Qing Yan

Psychoneuroimmunology

Systems Biology Approaches to Mind-Body Medicine

Springer

Psychoneuroimmunology

Qing Yan

Psychoneuroimmunology

Systems Biology Approaches to Mind-Body Medicine

Springer

Qing Yan
PharmTao
Santa Clara, CA, USA

ISBN 978-3-319-45109-1 ISBN 978-3-319-45111-4 (eBook)
DOI 10.1007/978-3-319-45111-4

Library of Congress Control Number: 2016953184

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Psychoneuroimmunology (PNI) is an emerging area that has developed rapidly during the last 40 years. As a multidisciplinary field, PNI may provide the scientific basis for mind-body relationships toward the development of personalized medicine. This book provides a comprehensive overview of the cutting-edge discoveries and the systems approaches in the area.

This book has several features that readers may find helpful. The first part of the book focuses on the PNI theories based on systems biology methodologies. The recognition of systemic biomarkers and networks may provide insights into the complex multidirectional interactions among various systems. The integrative biopsychosocial model is becoming the central theme for understanding health and diseases. For example, as the stress-inflammation connections are critical among different diseases, the elucidation of the complex associations may contribute to the findings of personalized and systems-based therapeutic targets.

The second part of this book focuses on the translation of PNI approaches into clinical practice. One of the major challenges in current bioscience is the translation of basic scientific discoveries into better clinical outcomes. This book is written in response to this challenge by highlighting the translational implications of PNI with the application of integrative interventions including meditation, nutritional supplements, and other mind-body strategies.

Specifically, PNI and systems biology studies support the establishment of integrative biopsychosocial models and multidimensional frameworks to connect the dynamical patterns of genetics, behaviors, environment, physiology, and pathology within various timeframes. On the basis of systemic PNI profiles, patient subgroups can be identified for personalized interventions toward the human-centered systems and dynamical medicine (see Chap. 1).

Novel models based on PNI and systems biology may provide the insights into the basic mechanisms at different levels of the human complex adaptive system (CAS). The understanding of the stress-inflammation networks would enable better therapeutic outcomes for various diseases including multiple sclerosis, cancer, and cardiovascular diseases (see Chap. 2).

In addition, the rhythmic patterns in the hypothalamic-pituitary-adrenocortical (HPA) axis have profound impacts on health and diseases. The molecular feedback and feedforward loops are essential in the neuroendocrine-immune networks. The dynamical systems approach may be appropriate to analyze the resilience and robustness of the HPA-leptin axis (see Chap. 3).

The cytokine networks may have impacts on the HPA axis in neuropsychiatric dysfunctions such as anxiety, depression, fatigue, cognitive problems, schizophrenia, and sleep disorders. Dynamical studies of the inflammatory biomarkers and pathways need to become a high priority in systemic PNI profiling (see Chap. 4).

Inflammation is considered a biological pathway that may connect sleep problems with the higher risks of disorders including depression and pain. Improving sleep quality and duration may be effective mind-body interventions (see Chap. 5).

The identification of systems-based biomarkers of depression is crucial for the translation of the discoveries in PNI into better clinical interventions. The depression-associated inflammatory networks and HPA axis-mediated interactions often have overlaps with physical disorders including rheumatoid arthritis, cardiovascular diseases, obesity, and cancer (see Chap. 6).

In schizophrenia, the complex interactions among the immune, endocrine, and nervous systems may be the essential mechanisms. The functions of the HPA-gonadal (HPAG) axis have been correlated to schizophrenia. The elucidation of these pathways is critical as the common inflammatory networks may be involved in both depression and schizophrenia (see Chap. 7).

Inflammatory biomarkers have an essential role in the psychological stress and behavioral symptoms of those with obesity. The elucidation of the cellular networks may contribute to the development of effective interventions for obesity and associated metabolic diseases including diabetes and cardiovascular diseases (see Chap. 8).

The bidirectional interactions between the nervous and immune systems have the major roles in inflammation, providing the connections among psychosocial stress, aging, and chronic diseases. The inflammatory, synaptic, and neurotrophic pathways have been related to the aging process and associated neurodegenerative diseases (see Chap. 9).

The PNI principles can be applied to understand the mechanisms in the comorbid disorders including cardiovascular diseases and psychiatric problems. The research in systems biology and PNI would help with the discovery of systems-based biomarkers including the inflammatory pathways for the diagnosis and treatment of cardiovascular diseases (see Chap. 10).

The individual variations and risk factors that may affect the psycho-neurological symptoms in cancer patients include perceived stress, cognitive deficits, malfunctions in the HPA axis, and inflammation. Such mechanisms indicate a framework for personalized medicine for different diseases sharing the common pathways in the inflammatory microenvironment (see Chap. 11).

Many evidences have addressed the stress-caused alterations in immune imbalance in chronic skin disorders including atopic dermatitis, psoriasis, and malignant melanoma. Various inflammatory pathways have been identified in fibrotic disorders

including localized scleroderma, pediatric and adult lichen sclerosus, and eosinophilic fasciitis (see Chap. 12).

The integrative PNI framework may help interpret the underlying mechanisms of mind-body medicine. Taking more adaptive ways and more effective coping strategies when facing life challenges may help improve the behaviors, psychophysiological responses, and overall health (see Chap. 13).

By covering topics from important concepts to recent development, from theoretical frameworks to clinical practice, this book intends to assist the understanding of PNI and mind-body methods toward the development of systems and dynamical medicine. It tries to present a state-of-the-art and holistic view for the translation of PNI into better preventive and personalized medical practice.

I would like to thank the editors from Springer for their support in this exciting project.

Santa Clara, CA, USA Qing Yan

Contents

Part I
Psychoneuroimmunology and Systems Biology Mechanisms

Chapter 1
From Psychoneuroimmunology to Personalized, Systems, and Dynamical Medicine

1.1 Psychoneuroimmunology (PNI) and Systems Biology

Biomedicine is getting to a revolutionary tipping point with the fast development in scientific discoveries. The current trend is moving from the reductionist-driven methods toward the systematic understanding of the whole system rather than separated components or factors (Gebicke-Haerter 2008; Yan 2010). Such approaches would incorporate multidimensional factors including the environmental, social, behavioral, and biological aspects (Mabry et al. 2008). These efforts require interdisciplinary works to construct biobehavioral–social–ecological models covering the molecular, cellular, physiological, psychosocial, and environmental levels (Yan 2011b). Such strategies would pave the ground for personalized and systems medicine.

The emerging field of psychoneuroimmunology (PNI) may serve as a platform for such multidisciplinary collaborations from the areas including psychology, neurobiology, immunology, endocrinology, pharmacology, and toxicology (Prolo et al. 2002). In the last four decades, PNI has been developing rapidly with profound impacts on various disciplines across the biomedical society. With the elucidation of the interconnections between behaviors and the nervous, immune, and endocrine systems, PNI studies may help understand the interactive and cooperative relationships in the integrated adaptive processes (Zachariae 2009; Kemeny 2009; Irwin 2008).

Because of the interdisciplinary features, the application of systems biology methods in PNI may promote its development in various aspects. Using experimental, computational, and high-throughput (HTP) approaches, systems biology investigates the interrelationships among biological components at various levels including molecules, cells, organisms, and environment (Yan 2005). The combination of PNI and systems biology may contribute to novel preventive and therapeutic methods for the development of systems medicine.

Specifically, in psychiatric studies, systems biology models may be especially helpful for the elucidation of the structural–functional complexity of the brain to

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_1

meet the challenges in describing mental disorders comprehensively and quantitatively (Tretter and Albus 2008). For example, the network-based methods may be useful for the better illustration of the crosstalk among pathways in different brain areas associated with Alzheimer's disease (AD) progression (Liu et al. 2010).

As another example, in the research about schizophrenia, systems biology methods have been applied for detecting potential biomarkers via the analyses in metabolomics, transcriptomics, proteomics, protein–protein interactions, and behavioral studies (Giegling et al. 2008). Such comprehensive investigations would be helpful for understanding the complexity of the brain and behaviors for the construction of models at various systems levels.

At the molecular level, neuroendocrine hormones such as the corticotrophin-releasing hormone may affect various cytokines generated by the immune system (Ziemssen and Kern 2007). At the system level, the brain can communicate with the immune system directly via the connections between sympathetic/parasympathetic nerves and lymphoid organs. The immune system may also influence the brain activities with the reflections in sleep and body temperature.

At the organism level, the mind–body connections and psychophysiological interactions have been confirmed by historical, experimental, and clinical evidences. For instance, attitudes and social supports may influence the susceptibility of physical diseases and life expectancy (Leonard and Myint 2009). Behavioral and life style changes can affect treatment results. Physical disorders often cause psychological problems in mood, behavior, and memory.

The functional and structural connections with reciprocal interactions among the multiple systems may facilitate the adaptive responses. Alterations in these activities and responses may result in various diseases. As an example, immune dysfunction may lead to various aging-associated problems including cardiovascular disease, cancers, type 2 diabetes, arthritis, and cognitive decline (Kiecolt-Glaser et al. 2002). Negative emotions and abnormal psychological activities may be involved in such processes by affecting the generation of proinflammatory cytokines in inflammatory conditions.

In summary, PNI studies based on systems biology methods may contribute to the philosophical solution between holism and reductionism via the integrative models connecting the communications among different levels. Such approaches may also help satisfy the demands in understanding mind–body medicine. With the better understanding of the structure–function, genotype–phenotype, and gene–environment interactions at different systems levels, the relevant findings can be translated into personalized and systems medicine (Yan 2011b).

1.2 Emotions, Stress, Inflammation, and Diseases

Studies in PNI have been focusing on the important topics such as how stress and negative emotions may affect the immune system. From the systems biology point of view, such connections can be studied at various levels. At the molecular level,

the serotonergic dysfunctions and the elevations of proinflammatory cytokines, glucocorticoids, catecholamines have been observed in those with chronic stress and depression (Leonard and Myint 2009; Goncharova and Tarakanov 2007).

At the cellular level, chronic stress can influence the corticotropin-releasing hormone system and the glucocorticoid receptor signaling pathways (Touma 2011). On immune cells, glucocorticoid receptors and cortisol may affect nuclear factor-kB (NF-kB) and relevant inflammatory pathways (Goncharova and Tarakanov 2007). More detailed discussions of the associations between stress and inflammation will be available in Chap. 2.

At the system level, chronic stress has been closely associated with anxiety and depression with the impacts on the hypothalamic–pituitary–adrenal (HPA) and sympathetic–adrenal–medullary axes, as well as the immune system (Leonard and Myint 2009; Goncharova and Tarakanov 2007). Such effects may lead to neurodegenerative alterations in the brain regions including hippocampus, prefrontal cortex, as well as amygdalae (Leonard and Myint 2009).

The alterations at different levels can often lead to systemic psychiatric and/or pathological results. For instance, the changes in the production patterns of vasopressin, dopamine, and serotonin can have impacts on emotionality, cognition, and social behaviors. The changes in gene expression patterns associated with glucocorticoid hormones and catecholamines can lead to immune dysfunctions (Goncharova and Tarakanov 2007). Such alterations can cause complex pathological problems by linking chronic stress and depression with the aging-associated illnesses including dementia and Alzheimer's disease (Leonard and Myint 2009; Kiecolt-Glaser 2009).

In other examples, distress may decelerate the wound healing process, elevate the risks to infections, and diminish the immune responses to vaccines. Studies have found that among the women with cervical dysplasia, stress was related to reduced HPV-specific immune responses by negatively affecting the antibody and T-cell immunity (Fang et al. 2008). These evidences have indicated the tight correlations between psychological factors and a wide range of neuroimmune functions.

1.3 The Dynamical Biopsychosocial Models on the Basis of PNI and Systems Biology

As discussed earlier, system biology-based studies of behavioral and physiological factors at various levels may contribute to the construction of biopsychosocial models. Such integrative models would be very helpful for the better understanding of health, wellness, diseases, as well as for the development of personalized and systems medicine.

As illustrated in Fig. 1.1, at the molecular level, functional genetic variances and genomic features are essential for detecting individual reactions to stress, environmental changes, pathological stimulations, and drugs. At the cellular level, protein–protein interactions and signaling pathways are pivotal for connecting the

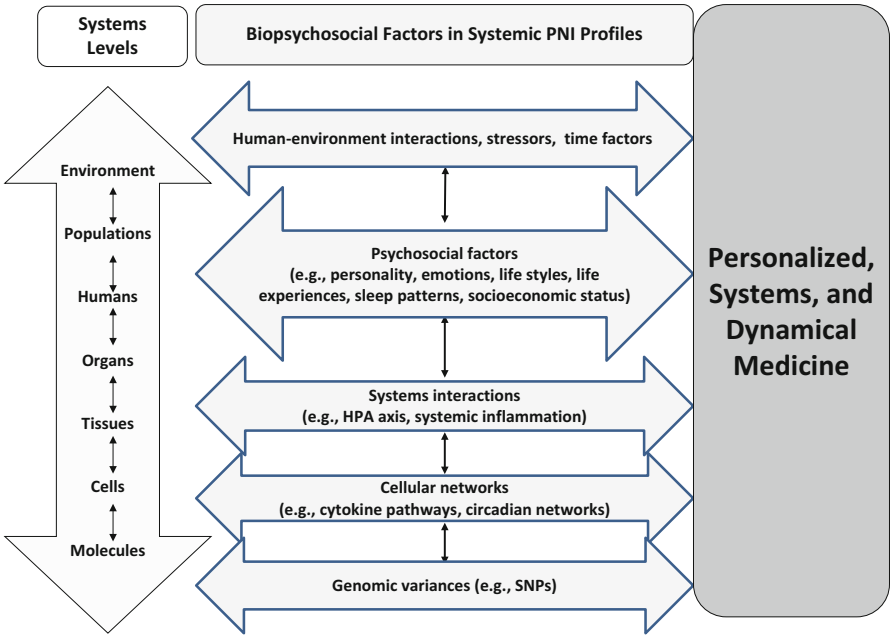

Fig. 1.1 The systems biology and PNI-based biopsychosocial model for the development of personalized, systems, and dynamical medicine

mechanisms at molecular and system levels, such as the links between inflammatory markers and systemic inflammation. Examples and more detailed discussions will be provided in the following chapters.

Furthermore, complex and dynamical interrelationships between different levels within different time dimensions such as the gene–environment interactions at different stages in the whole life span are also important (Yan 2014). Specifically, chronic stress cannot be explained in a simple HPA response (Friedman 2008). Instead, "A new wave of theories needs to be developed to incorporate the moderating influences of timing, nature of stress, controllability, and individual psychiatric response" (Miller et al. 2007).

Such models based on dynamical systems biology would contribute to the identification of dynamical patterns in PNI toward the development of both systems and dynamical medicine (Yan 2014, also see Chaps. 3 and 4). Among all of the factors, individual differences and the patterns of personalities, coping styles, emotionality, as well as cognitive and behavioral responses have the significant roles in immune-associated conditions and diseases (Kemeny and Schedlowski 2007).

As an example, bereavement is a stressful condition that can affect the activities of natural killer (NK) cells (Kemeny and Laudenslager 1999). Personality is an important factor in such conditions as those with the trait "negative affectivity" are more prone to have depression and anxiety when compared with those who don't have the negative traits (Kemeny and Laudenslager 1999).

Individual patterns in psychophysiological reactions such as the offensive aggressive behavior have been identified as the best predictor for the immune-associated risk factors for many diseases (Koolhaas 2008). An example is that cynical hostility may be a reliable predictor for cardiovascular diseases (Friedman 2008). Such observations indicate that individual psychological conditions such as personality may be critical for detecting personalized psychological and physiological changes.

These "internal elements" may have more important effects on health outcomes than the stressful environment or external stimulants. Causal linkages and multidirectional pathways have been identified among personality, health, disorders, and longevity (Friedman 2008). Unhealthy behavioral patterns including poor diet habits and smoking may have direct connections with pathological results.

Such mechanisms indicate that integrative mind–body interventions targeting personalities may be more effective than simple drug administrations. An example is that regular drug treatment of depression may not be very successful for the prevention of cardiovascular diseases, because personality components are also critical (Friedman 2008).

In addition, various environmental and socioeconomic components need to be incorporated into the systemic map of personalized medicine (see Fig. 1.1). For example, pollutants including tobacco smoke, diesel-associated particles, drugs, pesticides, and industrial contaminants may cause dysfunctions in the neuroendocrine pathways (Waye and Trudeau 2011; Wright and Subramanian 2007). Lower socioeconomic status and chronic social status threat such as discrimination and devaluation may result in the disruptions of the neurohormonal pathways and the HPA axis with the higher levels of proinflammatory cytokines and glucocorticoid changes (Kemeny 2009).

These evidences support the establishment of the dynamical biopsychosocial models and multidimensional frameworks to connect the patterns of genetics, personality, behaviors, environment, physiology, and pathology within various timeframes (see Fig. 1.1). Such models may also contribute to the transition from the disease-centered medicine to human-centric medicine (Yan 2011a). Specifically, systemic alterations in the inflammatory networks that are shared in different disorders can be applied as the common preventive and treatment targets for multiple illnesses rather than a single disease. Some of the examples can be found in the following chapters.

1.4 Systemic PNI Profiles for Personalized, Systems, and Dynamical Medicine

The integrative biopsychosocial models based on PNI and systems biology represent the complex interactions and dynamical events in the whole system (see Fig. 1.1). Such models may be useful for the prediction of the behaviors of the whole organism including drug responses and therapeutic outcomes.

To translate such models into better clinical practice, systemic PNI profiles can be established. Such comprehensive profiles can incorporate parameters at various levels from cytokine gene expression to cellular signaling pathways, from brain images to behavioral phenotypes (see the following chapters).

Such integrative behavioral and pathophysiological profiles may reveal the underlying genotype–phenotype correlations rather than the conventional classification of the isolated "subtypes" of a disease. Specifically, the behavioral sections of the profiles can be a comprehensive summary of the emotional properties, personality, and neurocognitive activities of each individual patient (Bloss et al. 2010; also see Fig. 1.1).

Based on such systemic PNI profile, patient subgroups can be identified for more precise diagnosis, prognosis, and individualized interventions. For instance, the common features of different neuropsychiatric diseases including schizophrenia and bipolar disorder can be identified and treated more effectively. Such approaches would enable the transition from the single-method and disease-based medicine to human-centric medicine.

For example, predictive models can be constructed by analyzing systemic behaviors, cellular pathways, and neuronal networks such as the prefrontal cortical working memory circuits associated with schizophrenia (Tretter and Albus 2008; also see Fig. 1.1). With such understanding of the spatiotemporal interactions in the PNI systems, more effective strategies can be developed for personalized, systems, and dynamical medicine.

References

Bloss, C. S., Schiabor, K. M., & Schork, N. J. (2010). Human behavioral informatics in genetic studies of neuropsychiatric disease: Multivariate profile-based analysis. *Brain Research Bulletin, 83*, 177–188.

Fang, C. Y., Miller, S. M., Bovbjerg, D. H., Bergman, C., Edelson, M. I., & Rosenblum, N. G. (2008). Perceived stress is associated with impaired T-cell response to HPV16 in women with cervical dysplasia. *Annals of Behavioral Medicine, 35*, 87–96.

Friedman, H. S. (2008). The multiple linkages of personality and disease. *Brain, Behavior, and Immunity, 22*, 668–675.

Gebicke-Haerter, P. J. (2008). Systems biology in molecular psychiatry. *Pharmacopsychiatry, 41*(Suppl 1), S19–S27.

Giegling, I., Hartmann, A. M., Genius, J., Benninghoff, J., Möller, H.-J., & Rujescu, D. (2008). Systems biology and complex neurobehavioral traits. *Pharmacopsychiatry, 41*(Suppl 1), S32–S36.

Goncharova, L. B., & Tarakanov, A. O. (2007). Molecular networks of brain and immunity. *Brain Research Reviews, 55*(1), 155–166.

Irwin, M. R. (2008). Human psychoneuroimmunology: 20 years of discovery. *Brain, Behavior, and Immunity, 22*, 129–139.

Kemeny, M. E. (2009). Psychobiological responses to social threat: Evolution of a psychological model in psychoneuroimmunology. *Brain, Behavior, and Immunity, 23*, 1–9.

Kemeny, M. E., & Laudenslager, M. L. (1999). Introduction beyond stress: The role of individual difference factors in psychoneuroimmunology. *Brain, Behavior, and Immunity, 13*, 73–75.

Kemeny, M. E., & Schedlowski, M. (2007). Understanding the interaction between psychosocial stress and immune-related diseases: A stepwise progression. *Brain, Behavior, and Immunity, 21*, 1009–1018.

Kiecolt-Glaser, J. K. (2009). Psychoneuroimmunology psychology's gateway to the biomedical future. *Perspectives on Psychological Science, 4*, 367–369.

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Psychoneuroimmunology: Psychological influences on immune function and health. *Journal of Consulting and Clinical Psychology, 70*, 537–547.

Koolhaas, J. M. (2008). Coping style and immunity in animals: Making sense of individual variation. *Brain, Behavior, and Immunity, 22*, 662–667.

Leonard, B. E., & Myint, A. (2009). The psychoneuroimmunology of depression. *Human Psychopharmacology, 24*, 165–175.

Liu, Z.-P., Wang, Y., Zhang, X.-S., & Chen, L. (2010). Identifying dysfunctional crosstalk of pathways in various regions of Alzheimer's disease brains. *BMC Systems Biology, 4*(Suppl 2), S11.

Mabry, P. L., Olster, D. H., Morgan, G. D., & Abrams, D. B. (2008). Interdisciplinarity and systems science to improve population health: A view from the NIH Office of Behavioral and Social Sciences Research. *American Journal of Preventive Medicine, 35*(2 Suppl), S211–S224.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin, 133*, 25–45.

Prolo, P., Chiappelli, F., Fiorucci, A., Dovio, A., Sartori, M. L., & Angeli, A. (2002). Psychoneuroimmunology: New avenues of research for the twenty-first century. *Annals of the New York Academy of Sciences, 966*, 400–408.

Touma, C. (2011). Stress and affective disorders: Animal models elucidating the molecular basis of neuroendocrine-behavior interactions. *Pharmacopsychiatry, 44*(Suppl 1), S15–S26.

Tretter, F., & Albus, M. (2008). Systems biology and psychiatry—Modeling molecular and cellular networks of mental disorders. *Pharmacopsychiatry, 41*(Suppl 1), S2–S18.

Waye, A., & Trudeau, V. L. (2011). Neuroendocrine disruption: More than hormones are upset. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews, 14*, 270–291.

Wright, R. J., & Subramanian, S. V. (2007). Advancing a multilevel framework for epidemiologic research on asthma disparities. *Chest, 132*(Suppl), 757S–769S.

Yan, Q. (2005). Pharmacogenomics and systems biology of membrane transporters. *Molecular Biotechnology, 29*, 75–88.

Yan, Q. (2010). Translational bioinformatics and systems biology approaches for personalized medicine. *Methods in Molecular Biology, 662*, 167–178.

Yan, Q. (2011a). Toward the integration of personalized and systems medicine: Challenges, opportunities and approaches. *Personalized Medicine, 8*, 1–4.

Yan, Q. (2011b). Translation of psychoneuroimmunology into personalized medicine: A systems biology perspective. *Personalized Medicine, 8*, 641–649.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Zachariae, R. (2009). Psychoneuroimmunology: A bio-psycho-social approach to health and disease. *Scandinavian Journal of Psychology, 50*(6), 645–651.

Ziemssen, T., & Kern, S. (2007). Psychoneuroimmunology—Cross-talk between the immune and nervous systems. *Journal of Neurology, 254*(Suppl 2), II8–II11.

Chapter 2
Stress and Inflammation: Translational Implications in Mind–Body Medicine

2.1 Stress and Inflammation: A Systems Biology Perspective

Stress and disrupted homeostasis can be caused by environmental changes and stimulations. However, the same stressor may result in different responses in different individuals, such as behavioral alterations or pathological dysfunctions in some people but little or no effects on other people. Different coping strategies and adaptive capabilities may account for such different impacts (Leonard and Myint 2009).

Stress can be acute or chronic. Acute stress responses can be protective in the adaptive processes for potential adverse environments. Chronic and constant stress may damage the ability of adaptation with changes in the immune system and hypothalamic–pituitary–adrenal (HPA) axis. Such changes may lead to pathological problems such as hypercortisolism, hypertension, and psychiatric disorders such as anxiety and depression (Leonard and Myint 2009).

Psychoneuroimmunology (PNI) studies may help explain the complex mechanisms underlying such processes. In stress responses, the endocrine and neurotransmitter systems are closely associated with the immune system with a wide range of molecules involved such as catecholamines, glucocorticoids, endorphins, and other neuropeptides (Leonard and Myint 2009). Stress and negative emotions may cause sympathetic hyperactivity and higher oxidative stress through cytokine receptors on endocrine cells and neurons, as well as hormone and neurotransmitter receptors on immune cells (Kemeny 2009; Irwin 2008; Alford 2007).

PNI studies based on systems biology approaches would enable the systemic insights into the complex stress–inflammation–disease correlations. The understanding of such interrelationships may be critical for the practice of human-centric personalized medicine by treating the shared pathological mechanisms instead of an isolated illness (see Chap. 1).

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_2

Inflammation has a significant role in adverse stress responses and various diseases. For instance, problems including anxiety, depression, and posttraumatic stress disorder (PTSD) have been associated with the elevated proinflammatory cytokines such as interleukin-6 (IL-6) and inflammatory networks such as the NF-kB pathway (Haroon et al. 2011; Segerstrom and Miller 2004; Carpenter et al. 2010). At the cellular and behavioral levels, relevant factors include T-cell subpopulations, dietary intake, adiposity, and the bacterial composition of the gut microbiota (Haroon et al. 2011).

The inflammatory mechanisms provide the common linkages among the leading causes of mortality (Aggarwal et al. 2006). For example, the proinflammatory cytokines including IL-6 and IL-1beta are the key factors in cardiovascular diseases, cancers, type II diabetes, arthritis, Alzheimer's disease, as well as skin disorders including psoriasis (Kiecolt-Glaser et al. 2002). Elevated proinflammatory cytokine levels triggered by stress and depression are associated with prolonged infectious periods and delayed wound healing (Glaser and Kiecolt-Glaser 2005).

In addition, various evidences have connected childhood maltreatment and adverse experiences with poor health in the adulthood. Inflammation is a pivotal mediator in such linkages as those adults with early life stress often have higher systemic inflammatory responses to acute stressors including elevated IL-6 levels (Carpenter et al. 2010). Early life stress experiences have also been related to the higher risks for adult obesity (D'Argenio et al. 2009).

2.2 The PNI Networks, Systems-Based Biomarkers, and Mind–Body Mechanisms

The integration of multiple emerging scientific disciplines including PNI, psychosocial genomics, and systems biology may pave the scientific ground for the translation and practice of mind–body medicine. The dynamical biopsychosocial models may provide the insights into the basic mechanisms at different systems levels of the human complex adaptive system (CAS) (see Chap. 1). These multiple levels expand from gene expression and neurogenesis to human experiencing, behavior, and consciousness (Rossi 2002).

Such dynamical biopsychosocial models emphasize the integrative psychoneuroendocrine-immune networks and the impacts of both stress and relaxation on the immune functions. The frameworks may help interpret the underlying mechanisms of mind–body medicine via the description of the multidirectional pathways that convey information between the central nervous system (CNS) and the peripheral systems. Such information exchanges are involved in the affective, autonomic, hormonal, and immune responses (Taylor et al. 2010).

Systemic factors can be used as the potential biomarkers for the central–peripheral communications and homeostasis in such integrative frameworks, including the

heart rate variability (HRV) and inflammatory markers. Specifically, certain frontotemporal cortical areas are pivotal in showing and regulating adverse symptoms in chronic diseases (Taylor et al. 2010). These areas may communicate reciprocally with subcortical structures associated with stress responses and homeostasis.

At the molecular and cellular levels, many factors may be involved in the complex networks, including endocrine components corticotrophin releasing factor (CRF), adrenocorticotropic hormone (ACTH), glucocorticoids (GC), alpha-endorphin, as well as Met-enkephalin (Mahbub-E-Sobhani et al. 2011). The immune factors include T cells; B cells; monocytes/macrophages; natural killer (NK) cells; as well as cytokines such as tumor necrosis factor-α (TNF-α), interferon-α (IFN-α), and interleukins such as IL-1, IL-2, IL-4, IL-6, IL-10, and IL-12.

In addition, stressful emotions may affect white blood cell functions by weakening their responses to viral infected cells and cancer cells (Littrell 2008). Vaccination has been found less effective and wounds may heal more slowly among the stressed people. However, stress may worsen certain types of autoimmune disease associated with some subsets of white blood cells.

At the system levels, both of the psychological and physical benefits of mind–body approaches have been explored. Emerging evidences are revealing the effects of these approaches on the immune system, especially on the inflammatory biomarkers and antiviral associated immune responses (see Chap. 13).

Different types of stress such as acute, brief naturalistic, and chronic stress may lead to different immune processes that affect the homeostasis (Mahbub-E-Sobhani et al. 2011). On the other hand, relaxation techniques may help keep the homeostasis. For instance, the PNI framework has been found especially appropriate in inflammatory bowel disease (IBD) as it involves intense immune reactions (Smith and Bryant 2002). Because of the strong mind–gut links, the behavioral interventions such as those applied by professional nurses may promote the quality of life by controlling symptoms for the IBD patients.

2.3 The Stress–Inflammation–Disease Associations: Translational Implications of PNI

The systems-based PNI studies on the stress–inflammation correlations have the translational implications in a wide range of diseases. According to the biopsychosocial models, the different ways that different individuals respond to stressors have the profound meanings to health, wellness, and illnesses (Lutgendorf and Costanzo 2003; also see Chap. 1). For example, stress and depression may have the impacts on food choices especially unhealthy choices such as the preferences for snack foods rather than fresh fruits (Kiecolt-Glaser 2010).

Stress can alter the gastroduodenal and colonic motilities (Yin et al. 2004). Experiments using a laboratory stressor showed that about 14 % longer time than

normal would be needed for the clearance of a fat load (Stoney et al. 2002). The hyperactivity of the sympatho-adrenal system associated with chronic stress may disturb metabolic homeostasis and result in fat accumulation, hypertension, and diabetes.

Although depression is a psychiatric disorder, it has profound influences on the neuroendocrine-immune systems. Those with chronic stress and depression often have the higher levels of inflammatory biomarkers such as C-reactive protein (CRP) and TNF-α (Leonard and Myint 2009). As proinflammatory cytokines are associated with neurotransmitter metabolism and synaptic plasticity, they may have impacts on various pathophysiological processes (Shelton and Miller 2010).

Specifically, the changes at the molecular and cellular levels including the stimulated microglia with activated proinflammatory cytokines have been associated with neurodegeneration and Alzheimer's disease (Leonard and Myint 2009). In the meantime, decreased levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) can cause slower neuronal repair (see Chap. 4). Changes at the tissue and organ levels include the alterations in the regions of the hippocampus, frontal cortex, and amygdalae (Leonard and Myint 2009).

In addition, complex correlations have been identified among stress, depression, and obesity, multiple sclerosis, psoriasis, rheumatoid arthritis, cancers, as well as cardiovascular diseases (Shelton and Miller 2010). The higher incidences of obesity and metabolic syndromes have been observed among patients with posttraumatic stress disorder (PTSD), possibly mediated via the neuropeptide Y (NPY) and glucocorticoid systems (Rasmusson et al. 2010). On the other hand, weight loss interventions may lead to the lower levels of inflammatory markers with better emotional status (Capuron et al. 2010).

Psychosocial stress has been related to coronary artery disease (CAD), thrombus formation, and myocardial infarction through affecting the immune system (Ho et al. 2010). Various aspects can be influenced, including the endothelial functions, NK cells, and acute phase proteins. However, those with the relevant cardiovascular risk factors can benefit from mind–body approaches including exercises, healthy diet plans, as well as antidepressants (Irwin 2008).

Cancer also has the tight linkages with stress via the suppression of lymphocyte proliferation and NK cell activities (Tausk et al. 2008). Studies have found that stress management methods including relaxation training may benefit the survival of cancer patients probably by improving the cytotoxic and NK cell functions.

Furthermore, emotional stressors have been related to various skin disorders including acne, atopic eczema, herpes simplex infections, psoriasis, and vitiligo (Tausk et al. 2008). Psoriasis patients often have dysfunctions in the HPA axis with hypertension and higher heart rates upon stress stimulations. Mind–body techniques such as meditation and hypnosis have been found helpful for the quicker clearance of psoriasis (Tausk et al. 2008). More discussions about the clinical implications of stress, inflammation, and various diseases will be available in the following chapters.

2.4 Targeting the Stress and Inflammation-Associated Networks

The dynamical biopsychosocial models based on PNI and systems biology can be applied for drug design targeting the shared pathways of different illnesses instead of a single isolated problem. As discussed previously, such approaches will facilitate the conversion from the disease-centered drugs to human-centric medicine, the main goal of personalized medicine (see Chap. 1).

Specifically, targeting the stress and inflammation-associated networks including IL-6, NFkB, and p38 MAPK signaling cascades may benefit a broad spectrum of disorders including depression, cancer, and cardiovascular disease (Yan 2011b). Such methods would allow for the more efficient drug strategies by using conventional drugs for better clinical outcomes and reducing the drug development costs (Yan 2011a).

For instance, drugs such as etanercept, infliximab, and anakinra that are conventionally used for rheumatoid arthritis may have potential applications for mood disorders. Etanercept administration has been shown to have beneficial effects on depression in psoriasis patients (Irwin and Miller 2007).

In summary, the understanding of the stress–inflammation networks in the behavior-neuroendocrine-immune communications would enable health practitioners to achieve better therapeutic outcomes with higher quality of life among patients. For instance, in intensive care units, patients' immune dysfunctions have been correlated to the stressors including trauma, anxiety, fear, and sleep disturbance (DeKeyser 2003). The integrative PNI models can be applied by physicians and nurses for stress reduction via empathetic methods and better coping strategies (Langley et al. 2006; Starkweather et al. 2005; McCain et al. 2005).

References

Aggarwal, B. B., Shishodia, S., Sandur, S. K., Pandey, M. K., & Sethi, G. (2006). Inflammation and cancer: How hot is the link? *Biochemical Pharmacology, 72*, 1605–1621.

Alford, L. (2007). Findings of interest from immunology and psychoneuroimmunology. *Manual Therapy, 12*, 176–180.

Capuron, L., Poitou, C., Machaux-Tholliez, D., Frochot, V., Bouillot, J. L., Basdevant, A., et al. (2010). Relationship between adiposity, emotional status and eating behaviour in obese women: Role of inflammation. *Psychological Medicine, 41*, 1517–1528.

Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology, 35*, 2617–2623.

D'Argenio, A., Mazzi, C., Pecchioli, L., Di Lorenzo, G., Siracusano, A., & Troisi, A. (2009). Early trauma and adult obesity: Is psychological dysfunction the mediating mechanism? *Physiology & Behavior, 98*, 543–546.

DeKeyser, F. (2003). Psychoneuroimmunology in critically ill patients. *AACN Clinical Issues, 14*, 25–32.

Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: Implications for health. *Nature Reviews Immunology, 5*, 243–251.

Haroon, E., Raison, C. L., & Miller, A. H. (2011). Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology, 37*(1), 137–162.

Ho, R. C. M., Neo, L. F., Chua, A. N. C., Cheak, A. A., & Mak, A. (2010). Research on psychoneuroimmunology: Does stress influence immunity and cause coronary artery disease? *Annals of the Academy of Medicine, Singapore, 39*, 191–196.

Irwin, M. R. (2008). Human psychoneuroimmunology: 20 years of discovery. *Brain, Behavior, and Immunity, 22*, 129–139.

Irwin, M. R., & Miller, A. H. (2007). Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity, 21*, 374–383.

Kemeny, M. E. (2009). Psychobiological responses to social threat: Evolution of a psychological model in psychoneuroimmunology. *Brain, Behavior, and Immunity, 23*, 1–9.

Kiecolt-Glaser, J. K. (2010). Stress, food, and inflammation: Psychoneuroimmunology and nutrition at the cutting edge. *Psychosomatic Medicine, 72*, 365–369.

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Psychoneuroimmunology: Psychological influences on immune function and health. *Journal of Consulting and Clinical Psychology, 70*, 537–547.

Langley, P., Fonseca, J., & Iphofen, R. (2006). Psychoneuroimmunology and health from a nursing perspective. *British Journal of Nursing, 15*, 1126–1129.

Leonard, B. E., & Myint, A. (2009). The psychoneuroimmunology of depression. *Human Psychopharmacology, 24*, 165–175.

Littrell, J. (2008). The mind-body connection: Not just a theory anymore. *Social Work in Health Care, 46*, 17–37.

Lutgendorf, S. K., & Costanzo, E. S. (2003). Psychoneuroimmunology and health psychology: An integrative model. *Brain, Behavior, and Immunity, 17*, 225–232.

Mahbub-E-Sobhani, Haque, N., Salma, U., & Ahmed, A. (2011). Immune modulation in response to stress and relaxation. *Pakistan Journal of Biological Sciences, 14*, 363–374.

McCain, N. L., Gray, D. P., Walter, J. M., & Robins, J. (2005). Implementing a comprehensive approach to the study of health dynamics using the psychoneuroimmunology paradigm. *ANS Advances in Nursing Science, 28*, 320–332.

Rasmusson, A. M., Schnurr, P. P., Zukowska, Z., Scioli, E., & Forman, D. E. (2010). Adaptation to extreme stress: Post-traumatic stress disorder, neuropeptide Y and metabolic syndrome. *Experimental Biology and Medicine (Maywood), 235*, 1150–1162.

Rossi, E. L. (2002). Psychosocial genomics: Gene expression, neurogenesis, and human experience in mind-body medicine. *Advances in Mind-Body Medicine, 18*, 22–30.

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin, 130*, 1–37.

Shelton, R. C., & Miller, A. H. (2010). Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression. *Progress in Neurobiology, 91*, 275–299.

Smith, M. M., & Bryant, J. L. (2002). Mind-body and mind-gut connection in inflammatory bowel disease. *Gastroenterology Nursing, 25*, 213–217.

Starkweather, A., Witek-Janusek, L., & Mathews, H. L. (2005). Applying the psychoneuroimmunology framework to nursing research. *Journal of Neuroscience Nursing, 37*, 56–62.

Stoney, C. M., West, S. G., Hughes, J. W., Lentino, L. M., Finney, M. L., Falko, J., et al. (2002). Acute psychological stress reduces plasma triglyceride clearance. *Psychophysiology, 39*, 80–85.

Tausk, F., Elenkov, I., & Moynihan, J. (2008). Psychoneuroimmunology. *Dermatology and Therapy, 21*, 22–31.

Taylor, A. G., Goehler, L. E., Galper, D. I., Innes, K. E., & Bourguignon, C. (2010). Top-down and bottom-up mechanisms in mind-body medicine: Development of an integrative framework for psychophysiological research. *Explore (NY), 6*, 29–41.

Yan, Q. (2011a). Toward the integration of personalized and systems medicine: Challenges, opportunities and approaches. *Personalized Medicine, 8*, 1–4.

Yan, Q. (2011b). Translation of psychoneuroimmunology into personalized medicine: A systems biology perspective. *Personalized Medicine, 8*, 641–649.

Yin, J., Levanon, D., & Chen, J. D. Z. (2004). Inhibitory effects of stress on postprandial gastric myoelectrical activity and vagal tone in healthy subjects. *Neurogastroenterology and Motility, 16*, 737–744.

Chapter 3
Biological Rhythms and the HPA Axis in Psychoneuroimmunology

3.1 The Rhythmic Patterns of the PNI Networks: Systems Biology Approaches

Intrinsic biological rhythms are the key features of the dynamical biopsychosocial models with the essential roles in health and aging. The complexity of the rhythmic variability such as the heart rate variability reflects the network interconnectedness (Sturmberg et al. 2015). Specifically, circadian rhythms have been found to play the critical roles in various psychoneuroimmunology (PNI)-associated activities such as sleep and eating behaviors.

Having endogenous biological clocks and oscillators is a benefit for adaptation. The clocks can help the organism foresee environmental changes and make adjustments, such as by utilizing energy resources more efficiently (Zhang and Kay 2010). They are also critical for maintaining health. As an intrinsic oscillator, the circadian clock controls the daily rhythms in both physiological and psychological activities (Baggs and Hogenesch 2010).

The elucidation of the behaviors of the interactive oscillations at multiple systems levels would be helpful for the understanding of psychological processes including learning and memory. Such rhythmic patterns have been identified from molecules to cellular pathways, from the brain networks to the immune system (Gebicke-Haerter et al. 2013; Yan 2014).

Specifically, more and more evidences are showing that circadian rhythms play a critical role in the regulation of the immune system (Mavroudis et al. 2013). A variety of immune variables have been found to go through daily fluctuations. These immune variables include the count of peripheral blood mononuclear cells and red blood cells. The levels of the essential immune factors including cytokines are also influenced by such rhythms.

Studies have revealed that the daily patterns of autonomic and endocrine rhythms may be involved in the processes of how the circadian information affects immune tissues (Mavroudis et al. 2013). The immune mediators including cytokines are

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_3

involved in the networks of neuroendocrine-immune interactions, maintaining a multidirectional flow of information that may affect the stage of the circadian clock.

To translate the understanding of such mechanisms into better clinical outcomes, some potential methods have been proposed to moderate homeostatic circadian operations, such as the reprogramming of biological rhythms (Mavroudis et al. 2013). To achieve the optimized strategies for effective interventions, the elucidation of the relevant signaling pathways and networks involved in the host responses and homeostatic regulations would be necessary.

In recent years, studies in systems biology have revealed the mechanistic properties and robustness of circadian oscillators by using the methods such as gene expression profiling and perturbation analysis (Zhang and Kay 2010; Baggs and Hogenesch 2010). The description and assessment at various systems levels would be very helpful for providing insights into the basic features of these complex systems.

For example, the disrupted rhythmic behaviors in mental disorders may be associated with varied oscillatory behaviors of gene expressions (Zhang and Kay 2010). Chronic stress may lead to abnormal endocrine signals that disturb the rhythmic patterns.

Using systems biology methods, a multiscale understanding of the circadian systems can be formed, expanding from the molecular level to the whole organism (Yan 2014). Proteomic analysis and cell-based screening methods would allow for the detection of clock components and regulators (Baggs and Hogenesch 2010).

Furthermore, the recent advancement in high-throughput (HTP) technologies such as microarrays and epigenetic profiling may also contribute to such understanding. Mathematical and computational methods can be applied for studying the small-world topology of the synchronized firing via neuron–neuron connections and neuron–glia gap junctions (Gebicke-Haerter et al. 2013).

Based on the systemic understanding, computational algorithms and laboratory experiments for the time-series analyses using various temporary scales are becoming important for identifying the rhythmic gene expressions and clustering patterns (Yan 2014). Such insights may also contribute to the discovery of novel therapeutic schemes.

3.2 Chronic Stress and the Dynamics of the HPA Axis

3.2.1 The Rhythmic Patterns of the HPA Axis in Association with Stress Responses

As illustrated in Fig. 3.1, the circadian and ultradian rhythms have the essential roles in the physiological and pathological activities of various organs and systems. For example, the hypothalamic–pituitary–adrenal (HPA) axis is the key neuroendocrine system involved in stress responses. It controls the circulating levels of

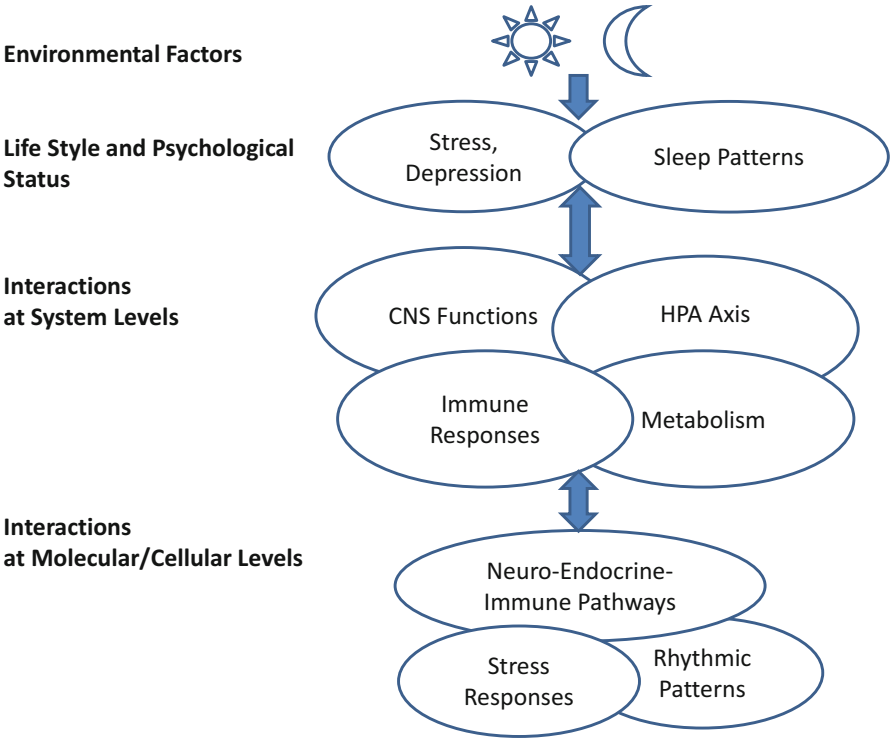

Fig. 3.1 The rhythmic patterns of the HPA axis in association with stress responses at various systems levels

glucocorticoid hormones. In normal and unstressed situations, glucocorticoids are generated with evident circadian rhythms (Spiga et al. 2014).

During the active stages such as daytime in humans and nighttime in nocturnal mammals including mice and rats, the levels of glucocorticoids reach the peak. Studies of the circadian rhythms of the HPA axis have identified a pulsatile generation of glucocorticoids from the adrenal gland (Spiga et al. 2014). Upon this release, immediate ultradian oscillations of the hormone levels can be observed in the blood as well as the target tissues such as the brain.

With their effects on the physiology, behaviors, and pathology in certain conditions, the circadian and ultradian HPA rhythms have profound impacts on health and diseases. Because of the multiple spatiotemporal factors, the dynamics of the HPA axis is quite complex. These factors include the different metabolic loads in different individuals, the mental and physical conditions, the circadian rhythms of the day and night, the ultradian phases, as well as the socioenvironmental influences (Marković et al. 2011; also see Fig. 3.1).

Such complexity makes it hard to assess the HPA axis activity among different individuals. The single time-point analysis of the cortisol levels would be inappropriate to describe the general condition of the HPA axis in an individual (Marković

et al. 2011). However, the understanding of the complexity would be meaningful for improving pharmacotherapy with glucocorticoids.

3.2.2 *The Circadian and Homeostatic Mechanisms of the HPA Axis at Various Levels*

The joined molecular feedback and feedforward loops are essential in the neuroendocrine-immune networks, allowing for synchronized functions that may be essential to optimize the immune reactions (Mavroudis et al. 2013). Diurnal rhythms may influence many different aspects of human behaviors including sleep, olfaction, memory, and learning. However, the potential impacts on physiological and pathological responses such as the brain activities at different time points of a day are hardly considered in conventional medicine.

Factors at various systems levels may disturb the inherent rhythmic composition and patterns, such as genetic mutations among the important rhythmic components. The rhythmic disruptions caused by environmental and epigenetic alterations have been found as the important risk factors for many diseases (Gebicke-Haerter et al. 2013).

The understanding of these different factors may enable a more complete view of health problems, especially the interactions among stress, depression, and the alterations of hormone dynamics in the HPA axis (see Fig. 3.1). Some of the factors may be the dysregulations of the proteins such as the corticotrophin-releasing hormone (CRH) and its receptor corticotrophin-releasing hormone receptor 1 (CRHR1). The elucidation of such molecular mechanisms would be helpful for a better understanding of the dynamical links between depression and the HPA axis.

For instance, in a recent study using rat models under the condition of chronic unpredictable mild stress (CUMS) for 21 days, the expression levels of CRHR1 in the hypothalamus were measured to analyze the effects of depression (Wan et al. 2014). The histone methylation at the CRHR1 gene promoter was also examined. The study assessed the levels of histone H3 trimethylation at lysines 4 (H3K4) and 9 (H3K9) to detect the transcriptional activities.

The study found that those rats under CUMS had the lower levels of locomotion and sucrose preference. These stress-induced behavioral changes were linked to the higher expression levels of CRHR1 with the reduced levels of H3K9 trimethylation (Wan et al. 2014). Such connections may be helpful for further understanding of stress-related problems such as depression.

In addition, studies have shown that the clockwork in macrophages may serve as the temporal gating of systemic reactions toward endotoxins (Gibbs et al. 2012). In such processes, Rev-erbα (NR1D1) has been identified as the primary link between the temporal pattern and immune reactions.

To compare various dynamic conditions of the HPA axis, different parameters need to be defined to illustrate the self-regulation processes in different circumstances

such as acute and/or chronic stress. In one study, a four-dimensional stoichiometric model was proposed to represent and predict the activities of the HPA axis in response to acute and chronic stress (Marković et al. 2011). In this model, a sudden change in the cortisol level in the process of numerical integration was used to represent the acute stress. The alterations in the mean stationary state levels of CRH were used to represent chronic stress.

The model was applied to analyze various parameters including the influences of acute stress intensity and the temporal factors of the onset regarding the ultradian amplitude and phase. The activities of the HPA axis in response to chronic stress were assessed using bifurcation analysis (Marković et al. 2011). These applications can be useful for making predictions in pharmacotherapy.

In addition, a recent study detected how the circadian and homeostatic functions affect the functional connectivity (FC) and cerebral blood flow (rCBF) in the different areas of the brain among healthy human volunteers (Hodkinson et al. 2014). To monitor the normal activities of the circadian alterations and the HPA axis, the samples of salivary cortisol were also collected in the study.

The study found that with the change of time from morning to afternoon, the FC and rCBF altered with the essential reduction in the functional integration of the default mode network (DMN) (Hodkinson et al. 2014). The observation of the anterior cingulate cortex (ACC) showed that the levels of morning cortisol were negatively connected to rCBF. These findings suggest that the functional integrity of the DMN especially the ACC might be regulated by the homeostatic mechanisms of the HPA axis. Furthermore, the time of the day is critical and the effects of circadian rhythms need to be considered for a better understanding of the various activities at various systems levels.

3.3 The Dynamics of the HPA Axis in Association with Diseases

3.3.1 Depression and Cancer

The PNI studies of anxiety, posttraumatic stress, and obsessive compulsive disorders have emphasized the dysfunctions in the immune system and the HPA axis (Furtado and Katzman 2015). Such dysregulations may be reflected in the alterations in the levels of cortisol and pro- and anti-inflammatory cytokines. The elucidation of the underlying mechanisms would contribute to the development of preventive and therapeutic strategies with reductions in societal and economic burdens.

Among patients with depression, the alterations in the complex neuro-immune-endocrine interactions and chronobiological rhythms have been revealed as the prominent properties (Antonioli et al. 2012; also see Fig. 3.1). These features include the increased levels of circulating corticosteroids and proinflammatory

cytokines. Other important features are the disentrainment of circadian rhythms and the decreased levels of melatonin in the plasma and urine (Antonioli et al. 2012).

Chronic stress and the higher levels of proinflammatory cytokines may result in chronic neuroinflammation and depression. In such processes, hippocampal glucocorticoid receptors (GRs) and the HPA axis have important impacts on the proinflammatory cytokines. The higher levels of proinflammatory cytokines and GR functional resistance may form a vicious circle (Kim et al. 2016). Chronic neuroinflammation may suppress the normal GR function. Such effects may elevate the activities of proinflammatory cytokines and worsen the conditions of chronic neuroinflammation.

Clinical evidences also support the close associations between the dysregulation of the rhythmic patterns in the HPA axis with the pathophysiology of depression (see Fig. 3.1). For instance, depressed women have shown flatter diurnal cortisol rhythms with more impaired inhibition of cortisol after the dexamethasone administration (Jarcho et al. 2013). In addition, the flatter diurnal cortisol slopes were related to the severity of self-reported depression.

Such observations indicate that the HPA axis dysfunctions are the important properties of depression. Because the dysfunctions of the HPA axis have the critical roles in both mental and somatic conditions, the understanding of such mechanisms may be helpful for the prevention and treatment of depression and associated physical illnesses.

In addition, the deregulations of the HPA axis are the common features among cancer patients. For example, in prostate cancer patients, the dysfunctions in the HPA activities have been considered the underlying mechanisms that may explain the effects of sleep disruption on depression (Hoyt et al. 2016).

A recent study analyzed the correlations among HPA activities, tumor-related inflammation, and the survival rates among ovarian cancer patients. The study found that abnormal cortisol rhythms were related to the lower survival rates and higher inflammation close to the tumor areas (Schrepf et al. 2015). The study confirmed the correlations among HPA dysfunctions, tumor-related inflammation, as well as the disturbance of circadian rhythms.

3.3.2 The Cholesterol Levels and Obesity

Cholesterol is the key precursor of steroid hormones. It may play a critical role in the ultradian and circadian activities of the HPA axis. Recently, a mathematical model was constructed for simulating such interactions between cholesterol and the HPA axis using cholesterol as a dynamical variable (Marković et al. 2014). The predictions from the model were consistent with the previous experimental discoveries that the cholesterol levels have an essential role in the overall dynamics of the HPA axis.

The dynamical regulatory mechanisms suggest that the impairments in the interactions may be closely associated with various diseases that have been caused by

the modern lifestyle, such as obesity and cardiovascular diseases (see Chap. 8). As mentioned in Chap. 1, the combination of both experimental and theoretical analyses would be beneficial for a better understanding of such dynamic interactions.

In addition, sleep deprivation studies have identified the lower levels of nocturnal ghrelin in insomnia (Motivala et al. 2009). Insomnia patients often have the problem of dysregulations in energy balance. Such altered rhythmic patterns and dysfunctions may also explain the frequency of weight gain among this population (see Chap. 8).

Although glucocorticoids have been closely associated with obesity and metabolic syndrome, the detailed processes of their involvements are still unknown (Aschbacher et al. 2014). The elucidation of the underlying mechanisms at various systems levels would be helpful for prognostic and preventive methods (see Fig. 3.1).

In a recent study, the levels of cortisol, adrenocorticotropin releasing hormone (ACTH), and leptin from the blood samples were tested among 18 obese premenopausal women every 10 min over 24 h (Aschbacher et al. 2014). In the study, the relationships between three parameters were examined: the signaling of cortisol inhibitory feedback, ACTH-adrenal signaling, as well as the leptin–cortisol antagonism. In addition, the metabolic risk profiles were measured including the levels of fat, lean body mass (LBM), as well as insulin resistance.

The study found that the lower levels of cortisol inhibitory feedback signaling were closely connected to the higher levels of metabolic risks including fat and insulin resistance but not LBM (Aschbacher et al. 2014). In addition, leptin was found to antagonize the cortisol dynamics among eight women who had decreased mean leptin levels and LBM over 24 h with increased ACTH-adrenal signaling at night. Furthermore, the leptin–cortisol antagonism represented a “neuroendocrine starvation” reaction.

While it is hard to use conventional neuroendocrine methods to represent and predict metabolic health, the dynamical systems approaches may be appropriate to analyze the resilience and robustness of the HPA-leptin axis (see Fig. 3.1). Further discussions of the correlations among PNI, stress, circadian rhythms, sleep, and the implications in health and diseases will be available in Chaps. 4 and 5.

References

Antonioli, M., Rybka, J., & Carvalho, L. A. (2012). Neuroimmune endocrine effects of antidepressants. *Neuropsychiatric Disease and Treatment, 8*, 65–83.

Aschbacher, K., Rodriguez-Fernandez, M., van Wietmarschen, H., Tomiyama, A. J., Jain, S., Epel, E., et al. (2014). The hypothalamic-pituitary-adrenal-leptin axis and metabolic health: A systems approach to resilience, robustness and control. *Interface Focus, 4*(5), 20140020. doi:10.1098/rsfs.2014.0020.

Baggs, J. E., & Hogenesch, J. B. (2010). Genomics and systems approaches in the mammalian circadian clock. *Current Opinion in Genetics & Development, 20*(6), 581–587. doi:10.1016/j.gde.2010.08.009.

Furtado, M., & Katzman, M. A. (2015). Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. *Psychiatry Research, 229*, 37–48.

Gebicke-Haerter, P. J., Pildaín, L. V., Matthäus, F., Schmitt, A., & Falkai, P. (2013). Circadian rhythms investigated on the cellular and molecular levels. *Pharmacopsychiatry, 46*(Suppl 1), S22–S29. doi:10.1055/s-0033-1337923.

Gibbs, J. E., Blaikley, J., Beesley, S., Matthews, L., Simpson, K. D., Boyce, S. H., et al. (2012). The nuclear receptor REV-ERBα mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proceedings of the National Academy of Sciences of the United States of America, 109*, 582–587.

Hodkinson, D. J., O'Daly, O., Zunszain, P. A., Pariante, C. M., Lazurenko, V., Zelaya, F. O., et al. (2014). Circadian and homeostatic modulation of functional connectivity and regional cerebral blood flow in humans under normal entrained conditions. *Journal of Cerebral Blood Flow and Metabolism, 34*(9), 1493–1499. doi:10.1038/jcbfm.2014.109.

Hoyt, M. A., Bower, J. E., Irwin, M. R., Weierich, M. R., & Stanton, A. L. (2016). Sleep quality and depressive symptoms after prostate cancer: The mechanistic role of cortisol. *Behavioral Neuroscience, 130*, 351–356.

Jarcho, M. R., Slavich, G. M., Tylova-Stein, H., Wolkowitz, O. M., & Burke, H. M. (2013). Dysregulated diurnal cortisol pattern is associated with glucocorticoid resistance in women with major depressive disorder. *Biological Psychology, 93*, 150–158.

Kim, Y.-K., Na, K.-S., Myint, A.-M., & Leonard, B. E. (2016). The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. *Progress in Neuropsychopharmacology and Biological Psychiatry, 64*, 277–284.

Marković, V. M., Cupić, Z., Maćešić, S., Stanojević, A., Vukojević, V., & Kolar-Anić, L. (2014). Modelling cholesterol effects on the dynamics of the hypothalamic-pituitary-adrenal (HPA) axis. *Mathematical Medicine and Biology, 33*(1), 1–28. pii: dqu020.

Marković, V. M., Čupić, Ž., Vukojević, V., & Kolar-Anić, L. (2011). Predictive modeling of the hypothalamic-pituitary-adrenal (HPA) axis response to acute and chronic stress. *Endocrine Journal, 58*(10), 889–904.

Mavroudis, P. D., Scheff, J. D., Calvano, S. E., & Androulakis, I. P. (2013). Systems biology of circadian-immune interactions. *Journal of Innate Immunity, 5*, 153–162.

Motivala, S. J., Tomiyama, A. J., Ziegler, M., Khandrika, S., & Irwin, M. R. (2009). Nocturnal levels of ghrelin and leptin and sleep in chronic insomnia. *Psychoneuroendocrinology, 34*, 540–545.

Schrepf, A., Thaker, P. H., Goodheart, M. J., Bender, D., Slavich, G. M., Dahmoush, L., et al. (2015). Diurnal cortisol and survival in epithelial ovarian cancer. *Psychoneuroendocrinology, 53*, 256–267.

Spiga, F., Walker, J. J., Terry, J. R., & Lightman, S. L. (2014). HPA axis-rhythms. *Comprehensive Physiology, 4*, 1273–1298.

Sturmberg, J. P., Bennett, J. M., Picard, M., & Seely, A. J. E. (2015). The trajectory of life. Decreasing physiological network complexity through changing fractal patterns. *Frontiers in Physiology, 6*, 169.

Wan, Q., Gao, K., Rong, H., Wu, M., Wang, H., Wang, H., et al. (2014). Histone modifications of the Crhr1 gene in a rat model of depression following chronic stress. *Behavioural Brain Research, 271*, 1–6. doi:10.1016/j.bbr.2014.05.031.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Zhang, E. E., & Kay, S. A. (2010). Clocks not winding down: Unravelling circadian networks. *Nature Reviews Molecular Cell Biology, 11*(11), 764–776. doi:10.1038/nrm2995.

Chapter 4
The Inflammatory Networks and Dynamical Patterns in Psychoneuroimmunology

4.1 Inflammatory Networks and Systemic PNI Profiling

Systemic psychoneuroimmunology (PNI) profiles can be constructed with the identification of inflammatory biomarkers, cytokine networks, and immune-brain-behavior communications (see Chap. 1). Such profiles can be useful for the discovery of potential therapeutic targets in personalized, systems, and dynamical medicine (Yan 2014). For instance, the plasma levels of the components in inflammatory pathways can be assessed for the diagnosis and treatment efficacies of antidepressants. Advancements in such paths can help overcome the obstacles in the current medical practice including adverse effects (Yan 2011).

As discussed in the previous chapters, the elucidation of the common systemic biomarkers such as the cellular pathways in different diseases may help make the progress from the disease-centered medicine to human-centered medicine. Such shared networks rather than the single disease may become the general therapeutic targets (Yan 2011; also see Chap. 1).

For example, psychological stressors may lead to the dysfunctions in the neurotransmitter systems including GABAergic and monoamine functioning. Such alterations may affect the growth factors and cellular viability including the networks associated with BDNF, NF-kB, and MAP kinase (Yin et al. 2004). These pathways are critical in various stress-associated disorders including depression, Parkinson's disease, Alzheimer's disease, and cardiovascular diseases.

At the molecular and cellular levels, the networks of cytokines and other molecules including neurotransmitters and neuropeptides mediate the interconnections among the nervous, endocrine, and immune systems. The cytokine networks may convey the communications between neurons and glial cells with the impacts on the hypothalamic–pituitary–adrenal (HPA) axis in stress and depression (Kemeny and Schedlowski 2007). At the system level, the complex communications such as those between the central nervous system (CNS) and the peripheral immune system are essential in emotionality and the regulations of mood, motivation, and alarm (Ziemssen and Kern 2007; Kemeny and Schedlowski 2007).

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_4

These factors are pivotal in neuropsychiatric dysfunctions including anxiety, depression, anorexia, fatigue, cognitive problems, and sleep disorders. For instance, brain cytokines such as interleukin 6 (IL-6) have been associated with various problems from food intake to anxiety-like behaviors (Yan 2011). Such evidences indicate that the studies of the inflammatory biomarkers and relevant pathways need to become a high priority in systemic PNI profiling with their key roles in the wide range of problems including mood disorders and schizophrenia (see Chaps. 6 and 7).

Furthermore, plentiful experimental evidences have referred to the essential role of the circadian system in mood disorders (Monje et al. 2011). Because proinflammatory cytokine networks such as the NF-kB signaling pathway are critical in the pathogenesis of depression, their rhythmic patterns are also the significant factors for the diagnosis, prevention, and treatment of the disorders. In the following sections, the examples of such potential biomarkers and networks will be discussed with their dynamical patterns and roles in various biopsychological disorders. A more complete list of the relevant factors can be found in the Database of Psychoneuroimmunology (DPNI 2016).

4.2 IL-6 and Associated Networks

Interleukin 6 (IL-6) is a cytokine that can be induced by stress. Its proinflammatory functions may be mediated through the soluble IL-6 receptor/trans-signaling (Fonseka et al. 2015). During chronic stress exposures, IL-6 can signal via the gp130 and IL-6Rα receptors to trigger the JAK/STAT3 signaling pathways (Girotti et al. 2013).

The pathophysiology of depression has been closely associated with the higher levels of IL-6 with the lower levels of brain-derived neurotrophic factor (BDNF) (Jehn et al. 2015; Fonseka et al. 2015; also see Chap. 6). IL-6 may be involved in depression via its impacts on the HPA axis (Girotti et al. 2013). Based on these mechanisms, potential antidepressant strategies have been proposed to selectively target the IL-6 trans-signaling pathways (Fonseka et al. 2015).

In addition, the levels of IL-6 have also been associated with insufficient sleep and disrupted sleep homeostasis (Möller-Levet et al. 2013). The inflammatory responses of microglia may be regulated by the intrinsic circadian clock. Studies have shown that microglia have robust rhythms in the expressions of cytokines including IL-6, IL-1β, and TNF-α (Fonken et al. 2015).

As an important inflammatory marker, IL-6 has distinctive diurnal patterns. Studies have found that in healthy subjects, the salivary IL-6 levels may reach the peak after awakening, slowly drop from morning to noon, and reach the peak again close to midnight before the sleep time (Izawa et al. 2013).

Such patterns suggest that timing is a key factor for inflammatory treatments including surgeries and immunotherapies (also see Chap. 13). Clinically, the morning symptoms of rheumatoid arthritis (RA) have been closely associated with the higher

nocturnal levels of proinflammatory cytokines especially IL-6 (Perry et al. 2009). Such effects have indicated the methods in chronotherapy using modified-release prednisone for RA patients to achieve better treatment outcomes (Alten 2012).

In addition, the coronary concentrations of IL-6 among patients with the ST segment elevation myocardial infarction (STEMI) may be higher in the afternoon than in the morning (Bonda et al. 2010). Such circadian variations of IL-6 in the coronary circulations may help explain the higher morbidity of the patients with myocardial infarction. The understanding of these mechanisms may contribute to the development of dynamical medicine (Yan 2014; also see Chaps. 1 and 13).

4.3 TNF and Associated Networks

Together with IL-6, tumor necrosis alpha (TNF-α) may be involved in the modulation of the hypothalamic–pituitary–adrenal (HPA) axis in systemic immune diseases (Straub et al. 2011). The dysfunction of the HPA axis may be associated with the effects of inflammatory mediators on the hypothalamic centers and the circadian disruptions of various hormones and cytokines (Li et al. 2004; also see Chap. 3).

For instance, acute psychosocial stress may lead to higher body mass index (BMI) with lower inhibition by glucocorticoids on the production of TNF-α (Wirtz et al. 2008). This mechanism may provide the connection between BMI and the higher risks for adverse cardiovascular events caused by stress.

Furthermore, TNF-α may have a critical role in depression induced by myocardial infarction (Liu et al. 2013). TNF-α may lead to the alterations of the blood–brain barrier and inflammation. It may become the target for anti-inflammatory treatment for the prevention of depressive symptoms to improve the cardiovascular outcomes.

Studies using rat models have found that during chronic stress conditions, TNF-α may be involved in the sensitization of pancreatic acinar cells. Such changes may lead to the higher risks for the development of pancreatitis (Binker et al. 2010).

Hippocampal expressed TNF-α has been suggested as a potential therapeutic target for the comorbid disorders such as chronic pain and major depressive disorder (MDD). TNF-α is an important common neuromodulator in these disorders (Fasick et al. 2015). These disorders also have shared neurotransmitters, neuroanatomical pathways, as well as structures such as the hippocampal brain area.

In addition, the altered concentrations of inflammatory cytokines such as TNF-α have been associated with circadian disruptions, fatigue, and cancer (Guess et al. 2009). TNF-α has also been considered as a critical mediator of inflammation in rheumatoid arthritis (RA). In rheumatoid synovial cells, TNF-α may affect the expression of the clock gene PER2 via the D-box binding proteins DBP, HLF, TEF, and E4BP4 (Yoshida et al. 2013). This mechanism has been correlated with the pathogenesis of RA. Together with adenosine A(2A) receptors (A(2A)R), TNF-α may regulate the endogenous circadian clock in immune cells and contribute to the pathologic alterations in the circadian patterns in RA (Perez-Aso et al. 2013).

4.4 NF-kB and Associated Networks

Chronic stress may influence the T cells via the activation of the NF-kB pathways (Silberman et al. 2005). Such process is protein kinase C (PKC) dependent. The NF-kB signaling pathway is also crucial in the IL-6-dependent depression-like behaviors induced by constant darkness (Monje et al. 2011).

Studies of chronic unpredictable mild stress (CUMS)-induced atherosclerosis using mice models have indicated the importance of the TLR4/NF-kB signaling pathways (Tang et al. 2015). Various cascades of proinflammatory cytokines can be activated via the TLR4/NF-kB networks. Such mechanisms suggest the possible treatment targets for the prevention of CUMS-caused atherosclerosis.

The activation of the transcription factor NF-kB is involved in the immune responses that may be regulated by the circadian clock. The association between NF-kB, cancer, and circadian rhythms may be mediated via the circadian protein cryptochrome (CRY) that controls the expression of proinflammatory cytokines.

The lower levels of the CRY proteins may lead to the lack of suppression on cAMP generation, resulting in the higher levels of cAMP and PKA (Narasimamurthy et al. 2012). Such changes may cause the higher levels of NF-kB activation via the phosphorylation of p65 at S276. These interactions may help explain the connections between circadian disturbances and the higher susceptibility to chronic inflammatory disorders including cancer.

In addition, the core circadian protein CLOCK has been considered as a positive controller of NF-kB-mediated transcription. Based on periodic oscillations in gene expression, the circadian patterns may be mediated by the transcriptional activities of the CLOCK/BMAL1 complex. Specifically, the daily oscillations in NF-kB responses to immunomodulators may be influenced by the core circadian protein CLOCK (Spengler et al. 2012). When the level of BMAL1 is low, CLOCK may up-regulate NF-kB-associated transcription. However, BMAL1 may counteract the CLOCK-associated elevation of NF-kB-responsive genes.

Furthermore, CLOCK has been detected in the protein complexes with the p65 subunit of NF-kB. The overexpression of CLOCK has been related to the elevation of phosphorylated and acetylated transcriptionally active types of p65 (Spengler et al. 2012). These molecular and cellular linkages among the essential components of the circadian and immune processes including NF-kB, CLOCK, and CRY may provide further implications for chronotherapy and dynamical medicine for cancer treatment (see Chaps. 1 and 13).

4.5 BDNF and Associated Networks

Brain-derived neurotrophic factor (BDNF) has the essential roles in many functions including cell survival, neural plasticity, stress regulation, as well as learning ability (Yu et al. 2012). Both basic scientific and clinical studies have indicated the

importance of BDNF in the pathophysiology of stress-associated mood disorders (Giese et al. 2014). The levels of BDNF in the human serum have been measured as a marker for the efficacy of antidepressants in certain psychiatric disorders.

Specifically, chronic mild stress may lead to the functional alterations of BDNF in rat hippocampal slices (Molteni et al. 2016). Normal BDNF functions are crucial in the synaptic and neuronal plasticity. The stress-induced changes in BDNF may result in long-lasting and fundamental alterations in the hippocampus with the higher susceptibility to stress-associated disorders.

In the pathophysiology of depression and the mechanisms of antidepressants, the pivotal roles have been found for the signaling pathways involving BDNF and its receptor tropomyosin receptor kinase B (TrkB) (Zhang et al. 2016). Because the importance of the tryptophan-kynurenine and BDNF-TrkB signaling pathways, they have been suggested as the potential treatment targets for inflammation-associated depression (see Chap. 6).

In addition, the alterations in both BDNF protein levels and circadian patterns have been considered the risk factors for depressive behaviors (Schulte-Herbrüggen et al. 2007). In a study using healthy young women as samples, the daily fluctuations of BDNF in the human saliva and serum were observed (Tirassa et al. 2012). The correlations have been established among the diurnal oscillations in BDNF, the morning–evening personality traits, as well as body rhythms.

In a study using a mouse model, dim light at night (dLAN) has been found to elevate the depressive-like responses via the decrease of BDNF expression in the hippocampus (Fonken and Nelson 2013). Such correlations indicate that salivary BDNF patterns can be measured as a useful biomarker for the stress-associated studies in both basic scientific and clinical settings.

Strong associations have also been established between BDNF and antidepressant responses. Among MDD patients, the elasticity in diurnal serum BDNF variation has been related to favorable treatment responses to the method of partial sleep deprivation (PSD) (Giese et al. 2014).

Currently available medications for depression have the limitations including low efficacy and response delay. The normalized BDNF serum profile that oscillates with a circadian pattern may occur before but not after a beneficial treatment result. Such observations of the quick BDNF elevation and diurnal BDNF oscillations related to therapeutic responses may be helpful for the improvement of the treatment strategies.

Furthermore, the variants in the BDNF gene may affect the vulnerability to stress and the treatment responses to antidepressants. In a study using a mouse model, the polymorphism of Val66Met in BDNF was associated with the hyper-reactivity in the HPA axis, depressive-like and anxiety-like behaviors, as well as weakened working memory after stress stimulations (Yu et al. 2012). In another study of at-risk adolescents, the variants in BDNF and 5-HTTLPR were associated with the higher morning salivary cortisol and the risks for subsequent depression (Goodyer et al. 2010).

In addition, certain classes of antidepressant such as desipramine but not fluoxetine may have better effects with the Val66Met variant in BDNF (Yu et al. 2012).

In the treatment of bipolar disorder using lithium, the treatment response has been associated with the genotypes and serum levels of the BDNF. A better response to lithium was observed in those carrying the BDNF Val/Met polymorphism with a hyperthymic temperament (Rybakowski 2014).

4.6 PPARs and Associated Networks

Peroxisome proliferator-activated receptors (PPAR α, β, and γ) have the key roles in the regulations of cellular metabolic processes in the heart muscle tissues, including glucose and lipid metabolism, inflammation, and oxidative stress (Lecarpentier et al. 2010, 2014). PPARs may also facilitate the interactions among the circadian, metabolic, and cardiovascular pathways.

For the treatment of the affective, cognitive, and systemic symptoms of major depressive disorder, PPAR-γ have been proposed as one of the three closely interrelated mediators to effectively inhibit parainflammation and ER stress (Gold et al. 2013). The other two are the central insulin and klotho. For example, the open-label administration of the PPAR-γ agonist pioglitazone has been found to result in decreased severity of depressive symptoms with lower cardiometabolic risks (Kemp et al. 2014).

In addition, circadian disruption is a property of the interrelated pathogenesis including sympathetic/parasympathetic dysfunctions, neurodegenerative disorders, cardiovascular diseases, diabetes, and cancer. The critical role of the PPAR α/γ profiles may provide a common link for these different disorders, especially primary or secondary cardiac dysfunctions (Lecarpentier et al. 2014). Such shared links are meaningful for the transition from disease-centered to personalized human-centered medicine.

For instance, with the critical functions in vascular muscles, PPAR-γ is involved in the regulation of blood pressure. The dysfunctions of PPAR-γ in the smooth muscles may lead to abnormal vascular functions and hypertension (Halabi et al. 2008). A study using a mouse model found that systemic PPAR-γ deletion may damage the circadian patterns of behavior and metabolism, including food and water intake, locomotor activity, oxygen consumption, and cardiovascular parameters (Yang et al. 2012).

At the cellular level, PPARs have the important roles in the cellular oscillatory processes including the Wnt/β-catenin pathway and glycolysis metabolic networks (Lecarpentier et al. 2010). As a critical component of the vascular clock interacting with BMAL1, vascular PPAR-γ is a peripheral controller of cardiovascular rhythms in the blood pressure and heart rate (Lecarpentier et al. 2014; Wang et al. 2008). The alterations in the Wnt/β-catenin and PPARs pathways have been associated with circadian disruptions and cardiac dysfunctions.

Specifically, the inactivation of the Wnt/β-catenin pathway has been linked to higher expression of PPAR-γ and arrhythmogenic right ventricular cardiomyopathy (Lecarpentier et al. 2014). On the other hand, the activation of the Wnt/β-catenin

pathway has been linked to the lower expression of PPAR-γ and type 2 diabetes. With the important roles in the disorders including metabolic syndrome, obesity, hyperphagia, myocardial infarction, sudden cardiac death, and associated mental problems, the PPARs pathways can become the potential therapeutic targets for different diseases (Lecarpentier et al. 2010).

References

Alten, R. (2012). Chronotherapy with modified-release prednisone in patients with rheumatoid arthritis. *Expert Review of Clinical Immunology, 8*, 123–133.

Binker, M.-G., Binker-Cosen, A.-A., Richards, D., Gaisano, H.-Y., de Cosen, R.-H., & Cosen-Binker, L.-I. (2010). Chronic stress sensitizes rats to pancreatitis induced by cerulein: Role of TNF-α. *World Journal of Gastroenterology, 16*, 5565–5581.

Bonda, T., Kaminski, K. A., Kozuch, M., Kozieradzka, A., Wojtkowska, I., Dobrzycki, S., et al. (2010). Circadian variations of interleukin 6 in coronary circulations of patients with myocardial infarction. *Cytokine, 50*, 204–209.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Fasick, V., Spengler, R. N., Samankan, S., Nader, N. D., & Ignatowski, T. A. (2015). The hippocampus and TNF: Common links between chronic pain and depression. *Neuroscience and Biobehavioral Reviews, 53*, 139–159.

Fonken, L. K., Frank, M. G., Kitt, M. M., Barrientos, R. M., Watkins, L. R., & Maier, S. F. (2015). Microglia inflammatory responses are controlled by an intrinsic circadian clock. *Brain, Behavior, and Immunity, 45*, 171–179.

Fonken, L. K., & Nelson, R. J. (2013). Dim light at night increases depressive-like responses in male C3H/HeNHsd mice. *Behavioural Brain Research, 243*, 74–78.

Fonseka, T. M., McIntyre, R. S., Soczynska, J. K., & Kennedy, S. H. (2015). Novel investigational drugs targeting IL-6 signaling for the treatment of depression. *Expert Opinion on Investigational Drugs, 24*, 459–475.

Giese, M., Beck, J., Brand, S., Muheim, F., Hemmeter, U., Hatzinger, M., et al. (2014). Fast BDNF serum level increase and diurnal BDNF oscillations are associated with therapeutic response after partial sleep deprivation. *Journal of Psychiatric Research, 59*, 1–7.

Girotti, M., Donegan, J. J., & Morilak, D. A. (2013). Influence of hypothalamic IL-6/gp130 receptor signaling on the HPA axis response to chronic stress. *Psychoneuroendocrinology, 38*, 1158–1169.

Gold, P. W., Licinio, J., & Pavlatou, M. G. (2013). Pathological parainflammation and endoplasmic reticulum stress in depression: Potential translational targets through the CNS insulin, klotho and PPAR-γ systems. *Molecular Psychiatry, 18*, 154–165.

Goodyer, I. M., Croudace, T., Dudbridge, F., Ban, M., & Herbert, J. (2010). Polymorphisms in BDNF (Val66Met) and 5-HTTLPR, morning cortisol and subsequent depression in at-risk adolescents. *British Journal of Psychiatry, 197*, 365–371.

Guess, J., Burch, J. B., Ogoussan, K., Armstead, C. A., Zhang, H., Wagner, S., et al. (2009). Circadian disruption, Per3, and human cytokine secretion. *Integrative Cancer Therapies, 8*, 329–336.

Halabi, C. M., Beyer, A. M., de Lange, W. J., Keen, H. L., Baumbach, G. L., Faraci, F. M., et al. (2008). Interference with PPAR gamma function in smooth muscle causes vascular dysfunction and hypertension. *Cell Metabolism, 7*, 215–226.

Izawa, S., Miki, K., Liu, X., & Ogawa, N. (2013). The diurnal patterns of salivary interleukin-6 and C-reactive protein in healthy young adults. *Brain, Behavior, and Immunity, 27*, 38–41.

Jehn, C. F., Becker, B., Flath, B., Nogai, H., Vuong, L., Schmid, P., et al. (2015). Neurocognitive function, brain-derived neurotrophic factor (BDNF) and IL-6 levels in cancer patients with depression. *Journal of Neuroimmunology, 287*, 88–92.

Kemeny, M. E., & Schedlowski, M. (2007). Understanding the interaction between psychosocial stress and immune-related diseases: A stepwise progression. *Brain, Behavior, and Immunity, 21*, 1009–1018.

Kemp, D. E., Schinagle, M., Gao, K., Conroy, C., Ganocy, S. J., Ismail-Beigi, F., et al. (2014). PPAR-γ agonism as a modulator of mood: Proof-of-concept for pioglitazone in bipolar depression. *CNS Drugs, 28*, 571–581.

Lecarpentier, Y., Claes, V., Duthoit, G., & Hébert, J.-L. (2014). Circadian rhythms, Wnt/beta-catenin pathway and PPAR alpha/gamma profiles in diseases with primary or secondary cardiac dysfunction. *Frontiers in Physiology, 5*, 429.

Lecarpentier, Y., Claes, V., & Hébert, J.-L. (2010). PPARs, cardiovascular metabolism, and function: Near- or far-from-equilibrium pathways. *PPAR Research, 2010*.

Li, S., Lu, A., Li, B., & Wang, Y. (2004). Circadian rhythms on hypothalamic-pituitary-adrenal axis hormones and cytokines of collagen induced arthritis in rats. *Journal of Autoimmunity, 22*, 277–285.

Liu, H., Luiten, P. G. M., Eisel, U. L. M., Dejongste, M. J. L., & Schoemaker, R. G. (2013). Depression after myocardial infarction: TNF-α-induced alterations of the blood-brain barrier and its putative therapeutic implications. *Neuroscience and Biobehavioral Reviews, 37*, 561–572.

Möller-Levet, C. S., Archer, S. N., Bucca, G., Laing, E. E., Slak, A., Kabiljo, R., et al. (2013). Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proceedings of the National academy of Sciences of the United States of America, 110*, E1132–E1141.

Molteni, R., Rossetti, A. C., Savino, E., Racagni, G., & Calabrese, F. (2016). Chronic mild stress modulates activity-dependent transcription of BDNF in rat hippocampal slices. *Neural Plasticity, 2016*, 2592319.

Monje, F. J., Cabatic, M., Divisch, I., Kim, E.-J., Herkner, K. R., Binder, B. R., et al. (2011). Constant darkness induces IL-6-dependent depression-like behavior through the NF-kB signaling pathway. *Journal of Neuroscience, 31*, 9075–9083.

Narasimamurthy, R., Hatori, M., Nayak, S. K., Liu, F., Panda, S., & Verma, I. M. (2012). Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. *Proceedings of the National academy of Sciences of the United States of America, 109*, 12662–12667.

Perez-Aso, M., Feig, J. L., Mediero, A., Aránzazu, M., & Cronstein, B. N. (2013). Adenosine A2A receptor and TNF-α regulate the circadian machinery of the human monocytic THP-1 cells. *Inflammation, 36*, 152–162.

Perry, M. G., Kirwan, J. R., Jessop, D. S., & Hunt, L. P. (2009). Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. *Annals of the Rheumatic Diseases, 68*, 63–68.

Rybakowski, J. K. (2014). Factors associated with lithium efficacy in bipolar disorder. *Harvard Review of Psychiatry, 22*, 353–357.

Schulte-Herbrüggen, O., Hellweg, R., Chourbaji, S., Ridder, S., Brandwein, C., Gass, P., et al. (2007). Differential regulation of neurotrophins and serotonergic function in mice with genetically reduced glucocorticoid receptor expression. *Experimental Neurology, 204*, 307–316.

Silberman, D. M., Zorrilla-Zubilete, M., Cremaschi, G. A., & Genaro, A. M. (2005). Protein kinase C-dependent NF-kappaB activation is altered in T cells by chronic stress. *Cellular and Molecular Life Sciences, 62*, 1744–1754.

Spengler, M. L., Kuropatwinski, K. K., Comas, M., Gasparian, A. V., Fedtsova, N., Gleiberman, A. S., et al. (2012). Core circadian protein CLOCK is a positive regulator of NF-kB-mediated transcription. *Proceedings of the National academy of Sciences of the United States of America, 109*, E2457–E2465.

Straub, R. H., Buttgereit, F., & Cutolo, M. (2011). Alterations of the hypothalamic-pituitary-adrenal axis in systemic immune diseases—A role for misguided energy regulation. *Clinical and Experimental Rheumatology, 29*, S23–S31.

Tang, Y. L., Jiang, J. H., Wang, S., Liu, Z., Tang, X. Q., Peng, J., et al. (2015). TLR4/NF-kB signaling contributes to chronic unpredictable mild stress-induced atherosclerosis in ApoE-/- mice. *PLoS One, 10*, e0123685.

Tirassa, P., Iannitelli, A., Sornelli, F., Cirulli, F., Mazza, M., Calza, A., et al. (2012). Daily serum and salivary BDNF levels correlate with morning-evening personality type in women and are affected by light therapy. *Rivista di Psichiatria, 47*, 527–534.

Wang, N., Yang, G., Jia, Z., Zhang, H., Aoyagi, T., Soodvilai, S., et al. (2008). Vascular PPARgamma controls circadian variation in blood pressure and heart rate through Bmal1. *Cell Metabolism, 8*, 482–491.

Wirtz, P. H., Ehlert, U., Emini, L., & Suter, T. (2008). Higher body mass index (BMI) is associated with reduced glucocorticoid inhibition of inflammatory cytokine production following acute psychosocial stress in men. *Psychoneuroendocrinology, 33*, 1102–1110.

Yan, Q. (2011). Toward the integration of personalized and systems medicine: Challenges, opportunities and approaches. *Personalized Medicine, 8*, 1–4.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Yang, G., Jia, Z., Aoyagi, T., McClain, D., Mortensen, R. M., & Yang, T. (2012). Systemic PPARγ deletion impairs circadian rhythms of behavior and metabolism. *PLoS One, 7*, e38117.

Yin, J., Levanon, D., & Chen, J. D. Z. (2004). Inhibitory effects of stress on postprandial gastric myoelectrical activity and vagal tone in healthy subjects. *Neurogastroenterology and Motility, 16*, 737–744.

Yoshida, K., Hashiramoto, A., Okano, T., Yamane, T., Shibanuma, N., & Shiozawa, S. (2013). TNF-α modulates expression of the circadian clock gene Per2 in rheumatoid synovial cells. *Scandinavian Journal of Rheumatology, 42*, 276–280.

Yu, H., Wang, D.-D., Wang, Y., Liu, T., Lee, F. S., & Chen, Z.-Y. (2012). Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants. *Journal of Neuroscience, 32*, 4092–4101.

Zhang, J.-C., Yao, W., & Hashimoto, K. (2016). Brain-derived neurotrophic factor (BDNF)—TrkB signaling in inflammation-related depression and potential therapeutic targets. *Current Neuropharmacology, 14*, 721–731.

Ziemssen, T., & Kern, S. (2007). Psychoneuroimmunology—Cross-talk between the immune and nervous systems. *Journal of Neurology, 254*(Suppl 2), II8–II11.

Part II
Psychoneuroimmunology, Diseases, and Mind-Body Medicine

Chapter 5
Sleep, Psychoneuroimmunology, and Mind–Body Medicine

5.1 Sleep Disturbances, Systemic Inflammation, and Mind–Body Techniques

Sleep is an essential dynamic behavioral state. It is pivotal in neuroendocrine processes and the maintenance of the overall homeostasis. Sleep has the profound effects on the immune system. The correlations between sleep and inflammation have broad clinical implications while therapeutics targeting sleep disorders may have anti-inflammatory effects to prevent a wide range of chronic diseases.

Specifically, evidences from experimental sleep deprivation and clinical studies have indicated a bidirectional association between sleep and inflammatory cytokines (Motivala 2011). Sleep loss may result in the higher levels of the proinflammatory cytokines. Disturbed sleep may cause the dysfunctions of the bidirectional networks between the brain and the immune system, leading to the higher levels of inflammatory mediators correlated with cardiovascular diseases (Motivala 2011).

Sleep disturbances and social isolation may enhance the risks for morbidity and mortality. Systemic inflammation has been suggested as a possible mechanism underlying these correlations. A recent population-based longitudinal study observed that sleep disturbance was a predictor for the elevated systemic inflammation measured by circulating C-reactive protein (CRP) over a 5-year follow-up (Cho et al. 2015). Such connection was remarkably stronger among those with the feelings of social isolation.

According to the dynamical biopsychosocial models, sleep disturbances can be the important targets of mind–body interventions toward the development of systems and dynamical medicine (Yan 2014; also see Chaps. 1 and 3). For example, a study compared the effects of cognitive behavioral therapy (CBT), tai chi chih (TCC), and a sleep seminar control (SS) on the biomarkers among older adults with chronic and primary insomnia (Carroll et al. 2015b). The study suggests that the mind–body techniques may be helpful for improving sleep quality and lowering the risks of chronic disorders among the older adults. More studies about the PNI mechanisms of sleep, health, and aging would contribute to the better understanding of mind–body medicine.

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_5

5.2 Sleep Problems and Aging

Older adults often have insomnia-related complaints. Aging-associated diseases have been related to sleep problems including short sleep duration and sleep disturbances. Essential cellular alterations associated with aging and related diseases have been observed especially sensitive to sleep loss (Carroll et al. 2016).

Inflammation is considered the biological pathway that may connect sleep problems with the higher risks for aging-associated disorders including depression, pain, and infectious diseases. Sleep disturbances including insomnia problems have been closely related to systemic inflammation featured with proinflammatory transcriptional profiles in circulating leukocytes (Carroll et al. 2016).

A recent study causally connected sleep deprivation with the molecular processes in aging. The study was done among community-dwelling older adults with partial sleep deprivation (PSD) (Carroll et al. 2016). The study assessed the effects of PSD by measuring leukocyte gene expression showing DNA damage responses (DDR) and the senescence-associated secretory phenotype (SASP). Other parameters measured included the peripheral blood mononuclear cell (PBMC) gene expression and the senescence marker p16(INK4a).

The study results revealed the higher levels of SASP and DDR after PSD nights. Altered gene expressions were found in NFKB2, NBS1, CHK2, as well as p16(INK4a) (CDKN2A). These findings indicate that PSD would change the PBMC gene expression patterns and aggravate the SASP with the higher levels of DNA damages, cell cycle arrest, as well as cellular senescence (Carroll et al. 2016).

Another study compared the influences of sleep deprivation on toll-like receptor (TLR) activation of monocytic inflammation among younger versus older adults (Carroll et al. 2015a). The study observed that PSD resulted in the higher generation of the inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Such alterations continued even after a night of recovery sleep. In addition, older adults had lower TLR-4-induced cellular inflammation than in younger adults. These observations indicate that sleep loss may lead to cellular inflammation in younger adults. The blunted TLR activation among older adults may elevate the risks for infectious diseases associated with aging (Carroll et al. 2015a).

5.3 Psychosocial Stress, Poor Sleep Quality, and Obesity

Insufficient sleep has been considered a significant causal factor to the rising rates among both childhood and adult obesity, as well as chronic diseases. For instance, a study of 819 children (8–11 years old) suggested a tight relationship between shorter sleep duration and a higher probability of being obese (Ievers-Landis et al. 2008).

The interactions between chronic stress and obesity may desynchronize the temporal patterns of the serum levels of the markers including leptin and triglycerides, and result in the development of metabolic disorders. Specifically, the interactions have been detected among time points, chronic stress, obesity, as well as adiponectin

and corticosterone levels (de Oliveira et al. 2014). Such correlations may help explain the mechanisms of the vicious circle among obesity, stress, and sleep loss. The altered functions of the hypothalamic–pituitary–adrenal (HPA) axis may also have a crucial role in this vicious circle (Lucassen and Cizza 2012).

Such connections have been demonstrated by various studies. For example, a study of 927 women aged 16–40 years with lower socioeconomic status (SES) observed that poor sleep quality, high stress, and obesity were common in the group (Tom and Berenson 2013). In another study of a sample of 1515 African Americans (AA), sleep quality was related to obesity among women (Bidulescu et al. 2010). The correlation between sleep quality and obesity was affected by perceived stress, with the higher likelihood of obesity in the medium stress category.

These evidences indicate that improving sleep quality and duration may be effective mind–body interventions for obesity. Obese people with short sleep are often psychosocially stressed and are likely to have unhealthy behaviors (Vgontzas and Bixler 2008). Better sleep quality, the reduction of chronic stress, and the promotion of healthier behaviors have been considered the important suggestions for almost half of the obese individuals in the general population.

5.4 Mind–Body Methods for Improving Sleep Quality

Better sleep quality has been viewed essential in promoting successful and resilient aging (Irwin 2014). Because sleep has the key role in the inflammatory pathways affecting both mental and physical health, promoting sleep quality may also help lower inflammation to achieve healthy aging.

In a recent randomized trial, the effects of cognitive-behavioral therapy for insomnia (CBT-I), tai chi chih (TCC), and sleep seminar education were analyzed among 123 older adults with insomnia (Irwin et al. 2015). By analyzing genome-wide transcriptional profiles, the study found that both CBT-I and TCC resulted in the lower levels of CRP and TLR-4 activated monocyte generation of proinflammatory cytokines. These two practices also led to the lower activity of nuclear factor-kB (NFkB) and AP-1.

The study results suggest that CBT-I could lower systemic inflammation and TCC could lower cellular inflammatory responses in older adults with insomnia (Irwin et al. 2015). These discoveries may have the implications not just for insomnia and aging, but also the interventions for the relevant risks from inflammatory disorders.

In another study of 109 older adults with chronic and primary insomnia, the effects of better sleep quality were tested on the biomarkers of diabetes and cardiovascular diseases (Carroll et al. 2015b). The practices of CBT, TCC, and a sleep seminar control (SS) were evaluated as the means to improve sleep quality. The biomarkers included high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, hemoglobinA1c, glucose, insulin, CRP, and fibrinogen. These biomarkers were applied to measure the risks for developing cardiovascular, metabolic, and inflammatory disorders.

The study showed that after 16 months of the treatments, both CBT and TCC led to significantly reduced risk scores with better sleep quality as compared with those of the SS group (Carroll et al. 2015b). In addition, the CBT group showed the reduced risk at the two time points of 4-months and 16-months. The TCC groups showed the lower risk at 16-months but not at 4 months. More comprehensive PNI studies may help elucidate the complex mechanisms underlying these mind–body approaches for the development of the optimal interventions.

References

Bidulescu, A., Din-Dzietham, R., Coverson, D. L., Chen, Z., Meng, Y.-X., Buxbaum, S. G., et al. (2010). Interaction of sleep quality and psychosocial stress on obesity in African Americans: The Cardiovascular Health Epidemiology Study (CHES). *BMC Public Health, 10*, 581.

Carroll, J. E., Carrillo, C., Olmstead, R., Witarama, T., Breen, E. C., Yokomizo, M., et al. (2015a). Sleep deprivation and divergent toll-like receptor-4 activation of cellular inflammation in aging. *Sleep, 38*, 205–211.

Carroll, J. E., Cole, S. W., Seeman, T. E., Breen, E. C., Witarama, T., Arevalo, J. M. G., et al. (2016). Partial sleep deprivation activates the DNA damage response (DDR) and the senescence-associated secretory phenotype (SASP) in aged adult humans. *Brain, Behavior, and Immunity, 51*, 223–229.

Carroll, J. E., Seeman, T. E., Olmstead, R., Melendez, G., Sadakane, R., Bootzin, R., et al. (2015b). Improved sleep quality in older adults with insomnia reduces biomarkers of disease risk: Pilot results from a randomized controlled comparative efficacy trial. *Psychoneuroendocrinology, 55*, 184–192.

Cho, H. J., Seeman, T. E., Kiefe, C. I., Lauderdale, D. S., & Irwin, M. R. (2015). Sleep disturbance and longitudinal risk of inflammation: Moderating influences of social integration and social isolation in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Brain, Behavior, and Immunity, 46*, 319–326.

de Oliveira, C., Scarabelot, V. L., de Souza, A., de Oliveira, C. M., Medeiros, L. F., de Macedo, I. C., et al. (2014). Obesity and chronic stress are able to desynchronize the temporal pattern of serum levels of leptin and triglycerides. *Peptides, 51*, 46–53.

Ievers-Landis, C. E., Storfer-Isser, A., Rosen, C., Johnson, N. L., & Redline, S. (2008). Relationship of sleep parameters, child psychological functioning, and parenting stress to obesity status among preadolescent children. *Journal of Developmental and Behavioral Pediatrics, 29*, 243–252.

Irwin, M. R. (2014). Sleep and inflammation in resilient aging. *Interface Focus, 4*, 20140009.

Irwin, M. R., Olmstead, R., Breen, E. C., Witarama, T., Carrillo, C., Sadeghi, N., et al. (2015). Cognitive behavioral therapy and tai chi reverse cellular and genomic markers of inflammation in late-life insomnia: A randomized controlled trial. *Biological Psychiatry, 78*, 721–729.

Lucassen, E. A., & Cizza, G. (2012). The hypothalamic-pituitary-adrenal axis, obesity, and chronic stress exposure: Sleep and the HPA axis in obesity. *Current Obesity Reports, 1*, 208–215.

Motivala, S. J. (2011). Sleep and inflammation: Psychoneuroimmunology in the context of cardiovascular disease. *Annals of Behavioral Medicine, 42*, 141–152.

Tom, S. E., & Berenson, A. B. (2013). Associations between poor sleep quality and psychosocial stress with obesity in reproductive-age women of lower socioeconomic status. *Womens Health Issues, 23*, e295–e300.

Vgontzas, A. N., & Bixler, E. O. (2008). Short sleep and obesity: Are poor sleep, chronic stress, and unhealthy behaviors the link? *Sleep, 31*, 1203.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Chapter 6
Psychoneuroimmunology of Depression

6.1 PNI and the Biopsychosocial Models

Depression is an important cause of disability worldwide. However, the etiology of depression is still not completely understood (Souza-Teodoro et al. 2016). The unsatisfactory results of pharmacotherapy and the high incidence of associated physical disorders refer to the inadequacy of the single molecule theories such as those focusing on the monoaminergic neurotransmitter system, especially the serotonergic system (Su 2015; Toben and Baune 2015).

These challenges indicate that more systemic studies in psychoneuroimmunology (PNI) are needed to improve the current situations. The dynamical biopsychosocial models may be useful for understanding the key roles of the immune system in the interactions with the central nervous systems (CNS) and peripheral organ systems (see Chap. 1).

For example, at the cellular level, T lymphocytes are critical in the susceptibility or resilience to major depressive disorder (MDD). During depression, T lymphocytes have the essential roles in the neuroimmune network in balancing the adaptive and maladaptive immune responses (Toben and Baune 2015). T lymphocytes have been associated with the production of certain neurotrophic factors and cytokines in the brain in the condition of stress-induced depression.

In addition, in chronic stress-induced neuroinflammation and depression, T cells are crucial in the maladaptive immunity associated with neurodegeneration (Toben and Baune 2015). Understanding of the cellular and molecular mechanisms of these activities may help elucidate the neurodegenerative and neuroregenerative functions in order to restore the neuroimmune homeostasis in depression.

Inflammation has the essential role in these processes at various systems biology levels. More and more evidences are referring to the close associations between inflammation and the pathophysiology of depression (Su 2015). Proinflammatory cytokines have been found to cause psychiatric symptoms including those of the MDD. The higher levels of inflammatory biomarkers such as IFN-α have been observed as a feature among the patients with depression (Su 2015).

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_6

In summary, the inflammatory mechanisms may help explain the neuropsychiatric symptoms in depression and link the interface between the mind and the body. The understandings of the PNI of depression have led to some novel and integrative antidepressant interventions such as the anti-inflammatory compounds including omega-3 polyunsaturated fatty acids, i.e., omega-3 PUFAs or n-3 PUFAs (Su 2015).

6.2 The PNI Implications in Personalized, Systems, and Dynamical Medicine

The PNI studies of depression in different groups of people may contribute to the development of personalized, systems, and dynamical medicine (see Chap. 1). For instance, in children, the depression–immunity correlations have been confirmed and the interactions may be influenced by adrenarcheal timing. A study of 103 children indicated that the immune markers such as C-reactive protein (CRP) and the secretory immunoglobulin A (SIgA) were related to the negative mood/physical symptoms (NM/PS) (Delany et al. 2016). In addition, the factor of adrenarcheal timing was found an important parameter among the younger populations.

Among the elderly, the lower levels of dehydroepiandrosterone (DHEA) sulfated form DHEA(S) could predict higher ratios of depression. According to the analysis of data from the English Longitudinal Study of Aging (ELSA) including 3083 subjects, the higher serum levels of DHEA(S) were related to the lower risks of the development of depressive symptoms among older men and women (Souza-Teodoro et al. 2016). The study indicates that DHEA(S) may have critical roles in both mood and aging.

In cancer patients, depression is one of the most common psychological symptoms that affect the quality of life and treatment outcomes. Depression has been related to the immune dysfunctions and poor survival rates among cancer patients (Barrera and Spiegel 2014). Various biopsychological mechanisms and neural-immune-endocrine pathways may be involved in cancer-associated depression, including chronic stress responses, tissue damages, and inflammatory mediators (Smith 2015).

On the other hand, psychotherapeutic interventions have been found helpful for relieving the symptoms of depression with the potential effects on disease progression and mortality (Barrera and Spiegel 2014). Because depression has significant effects on the morbidity and mortality in many chronic diseases including cancer, diabetes, and heart disease, synergistic mental health and primary care approaches have been suggested. Such approaches should embrace both psychotherapeutic and psychopharmacologic interventions (Voinov et al. 2013).

6.3 Potential Systemic Biomarkers in Depression

The identification of systemic biomarkers of depression is crucial not only for better diagnosis, but also for the translation of the PNI discoveries into better clinical interventions and outcomes. Tight connections have been confirmed among depression, inflammation, and various aging-associated disorders such as cardiovascular diseases (Yan 2012). Inflammatory biomarkers such as cytokine signaling pathways in the brain may have the special roles in association with behavioral alterations.

Specifically, stress, depression, and troubled relationships have been closely related to the higher levels of inflammation and risks for the disorders including obesity, type 2 diabetes, and cardiovascular diseases (Jaremka et al. 2013). Such correlations may be synergistic and bidirectional. Troubled relationships often lead to the higher levels of stress and depression, while depression may promote inflammation with the effects that may worsen depression.

In addition, the adipose tissue is a critical supplier of proinflammatory cytokines. Metabolic syndrome and obesity may aggravate the conditions of stress and depression. Such mechanisms indicate that psychosocial interventions may counteract the negative effects caused by stress and depression and break the vicious circle among the associated disorders (Jaremka et al. 2013).

Studies about the potential systemic biomarkers may be meaningful for understanding the PNI of depression and the immune-modulating mechanisms of antidepressants (Hou et al. 2013). The identification of the inflammatory markers, cytokine pathways, and the immune-brain-behavior networks would contribute to the establishment of systemic PNI profiles for discovering the potential targets for personalized interventions (Yan 2012; also see Chap. 1).

6.4 Stress Response and Inflammatory Pathways in Depression

As discussed earlier, in recent years more and more evidences from PNI studies have revealed the robust connections among stress, depression, and inflammatory pathways (Noto et al. 2014). These findings may provide the implications for the development of novel therapeutic strategies targeting the inflammatory networks for individual care in MDD. However, the sporadic findings on such topics still need to be organized to be translated into more effective treatments for depression.

6.4.1 The Immune-Kynurenine Pathway

Table 6.1 lists some stress response pathways associated with depression. Many of these pathways are also involved in the inflammatory processes. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

Table 6.1 Examples of stress and inflammation-related pathways in depression

Pathways and interactions	Associated pathogenesis/diseases	References
The immune-kynurenine pathways (e.g., IDO, kynurenines)	Stress responses, glial-neuronal network dysfunctions, inflammation	Won and Kim 2016; Christmas et al. 2011
The HPA axis-mediated interactions (e.g., 5-HT, CREB, BDNF, TRkB)	Stress responses, depression	Moreno-Ramos et al. 2013
The leptin pathways and HPA axis (e.g., leptin, leptin receptor (LEPR))	Stress-induced depression	Ge et al. 2013
The ERK1/2 signaling pathways (e.g., ERK1, ERK2, RSK1, MSK1)	Stress-induced depression	Dwivedi and Zhang 2016
The MEK/ERK signaling pathways	Chronic restraint stress, depressive-like behavior	Leem et al. 2014
The GSK3-dependent TLR4 signaling (e.g., TLR4, GSK3, NF-kB)	Stress-induced neuroinflammation, depression-like behavior	Cheng et al. 2016

For instance, the immune-kynurenine pathway mediates the critical interactions among stress, the autonomic nervous system, and the immune system in MDD (Won and Kim 2016). Chronic stress may enhance the levels of proinflammatory cytokines, leading to the higher activities of indoleamine 2,3-dioxygenase (IDO), the first enzyme in the kynurenine pathway.

The imbalances in the downstream kynurenine metabolites may cause neurotoxic alterations in the brain with the dysfunctions in the glial-neuronal network and higher susceptibilities to depression (Won and Kim 2016, also see Table 6.1). Providing the linkages among stress, inflammation, and depression, this pathway may have the implications as novel antidepressant targets (Christmas et al. 2011).

6.4.2 The HPA Axis and Associated Pathways

Another important network is the hypothalamic–pituitary–adrenal (HPA) axis-mediated interactions between the serotonin regulation pathway and the stress response pathway (Moreno-Ramos et al. 2013, also see Table 6.1). Gene–environment interactions have critical roles in the multifactorial disorder. These environmental factors include childhood maltreatment and stressful life events (SLEs). Various genes may be involved in such interactions and the neurotrophin pathway, including cAMP response element binging protein (CREB), brain-derived neurotrophic factor (BDNF), and its receptor TRkB (Moreno-Ramos et al. 2013; also see Chap. 4).

Studies using the chronic unpredictable stress (CUS) model found that the antidepressant, the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine may

regulate glutamate transporter 1 (GLT-1) through the BDNF-TrkB signaling pathway (Liu et al. 2016). In addition, the hyperactivity of HPA axis has been found as an important feature in depression-like behaviors caused by CUS, together with the imbalance in the leptin pathway and altered synaptic plasticity in the hypothalamus (Ge et al. 2013, also see Table 6.1).

6.4.3 The ERK1/2 and MAPK Signaling Pathways

A study using the model of learned helplessness (LH) rats showed that the alterations in the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway may be associated with the higher vulnerability to developing stress-induced depression (Dwivedi and Zhang 2016). Such changes included the lower expressions of ERK1 and ERK2 with lower activities in cytosolic and nuclear fractions. Other changes included the lower levels of phosphorylation of the downstream substrates RSK1 (cytosolic and nuclear) and MSK1 (nuclear) in the brain areas such as frontal cortex and hippocampus (see Table 6.1).

In a study using chronic restraint stress mouse model of depression, the MEK/ERK signaling pathway was found to be disrupted with the lower levels of immunoreactivity in the medial orbital (MO) cortex and dorsal endopiriform nuclei (DEn) of the prefrontal cortex (Leem et al. 2014; also see Table 6.1). In the study, the depressive-like behavior was induced by repeated restraint stress with the higher levels of social avoidance in the social interaction test. In addition, the antidepressant imipramine was observed to ameliorate the depressive behavior.

Other studies have confirmed that the gene–environment interactions such as those between genetic vulnerability and early life stress may lead to depressive-like behavior mediated by lifelong synaptic dysfunctions. The alterations in the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK-MAPK) pathways are critical in such processes (Musazzi et al. 2010).

In addition, the Epac-dependent central corticotropin releasing factor (CRF) (1) receptor signaling through the ERK-MAPK pathway may also promote the BDNF-stimulated TrkB signaling. The dysfunctions of the G protein-coupled receptor kinase (GRK) and β-arrestin have been suggested as the important factors in the pathophysiology of stress-induced depression (Hauger et al. 2009).

6.4.4 The GSK3-Dependent TLR4 Signaling Pathways

Various signaling pathways in the brain are involved in the susceptibility to depression. For example, neuroinflammation caused by stress may be mediated via the glycogen synthase kinase-3 (GSK3)-dependent toll-like receptor 4 (TLR4) signaling pathway with the higher risks for depression-like behaviors (Cheng et al. 2016, also see Table 6.1).

Stress may lead to a broad inflammatory response with the higher levels of cytokines and chemokines in the hippocampus of mouse models, peaking from 6 to 12 h after the stress stimulation. The higher hippocampal levels of the danger-associated molecular pattern (DAMP) protein high mobility group box 1 (HMGB1) may be involved in the process, with the activation of the inflammatory transcription factor NF-kB (Cheng et al. 2016).

On the other hand, the treatment using leptin was found to have effects on chronic stress and glucocorticoid-caused inhibition of hippocampal neurogenesis by affecting the GSK-3β/β-catenin signaling pathways (Garza et al. 2012). Leptin may promote the levels and nuclear translocation of β-catenin, the essential substrate of GSK-3β and the major regulator involved in hippocampal neural progenitor cell proliferation.

6.5 The Inflammatory Networks: The Links Between Depression and Other Diseases

The depression pathogenesis often has overlaps with physical disorders including asthma, rheumatoid arthritis, cardiovascular diseases, obesity, cancer, and neurodegenerative diseases (Slavich and Irwin 2014). Inflammation may be the pivotal mechanisms connecting life stressors such as interpersonal stress and social rejection with genomic and physiological alterations. In addition to MDD alone, the inflammatory signaling pathways may provide the central linkages between depression and the morbidity of various physical systems. Table 6.2 lists some examples of such connections. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

6.5.1 Cancer

Among breast cancer patients, childhood trauma has been found prevalent with the higher levels of stress, depression, and fatigue (Han et al. 2016). The higher expressions of the gene transcripts associated with the inflammatory signaling pathways including CRP, interleukin (IL)-6, and IL-1 receptor antagonist have been shown closely related to these symptoms (also see Table 6.2).

In a study of colorectal cancer patients, childhood trauma and recent life events were observed as the risk factors for the increased levels of depressive symptoms (Archer et al. 2012). Childhood trauma was also positively related to the levels of the inflammatory markers including tumor necrosis factor-α (TNF-α) and CRP among the patients (see Table 6.2). Such significant connections may provide the implications for potential preventive and therapeutic targets.

Table 6.2 Examples of the depression-inflammation-disease associations and pathways

Inflammatory pathways and interactions	Stress and comorbidity	References
The inflammatory signaling pathways (e.g., CRP, IL-6)	Childhood trauma, stress; breast cancer, depression, fatigue	Han et al. 2016
The inflammatory signaling pathways (e.g., TNF-α)	Unpredictable chronic mild stress (UCMS); depression, vascular inflammation	Demirtaş et al. 2014
The inflammatory signaling pathways (e.g., TNFα, CRP)	Childhood trauma, stress events; colorectal cancer, depressive symptoms	Archer et al. 2012
The inflammatory signaling pathways and the dysregulation of cortisol rhythmicity	Depressive symptoms, renal cell carcinoma	Cohen et al. 2012
The IO&NS pathways (e.g., IL-6)	Multiple sclerosis (MS), depression	Kallaur et al. 2016
The IO&NS pathways (e.g., IL-1β, IL-2, IL-6, IL-8, IL-12, TNF-α, INF-γ, CRP)	Cardiovascular disorder (CVD), major depression	Maes et al. 2011
The inflammatory and IO&NS pathways (e.g., IL-6, TNF-α, CRP); the gut–brain pathways	Inflammatory bowel disease (IBD), depression	Martin-Subero et al. 2016
The inflammatory signaling pathways (e.g., CRP, IL-6); HPA axis; the kynurenine pathways	Coronary heart disease (CHD), depression	Nikkheslat et al. 2015

Furthermore, the depressive symptoms have been identified as the essential predictor for survival among the patients with renal cell carcinoma (Cohen et al. 2012). Such associations can be explained by the possible correlations with inflammatory signaling pathways and the dysregulations of cortisol rhythmicity (see Table 6.2).

6.5.2 Cardiovascular Diseases

More and more evidences are referring to the bidirectional association between major depression and cardiovascular diseases (CVD) (Maes et al. 2011). While patients with depression have the higher risks for cardiac morbidity and mortality, CVD patients have the higher possibility to develop depression.

Specifically, coronary heart disease (CHD) and depression are often occurred together, and inflammation has been suggested as the key linkage between these two disorders (Nikkheslat et al. 2015). Depression may not only cause social morbidity but also worsen the adverse cardiac outcomes among CHD patients.

Studies on the common pathophysiology of both CVD and major depression have indicated the importance of the complex networks involving inflammatory, oxidative, and nitrosative stress (IO&NS) pathways (Nikkheslat et al. 2015; also see

Table 6.2). The inflammatory signaling pathways may serve as the key connections among unpredictable chronic mild stress (UCMS), depression, and cardiovascular dysfunctions. In the model of stress-induced depression, TNF-α was revealed as the major cytokine in the neuroendocrine, immune, and behavioral response pathways (Demirtaş et al. 2014). It may cause the lower expression of endothelial nitric oxide synthase (eNOS) as well as vascular dysfunctions.

The alterations in these pathways have been associated with the shared risks for both diseases. Such alterations include the higher levels of proinflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, IL-12, TNF-α, and interferon-γ (INF-γ) (Maes et al. 2011). Other features include the higher levels of CRP, IDO, and tryptophan catabolites, as well as the higher levels of O&NS and DNA damages. In addition, bacterial translocation and gut-derived inflammation have been observed (see Table 6.2).

Compared with the nondepressed CHD patients, those with depression often have increased levels of CRP, IL-6, and plasma vascular endothelial growth factor (VEGF) (Nikkheslat et al. 2015). Depressed patients may also have lower tryptophan levels and higher kynurenine/tryptophan ratio. Moreover, studies have indicated that CHD patients with depression may have the higher levels of inflammation with altered HPA axis activity, the glucocorticoid receptor (GR) resistance, with the altered activation of the kynurenine pathway (Nikkheslat et al. 2015; also see Tables 6.1 and 6.2).

6.5.3 Other Relevant Diseases

In addition to CVD, the complex IO&NS pathways are also critical in the pathophysiology of multiple sclerosis (MS) and depression (Kallaur et al. 2016). MS patients with depression have shown the signs of peripheral inflammation including the higher serum levels of IL-6, gastrointestinal and visual symptoms, as well as more disease progression and disability (see Table 6.2).

The pathogenesis of inflammatory bowel disease (IBD) is another example. The high incidence of depression among the IBD patients has been related to the lower quality of life and higher morbidity (Martin-Subero et al. 2016). Such connections suggest the importance of depression in the pathophysiology of IBD.

The common IO&NS pathways with altered gut–brain pathways in the co-occurrence of IBD and depression highlight the key roles of these complex networks (see Table 6.2). The evidences supporting such connections in the comorbidity included the higher proinflammatory cytokine levels such as IL-1, IL-6, and TNF-α, with the higher levels of positive acute phase reactants including haptoglobin and CRP (Martin-Subero et al. 2016).

Meanwhile, the lowered levels were observed for negative acute phase reactants including albumin, transferrin, and zinc, as well as anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF-β) (Martin-Subero et al. 2016). Other signs included the higher levels of DNA damages, nitric oxide (NO), trypto-

phan catabolite (TRYCAT), as well as autoimmune responses and bacterial translocation (see Table 6.2). The systemic framework of such complex pathways would have significant implications for the development of novel strategies targeting the common networks in multiple disorders (also see Chap. 1).

References

Archer, J. A., Hutchison, I. L., Dorudi, S., Stansfeld, S. A., & Korszun, A. (2012). Interrelationship of depression, stress and inflammation in cancer patients: A preliminary study. *Journal of Affective Disorders, 143*, 39–46.

Barrera, I., & Spiegel, D. (2014). Review of psychotherapeutic interventions on depression in cancer patients and their impact on disease progression. *International Review of Psychiatry, 26*, 31–43.

Cheng, Y., Pardo, M., de Souza Armini, R., Martinez, A., Mouhsine, H., Zagury, J.-F., et al. (2016). Stress-induced neuroinflammation is mediated by GSK3-dependent TLR4 signaling that promotes susceptibility to depression-like behavior. *Brain, Behavior, and Immunity, 53*, 207–222.

Christmas, D. M., Potokar, J., & Davies, S. J. (2011). A biological pathway linking inflammation and depression: Activation of indoleamine 2,3-dioxygenase. *Neuropsychiatric Disease and Treatment, 7*, 431–439.

Cohen, L., Cole, S. W., Sood, A. K., Prinsloo, S., Kirschbaum, C., Arevalo, J. M. G., et al. (2012). Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: Role of inflammatory signaling. *PLoS One, 7*, e42324.

Delany, F. M., Byrne, M. L., Whittle, S., Simmons, J. G., Olsson, C., Mundy, L. K., et al. (2016). Depression, immune function, and early adrenarche in children. *Psychoneuroendocrinology, 63*, 228–234.

Demirtaş, T., Utkan, T., Karson, A., Yazır, Y., Bayramgürler, D., & Gacar, N. (2014). The link between unpredictable chronic mild stress model for depression and vascular inflammation? *Inflammation, 37*, 1432–1438.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Dwivedi, Y., & Zhang, H. (2016). Altered ERK1/2 signaling in the brain of learned helpless rats: Relevance in vulnerability to developing stress-induced depression. *Neural Plasticity, 2016*, 7383724.

Garza, J. C., Guo, M., Zhang, W., & Lu, X.-Y. (2012). Leptin restores adult hippocampal neurogenesis in a chronic unpredictable stress model of depression and reverses glucocorticoid-induced inhibition of GSK-3β/β-catenin signaling. *Molecular Psychiatry, 17*, 790–808.

Ge, J.-F., Qi, C.-C., & Zhou, J.-N. (2013). Imbalance of leptin pathway and hypothalamus synaptic plasticity markers are associated with stress-induced depression in rats. *Behavioural Brain Research, 249*, 38–43.

Han, T. J., Felger, J. C., Lee, A., Mister, D., Miller, A. H., & Torres, M. A. (2016). Association of childhood trauma with fatigue, depression, stress, and inflammation in breast cancer patients undergoing radiotherapy. *Psychooncology, 25*, 187–193.

Hauger, R. L., Risbrough, V., Oakley, R. H., Olivares-Reyes, J. A., & Dautzenberg, F. M. (2009). Role of CRF receptor signaling in stress vulnerability, anxiety, and depression. *Annals of the New York Academy of Sciences, 1179*, 120–143.

Hou, R., Tang, Z., & Baldwin, D. S. (2013). Potential neuroimmunological targets in the treatment of anxiety disorders. *Modern Trends in Pharmacopsychiatry, 29*, 67–84.

Jaremka, L. M., Lindgren, M. E., & Kiecolt-Glaser, J. K. (2013). Synergistic relationships among stress, depression, and troubled relationships: Insights from psychoneuroimmunology. *Depression and Anxiety, 30*, 288–296.

Kallaur, A. P., Lopes, J., Oliveira, S. R., Simão, A. N. C., Reiche, E. M. V., de Almeida, E. R. D., et al. (2016). Immune-inflammatory and oxidative and nitrosative stress biomarkers of depression symptoms in subjects with multiple sclerosis: Increased peripheral inflammation but less acute neuroinflammation. *Molecular Neurobiology, 53*, 5191–5202.

Leem, Y.-H., Yoon, S.-S., Kim, Y.-H., & Jo, S. A. (2014). Disrupted MEK/ERK signaling in the medial orbital cortex and dorsal endopiriform nuclei of the prefrontal cortex in a chronic restraint stress mouse model of depression. *Neuroscience Letters, 580*, 163–168.

Liu, W.-X., Wang, J., Xie, Z.-M., Xu, N., Zhang, G.-F., Jia, M., et al. (2016). Regulation of glutamate transporter 1 via BDNF-TrkB signaling plays a role in the anti-apoptotic and antidepressant effects of ketamine in chronic unpredictable stress model of depression. *Psychopharmacology, 233*, 405–415.

Maes, M., Ruckoanich, P., Chang, Y. S., Mahanonda, N., & Berk, M. (2011). Multiple aberrations in shared inflammatory and oxidative & nitrosative stress (IO&NS) pathways explain the co-association of depression and cardiovascular disorder (CVD), and the increased risk for CVD and due mortality in depressed patients. *Progress in Neuropsychopharmacology & Biological Psychiatry, 35*, 769–783.

Martin-Subero, M., Anderson, G., Kanchanatawan, B., Berk, M., & Maes, M. (2016). Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways. *CNS Spectrums, 21*, 184–198.

Moreno-Ramos, O. A., Lattig, M. C., & González Barrios, A. F. (2013). Modeling of the hypothalamic-pituitary-adrenal axis-mediated interaction between the serotonin regulation pathway and the stress response using a Boolean approximation: A novel study of depression. *Theoretical Biology and Medical Modelling, 10*, 59.

Musazzi, L., Mallei, A., Tardito, D., Gruber, S. H. M., El Khoury, A., Racagni, G., et al. (2010). Early-life stress and antidepressant treatment involve synaptic signaling and Erk kinases in a gene-environment model of depression. *Journal of Psychiatric Research, 44*, 511–520.

Nikkheslat, N., Zunszain, P. A., Horowitz, M. A., Barbosa, I. G., Parker, J. A., Myint, A.-M., et al. (2015). Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain, Behavior, and Immunity, 48*, 8–18.

Noto, C., Rizzo, L. B., Mansur, R. B., McIntyre, R. S., Maes, M., & Brietzke, E. (2014). Targeting the inflammatory pathway as a therapeutic tool for major depression. *Neuroimmunomodulation, 21*, 131–139.

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin, 140*, 774–815.

Smith, H. R. (2015). Depression in cancer patients: Pathogenesis, implications and treatment (Review). *Oncology Letters, 9*, 1509–1514.

Souza-Teodoro, L. H., de Oliveira, C., Walters, K., & Carvalho, L. A. (2016). Higher serum dehydroepiandrosterone sulfate protects against the onset of depression in the elderly: Findings from the English Longitudinal Study of Aging (ELSA). *Psychoneuroendocrinology, 64*, 40–46.

Su, K.-P. (2015). Nutrition, psychoneuroimmunology and depression: The therapeutic implications of omega-3 fatty acids in interferon-α-induced depression. *Biomedicine (Taipei), 5*, 21.

Toben, C., & Baune, B. T. (2015). An act of balance between adaptive and maladaptive immunity in depression: A role for T lymphocytes. *Journal of Neuroimmune Pharmacology, 10*, 595–609.

Voinov, B., Richie, W. D., & Bailey, R. K. (2013). Depression and chronic diseases: It is time for a synergistic mental health and primary care approach. *Primary Care Companion for CNS Disorders, 15*.

Won, E., & Kim, Y.-K. (2016). Stress, the autonomic nervous system, and the immune-kynurenine pathway in the etiology of depression. *Current Neuropharmacology, 14*, 665–673.

Yan, Q. (2012). Translational implications of inflammatory biomarkers and cytokine networks in psychoneuroimmunology. *Methods in Molecular Biology, 934*, 105–120.

Chapter 7
Psychoneuroimmunology of Schizophrenia

7.1 The Stress–Inflammation Associations and the Biopsychosocial Models

Schizophrenia is a complex trait disorder with serious neurocognitive dysfunctions. It often causes lifelong disability. As a neuropsychiatric disease with heterogeneous properties and various clinical manifestations, schizophrenia is influenced by many factors including gene–environment interactions and epigenetic elements.

For instance, genetic studies have identified the strong connections between schizophrenia and chromosome 6p22.1, a location associated with the human leucocyte antigen (HLA) system and various immune functions (Müller et al. 2015). Decades of studies have reported immunological alterations as an important feature of schizophrenia patients, including gene expression changes in the immune pathways and the dysfunction of immune cells (Sperner-Unterweger and Fuchs 2015).

Among all of the factors, the immune system is especially significant as demonstrated by the anti-inflammatory therapies (Müller and Dursun 2011). Many evidences have referred to the essential role of inflammation in schizophrenia. These evidences include the anti-inflammatory effects of antipsychotics, the clinical effects of the anti-inflammatory drugs, together with other genetic and immunological discoveries (Müller et al. 2015). For example, cyclo-oxygenase-2 inhibitors have been found to be beneficial during the early stages of schizophrenia (Müller et al. 2015). On the other hand, antipsychotic drugs are known to have immunomodulatory properties.

Chronic stress has been closely linked to immune responses and may enhance the levels of proinflammatory cytokines, leading to continuous inflammatory conditions (Müller et al. 2015). Based on this mechanism, the dynamical biopsychosocial models of schizophrenia addressing the stress–inflammation correlations may contribute to the development of systems and dynamical medicine for the disorder (Yan 2014; also see Chap. 1).

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_7

7.2 The Interactions Among the Immune, Endocrine, Nervous Systems, and Cognition

According to the dynamical biopsychosocial models, the complex interactions among the immune, endocrine, and nervous systems via cytokines, hormones, and neurotransmitters are essential in schizophrenia with etiological implications (see Chap. 1). For instance, the neuroimaging studies of schizophrenia patients have indicated the decreased volumes of the central nervous system (CNS) and the stimulation of microglia with a low level of inflammatory neurotoxic activities (Müller et al. 2015).

The understanding of the complex interactions may enable more accurate diagnostic methods with the potential for the design of neuroimmune-associated interventions. Various immune dysfunctions may affect the neurobiological circuits by altering neurotransmitter metabolisms, leading to the pathophysiological processes in schizophrenia (Sperner-Unterweger and Fuchs 2015). Such immune dysregulations can be stimulated by many reasons, including infections, higher autoimmune activities, and altered inflammatory responses.

Specifically, increased levels of proinflammatory cytokines have been observed in the blood and cerebrospinal fluid of schizophrenia patients (Müller et al. 2015). Studies of schizophrenia have indicated that that immune dysfunctions during early life including infections may cause lifelong higher immune responses. Serious infectious diseases and autoimmune disorders have been confirmed as risk factors for schizophrenia (Müller et al. 2015).

As discussed earlier, peripheral and central cytokine alterations are critical in the processes of neuropathology in schizophrenia. Clinically such activities have been demonstrated by many studies showing that antipsychotic drugs also have important effects on the cytokine network systems (Drzyzga et al. 2006). Such modulating effects of antipsychotics have been suggested to contribute to their clinical efficacy in patients with schizophrenia.

One of the important features of schizophrenia is social cognitive deficits, such as the deficits in the capability to recognize the emotional states of other people. Such concepts are in the boundary of social cognition and defined with the term of "theory of mind (ToM)" (Moieni et al. 2015). Because inflammation is a critical mechanism in the pathology of schizophrenia, it is necessary to explore the possible correlations between inflammation and the impairments in social cognition.

For instance, a recent study assessed the relationships between experimental inflammatory challenges and the alterations in ToM among 115 healthy participants (Moieni et al. 2015). The study found that acute inflammation resulted in the decline of the ability to precisely understand emotional information from other people. Such findings may be meaningful for the establishment of the connections among inflammation, the deficits in ToM and social cognition, as well as neuropsychiatric diseases including schizophrenia.

7.3 PNI and Potential Immunomodulation Strategies

As described earlier, psychoneuroimmunology (PNI) studies on the immunological, neurological, and cognitive dysfunctions of schizophrenia may lead to the breakthroughs in not just the pathophysiological aspects of schizophrenia. The understanding of continuous systemic inflammation especially neuroinflammation associated with microglia activities may also have the potential benefits for discovering novel therapeutic strategies using immunomodulation mechanisms (Debnath and Venkatasubramanian 2013).

For example, a recent randomized clinical study of 40 schizophrenia patients assessed the immunomodulatory effects of the drug anaferon containing the ultra-high dilutions of antibodies to interferon γ (INF-γ) in a complex therapy (Vetlugina et al. 2016). Before the combined therapy, the patients had lower levels of interferon-producing potential by the immunocompetent cells when compared with normal values. After the anaferon treatment, the higher levels of INF-γ were observed together with favorable improvements in the psychopathological symptoms (Vetlugina et al. 2016). The study indicates that the drug anaferon may help enhance the efficacy with its effects of psycho-immunomodulation in the complex therapy for patients with schizophrenia.

Although the conventional antipsychotic drugs may help control certain positive symptoms, they may not have the sufficient effects for regulating immune functions. To improve such situations, alternative therapeutics such as anti-inflammatory and other nonsteroidal drugs have been suggested as the adjunct therapies for schizophrenia. Such groups of drugs have shown higher target specificity and effectiveness in relieving the symptom severity (Debnath and Venkatasubramanian 2013).

These immunomodulation drugs may not just lower the levels of proinflammatory cytokines. They can also adjust the microglia activities to promote the treatment outcomes. However, the applications of anti-inflammatory in schizophrenia still need improvement to promote their methodological robustness (Debnath and Venkatasubramanian 2013).

To meet such demands, systemic drug target identifications would be needed on the basis of systems biology methods and the dynamical biopsychosocial models with the integration of the cellular pathways and networks (see Chap. 1). Such strategies may upgrade the methods of immunomodulation for schizophrenia toward a more effective and comprehensive level.

7.4 Stress Response and Inflammatory Pathways in Schizophrenia

7.4.1 Metabolic and Inflammatory Pathways

Because of the complex interactions between the immune and nervous systems, multiple pathways are involved in the disorder of schizophrenia. The elucidation of these pathways is critical in PNI research as the common inflammatory networks

may be involved in the pathological mechanisms in both depression and schizophrenia (Müller and Schwarz 2008). Such mechanisms may have the implications for applying the shared strategies of anti-inflammatory treatment for both disorders. Such strategies would promote the transition from disease-centered medicine to personalized human-centered medicine (see Chap. 1).

Table 7.1 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016). For instance, immune changes may affect the dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission (Müller et al. 2015). The immune activation may alter the enzyme indoleamine 2,3-dioxygenase (IDO) of the tryptophan/kynurenine metabolism (see Table 7.1). Such activities may affect neuroactive metabolites including kynurenic acid with the impacts on the serotonergic and glutamatergic neurotransmission.

The glutamatergic dysfunction has been tightly related to the dopaminergic dysfunction in patients with schizophrenia (Miüller and Schwarz 2007). The endogenous NMDA (*N*-methyl-D-aspartate) receptor antagonist kynurenic acid (KYN-A) is critical in the glutamatergic dysfunction. In the key CNS areas of schizophrenics, the higher levels of KYN-A may block the nicotinergic acetylcholine receptor, contributing to the psychotic symptoms and cognitive declination.

In addition, the immune dysfunctions among schizophrenic patients are featured with the imbalance between the type-1 and type-2 immune reactions. While the type-1 immune reactions are often partially suppressed, the elevated levels of the type-2 responses are often observed at the same time (Miüller and Schwarz 2007). The type-2 cytokines may suppress the IDO enzyme and lead to the metabolism of tryptophan by tryptophan 2,3-dioxygenase (TDO) in astrocytes with the activation of these cells in schizophrenia (see Table 7.1).

The higher levels of TDO activity and KYN-A in the CNS, as well as the immune-associated glutamatergic-dopaminergic dysfunctions may result in the clinical symptoms of schizophrenia. Such mechanisms may help explain the potential applications of anti-inflammatory cyclooxygenase-2 inhibitors in reducing the levels of KYN-A for the treatment of the disorder (Miüller and Schwarz 2007).

Furthermore, the higher levels of plasmatic angiotensin-I converting enzyme (ACE) activity have also been related to poor cognitive functioning among schizophrenia patients. As the major product of ACE, angiotensin II (Ang-II) has proinflammatory features. A recent study analyzed the relationships between the plasma ACE activity and inflammatory markers including interleukins, tumor necrosis factor (TNF-α), and IFN-γ among 33 schizophrenia patients (Gadelha et al. 2015). The study identified a significant correlation between the ACE enzymatic activity and the levels of IL-17a and IFN-γ among the patients but not healthy controls (see Table 7.1).

Moreover, peroxisome proliferator-activated receptors (PPARs) are nuclear receptors involved in the regulation of the gene expressions associated with the glucid–lipid and the inflammatory pathways (Rolland et al. 2013; also see Chap. 4). The PPARs agonists have been applied for metabolic disorders with the therapeutic

Table 7.1 Examples of stress and inflammation related pathways in schizophrenia

Pathways and interactions	Associated pathology/diseases	References
The kynurenine metabolism pathways	Inflammatory CNS disorders including schizophrenia	Müller and Schwarz 2008
The glutamatergic–dopaminergic and serotonergic pathways	Schizophrenia	Miüller and Schwarz 2007; Müller et al. 2015
The ACE and cytokine pathways (e.g., IL-17a and IFN-γ)	Schizophrenia	Gadelha et al. 2015
The PPAR-associated inflammatory pathways	Schizophrenia spectrum disorders, mood disorders, posttraumatic stress disorder (PTSD), personality disorders	Rolland et al. 2013
The IL17 pathways (e.g., IL-1β, IL1ra, IL-3, IL-6, IL-9, IL-10, sCD40L, TNF-β)	Psychotic symptoms in schizophrenia	Dimitrov et al. 2013
The IL-2 associated dynamics and pathways	Cognitive deterioration and negative symptomatology in schizophrenia, neurodegenerative diseases (e.g., Alzheimer's disease), neurodevelopmental disorders (e.g., autism, schizophrenia), autoimmune diseases (e.g., multiple sclerosis)	Asevedo et al. 2014; Petitto et al. 2012
The NF-kB signaling pathways	Schizophrenia	Roussos et al. 2013
The epidermal growth factor receptor signaling pathways	Pathological implications of oxidative stress in schizophrenia	Nagano et al. 2015
The signaling pathways of neurotransmitter dopamine (DA) and DA receptors	Immune dysfunctions in disorders including schizophrenia and Parkinson's disease	Sarkar et al. 2010
The BDNF-TrkB signaling pathways	The pathophysiology and treatment of schizophrenia	Pandya et al. 2013
The microglial intracellular Ca^{2+} signaling pathways	Schizophrenia	Mizoguchi et al. 2014
The neuronal signaling and immune pathways (e.g., WNT signaling)	Cognitive decline in schizophrenia	Wu et al. 2016
The Wnt and GSK3 signaling pathways	Schizophrenia	Singh 2013
The AKT/GSK3 signaling pathway	Schizophrenia	Emamian 2012
The PI3K signaling pathway	Synapse dysfunctions and pathological behaviors, autism, schizophrenia	Enriquez-Barreto and Morales 2016
The HPA axis (e.g., insulin and other neuroendocrine hormones)	Schizophrenia	Guest et al. 2011
The insulin and growth factor signaling pathways	Schizophrenia	van Beveren et al. 2014

potentials for inflammation-associated pathogenesis, such as the psychiatric disorders including schizophrenia and mood disorders. PPARs' roles in metabolic regulations may also be useful for preventing or treating the metabolic problems caused by some psychiatric medications and antipsychotics.

In addition to their anti-inflammatory properties, PPARs may regulate the expression of various neurotransmission factors and the information processing activities (Rolland et al. 2013). The multiple action profiles of PPARs regulators have been suggested useful as the therapeutic strategies for schizophrenia and mood disorders, as well as posttraumatic stress disorder (PTSD) and personality disorders (see Table 7.1). Further PNI studies of PPARs may help with more effective prevention and treatment for schizophrenia and associated psychiatric disorders.

7.4.2 Important Cytokine Networks

Many research evidences have shown increased levels of proinflammatory cytokines as a feature among schizophrenia patients. The levels of these cytokines have been correlated with the severity of the psychotic symptoms. In a recent study, the levels of 38 cytokines/chemokines were assessed from the serum samples of schizophrenia patients and healthy controls (Dimitrov et al. 2013). The higher levels of GRO, MCP-1, MDC, and sCD40L and lower levels of IFN-γ, IL-2, IL-12p70, and IL-17 were observed among the patients. In addition, positive associations were identified between the Positive and Negative Symptoms Scale (PANSS) scores and the levels of G-CSF, IL-1β, IL-3, IL-6, IL-9, IL-10, sCD40L, and TNF-β (Dimitrov et al. 2013). These cytokines have important roles in the IL-17 pathway. Such findings indicate that the alterations in the IL-17 pathway may have close relationships with the severity of psychotic symptoms in schizophrenia (see Table 7.1).

Several studies have emphasized the roles of the cytokine IL-2 in schizophrenia. IL-2 has critical functions in neurodevelopment and the peripheral immune system, with the essential activities in the CNS. Studies using mouse models investigated the complex biology of IL-2 and recognized its synchronized and dynamic functions in various systems, such as the effects on the homeostasis of the CNS and immune system (Petitto et al. 2012). The decrease of the brain IL-2 gene expression has been associated with neuroimmunological changes and CNS autoimmunity (see Table 7.1).

The understanding of the different functions of IL-2 in different conditions and stages may help elucidate the multifaceted effects of IL-2 on CNS and psychiatric disorders. For example, a recent study analyzed the correlations between the peripheral IL-2 levels and the symptoms and cognitive performance among schizophrenia patients (Asevedo et al. 2014). The study compared the plasma levels of IL-2 between chronically medicated schizophrenia outpatients and healthy controls. The patients were assessed using various scales including the PANSS and the Global

Assessment of Functioning (GAF). The study also applied the computerized neuropsychological battery to examine the abilities in verbal learning, working memory, executive function, as well as intelligence.

The study found that the schizophrenia patients had the decreased levels of IL-2 when compared with the healthy controls (Asevedo et al. 2014). In addition, the IL-2 levels were positively associated with the scores of intelligence and negatively associated with the total score in the negative subscale of PANSS. The results refer to the possible roles of IL-2 in cognitive decline and negative symptomatology among schizophrenia patients (see Table 7.1).

Furthermore, studies have found that the signaling pathways associated with nuclear factor-kB (NF-kB) have essential functions in neurons. NF-kB is involved in neurite outgrowth, activity-dependent plasticity, as well as cognitive processes (see Chap. 4). In a recent study, the analysis of microarray data from the profiles of four different brain regions indicated lower protein levels of NF-kB and nuclear activation in the superior temporal gyrus of schizophrenia patients (Roussos et al. 2013). The dysregulation was observed among the upstream NF-kB genes associated with translocation. The reduced levels of KPNA4 were also observed among schizophrenia patients. KPNA4 is one of the proteins involved in the translocation of NF-kB to the nucleus. These results suggest the important roles of the altered NF-kB signaling pathway in schizophrenia (see Table 7.1).

The earlier evidences support the correlations between proinflammatory cytokines and the alterations of the brain development and neurotransmission in psychiatric disorders including schizophrenia and depression. Furthermore, these cytokines may cause the generation of reactive oxygen species (ROS) by mitochondria and affect cell survival and proliferation (Nagano et al. 2015). The proinflammatory cytokines can be induced by the conditions such as ischemia and seizure-like neural activities with the overproduction of ROS targeting protein phosphatases associated with the basal silencing of cytokine receptor activation. Such alterations may result in the brain dysfunctions and psychiatric symptoms (see Table 7.1).

On the other hand, the ROS scavengers including polyphenols and unsaturated fatty acids may help regulate the cytokine signaling associated with the psychiatric symptoms (Nagano et al. 2015). The elucidation of the interactions between ROS and cytokine signaling pathways in schizophrenia would be helpful for understanding the pathological mechanisms of ROS as well as the potential antipsychotic functions of the ROS scavengers.

7.4.3 Neurotransmitters and Neuronal Signaling Pathways

Neurotransmitters such as dopamine (DA) may have the key roles in bridging the interactions between the nervous and the immune systems. Via the operation of its receptors, DA may regulate the activities of immune effector cells in an autocrine/paracrine way. A special feature of DA is that it has opposite effects on T cell

activities by activating naïve or resting T cells but suppressing the activated T cells (Sarkar et al. 2010).

In illnesses such as schizophrenia and Parkinson's disease, the alterations in the expression of DA receptors and associated signaling pathways such as those in the T cells have been related to immune dysfunctions (see Table 7.1). Such complexed functions of DA, especially its correlations with the altered immunity have indicated its utilizations in immune-regulatory strategies. For instance, the DA receptor agonists and antagonists have been suggested to target DA receptors and their signaling pathways for the treatment of the disorders such as schizophrenia (Sarkar et al. 2010).

In addition, neurotrophins including brain-derived neurotrophic factor (BDNF) have the essential functions in neuronal survival, synaptic plasticity, as well as cognitive activities (see Chap. 4). BDNF is involved in different intracellular signaling pathways associated with tyrosine kinase receptor B (TrkB). Many evidences have referred to the importance of neuroplasticity in schizophrenia (Pandya et al. 2013). Such mechanisms emphasize the key roles of the BDNF signaling pathways in neuroprotection, cell survival, and the pathogenesis of schizophrenia. Studies of schizophrenia patients and animal models have indicated that antipsychotic drugs may affect the BDNF levels in a time-dependent manner (see Chap. 4). The diverse effects of BDNF signaling pathways have the potential implications in understanding the pathophysiology and therapeutics of schizophrenia (see Table 7.1).

Furthermore, recent reports have indicated the importance of microglia-mediated inflammatory reactions in the pathophysiology of schizophrenia (Mizoguchi et al. 2014). Upon immunological stimulation, microglia are also innate immune cells that may generate components such as proinflammatory cytokines, nitric oxide (NO), as well as neurotrophic factors. Normal microglial functions rely on the intracellular Ca^{2+} signaling pathways regulated by the endoplasmic reticulum (ER). However, the dysfunctions in this signaling pathways may be involved in the pathophysiology of schizophrenia (see Table 7.1). Antipsychotics have been found to influence the intracellular Ca^{2+} signaling and mobilization among microglial cells (Mizoguchi et al. 2014). These mechanisms also imply the potential roles of the ER in the microglial cells as the possible target for the intervention of schizophrenia.

7.4.4 Multiple Signaling Pathways

As a disabling disease, schizophrenia only has limited therapeutic options with unclear pathophysiology caused by its heterogeneous factors. Because of the difficulties in the identification of the relevant genetic biomarkers, more understandings are needed about its complex genetic risk factors at the system level, especially the associated signaling pathways.

Recent studies have identified multiple signaling pathways involved in the pathogenesis of schizophrenia, such as WNT and glycogen synthase kinase 3 (GSK3) signaling pathways (Wu et al. 2016; Singh 2013; Emamian 2012). These pathways can become the potential pharmaceutical targets for novel treatment strategies.

For example, the AKT/GSK3 signaling pathways are important in the development of schizophrenia among various population groups. The lower levels of AKT1 proteins and GSK-3β phosphorylation have been observed in the peripheral lymphocytes and brains of patients with schizophrenia (Emamian 2012). An AKT1 haplotype has been closely related to the disorder. AKT1 deficiency may result in the higher sensitivity to the sensorimotor gating-disruptive effect of amphetamine. The hypo-activity of the AKT signaling pathway may affect the transcriptional mechanisms and other pathways associated with the complex pathogenesis of schizophrenia (see Table 7.1).

In schizophrenia, cognitive deficits are the major problems associated with functional disability. In a recent assessment using transcriptome data from peripheral blood mononuclear cells (PBMCs), various pathways related to schizophrenia were analyzed in respect of the subtypes including "cognitive deficit (CD)" and "cognitively spared (CS)" (Wu et al. 2016). The study identified the dysfunctions in 27 pathways including 19 up-regulated and 8 down-regulated pathways in the combined schizophrenia group. The analysis of the CD subgroup identified four down-regulated and one up-regulated pathways. In the CS subgroup, six pathways were found up-regulated.

Furthermore, the analysis based on transcriptome profiling and cognitive subtypes found that the up-regulated pathways were mostly associated with immune dysfunctions (such as antigen presentation) and energy metabolism (such as oxidative phosphorylation) (Wu et al. 2016). The down-regulated pathways were mostly related to neuronal signaling, especially the WNT signaling pathway (in the CD subgroup) and the ERBB pathway (in general schizophrenia) (see Table 7.1).

The WNT signaling pathway is critical in the development and normal activities of the CNS and peripheral tissues. Its dysfunctions in PBMCs refer to the importance of the genomic axis associated with the cognitive functions in the neuropathology of schizophrenia (Wu et al. 2016). The correlations between the inhibition of the WNT signaling pathway and the cognitive deterioration in schizophrenia may have potential implications in the treatment of the disease.

Another important factor is the PI3K signaling pathway. The elements of the PI3K pathway are critical in the synaptic formation and plasticity in the brain. The alterations in this pathway may result in synapse dysfunctions and sickness behaviors. Such correlations may occur in the early or late stages of the brain synaptic circuit's development (Enriquez-Barreto and Morales 2016). Genetic mutations in the PI3K signaling pathway may be important factors. The imbalance of the components in the PI3K signaling pathway has been considered the major factors in the pathophysiology of both autism and schizophrenia (see Table 7.1). Such pathways have also been suggested as the plausible novel pharmacological targets.

7.4.5 The HPA Axis and Associated Pathways

In addition to the earlier pathways, the dysfunctions of the multiple elements in the hypothalamic–pituitary–adrenal–gonadal (HPAG) axis have been correlated with schizophrenia (see Table 7.1). For example, the higher circulating levels of insulin-related peptides and the secretory granule protein chromogranin A were observed among the first onset and recent onset schizophrenia patients (Guest et al. 2011). The higher levels of pancreatic polypeptide, prolactin, progesterone, and cortisol were also observed (see Table 7.1). Among chronic schizophrenia patients, the lower levels of growth hormones were detected in postmortem pituitaries.

As shown in the earlier examples, evidences have indicated that molecular malfunctions in the metabolic, hormonal, and immune pathways have the essential roles in the subgroups of schizophrenia patients. To characterize the potential risk factors, biomarkers, and disease vulnerability, a recent study evaluated the levels of 184 molecules in the serum from 112 schizophrenia patients and 133 siblings (van Beveren et al. 2014). The results of the study supported the earlier findings with the indications of elevated serum levels of insulin, C-peptide, and proinsulin among schizophrenia patients (see Table 7.1). Other changes include the lower levels of growth hormone and abnormal levels of inflammation-associated molecules.

Furthermore, significant differences were identified in many of the protein levels between the siblings with mood disorders and the unaffected siblings (van Beveren et al. 2014). The elevated insulin/growth hormone ratio was observed when compared with the healthy controls. These results confirmed the roles of the impaired insulin signaling pathways as the potential risk factors and therapeutic targets for schizophrenia.

The earlier findings highlight the significance of the HPA axis and various signaling pathways in the discovery of systemic biomarkers (see Table 7.1). Such methods in patient stratification may also contribute to the development of diagnostic and therapeutic strategies for personalized, systems, and dynamical medicine (see Chap. 1).

References

Asevedo, E., Rizzo, L. B., Gadelha, A., Mansur, R. B., Ota, V. K., Berberian, A. A., et al. (2014). Peripheral interleukin-2 level is associated with negative symptoms and cognitive performance in schizophrenia. *Physiology and Behavior, 129*, 194–198.

Debnath, M., & Venkatasubramanian, G. (2013). Recent advances in psychoneuroimmunology relevant to schizophrenia therapeutics. *Current Opinion in Psychiatry, 26*, 433–439.

Dimitrov, D. H., Lee, S., Yantis, J., Valdez, C., Paredes, R. M., Braida, N., et al. (2013). Differential correlations between inflammatory cytokines and psychopathology in veterans with schizophrenia: Potential role for IL-17 pathway. *Schizophrenia Research, 151*, 29–35.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Drzyzga, L., Obuchowicz, E., Marcinowska, A., & Herman, Z. S. (2006). Cytokines in schizophrenia and the effects of antipsychotic drugs. *Brain, Behavior, and Immunity, 20*, 532–545.

Emamian, E. S. (2012). AKT/GSK3 signaling pathway and schizophrenia. *Frontiers in Molecular Neuroscience, 5*, 33.

Enriquez-Barreto, L., & Morales, M. (2016). The PI3K signaling pathway as a pharmacological target in Autism related disorders and Schizophrenia. *Molecular and Cellular Therapies, 4*, 2.

Gadelha, A., Yonamine, C. M., Nering, M., Rizzo, L. B., Noto, C., Cogo-Moreira, H., et al. (2015). Angiotensin converting enzyme activity is positively associated with IL-17a levels in patients with schizophrenia. *Psychiatry Research, 229*, 702–707.

Guest, P. C., Schwarz, E., Krishnamurthy, D., Harris, L. W., Leweke, F. M., Rothermundt, M., et al. (2011). Altered levels of circulating insulin and other neuroendocrine hormones associated with the onset of schizophrenia. *Psychoneuroendocrinology, 36*, 1092–1096.

Miüller, N., & Schwarz, M. J. (2007). The immunological basis of glutamatergic disturbance in schizophrenia: Towards an integrated view. *Journal of Neural Transmission. Supplementa, 72*, 269–280.

Mizoguchi, Y., Kato, T. A., Horikawa, H., & Monji, A. (2014). Microglial intracellular Ca(2+) signaling as a target of antipsychotic actions for the treatment of schizophrenia. *Frontiers in Cellular Neuroscience, 8*, 370.

Moieni, M., Irwin, M. R., Jevtic, I., Breen, E. C., & Eisenberger, N. I. (2015). Inflammation impairs social cognitive processing: A randomized controlled trial of endotoxin. *Brain, Behavior, and Immunity, 48*, 132–138.

Müller, N., & Dursun, S. M. (2011). Schizophrenia genes, epigenetics and psychoneuroimmunology therapeutics: All make sense now? *Journal of Psychopharmacology (Oxford), 25*, 713–714.

Müller, N., & Schwarz, M. J. (2008). A psychoneuroimmunological perspective to Emil Kraepelins dichotomy: Schizophrenia and major depression as inflammatory CNS disorders. *European Archives of Psychiatry and Clinical Neuroscience, 258*(Suppl 2), 97–106.

Müller, N., Weidinger, E., Leitner, B., & Schwarz, M. J. (2015). The role of inflammation in schizophrenia. *Frontiers in Neuroscience, 9*, 372.

Nagano, T., Mizuno, M., Morita, K., & Nawa, H. (2015). Pathological implications of oxidative stress in patients and animal models with schizophrenia: The role of epidermal growth factor receptor signaling. *Current Topics in Behavioral Neurosciences, 29*, 429–446.

Pandya, C. D., Kutiyanawalla, A., & Pillai, A. (2013). BDNF-TrkB signaling and neuroprotection in schizophrenia. *Asian Journal of Psychiatry, 6*, 22–28.

Petitto, J. M., Meola, D., & Huang, Z. (2012). Interleukin-2 and the brain: Dissecting central versus peripheral contributions using unique mouse models. *Methods in Molecular Biology, 934*, 301–311.

Rolland, B., Deguil, J., Jardri, R., Cottencin, O., Thomas, P., & Bordet, R. (2013). Therapeutic prospects of PPARs in psychiatric disorders: A comprehensive review. *Current Drug Targets, 14*, 724–732.

Roussos, P., Katsel, P., Davis, K. L., Giakoumaki, S. G., Lencz, T., Malhotra, A. K., et al. (2013). Convergent findings for abnormalities of the NF-kB signaling pathway in schizophrenia. *Neuropsychopharmacology, 38*, 533–539.

Sarkar, C., Basu, B., Chakroborty, D., Dasgupta, P. S., & Basu, S. (2010). The immunoregulatory role of dopamine: An update. *Brain, Behavior, and Immunity, 24*, 525–528.

Singh, K. K. (2013). An emerging role for Wnt and GSK3 signaling pathways in schizophrenia. *Clinical Genetics, 83*, 511–517.

Sperner-Unterweger, B., & Fuchs, D. (2015). Schizophrenia and psychoneuroimmunology: An integrative view. *Current Opinion in Psychiatry, 28*, 201–206.

van Beveren, N. J. M., Schwarz, E., Noll, R., Guest, P. C., Meijer, C., de Haan, L., et al. (2014). Evidence for disturbed insulin and growth hormone signaling as potential risk factors in the development of schizophrenia. *Translational Psychiatry, 4*, e430.

Vetlugina, T. P., Lobacheva, O. A., Sergeeva, S. A., Nikitina, V. B., Nevidimova, T. I., & Semke, A. V. (2016). Adjunctive use of interferon γ inducer for treatment of patients with schizophrenia. *Acta Neuropsychiatrica, 28*, 149–156.

Wu, J. Q., Green, M. J., Gardiner, E. J., Tooney, P. A., Scott, R. J., Carr, V. J., et al. (2016). Altered neural signaling and immune pathways in peripheral blood mononuclear cells of schizophrenia patients with cognitive impairment: A transcriptome analysis. *Brain, Behavior, and Immunity, 53*, 194–206.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Chapter 8
Obesity, Stress, Inflammation, and Psychoneuroimmunology

8.1 Obesity, PNI, and the Biopsychosocial Models

Obesity is becoming an epidemic problem worldwide with a high incidence of secondary diseases and remarkably increased healthcare costs. Obesity has been connected to the higher risks for various chronic diseases including multiple sclerosis (MS). For example, a population-based case–control study indicated that those with adolescent obesity had a 90 % higher risk for having MS (Hedström et al. 2016).

Obesity may also be a critical factor that interferes with the immunological activities in the brain and enhances the progression of Alzheimer's disease (Heneka et al. 2015). Low-grade inflammation is a prominent feature of obesity (Yan 2012b). The understanding of the roles of obesity and systemic inflammation would be helpful for the discovery of effective preventive and therapeutic strategies for many diseases.

Studies in psychoneuroimmunology (PNI) based on the biopsychosocial models would support the development of personalized, systems, and dynamical medicine toward the integrative interventions for obesity (Yan 2014; also see Chap. 1). Close associations have been identified among stress, depression, inflammation, and disorders such as obesity, diabetes, and cardiovascular diseases (Yan 2012a; Aguilar-Valles et al. 2015).

Inflammation has an essential role in psychological stress and the behavioral symptoms of those with obesity (Yan 2012b). Evidences have been found that stressed or depressed people are often overweight too, while the adipose tissue is a key resource of proinflammatory cytokines (Jaremka et al. 2013). Depression may induce weight accumulation. The weight increase may activate the inflammatory responses via the higher production of interleukin-6 (IL-6) in the expanded adipose tissue and white blood cells induced by leptin (Miller et al. 2003).

Studies on the correlations among adiposity, inflammation, eating behavior, and emotional conditions in obese women have connected body mass index (BMI) with inflammatory biomarkers such as IL-6 and high-sensitivity C-reactive protein (hsCRP) (Capuron et al. 2011). These biomarkers are also critical in the depression and anxiety properties of neuroticism.

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_8

On the other hand, weight loss (e.g., via surgery) has been linked to the lower levels of inflammation and adipokines, with remarkable improvement in emotional conditions and eating habits (Capuron et al. 2011). Adipokines such as leptin and adiponectin have important roles in the neuro-immune networks, neuroinflammation, and brain disorders (Aguilar-Valles et al. 2015).

8.2 Psychological Stress, Obesity, and Associated Diseases

Social and psychological factors may interact with genetic predisposition, dietary patterns, and lifestyle to influence weight gain and the condition of obesity. Chronic stress refers to a prolonged state of the disturbance of homeostasis that can be triggered by intense and frequently enforced stressors (Kyrou and Tsigos 2008). Chronic psychosocial stress has been connected with the development of obesity as an important environmental factor (Scott et al. 2012).

For example, a study of 7443 Swedish families indicated that psychological stress in the family was a causal factor for childhood obesity (Koch et al. 2008). Such correlation highlights the importance of psychological and social support for obese children and their families.

According to a study of 5077 Hispanic/Latino adults, when compared with no stressors, multiple chronic stressors were related to the higher probabilities of obesity and the percentages of body fat with larger waist circumference (Isasi et al. 2015). The connections between stress and adiposity measures indicate that stress management methods can be helpful for the prevention and treatment of obesity among Hispanic/Latino populations.

The individual maladaptation to chronic environmental stress exposure may contribute to obesity, especially the type of abdominal obesity (Pasquali 2012). Such effects may be mediated by the dysregulation of associated neuroendocrine axes. Social stress may influence the patterns of dietary preference, food consumption, as well as the distribution of adipose tissues. Chronic stress may interact with the mechanisms of energy intake and expenditure by promoting appetite while reducing physical activity (De Vriendt et al. 2009). Such mechanisms may lead to the accumulation of visceral fat and abdominal obesity.

The interactions between chronic stress and obesity may have various physiological consequences, such as the effects on the cardiovascular reactivity. Obesity and chronic stress may disturb the normal metabolic process and progressively result in a range of metabolic complications including diabetes, hypertension, and cardiovascular diseases (Macedo et al. 2012; Kyrou and Tsigos 2008). While chronic stress may induce weight gain, excessive fat accumulation may in turn lead to the development of a chronic stressful state.

For example, a study of 122 undergraduate students taking stressful tasks suggested that higher abdominal obesity had predictive values for blunted systolic blood pressure (SBP) and mean arterial pressure (MAP) changes (Singh and Shen 2013). A significant interaction effect was observed between abdominal obesity and

chronic stress on the SBP and MAP changes. The findings indicate that abdominally obese individuals may have difficulties in having appropriate cardiovascular reactivity in response to the high levels of chronic stress (Singh and Shen 2013).

In another study using a rat model, the interaction between hypercaloric diet and stress was shown by the higher levels of serum leptin (Macedo et al. 2012). In a study of a population-based sample of 3759, perceived stress was found useful for the prediction of abnormal glucose metabolism including abnormal fasting glucose and impaired glucose tolerance among women (Williams et al. 2013). The studies suggest that psychosocial adversity should be considered in the risk factor profiles for the development of diabetes.

8.3 Potential Stress and Inflammatory Biomarkers in Obesity

As discussed earlier, inflammation has been suggested to serve as a transitional pathway providing the connection between psychosocial stress and obesity. Table 8.1 provides a sample list of potential stress and inflammation-associated biomarkers in obesity. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

For example, a study of 7540 individuals demonstrated that the likely mediators included inflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen (Hamer and Stamatakis 2008, also see Table 8.1). These inflammatory biomarkers alone may attribute to about 25 % of the link between stress and obesity. In addition, health behaviors such as physical activity and dietary intake are also significant factors.

Table 8.1 Potential stress and inflammatory biomarkers in association with obesity

Potential biomarkers	Associated pathogenesis/diseases	References
C-reactive protein (CRP), fibrinogen	Stress, obesity	Hamer and Stamatakis 2008
CRP, fibrinogen	Obesity-associated diabetes and hypertension	Nguyen et al. 2009
CRP	Obesity	Stępień et al. 2014
IL-6, urinary albumin, and ischemia-modified albumin (IMA)	Obesity	Piva et al. 2013
IL-6, hsCRP, leukocytes, granulocytes, $CD3^+$ cells	Stress, obesity in women	Benson et al. 2009
Leptin, resistin	Childhood obesity	Leoni et al. 2010
TNF-α	Obesity	Lasselin et al. 2014
Catecholamines and IL-1β	Acute mental stress, obesity, cardiovascular disease (CVD)	Caslin et al. 2016
TNF-α, hsCRP	Obesity	Marques-Vidal et al. 2012

Direct connections have been confirmed between the elevated levels of inflammatory biomarkers and obese levels as well as obesity-associated comorbidities including diabetes and hypertension. The study of the US participants of the 1999–2004 National Health and Nutrition Examination Survey (NHANES) evaluated the biomarker levels across various weight classes of normal weight, overweight, and obesity classes 1, 2, and 3 (Nguyen et al. 2009).

The study found that the serum levels of CRP nearly doubled with each increase in the weight class from overweight to obesity class 3 (Nguyen et al. 2009). In addition, the levels of fibrinogen elevated with higher weight class. The elevated levels of CRP and fibrinogen were also observed among those with hypertension or diabetes when compared with those who did not have the disorders (see Table 8.1).

In another study of 65 obese adult subjects, the serum levels of high sensitivity CRP (hsCRP) were found as a more sensitive biomarker than IL-6 and TNF-α in association with obesity (Stępień et al. 2014). In addition, the treatments targeting lowering lipid levels were found to affect the levels of chronic inflammation.

Studies have shown that various inflammatory and oxidative biomarkers have been associated with body mass index (BMI) and obesity. For example, a study of 93 subjects revealed the significant associations between BMI and the higher levels of IL-6, urinary albumin, and ischemia-modified albumin (IMA) (Piva et al. 2013). In the meantime, the decreased levels of nitrate/nitrite (NOx) were observed among obese patients (see Table 8.1). These correlations indicate the interactions among the conditions of inflammation, oxidative stress, and endothelial dysfunctions in obesity.

The obese condition may affect inflammatory cytokines and leptin levels upon acute mental or psychosocial stress. For example, a strong connection has been established between obesity and chronic low-grade inflammation among premenopausal women (Benson et al. 2009). The combination of the proinflammatory condition and altered neuroendocrine and cardiovascular stress reactions has been suggested to explain the mechanisms connecting psychological stress with the health risks caused by obesity.

Specifically, a study found that the cortisol stress response was remarkably higher among the obese women (Benson et al. 2009). Psychological stress induced higher levels of serum IL-6, heart rate, and diastolic blood pressure. In addition, higher baseline numbers of circulating leukocytes, granulocytes, $CD3^+$ cells, and hsCRP levels were also observed in the obese women (see Table 8.1).

In a study of blood samples from 47 obese children, the anthropometric parameters and levels of adipocytokines and inflammatory cytokines were assessed (Leoni et al. 2010). Strong correlations were observed between the levels of plasma leptin and resistin and the anthropometric parameters, showing as the potential biomarkers of childhood obesity (see Table 8.1).

Furthermore, the inflammatory conditions of the adipose tissue may result in systemic inflammation in obesity. Macrophages and T cells may be involved in adipose inflammation and affect the treatment outcomes of obesity. Specifically, the gene expression of several cytokines has been associated with the visceral adipose tissue, such as the adipose expression of TNF-α (Lasselin et al. 2014, also see

Table 8.1). Elevated inflammatory conditions of the adipose tissue were associated with a lower BMI reduction after bariatric surgery intended for weight reduction.

The association between obesity and higher cardiovascular disease (CVD) risks may also be mediated via the chronic systemic inflammation and impaired immune reactions to stressors. A study of 20 college-aged males indicated that acute mental stressors caused the higher levels of heart rate, catecholamines, and interleukin-1β (IL-1β) (Caslin et al. 2016). In addition, adiposity in males was found to affect leptin and inflammatory signaling mechanisms after acute mental stress (see Table 8.1).

In a study of 2884 men and 3201 women in a Swiss population-based sample, the obesity markers were found to be differentially related to the cytokine levels (Marques-Vidal et al. 2012). The percentages of body fat were negatively related to IL-1β. The levels of the cytokine TNF-α were found to be related to the status of BMI among women and waist circumferences among men. Furthermore, the hsCRP levels were positively related to all obesity markers (see Table 8.1).

8.4 Obesity-Associated Inflammatory Pathways

Various signaling pathways and cellular networks may be involved in the processes of obesity-associated inflammation. Table 8.2 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

For example, the transcriptome analysis of human adipocytes discovered that the interactions among IFNγ, the NOD-like receptor pathway components such as NLRP3, and adipocyte class II major histocompatibility complex (MHCII) may cause adipose inflammation in obesity (Yin et al. 2014, also see Table 8.2).

A study using mice models found that high-fat diet (HFD) may induce the dysregulation of the gut microbiota and worsen the conditions of inflammation and obesity through the toll-like receptor 4 (TLR4) signaling pathway (Kim et al. 2012, also see Table 8.2). HFD may lead to macrophage infiltration and inflammation in the adipose tissue with the higher levels of the circulating proinflammatory cytokines. This type of diet may result in colonic inflammation and elevated levels of TLR4, iNOS, COX-2, and NF-kB in the colon.

Proinflammatory networks such as the NF-kB pathway have been identified as the essential mechanisms underlying the transformation from overnutrition into intracellular stresses and brain inflammation (Cai and Liu 2012; also see Table 8.2). The inflammatory status in the central nervous system (CNS) has been associated with the neural dysregulations of energy and glucose, as well as the disturbance of the cardiovascular homeostasis. These alterations may result in metabolic syndrome and associated disorders including obesity and hypertension.

In addition, the lower expressions of Baf60c and Deptor were observed in the skeletal muscles in obese mice (Meng et al. 2014). The altered Baf60c/Deptor pathways may connect skeletal muscle inflammation with the disturbance of glucose

Table 8.2 Examples of the inflammatory pathways and HPA-axis in association with obesity

Pathways	Associated pathogenesis/diseases	References
The NOD-like receptor pathways (e.g., NLRP3, MHCII)	Adipose inflammation in obesity	Yin et al. 2014
The TLR4 signaling pathways (e.g., TLR4, iNOS, COX-2, NF-kB)	Inflammation in the adipose tissue, colonic inflammation	Kim et al. 2012
The NF-kB pathways	Intracellular stresses, brain inflammation, disturbance of the cardiovascular homeostasis, metabolic syndrome, obesity, hypertension	Cai and Liu 2012
The Baf60c/Deptor pathways	Skeletal muscle inflammation, disturbance of glucose homeostasis in obesity, insulin resistance	Meng et al. 2014
The GR-GILZ axis	Obesity-induced liver inflammation	Robert et al. 2016
The HPA axis (altered diurnal cortisol patterns)	Stress and waist circumference	Farag et al. 2008
The HPA axis (altered diurnal cortisol patterns)	Obesity in adolescent girls	Hillman et al. 2012
The altered basal HPA activity	Obesity-associated increase in cholesterol and glucose levels	Evans et al. 2013
The HPA-axis (altered 11β-HSD(1))	Obesity	Lucassen and Cizza 2012
HPA-axis dysregulations	Upper body obesity, sleep deprivation, metabolic diseases	Bose et al. 2009

homeostasis in obesity (see Table 8.2). Such finding suggests that the Baf60c/Deptor pathways could be the targets of proinflammatory signaling that associate meta-inflammation with insulin resistance in type 2 diabetes.

Furthermore, obesity has been related to the downregulation of the glucocorticoid receptor (GR) and glucocorticoid-induced leucine zipper (GILZ) pathway in the Kupffer cells (KC) (Robert et al. 2016). Such alterations may lead to the pathophysiology of obesity-induced liver inflammation. As KC are critical in the inflammatory processes in nonalcoholic steatohepatitis, the GR-GILZ axis in KC has been considered an essential target for the treatment of liver inflammation in obesity (see Table 8.2).

8.5 Obesity and the HPA Axis

Stress may increase the craving for "comfort foods." Studies using human and animal models have correlated visceral obesity with the malfunction of the sympathetic nervous system and the hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis (Scott et al. 2012; Pasquali 2012; also see Chap. 3).

Obesity, especially the visceral body fat distribution (V-BFD), has been considered a maladaptation in responses to stress (Vicennati et al. 2014). The alterations in the HPA axis may provide the important mediators linking chronic stress with higher risks for obesity and various metabolic diseases (Bose et al. 2009).

For instance, in a study of 78 women aged 24–72 years, psychological stress was found to be a significant predictor of the dysfunctions of the HPA axis and altered diurnal cortisol patterns (Farag et al. 2008). The disruption of the cortisol patterns across the day may indicate the impairment in the HPA functions (see Table 8.2). Among overweight women, both perceived stress and waist circumference were found important in the prediction of the levels of adrenal cortisol productions.

In another study of 262 adolescent girls, the connections between altered HPA axis activities and obesity were also identified (Hillman et al. 2012). In this study, lower cortisol levels during the day and higher levels at night were associated with the higher levels of adiposity. Such findings demonstrate the pattern alterations in the circadian rhythms of cortisol levels in obesity (see Table 8.2).

In a study using the diet-induced obese mice, strong correlations were revealed between total cholesterol, LDL-cholesterol, glucose, and HPA axis hormones (Evans et al. 2013). The findings confirm the connections between obesity-associated increase in cholesterol and glucose levels with altered basal HPA activities (see Table 8.2).

Furthermore, obese individuals often have the higher levels of cortisol in the adipose tissue with higher local activity of 11β-hydroxysteroid dehydrogenase (HSD) type 1 (Lucassen and Cizza 2012; also see Table 8.2). The HPA-axis alterations may have negative effects on sleep. These mechanisms suggest the potential treatment strategies for obesity by regulating the cortisol levels in the adipose tissue using 11β-HSD(1) inhibitors.

The dysregulations in the HPA axis may have close relationships with upper body obesity and conditions such as sleep deprivation in metabolic disorders (Bose et al. 2009; also see Table 8.2). The elucidation of such interactions may contribute to the development of effective interventions for obesity and associated diseases.

8.6 Potential Therapeutic Targets in Association with Stress and Obesity

The understanding of the connections between chronic stress and obesity may help identify the molecular targets for metabolic regulations. For example, the FK506-binding protein 51 (FKBP51, gene: Fkbp5) is an important gene involved in the metabolic processes and the development of stress-related psychiatric disorders (Balsevich et al. 2014).

In a recent study using mice, the expression of Fkbp5 was found to be responsive to the high-fat diet and chronic stress in the hypothalamus and hippocampus, respectively (Balsevich et al. 2014). The increased levels of hypothalamic Fkbp5 expres-

sion were associated with higher body weight gain. The study showed that Fkbp5 could serve as a molecular target for metabolic regulations with its critical role in the interplay between chronic stress and obesity.

In addition, the combination of chronic stress and a high-fat, high-sugar (HFS) diet has been found to result in abdominal obesity via the promotion of the sympathetic neurotransmitter neuropeptide Y (NPY) in the adipose tissue (Kuo et al. 2008). Both in vitro and in vivo studies showed that chronic stress may affect the NPY-NPY-Y2 receptors (Y2Rs) pathway and enhance diet-induced obesity and the metabolic syndrome. Based on this finding, local administration of Y2R antagonists has been proposed as a method for the treatment of obesity (Kuo et al. 2008).

In addition to these proposed targets, the potential biomarkers and networks described earlier can also become the candidate targets for the discovery of more effective interventions. The comprehensive methods may contribute to the practice of personalized, systems, and dynamical medicine (see Chap. 1).

References

Aguilar-Valles, A., Inoue, W., Rummel, C., & Luheshi, G. N. (2015). Obesity, adipokines and neuroinflammation. *Neuropharmacology, 96*, 124–134.

Balsevich, G., Uribe, A., Wagner, K. V., Hartmann, J., Santarelli, S., Labermaier, C., et al. (2014). Interplay between diet-induced obesity and chronic stress in mice: Potential role of FKBP51. *Journal of Endocrinology, 222*, 15–26.

Benson, S., Arck, P. C., Tan, S., Mann, K., Hahn, S., Janssen, O. E., et al. (2009). Effects of obesity on neuroendocrine, cardiovascular, and immune cell responses to acute psychosocial stress in premenopausal women. *Psychoneuroendocrinology, 34*, 181–189.

Bose, M., Oliván, B., & Laferrère, B. (2009). Stress and obesity: The role of the hypothalamic-pituitary-adrenal axis in metabolic disease. *Current Opinion in Endocrinology, Diabetes, and Obesity, 16*, 340–346.

Cai, D., & Liu, T. (2012). Inflammatory cause of metabolic syndrome via brain stress and NF-kB. *Aging (Albany NY), 4*, 98–115.

Capuron, L., Poitou, C., Machaux-Tholliez, D., Frochot, V., Bouillot, J.-L., Basdevant, A., et al. (2011). Relationship between adiposity, emotional status and eating behaviour in obese women: Role of inflammation. *Psychological Medicine, 41*, 1517–1528.

Caslin, H. L., Franco, R. L., Crabb, E. B., Huang, C. J., Bowen, M. K., & Acevedo, E. O. (2016). The effect of obesity on inflammatory cytokine and leptin production following acute mental stress. *Psychophysiology, 53*, 151–158.

De Vriendt, T., Moreno, L. A., & De Henauw, S. (2009). Chronic stress and obesity in adolescents: Scientific evidence and methodological issues for epidemiological research. *Nutrition, Metabolism, and Cardiovascular Diseases, 19*, 511–519.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Evans, J. F., Islam, S., Urade, Y., Eguchi, N., & Ragolia, L. (2013). The lipocalin-type prostaglandin D2 synthase knockout mouse model of insulin resistance and obesity demonstrates early hypothalamic-pituitary-adrenal axis hyperactivity. *Journal of Endocrinology, 216*, 169–180.

Farag, N. H., Moore, W. E., Lovallo, W. R., Mills, P. J., Khandrika, S., & Eichner, J. E. (2008). Hypothalamic-pituitary-adrenal axis function: Relative contributions of perceived stress and obesity in women. *Journal of Women's Health (Larchmt), 17*, 1647–1655.

Hamer, M., & Stamatakis, E. (2008). Inflammation as an intermediate pathway in the association between psychosocial stress and obesity. *Physiology and Behavior, 94*, 536–539.

Hedström, A. K., Olsson, T., & Alfredsson, L. (2016). Body mass index during adolescence, rather than childhood, is critical in determining MS risk. *Multiple Sclerosis, 22*, 878–883.

Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., et al. (2015). Neuroinflammation in Alzheimer's disease. *Lancet Neurology, 14*, 388–405.

Hillman, J. B., Dorn, L. D., Loucks, T. L., & Berga, S. L. (2012). Obesity and the hypothalamic-pituitary-adrenal axis in adolescent girls. *Metabolism: Clinical and Experimental, 61*, 341–348.

Isasi, C. R., Parrinello, C. M., Jung, M. M., Carnethon, M. R., Birnbaum-Weitzman, O., Espinoza, R. A., et al. (2015). Psychosocial stress is associated with obesity and diet quality in Hispanic/Latino adults. *Annals of Epidemiology, 25*, 84–89.

Jaremka, L. M., Lindgren, M. E., & Kiecolt-Glaser, J. K. (2013). Synergistic relationships among stress, depression, and troubled relationships: Insights from psychoneuroimmunology. *Depression and Anxiety, 30*, 288–296.

Kim, K.-A., Gu, W., Lee, I.-A., Joh, E.-H., & Kim, D.-H. (2012). High fat diet-induced gut microbiota exacerbates inflammation and obesity in mice via the TLR4 signaling pathway. *PLoS One, 7*, e47713.

Koch, F.-S., Sepa, A., & Ludvigsson, J. (2008). Psychological stress and obesity. *Journal of Pediatrics, 153*, 839–844.

Kuo, L. E., Czarnecka, M., Kitlinska, J. B., Tilan, J. U., Kvetnanský, R., & Zukowska, Z. (2008). Chronic stress, combined with a high-fat/high-sugar diet, shifts sympathetic signaling toward neuropeptide Y and leads to obesity and the metabolic syndrome. *Annals of the New York Academy of Sciences, 1148*, 232–237.

Kyrou, I., & Tsigos, C. (2008). Chronic stress, visceral obesity and gonadal dysfunction. *Hormones (Athens), 7*, 287–293.

Lasselin, J., Magne, E., Beau, C., Ledaguenel, P., Dexpert, S., Aubert, A., et al. (2014). Adipose inflammation in obesity: Relationship with circulating levels of inflammatory markers and association with surgery-induced weight loss. *Journal of Clinical Endocrinology and Metabolism, 99*, E53–E61.

Leoni, M. C., Valsecchi, C., Mantelli, M., Marastoni, L., Tinelli, C., Marchi, A., et al. (2010). Impact of child obesity on adipose tissue physiology: Assessment of adipocytokines and inflammatory cytokines as biomarkers of obesity. *Pediatric Reports, 2*, e19.

Lucassen, E. A., & Cizza, G. (2012). The hypothalamic-pituitary-adrenal axis, obesity, and chronic stress exposure: Sleep and the HPA axis in obesity. *Current Obesity Reports, 1*, 208–215.

Macedo, I. C., Medeiros, L. F., Oliveira, C., Oliveira, C. M., Rozisky, J. R., Scarabelot, V. L., et al. (2012). Cafeteria diet-induced obesity plus chronic stress alter serum leptin levels. *Peptides, 38*, 189–196.

Marques-Vidal, P., Bochud, M., Bastardot, F., Lüscher, T., Ferrero, F., Gaspoz, J.-M., et al. (2012). Association between inflammatory and obesity markers in a Swiss population-based sample (CoLaus Study). *Obesity Facts, 5*, 734–744.

Meng, Z.-X., Wang, L., Xiao, Y., & Lin, J. D. (2014). The Baf60c/Deptor pathway links skeletal muscle inflammation to glucose homeostasis in obesity. *Diabetes, 63*, 1533–1545.

Miller, G. E., Freedland, K. E., Carney, R. M., Stetler, C. A., & Banks, W. A. (2003). Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. *Brain, Behavior, and Immunity, 17*, 276–285.

Nguyen, X.-M. T., Lane, J., Smith, B. R., & Nguyen, N. T. (2009). Changes in inflammatory biomarkers across weight classes in a representative US population: A link between obesity and inflammation. *Journal of Gastrointestinal Surgery, 13*, 1205–1212.

Pasquali, R. (2012). The hypothalamic-pituitary-adrenal axis and sex hormones in chronic stress and obesity: Pathophysiological and clinical aspects. *Annals of the New York Academy of Sciences, 1264*, 20–35.

Piva, S. J., Tatsch, E., De Carvalho, J. A. M., Bochi, G. V., Kober, H., Duarte, T., et al. (2013). Assessment of inflammatory and oxidative biomarkers in obesity and their associations with body mass index. *Inflammation, 36*, 226–231.

Robert, O., Boujedidi, H., Bigorgne, A., Ferrere, G., Voican, C. S., Vettorazzi, S., et al. (2016). Decreased expression of the glucocorticoid receptor-GILZ pathway in Kupffer cells promotes liver inflammation in obese mice. *Journal of Hepatology, 64*, 916–924.

Scott, K. A., Melhorn, S. J., & Sakai, R. R. (2012). Effects of chronic social stress on obesity. *Current Obesity Reports, 1*, 16–25.

Singh, K., & Shen, B.-J. (2013). Abdominal obesity and chronic stress interact to predict blunted cardiovascular reactivity. *International Journal of Psychophysiology, 90*, 73–79.

Stępień, M., Stępień, A., Wlazeł, R. N., Paradowski, M., Banach, M., & Rysz, J. (2014). Obesity indices and inflammatory markers in obese non-diabetic normo- and hypertensive patients: A comparative pilot study. *Lipids in Health and Disease, 13*, 29.

Vicennati, V., Garelli, S., Rinaldi, E., Di Dalmazi, G., Pagotto, U., & Pasquali, R. (2014). Cross-talk between adipose tissue and the HPA axis in obesity and overt hypercortisolemic states. *Hormone Molecular Biology and Clinical Investigation, 17*, 63–77.

Williams, E. D., Magliano, D. J., Tapp, R. J., Oldenburg, B. F., & Shaw, J. E. (2013). Psychosocial stress predicts abnormal glucose metabolism: The Australian Diabetes, Obesity and Lifestyle (AusDiab) study. *Annals of Behavioral Medicine, 46*, 62–72.

Yan, Q. (2012a). The role of psychoneuroimmunology in personalized and systems medicine. *Methods in Molecular Biology, 934*, 3–19.

Yan, Q. (2012b). Translational implications of inflammatory biomarkers and cytokine networks in psychoneuroimmunology. *Methods in Molecular Biology, 934*, 105–120.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Yin, Z., Deng, T., Peterson, L. E., Yu, R., Lin, J., Hamilton, D. J., et al. (2014). Transcriptome analysis of human adipocytes implicates the NOD-like receptor pathway in obesity-induced adipose inflammation. *Molecular and Cellular Endocrinology, 394*, 80–87.

Chapter 9
Psychoneuroimmunology of Aging

9.1 Aging, PNI, and the Systems Biology Models

The crosstalk among the immune, nervous, and endocrine systems relies on the feedback loops and networks to maintain the homeostasis and stress responses. The higher frequencies of autoimmune, infectious, and neoplastic illnesses among the elderly refer to the importance of psychoneuroimmune interactions in the old age (Guidi et al. 1998).

The aging process is often related to social changes, psychological stress, and depression. These factors can have significant impacts on the brain activities and immune functions. The brain–body communications carry out the multidirectional flow of information involving hormones, neurotransmitters, neuropeptides, as well as cytokines (Vitetta et al. 2005).

Specifically, the innate immune system of the brain mainly contains microglial cells and astrocytes. The activation of these cells provides the protection for neurons against stimulants including infectious materials and lesions (Layé 2010). Even during the normal aging process, the microglia and astrocytes are getting more reactive (Godbout and Johnson 2009).

Such changes in the innate immune cells may enhance the brain inflammatory cytokine activities and worsen the conditions of neuroinflammation. These mechanisms may lead to the alterations in cognition and mood, as well as sickness behaviors upon peripheral immune responses. As a consequence, proinflammatory cytokines may be related to depression and various neurodegenerative disorders associated with aging (Layé 2010).

Higher levels of inflammatory cytokines in the brain may damage the neuronal plasticity with elevated neuroinflammatory reactions among the aged. These alterations may result in neurobehavioral problems and cognitive deficits including delirium, depression, as well as various neurologic diseases (Godbout and Johnson 2006, 2009). Interventions to reduce the levels of neuroinflammation would be necessary for the treatment and recovery of neurobehavioral disorders in the elderly.

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_9

With the understanding in the interconnected complex adaptive systems (CASs), systems biology models based on physiology and nonlinear dynamics may be established for aging. Embracing the PNI mechanisms including stress systems, immune functions, and mitochondrial bioenergetics, the dynamical biopsychosocial models would enable the better insights into the complex aging process toward better patient care (see Chap. 1).

Specifically, the trajectory of life span is featured with the growth, plateauing, the loss of adaptive functions, and the lower levels of the coordination among systems (Sturmberg et al. 2015). In the process of aging, the interdependence among various organ systems and the network interconnectedness are especially important. Such complexity can be evaluated by analyzing the variability in biologic rhythms, such as the heart rate variability and the genetic rhythmic patterns (see Chaps. 3 and 4). Aging is featured with the loss of the variability at different scales, including the functional units at the small scale and the diagnostic biomarkers at the larger scale (Sturmberg et al. 2015).

Various investigations have revealed that the overall integrity of physiological complexity may be shown in the degree and variability of biologic rhythms (see Chaps. 3 and 4). Such mechanisms have been suggested as the essential properties of health. On the other hand, aging is associated with the loss of such complex properties (Sturmberg et al. 2015). Such understanding may have profound meanings for the development of novel preventive and therapeutic strategies in systems and dynamical medicine for aging-associated disorders and for health promotion across the trajectory of life (Yan 2014).

9.2 The Stress–Inflammation Correlations in Aging

While both of the aging process and mental stress can lead to immune dysfunctions, stress and age are the factors that can also interact with each other. Mental stress may aggravate the aging process, and stress often causes more significant immune dysregulations among older adults than in younger adults (Graham et al. 2006). Childhood stressful experiences may also lead to the alterations in the nervous and immune systems in later life. The understanding of the stress–age interactions is important for the development of interventions during both early and late life.

Specifically, the bidirectional interactions between the nervous and immune systems have the major roles in peripheral inflammation, providing the connections among psychosocial stress, aging, and chronic diseases. The term “inflammaging” refers to the condition of premature aging based on chronic inflammations and proinflammatory mechanisms (Liezmann et al. 2012).

Normally, the neuroendocrine-immune plasticity provides the immune adaptation in response to environmental and endogenous stressors. However, chronic and excessive stress may lead to maladaptive plasticity and inflammaging with chronic inflammatory states. The stress mediators including neurotransmitters, neuropeptides, as

well as neurotrophins have the key roles in the immune responses in the spleen (Liezmann et al. 2012).

Numerous laboratory and clinical evidences have demonstrated that chronic stress is closely related to immune dysfunctions and premature aging. PNI studies have indicated that stress conditions may lead to the dysregulations of various components of both innate and adaptive immunity. For example, family dementia caregiving providers are often affected by chronic stress. Compared with other older adults, elderly caregivers may have poor vaccine responses, elevated levels of inflammatory mediators, as well as accelerated cellular aging (Gouin et al. 2008). Such chronic stress-caused immune dysfunctions among older caregivers may have negative impacts on both mental and physical health.

Stressful experiences and negative emotions may stimulate the complex pathways of proinflammatory cytokines. As a result, inflammation has been tightly connected to a variety of aging-associated disorders including periodontal diseases, arthritis, cardiovascular diseases, gastrointestinal distress, type 2 diabetes, cancers, as well as Alzheimer's disease (Kiecolt-Glaser et al. 2002; Vitetta et al. 2005). Other results include prolonged infections and slow wound healing, which may also promote the continuous release of proinflammatory cytokines.

9.3 Inflammatory Pathways: The Links Among Stress, Aging, and Chronic Diseases

9.3.1 Cardiovascular Aging and Diseases

Cardiovascular diseases (CVD) have a high incidence in the elderly population. This may be caused by the interactive effects of age-associated alterations in both of the heart morphology and functions, as well as the continuous exposure to CVD risk factors such as oxidative stress (Silva-Palacios et al. 2016). Table 9.1 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

Chronic psychological stress has been related to accelerated aging and the higher risk for aging-associated disorders such as CVD. Specifically, cumulative lifetime stress has been found to accelerate epigenetic aging with glucocorticoid-related epigenetic alterations (Zannas et al. 2015). Lifetime stressors may influence the DNA methylation-based age predictor and the epigenetic clock. In addition, cumulative lifetime stress but not childhood maltreatment or current stress alone has predictive values in accelerated epigenetic aging.

For example, glucocorticoid signaling pathways may be involved in such epigenetic effects as demonstrated by increased epigenetic clock CpG sites in glucocorticoid response elements. The evaluation of the effects of glucocorticoids upon exposure to the glucocorticoid receptor agonist dexamethasone showed the dynamic alterations in the methylation of the CpGs (Zannas et al. 2015). The genes regulated

Table 9.1 Examples of stress and inflammation-related pathways in aging

Pathways and interactions	Associated pathogenesis/diseases	References
The glucocorticoid signaling pathways	Epigenetic aging, coronary artery disease (CAD), arteriosclerosis, leukemias	Zannas et al. 2015
The IL-6 pathways	Age-related disorders (e.g., atherosclerosis, CAD, peripheral vascular disease, osteoporosis, diabetes, dementia, Alzheimer's disease, arthritis, cancer)	Omoigui 2007
The Arg-II, p38, and S6K1 pathways	Endothelial senescence, cardiovascular aging	Wu et al. 2015
The Nrf2 signaling pathways	Cardiovascular diseases (CVD), hypertension	Silva-Palacios et al. 2016
The inflammatory, synaptic, neurotrophic pathways (e.g., NF-kB, TRAF6, TLR4, IL1R1, TSPO, GFAP, BDNF, NGF, PDGFA, SYN, DBN1)	Aging, neuroinflammation	Primiani et al. 2014
The IDO and GTP-CH1 pathways	Age-associated neuropsychiatric symptoms, depression, inflammation	Capuron et al. 2011
The mTOR signaling pathways	Age-related cognitive decline, Alzheimer disease	Perluigi et al. 2015
The mTOR signaling pathways	Aging, obesity, cancer, systemic lupus erythematosus, autoimmune diseases	Perl 2015
The RAGE/NF-kB/JNK and melatonin-associated pathways	Neuroinflammation, age-related neurodegenerative diseases, Alzheimer's disease	Ali et al. 2015
The RIG-I/NF-kB signaling pathways	Aging-related renal injury, chronic kidney disease (CKD)	Zeng et al. 2016
The Wnt4, NF-kB, and Tak1-associated signaling pathways	Skeletal aging, osteoporosis	Yu et al. 2014
The TGFβ signaling pathways	Aging, osteoarthritis	Baugé et al. 2014
The JAK–STAT3 signaling pathways	Inflammaging, sarcopenia, or muscular dystrophies	Chazaud and Mouchiroud 2014
The CCL2–CCR2 signaling pathways	Choroidal neovascularization (CNV), age-associated macular degeneration in the eye, age-related inflammatory diseases	Robbie et al. 2016
The FOXO3 signaling pathways	Lung tissue aging, chronic obstructive pulmonary disease (COPD)	Yuan et al. 2015
The mitochondrial stress response pathways	Systemic inflammatory responses	Hill and Van Remmen 2014

by dexamethasone have close relationships with aging-associated diseases such as coronary artery disease (CAD), arteriosclerosis, and leukemias (see Table 9.1).

The inflammatory pathways involved in the connections between cholesterol and aging are essential for various chronic diseases. For instance, interleukin-6 (IL-6)-mediated inflammation has been closely related to various aging-associated diseases (see Table 9.1). These disorders include dementia and Alzheimer's disease, type 2 diabetes, atherosclerosis, coronary artery disease (CAD), peripheral vascular disease, osteoporosis, as well as arthritis and cancer (Omoigui 2007).

The inhibition of IL-6-associated inflammatory pathways has been suggested as the common therapeutic targets for the management of these aging-associated diseases. For instance, statins and bisphosphonates may suppress the IL-6-associated inflammatory pathways indirectly via the control of endogenous cholesterol synthesis and isoprenoid depletion (Omoigui 2007). In addition, polyphenolic compounds derived from plants, fruits, and vegetables may also suppress the signal transduction inflammatory pathways directly.

Moreover, the pathways associated with p38 mitogen-activated protein kinase (p38 MAPK) have the pivotal roles in cellular senescence and senescence-related secretory phenotype (SASP) with the release of cytokines and/or chemokines (Wu et al. 2015). The higher levels of the interactions between arginase-II (Arg-II) and S6K1 may enhance the endothelial senescence via the uncoupling of endothelial nitric oxide synthase (eNOS) (see Table 9.1).

In the heart and aortas of aging mice, higher levels of p38 activation and the expression of IL-6 and IL-8 homolog have been observed (Wu et al. 2015). Meanwhile, antioxidants and the suppression of p38 may recouple the eNOS function with the lower levels of IL-6 and IL-8. These indicate the circuit among the interactions of Arg-II, p38, and S6K1 in the process of endothelial senescence and cardiovascular aging.

As a feature of aging, oxidative stress is a key factor in the pathogenesis of obesity, diabetes, as well as CVD including hypertension. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway has been found important in the cellular redox homeostasis, antioxidant regulation, and phase II detoxification reactions (Silva-Palacios et al. 2016; also see Table 9.1). Strategies of promoting the endogenous antioxidant mechanisms may be applied to prevent the aging-associated CVD and to improve the quality of life. The supplements of exogenous antioxidants to suppress oxidative stress could be useful.

9.3.2 Brain Aging and Neuropsychiatric Symptoms

The inflammatory, synaptic, and neurotrophic pathways have been associated with the alterations in the aging process and neurodegenerative diseases. In the brain, these cellular networks have pivotal roles in the structural and functional activities over the life span. By analyzing a large-scale microarray dataset from human

prefrontal cortex, a study examined the transcription levels of 39 genes associated with aging (Primiani et al. 2014; also see Table 9.1).

The study revealed different trajectories of the gene expression levels over the life span. The changes in the clusters of genes were found to be intercorrelated. For example, higher levels of expression were observed among the potentially proinflammatory genes including NFKB1, TRAF6, TLR4, IL1R1, TSPO, and GFAP (Primiani et al. 2014). In addition, lower levels were observed among the neurotrophic and synaptic integrity genes including BDNF, NGF, PDGFA, SYN, and DBN1. Proinflammatory gene networks and synaptic loss are especially important in the late aging stage. The identification of the changes in the transcription cascades throughout the life span would contribute to the understanding of the phenotypic alterations in the aging process.

In addition, the alterations in several enzymatic pathways associated with monoamine metabolism have been found critical in chronic low-grade inflammation in aging (Capuron et al. 2011). Such inflammatory status may contribute to the pathophysiology of neuropsychiatric symptoms, the common complaints among elderly persons. Two of these enzymatic pathways have been found essential in the biosynthesis of monoamines, including the indoleamine-2,3-dioxygenase (IDO) and the guanosine-triphosphate-cyclohydrolase-1 (GTP-CH1) pathways (see Table 9.1).

In a study of 284 healthy elderly subjects, assessments were made using inflammatory markers such as IL-6 and C-reactive-protein (CRP), and the index of IDO activity such as tryptophan, kynurenine, and their ratio (Capuron et al. 2011). The study confirmed that the levels of immune markers and neuropsychiatric symptoms had tight correlations with age. Higher levels of inflammation were associated with lower tryptophan levels and higher kynurenine levels, indicating IDO caused higher tryptophan catabolism. Inflammation was also the key in higher neopterin, nitrite, and phenylalanine levels.

Furthermore, higher levels of tryptophan catabolism were also correlated with the depressive symptoms including lassitude, lower motivation, anorexia, and pessimism (Capuron et al. 2011). The alterations in the markers of GTP-CH1 activity were related to neurovegetative symptoms such as sleep disturbance, digestive problems, fatigue, as well as motor symptoms.

9.3.3 The mTOR Signaling Pathways, Alzheimer's Disease, and Autoimmune Disorders

Evidences have proven that in cellular aging, organismal aging, as well as aging-associated diseases, the mammalian target of rapamycin (mTOR) signaling pathway has essential roles (Perluigi et al. 2015; also see Table 9.1). As a ubiquitous serine/threonine kinase, mTOR is a component of the two interacting protein complexes mTORC1 and mTORC2. mTOR is pivotal in integrating cellular growth signals, metabolism, and cellular energy conditions.

Under stress conditions, mTOR has been found to support proliferation, survival, and protein translation (Perl 2015). It is involved in the promotion of the transcription of genes associated with carbohydrate metabolism and lipogenesis, as well as the inhibition of autophagy. In the immune system, mTOR may act as a major regulator of metabolism associated with lineage specification. In the condition of oxidative stress, the mTORC1 pathway may be involved in the pathogenesis of systemic lupus erythematosus (SLE) and various autoimmune disorders (see Table 9.1).

The alterations in the mTOR signaling pathway in the brain have been found to influence various pathways associated with glucose metabolism, energy generation, as well as mitochondrial functions (Perluigi et al. 2015). These dysfunctions are critical in age-associated cognitive decline and the development of Alzheimer disease (AD). Further studies based on systems biology may help elucidate the comprehensive mechanisms of the mTOR pathways in the CNS, with the complex signals as the potential biomarkers and therapeutic targets for AD.

With the understanding of these mechanisms, rapamycin and different classes of mTOR inhibitors have been proposed to block transplant rejection and autoimmunity (Perl 2015). They may also be applied for the treatment of obesity and different types of cancer. The mTOR-associated pathways have been suggested as the targets for disease prevention, personalized interventions, as well as life span extension.

9.3.4 Melatonin-Associated Pathways and Age-Associated Neurodegenerative Disorders

As a pleiotropic agent, melatonin has been suggested as helpful for age-associated neurodegenerative disorders. It may have neuroprotective effects and attenuate the levels of neuroinflammation. For example, a recent study demonstrated that chronic melatonin intervention could help ease D-galactose-caused memory loss (Ali et al. 2015). It could promote the levels of memory-associated pre-and postsynaptic protein biomarkers to counteract synaptic alterations. It may also inhibit the levels of reactive oxygen species (ROS) and receptor for advanced glycation end products (RAGE) to improve memory functions.

In addition, melatonin could reduce the levels of microgliosis (Iba-1), astrocytosis (GFAP), as well as inflammatory markers including p-IKKβ, p-NF-K B65, COX2, NOS2, IL-1β, and TNFα (Ali et al. 2015). Such mechanism could lower the levels of neuroinflammation. It may provide the protection and prevention from neurodegeneration by inhibiting the oxidative stress kinase p-JNK and apoptotic markers including cytochrome C, caspase-9, caspase-3, and PARP-1.

These observations revealed that melatonin may supply the protection from memory loss, neuroinflammation, and neurodegeneration via the effects on the RAGE/NF-kB/JNK pathways (Ali et al. 2015; also see Table 9.1). These mechanisms indicate its potential usage as an endogenous antioxidant for age-associated neurodegenerative disorders including Alzheimer's disease.

9.3.5 The Kidney–Brain Axis and Chronic Kidney Disease (CKD)

The interactions between different organs may have important roles in both aging and inflammation. The aging process is often associated with the dysfunction of the kidney–brain axis. For example, the abundance of the antiaging Klotho protein in both of the kidneys and the brain may provide the protection against the destructive processes. The lower levels of Klotho have been related to aging-associated cognitive impairments, inflammation, and renal injury (Zeng et al. 2016).

Studies have linked early stage chronic kidney disease (CKD) with the higher levels of the urinary albumin-to-creatinine ratio, inflammatory cell infiltration, glomerulosclerosis, as well as tubulointerstitial fibrosis (Zeng et al. 2016). When compared with normal controls, the aging-associated decline of Klotho was associated with the activation of the retinoic acid-inducible gene 1/nuclear factor-kB (RIG-I/NF-kB) signaling pathways. The subsequent results included higher levels of the proinflammatory markers such as tumor necrosis factor α (TNF-α), IL-6, and nitric oxide synthase (NOS) in the kidneys of aged mice models.

The findings correlate aging-associated inflammation and the pathogenesis of early stage CKD with the lower levels of Klotho and the activation of the RIG-I/NF-kB signaling pathways (Zeng et al. 2016; also see Table 9.1). These evidences about the cognitive deficits and renal damages have highlighted the importance of the kidney–brain axis and the inflammatory biomarkers and pathways in the aging process.

9.3.6 Bone Loss, Osteoporosis, and Muscle Dysfunctions

Bone loss and osteoporosis are commonly seen aging-associated problems that influence the quality of life among millions of people. Chronic inflammation in the aging process may lead to bone resorption with damages in the bone formation. Studies have indicated that Wnt4 and noncanonical Wnt signaling pathways may suppress the cytokine activities of NF-kB mediated by transforming growth factor-β-activated kinase-1 (Tak1) in macrophages and osteoclast precursors (Yu et al. 2014; also see Table 9.1).

Wnt4 has been found to diminish bone loss in osteoporosis and skeletal aging and provide the protection from chronic inflammation caused by ovariectomy or TNF (Yu et al. 2014). It may suppress the osteoclast formation and bone resorption. Such mechanisms of the Wnt signaling pathways in the promotion of bone formation indicate their potential applications as the preventive and treatment targets for osteoporosis and skeletal aging.

In joints, the cytokine network of transforming growth factor-β (TGF-β) is a critical signaling pathway associated with the cellular processes in cartilage (Baugé et al. 2014; also see Table 9.1). They may be involved in the support of chondrocyte

differentiation and cartilage repair. On the other hand, TGF-β has been found to have deleterious effects related to hypertrophy. These mechanisms highlight the importance of the TGF-β signaling pathways in joints and the aging-associated disorders such as osteoarthritis (Baugé et al. 2014).

The muscle dysfunctions are commonly seen in aging and aging-associated diseases. The JAK-STAT signaling pathways are critical in myogenic differentiation (Chazaud and Mouchiroud 2014; also see Table 9.1). The dysfunctions in these pathways may result in a shrinking reservoir of muscle stem cells. Evidences have shown that genetic and drug targets for inhibiting the STAT3 signaling pathways may help promote the stem cell homeostasis and the recovery of aged and dystrophic muscles.

9.3.7 Age-Related Macular Degeneration in the Eye

The age-related alterations may affect resident and circulating myeloid cells in association with various inflammatory disorders (Robbie et al. 2016). The effects of age-related macular degeneration in the eye may lead to serious choroidal neovascularization (CNV) with a critical sight-threatening result.

A recent study analyzed the molecular pathways and myeloid cell populations associated with the higher neovascular response by assessing the immune conditions of murine choroid and retina in the aging process (Robbie et al. 2016). The study showed that the aging process was related to higher proinflammatory levels of CCL2–CCR2 signaling pathway in the choroid but not in the retina (see Table 9.1). Another evidence was that the genetic excision of CCL2 reduced the age-related inflammatory alterations in the choroid with lower levels of proinflammatory myeloid cells and CNV.

These evidences suggest that the CCL2-caused gathering of myeloid cells may result in higher severity of CNV in the aging process (Robbie et al. 2016). Further studies would be helpful to find out if the associated pathways and mechanisms are common in other age-related inflammatory disorders.

9.3.8 Chronic Obstructive Pulmonary Disease (COPD)

In the lungs, the smoking behavior and aging activities may influence the transcription factor forkhead box O3 (FOXO3) signaling pathways (Yuan et al. 2015). A recent study using mice models showed that the signal transduction pathways associated with FOXO3a including the PI3K/Akt pathway may be related to the accelerated aging of the lung tissues in chronic obstructive pulmonary disease (COPD).

The behavior of smoking may cause the lower levels of FOXO3, sirtuin 1, manganese superoxide dismutase, and phosphatidylinositol 3-kinase (PI3K)/Akt (Yuan et al. 2015; also see Table 9.1). Such alterations may accelerate the aging process in the lung tissues in COPD.

9.3.9 *The Mitochondrial Signaling Pathways and Systemic Inflammation*

At the cellular level, mitochondria are essential in various cellular functions and metabolic processes including the homeostasis of energy and calcium, apoptosis, as well as the electron transport chain (Hill and Van Remmen 2014). Mitochondria are also critical in the redox signaling involving the reactive oxygen species (ROS). The complex mitochondrial–nuclear interactions and the extracellular release of mitochondrial elements as signaling molecules are essential in supporting the cellular and tissue functions.

In stress responses, the mitochondrial–nuclear interactions are the key for the transcriptional activation of nuclear genes associated with metabolism to support fission and fusion events as well as the mitochondrial unfolded protein response (UPR^{mt}). The mitochondrial signaling pathways in various tissues may promote the cytoprotective functions to improve healthy aging (Hill and Van Remmen 2014). On the other hand, mitochondria signaling pathways may also be involved in innate immunity and systemic inflammatory reactions with the higher levels of inflammation in the aging process (see Table 9.1). More studies are still needed to understand the complex roles of mitochondrial stress response pathways in aging, stress responses, and longevity.

References

Ali, T., Badshah, H., Kim, T. H., & Kim, M. O. (2015). Melatonin attenuates D-galactose-induced memory impairment, neuroinflammation and neurodegeneration via RAGE/NF-K B/JNK signaling pathway in aging mouse model. *Journal of Pineal Research, 58*, 71–85.

Baugé, C., Girard, N., Lhuissier, E., Bazille, C., & Boumediene, K. (2014). Regulation and role of TGFβ signaling pathway in aging and osteoarthritis joints. *Aging and Disease, 5*, 394–405.

Capuron, L., Schroecksnadel, S., Féart, C., Aubert, A., Higueret, D., Barberger-Gateau, P., et al. (2011). Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: Role in neuropsychiatric symptoms. *Biological Psychiatry, 70*, 175–182.

Chazaud, B., & Mouchiroud, G. (2014). Inflamm-aging: STAT3 signaling pushes muscle stem cells off balance. *Cell Stem Cell, 15*, 401–402.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Godbout, J. P., & Johnson, R. W. (2006). Age and neuroinflammation: A lifetime of psychoneuroimmune consequences. *Neurologic Clinics, 24*, 521–538.

Godbout, J. P., & Johnson, R. W. (2009). Age and neuroinflammation: A lifetime of psychoneuroimmune consequences. *Immunology and Allergy Clinics of North America, 29*, 321–337.

Gouin, J.-P., Hantsoo, L., & Kiecolt-Glaser, J. K. (2008). Immune dysregulation and chronic stress among older adults: A review. *Neuroimmunomodulation, 15*, 251–259.

Graham, J. E., Christian, L. M., & Kiecolt-Glaser, J. K. (2006). Stress, age, and immune function: Toward a lifespan approach. *Journal of Behavioral Medicine, 29*, 389–400.

Guidi, L., Tricerri, A., Frasca, D., Vangeli, M., Errani, A. R., & Bartoloni, C. (1998). Psychoneuroimmunology and aging. *Gerontology, 44*, 247–261.

Hill, S., & Van Remmen, H. (2014). Mitochondrial stress signaling in longevity: A new role for mitochondrial function in aging. *Redox Biology, 2*, 936–944.

Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Emotions, morbidity, and mortality: New perspectives from psychoneuroimmunology. *Annual Review of Psychology, 53*, 83–107.

Layé, S. (2010). Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins, Leukotrienes, and Essential Fatty Acids, 82*, 295–303.

Liezmann, C., Stock, D., & Peters, E. M. J. (2012). Stress induced neuroendocrine-immune plasticity: A role for the spleen in peripheral inflammatory disease and inflammaging? *Dermatoendocrinology, 4*, 271–279.

Omoigui, S. (2007). The Interleukin-6 inflammation pathway from cholesterol to aging—Role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases. *Immunity & Ageing, 4*, 1.

Perl, A. (2015). mTOR activation is a biomarker and a central pathway to autoimmune disorders, cancer, obesity, and aging. *Annals of the New York Academy of Sciences, 1346*, 33–44.

Perluigi, M., Di Domenico, F., & Butterfield, D. A. (2015). mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy. *Neurobiology of Disease, 84*, 39–49.

Primiani, C. T., Ryan, V. H., Rao, J. S., Cam, M. C., Ahn, K., Modi, H. R., et al. (2014). Coordinated gene expression of neuroinflammatory and cell signaling markers in dorsolateral prefrontal cortex during human brain development and aging. *PLoS One, 9*, e110972.

Robbie, S. J., Georgiadis, A., Barker, S. E., Duran, Y., Smith, A. J., Ali, R. R., et al. (2016). Enhanced Ccl2-Ccr2 signaling drives more severe choroidal neovascularization with aging. *Neurobiology of Aging, 40*, 110–119.

Silva-Palacios, A., Königsberg, M., & Zazueta, C. (2016). Nrf2 signaling and redox homeostasis in the aging heart: A potential target to prevent cardiovascular diseases? *Ageing Research Reviews, 26*, 81–95.

Sturmberg, J. P., Bennett, J. M., Picard, M., & Seely, A. J. E. (2015). The trajectory of life. Decreasing physiological network complexity through changing fractal patterns. *Frontiers in Physiology, 6*, 169.

Vitetta, L., Anton, B., Cortizo, F., & Sali, A. (2005). Mind-body medicine: Stress and its impact on overall health and longevity. *Annals of the New York Academy of Sciences, 1057*, 492–505.

Wu, Z., Yu, Y., Liu, C., Xiong, Y., Montani, J.-P., Yang, Z., et al. (2015). Role of p38 mitogen-activated protein kinase in vascular endothelial aging: Interaction with Arginase-II and S6K1 signaling pathway. *Aging (Albany NY), 7*, 70–81.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Yu, B., Chang, J., Liu, Y., Li, J., Kevork, K., Al-Hezaimi, K., et al. (2014). Wnt4 signaling prevents skeletal aging and inflammation by inhibiting nuclear factor-kB. *Nature Medicine, 20*, 1009–1017.

Yuan, Y. M., Luo, L., Guo, Z., Yang, M., Lin, Y. F., & Luo, C. (2015). Smoking, aging, and expression of proteins related to the FOXO3 signaling pathway in lung tissues. *Genetics and Molecular Research, 14*, 8547–8554.

Zannas, A. S., Arloth, J., Carrillo-Roa, T., Iurato, S., Röh, S., Ressler, K. J., et al. (2015). Lifetime stress accelerates epigenetic aging in an urban, African American cohort: Relevance of glucocorticoid signaling. *Genome Biology, 16*, 266.

Zeng, Y., Wang, P.-H., Zhang, M., & Du, J.-R. (2016). Aging-related renal injury and inflammation are associated with downregulation of Klotho and induction of RIG-I/NF-kB signaling pathway in senescence-accelerated mice. *Aging Clinical and Experimental Research, 28*, 69–76.

Chapter 10
Psychoneuroimmunology of Cardiovascular Diseases

10.1 Psychological Stress, Depression, and Cardiovascular Diseases

Cardiovascular disease is one of the leading causes of morbidity and mortality. Chronic inflammation has an essential role in the development of cardiovascular disease. Psychoneuroimmunology (PNI) studies about the impacts of psychological stressors on the immune functions and coronary artery disease (CAD) have revealed that such stressors may alter the endothelial functions and result in chemotaxis (Ho et al. 2010).

The bidirectional communications between the brain and peripheral tissues such as the cardiovascular and immune systems have been found pivotal to both psychological and physical health (Taylor et al. 2010). To achieve more accurate diagnosis and more effective treatment, the functional mind–body connections need to be addressed.

The dynamical biopsychosocial models are needed to understand the mind–body interactions in cardiovascular diseases at various system levels (see Chap. 1). PNI studies based on systems biology would improve the understanding of the relevant biobehavioral mechanisms to support the development of systems and dynamical medicine (Yan 2014).

Specifically, acute psychological stressors may cause leukocytosis and elevated natural killer cell cytotoxicity, with the decreased proliferative responses to mitogens. Chronic psychological stressors may cause cardiovascular dysfunctions and the onset of CAD (Ho et al. 2010). Both acute and chronic psychological stressors may elevate the hemostatic factors and acute phase proteins with the potential results of thrombus formation and myocardial infarction.

These mechanisms refer to the importance of the psychological stress conditions as well as the early detection of immunological alterations associated with cardiovascular risks. The PNI principles can be applied to understand the underlying mechanisms such as the neurohormonal and cytokine activations in the comorbid disorders of cardiovascular diseases and psychiatric problems.

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_10

For example, in the case of heart failure (HF), those patients with depression often have worse clinical outcomes when compared with the nondepressed controls (Jiménez and Mills 2012). In a study of 5525 elderly men and women, a significant connection was identified between depressive symptoms and the risk of ischemic stroke (Arbelaez et al. 2007).

In addition, life experience may have profound influences on both mental and physical health. For example, childhood abuse may enhance the risks in multiple physiological systems for morbidity and mortality during adulthood. A study using comprehensive biomarkers found that the low levels of love and affection and the high levels of abuse in childhood had the highest multisystem risks (Carroll et al. 2013).

According to the Coronary Artery Risk Development in Young Adults (CARDIA) study, early life stress assessed at Year 15 was related to adulthood fatigue at Year 20 (which was 5 years later) (Cho et al. 2012). A proposed explanation was that early biological programming of the neural circuitry may affect the stress response patterns on later life and lead to wear and tear across multiple physiological systems (Carroll et al. 2013). The comprehensive understanding of these complex mechanisms would contribute to the development of personalized, systems, and dynamical medicine (see Chap. 1).

10.2 The Complex PNI Interactions and Inflammatory Biomarkers

The affective, autonomic, hormonal, and immune responses are influenced by the bidirectional PNI pathways and the communications of information between the CNS and the periphery tissues. Certain frontotemporal cortical areas in the brain associated with adverse symptoms have mutual communications with subcortical structures related to homeostasis and stress responses (Taylor et al. 2010). The heart rate variability (HRV) and inflammatory biomarkers are critical in such central–peripheral integration and homeostatic networks.

A recent study of a middle-aged population analyzed the correlations between psychological resources and inflammatory biomarkers in connection with coronary heart disease (CHD). The study found that psychological resources such as self-esteem was related to the inflammatory biomarkers including interleukin (IL)-6, C-reactive protein (CRP), and matrix metalloproteinase (MMP)-9 (Marteinsdottir et al. 2016).

According to the study, the quality of life (or "the ladder of life") was also related to IL-6 and CRP (Marteinsdottir et al. 2016). The psychological resource of coping and the psychological risk factors including vital exhaustion and depressive symptoms were linked to IL-6. In addition, the psychological resource of the sense of coherence (SOC) was connected to MMP-9. The psychological risk factors were

closely related to the lifestyle factors including smoking, physical activity, and body mass index (BMI) (Marteinsdottir et al. 2016).

Among heart failure (HF) patients, inflammation and psychological conditions especially depression have been suggested as possible risk factors for unfavorable outcomes. Studies have shown that in HF patients, depressive symptoms are commonly observed and have significant associations with soluble tumor necrosis factor receptor 2 (sTNR2) and IL-6 (Moughrabi et al. 2014). Because of such correlations between the inflammatory biomarkers and depression in HF patients, psychological screening has been suggested to improve the clinical outcomes.

In addition, evidences have indicated that serum brain-derived neurotrophic factor (BDNF) may be correlated with cardiorespiratory fitness (CRF) with impacts on cardiovascular diseases (Jung et al. 2011). In a study of healthy men, a significant inverse correlation was identified between serum BDNF and relative VO(2)max and heart rate reserve. Serum BDNF was positively linked to body mass index, total cholesterol, and triglyceride.

Furthermore, sleep quality is another pivotal PNI factor (see Chap. 5). Poor sleep may be associated with cardiovascular mortality. Inflammation has been suggested as an essential mechanism connecting poor sleep with cardiovascular diseases. Specifically, signaling cytokine pathways may be involved with critical roles in the development of atherosclerotic plaques (Motivala 2011).

10.3 Inflammatory Pathways: The Links Between Stress and Cardiovascular Diseases

10.3.1 Emotional Problems, Inflammation, and Atherosclerosis

At the system level, the cognitive regulation of emotions may be correlated to CVD risks via a pathway of the functional communication between the anterior cingulate area of the prefrontal cortex and inflammatory processes (Gianaros et al. 2014). Areas of the prefrontal cortex are involved in the visceral control functions associated with the regulation of the immune system. Immune functions are critical in the pathophysiology of atherosclerotic cardiovascular disease (CVD).

Importantly, inflammatory conditions have been found comorbid with affective disorders and emotional problems. Studies have related the prefrontal dysfunctions to atherosclerotic CVD risks, possibly mediated via inflammatory processes. For instance, the dorsal anterior cingulate cortex has been linked to preclinical atherosclerosis and the proinflammatory cytokine IL-6 (Gianaros et al. 2014). In other words, the IL-6-associated pathways may mediate the connections between dorsal anterior cingulate cortex dysfunctions and preclinical atherosclerosis (see Table 10.1).

Table 10.1 Examples of stress and inflammation related pathways in cardiovascular diseases (CVDs)

Pathways and interactions	Associated pathogenesis/diseases	References
The interactions between the anterior cingulate region of the prefrontal cortex and inflammatory networks (e.g., IL-6)	The emotion-related CVD risks	Gianaros et al. 2014
The IL-1 pathways	Type 2 diabetes (T2D), associated cardiovascular complications	Herder et al. 2015
The IL-33/ST2 pathways	Chronic inflammatory cardiovascular diseases	Willems et al. 2012; Miller and Liew 2011
The IL-12/IL-18-dependent IFN-γ pathways	Coronary atherosclerosis	Ranjbaran et al. 2007
The NF-kB pathways, the renin–angiotensin system (RAS)	Cardiovascular diseases	Ruiz-Ortega et al. 2007
The TLR signaling pathways (e.g., LBP, CD14, MD-2, TLR4, MyD88, NF-kB)	Cardiovascular diseases, reperfusion ischemia (myocardial infarction), arteriosclerosis, valvulopathy	Bustamante et al. 2012; Stoll et al. 2006
The kynurenine pathways of tryptophan metabolism	Cardiovascular risk factors (e.g., hypertension, obesity, lipid metabolism, diabetes mellitus, atherosclerotic CVD)	Polyzos and Ketelhuth 2015
The inflammatory and kynurenine associated pathways (e.g., neopterin, CRP, tryptophan, kynurenines)	Cardiovascular disease mortality	Zuo et al. 2016
The 5-lipoxygenase associated pathways	Cardiovascular risks, arterial thrombosis	Camacho et al. 2012
The heme oxygenase (HO) pathways	CVD risks	Fredenburgh et al. 2015
The Notch signaling pathways (e.g., NFkB, MAPK, TLR, TGFβ, NO, hypoxia signaling)	Cardiovascular diseases	Quillard and Charreau 2013

10.3.2 The IL-1 Family

The ongoing research in systems biology and PNI would help with the discovery of systems-based biomarkers for the diagnosis and treatment of cardiovascular diseases and associated problems. Table 10.1 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

For example, among the patients with type 2 diabetes (T2D), the chronic activation of the innate immune system has been found as a feature in pancreatic islets, insulin-sensitive tissues, and at locations of diabetic complications. The proinflammatory cytokine interleukin-1 (IL-1) may connect obesity and dyslipidemia.

Epidemiological, molecular, and animal studies have associated IL-1β in T2D with metabolic stress and tissue inflammation, which may provide the correlations with cardiovascular complications (Herder et al. 2015). The IL-1β-associated pathways have been suggested as the potential targets for improving insulin production, as well as preventing cardiovascular and relevant complications (see Table 10.1).

In addition, Interleukin (IL)-33 belongs to the IL-1 family and promotes the Th2 type immune reactions by signaling via the ST2L and IL-1RAcP dimeric receptor complex (Miller and Liew 2011, also see Table 10.1). With alternative splicing, ST2 may exist in the transmembrane (ST2L) or as a soluble form sST2.

The effects of IL-33 may be suppressed by the soluble decoy form of ST2 (sST2), a potential predictive cardiovascular biomarker for adverse cardiovascular events including heart failure and myocardial infarction. The higher serum levels of sST2 have been reported among cardiovascular disease patients (Willems et al. 2012). ST2 has been suggested to have a causal role in chronic cardiovascular conditions including atherosclerosis and heart failure.

In atherosclerosis and obesity, IL-33 and ST2L have been found protective (Miller and Liew 2011). IL-33 and the receptor ST2L-associated pathways may have the potential roles in the treatment of cardiovascular diseases. Studies using mouse models have indicated that the signaling pathways of IL-33 may be cardioprotective for myocardial infarction, heart transplantation, as well as cardiac hypertrophy and fibrosis (Willems et al. 2012). Treatment with IL-33 has been shown to inhibit the development of plaques in atherosclerotic mice. These evidences support the important role of the IL-33/ST2 pathways in various chronic inflammatory cardiovascular disorders (see Table 10.1).

10.3.3 The Networks of Multiple Cytokines

The multiple networks involved in innate immune responses may be associated with the generation of proarteriosclerotic Th1-type cytokines in coronary atherosclerosis. For example, circulating IL-12 has been suggested as the connection between inflammation and Th1-type cytokine generations in coronary atherosclerosis (Ranjbaran et al. 2007).

The higher plasma levels of IL-12 and IL-18 have been related to an IFN-γ axis including IFN-γ and IFN-γ-inducible chemokines (Ranjbaran et al. 2007). Systemic inflammation driven by cardiopulmonary bypass may also lead to higher plasma levels of the IFN-γ axis (see Table 10.1). In the arterial wall, T cells may be the major resource of IFN-γ upon the IL-12/IL-18 stimulations. The IL-12/IL-18-dependent IFN-γ productions could be blocked by a p38 MAPK inhibitor (Ranjbaran et al. 2007). Such complex cytokine networks and mechanisms may be useful for biomarker and target selections (see Table 10.1).

Furthermore, the renin–angiotensin system (RAS) has also been correlated with the pathogenesis of cardiovascular diseases. Specifically, angiotensin IV (AngIV) is an N-terminal angiotensin degradation product with functions in cognition and

renal metabolism (Ruiz-Ortega et al. 2007). AngIV has been related to the vascular inflammatory responses and cardiovascular damages. It is involved in the regulations of cell growth in cardiac fibroblasts, endothelial cells, and vascular smooth muscle cells (VSMCs).

In endothelial cells and VSMCs, AngIV may lead to the higher levels of plasminogen activator inhibitor-1 expression and thrombus formation (Ruiz-Ortega et al. 2007). In VSMC, AngIV may trigger the nuclear factor-kB (NF-kB) pathway and increase the associated genes such as the cytokines IL-6 and tumor necrosis factor α (TNF-α). These complex interactions and pathways may have the essential roles in cardiovascular diseases (see Table 10.1).

10.3.4 The Signaling Pathway of Toll-Like Receptors (TLR)

The advancements in systems biology are improving the understanding of the physiopathology and evolution of different immunological activities, especially those correlated with the cardiovascular functions. For instance, the signaling pathway of toll-like receptors (TLR) is strongly associated with the regulations of the inflammatory responses to tissue damages in various cardiovascular diseases (Bustamante et al. 2012). The relevant changes may affect the tissue homeostasis in a broad range of conditions including reperfusion ischemia (myocardial infarction), arteriosclerosis, as well as cardiac valvulopathy.

The TLR signaling pathways have been proposed as the promising targets to decrease inflammation in atherosclerosis (Stoll et al. 2006). The innate immunity and endotoxin/TLR4 signaling may provide the key connections between cardiovascular diseases and inflammation. The associated cellular signaling pathways contain various molecules including lipopolysaccharide-binding protein (LBP), CD14, MD-2, TLR4, MyD88, as well as NF-kB (see Table 10.1).

The regulations of these cellular signaling pathways have been suggested as the potential preventive and therapeutic strategies for cardiovascular diseases. Specific vaccine development and drugs with anti-inflammatory functions such as statins may be helpful (Stoll et al. 2006). Because of the disease complexity, integrated methods that combine different strategies targeting the inflammatory activities may be more effective.

10.3.5 The Kynurenine Pathway and Metabolic Networks

Coronary heart disease and stroke are the most serious types of cardiovascular diseases (CVD). They are primarily caused by atherosclerosis and the chronic inflammation of the artery wall triggered by maladaptive immune reactions (Polyzos and Ketelhuth 2015). Inflammatory pathways are the essential components in the pathogenesis of coronary atherosclerosis. The systemic pathogenic activities can be

complicated by many risk factors and other illnesses such as dyslipidemia, obesity, and diabetes.

Various plasma inflammatory biomarkers and the kynurenine pathway have been related to the risks of CVD mortality and cancer (Zuo et al. 2016). These markers include neopterin, the kynurenine:tryptophan ratio, and C-reactive protein (CRP). Many molecules involved in the cytokine networks have been implicated in the pathogenesis of cardiovascular diseases (see Table 10.1).

Indoleamine 2,3-dioxygenase (IDO) is an enzyme in the kynurenine pathway of tryptophan degradation. It can be stimulated by inflammation in various tissues such as the artery wall. IDO may support homeostasis, enhance immune tolerance, suppress excessive immune responses, and inhibit inflammation (Polyzos and Ketelhuth 2015). Such mechanism emphasizes IDO-associated tryptophan metabolism and the kynurenine pathways in the regulations of the complex cardiovascular risk factors including obesity, diabetes, hypertension, and atherosclerosis (see Table 10.1).

In addition, leukotrienes (LT) have been associated with different pathological conditions including inflammation, cardiovascular diseases, and cancer. Many genes have been related to the variability of LT-related phenotypes. For example, the components of the 5-Lipoxygenase pathway have been correlated with arterial thrombosis (see Table 10.1). These components include 5-Lipoxygenase, five lipoxygenase activating protein (FLAP), LTA(4)-hydrolase, and LTB(4) (Camacho et al. 2012).

Furthermore, the heme oxygenase (HO) pathway may also be involved in the risks for CVD events as the potential prognostic markers (Fredenburgh et al. 2015). With the vasoregulatory features, the HO pathway may serve as an endogenous regulator of oxidative, inflammatory, and cytotoxic stress (see Table 10.1). Its activities can be affected by various factors including genetic traits, environmental stimuli, as well as drug treatments. These mechanisms suggest that the HO pathway may be utilized as a potential target for decreasing the overall problems of CVD (Fredenburgh et al. 2015).

10.3.6 The Complex Notch Signaling Pathway

Another important pathway is the Notch signaling pathway. Notch is involved in vascular homeostasis via the regulation of the essential cell functions including differentiation, proliferation, apoptosis/survival, and activation (Quillard and Charreau 2013). Such functions emphasize the key role of Notch in inflammatory processes in endothelial cells, smooth muscle cells, or vascular infiltrating cells associated with cardiovascular diseases.

The crosstalk among Notch and inflammatory signaling pathways is complex including multifaceted communications among Notch, NFkB, mitogen-activated protein kinase (MAPK), and TLR (Quillard and Charreau 2013). In addition, transforming growth factor (TGFβ), NO, and hypoxia signaling pathways are also involved (see Table 10.1). The complex Notch signaling pathways are pivotal in the

dynamic interactions and cellular adaptations among immune, vascular, and cardiac cells.

PNI studies of such mechanisms are especially meaningful for the modulation of the inflammatory responses in the damaged cardiovascular tissues. The understanding of the relevant pathways is crucial for identifying effective biomarkers and therapeutic strategies for the pathological context of CVD.

References

Arbelaez, J. J., Ariyo, A. A., Crum, R. M., Fried, L. P., & Ford, D. E. (2007). Depressive symptoms, inflammation, and ischemic stroke in older adults: A prospective analysis in the cardiovascular health study. *Journal of American Geriatrics Society, 55*, 1825–1830.

Bustamante, J., Tamayo, E., & Herreros, J. (2012). Genomics in cardiovascular diseases: Analysis of the importance of the toll-like receptor signaling pathway. *International Journal of General Medicine, 5*, 849–859.

Camacho, M., Martinez-Perez, A., Buil, A., Siguero, L., Alcolea, S., López, S., et al. (2012). Genetic determinants of 5-lipoxygenase pathway in a Spanish population and their relationship with cardiovascular risk. *Atherosclerosis, 224*, 129–135.

Carroll, J. E., Gruenewald, T. L., Taylor, S. E., Janicki-Deverts, D., Matthews, K. A., & Seeman, T. E. (2013). Childhood abuse, parental warmth, and adult multisystem biological risk in the Coronary Artery Risk Development in Young Adults study. *Proceedings of the National academy of Sciences of the United States of America, 110*, 17149–17153.

Cho, H. J., Bower, J. E., Kiefe, C. I., Seeman, T. E., & Irwin, M. R. (2012). Early life stress and inflammatory mechanisms of fatigue in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Brain, Behavior, and Immunity, 26*, 859–865.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Fredenburgh, L. E., Merz, A. A., & Cheng, S. (2015). Haeme oxygenase signalling pathway: Implications for cardiovascular disease. *European Heart Journal, 36*, 1512–1518.

Gianaros, P. J., Marsland, A. L., Kuan, D. C.-H., Schirda, B. L., Jennings, J. R., Sheu, L. K., et al. (2014). An inflammatory pathway links atherosclerotic cardiovascular disease risk to neural activity evoked by the cognitive regulation of emotion. *Biological Psychiatry, 75*, 738–745.

Herder, C., Dalmas, E., Böni-Schnetzler, M., & Donath, M. Y. (2015). The IL-1 pathway in type 2 diabetes and cardiovascular complications. *Trends in Endocrinology and Metabolism, 26*, 551–563.

Ho, R. C. M., Neo, L. F., Chua, A. N. C., Cheak, A. A. C., & Mak, A. (2010). Research on psychoneuroimmunology: Does stress influence immunity and cause coronary artery disease? *Annals of the Academy of Medicine, Singapore, 39*, 191–196.

Jiménez, J. A., & Mills, P. J. (2012). Neuroimmune mechanisms of depression in heart failure. *Methods in Molecular Biology, 934*, 165–182.

Jung, S. H., Kim, J., Davis, J. M., Blair, S. N., & Cho, H. (2011). Association among basal serum BDNF, cardiorespiratory fitness and cardiovascular disease risk factors in untrained healthy Korean men. *European Journal of Applied Physiology, 111*, 303–311.

Marteinsdottir, I., Ernerudh, J., Jonasson, L., Kristenson, M., & Garvin, P. (2016). Psychological resources are independently associated with markers of inflammation in a middle-aged community sample. *International Journal of Behavioral Medicine*, doi:10.1007/s12529-016-9553-z.

Miller, A. M., & Liew, F. Y. (2011). The IL-33/ST2 pathway—A new therapeutic target in cardiovascular disease. *Pharmacology and Therapeutics, 131*, 179–186.

Motivala, S. J. (2011). Sleep and inflammation: Psychoneuroimmunology in the context of cardiovascular disease. *Annals of Behavioral Medicine, 42*, 141–152.

Moughrabi, S., Evangelista, L. S., Habib, S. I., Kassabian, L., Breen, E. C., Nyamathi, A., et al. (2014). In patients with stable heart failure, soluble TNF-receptor 2 is associated with increased risk for depressive symptoms. *Biological Research for Nursing, 16*, 295–302.

Polyzos, K. A., & Ketelhuth, D. F. J. (2015). The role of the kynurenine pathway of tryptophan metabolism in cardiovascular disease. An emerging field. *Hamostaseologie, 35*, 128–136.

Quillard, T., & Charreau, B. (2013). Impact of notch signaling on inflammatory responses in cardiovascular disorders. *International Journal of Molecular Sciences, 14*, 6863–6888.

Ranjbaran, H., Sokol, S. I., Gallo, A., Eid, R. E., Iakimov, A. O., D'Alessio, A., et al. (2007). An inflammatory pathway of IFN-gamma production in coronary atherosclerosis. *Journal of Immunology, 178*, 592–604.

Ruiz-Ortega, M., Esteban, V., & Egido, J. (2007). The regulation of the inflammatory response through nuclear factor-kappab pathway by angiotensin IV extends the role of the renin angiotensin system in cardiovascular diseases. *Trends in Cardiovascular Medicine, 17*, 19–25.

Stoll, L. L., Denning, G. M., & Weintraub, N. L. (2006). Endotoxin, TLR4 signaling and vascular inflammation: Potential therapeutic targets in cardiovascular disease. *Current Pharmaceutical Design, 12*, 4229–4245.

Taylor, A. G., Goehler, L. E., Galper, D. I., Innes, K. E., & Bourguignon, C. (2010). Top-down and bottom-up mechanisms in mind-body medicine: Development of an integrative framework for psychophysiological research. *Explore (NY), 6*, 29–41.

Willems, S., Hoefer, I., & Pasterkamp, G. (2012). The role of the Interleukin 1 receptor-like 1 (ST2) and Interleukin-33 pathway in cardiovascular disease and cardiovascular risk assessment. *Minerva Medica, 103*, 513–524.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Zuo, H., Ueland, P. M., Ulvik, A., Eussen, S. J. P. M., Vollset, S. E., Nygård, O., et al. (2016). Plasma biomarkers of inflammation, the kynurenine pathway, and risks of all-cause, cancer, and cardiovascular disease mortality: The Hordaland Health Study. *American Journal of Epidemiology, 183*, 249–258.

Chapter 11
Psychoneuroimmunology and Cancer

11.1 The Systems-Based PNI Frameworks

More and more evidences are showing that psychosocial factors may affect cancer development and progression. Systems-based psychoneuroimmunology (PNI) frameworks and the dynamical psychosocial models may help understand the changing demographics in cancer treatment and outcomes (Green McDonald et al. 2013; also see Chap. 1).

Although psychosocial care for cancer patients has been ignored historically, such quality clinical care has been recommended across various stages of treatment recently (Artherholt and Fann 2012). For instance, in a meta-analysis of 24 cancer-specific studies of psychosocial interventions that applied PNI-based outcome measures, cognitive-behavioral therapies were shown to have the most significant success using functional measures such as cytokines (Subnis et al. 2014).

Distress has been suggested as the sixth vital sign in the examination of cancer patients. Evidences from the studies in psycho-oncology have associated psychosocial factors with cancer, including distress, cognitive deficits, psychiatric morbidity, as well as coping methods applied by cancer survivors (Chaturvedi and Venkateswaran 2008). A recent study using rat models showed that isolation stress may have impacts on the development of tumors, even though stress itself is not a sufficient risk factor in cancer occurrence (De la Roca-Chiapas et al. 2016).

As an important psychological factor, stress is often experienced in cancer patients and harms the protective functions of the immune system. Various diverse interactions have been identified between malignant tissues and immunocytes. Animal studies have demonstrated that neuroendocrine and immunological mediators of stress have impacts on the sympathetic nervous system, NK cell activities, and cancer progression (Ben-Eliyahu et al. 2007).

As an example, breast cancer patients often blame "stress" as an important factor in the disease development. PNI studies have revealed the effects of stress on molecular and cellular pathways involved in carcinogenesis, especially the roles of immune cells in the development and progression of epithelial cancer (Pant and

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_11

Ramaswamy 2009). In addition, psychosocial factors including stress, pessimism, and sleep quality may be critical factors in the development of HPV-mediated cervical neoplasia among HIV-positive patients (Jensen et al. 2007).

In a recent study of 379 patients with breast cancer undergoing treatment, social support and positive worldviews were observed to have the most significant influences on survivorship experiences (Hulett et al. 2015). The study suggests that because breast cancer is an immune-associated disease, the care for long-term survivors needs to embrace psychosocial factors such as distress with influences on immune functions.

In the regulation of cancer progression, key roles have been identified for catecholamine hormones including norepinephrine and epinephrine, as well as their receptors including the β-adrenergic receptors (β-ARs) (Yang and Eubank 2013). These catecholamines may mediate the impacts of psychological stress on different stages of tumor progression such as proliferation, angiogenesis, and metastasis. Because of the important roles of β-ARs, the potential applications of β-blockers have been suggested for adjuvant cancer therapy (Yang and Eubank 2013). Such mechanisms emphasize the translational importance of biobehavioral impacts on tumor biology and cancer therapeutic outcomes.

Recent development in personalized medicine is improving the survival rate among breast cancer patients. However, many of the survivors still suffer from co-occurring psychoneurological symptoms with adverse influences on their quality of life. These co-occurring symptoms are also called "symptoms clusters" with the underlying epigenetic and genomic mechanisms associated with the interindividual variability during and after treatments (Starkweather et al. 2013).

Systems biology-based PNI studies including the elucidation of the stress response networks and inflammatory pathways may connect the genotypes with the phenotypic "symptoms clusters" to support the practice of personalized medicine. Because inflammation is a key factor in cancer development, the better understanding of the inflammatory networks is becoming more and more important. For more effective prevention and treatment, approaches including psychosocial instruments, systemic biomarkers, and PNI-based measures would be helpful toward the development of systems and dynamical medicine (Yan 2014; also see Chap. 1).

11.2 Inflammatory Pathways in Different Types of Cancer

11.2.1 Pancreatic Cancer and the NFATc2-STAT3-GSK-3β Pathway

Epidemiological evidences have demonstrated that chronic inflammation is one of the key risk factors for different types of cancer (Fan et al. 2013). Table 11.1 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

Table 11.1 Examples of stress- and inflammation-related pathways in cancers

Pathways and interactions	Associated pathogenesis/diseases	References
Inflammation-induced NFATc2 and STAT3 transcriptional networks, GSK-3β	Pancreatic cancer progression and growth	Baumgart et al. 2016
The β-Catenin signaling pathways	Inflammation, fibrosis, hepatocellular carcinoma (HCC)	Lee et al. 2014
The TGF-β signaling pathways	Inflammation, DNA damage in the forestomach, invasive squamous cell carcinoma (SCC)	Achyut et al. 2013
The PPARδ and PGE2 signaling pathways	Colorectal cancer (CRC)	Wang and DuBois 2014
The toll-like receptors (TLRs) signaling pathways	Colorectal inflammation and cancer	Fűri et al. 2013
The JNK1 stress signaling pathways	High breast density and the tumor stroma	Lisanti et al. 2014
The NF-kB signaling pathways	Chronic inflammation and cancer	Verstrepen and Beyaert 2014
The NF-kB signaling pathways (e.g., STAT3, p53, GSK3-β, p38, PI3K, TLRs)	Inflammation and cancer	Hoesel and Schmid 2013
The NF-kB and STAT3 signaling pathways	Tumor angiogenesis and invasiveness	Fan et al. 2013
The TNF signaling pathways, interactions with mutant p53, DAB2IP	Inflammation in cancer	Di Minin et al. 2014
The IL-1 associated signaling pathways (e.g., apoptosis, TLR, MAPK, NLR, and NF-kB)	Cancer, chronic inflammation	Acuner Ozbabacan et al. 2014
The IL-1 receptor-associated kinase signaling pathways	Tumor growth, metastasis, immune suppression, chemotherapy resistance	Jain et al. 2014
The IL-1β-mediated inflammatory pathways	Central nervous system (CNS) inflammation, cancer treatment-related symptoms (CTRSs)	Wood and Weymann 2013
The inflammatory signaling pathways (e.g., MMIF)	Microbial-triggered carcinogenesis	Kipanyula et al. 2013
The epithelial IL-6 signaling pathways (microbiota induced)	Inflammation-induced colorectal cancer (CRC) formation	Hu et al. 2013
The VEGF-associated pathways	Hematopoietic stem cell transplant (HSCT)	Knight et al. 2013
The HPA and SNS axes	HSCT	Costanzo et al. 2013
The HPA axis	Inflammation and cancer	Starkweather et al. 2013
The macrophage migration inhibitory factor-mediated signaling pathways	Prostate cancer cells proliferation and survival	Tawadros et al. 2013
The AMPK and autophagy signaling pathways	Prostate cancer (PCa) with neuroendocrine differentiation (NED)	Lin et al. 2016
The Erk/MAP kinase signaling pathway	NED of small-cell lung cancers (SCLC)	Chen et al. 2014

For instance, in pancreatic cancer, glycogen synthase kinase 3β (GSK-3β) is involved in the networks associated with proinflammatory oncogenic transcription factor nuclear factor of activated T cells (NFATc2) and STAT3 complexes (Baumgart et al. 2016; also see Table 11.1). Such interactions integrate the upstream signaling activities that control pancreatic cancer progression and growth. With the GSK-3β-associated phosphorylation of STAT3 and the formation of the NFATc2-STAT3 complex, the NFAT target promoters including cyclin-dependent kinase-6 may be stimulated to enhance tumor growth (Baumgart et al. 2016).

Experiments using mice models indicated that targeting the NFATc2-STAT3-GSK-3β module could suppress the proliferation and tumor growth, as well as block the inflammation-caused pancreatic cancer progression (Baumgart et al. 2016). The relevant networks have been suggested as the potential therapeutic targets for pancreatic cancer.

11.2.2 Hepatocellular Carcinoma (HCC) and the β-Catenin Signaling Pathway

The β-Catenin signaling pathway has been correlated with hepatocellular carcinoma (HCC) with a complex role in inflammation and fibrosis. A recent study using mice and human models addressed the importance of the abnormal intratumoral β-catenin stabilization (Lee et al. 2014; also see Table 11.1). Those who had predominant cytoplasmic with occasional nuclear (C/N) localization were associated with higher levels of intratumoral inflammation and proliferation.

11.2.3 Squamous Cell Carcinoma (SCC) and the Pathways of Tgfbr2, p21

Because stroma is pivotal in epithelial homoeostasis, the lack of tumor suppressor genes in stromal fibroblasts has been correlated with epithelial cancer development. In the neighboring epithelia of the forestomach, the lower levels of TGFβ receptor 2 (Tgfbr2) in the stromal fibroblasts (Tgfbr2(fspKO)) may cause inflammation and DNA damages (Achyut et al. 2013; also see Table 11.1). Such changes may lead to the lower levels of cyclin-dependent kinase inhibitors p15, p16, and p21, resulting in the development of invasive squamous cell carcinoma (SCC).

Because inflammation is essential in the epigenetic silencing of p21 in the tumor progression processes, anti-inflammation therapies have been found to restore p21 expression and block tumorigenesis (Achyut et al. 2013). These findings refer to the option of anti-inflammation for the therapy of human SCCs with the lower levels of TβRII in the stroma.

11.2.4 Colorectal Cancer and the Signaling Pathways of TLRs and PPARδ

The nuclear hormone receptor peroxisome proliferator-activated receptor δ (PPARδ) has been found essential for the chronic colonic inflammation and colitis-related carcinogenesis (Wang and DuBois 2014). It has also been correlated with fatty acid metabolism, obesity, and wound healing.

The COX-2-derived PGE_2 signaling pathway is a PPARδ downstream pathway that facilitates the communications between tumor epithelial cells and macrophages (Wang and DuBois 2014; also see Table 11.1). Such activities may enhance chronic inflammation and colitis-related tumor genesis. With its critical roles in inflammatory bowel disease (IBD) and colorectal cancer (CRC), the PPARδ-associated network may be the potential targets for the discovery of novel therapeutics of IBD and CRC.

In addition, the signaling pathway of toll-like receptors (TLRs) has been associated with the pathogenesis and treatment of inflammatory bowel diseases and colorectal cancer (Fűri et al. 2013; also see Table 11.1). TLR9 is one of the TLRs and its signaling is involved in colorectal carcinogenesis and colonic inflammation. It may facilitate cytokine productions in the colonic mucosa.

TLR9 can be stimulated by bacterial or viral DNA fragments, immunoglobulin–DNA complexes, or synthetic oligonucleotides (Fűri et al. 2013). These stimulants have unmethylated cytosine–guanine nucleotide sequences (CpGs). The stimulation of TLR9 through CpGs has been proposed as a possible therapeutic target for cancerous and inflammatory disorders.

11.2.5 Breast Cancer and Various Signaling Pathways

The gene set enrichment analysis (GSEA) of genome-wide transcriptional profiling data from low-density (LD) and high-density (HD) mammary fibroblasts has shown that HD fibroblasts have higher activities of the essential cellular processes (Lisanti et al. 2014). These processes include stress responses and inflammation. The transcriptional profiles of HD fibroblasts have indicated the functional similarities with those cancer-associated fibroblasts (CAFs) in the head and neck, liver, thyroid, lung, and breast cancers.

The GSEA also suggests that different signaling pathways can be relevant in the processes, such as those of the JNK1, iNOS, Rho GTPase(s), FGF-R, EGF-R, and PDGF-R-associated signal transductions (Lisanti et al. 2014; also see Table 11.1). These connections may generate a microenvironment that is proinflammatory, proproliferative, and cytokine rich. Other relevant gene profiles include those from smooth muscle cells under stress (JNK1) and activated/infected macrophages (iNOS). The JNK1 stress signaling has been related to tumor recurrence, the transition to malignancy, and the pathogenesis of breast cancer.

The shared features have been recognized among the genetic profiles of the HD fibroblast, wound healing, and the cancer-associated fibroblast phenotypes (Lisanti et al. 2014). Such mechanisms may indicate a framework of personalized medicine for different diseases sharing the common pathways such as those in the inflammatory microenvironment (also see Chap. 1).

11.3 The NF-kB- and p53-Associated Pathways

The family of the transcription factor NF-kB is essential in various cellular activities such as innate and adaptive immune signaling, inflammation, proliferation, and survival (see Chap. 4). The alterations in the NF-kB-associated pathways have been related to autoimmunity, chronic inflammation, and various stages of cancer initiation and progression (Verstrepen and Beyaert 2014; Hoesel and Schmid 2013).

The activation of NF-kB needs IkB kinase (IKK)α or β and can be affected by phosphorylation via certain IKK kinases and autophosphorylation. Various classes of molecules may be involved in the NF-kB-associated interactions, including reactive oxygen species (ROS) and miRNAs. Components associated with the canonical NF-kB signaling pathway also include lipopolysaccharides (LPS) and toll-like receptors (TLRs) (Hoesel and Schmid 2013).

Complex crosstalk has been identified between NF-kB and various transcription factors including the signal transducer and activator of transcription 3 (STAT3) and p53 or the ETS related gene (ERG) (Hoesel and Schmid 2013). The crosstalk may be mediated through different kinases including GSK3-β, p38, PI3K, c-Jun N-terminal kinases (JNKs), and can influence the upstream signaling pathways (see Table 11.1).

Recent studies have emphasized the interactions between NF-kB and STAT3 in colon, gastric, and liver cancers (Fan et al. 2013). STAT3 interacts with many genes in cellular responses, cell growth, and apoptosis. The STAT3 and NF-kB interaction is critical in the regulation of the communications between cancer cells and inflammatory cells, as well as tumor angiogenesis and invasiveness. The elucidation of NF-kB-associated signaling pathways such as the NF-kB and STAT3 cooperation may be helpful for finding novel chemopreventive and chemotherapeutic strategies (Fan et al. 2013; also see Table 11.1).

In addition, the tumor suppressor p53 is often mutated in cancer and the p53 missense mutants (mutp53) may have oncogenic features (Di Minin et al. 2014). The interactions between mutp53 and inflammatory cytokines may enhance the invasive activities of cancer cells. Specifically, mutp53 may stimulate NF-kB activation but inhibit the activation of ASK1/JNK by TNFα (Di Minin et al. 2014; also see Table 11.1). The mutant p53-associated networks may affect tumor evolution and the complex processes in inflammation.

Furthermore, the positive and negative feedback mechanisms may add another level of complexity to the NF-kB signaling pathways. For instance, the positive feedback molecules may include the X-linked inhibitor of apoptosis protein (XIAP), tumor necrosis factor α (TNFα), and interleukin-1 (IL-1) (Hoesel and Schmid 2013). The negative feedback circuits may include the NF-kB target genes such as

IkBα, Cylindromatosis (CYLD), and A20. The NF-kB-associated pathways have been proposed as the potential treatment targets for inflammatory disorders and cancer (Verstrepen and Beyaert 2014; also see Table 11.1).

11.4 The Interleukin-1 (IL-1) Cytokine Family and Associated Pathways

Interleukin-1 (IL-1) is a large cytokine family involved in innate immunity, chronic inflammation, oncogenic mutations, and cancer development. IL-1 proteins are critical in signaling pathways including those of apoptosis, TLR, MAPK, and NF-kB. In silico analysis and the comparison of the mutagenesis and binding energies have indicated that single nucleotide polymorphism (SNP) mutations may affect the complex interactions (Acuner Ozbabacan et al. 2014).

An important pathway that links chronic inflammation with the development of cancer is related to IL-1 receptor-associated kinases (IRAK). The IRAK family has four members including IRAK-1, IRAK-2, IRAK-3 (also named as IRAK-M), and IRAK-4. The IRAK-associated interactions are involved in the regulation of tumor growth, metastasis, immune inhibition, as well as chemotherapy resistance. The dysfunctions in the IRAK signaling pathway among cancer cells may enhance the inflammatory tumor microenvironment and result in cancer progression (Jain et al. 2014; also see Table 11.1).

In addition, the treatment using cytotoxic chemotherapeutic agents (CCAs) may induce a cluster of treatment-associated symptoms among cancer patients (Wood and Weymann 2013). Such cancer treatment-related symptoms (CTRSs) are often shown as fatigue, low appetite, sleep problems, depression, cognitive decline, and alterations in body composition. These symptoms may cause lower levels of quality of life, as well as physical and social difficulties.

Studies have revealed that CTRS may be strongly associated with CCA-caused interleukin-1β (IL-1β) signaling pathways (Wood and Weymann 2013; also see Table 11.1). CCAs may trigger the intracellular stress response networks with the higher levels of IL-1β, IL-6, IL-1 receptor antagonist, and soluble TNF receptor-I/II. Another important factor may be IL-1β-associated central nervous system (CNS) inflammation with the alterations in the hypothalamic and hippocampal functions. These mechanisms provide the implications for potential therapeutic strategies in relieving these symptoms among cancer patients.

11.5 Inflammatory Pathways in the Microbiota

Gut microbiota bacteria are mutualistic microorganisms in the gastrointestinal tract. They are essential in digestion, immunity, and cancer prevention. The alterations in the microbiota environment have been identified pivotal in the pathogenesis of inflammatory bowel disease (IBD)-related and inflammation-caused colorectal

cancer (CRC) (Hu et al. 2013; Kipanyula et al. 2013). Abnormal inflammatory conditions in microbiota have been correlated with CRC development.

In mice models, the deficiencies in the NOD-like receptor family pyrin domain containing 6 (NLRP6) and IL-18 were related to inflammation-caused CRC formation (Hu et al. 2013). Higher levels of tumorigenesis have been associated with inflammation that is microbiota caused and chemokine (C-C motif) ligand 5 (CCL5) driven. Such conditions may activate the IL-6 pathway and enhance epithelial cell proliferation, resulting in cancer formation (see Table 11.1). Moreover, in certain situations the components of microbiota may transmit the susceptibility of CRC between individuals.

These emerging evidences are supporting the correlations between inflammatory signaling pathways and microbial-stimulated carcinogenesis (Kipanyula et al. 2013; also see Table 11.1). Although microbial-stimulated inflammation may provide the protection against pathogens, persistent inflammatory responses may cause secondary damages to the host tissues and lead to tissue fibrosis and carcinogenesis.

For example, genotoxic and mutagenic pathogens such as *Escherichia coli* may lead to DNA damages in different cell types. Inflammatory responses caused by chronic infections from pathogens may also stimulate the carcinogenic activities. An altered microenvironment with increased levels of inflammatory signaling molecules may promote the carcinogenic conversion of host cells (Kipanyula et al. 2013).

The molecules generated during immune responses may result in further DNA damages and the oncogenic mutations. These molecules include the macrophage migration inhibitory factor (MMIF), the reactive oxygen, and nitrogen species' products superoxide and peroxynitrite (Kipanyula et al. 2013). Furthermore, proinflammatory cytokines, adhesion molecules, and growth factors may affect the microenvironment and enhance neoplastic cell survival and proliferation. These mechanisms suggest the importance of microbiota regulations in cancer prevention and treatment.

11.6 Biobehavioral Pathways in Hematopoietic Stem Cell Transplant Patients

As the psychosocial factors may affect cancer progression through biobehavioral pathways, such correlations may also be important among hematopoietic stem cell transplant (HSCT) patients (Knight et al. 2013). These pathways include the inflammatory signaling networks and the vascular endothelial growth factor (VEGF)-associated pathways.

Studies have demonstrated that psychosocial factors may influence the hormonal, messenger, and immune systems. Mediated by the biobehavioral pathways, such effects may have impacts on the overall success of HSCT including the mortality, relapse, progression, and survival (Knight et al. 2013; also see Table 11.1).

The correlations among psychosocial factors, immune functions, and clinical results are significant for the timely immune recovery, the immune control of infections, as well as the elimination of cancer cells (Costanzo et al. 2013). PNI research has indicated that the recovery stage after HSCT may be a "window of opportunity" because stress-associated behavioral factors may affect the survival and well-being of the HSCT recipients.

Specifically, these stress factors may influence the functions of the hypothalamic–pituitary–adrenocortical (HPA) and sympathetic nervous system (SNS) axes (Costanzo et al. 2013; also see Table 11.1). The molecules such as glucocorticoids and catecholamines associated with these networks may affect the bone marrow microenvironment and cell recovery processes. An inflammatory environment may be induced with possible results of severe graft versus host disease (GVHD). These mechanisms highlight the PNI factors in disease recurrence, survival, and quality of life.

11.7 The HPA Axis and the Roles of Melatonin

The individual variations and risk factors that may affect the psychoneurological symptoms in breast cancer patients include perceived stress, malfunctions in the HPA axis, and inflammation (Starkweather et al. 2013; also see Table 11.1). PNI studies of these factors and mechanisms may contribute to the understudied area of cancer research and improve the psychoneurological conditions among cancer patients and survivors.

Specifically, anticancer immunity is affected by psychoneuroendocrine functions including the pineal gland and brain opioid system. Immunosuppression therapies targeting cancer cells may rely on the neuroimmuno-modulation effects, which can be influenced by the blood levels of the pineal hormone melatonin (MLT) (Lissoni et al. 2008).

A study of 846 patients with metastatic solid tumors including non-small-cell lung cancer and gastrointestinal tract tumors showed that the administration of MLT alone could promote disease stabilization and survival time when compared with supportive care alone (Lissoni et al. 2008). The administration of both IL-2 and MLT provided a further improvement in tumor regressions and survival when compared with MLT alone.

11.8 Inflammatory Pathways Associated with Neuroendocrine (NE) Differentiation

In prostate cancer (PCa) cells, the neuroendocrine (NE) cells have been found to affect tumor growth and progression (Tawadros et al. 2013). The underlying mechanisms have been correlated with hormone refractory PCa (HRPC) and the repressor

element-1 silencing transcription factor (REST) (Lin et al. 2016). REST is a transcriptional inhibitor of neuronal genes associated with androgen deprivation and IL-6-caused NE differentiation (NED). It has a key role in hypoxia-caused NED of PCa cells.

Bioinformatics, gene ontology (GO), and gene set enrichment analysis (GSEA) of the transcriptome profiles have revealed the tight relationships among HRPC, REST reduction, and hypoxia-caused tumorigenesis (Lin et al. 2016). The activation of the AMPK signaling pathway and NE development is also essential (see Table 11.1). The elucidation of such mechanisms may contribute to potential therapeutic approaches for the treatment of HRPC, the aggressive type of cancer that is difficult to treat.

In addition, the proinflammatory cytokine macrophage migration inhibitory factor (MIF) has been closely associated with oncogenic activities and the aggressiveness of PCa (Tawadros et al. 2013). Higher levels of MIF during NED in PCa may mediate cancer progression or recurrence, especially in the condition of androgen deficiency. MIF may interact with the AKT and ERK1/2 signaling pathways and result in the cancer cell proliferation and resistance to paclitaxel and thapsigargin-caused apoptosis (see Table 11.1). The MIF-associated pathways have been suggested as the potential target for PCa treatment.

Furthermore, NED has been observed in almost all of the small-cell lung cancers (SCLC) and carcinoid tumors (Chen et al. 2014). In non-small-cell lung cancers (NSCLC), about 10–20 % have been related to NED. NED of NSCLC has been associated with various signaling pathways including the activation of Erk1/2-mitogen-activated protein kinases (MAPK) signal transductions (see Table 11.1). In addition, the suppression of the Akt signal transduction pathway may also be related. Further explorations of the complex Erk/MAPK signal transduction pathways may be helpful for identifying new targets for the therapy of NSCLC with NED.

References

Achyut, B. R., Bader, D. A., Robles, A. I., Wangsa, D., Harris, C. C., Ried, T., et al. (2013). Inflammation-mediated genetic and epigenetic alterations drive cancer development in the neighboring epithelium upon stromal abrogation of TGF-β signaling. *PLoS Genetics, 9*, e1003251.

Acuner Ozbabacan, S. E., Gursoy, A., Nussinov, R., & Keskin, O. (2014). The structural pathway of interleukin 1 (IL-1) initiated signaling reveals mechanisms of oncogenic mutations and SNPs in inflammation and cancer. *PLoS Computational Biology, 10*, e1003470.

Artherholt, S. B., & Fann, J. R. (2012). Psychosocial care in cancer. *Current Psychiatry Reports, 14*, 23–29.

Baumgart, S., Chen, N.-M., Zhang, J.-S., Billadeau, D. D., Gaisina, I. N., Kozikowski, A. P., et al. (2016). GSK-3β governs inflammation-induced NFATc2 signaling hubs to promote pancreatic cancer progression. *Molecular Cancer Therapeutics, 15*, 491–502.

Ben-Eliyahu, S., Page, G. G., & Schleifer, S. J. (2007). Stress, NK cells, and cancer: Still a promissory note. *Brain, Behavior, and Immunity, 21*, 881–887.

Chaturvedi, S. K., & Venkateswaran, C. (2008). New research in psychooncology. *Current Opinion in Psychiatry, 21*, 206–210.

Chen, Y., Nowak, I., Huang, J., Keng, P. C., Sun, H., Xu, H., et al. (2014). Erk/MAP kinase signaling pathway and neuroendocrine differentiation of non-small-cell lung cancer. *Journal of Thoracic Oncology, 9*, 50–58.

Costanzo, E. S., Juckett, M. B., & Coe, C. L. (2013). Biobehavioral influences on recovery following hematopoietic stem cell transplantation. *Brain, Behavior, and Immunity, 30*(Suppl), S68–S74.

De la Roca-Chiapas, J. M., Barbosa-Sabanero, G., Martínez-García, J. A., Martínez-Soto, J., Ramos-Frausto, V. M., González-Ramírez, L. P., et al. (2016). Impact of stress and levels of corticosterone on the development of breast cancer in rats. *Psychology Research and Behavior Management, 9*, 1–6.

Di Minin, G., Bellazzo, A., Dal Ferro, M., Chiaruttini, G., Nuzzo, S., Bicciato, S., et al. (2014). Mutant p53 reprograms TNF signaling in cancer cells through interaction with the tumor suppressor DAB2IP. *Molecular Cell, 56*, 617–629.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Fan, Y., Mao, R., & Yang, J. (2013). NF-kB and STAT3 signaling pathways collaboratively link inflammation to cancer. *Protein & Cell, 4*, 176–185.

Fűri, I., Sipos, F., Germann, T. M., Kalmár, A., Tulassay, Z., Molnár, B., et al. (2013). Epithelial toll-like receptor 9 signaling in colorectal inflammation and cancer: Clinico-pathogenic aspects. *World Journal of Gastroenterology, 19*, 4119–4126.

Green McDonald, P., O'Connell, M., & Lutgendorf, S. K. (2013). Psychoneuroimmunology and cancer: A decade of discovery, paradigm shifts, and methodological innovations. *Brain, Behavior, and Immunity, 30*(Suppl), S1–S9.

Hoesel, B., & Schmid, J. A. (2013). The complexity of NF-kB signaling in inflammation and cancer. *Molecular Cancer, 12*, 86.

Hu, B., Elinav, E., Huber, S., Strowig, T., Hao, L., Hafemann, A., et al. (2013). Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. *Proceedings of the National academy of Sciences of the United States of America, 110*, 9862–9867.

Hulett, J. M., Armer, J. M., Stewart, B. R., & Wanchai, A. (2015). Perspectives of the breast cancer survivorship continuum: Diagnosis through 30 months post-treatment. *Journal of Personalized Medicine, 5*, 174–190.

Jain, A., Kaczanowska, S., & Davila, E. (2014). IL-1 receptor-associated kinase signaling and its role in inflammation, cancer progression, and therapy resistance. *Frontiers in Immunology, 5*, 553.

Jensen, S. E., Lehman, B., Antoni, M. H., & Pereira, D. B. (2007). Virally mediated cervical cancer in the iatrogenically immunocompromised: Applications for psychoneuroimmunology. *Brain, Behavior, and Immunity, 21*, 758–766.

Kipanyula, M. J., Seke Etet, P. F., Vecchio, L., Farahna, M., Nukenine, E. N., & Nwabo Kamdje, A. H. (2013). Signaling pathways bridging microbial-triggered inflammation and cancer. *Cellular Signalling, 25*, 403–416.

Knight, J. M., Lyness, J. M., Sahler, O. J. Z., Liesveld, J. L., & Moynihan, J. A. (2013). Psychosocial factors and hematopoietic stem cell transplantation: Potential biobehavioral pathways. *Psychoneuroendocrinology, 38*, 2383–2393.

Lee, J. M., Yang, J., Newell, P., Singh, S., Parwani, A., Friedman, S. L., et al. (2014). β-Catenin signaling in hepatocellular cancer: Implications in inflammation, fibrosis, and proliferation. *Cancer Letters, 343*, 90–97.

Lin, T.-P., Chang, Y.-T., Lee, S.-Y., Campbell, M., Wang, T.-C., Shen, S.-H., et al. (2016). REST reduction is essential for hypoxia-induced neuroendocrine differentiation of prostate cancer cells by activating autophagy signaling. *Oncotarget, 7*, 26137–26151.

Lisanti, M. P., Tsirigos, A., Pavlides, S., Reeves, K. J., Peiris-Pagès, M., Chadwick, A. L., et al. (2014). JNK1 stress signaling is hyper-activated in high breast density and the tumor stroma: Connecting fibrosis, inflammation, and stemness for cancer prevention. *Cell Cycle, 13*, 580–599.

Lissoni, P., Brivio, F., Fumagalli, L., Messina, G., Vigoré, L., Parolini, D., et al. (2008). Neuroimmunomodulation in medical oncology: Application of psychoneuroimmunology with subcutaneous low-dose IL-2 and the pineal hormone melatonin in patients with untreatable metastatic solid tumors. *Anticancer Research, 28*, 1377–1381.

Pant, S., & Ramaswamy, B. (2009). Association of major stressors with elevated risk of breast cancer incidence or relapse. *Drugs Today, 45*, 115–126.

Starkweather, A. R., Lyon, D. E., Elswick, R. K., Montpetit, A. J., Conley, Y., & McCain, N. L. (2013). A conceptual model of psychoneurological symptom cluster variation in women with breast cancer: Bringing nursing research to personalized medicine. *Current Pharmacogenomics and Personalized Medicine, 11*, 224–230.

Subnis, U. B., Starkweather, A. R., McCain, N. L., & Brown, R. F. (2014). Psychosocial therapies for patients with cancer: A current review of interventions using psychoneuroimmunology-based outcome measures. *Integrative Cancer Therapies, 13*, 85–104.

Tawadros, T., Alonso, F., Jichlinski, P., Clarke, N., Calandra, T., Haefliger, J.-A., et al. (2013). Release of macrophage migration inhibitory factor by neuroendocrine-differentiated LNCaP cells sustains the proliferation and survival of prostate cancer cells. *Endocrine-Related Cancer, 20*, 137–149.

Verstrepen, L., & Beyaert, R. (2014). Receptor proximal kinases in NF-kB signaling as potential therapeutic targets in cancer and inflammation. *Biochemical Pharmacology, 92*, 519–529.

Wang, D., & DuBois, R. N. (2014). PPARδ and PGE2 signaling pathways communicate and connect inflammation to colorectal cancer. *Inflammation and Cell Signaling, 1*.

Wood, L. J., & Weymann, K. (2013). Inflammation and neural signaling: Etiologic mechanisms of the cancer treatment-related symptom cluster. *Current Opinion in Supportive and Palliative Care, 7*, 54–59.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Yang, E. V., & Eubank, T. D. (2013). The impact of adrenergic signaling in skin cancer progression: Possible repurposing of β-blockers for treatment of skin cancer. *Cancer Biomarkers, 13*, 155–160.

Chapter 12
Psychoneuroimmunology of Skin Diseases

12.1 The PNI Mechanisms of Skin Disorders at Various Levels

Increasing evidences are connecting psychosocial stress with physical diseases. Psychosomatic factors have been considered critical in more than one-third of the patients with skin disorders (Lotti et al. 2008). The management of the related psychological factors may help improve the treatment of skin problems.

In psychodermatology, three types of diseases have been illustrated (Filaković et al. 2009). The type of primary psychiatric disorders includes skin problems caused by the mental diseases and/or therapies. The type of secondary psychiatric disorders includes mental diseases caused by skin disorders and treatments. The type of psychophysiological disorders refers to both psychiatric and skin disorders caused by stressors (Filaković et al. 2009).

Studies in epidemiology, psychoneuroimmunology (PNI), and molecular psychosomatics have confirmed the complex interactions among the endocrine, nervous, and immune systems to support the dynamical biopsychosocial models (see Chap. 1). The communications between the mind and the skin emphasize the psycho-immuno-endocrine-cutaneous networks involving various neuropeptides, interleukins, and immune messengers (Lugović-Mihić et al. 2013).

These interrelationships emphasize the stress-caused alterations in immune imbalance in the chronic skin disorders including atopic dermatitis, psoriasis, and malignant melanoma (Peters 2016). The effects of chronic stress on the immune functions and skin diseases have been demonstrated by the effectiveness of psychosocial interventions (Tausk et al. 2008).

From the systems biology point of view, the skin is a complex and dynamic organ at various levels. At the molecular and cellular levels, the skin health depends on the interactions among various signaling pathways and cell types. The underlying molecular and cellular mechanisms of the skin disorders indicate the bidirectional somatic-mental communications.

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_12

Specifically, the immune cells are regulated by neurotransmitters, neuropeptides, and hormones, while cytokines are the keys in the communications between the immune cells and nervous tissues (Tausk et al. 2008). The central nervous system (CNS) and nerves are crucial in keeping the normal status between cell-mediated (Th1) and humoral (Th2) immune responses.

At the organ level, the skin needs to maintain the normal functions and interrelations among its own appendages as well as with other organs including the sebaceous glands, hair follicles, adrenal glands, and the kidney (Hochman et al. 2015). For example, clinical and experimental studies have proved that the brain may initiate, affect, and block biological skin events (Urpe et al. 2005).

The skin has been suggested as an important component of the "diffuse brain" by involving in the perceptions and feelings (Urpe et al. 2005). The immune–endocrine interactions are also critical in the regulation of these skin events. Meanwhile, psychosocial stressors have the essential role in these complex interactions with profound implications for finding novel interventions for dermatologists.

At the system level, various connections among the immune system and the CNS, as well as the hypothalamic–pituitary–adrenal (HPA) axis provide the adaptability in the skin physiology and pathology. The agents involved in the HPA axis have special roles in dermatologic diseases and skin lesions (Hochman et al. 2015; Lugović-Mihić et al. 2013).

In the cases of skin injuries, a cascade of PNI intercommunications are involved in the efforts for recovering the integrity and homeostatic status. In most skin disorders including psoriasis and atopic dermatitis, psychogenic factors have been found critical in the pathophysiology with abnormal activities in the nervous, immune, and endocrine systems (Hochman et al. 2015). The elucidation of the complex mechanisms would support the development of systems and dynamical medicine (Yan 2014; also see Chap. 1).

12.2 Emotional Tension and Immune Responses

Emotional factors have been found critical in most of the skin disorders. Close associations have been established between stressful life events and the onset of skin diseases (Locala 2009). Such connections have led to the recommendations for psychosocial interventions among dermatology patients.

Certain types of psycho-associated pathogenesis and cytokines in the skin tissues have been identified in the development of skin lesions in various dermatologic diseases. Strong connections have been observed between emotional stressors, psychiatric disorders, and disorders including acnes, alopecia, atopic dermatitis, herpes simplex, prurigo, psoriasis, urticaria, viral warts, and vitiligo (Lugović-Mihić et al. 2013).

For example, among predisposed subjects, emotional tensions have been found critical in provoking the pruritic sensation and scratching. The self-perpetuating mechanism and psychogenic factors are important in the cutaneous entities including

prurigo nodularis and lichen simplex chronicus (Lotti et al. 2008). These two conditions are often related to depression and dissociative experiences.

These links have led to the studies of psychodermatology that investigates the associations between psychological factors and skin disorders. Those who have real or perceived problems in certain areas of the body such as face, scalp, and hands have been found more susceptible to psychological distress (Lotti et al. 2008). On the other hand, cutaneous disorders in turn may also result in elevated levels of stress experiences.

Depressive disorders are often seen among patients with dermatological diseases. The percentage of the comorbidity of depression and skin disorders is about 30 % (Filaković et al. 2009). In depression and skin disorders, the cytokines involved in the immune responses and inflammatory activities may result in recurrent hormonal secretions and influence the functions of the vegetative and central nervous system.

Phenotypically, such alterations may result in "sickness behaviors" and depressive symptoms featured with the loss of appetite, anhedonia, anxiety, lack of concentration, as well as the loss of interest (Filaković et al. 2009). Such complex mechanisms require integrative interventions for both depressive and dermatological problems. The translation of the relevant PNI discoveries into clinical practice may help bridge the gaps between the psychiatric and physical disorders.

12.3 PNI of Atopic Dermatitis (AD) and Other Skin Diseases

12.3.1 Atopic Dermatitis (AD)

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disorder featured with serious and extensive pruritus, eczematous inflammation, impaired epidermal barrier functions, as well as chronical relapses (Suárez et al. 2012; Buske-Kirschbaum et al. 2001). Many young people are troubled by this disease. Evidences have linked psychological distress and personality with the disease's pathogenesis, onset, symptomatology, and clinical progression.

Recent studies have shown that complex interactions of the genetic, environmental, and pharmacological factors are involved in AD (Raap and Kapp 2005). Specific psychological profiles featured with anxiety, depression, and emotional instability have been associated with those who have allergic problems especially AD.

PNI studies have confirmed the connections between anxiety and hypersensitivity responses in allergic individuals (Hashizume and Takigawa 2006). Emotional stress may trigger allergic symptoms with higher anxiety levels and immune dysfunctions. A vicious circle between anxiety and the AD symptoms has been observed among the AD patients with emotional problems. Acute stressors may have continuous and chronic effects on the AD patients and increase the levels of anxiety. Such psychological impacts in turn may elevate the Th2-type responses and aggregate the allergic symptoms (Hashizume and Takigawa 2006).

As a potential risk factor, stress may affect the neuroimmune functions with the induction of hypersensitivity responses (Pallanti et al. 2005). In such processes, inflammation can be induced by immunoglobulin E (IgE) with the alterations in helper T-cell 2 and eosinophilia. Stress responses may lead to the elevation of the neuropeptide mediators in the CNS, peripheral nervous system (PNS), and the endocrine system with effects on the immune cells in the skin. Specifically, AD patients have shown higher levels of mast cells and mast cell-nerve fiber contacts (Suárez et al. 2012). The neuromediators secreted from the sensory nerves in stress responses may induce inflammatory responses and affect the barrier functions.

The higher levels of neuropeptides and higher density of neuropeptide-positive nerve fibers have been observed in the AD lesions (Raap and Kapp 2005). Neurotrophins and neuropeptides regulate the functional processes of sensory neurons and immune cells, with a bidirectional communication between neuronal cells and the target effector cells including eosinophils. The neuroimmune network between the target effector cells and sensory nerves provides the connections underlying the pathogenic mechanisms of the cutaneous immune and peripheral nervous systems in AD (Raap and Kapp 2005).

Based on these mechanisms, psychopharmacologic agents can be discovered to regulate the neuronal receptors and/or the inflammatory circuits for the treatment of stress-associated inflammatory skin disorders including AD (Suárez et al. 2012). For example, Tandospirone is a 5-hydroxytryptamine 1A receptor agonist. It has anxiolytic and antidepressant functions that may ease itching via the regulation of the emotional problems (Hashizume and Takigawa 2006). Various drugs with anxiolytic effects have been suggested for the management of stress-related itching among AD patients. Furthermore, psychosocial strategies such as the periodic inspection of anxiety levels, together with the checking of immune functions and skin conditions may become the essential strategies for the treatment of AD patients with emotional difficulties.

12.3.2 Other Relevant Skin Disorders

As discussed earlier, the AD problem is not limited to physical disorders but may also have certain psychiatric consequences. For example, epidemiological data have shown that atopic eczema (AE) during the infant stage may be associated with higher risks for attention deficit/hyperactivity disorder (ADHD) during later life (Buske-Kirschbaum et al. 2013). The combination of higher levels of psychological stress and the allergic inflammation in AD may induce the higher levels of inflammatory cytokines. Such changes may impede the maturation processes of the prefrontal cortex areas and affect the neurotransmitter activities related to the pathology of ADHD.

On the other hand, higher stress levels in ADHD patients may in turn worsen the conditions of AE through the neuroimmunological pathways (Buske-Kirschbaum et al. 2013). Although AE and ADHD are two different diseases, they share some

risk factors including genetic factors and prenatal stress. These common risk factors may elevate the susceptibility for both diseases and result in the comorbidity of both AE and ADHD. Further PNI studies would enable more effective strategies for the prevention and therapy of both diseases.

In addition to the AD problems, recent discoveries have also demonstrated that fibroproliferative disorders of wound healing including hypertrophic scar and keloid are also strongly correlated to psychosocial stress. The mechanisms of the "brain–skin connection" have categorized the keloid problem as a psycho-associated disorder (Hochman et al. 2015).

In a systematic review and meta-analysis, the influences of stress on the healing of various wound types were evaluated, such as the acute and chronic clinical wounds, blister wounds, and minor skin damages (Walburn et al. 2009). The results of studies confirm that psychological stress is closely related to the diminished healing processes or the dysregulations of biomarkers associated with wound healing.

In the case of skin cancer, factors other than UV radiation exposure such as psychosocial stressors and physical inactivity have also been found important in the elevating tumor incidences (Peters 2012). The HPA axis, the sympathetic axis, and natural killer cells may have the critical roles in the interactions between psychological stress and cancer pathogenesis. The stress pathways involving neurotrophins and neuropeptides are also crucial. These mechanisms refer to the importance of the length and intensity of integrative and psychosocial interventions for promoting the quality of life and skin health.

12.4 Stress Response and Inflammatory Networks in Skin Disorders

12.4.1 Stress and the Neurotrophin Nerve Growth Factor (NGF) Pathway

As discussed earlier, PNI studies have demonstrated that the dysregulations in the neuroimmune pathways have the key roles in atopic diseases. Table 12.1 lists some examples of the associated cellular networks. A more complete list can be found in the Database of Psychoneuroimmunology (DPNI 2016).

For instance, the neurotrophin nerve growth factor (NGF) may be triggered by psychological stress and aggravate the conditions of cutaneous inflammation (Peters et al. 2011). Serving as a local stress mediator, higher levels of NGF may cause higher levels of epidermal hyperplasia, proallergic cytokines, and allergy-featured cellular infiltration. A study using a mouse model showed that stress may result in the higher levels of cutaneous NGF and various inflammatory and growth factors related to the NGF pathways in the skin (Peters et al. 2011; also see Table 12.1).

On the other hand, NGF-neutralizing antibodies were found to lower the levels of epidermal thickening and neurotrophin receptors including tyrosine kinase A and

Table 12.1 Examples of stress- and inflammation-related pathways in skin diseases

Pathways and interactions	Associated pathogenesis/diseases	References
Neurotrophin nerve growth factor (NGF), inflammatory and growth factors (e.g., neurotrophin receptor, TGF-β)	Allergic dermatitis	Peters et al. 2011
Neurotrophin signaling pathways, enzymes, associated coreceptors, and intracellular adaptor molecules	Cutaneous diseases, atopic dermatitis, neurogenic inflammation, peripheral nerve degeneration, wound healing, psoriasis	Peters et al. 2007
TNFα, LTß, and TNFR1 signaling pathways	Chronic skin inflammation, thymic atrophy, psoriasis	Belhacéne et al. 2012
TNF receptor signaling pathways (e.g., TNFR1, NF-kB, ERK, IL-24, IL-22R1, and STAT3 signaling)	Skin inflammation in psoriasis	Kumari et al. 2013
The IL-6–STAT3–SOCS3 axis	Skin inflammation	Uto-Konomi et al. 2012
IL-1α and IL-1R1 signaling pathways	Microabscess formation, neutrophil recruiting chemokine expression, acanthosis in psoriasis-like skin inflammation	Uribe-Herranz et al. 2013
The ROS–NLRP3–caspase-1 pathways	Inflammatory skin diseases	Cho et al. 2012
The JAK–STAT pathways	Chronic inflammatory skin disease, atopic dermatitis	Bao et al. 2013
The histamine receptor H1 (H1R) signaling pathways	T cell-mediated skin inflammation, atopic dermatitis	Vanbervliet et al. 2011
The antigen processing and interferon pathways	Inflammatory fibrotic skin diseases (e.g., localized scleroderma, pediatric and adult lichen sclerosus, eosinophilic fasciitis, and systemic sclerosis)	Limpers et al. 2014
The inflammatory networks (e.g., TNF-α, NFkB, IL-22, IL-1b, Cxcl1, Cxcl2, and Cxcl5)	Skin tumor	Shen et al. 2012
The hypothalamus–pituitary–adrenal (HPA) axis, nonneuronal cholinergic system (NNCS)	Atopic dermatitis	Peters et al. 2014
The adrenergic signaling pathways, catecholamine hormones, and receptors (β-ARs)	Skin tumor progression (proliferation, angiogenesis, and metastasis)	Yang and Eubank 2013
The Cldn-1 and Cldn-4 pathways (including IL-4, IL-13, and IL-31)	Inflammation, atopic dermatitis	Gruber et al. 2015
The VEGF-C/VEGFR3 signaling pathways	Inflammatory skin diseases	Hagura et al. 2014

p75 neurotrophin receptors (Peters et al. 2011). Other changes caused by the neutralizing antibodies included the lower expression levels of transforming growth factor (TGF)-β and cutaneous tumor necrosis factor-α (TNF-α). These observations indicate the communications of the components in the NGF-associated PNI pathways in the conditions of stress and skin inflammation.

Such mechanisms put the neuroendocrine peptide family and the signaling pathways of neurotrophins in the pivotal role in the regulation of skin homeostasis. Neurotrophins serve as the growth and motility factors on skin cells including keratinocytes and fibroblasts (Peters et al. 2007). They are involved in the cutaneous immune functions and act as stress mediators in skin physiology and pathology. They interact with high affinity specific tyrosine kinase receptors and the Janus-faced p75 receptor.

PNI studies of the skin diseases need to incorporate the neurotrophin expression patterns and associated cellular networks into the complex profiles of the skin pathogenesis. Such profiles should include the roles of neurotrophin processing enzymes, relevant coreceptors, and intracellular adaptor molecules in various cutaneous cell groups (Peters et al. 2007; also see Table 12.1). The profiling of the neurotrophin-associated pathogenesis pathways may contribute to the precise identification of systems-based biomarkers and therapeutics for cutaneous diseases including atopic dermatitis, psoriasis, as well as wound healing.

12.4.2 Multiple Cytokine Networks and Skin Homeostasis

Evidences have shown that multiple cytokines are involved in skin diseases and it is necessary to elucidate such cytokine networks. As an example, psoriasis is a chronic inflammatory skin disorder. It is known that the cytokine TNFα is critical in the pathogenesis of psoriasis. Studies using mice models have indicated that chronic inflammation may lead to thymic atrophy and disturb spleen homeostasis via the higher levels of TNFα and TNFR1 signaling (Belhacéne et al. 2012; also see Table 12.1). Recent studies have revealed a keratinocyte-intrinsic mechanism connecting multiple molecules and pathways with the disease onset involving TNFR1, NF-kB, ERK, IL-24, IL-22R1, and STAT3 signaling (Kumari et al. 2013; also see Table 12.1).

The homeostatic management of epidermal keratinocytes is decided by the environment of the local cytokine networks. In this environment, the suppressor of cytokine signaling (SOCS) acts as the negative feedback controller of the cytokine networks in the maintenance of skin homeostasis. The keratinocyte-specific deletion of SOCS3 was found to result in serious skin inflammation with elevated generation of IgE and epidermal hyperplasia (Uto-Konomi et al. 2012).

In addition, the higher levels of STAT3, IL-6, IL-19, IL-20, IL-24, and IL-20 receptor (IL-20R)-associated cytokines may also be involved in the skin inflammation (Uto-Konomi et al. 2012). The higher levels of IL-6 and IL-20R-associated cyto-

kines may lead to STAT3 hyperactivation, epidermal hyperplasia, as well as neutrophilia.

These interactions indicate that skin homeostasis is firmly controlled by the IL-6–STAT3–SOCS3 axis (Uto-Konomi et al. 2012; also see Table 12.1). Such mechanisms also suggest that the SOCS3-associated negative feedback loop in keratinocytes may be essential in the prevention and treatment of skin inflammation related to the hyperactivation of STAT3.

12.4.3 Inflammatory Networks in Association with Various Skin Disorders

As discussed before, various inflammatory networks have been associated with different skin diseases. For example, the functions of the vascular endothelial growth factor (VEGF)-C/VEGF receptor (VEGFR)-3 signaling pathway have been found crucial in chronic skin inflammation (Hagura et al. 2014; also see Table 12.1). To keep normal tissue pressure and immune responses, the lymphatic vessels need to drain the protein-rich lymph from the extracellular space. Such function is especially important during inflammatory conditions.

Evidences have revealed that VEGF-C may improve the drainage of interstitial fluid and inflammatory cells through lymphatic vessels (Hagura et al. 2014). On the other hand, the blockade of VEGFR3 may suppress the drainage function of the lymphatic system, causing delays in the recovery from skin inflammation. Because the VEGF-C/VEGFR3 signaling pathway is essential in the resolution of skin inflammation, it may be an important target for the regulation of lymphatic functions for the management of inflammatory skin diseases.

In psoriasis, the IL-1α and IL-1R1 signaling pathways have been found crucial. According to a study of the skin inflammation induced by imiquimod, the relevant pathways were involved in the microabscess formation, neutrophil chemokine accumulation, as well as acanthosis (Uribe-Herranz et al. 2013; also see Table 12.1).

The production of the cytokines from keratinocytes such as IL-1β is a key mechanism in the pathogenesis of inflammatory skin disorders. Cytokines from T(h)17 cells may trigger IL-1β-associated skin inflammation and lead to the phenotypic changes of keratinocytes through a feedback loop (Cho et al. 2012; also see Table 12.1). T(h)17 cells are a subset of T(h) cells associated with autoimmunity and inflammation. These cells have IL-1β receptors and generate cytokines including IL-17 and IL-22 upon the stimulation from IL-1β. Mutations in the protein NLRP3 (NACHT, LRR, and PYD domains-containing protein 3) may lead to the overproduction of IL-1β and amplify the T(h)17-related pathology (Cho et al. 2012).

A significant feature of atopic dermatitis (AD), the chronic inflammatory skin disorder, is the inflammatory cell skin infiltration. The JAK–STAT pathway is critical in the abnormal immune responses in AD (Bao et al. 2013). At the cellular level, these responses include the overreaction of Th2 cells, the stimulation of eosinophils,

the maturation of B cells, as well as the inhibition of regulatory T cells (Tregs). The JAK–STAT pathway may be triggered by IL-4. The pathway may be involved in the pathogenesis of AD via stimulating epidermal chemokines, proinflammatory cytokines, as well as proangiogenic factors (Bao et al. 2013; also see Table 12.1). The pathway may also be associated with the lower levels of antimicrobial peptides (AMPs) and factors related to normal skin barrier functions.

During the initial stage of the T cell-mediated skin pathology in dermatitis, the type 1 receptor (H1R) has been found to mediate the allergic and inflammatory activities of histamine. The histamine signaling via the H1R pathway on dendritic cells (DCs) may be an essential early step in the skin immune response (Vanbervliet et al. 2011; also see Table 12.1).

In addition, tight junctions are essential for maintaining the normal skin barrier functions. The lower levels of claudin 1 (Cldn-1), a tight junction protein, have been observed in the nonlesional skin among patients with atopic dermatitis (AD). A recent study of Cldn-1 also found its lower levels in the epidermal layers of lesional skin (Gruber et al. 2015). Higher levels of Cldn-4 were detected in nonlesional but not lesional AD skin.

The studies using mouse models have shown that the down-regulation of Cldn-1 may be affected by dermal inflammation in association with the features of eczema (Gruber et al. 2015). These features include the elevated keratinocyte proliferation and epidermal thickness, damaged barrier functions, as well as changes in keratinocyte differentiation. In addition, human epidermal studies have found that the higher levels of IL-4, IL-13, and IL-31 may lead to the down-regulation of Cldn-1 (Gruber et al. 2015; also see Table 12.1). Thus, the pathways of Cldn-1 and Cldn-4 may be differentially associated with AD pathogenesis. Such mechanisms also address the importance of inflammation and Cldn-1 in the AD eczema formation.

Furthermore, the studies using AD mouse models identified the importance of the HPA axis dysfunctions and neuropeptide-associated inflammation in stress-provoked disease onset (Peters et al. 2014; also see Table 12.1). In these processes, the cholinergic signaling pathway may provide the connections between stress responses with innate and adaptive immunity, as well as chronic inflammation. Such interactions may lead to the alterations in the expressions of nonneuronal cholinergic system (NNCS) markers (Peters et al. 2014).

Different molecular pathways have been identified in different inflammatory fibrotic disorders including eosinophilic fasciitis. Gene expression microarray studies indicated unique gene expression features in different problems. However, the antigen processing and interferon networks have been observed as the common pathways among the adult and pediatric lichen sclerosus as well as localized scleroderma (Limpers et al. 2014; also see Table 12.1). Further elucidation of these pathways may be helpful for more effective treatment of the disorders.

In skin tumors, the differential expression of the genes associated with inflammatory pathways in epidermis has been identified as the essential factors for the predisposition to the disease. A proteomic study recognized 19 differentially expressed proteins, and 5 of them were the calcium-binding proteins including annexin A1,

parvalbumin α, S100A8, S100A9, and S100A11 (Shen et al. 2012). The higher levels of TNF, NF-kB1, IL-22, IL-1b, CXCL1, CXCL2, and CXCL5 mRNAs were also detected in epidermis. The pathway analysis correlated these proteins with several inflammatory networks in the skin tumor development, especially the pathways of TNF-α and NF-kB (Shen et al. 2012; also see Table 12.1).

Moreover, the adrenergic signaling pathways including catecholamine hormones (norepinephrine and epinephrine) and their receptors (the β-adrenergic receptors; β-ARs) have been associated with the processes of skin tumor progression (Yang and Eubank 2013; also see Table 12.1). The processes include the proliferation, angiogenesis, and metastasis of the tumor cells.

In summary, the earlier evidences emphasize the interactions between psychoemotional stress and chronic inflammation with important impacts on the cutaneous neuroimmune communications (Peters et al. 2014). These mechanisms are meaningful for the development of systems-based preventive and therapeutic strategies for the skin problems.

References

Bao, L., Zhang, H., & Chan, L. S. (2013). The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. *JAKSTAT, 2*, e24137.

Belhacéne, N., Gamas, P., Gonçalvès, D., Jacquin, M., Beneteau, M., Jacquel, A., et al. (2012). Severe thymic atrophy in a mouse model of skin inflammation accounts for impaired TNFR1 signaling. *PLoS One, 7*, e47321.

Buske-Kirschbaum, A., Geiben, A., & Hellhammer, D. (2001). Psychobiological aspects of atopic dermatitis: An overview. *Psychotherapy and Psychosomatics, 70*, 6–16.

Buske-Kirschbaum, A., Schmitt, J., Plessow, F., Romanos, M., Weidinger, S., & Roessner, V. (2013). Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. *Psychoneuroendocrinology, 38*, 12–23.

Cho, K.-A., Suh, J. W., Lee, K. H., Kang, J. L., & Woo, S.-Y. (2012). IL-17 and IL-22 enhance skin inflammation by stimulating the secretion of IL-1β by keratinocytes via the ROS-NLRP3-caspase-1 pathway. *International Immunology, 24*, 147–158.

DPNI. (2016). The database of psychoneuroimmunology. Retrieved July 1, 2016, from http://pharmtao.com/health/psychoneuroimmunology-database/

Filaković, P., Petek, A., Koić, O., Radanović-Grgurić, L., & Degmecić, D. (2009). Comorbidity of depressive and dermatologic disorders—Therapeutic aspects. *Psychiatria Danubina, 21*, 401–410.

Gruber, R., Börnchen, C., Rose, K., Daubmann, A., Volksdorf, T., Wladykowski, E., et al. (2015). Diverse regulation of claudin-1 and claudin-4 in atopic dermatitis. *American Journal of Pathology, 185*, 2777–2789.

Hagura, A., Asai, J., Maruyama, K., Takenaka, H., Kinoshita, S., & Katoh, N. (2014). The VEGF-C/VEGFR3 signaling pathway contributes to resolving chronic skin inflammation by activating lymphatic vessel function. *Journal of Dermatological Science, 73*, 135–141.

Hashizume, H., & Takigawa, M. (2006). Anxiety in allergy and atopic dermatitis. *Current Opinion in Allergy and Clinical Immunology, 6*, 335–339.

Hochman, B., Isoldi, F. C., Furtado, F., & Ferreira, L. M. (2015). New approach to the understanding of keloid: Psychoneuroimmune-endocrine aspects. *Clinical, Cosmetic and Investigational Dermatology, 8*, 67–73.

Kumari, S., Bonnet, M. C., Ulvmar, M. H., Wolk, K., Karagianni, N., Witte, E., et al. (2013). Tumor necrosis factor receptor signaling in keratinocytes triggers interleukin-24-dependent psoriasis-like skin inflammation in mice. *Immunity, 39*, 899–911.

Limpers, A., van Royen-Kerkhof, A., van Roon, J. A. G., Radstake, T. R. D. J., & Broen, J. C. A. (2014). Overlapping gene expression profiles indicative of antigen processing and the interferon pathway characterize inflammatory fibrotic skin diseases. *Expert Review of Clinical Immunology, 10*, 231–241.

Locala, J. A. (2009). Current concepts in psychodermatology. *Current Psychiatry Reports, 11*, 211–218.

Lotti, T., Buggiani, G., & Prignano, F. (2008). Prurigo nodularis and lichen simplex chronicus. *Dermatology and Therapy, 21*, 42–46.

Lugović-Mihić, L., Ljubesić, L., Mihić, J., Vuković-Cvetković, V., Troskot, N., & Situm, M. (2013). Psychoneuroimmunologic aspects of skin diseases. *Acta Clinica Croatica, 52*, 337–345.

Pallanti, S., Lotti, T., & Urpe, M. (2005). Psychoneuroimmunodermatology of atopic dermatitis: From empiric data to the evolutionary hypothesis. *Dermatologic Clinics, 23*, 695–701.

Peters, E. M. J. (2012). Psychological support of skin cancer patients. *British Journal of Dermatology, 167*(Suppl 2), 105–110.

Peters, E. M. J. (2016). Stressed skin?—A molecular psychosomatic update on stress-causes and effects in dermatologic diseases. *Journal der Deutschen Dermatologischen Gesellschaft, 14*, 233–252.

Peters, E. M. J., Liezmann, C., Spatz, K., Daniltchenko, M., Joachim, R., Gimenez-Rivera, A., et al. (2011). Nerve growth factor partially recovers inflamed skin from stress-induced worsening in allergic inflammation. *Journal of Investigative Dermatology, 131*, 735–743.

Peters, E. M. J., Michenko, A., Kupfer, J., Kummer, W., Wiegand, S., Niemeier, V., et al. (2014). Mental stress in atopic dermatitis—Neuronal plasticity and the cholinergic system are affected in atopic dermatitis and in response to acute experimental mental stress in a randomized controlled pilot study. *PLoS One, 9*, e113552.

Peters, E. M. J., Raap, U., Welker, P., Tanaka, A., Matsuda, H., Pavlovic-Masnicosa, S., et al. (2007). Neurotrophins act as neuroendocrine regulators of skin homeostasis in health and disease. *Hormone and Metabolic Research, 39*, 110–124.

Raap, U., & Kapp, A. (2005). Neuroimmunological findings in allergic skin diseases. *Current Opinion in Allergy and Clinical Immunology, 5*, 419–424.

Shen, J., Abel, E. L., Riggs, P. K., Repass, J., Hensley, S. C., Schroeder, L. J., et al. (2012). Proteomic and pathway analyses reveal a network of inflammatory genes associated with differences in skin tumor promotion susceptibility in DBA/2 and C57BL/6 mice. *Carcinogenesis, 33*, 2208–2219.

Suárez, A. L., Feramisco, J. D., Koo, J., & Steinhoff, M. (2012). Psychoneuroimmunology of psychological stress and atopic dermatitis: Pathophysiologic and therapeutic updates. *Acta Dermato-Venereologica, 92*, 7–15.

Tausk, F., Elenkov, I., & Moynihan, J. (2008). Psychoneuroimmunology. *Dermatology and Therapy, 21*, 22–31.

Uribe-Herranz, M., Lian, L.-H., Hooper, K. M., Milora, K. A., & Jensen, L. E. (2013). IL-1R1 signaling facilitates Munro's microabscess formation in psoriasiform imiquimod-induced skin inflammation. *Journal of Investigative Dermatology, 133*, 1541–1549.

Urpe, M., Buggiani, G., & Lotti, T. (2005). Stress and psychoneuroimmunologic factors in dermatology. *Dermatologic Clinics, 23*, 609–617.

Uto-Konomi, A., Miyauchi, K., Ozaki, N., Motomura, Y., Suzuki, Y., Yoshimura, A., et al. (2012). Dysregulation of suppressor of cytokine signaling 3 in keratinocytes causes skin inflammation mediated by interleukin-20 receptor-related cytokines. *PLoS One, 7*, e40343.

Vanbervliet, B., Akdis, M., Vocanson, M., Rozières, A., Benetière, J., Rouzaire, P., et al. (2011). Histamine receptor H1 signaling on dendritic cells plays a key role in the IFN-γ/IL-17 balance in T cell-mediated skin inflammation. *Journal of Allergy and Clinical Immunology, 127*, 943–953.e1–10.

Walburn, J., Vedhara, K., Hankins, M., Rixon, L., & Weinman, J. (2009). Psychological stress and wound healing in humans: A systematic review and meta-analysis. *Journal of Psychosomatic Research, 67*, 253–271.

Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Yang, E. V., & Eubank, T. D. (2013). The impact of adrenergic signaling in skin cancer progression: Possible repurposing of β-blockers for treatment of skin cancer. *Cancer Biomarkers, 13*, 155–160.

Chapter 13
The Translation of Psychoneuroimmunology into Mind–Body Medicine

13.1 From PNI to Mind–Body Medicine

With the elucidation of the PNI mechanisms of stress, healthcare professionals have been encouraged to promote stress management and translate the PNI discoveries into clinical practice with mind–body approaches (Pearson 2015). PNI studies have provided evidences for the connections between continuous psychological stress and chronic peripheral inflammation (Davies et al. 2015).

The research in PNI has suggested a reciprocal interaction between cognition and body as cognitive incidences may have somatic results with influences on the immune functions and disease development (Webber 2010). On the other hand, such alterations may cause maladaptive cognitive activities. Patients' thought processes and perceived quality of life can have impacts on their somatic and disease activities, while interventions targeting the mind–body level may affect their prognosis.

As discussed in the previous chapters, lifestyle stresses have been linked to the disorders including coronary heart disease, gastrointestinal distress, and cancer (Vitetta et al. 2005). The multidirectional flow of information is involved in the brain–body communication. Such information flow can be carried out by various molecules including hormones, neurotransmitters, and neuropeptides, as well as cytokines.

Conventional medical sciences have separated the mind from the body. Recent development in PNI has provided the evolved knowledge focusing on the interactions between psyche and soma (Mahbub-E-Sobhani et al. 2011). Based on the PNI theories, a "mindbody" coemergence concept has been proposed to represent the links between the internal biological processes and external interpersonal influences (Broom et al. 2012).

Together with systems biology, these concepts differentiate from the dualism of mind and body by integrating the "internal" bodily alterations with the external and environmental changes. The dynamical biopsychosocial models described in the previous chapters embrace such comprehensive concepts with the interpretations in

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4_13

health and diseases at various system levels for the development of systems and dynamical medicine (see Chap. 1).

The interrelationships between behaviors and health support the clinical practice of mind–body medicine by various healthcare professionals including nurses. The development in mind–body techniques in combination with healthier nutrition and lifestyles may contribute to health maintenance, disease prevention, and life span prolongation (Vitetta et al. 2005).

Mind–body techniques that regulate the psychological responses to diseases and surgery have been demonstrated beneficial with better recoveries and higher patient satisfaction rates (Tagge et al. 2013). For example, the talk-therapy interventions may have effects on improving immune parameters and promoting the body's disease-fighting abilities (Littrell 2008).

In summary, PNI provides the scientific groundwork for understanding integrative therapies. Several mechanisms underlying the PNI interventions and mind–body techniques have been proposed, including sensory, cognitive, expressive, and physical (Bauer-Wu 2002). The techniques or interventions can also be combined with clinical practice and pharmaceutical therapies.

As shown in Fig. 13.1, based on the systemic PNI profiles (see Chap. 1), comprehensive mind–body approaches can be taken to achieve the optimal outcomes. These methods include meditation, exercises, lifestyle changes, healthy diet plans

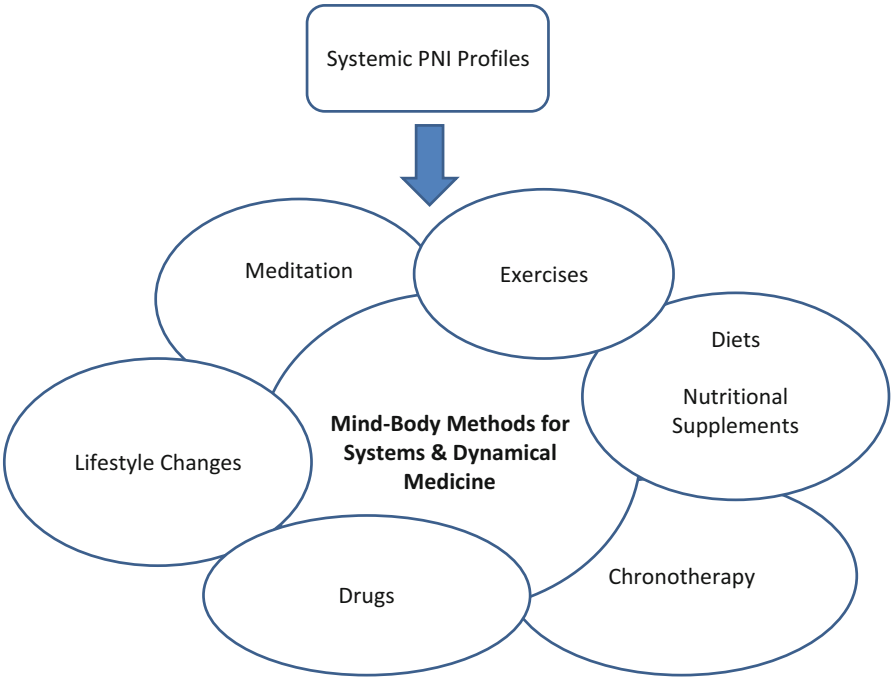

Fig. 13.1 Mind–body methods based on the systemic PNI profiles toward the achievement of systems and dynamical medicine

and nutrition, as well as drugs. The factors of biological rhythms can also be incorporated into these methods toward the practice of systems and dynamical medicine (Yan 2014).

13.2 The PNI Mechanisms of Meditation

In the recent decades, the applications of mind–body medicine such as the techniques in meditation, Tai Chi, Qigong, and yoga have been increasing solidly. As many of these methods may be helpful in relieving symptoms and promoting the quality of life, it is necessary to understand the biomedical mechanisms underlying these therapies, especially their effects on inflammation. Evidences from PNI studies provide the scientific support for the practice and improvement of these approaches.

For example, as a stable intervention with low cost and can be practiced in long term, mindfulness meditation (MfM) has been found promising in promoting health outcomes and the quality of life among veterans (Cuellar 2008). Mindfulness meditation provides a mental training framework for supporting the condition of mindful awareness in the everyday life. It may improve self-reported assessments of disease symptoms.

Mindfulness meditation training has shown the effects of stress reduction among different patient populations (Creswell et al. 2009). It has also been found to have impacts on the inflammatory markers, cell-mediated immunity, as well as biological aging (Black and Slavich 2016).

For example, a recent meta-study analyzed the immune outcomes from the practice of Tai Chi, Qigong, meditation, and Yoga. The study found that 7–16 weeks of mind–body interventions could lead to moderate decrease of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) (Morgan et al. 2014). In addition, higher levels of virus-specific immune responses to vaccination were also observed in some studies.

Another meta-study examined 26 randomized controlled trials about the impacts of mind–body therapies (MBTs) on the inflammatory markers (Bower and Irwin 2016). Reliable results were observed for genomic markers with lower expression of inflammation-associated genes and lower signaling via the proinflammatory transcription factor NF-kB.

With their impacts on the immune system, such mind–body approaches may have certain effects on various diseases. For example, a randomized clinical trial showed that Tai Chi intervention may have effects on the psychosocial parameters among HIV patients at different stages (Robins et al. 2006). Another study measured the effects of mindfulness meditation on the biomarkers of HIV-1 progression (Creswell et al. 2009). The results showed that the meditation training could buffer the decline of $CD4^+$ T lymphocytes among HIV-1-infected patients.

Another study assessed the effects of transcendental meditation (TM), a type of mantra meditation on the immune system including the leukocytes and lymphocytes

subsets (Infante et al. 2014). The results showed that the TM training may lead to higher levels of $CD3^+CD4^-CD8^+$ lymphocytes, B lymphocytes, and natural killer cells, with reductions of $CD3^+CD4^+CD8^-$ lymphocytes. Such findings revealed that the TM training may have significant impacts on the immune cells especially the circulating levels of lymphocyte subsets. The effects may be associated with the influences of TM on the neuroendocrine axis (Infante et al. 2014).

Furthermore, sleep disturbances are common problems among older adults. A randomized clinical trial evaluated the efficacy of mindfulness meditation on sleep quality among older adults with problems of sleep disturbances (Black et al. 2015). The study found that mindful awareness practices (MAPs) led to significant improvements in various aspects, not just sleep quality, but also the symptoms of insomnia, depression, fatigue interference, and fatigue severity.

The training of PsychoNeuroEndocrinoImmunology-based meditation (PNEIMED) is the combination of the teaching of philosophy and practice of Buddhist meditation with a basis in physiology from a systemic and integrative view. A recent study examined the effects of 4-day PNEIMED training (a total of 30 h) on stress among healthy adults (Bottaccioli et al. 2014). The study showed that PNEIMED program resulted in the significant decrease in self-rated distress scores (Bottaccioli et al. 2014). Together with the improvement in psychological well-being, lower levels of cortisol at awakening were also observed with the reduction in both of the amplitude and duration of the cortisol response.

These findings indicate that the meditation-based combination trainings may have immediate effects on decreasing distress symptoms and adrenocortical activities. Such mind–body approaches have been suggested as effective means for the management of stress and anxiety, especially job-associated stressors among health-care professionals (Bottaccioli et al. 2014).

13.3 PNI and Nutrition

13.3.1 Stress, Diets, and Inflammation

PNI mechanisms may provide the connections among emotional well-being, inflammation, chronic diseases, and nutritional status. As discussed in the previous chapters, inflammation may be the common pathway among may chronic diseases. Both diets and behaviors may influence inflammatory conditions (Kiecolt-Glaser 2010).

Specifically, stress can affect food choices and elevate maladaptive metabolic reactions to unhealthy meals. On the other hand, diets may have effects on mood and proinflammatory stress responses. Vagal activities are pivotal in the digestion, absorption, and metabolism of nutrients with significant influences on the metabolic reactions to diets and inflammation (Kiecolt-Glaser 2010). Stress and depression may have negative impacts on the vagal activities and affect the brain–gut interactions. The elucidation of the interactions among stressors, emotions, diets, and

inflammation will contribute to integrative approaches in mind–body medicine including behavioral and nutritional methods.

For instance, chronic low-grade inflammation is a key feature of obesity, which may result in emotional distress and behavioral problems (see Chap. 8). Strong connections have been identified among adiposity, inflammation, and affectivity among those with obese problems (Capuron et al. 2011). On the other hand, surgery-caused weight loss has been related to lower levels of inflammation and adipokines, as well as better emotional status and eating behaviors. Thus, the factors of inflammatory conditions may be crucial to emotional distress and psychological features among obese people.

Among diabetes patients, stress and emotional problems may also affect the quality of life. Type 2 diabetes has been related to altered innate immune functions with higher circulating levels of acute phase reactants, macrophage malfunctions, and chronic inflammation (O'Connor et al. 2006). In macrophages, the disease conditions may elevate proinflammatory responses while reduce anti-inflammatory reactions. These connections and mechanisms require integrative approaches from prevention to treatment.

13.3.2 Nutritional Interventions, Stress Responses, and Anti-inflammatory Effects

Nutritional elements may have deep impacts on the nervous system. Microglial cells and astrocytes are the major components of the innate immune system of the brain. Their activations may defend neurons against infectious agents and lesions. Activated glial cells may generate inflammatory cytokines and lead to neuroinflammation, causing changes in cognition, mood, and behaviors including depression and age-associated neurodegenerative disorders (Layé 2010). Certain nutritional and dietary components may interact with such processes with preventive and therapeutic potentials.

For example, polyunsaturated fatty acids (PUFA) are the key nutrients and components of neuronal and glial cell membranes. Dietary PUFA may influence the generation of prostaglandin and proinflammatory cytokines (Layé 2010). In addition, n-3 fatty acids have anti-inflammatory activities, and n-6 fatty acids are involved in the formation of prostaglandins. Unbalanced ratio of dietary n-6 and n-3 fatty acids has been correlated with neuroinflammation in the brain. Dietary PUFA such as n-3 fatty acids may have important impacts on age-associated neurodegenerative disorders (Layé 2010).

In depression, elevated levels of inflammatory biomarkers have been observed. Proinflammatory cytokines such as IFN-α may cause neuropsychiatric symptoms (Su 2015). The anti-inflammatory pathways may provide novel strategies for antidepressant treatment. For instance, omega-3 PUFAs (or n-3 PUFAs) are anti-inflammatory compounds that have been found helpful for the treatment of

depression in animal studies and clinical trials (Su 2015). The n-3 PUFAs may improve mood and vagal tone, inhibit NF-kB activation and reactions to endotoxin, and regulate the degree of proinflammatory stress responses (Kiecolt-Glaser 2010).

In postpartum depression (PPD), emerging evidences have indicated that PNI mechanisms may provide the linkages between the disorder and deficiencies in micronutrients including n-3 PUFA, B vitamins, vitamin D, and trace minerals such as Zn and Se (Ellsworth-Bowers and Corwin 2012).

Furthermore, poor nutritional habits have been correlated with chronic low-grade inflammation, a feature of aging with negative impacts on health and the quality of life. Studies have found that elderly subjects with poor physical health conditions had decreased circulating levels of vitamin E (alpha-tocopherol) and higher levels of inflammatory biomarkers (Capuron et al. 2009). Poor mental health conditions were also linked to decreased levels of alpha-tocopherol and tryptophan (TRP). These relationships suggest that nutritional status such as vitamin E may be critical for maintaining normal immune functions, mental health, and quality of life in the elderly.

13.4 Mind–Body Interventions for Cardiovascular Diseases

Mind–body interventions may be helpful for various diseases. For example, depression after cardiac surgery (CS) is often seen together with pain and lower sleep quality. Cognitive behavioral therapy (CBT) for depression has been found useful for promoting perceived control with lower levels of pain interference and pain severity among depressed cardiac surgery patients (Doering et al. 2015).

In addition, the practice of Tai Chi (TC) may have effects on biobehavioral factors related to the cardiovascular disease (CVD) risks among women. A recent randomized trial among women indicated that TC may help lower the levels of fatigue and granulocyte colony stimulating factor (Robins et al. 2015).

The study found that TC may help reduce the levels of proinflammatory cytokines related to the CVD risks such as IFN-γ, tumor necrosis factor (TNF), IL-8, and IL-4 (Robins et al. 2015). The TC practice has also been found to promote mindfulness, spiritual thoughts and behaviors, as well as self-compassion. Such findings have demonstrated that mind–body strategies such as TC may be beneficial for lowering CVD risks.

13.5 Mind–Body Interventions for Aging and Associated Disorders

Studies in PNI may contribute to the development and understanding of mind–body medicine by providing better nutrition and lifestyle choices toward health promotion, disease prevention, and healthier aging processes (Vitetta et al. 2005). The way

an individual understands and reacts to the environmental changes may decide stress responses, behaviors, the neuroendocrine and immune functions, as well as health and disease outcomes.

Taking more adaptive ways and more effective coping strategies when facing life challenges may help improve these behaviors, responses, and the overall health (Lutgendorf and Costanzo 2003). For example, the study of a behavioral intervention Tai Chi Chih (TCC) among 36 older adults showed that the 15-week training program resulted in higher varicella-zoster virus (VZV)-specific cell-mediated immunity (CMI) (Irwin et al. 2003). TCC is a movement-based relaxation practice. The older adults who had the most serious impairments of health conditions showed the most significant improvement, confirming the benefits of the behavioral intervention (Irwin et al. 2003).

Aging has been related to elevated sympathetic nervous system activation in association with hypertension and cardiovascular diseases. Studies have found that TCC practice has immediate inhibition effects on the sympathetic activities among older adults (Motivala et al. 2006). Such changes could not be caused by the physical activity alone.

13.6 Incorporating Chronotherapy into Systems and Dynamical Medicine

As discussed in Chaps. 3 and 4, the circadian rhythms are one of the essential properties of the immune and nervous systems. Methods in chronotherapy provide treatment regimens to address such diurnal body rhythms. Studies have confirmed that chronotherapy may promote the efficiency, safety and tolerability of drugs, especially in the diseases with abnormal immune activities (Glass-Marmor et al. 2007).

For example, a study found that following the nighttime therapies for multiple sclerosis, the clinical recovery was remarkably improved with reduced rates of side effects (Glass-Marmor et al. 2007). Most of the patients also reported the preference for nighttime rather than daytime administration of the drugs. Such observations indicate the potential benefits of chronotherapy for immune-associated diseases.

Because of the factors of the environment, lifestyle, and intrinsic "body clocks," circadian rhythms are essential to the variables of physical activities. Such features need to be incorporated into the practice of mind–body medicine. For instance, during physical exercise, the rhythms may have certain roles that special care is needed at certain time points of the day (Reilly et al. 2006).

These time points include those soon after waking (such as in the early morning) with higher risks of cardiovascular morbidity and possible spine damages (Reilly et al. 2006). In addition, the time points of late in the day are often associated with higher risks of respiratory difficulties.

Such factors need to be considered for planning physical exercises, especially at night and upon time-zone transitions. Based on the chronobiology mechanisms,

physical activity programs have been recommended to be taken during the middle of the waking day rather than immediately after waking up from a sleep or nap (Reilly et al. 2006).

Furthermore, lifestyle changes may help improve the circadian functions in the practice of various mind–body approaches including healthier dietary plans, physical activities, and meditation (see Fig. 13.1). Diets with anti-inflammatory ingredients can be taken at regular meal times to promote the normal circadian cycles. Appropriate daytime physical exercise and morning light exposure may also help entrain melatonin rhythms and improve sleep quality (Block et al. 2009). In addition, meditation may relieve anxiety and depressive symptoms associated with sleep disturbance.

As summarized in Fig. 13.1, comprehensive mind–body strategies can be designed and applied based on the systemic PNI profiles (see Chap. 1). These approaches include meditation, exercises, healthy dietary plans, nutritional supplements, lifestyle changes, drugs, and chronotherapy. Integrative methodologies incorporating dynamical networks and feedbacks would promote the overall well-being in the psychophysiological, social, and environmental dimensions toward the achievement of systems and dynamical medicine (Yan 2014; also see Chap. 1).

References

Bauer-Wu, S. M. (2002). Psychoneuroimmunology. Part II: Mind-body interventions. *Clinical Journal of Oncology Nursing, 6*, 243–246.

Black, D. S., O'Reilly, G. A., Olmstead, R., Breen, E. C., & Irwin, M. R. (2015). Mindfulness meditation and improvement in sleep quality and daytime impairment among older adults with sleep disturbances: A randomized clinical trial. *JAMA Internal Medicine, 175*, 494–501.

Black, D. S., & Slavich, G. M. (2016). Mindfulness meditation and the immune system: A systematic review of randomized controlled trials. *Annals of the New York Academy of Sciences, 1373*(1), 13–24.

Block, K. I., Block, P. B., Fox, S. R., Birris, J. S., Feng, A. Y., de la Torre, M., et al. (2009). Making circadian cancer therapy practical. *Integrative Cancer Therapies, 8*, 371–386.

Bottaccioli, F., Carosella, A., Cardone, R., Mambelli, M., Cemin, M., D'Errico, M. M., et al. (2014). Brief training of psychoneuroendocrinoimmunology-based meditation (PNEIMED) reduces stress symptom ratings and improves control on salivary cortisol secretion under basal and stimulated conditions. *Explore (NY), 10*, 170–179.

Bower, J. E., & Irwin, M. R. (2016). Mind-body therapies and control of inflammatory biology: A descriptive review. *Brain, Behavior, and Immunity, 51*, 1–11.

Broom, B. C., Booth, R. J., & Schubert, C. (2012). Symbolic diseases and "mindbody" co-emergence. A challenge for psychoneuroimmunology. *Explore (NY), 8*, 16–25.

Capuron, L., Moranis, A., Combe, N., Cousson-Gélie, F., Fuchs, D., De Smedt-Peyrusse, V., et al. (2009). Vitamin E status and quality of life in the elderly: Influence of inflammatory processes. *British Journal of Nutrition, 102*, 1390–1394.

Capuron, L., Poitou, C., Machaux-Tholliez, D., Frochot, V., Bouillot, J.-L., Basdevant, A., et al. (2011). Relationship between adiposity, emotional status and eating behaviour in obese women: Role of inflammation. *Psychological Medicine, 41*, 1517–1528.

Creswell, J. D., Myers, H. F., Cole, S. W., & Irwin, M. R. (2009). Mindfulness meditation training effects on CD4+ T lymphocytes in HIV-1 infected adults: A small randomized controlled trial. *Brain, Behavior, and Immunity, 23*, 184–188.

Cuellar, N. G. (2008). Mindfulness meditation for veterans—Implications for occupational health providers. *AAOHN Journal, 56*, 357–363.
Davies, C., Redmond, C., Toole, S. O., & Coughlan, B. (2015). Has bioscience reconciled mind and body? *Journal of Clinical Nursing*, doi:10.1111/jocn.12979.
Doering, L. V., McGuire, A., Eastwood, J.-A., Chen, B., Bodán, R. C., Czer, L. S., et al. (2015). Cognitive behavioral therapy for depression improves pain and perceived control in cardiac surgery patients. *European Journal of Cardiovascular Nursing*, doi:10.1177/1474515115592292.
Ellsworth-Bowers, E. R., & Corwin, E. J. (2012). Nutrition and the psychoneuroimmunology of postpartum depression. *Nutrition Research Reviews, 25*, 180–192.
Glass-Marmor, L., Paperna, T., Ben-Yosef, Y., & Miller, A. (2007). Chronotherapy using corticosteroids for multiple sclerosis relapses. *Journal of Neurology, Neurosurgery, and Psychiatry, 78*, 886–888.
Infante, J. R., Peran, F., Rayo, J. I., Serrano, J., Domínguez, M. L., Garcia, L., et al. (2014). Levels of immune cells in transcendental meditation practitioners. *International Journal of Yoga, 7*, 147–151.
Irwin, M. R., Pike, J. L., Cole, J. C., & Oxman, M. N. (2003). Effects of a behavioral intervention, Tai Chi Chih, on varicella-zoster virus specific immunity and health functioning in older adults. *Psychosomatic Medicine, 65*, 824–830.
Kiecolt-Glaser, J. K. (2010). Stress, food, and inflammation: Psychoneuroimmunology and nutrition at the cutting edge. *Psychosomatic Medicine, 72*, 365–369.
Layé, S. (2010). Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins, Leukotrienes, and Essential Fatty Acids, 82*, 295–303.
Littrell, J. (2008). The mind-body connection: Not just a theory anymore. *Social Work in Health Care, 46*, 17–37.
Lutgendorf, S. K., & Costanzo, E. S. (2003). Psychoneuroimmunology and health psychology: An integrative model. *Brain, Behavior, and Immunity, 17*, 225–232.
Mahbub-E-Sobhani, Haque, N., Salma, U., & Ahmed, A. (2011). Immune modulation in response to stress and relaxation. *Pakistan Journal of Biological Sciences, 14*, 363–374.
Morgan, N., Irwin, M. R., Chung, M., & Wang, C. (2014). The effects of mind-body therapies on the immune system: Meta-analysis. *PLoS One, 9*, e100903.
Motivala, S. J., Sollers, J., Thayer, J., & Irwin, M. R. (2006). Tai Chi Chih acutely decreases sympathetic nervous system activity in older adults. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 61*, 1177–1180.
O'Connor, J. C., Johnson, D. R., & Freund, G. G. (2006). Psychoneuroimmune implications of type 2 diabetes. *Neurologic Clinics, 24*, 539–559.
Pearson, T. (2015). Stopping the tsunami of stress in primary care. *The Nurse Practitioner, 40*, 1–6.
Reilly, T., Atkinson, G., Gregson, W., Drust, B., Forsyth, J., Edwards, B., et al. (2006). Some chronobiological considerations related to physical exercise. *Clinical Therapeutics, 157*, 249–264.
Robins, J. L., Elswick, R. K., Sturgill, J., & McCain, N. L. (2015). The effects of Tai Chi on cardiovascular risk in women. *American Journal of Health Promotion*, doi:10.4278/ajhp.140618-QUAN-287.
Robins, J. L. W., McCain, N. L., Gray, D. P., Elswick, R. K., Walter, J. M., & McDade, E. (2006). Research on psychoneuroimmunology: Tai chi as a stress management approach for individuals with HIV disease. *Applied Nursing Research, 19*, 2–9.
Su, K.-P. (2015). Nutrition, psychoneuroimmunology and depression: The therapeutic implications of omega-3 fatty acids in interferon-α-induced depression. *Biomedicine (Taipei), 5*, 21.
Tagge, E. P., Natali, E. L., Lima, E., Leek, D., Neece, C. L., & Randall, K. F. (2013). Psychoneuroimmunology and the pediatric surgeon. *Seminars in Pediatric Surgery, 22*, 144–148.
Vitetta, L., Anton, B., Cortizo, F., & Sali, A. (2005). Mind-body medicine: Stress and its impact on overall health and longevity. *Annals of the New York Academy of Sciences, 1057*, 492–505.
Webber, M. A. (2010). Psychoneuroimmunological outcomes and quality of life. *Transfusion and Apheresis Science, 42*, 157–161.
Yan, Q. (2014). From pharmacogenomics and systems biology to personalized care: A framework of systems and dynamical medicine. *Methods in Molecular Biology, 1175*, 3–17.

Index

Q. Yan, *Psychoneuroimmunology*, DOI 10.1007/978-3-319-45111-4

D