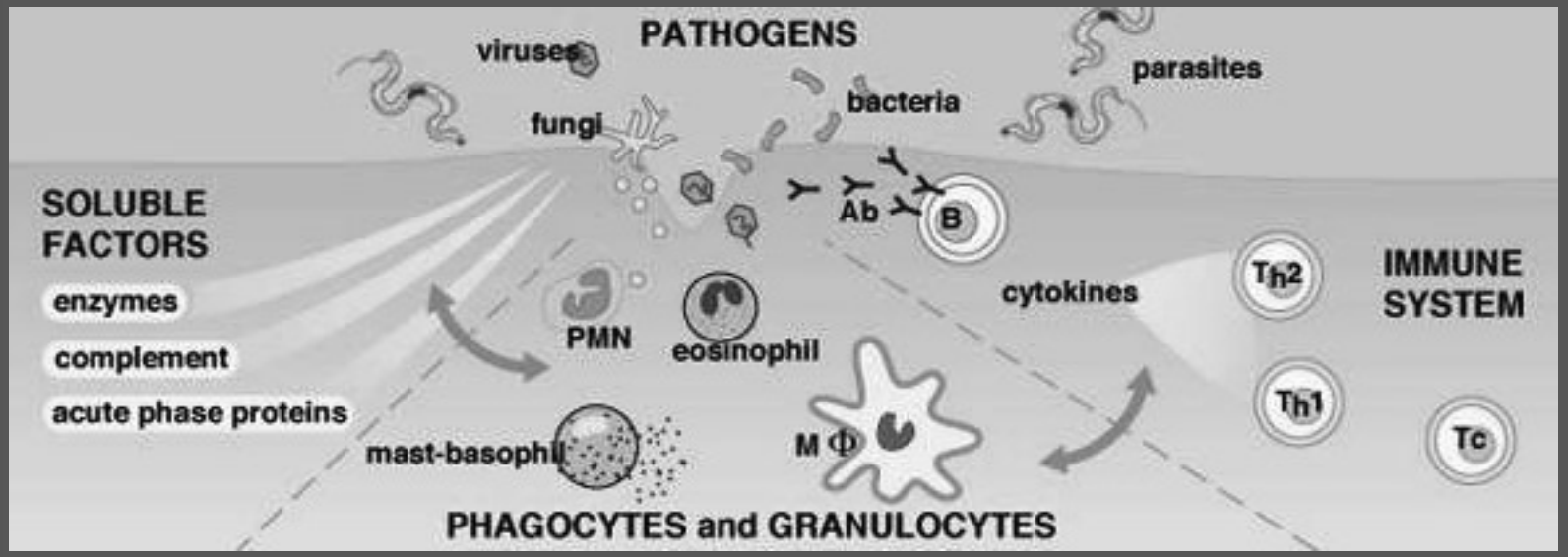
The Immune Response to Infectious Disease

The Immune System

- The principal function of the immune system is to protect the host against pathogenic microbes.
- Immunity may be innate or specific.



Pathogens & Disease

- Pathogens are defined as microbes capable of causing host damage.
- When host damage reaches a certain threshold, it can manifest itself as a disease.
  - The evolution of an infectious disease in an individual involves complex interactions between the pathogen and the host.

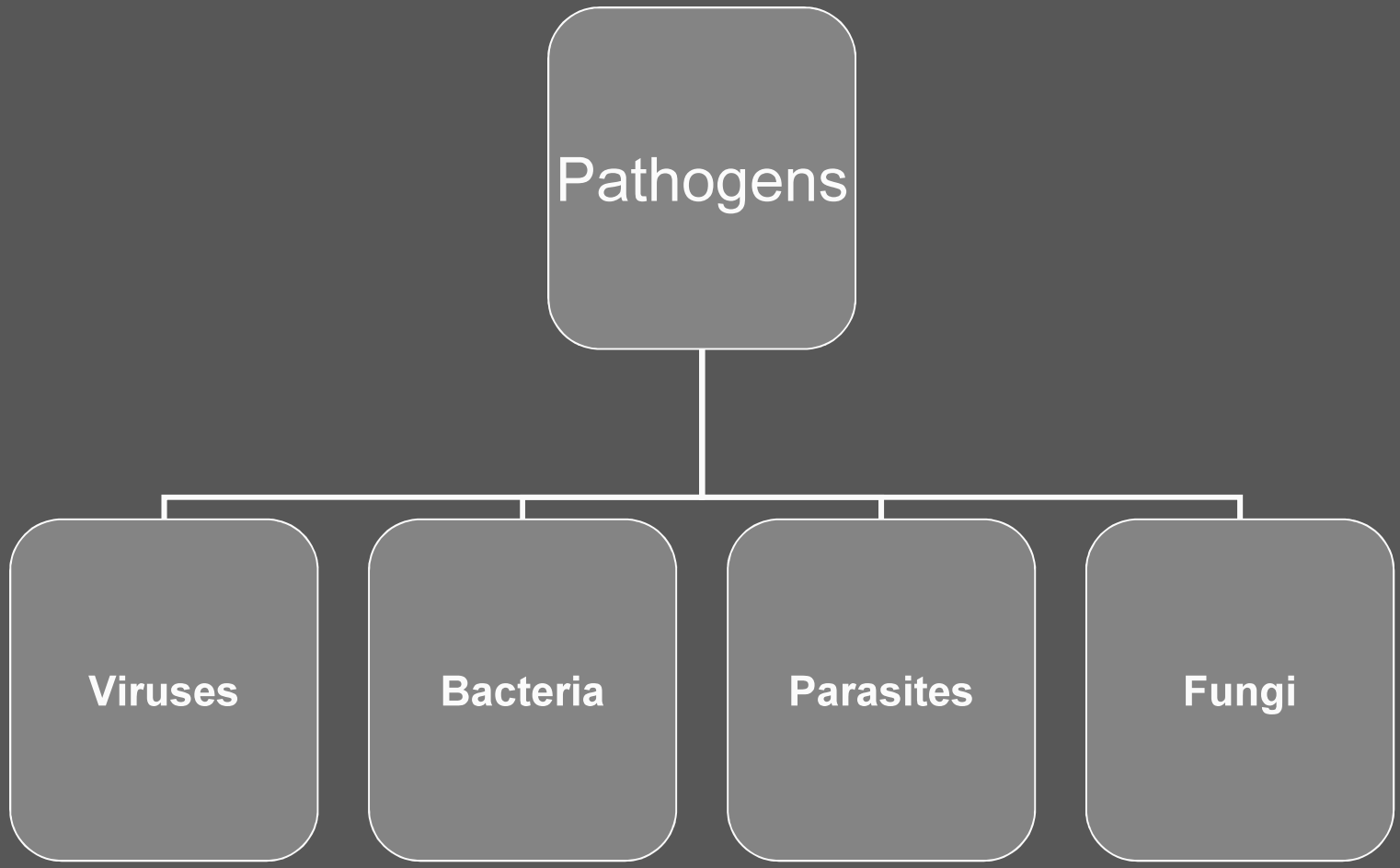
Important General Features of Immunity to Pathogens.

- *Defense against pathogens is mediated by both innate and specific immunity.*
- *The innate immune response to pathogens plays an important role in determining the nature of the specific immune response.*
- *The immune response is capable of responding in distinct and specialized ways to different pathogens in order to combat these infectious agents most effectively.*

- *The survival and pathogenicity of pathogens in a host are critically influenced by their ability to evade or resist protective immunity.*

- *Tissue injury and disease consequent to infections may be caused by the host response to the pathogen and its products rather than the pathogen itself.*

Agents That Cause Disease.



Viruses

- Obligatory intercellular pathogens that replicate within cells.
- Use the nucleic acid and protein synthetic machineries of the host cell.
- Infect a variety of cell populations by utilizing normal cell surface molecules as receptors to enter cell.

1)Host defenses against viral infection aim to first slow viral replication and then eradicate infection.

Innate Immune Response to Viruses

- Viral infection directly stimulates the production of interferons (INF).
  - Interferons are antiviral proteins, or glycoproteins produced by several types of cells in response to viral infection.
    - INFα by leucocytes
    - INFβ by fibroblast

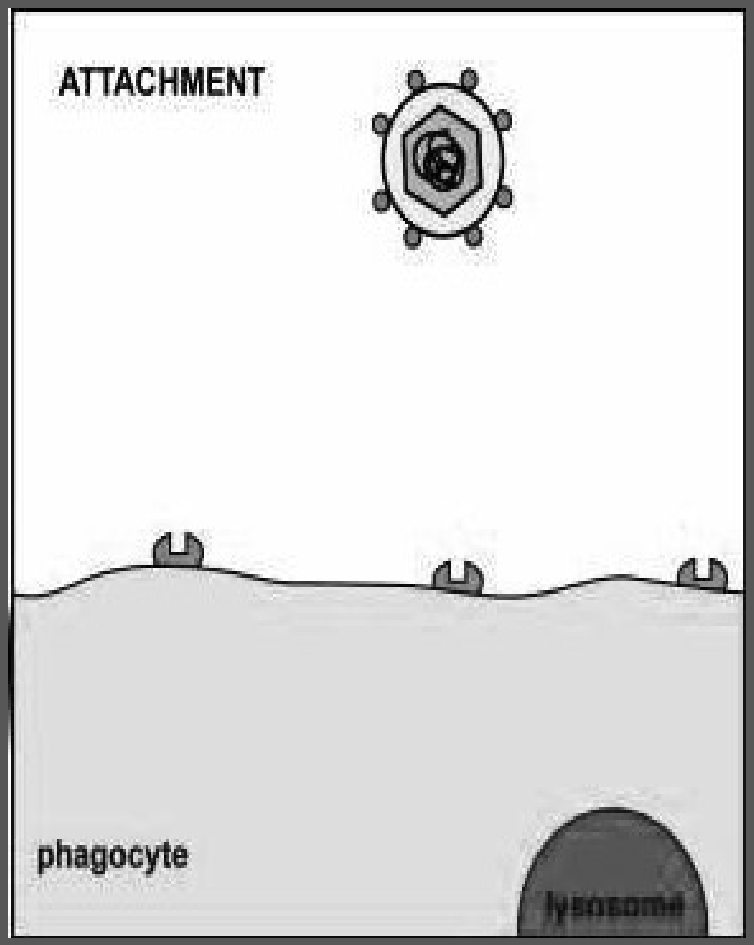
    → Activate gene that interfere with viral replication
    → Activate MHC-I
    → Activate NK-cell

    - INFγ by natural killers (NK) cells
- Natural killer (NK) cells →
  - lyse a wide variety of virally infected cells.
  - Principal mechanism before Ab production

Specific Immune Response to Viruses

- Mediated by a combination of humoral and cell mediated immune mechanisms.
  - Humoral mediated immune response.
    - Antibodies specific for viral surface antigens are often crucial in containing the spread of a virus during acute infection and in protecting against re-infection.
    - *Specific antibodies are important* in defense against viruses early in the course of infection and in defense against cytopathic viruses that are liberated from lysed infected cells.

Opsonization

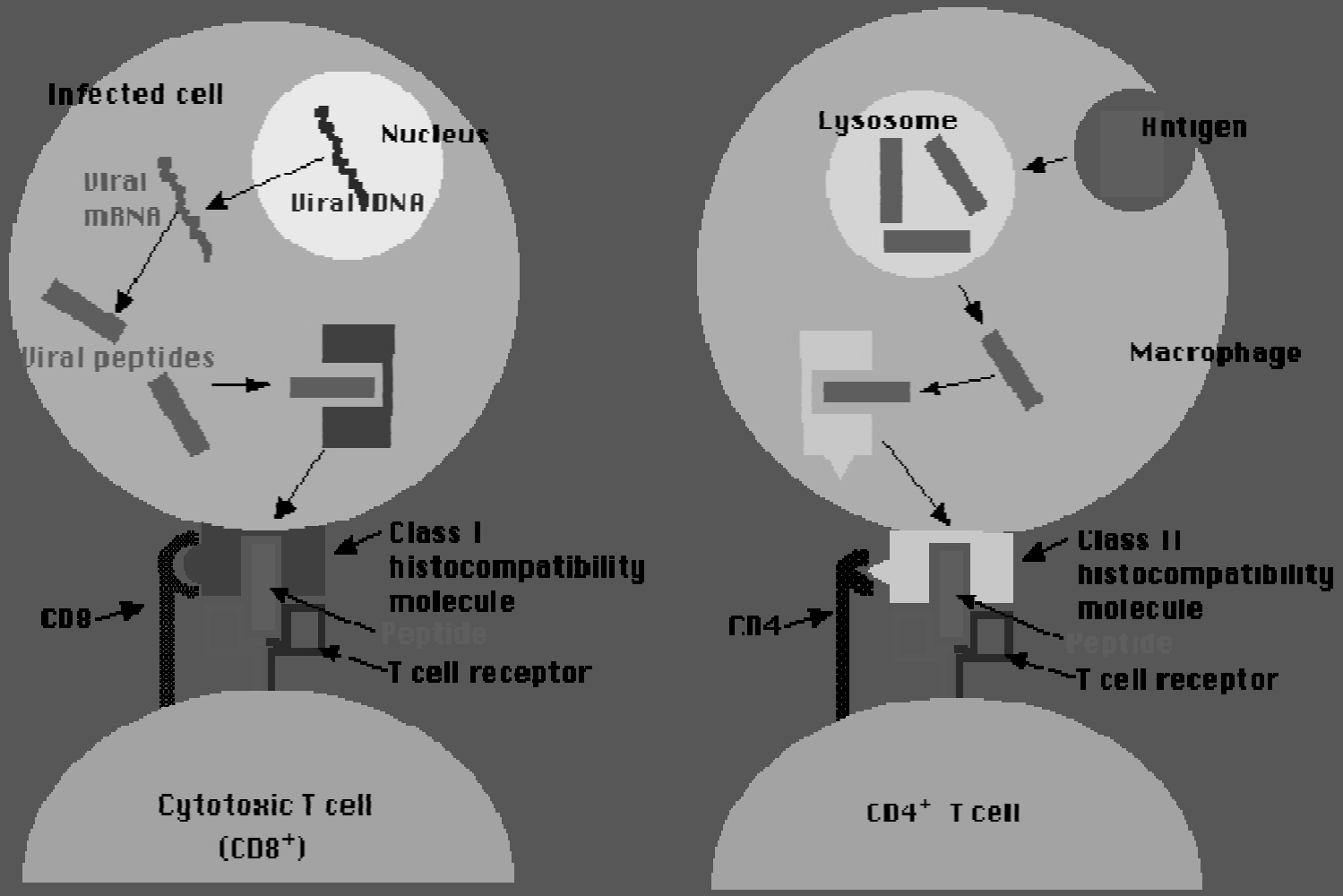


1. Opsonizing antibodies may enhance phagocytic clearance of viral particles.

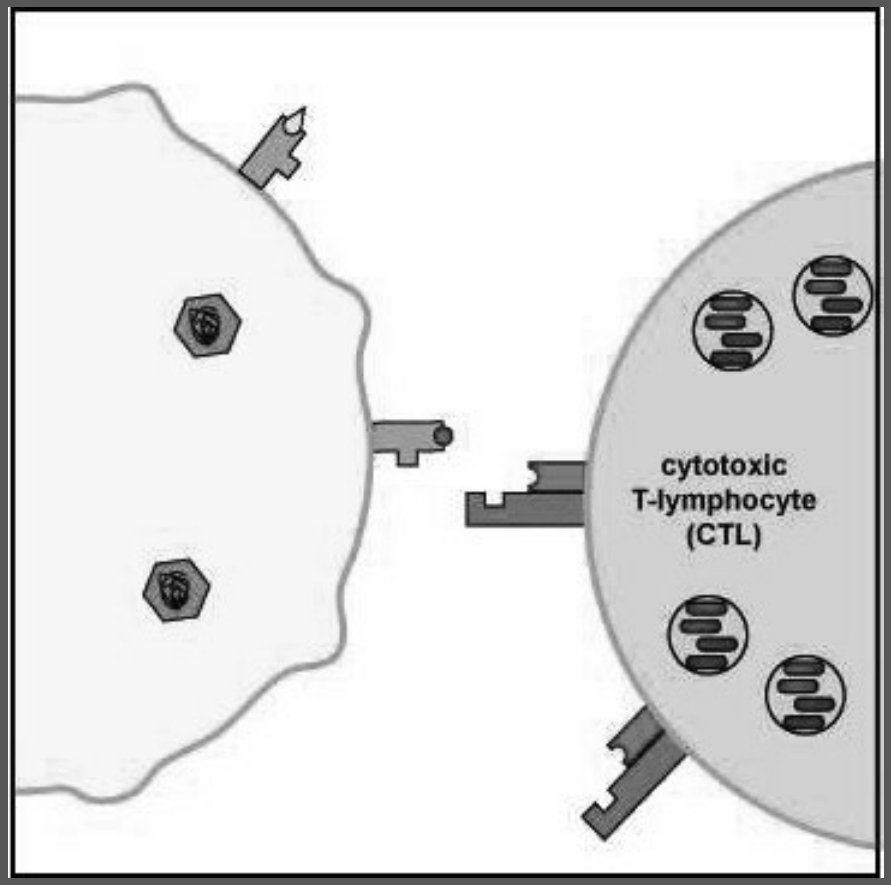
Specific Immune Response to Viruses

- Cell-mediated immune responses.
  - Most important in host defense, once a viral infection is established.
  - $CD8^+$ T_c cells (Cytotoxic T lymphocytes; CTLs) and $CD4^+$ t_h1 cells (helper T lymphocytes) are the main components of cell mediated antiviral defense.

CD8+ T and CD4+ T



CTL activating macrophage function



Tissue Injury

- In some cases, infections with non-cytopathic viruses, CTLs may be responsible for tissue damage to the host.

Evasion of Immune Mechanisms by Viruses

- Viruses have evolved numerous mechanisms for evading host immunity.

- A number of viruses have strategies to evade complement-mediated destruction.

Evasion of Immune Mechanisms by Viruses

- Viruses can also escape immune attack by changing their antigens.
- A large number of viruses evade the immune response by causing generalized immunosuppression.

Bacteria

- Immunity to bacterial infection is achieved by means of antibody unless the bacteria are capable of intracellular growth.

- Two types of bacteria infection.
  - Extracellular.
  - Intracellular.

Extracellular Bacteria

- Extracellular bacteria are capable of replicating outside of the host cells.
- They cause disease by two principle mechanisms.
  - They induce inflammation.
  - Many of these bacteria produce toxins.
    - Endotoxins.
    - Exotoxins.
- The immune responses against extracellular bacteria are aimed at eliminating the bacteria and at neutralizing the effects of their toxins.

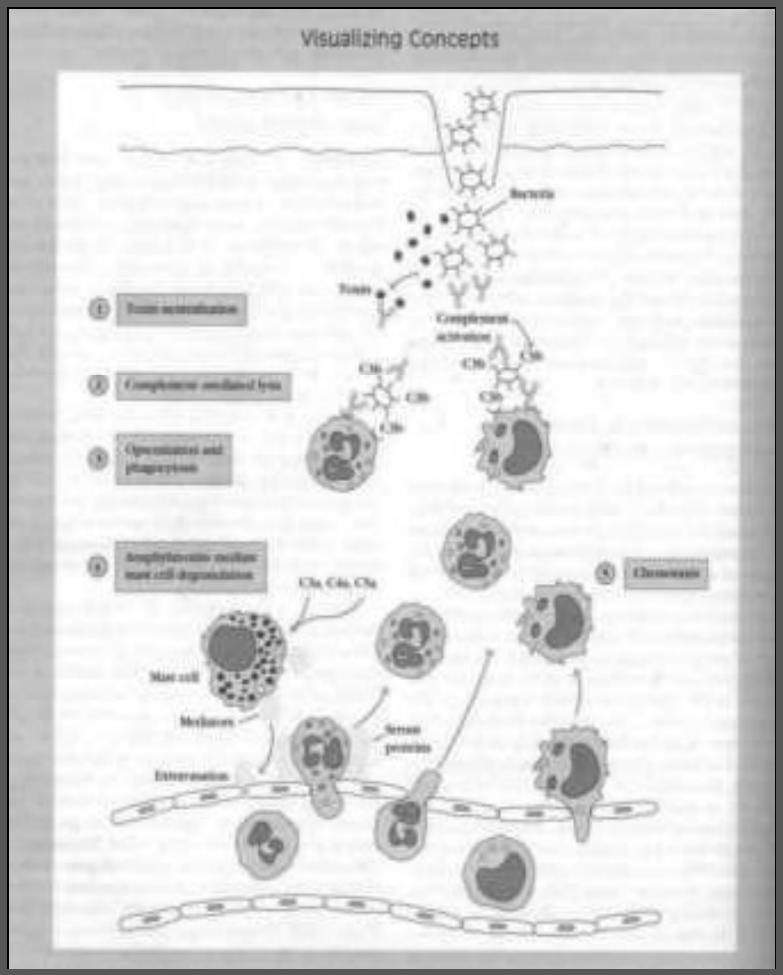
Innate Immunity Extracellular Bacteria

- Phagocytosis by neutrophils, monocytes, and the tissue macrophages.
- Activation of the compliment system, in the absence of antibody.

Specific Immunity Extracellular Bacteria

- Humoral immunity is the principle specific immune response against extracellular bacteria.
  - Strong IgM responses are caused by polysaccharides.
  - Antibodies IgM and IgG against bacteria surface antigens and toxins stimulate three types of effector mechanisms:

Three Types of Effector Mechanisms:



- 1. IgG antibodies opsonize bacteria and enhance phagocytosis.
- 2. Antibodies neutralize bacterial toxins.
- 3. IgM and IgG antibodies activate the complement system.

Tissue Injury

- Principal injuries of host responses to extracellular bacteria are:
  - Inflammation
  - Septic shock
    - cytokine-induced

Evasion of Immune Mechanisms by Extracellular Bacteria

- Genetic variation of the surface antigen is one of the mechanisms used by bacteria to evade specific immunity.
  - The capsule of many gram-negative and gram positive bacteria contain one or more sialic acid residues that inhibit complement activation by the alternative pathway

Intracellular Bacteria

- Intercellular bacteria have the ability to survive and even replicate within phagocytes where they are inaccessible to circulating antibodies.
  - Elimination of intracellular bacteria requires immune responses that are very different from the responses against extracellular bacteria.

Innate Immunity Intracellular Bacteria

- During the innate immune response to intracellular bacteria phagocytes ingest and attempt to destroy.
  - Intracellular bacteria are resistant to degradation within phagocytes.
  - Intracellular bacteria also activate NK cells, either directly or by stimulating macrophages production of IL-12, a powerful NK cell – activating cytokine.

Specific Immunity to Intracellular Bacteria

- Cell-mediated immune response is the major specific immune response against intracellular bacteria.
  - . There are two types of cell-mediated reactions:
    - Killing of phagocytosed intracellular bacteria as a result of macrophage activation by T cell – derived cytokines, particularly IFN-y.
    - Lysis of infected cells by CTLs.

Tissue Injury

- Tissue damage can be caused by macrophage activation that occurs in response to intracellular bacteria.
  - The macrophages accumulate and result in the formation of a granuloma.

Evasion of Immune Mechanisms by Intracellular Bacteria

- Intracellular bacteria's ability to resist elimination by phagocytes is an important mechanism for survival in evasion of the immune response.
  - Some intracellular bacteria do this by:
    - inhibiting phagolysosome fusion.
    - while others produce hemolysin that blocks bacterial killing in macrophages.

Fungi

- Fungal infections are eukaryotes that tend to cause serious infections primarily in individuals with impaired immunity

Innate Immunity Fungi

- The principal mediator of innate immunity against fungi is the neutrophils.
  - Neutrophils liberate fungicidal substances, such as reactive oxygen species and lysosome enzymes.
  - They also phagocytose fungi for intracellular killing.

Specific Immunity to Fungi

- Cell-mediated specific immunity is the major defense against fungal infections.
  - Fungi that are present intercellularly in macrophages are eliminated by the same cellular mechanisms that are effective against intracellular bacteria.

Evasion of Immune Mechanisms by Fungi

- Since individuals with healthy immune systems are not susceptible to opportunistic fungal infections, very little is know about the ability of fungi to evade host immunity

Parasites

- In infectious disease terminology, “ parasitic infection” refers to infection with animal parasites, such as protozoa, helminthes, and ectoparasites.
  - Humans are only part of the complex life cycle of parasites.

Innate Immunity Parasites

- Protozoa and helminthic parasites that enter the blood stream or tissue are often able to survive and replicate because they are resistant to host innate immune responses.
  - Parasites in humane host are usually resistant to complement.
  - Macrophages can phagocytose protozoa, but the tegument of helminthic parasites makes them resistant to the cytocidal effects of both neutrophils and macrophages.

Specific Immunity to Parasites

- Different parasites elicit quite distinct specific immune responses.
  - Cell-mediated immunity is the principal defense against protozoa that survive within macrophages.
  - Protozoa that replicate inside cells and lyse host cells stimulate specific CTL responses, similar to cytopathic viruses.
  - IgE antibodies and eosinophils mediate defense against many helminthic infections.

Tissue Injury

- Tissue injury can be caused when parasites deposited in the liver stimulate CD4+ T cell.
  - Cause macrophages to activate and induce DTH reactions.
  - Resulting in the formation of granulomas.

Evasion of Immune Mechanisms by Parasites

- Evolutionary adaptations give parasites their ability to evade and resist immune responses.
  - Some parasites survive and replicate inside cells.
  - Others develop cysts that are resistant to immune responses.
  - Antigen masking is an effective form of immune response evasion by some parasites.
  - Parasites can develop a tegument that is resistant to damage by antibodies and complement or CTLs.

Evasion of Immune Mechanisms by Parasites

- Some parasites have mechanisms for surface antigen variation.
  - There are two forms of antigenic variation:
    - Stage specific
    - Continuous variation of major surface antigens.

Conclusion

The immune responses to infectious disease are an efficient and effective mechanism against the bombardment of pathogens we face everyday.