

# Immune Response to Infectious Diseases

## ❖ Viral infection

A number of specific immune effector mechanisms, together with nonspecific defense mechanisms, are called into play to eliminate an infecting virus:

### 1. Innate immunity:

- The innate immune response to viral infection is primarily through the induction of **type I interferons (IFN- $\alpha$  and IFN- $\beta$ )** and the activation of **NK cells**.
- Double stranded RNA (dsRNA) produced during the viral life cycle can induce the expression of IFN- $\alpha$  and IFN- $\beta$  by the infected cell.
- Macrophages, monocytes, and fibroblasts also are capable of synthesizing these cytokines.
- IFN- $\alpha$  and IFN- $\beta$  can induce an antiviral response or resistance to viral replication by binding to the IFN  $\alpha/\beta$  receptor.
- Once bound, IFN- $\alpha$  and IFN- $\beta$  activate the JAK-STAT (transduction pathway), which in turn induces the transcription of several genes.
- One of these genes encodes an enzyme known as 2-5-oligo-adenylate synthetase, which activates a ribonuclease (RNase L) that degrades viral RNA.
- IFN- $\alpha/\beta$  binding induces a specific protein kinase called dsRNA-dependent protein kinase (PKR), which inactivates protein synthesis, thus blocking viral replication in infected cells.
- The binding of IFN- $\alpha$  and IFN- $\beta$  to NK cells induces lytic activity, making them very effective in killing virally infected cells. The activity of NK cells is also greatly enhanced by IL-12, a cytokine that is produced very early in a response to viral infection.

### 2. Antibodies can neutralize viruses

- Antibodies specific for viral surface antigens are often crucial in containing the spread of a virus during acute infection and in protecting against reinfection.
- Antibodies are particularly effective in protecting against infection if they are localized at the site of viral entry into the body.
- Most viruses express surface receptor molecules that enable them to initiate infection by binding to specific host-cell membrane molecules.
- If antibody to the viral receptor is produced, it can block infection altogether by preventing the binding of viral particles to host cells.
- Secretory IgA in mucous secretions plays an important role in host defense against viruses by blocking viral attachment to mucosal epithelial cells.

### 3. Cell mediated immunity in viral infections

- if the virus is capable of entering a latent state in which its DNA is integrated into host chromosomal DNA. Once an infection is established, cell-mediated immune mechanisms are most important in host defense.
- CD8<sup>+</sup> TC cells and CD4<sup>+</sup> TH1 cells are the main components of cell-mediated antiviral defense.
- Activated TH1 cells produce a number of cytokines, including IL-2, IFN- $\gamma$ , and TNF, that defend against viruses either directly or indirectly.
- IFN- $\gamma$  acts directly by inducing an antiviral state in cells. IL-2 acts indirectly by assisting in the recruitment of CTL precursors into an effector population.
- Both IL-2 and IFN- $\gamma$  activate NK cells, which play an important role in host defense during the first days of many viral infections until a specific CTL response develops.
- In most viral infections, specific CTL activity arises within 3–4 days after infection, peaks by 7–10 days, and then declines. Within 7–10 days of primary infection, most virions have been eliminated, paralleling the development of CTLs

### Viruses Can Evade Host Defense Mechanisms:

- some viruses have developed strategies to evade the action of IFN- $\alpha/\beta$ .
- These include hepatitis C virus, which has been shown to overcome the antiviral effect of the interferons by blocking or inhibiting the action of PKR (protein kinase).
- Inhibition of antigen presentation by infected host cells.
- down-regulate class I MHC expression shortly after infection.
- Reduce levels of class II MHC molecules on the cell surface, thus blocking the function of antigen-specific antiviral helper T cells.
- A number of viruses have strategies for evading complement-mediated destruction. Vaccinia virus, for example, secretes a protein that binds to the C4b complement component, inhibiting the classical complement pathway; and herpes simplex viruses have a glycoprotein component that binds to the C3b complement component, inhibiting both the classical and alternative pathways.
- A number of viruses escape immune attack by constantly changing their antigens. In the influenza virus, continual antigenic variation results in the frequent emergence of new infectious strains.
- A large number of viruses evade the immune response by causing generalized immunosuppression.
- Cytokines homologous ; EBV produce protein like IL-10 suppresses cytokine production by the TH1 subset, resulting in decreased levels of IL-2, TNF, and IFN- $\gamma$ .

## Bacterial Infections

- Immunity to bacterial infections is achieved by means of antibody unless the bacterium is capable of intracellular growth in which case delayed-type hypersensitivity has an important role.
- Depending on the number of organisms entering and their virulence, different levels of host defense are enlisted. If the inoculum size and the virulence are both low, then localized tissue phagocytes may be able to eliminate the bacteria with an innate, nonspecific defense. Larger inoculums or organisms with greater virulence tend to induce an adaptive, specific immune response.
- The humoral immune response is the main protective response against extracellular bacteria. The antibodies act in several ways to protect the host from the invading organisms, including removal of the bacteria and inactivation of bacterial toxins
- Antibody that binds to accessible antigens on the surface of a bacterium can, together with the C3b component of complement, act as an opsonin that increases phagocytosis and thus clearance of the bacterium
- intracellular bacteria can activate NK cells, which, in turn, provide an early defense against these bacteria.
- Intracellular bacterial infections tend to induce a cell-mediated immune response, specifically, delayed type hypersensitivity. In this response, cytokines secreted by CD4+ T cells are important—notably IFN- $\gamma$ , which activates macrophages to kill ingested pathogens more effectively.

## Bacteria Can Effectively Evade Host Defense Mechanisms

There are four primary steps in bacterial infection:

- \_ Attachment to host cells
- \_ Proliferation
- \_ Invasion of host tissue
- \_ Toxin-induced damage to host cells

Host-defense mechanisms act at each of these steps, and many bacteria have evolved ways to circumvent some of these host defenses

- A number of gram-negative bacteria, for instance, have pili (long hairlike projections), which enable them to attach to the membrane of the intestinal or genitourinary tract
- Secretory IgA antibodies specific for such bacterial structures can block bacterial attachment to mucosal epithelial cells and are the main host defense against bacterial attachment.
- some bacteria (e.g., *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) evade the IgA response by secreting proteases that cleave secretory IgA at the hinge region; the resulting Fab and Fc fragments have a shortened half-life in mucous secretions and are not able to agglutinate microorganisms.

- Some bacteria evade the IgA response of the host by changing these surface antigens. In *N. gonorrhoeae*, for example, pilin, the protein component of the pili, has a highly variable structure.
- Some bacteria possess surface structures that serve to inhibit phagocytosis. *Streptococcus pneumoniae*, whose polysaccharide capsule prevents phagocytosis very effectively.
- On other bacteria, such as *Streptococcus pyogenes*, a surface protein projection called the M protein inhibits phagocytosis.
- Some pathogenic staphylococci are able to assemble a protective coat from host proteins.
- These bacteria secrete a coagulase enzyme that precipitates a fibrin coat around them, shielding them from phagocytic cells.
- Mechanisms for interfering with the complement system help other bacteria survive.
- In some gram-negative bacteria, for example, long side chains on the lipid A moiety of the cell-wall core polysaccharide help to resist complement mediated lysis.
- *Pseudomonas* secretes an enzyme, elastase, that inactivates both the C3a and C5a anaphylatoxins, thereby diminishing the localized inflammatory reaction.
- A number of bacteria escape host defense mechanisms by their ability to survive within phagocytic cells.
- Some, such as *Listeria monocytogenes*, do this by escaping from the phagolysosome to the cytoplasm, which is a more favorable environment for their growth.
- Other bacteria, such as *Mycobacterium avium*, block lysosomal fusion with the phagolysosome; and some mycobacteria are resistant to the oxidative attack that takes place within the phagolysosome.

## Parasitic infections

Many protozoans have life-cycle stages in which they are free within the bloodstream, and it is during these stages that humoral antibody is most effective. Many of these same pathogens are also capable of intracellular growth; during these stages, cell-mediated immune reactions are effective in host defense

- As in plasmodium infection antibodies against sporozoites and merozoite will produced.
- A number of factors may contribute to the low levels of immune responsiveness to *Plasmodium*. The maturational changes from sporozoite to merozoite to gametocyte allow the organism to keep changing its surface molecules, resulting in continual changes in the antigens seen by the immune system.

- The intracellular phases of the life cycle in liver cells and erythrocytes also reduce the degree of immune activation generated by the pathogen and allow the organism to multiply while it is shielded from attack.
- the sporozoite, circulates in the blood for only about 30 min before it infects liver hepatocytes; it is unlikely that much immune activation can occur in such a short period of time.
- an effective humoral antibody response develops to the glycoprotein coat, called variant surface glycoprotein (VSG), that covers the trypanosomal surface.
- These antibodies eliminate most of the parasites from the bloodstream, both by complement-mediated lysis and by opsonization and subsequent phagocytosis.
- Several unusual genetic processes generate the extensive variation in trypanosomal VSG that enables the organism to escape immunologic clearance.
- *Leishmania* is a protozoan that lives in the phagosomes of macrophages.
- Resistance to the infection correlates well with the production of IFN- $\gamma$  and the development of a TH1 response.
- highly susceptible to *Leishmania*-induced fatality if they lose either IFN- $\gamma$  or the IFN- $\gamma$  receptor.
- Parasitic worms are responsible for a wide variety of diseases in both humans and animals.
- the symptoms of schistosomiasis are initiated by the eggs.
- As many as half of the eggs produced remain in the host, where they invade the intestinal wall, liver, or bladder and cause hemorrhage. A chronic state can then develop in which the adult worms persist and the unexcreted eggs induce cell-mediated delayed-type hypersensitive reactions, resulting in large granulomas that are gradually walled off by fibrous tissue.
- The schistosomules would appear to be the forms most susceptible to attack, but because they are motile, they can evade the localized cellular buildup of immune and inflammatory cells.
- Adult schistosome worms also have several unique mechanisms that protect them from immune defenses. The adult worm has been shown to decrease the expression of antigens on its outer membrane and also to enclose itself in a glycolipid and glycoprotein coat derived from the host, masking the presence of its own antigens.
- The humoral response to infection with worms is characterized by high titers of IgE antibodies, localized increases in mast cells and their subsequent degranulation, and increased numbers of eosinophils cytokines produced by a TH2-like subset are important for the immune response: IL-4, which induces B cells to classswitch to IgE production; IL-5, which induces bone-marrow precursors to differentiate into eosinophils; and IL-3, which (along with IL-4) stimulates growth of mast cells.

- Degranulation of mast cells releases mediators that increase the infiltration of such inflammatory cells as macrophages and eosinophils.
- The eosinophils express Fc receptors for IgE and IgG and bind to the antibody-coated parasite.
- Once bound to the parasite, an eosinophil can participate in antibody dependent cell-mediated cytotoxicity (ADCC), releasing mediators from its granules that damage the parasite .
- One eosinophil mediator, called basic protein, is particularly toxic to helminths.

### **Fungal infections**

- The barriers of innate immunity control most fungal infections
- Commensal organisms also control the growth of certain potential pathogens as demonstrated by long term treatment with broad-spectrum antibiotic, which destroy normal flora and lead to oral or vulvovaginal infection with *candida albicans*
- Phagocytosis by neutrophil is a strong defense against most fungi
- Alternative and lectin pathways of complement activation are triggered by components present in most fungal cell wall