Section D: Immunity in Health and Disease

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1. Immunity can be achieved naturally or artificially

- Immunity conferred by recovering from an infectious disease such as chicken pox is called **active immunity** because it depends on the response of the infected person’s own immune system.

  - Active immunity can be acquired naturally or artificially, by **immunization**, also known as **vaccination**.
  
  - Vaccines include inactivated toxins, killed microbes, parts of microbes, and viable but weakened microbes.
  
  - These no longer cause disease, but they can act as antigens, stimulating an immune response, and more important, immunological memory.
• A vaccinated person who encounters the actual pathogen will have the same quick secondary response based on memory cells as a person who has had the disease.

• Routine immunization of infants and children has dramatically reduced the incidence of infectious diseases such as measles and whooping cough, and has led to the eradication of smallpox, a viral disease.

• Unfortunately, not all infectious agents are easily managed by vaccination.

• For example, although researchers are working intensively to develop a vaccine for HIV, they face many problems, such as antigenic variability.
• Antibodies can be transferred from one individual to another, providing **passive immunity**.
  • This occurs naturally when IgG antibodies of a pregnant woman cross the placenta to her fetus.
  • In addition, IgA antibodies are passed from mother to nursing infant in breast milk, especially in early secretions called colostrum.
  • Passive immunity persists as long as these antibodies last, a few weeks to a few months.
    • This protects the infant from infections until the baby’s own immune system has matured.
• Passive immunity can be transferred artificially by injecting antibodies from an animal that is already immune to a disease into another animal.
  • This confers short-term, but immediate protection against that disease.
  • For example, a person bitten by a rabid animal may be injected with antibodies against rabies virus because rabies may progress rapidly, and the response to an active immunization could take too long to save the life of the victim.
  • Actually, most people infected with rabies virus are given both passive immunizations (the immediate fight) and active immunizations (longer term defense).
2. The immune system’s capacity to distinguish self from nonself limits blood transfusion and tissue transplantation

- In addition to attacking pathogens, the immune system will also attack cells from other individuals.
  - For example, a skin graft from one person to a nonidentical individual will look healthy for a day or two, but it will then be destroyed by immune responses.
  - Interestingly, a pregnant woman does not reject the fetus as a foreign body, as apparently, the structure of the placenta is the key to this acceptance.
One source of potential problems with blood transfusions is an immune reaction from individuals with incompatible blood types.

- In the **ABO blood groups**, an individual with type A blood has A antigens on the surface of red blood cells.
  - This is not recognized as an antigen by the “owner,” but it can be identified as foreign if placed in the body of another individual.
- B antigens are found on type B red blood cells.
- Both A and B antigens are found on type AB red blood cells.
- Neither antigen is found on type O red blood cells.
• A person with type A blood already has antibodies to the B antigen, even if the person has never been exposed to type B blood.
  
  • These antibodies arise in response to bacteria (normal flora) that have epitopes very similar to blood group antigens.
  
  • Thus, an individual with type A blood does make antibodies to A-like bacterial epitopes - these are considered self - but that person does make antibodies to B-like bacterial epitopes.
  
  • If a person with type A blood receives a transfusion of type B blood, the preexisting anti-B antibodies will induce an immediate and devastating transfusion reaction.
• Because blood group antigens are polysaccharides, they induce T-independent responses, which elicit no memory cells.
  
  • Each response is like a primary response, and it generates IgM anti-blood-group antibodies, not IgG.
  
  • This is fortunate, because IgM antibodies do not cross the placenta where they may harm a developing fetus with a blood type different from its mother’s.
• However, another blood group antigen, the **Rh factor**, can cause mother-fetus problems because antibodies produced to it are IgG.

• This situation arises when a mother that is Rh-negative (lacks the Rh factor) has a fetus that is Rh-positive, having inherited the factor from the father.

• If small amounts of fetal blood cross the placenta as may happen late in pregnancy or during delivery, the mother mounts a T-dependent humoral response against the Rh factor.

• The danger occurs in subsequent Rh-positive pregnancies, when the mother’s Rh-specific memory B cells produce IgG antibodies that can cross the placenta and destroy the red blood cells of the fetus.
• To prevent this, the mother is injected with anti-Rh antibodies after delivering her first Rh positive baby.

• She is, in effect, passively immunized (artificially) to eliminate the Rh antigen before her own immune system responds and generates immunological memory against the Rh factor, endangering her future Rh-positive babies.
• The major histocompatibility complex (MHC) is responsible for stimulating the rejection of tissue grafts and organ transplants.
  • Because MHC creates a unique protein fingerprint for each individual, foreign MHC molecules are antigenic, inducing immune responses against the donated tissue or organ.
  • To minimize rejection, attempts are made to match MCH of tissue donor and recipient as closely as possible.
    • In the absence of identical twins, siblings usually provide the closest tissue-type match.
• In addition to MHC matching, various medicines are necessary to suppress the immune response to the transplant.

• However, this strategy leaves the recipient more susceptible to infection and cancer during the course of treatment.

• More selective drugs, which suppress helper T cell activation without crippling nonspecific defense or T-independent humoral responses, have greatly improved the success of organ transplants.
• In bone marrow transplants, it is the graft itself, rather than the host, that is the source of potential immune rejection.

• Bone marrow transplants are used to treat leukemia and other cancers as well as various hematological diseases.

• Prior to the transplant, the recipient is typically treated with irradiation to eliminate the recipient’s immune system, leaving little chance of graft rejection.

• However, the donated marrow, containing lymphocytes, may react against the recipient, producing **graft versus host reaction**, unless well matched.
3. Abnormal immune function can lead to disease

- Malfunctions of the immune system can produce effects ranging from the minor inconvenience of some allergies to the serious and often fatal consequences of certain autoimmune and immunodeficiency diseases.
• Allergies are hypersensitive (exaggerated) responses to certain environmental antigens, called allergens.

• One hypothesis to explain the origin of allergies is that they are evolutionary remnants of the immune system’s response to parasitic worms.

• The humoral mechanism that combats worms is similar to the allergic response that causes such disorders as hay fever and allergic asthma.
• The most common allergies involve antibodies of the IgE class.

• Hay fever, for example, occurs when plasma cells secrete IgE specific for pollen allergens.

• Some IgE antibodies attach by their tails to mast cells present in connective tissue, without binding to the pollen.

• Later, when pollen grains enter the body, they attach to the antigen-binding sites of mast cell-associated IgE, cross-linking adjacent antibody molecules.
• This event triggers the mast cell to *degranulate* - that is, to release histamines and other inflammatory agents from vesicles called granules.
• High levels of histamines cause dilation and increased permeability of small blood vessels.

• These inflammatory events lead to typical allergy symptoms: sneezing, runny nose, tearing eyes, and smooth muscle contractions that can result in breathing difficulty.

• Antihistamines diminish allergy symptoms by blocking receptors for histamine.
Sometimes, an acute allergic response can result in **anaphylactic shock**, a life threatening reaction to injected or ingested allergens.

- Anaphylactic shock results when widespread mast cell degranulation triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure.
  - Death may occur within minutes.
- Triggers of anaphylactic shock in susceptible individuals include bee venom, penicillin, or foods such as peanuts or fish.
  - Some hypersensitive individuals carry syringes with epinephrine, which counteracts this allergic response.
Sometimes the immune system loses tolerance for self and turns against certain molecules of the body, causing one of many autoimmune diseases.

- In *systemic lupus erythematosus* (*lupus*), the immune system generates antibodies against all sorts of self molecules, including histamines.

  - Lupus is characterized by skin rashes, fever, arthritis, and kidney dysfunction.

- *Rheumatoid arthritis* leads to damage and painful inflammation of the cartilage and bone of joints.

- In *insulin-dependent diabetes mellitus*, the insulin-producing beta cells of the pancreas are the targets of autoimmune cell-mediated responses.
• *Multiple sclerosis (MS)* is the most common chronic neurological disease in developed countries,

• In MS, T cells reactive against myelin infiltrate the central nervous system and destroy the myelin of neurons.

• People with MS experience a number of serious neurological abnormalities.
• The mechanisms that lead to autoimmunity are not fully understood.
  
  • It was thought that people with autoimmune diseases had self-reactive lymphocytes that escaped elimination during their development.
  
  • We now know that healthy people also have lymphocytes with the capacity to react against self, but these cells are inhibited from inducing an autoimmune reaction by several regulatory mechanisms.
  
  • So, autoimmune disease likely arises from some failure in immune regulation, perhaps linked with particular MHC alleles.
• In immunodeficiency diseases, the function of either the humoral or cell-mediated immune defense is compromised.
  • In *severe combined immunodeficiency (SCID)*, both branches of the immune system fail to function.
  • For individuals with this disease, long-term survival requires a bone marrow transplant that will continue to supply functional lymphocytes.
  • Several gene therapy approaches are in clinical trials to attempt to reverse SCID, but results to this point have been equivocal.
• Immunodeficiency may also develop later in life.
  • For example, certain cancers suppress the immune system, especially Hodgkin’s disease, which damages the lymphatic system.
  • AIDS is another acquired immune deficiency.
Healthy immune system function appears to depend on both the endocrine system and the nervous system.

- For example, hormones secreted by the adrenal glands during stress affect the number of white blood cells and may suppress the immune system in other ways.
- Similarly, some neurotransmitters secreted when we are relaxed and happy may enhance immunity.
- Physiological evidence also points to an immune system-nervous system link based on the presence of neurotransmitter receptors on the surfaces of lymphocytes and a network of nerve fibers that penetrates deep into the thymus.
4. AIDS is an immunodeficiency disease caused by a virus

- In 1981, increased rates of two rare diseases, Kaposi’s sarcoma, a cancer of the skin and blood vessels, and pneumonia caused by the protozoan *Pneumocystis carinii*, were the first signals to the medical community of a new threat to humans, later known as acquired immunodeficiency syndrome, or AIDS.

- Both conditions were previously known to occur mainly in severely immunosuppressed individuals.

- People with AIDS are susceptible to opportunistic diseases.
• In 1983, a retrovirus, now called **human immunodeficiency virus (HIV)**, had been identified as the causative agent of AIDS.
• With the AIDS mortality close to 100%, HIV is the most lethal pathogen ever encountered.

  • Molecular studies reveal that the virus probably evolved from another HIV-like virus in chimpanzees in central Africa and appeared in humans sometimes between 1915 and 1940.

  • These first rare cases of infection and AIDS went unrecognized.
• There are two major strains of the virus, HIV-1 and HIV-2.
  • HIV-1 is the more widely distributed and more virulent.
• Both strains infect cells that bear CD4 molecules, especially helper T cells and class II MHC-bearing antigen-presenting cells, but also macrophages, some lymphocytes and some brain cells.
  • CD4 functions as the major receptor for the virus.
• The entry of the virus requires not only CD4 on the surface of the susceptible cells but also a second protein molecule, a coreceptor.

• Two of the coreceptors that have been identified normally function as receptors for chemokines.

• Some people who are innately resistant to HIV-1 owe their resistance to defective chemokine receptors which prevents HIV from binding and infecting cells.
• Once inside a cell, HIC RNA is reverse-transcribed, and the product DNA is integrated into the host genome.

• In this provirus form, the viral genome directs the production of new virus particles.

• Because a retrovirus exists as a provirus for the life of the infected cell, immune responses fail to eradicate it from the body.

• Even more challenging for the immune responses are the frequent mutational changes that occur in each round of virus replication.

• Indeed, most HIV particles produced in an infected person differ at least slightly from the original virus.
• In spite of these challenges, the immune system engages in a prolonged battle against HIV.

(1) The immune response diminishes the initial viral load, but HIV continues to replicate in lymphatic tissue.

(2) Viral load gradually rises as HIV is released from lymphatic tissue and helper T cell levels decrease.

(3) This results in extensive loss of humoral and cell-mediated immunity.
Fig. 43.20

Infection; minor symptoms such as swollen lymph nodes

Loss of immune function more apparent with the appearance of characteristic diseases such as yeast infections

AIDS

Relative antibody concentration

Relative HIV concentration

T-cell concentration

Helper T-cell concentration in blood (cells/mm³)

Years after infection

0 1 2 3 4 5 6 7 8 9 10

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• After an initial peak, virus levels in the blood fall as anti-HIV antibodies, produced 1 to 12 months after infection, rise.

• A person who is HIV-positive is infected, having tested positive for the presence of antibodies to the virus.

• The HIV antibody test has be used to screen all blood supplies in the U.S. since 1985.

• However, this does not completely guarantee a safe blood supply because an infected individual may require several weeks or months before anti-HIV antibodies become detectable.
• After the early drop in HIV levels in the blood, the virus continues to be produced by cells in the lymph nodes, causing structural and functional damage.

• In time, the concentration of HIV in the blood increases as a result of the breakdown of lymphatic tissue function, the release of virus from these tissues, and diminishing responses to the infection because of the depletion of helper T cells.
• The decline in helper T cells is primarily caused by direct mortality from HIV infection.

• There is some evidence that some depletion of T cells is through inappropriately timed apoptosis.

• The half-life of an actively infected helper T cell (one producing new copies of HIV) is less than 1.5 days.
• The time required for an HIV infection to progress from severe helper T cell depletion and AIDS varies greatly, but it currently averages about ten years.
  • During most of this time, the individual exhibits only moderate hints of illness, such as swollen lymph nodes and occasional fever.
  • Progress of the disease can be monitored by measuring changes in the level of T cells, although measures of viral load are a better indicator of disease prognosis and of the effectiveness of anti-HIV treatment.
• At this time, HIV infection cannot be cured, and the progression to AIDS cannot be prevented.
• New, expensive drug therapies can slow this progression.
  • These drugs slow viral replication by inhibiting DNA synthesis, reverse transcriptase, and protease.
  • Protease inhibitors prevents a key step in the synthesis of HIV proteins.
  • Combinations of these drugs decrease viral load and therefore allow the number of helper T cells to rise.
  • Other drugs treat the myriad of opportunistic diseases as they develop.
• Transmission of HIV requires the transfer of body fluids containing infected cells, such as semen or blood, from person to person.

• Unprotected sex (that is, without a condom) among male homosexuals and transmission via nonsterile needles (typically among intravenous drug users) account for most of the AIDS cases reported thus far in the United States and Europe.

• However, transmission of HIV among heterosexuals is rapidly increasing as a result of unprotected sex with infected partners.

• In Africa and Asia, transmission has been primarily by heterosexual sex, especially where there is a high incidence of genital lesions from other diseases.
• HIV is not transmitted by casual contact.
  • So far, only one case of HIV transmission by kissing has been reported, and both individuals had bleeding gums.
  • Transmission of HIV from mother to child can occur during fetal development or during nursing.
  • HIV screening has virtually eliminated blood transfusions as a route of transmission in developed countries.
• As of 2000 the Joint United Nations Program on AIDS estimates that 30 to 40 million people worldwide are living with HIV or HIV/AIDS.

• Of these, approximately 70% reside in sub-Saharan Africa.

• The number of people with AIDS is expected to grow by nearly 20% per year.
• The best approach for slowing the spread of HIV is to educate people about the practices that transmit the disease, such as using nonsterile needles and having sex without a condom.

• Although condoms do not completely eliminate the risk of transmitting HIV (or other similar transmitted viruses, such as the hepatitis B virus), they do reduce it.

• Any individual who has sex - vaginal, oral, or anal - with a partner who had unprotected sex with another person during the past two decades risks exposure to HIV.