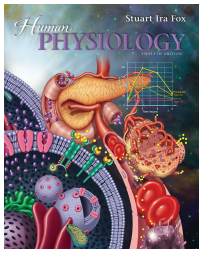
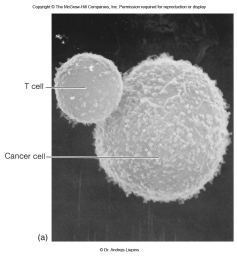


Chapter 15

Immune System

Lecture PowerPoint

I. Defense Mechanisms



Defense Mechanisms

- Protect against disease-causing agents called pathogens
- Make up the immune system
- Two types:
  - Innate (nonspecific) immunity
  - Adaptive (specific) immunity
    - There are some areas of overlap between the two.

Innate Immunity

- Inherited
- Serves as a first line of defense against pathogens
  - Examples: epithelial membranes, high acidity in stomach, cells that can engulf/kill pathogens, fever

Innate Immunity

Table 15.1 | Structures and Defense Mechanisms of Nonspecific (Innate) Immunity

	Structure	Mechanisms
External	Skin	Physical barrier to penetration by pathogens; secretions contain lysozyme (enzyme that destroys bacteria)
	Digestive tract	High acidity of stomach; protection by normal bacterial population of colon
	Respiratory tract	Secretion of mucus; movement of mucus by cilia; alveolar macrophages
	Genitourinary tract	Acidity of urine; vaginal lactic acid
Internal	Phagocytic cells	Ingest and destroy bacteria, cellular debris, denatured proteins, and toxins
	Interferons	Inhibit replication of viruses
	Complement proteins	Promote destruction of bacteria; enhance inflammatory response
	Endogenous pyrogen	Secreted by leukocytes and other cells; produces fever
	Natural killer (NK) cells	Destroy cells infected with viruses, tumor cells, and mismatched transplanted tissue cells
	Mast cells	Release histamine and other mediators of inflammation, and cytokines that promote adaptive immunity

Activation of Innate Immunity

- Cells distinguish “self” from “nonself” using pathogen-associated molecular patterns (PAMPs) unique to the pathogens.
  - Immune cells have toll-like receptors for PAMPs on their surface.
  - So far, 10 distinct toll-like receptors have been identified.
  - These cells respond by secreting cytokines to recruit more immune cells or activate specific immune cells.

Complement System

- Integrates innate and adaptive immune responses
- Consists of proteins in the plasma that become activated when antibodies bind to antigens
- Complement proteins promote phagocytosis, lysis of target cells, and inflammation.

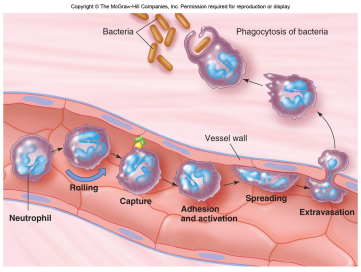
Phagocytosis

- Three types of phagocytic cells:
  - Neutrophils are the first to arrive at an infection.
  - Mononuclear phagocytic cells (monocytes in the blood and macrophages in the tissues) arrive later.
  - There are organ-specific phagocytes in the liver, spleen, lymph nodes, lungs, and brain.
    - Some of these, called fixed phagocytes, are immobile in the walls of these organs.

Phagocytosis in Tissues

- Neutrophils and monocytes squeeze through gaps in venule walls to enter tissue in a process called extravasation, or diapedesis.
- Attracted to site by cytokines

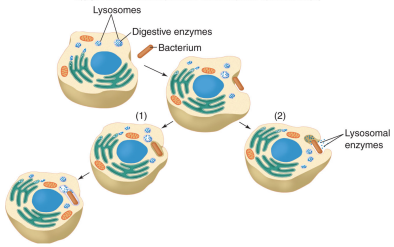
Phagocytosis in Tissues



Phagocytosis

- The pathogen becomes engulfed by pseudopods.
- The vacuole containing the pathogen fuses with a lysosome.
- The pathogen is digested.

Phagocytosis



Fever

- Regulated by hypothalamus
- A chemical called an endogenous pyrogen sets the body temperature higher.
  - Produced as a cytokine by leukocytes
  - Toxins from some bacteria stimulate leukocytes to produce these cytokines.
  - Along with fever, they also induce sleepiness and a fall in plasma iron concentration (which limits bacterial activity).

Interferons

- Antiviral polypeptides produced by infected cells
- Three types identified:
  - Alpha, beta ,gamma
- New antiviral drugs are being developed using interferons.

Interferons

Table 15.3 | Effects of Interferons

Stimulation	Inhibition
Macrophage phagocytosis	Cell division
Activity of cytotoxic ("killer") T cells	Tumor growth
Activity of natural killer cells	Maturation of adipose cells
Production of antibodies	Maturation of erythrocytes

Adaptive Immunity

- The acquired ability to defend against *specific* pathogens after exposure to these pathogens
  - Mediated by antigens and antibodies

Antigens

- Cell surface molecules that stimulate the production of specific antibodies
  - Foreign antigens illicit an immune response. The immune system can distinguish "self" from "nonself."
  - Antibodies bind to their specific antigens.
  - Large molecules can have several antigenic determinant sites that stimulate the production of and binding to antibodies.

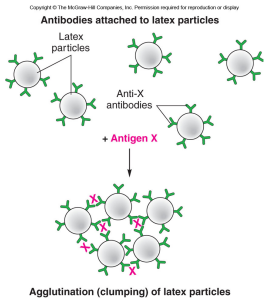
Haptens

- Smaller, nonantigenic molecules that can become antigens when bound to other proteins
  - These are useful for creating antigens for research and diagnosis.

Immunoassays

- Tests that use specific antibodies to identify specific antigens
- Binding causes agglutination, which can be seen.
- Used to determine blood type and detect pregnancy

Immunoassays



Lymphocytes

- Derived from stem cells in the bone marrow.
- These stem cells seed the thymus, spleen, and lymph nodes.
  - The thymus is the site of new T lymphocytes through late childhood. It degenerates in adulthood, and new T lymphocytes are made through mitosis in secondary lymphoid organs.
  - The bone marrow and thymus are considered primary lymphoid organs.

T Lymphocytes

- Lymphocytes that seed the thymus become T lymphocytes. These then seed the blood, lymph nodes, and spleen.
- T lymphocytes attack host cells that have become infected with a virus or fungus, transplanted human cells, and cancer cells.
- T lymphocytes do not produce antibodies.
- They must be in close proximity to the victim cell in order to destroy it.
- This is called cell-mediated immunity.

B Lymphocytes

- Lymphocytes that come directly from bone marrow to seed other organs (not the thymus) are called B lymphocytes.
- They combat bacterial and some viral infections.
- They secrete antibodies into blood and lymph so can be far from the victim.
- This is called humoral immunity or antibody-mediated immunity.

T and B Lymphoctes

Table 15.4 | Comparison of B and T Lymphocytes

Characteristic	B Lymphocytes	T Lymphocytes
Site where processed	Bone marrow	Thymus
Type of immunity	Humoral (secretes antibodies)	Cell-mediated
Subpopulations	Memory cells and plasma cells	Cytotoxic (killer) T cells, helper cells, suppressor cells
Presence of surface antibodies	Yes—IgM or IgD	Not detectable
Receptors for antigens	Present—are surface antibodies	Present—are related to immunoglobulins
Life span	Short	Long
Tissue distribution	High in spleen, low in blood	High in blood and lymph
Percentage of blood lymphocytes	10%–15%	75%–80%
Transformed by antigens into	Plasma cells	Activated lymphocytes
Secretory product	Antibodies	Lymphokines
Immunity to viral infections	Enteroviruses, poliomyelitis	Most others
Immunity to bacterial infections	*Streptococcus, Staphylococcus*, many others	Tuberculosis, leprosy
Immunity to fungal infections	None known	Many
Immunity to parasitic infections	Trypanosomiasis, maybe to malaria	Most others

Secondary Lymphoid Organs

- Lymph nodes, spleen, tonsils, and Peyer's patches (in mucosa of intestines)
- Capture and present pathogens to macrophages and house lymphocytes
- Lymphocytes migrate between lymphoid organs to sample blood and lymph.
  - The spleen filters blood for pathogens.
  - Other organs filter lymph for pathogens.

Local Inflammation

- Occurs when bacteria enter a break in the skin
- Initiated by nonspecific mechanisms of phagocytosis by toll-like receptors
  - Macrophages and mast cells release cytokines to attract phagocytic neutrophils.
  - Complement proteins are activated, which also attract phagocytic cells.

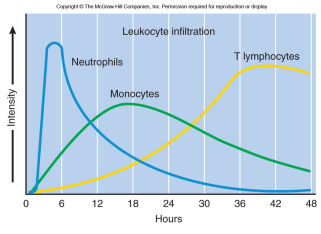
Local Inflammation

- As inflammation progresses, B lymphocytes produce antibodies against bacterial antigens.
  - Formation of antigen-antibody complexes amplifies nonspecific response, a process called opsinization.

Local Inflammation

- More phagocytic cells arrive via extravasation from nearby venules. T lymphocytes are the last to arrive.
- Neutrophils may spill protein-digesting enzymes into the surrounding tissues, causing pus.

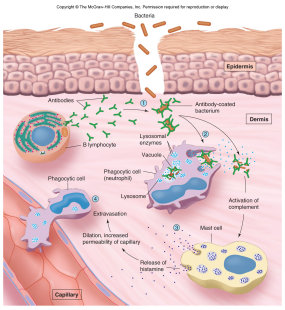
Local Inflammation



Local Inflammation

- Mast cells secrete heparin, histamine, prostaglandins, leukotrienes, cytokines, and TNF-α.
  - These produce warmth, swelling, and pain (classic symptoms).
  - They also recruit more leukocytes.

Local Inflammation



II. Functions of B Lymphocytes

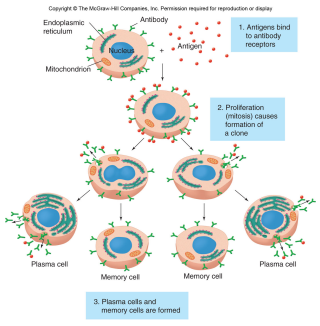
How B Lymphocytes Work

- Exposure to the specific antigen activates a B lymphocyte and causes it to undergo multiple cell divisions.

How B Lymphocytes Work

- Some become memory cells, which are used in a later infection by the same pathogen.
- Others become plasma cells, which produce 2,000 antibodies/second.

How B Lymphocytes Work



Antibodies

- Also known as immunoglobulins
- Five classes: IgG, IgA, IgM, IgD, and IgE

Antibodies

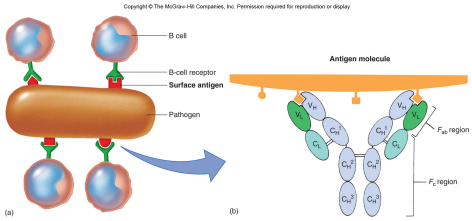
Table 15.6 | The Immunoglobulins

Immunoglobulin	Functions
IgG	Main form of antibodies in circulation: production increased after immunization; secreted during secondary response
IgA	Main antibody type in external secretions, such as saliva and mother's milk
IgE	Responsible for allergic symptoms in immediate hypersensitivity reactions
IgM	Function as antigen receptors on lymphocyte surface prior to immunization; secreted during primary response
IgD	Function as antigen receptors on lymphocyte surface prior to immunization; other functions unknown

Antibody Structure

- Y-shaped
  - 2 long, heavy (H) chains joined by 2 shorter, light (L) chains
  - The bottom (F_c) is constant across different antibodies, whereas the top (F_{ab}) varies and allows antigen specificity.

Antibody Structure



Diversity of Antibodies

- Everyone has 10^{20} antibody molecules.
  - There are a few million different specificities.
  - There should be an antibody for every antigen you might encounter.

Diversity of Antibodies

– There are so many because:

- A large percentage of our genetic code is dedicated to making antibodies. Some genes code for light chains and some for heavy chains, and then these are combined in different ways to get even more.
- These genes mutate easily, making more combinations.

How the Complement System Works

- Part of the nonspecific defense system
  - Activity is triggered by binding of antibodies to antigens (classic pathway) and by polysaccharides on bacterial membranes (alternative pathway).
- Binding of antibodies to antigens does not destroy the pathogen.
  - This labels targets for attack by phagocytic cells and stimulates opsonization.

The Complement System

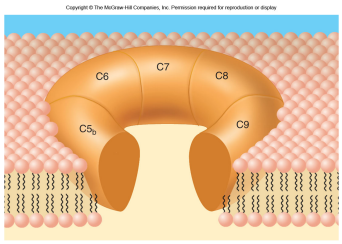
- Complement is a group of plasma proteins activated by the binding of antibodies to antigens.

How the Complement System Works

– Proteins are designated C1−C9.

- C1 serves as a recognition protein.
- C2, C3, and C4 serve as activators.
- C5−C9 attack by attaching to a cell membrane and destroying it.

How the Complement System Works



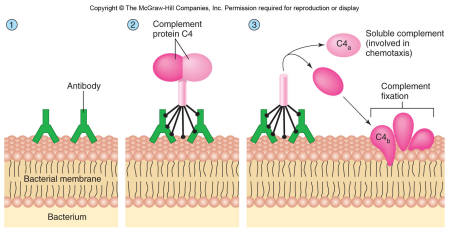
How the Complement System Works

- Classic pathway: more rapid and efficient; involves antibodies binding to antigens
  1. IgG and IgM activate C1, which splits C4 into two fragments, $C4_a$ and $C4_b$.
  2. $C4_b$ binds to the cell membrane and becomes active, splitting C2 into $C2_a$ and $C2_b$.
  3. $C2_a$ attaches to $C4_b$ and cleaves C3 into $C3_a$ and $C3_b$.

How the Complement System Works

4. $C3_b$ converts C5 into $C5_a$ and $C5_b$.
5. $C5_b$ and C6−C9 are inserted into the bacterial cell membrane, forming the membrane attack complex.
6. This creates a large pore in the membrane, causing influx of water into the cell = lysis.

Complement Fixation



Complement Fragments

- $C3_a$ and $C5_a$ stimulate mast cells to release histamine.
  - This increases blood flow to the area.
- $C5_a$ also attracts neutrophils and monocytes to the region.

III. Functions of T Lymphocytes

Cytotoxic T Lymphocytes

- Destroy body cells that harbor foreign antigens
  - Usually from a pathogen (virus or fungus), but can be due to a malignancy (cancer)
- Cell-mediated destruction means the T cells must touch the target victim.
  - Secrete perforins to create large pore in cell
  - Secrete granzymes to trigger apoptosis in cell

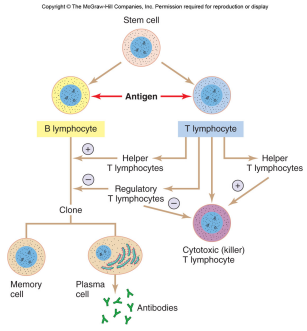
Helper T Lymphocytes

- Improve ability of B lymphocytes to become plasma cells and enhance ability of cytotoxic T cells to kill targets
  - Secretion of lymphokines

Regulatory T Lymphocytes

- Inhibit response of B lymphocytes and cytotoxic T lymphocytes
- Previously called suppressor T lymphocytes
- People with genetic deficiencies in regulatory T lymphocyte production may develop autoimmune diseases and allergies.

Effects of an Antigen in Summary



Lymphokines

- Cytokines specific to lymphocytes
  - Many stimulate B cell or cytotoxic T cell activity.

Lymphokines

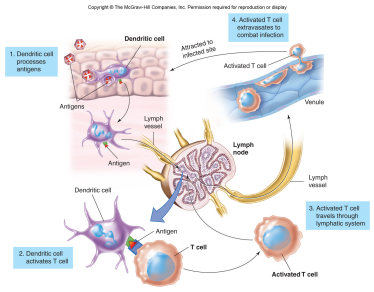
Table 15.7 | Some Cytokines That Regulate the Immune System

Cytokine	Biological Functions
Interleukin-1 (IL-1)	Induces proliferation and activation of T lymphocytes
Interleukin-2 (IL-2)	Induces proliferation of activated T lymphocytes
Interleukin-3 (IL-3)	Stimulates proliferation of bone marrow stem cells and mast cells
Interleukin-4 (IL-4)	Stimulates proliferation of activated B cells; promotes production of IgE antibodies; increases activity of cytotoxic T cells
Interleukin-5 (IL-5)	Induces activation of cytotoxic T cells; promotes eosinophil differentiation and serves as chemokine for eosinophils
Interleukin-6 (IL-6)	Stimulates proliferation and activation of T and B lymphocytes
Granulocyte/ monocyte-macrophage colony-stimulating factor (GM-CSF)	Stimulates proliferation and differentiation of neutrophils, eosinophils, monocytes, and macrophages

T Cell Receptor Proteins

- Antigen recognition proteins on the membranes of T cells
- These cannot bind directly to antigens.
- Antigen-presenting cells, such as dendritic cells and macrophages, help T cells bind to antigens.

T Cell Receptor Proteins



Dendritic Cells

- Originate in the marrow and migrate to most tissues (especially where pathogens might enter body)
- Engulf protein antigens, partially digest them, and display polypeptide fragments on surface for T cell to "see"
  - Associated with histocompatibility antigens
  - Secrete cytokines to attract lymphocytes.

Histocompatibility Antigens

- On surface of all body cells (except mature RBCs)
  - Also called human leukocyte antigens (HLAs)
- Coded for by four genes on chromosome 6 called major histocompatibility complex (MHC)
  - Many versions of each gene are possible, so most people have different combinations.
  - An organ transplant requires an MHC match.

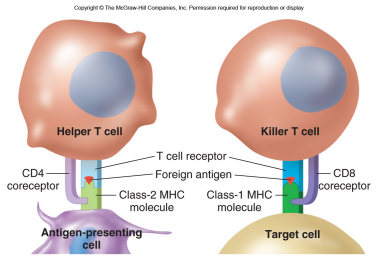
MHC

- MHC genes produce two classes of cell surface molecules: class 1 and class 2.
  - Class 1 is made by all cells except RBCs.
  - Class 2 is made by antigen-presenting cells and B cells

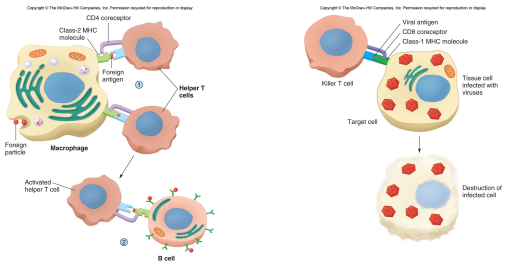
MHC

- Class 2 MHC molecules and foreign antigens are presented together to helper T lymphocytes.
- Class 1 MHC molecules and foreign antigens are presented together to activate cytotoxic T cells.

MHC



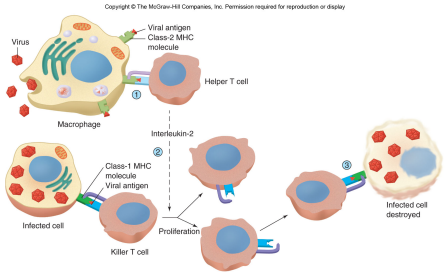
T lymphocyte Response to a Virus



T Lymphocyte and Macrophage Interactions

- Macrophages secrete interleukin-1, which stimulates helper T cell mitosis.
- Helper T cells secrete macrophage colony-stimulating factor and gamma interferon, which promote macrophage activity.
- T helpers secrete interleukin-2, which makes the macrophage produce tumor necrosis factor (against cancer) and activates cytotoxic T cell activity/mitosis.

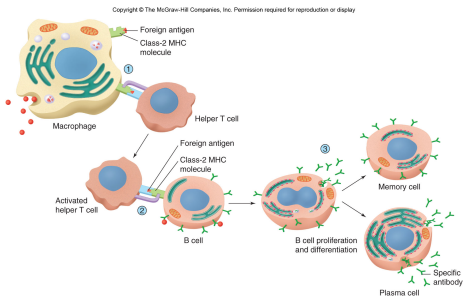
T Lymphocyte and Macrophage Interactions



Interactions with B Cells

- Activated helper Ts promote humoral response of B cells by binding to foreign antigens and MHC class 2s.
  - This stimulates mitosis of Bs, conversion to plasma cells, and production of antibodies.

Interactions with B Cells



Destruction of T Cells

- Activated T cells must be destroyed when the infection is over.
- Active T cells produce a surface receptor called FAS and later a protein called FAS ligand.
  - Binding of FAS to FAS ligand induces apoptosis.

IV. Active and Passive Immunity

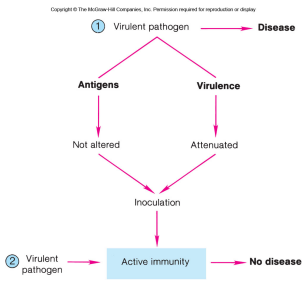
Active Immunity

- When exposed to foreign antigens, immune cells respond by making many copies of themselves.
  - This protects the body from future infections.
  - This protection is called active immunity.

Active Immunity

- Active immunity is also used to make vaccines.
- These vaccines include an antigen but are not virulent (disease-causing).

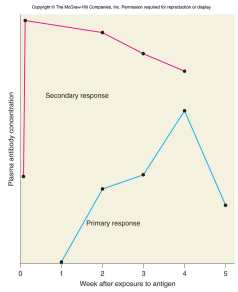
Active Immunity



Active Immunity

- After infection, it takes 5−10 days before antibodies are detected in the blood.
  - This is the primary response.
  - The person will get sick.
- Later exposure to the same infection results in maximum antibody production in less than 2 hours.
  - This is the secondary response.
  - The person will likely never get sick.

Active Immunity



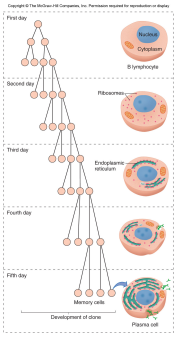
Clonal Selection Theory

- Explains how the secondary immune response works:
  - A person inherits lymphocytes specific to almost every pathogen, but there are few of each type.

Clonal Selection Theory

- The primary response triggers a massive production of cells that can respond to that antigen.
- These cells respond much quicker after exposure a second time.

Clonal Selection Theory



Vaccines

- Stimulate a primary response and active immunity without making the person sick.
- Three ways to accomplish this:
  - Use a killed virus
  - Use a live virus with attenuated virulence—i.e., the virus either cannot replicate or cannot infect target tissues (polio)
  - Use a genetically engineered recombinant virus (hepatitis B)

Immunological Tolerance

- It is important to avoid attacking "self" cells.
- The immune system develops a tolerance for "self" antigens in the fetal period.
- In some instances, "self" cells are attacked:
  - If mutations occur in lymphocytes (usually good and adds to what the body can defend against)
  - If cells in particular organs are never exposed to the immune system
  - These lymphocytes are called autoreactive.

Immunological Tolerance

- If lymphocytes do begin attacking cells, there are mechanisms to stop this:
  - In clonal deletion, these lymphocytes are destroyed (apoptosis).
  - In clonal anergy, these lymphocytes are prevented from becoming active. Regulatory T lymphocytes likely do this.

Passive Immunity

- Passing of antibodies from one individual to another
- Provides temporary protection:
  - From mother to fetus
  - From mother to child (in breast milk)
  - Artificially via immunization (snake anti-venom)

Passive Immunity

Table 15.9 | Comparison of Active and Passive Immunity

Characteristic	Active Immunity	Passive Immunity
Injection of person with	Antigens	Antibodies
Source of antibodies	The person inoculated	Natural—the mother; artificial—injection with antibodies
Method	Injection with killed or attenuated pathogens or their toxins	Natural—transfer of antibodies across the placenta; artificial—injection with antibodies
Time to develop resistance	5 to 14 days	Immediately after injection
Duration of resistance	Long (perhaps years)	Short (days to weeks)
When used	Before exposure to pathogen	Before or after exposure to pathogen

V. Tumor Immunology

Tumors

- Tumors are abnormal clonal cells that dedifferentiate to an embryonic state.
  - Tumor growth and dedifferentiation reveal antigens that can stimulate the destruction of the cell (by cytotoxic T cells).
  - Benign tumors are slow growing and limited to specific areas of the body.

Tumors

- Malignant tumors are fast growing and spread to other parts of the body.
- Cancers arise when the immune cells fail to stop the growth/spread of the tumors.

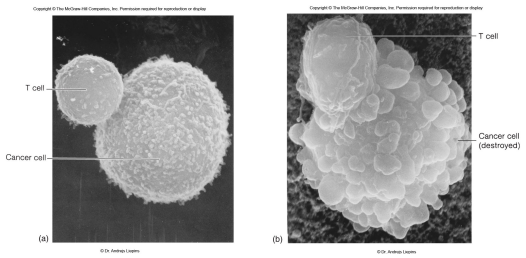
Tumor Antigens

- Some tumor antigens are due to dedifferentiated embryonic antigens not recognized by the immune system.
- Some arise due to mutations from carcinogens.
- Others are viral antigens from the virus that caused the tumor (human papillomavirus).
- Normally, over-expressed antigens may trigger an immune response.

Lymphocytes and Tumor Cells

- Lymphocytes provide immunological surveillance against cancer.
- Tumor cells can evade immune surveillance by suppressing immunity with secretions:
  - FAS ligand stimulates lymphocyte apoptosis.

Lymphocytes and Tumor Cells



Natural Killer Cells

- Related to T lymphocytes but part of innate immunity without the ability to recognize specific antigens
  - Can recognize malignant cells and cells infected with a virus
  - Must be activated by pro-inflammatory cytokines from dendritic cells

Natural Killer Cells

- Kill compromised cells in the same manner as cytotoxic T cells
- Cytokines released by natural killer cells activate both innate and adaptive immune cells.

Immunotherapy for Cancer

- Therapeutic antibodies, interferons, and interleukin-2 have been used to treat cancer.
  - None of these "cure" cancer, but they do help some people.
  - Other cytokines are currently being tested against cancer.

Aging and Stress

- Cancer risk increases with age.
  - This may be due to aging mutated lymphocytes.
  - Tumors also grow faster in lab animals under stress. Stress induces the release of cortisone, which is known to suppress the immune system.

VI. Diseases Caused by the Immune System

Autoimmunity

- Produced by failure of immune cells to tolerate "self" antigens
  - Autoreactive T lymphocytes and autoantibodies are produced, causing inflammation and organ damage.
  - Common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, Grave's disease, pernicious anemia, thyroiditis, psoriasis, and lupus

Autoimmunity

- Several factors may cause autoimmune diseases:
  - An antigen not normally exposed to the immune system becomes exposed.
    - Hashimoto's thyroiditis
  - A normally tolerated antigen is combined with a foreign hapten. This may occur when a drug such as aspirin combines with platelets, resulting in the destruction of platelets.
    - Thrombocytopenia

Autoimmunity

- Several factors may cause autoimmune diseases:
  - Antibodies are produced aimed at other antibodies.
    - Cause of inflammation in rheumatoid arthritis
  - Antibodies produced against foreign antigens cross-react with self antigens and begin attacking self cells (can occur in the heart or kidneys after a strep infection).
    - Rheumatic fever

Autoimmunity

- Several factors may cause autoimmune diseases:
  - Self antigens may be presented to T helper cells along with class 2 MHC molecules.
    - May occur after viral infection of cells
    - Occurs in diabetes type I
  - Inadequate regulatory T cell activity.

Immune Complex Diseases

- Involve free antigen-antibody complexes that stimulate complement proteins and inflammation
  - Usually self-regulating because complexes are removed via phagocytosis
  - Complex formation may be prolonged or spread to other organs, leading to prolonged inflammation.

Immune Complex Diseases

- May result from infections from bacteria, viruses, or parasites
  - Hepatitis B results in free complexes that cause damage to arteries due to inflammation.
- May also result from complexes formed by self antigens and autoantibodies
  - Rheumatoid arthritis and lupus

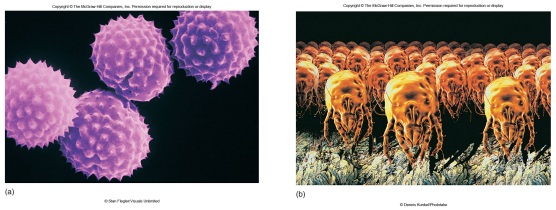
Allergies

- Also called hypersensitivity
- Abnormal response to allergens (antigens)
- Two types:
  - Immediate hypersensitivity
  - Delayed hypersensitivity

Immediate Hypersensitivity

- Abnormal B cell response to allergen
  - Effects seen seconds to minutes after exposure
  - Can be caused by foods, bee stings, pollen, etc.

Immediate Hypersensitivity



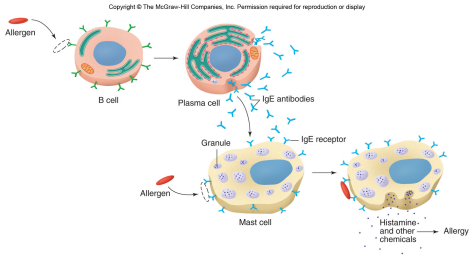
(a)

(b)

Immediate Hypersensitivity

- Dendritic cells stimulate a class of helper T cells to secrete interleukin-4 and interleukin-13, which stimulate B and plasma cells to secrete IgE antibodies.
- These antibodies do not circulate in the blood but attach to mast cells and basophils.
- When re-exposed to the same allergen, these antibodies bind with it and stimulate the production of histamine, leukotrienes, and prostaglandin D, producing allergy symptoms.

Immediate Hypersensitivity



Delayed Hypersensitivity

- Abnormal T cell response that produces symptoms 24−72 hours after exposure
  - Symptoms are caused by secretion of lymphokines, not histamine, so taking antihistamines has little effect.
  - Example: contact dermatitis caused by poison oak, ivy, or sumac