

Chapter 22b Lymphatics & Immunity

Introduction to Body Defenses

Immunity refers to the immune system's ability to defend against disease by recognizing and eliminating potentially pathogenic agents such as viruses, toxins, bacteria, parasites and fungi. In addition, the immune system also:

- Disposes of dysfunctional cells and cell debris
- Participates in healing wounds
- Often recognizes and eliminates mutant cells before they form cancer

Since the immune system detects foreign materials as anything “non-self”, it also rejects transplanted tissues and transfused blood unless the cellular markers resemble “self cells”. This is why ABO blood typing is so important when donating blood!

The presence of foreign/abnormal substances in the body usually evokes an immune response. It can even be evoked by harmless substances such as those that cause allergies...pollen (as is the case with allergies) and self cells/proteins (as in the case of autoimmune disease such as Type 1 Diabetes, MS or rheumatoid arthritis).

An *allergen* is a harmless substance that evokes an immune response.

The Anatomy of the Immune System includes leukocytes and lymphoid tissues and organs as well as any part of the 1st, 2nd or 3rd line of defense. This includes any tissues or secretions that prevent entry of pathogens into our body fluids, as well as the defense proteins and chemical messengers that assist immune cells.

Non-specific vs Specific Defenses

<i>Non Specific Defenses</i>	<i>Specific Defenses</i>
<ul style="list-style-type: none"> ○ Innate defenses (born with) ○ Provides a rapid, generalized response to any threat. ○ Aimed at preventing entry into body fluids, preventing the spread of infection once inside, and removing the threat from body. ○ Includes the 1st line of defense (physical and chemical barriers, and the 2nd line of defense (phagocytes and NK cells, interferons and complement proteins and inflammation & fever) 	<ul style="list-style-type: none"> ○ Specific resistance or adaptive defenses ○ 3rd line of defense ○ T and B Lymphocytes ○ The antibodies produced by B-cells ○ They detect and eliminate specific substances/pathogens ○ Memory cells provide long-term immunity against exposures to the same substance

The First Line of Defense consists of the chemical and physical barriers that keep pathogens from even getting inside the body.

One physical barrier is the skin!

- Epithelial TIGHT JUNCTIONS and the underlying basal lamina keep stuff out!
- Constant shedding of epithelial cells also sloughs off pathogens
- Low pH is inhospitable to pathogens
- Antimicrobial secretions such as enzymes, antibodies and antibiotics make for an inhospitable environment.

Another physical barrier are the mucus membranes!

- These are the respiratory, GI, Urinary and Reproductive tracts
- Mucus traps invaders which are removed by cilia and/or phagocytes.
- Mucus also often contains antimicrobial secretions (enzymes, antibodies, antibiotics)

Chemical barriers are things that are secreted onto the skin/mucus membrane to make for an inhospitable environment:

- Tears wash surface of the eye with fluid containing lysosomes
- Saliva in the mouth also washes the inside of the mouth
- Sebaceous glands secrete sebum and sweat which has antimicrobial properties
- Earwax traps pathogens and is a bitter repellent
- GI tract has HCL
- The low pH of urine makes the urinary tract inhospitable
- The low pH of mucus in the female reproductive tract is inhospitable

The Second Line of Defense

This line of defense includes phagocytic cells and proteins, as well as the processes of inflammation and fever.

Cells of the Second Line...

Most WBCs are phagocytic and use endocytosis to engulf their prey. Sometimes complement and antibodies are used to mark cells for removal by phagocytosis...the process of marking a cell is called OPSONIZATIONS, and the items used as markers are called OPSONINS. With opsonization, macrophages can more easily and quickly phagocytize a bad guy.

The **process of phagocytosis** involves adhesion, endocytosis, formation of phagosome and digestion.

The phagocytic cells are:

- Macrophages. These are leukocytes that phagocytize foreign cells, cell debris, old RBCs, bacteria, viruses...they are big eaters!
 - They circulate as monocytes in the blood before entering tissues...once in tissue they become a macrophage.
 - There are **two general macrophages**...fixed and free. FIXED MACROPHAGES are anchored to tissue (microglia, Kupffer cells) FREE

Four Components of the 2nd Line of Defense!

1. Cells
2. Proteins
3. Inflammation
4. Fever

MACROPHAGES wander around the body, traveling through lymph and blood, and can migrate through tissues to the site of injury/infection.

- Microphages are leukocytes that leave the blood via diapedesis to target infected/injured tissue.
 - Neutrophils become phagocytic in response to infection...their job is mainly to phagocytize bacteria. That is why when you have a high neutrophil count then you likely have a bacterial infection!
 - Eosinophils technically are phagocytes, but they kill their prey by bombarding parasitic worms digestive enzymes. If you have a high eosinophil count you have a parasite infection. Ick!

Other cells include the BASOPHILS which are non-phagocytic. They release chemical messengers such as histamines in response to infection and injury, which is part of the inflammatory response. Basophils typically help mast cells...the mast cells respond first and basophils arrive to help out.

The **MAST CELLS and DENDRITIC CELLS** are descendents of hematopoietic stem cells. They circulate temporarily and then enter tissues where they mature and hang out.

- Mast cells are in the skin and mucosal epithelium. They secrete histamine and can initiate inflammation from anywhere. They are not phagocytic.
- Dendrites are phagocytic. They help activate T-cells, and example are Langerhans cells, interstitial dendritic cells, lymphoid dendritic cells.

The **NATURAL KILLER (NK) Cells** are granular lymphocytes...recall that the T and B lymphocytes are agranular, so NKs are different in that way, and also in that they are part of the non-specific defense, while T and B are part of the specific defense. NK cells provide immunological surveillance and look for things that don't belong. NK cells specialize in responding to bacteria, mutant cells (tumors) and virus infected cells. They are **THE MOST IMPORTANT CELL FOR TUMOR SUPPRESSION!** They are also not phagocytic...they use perforins that cause holes in the target cell's membrane.

Proteins of the Second Line of Defense

The two proteins of the second line of defense are interferons and complement.

Interferons interfere with viral replication. They are secreted in two different ways:

1. *Virus infected cells secrete interferons* to protect neighboring cells. They then bind to the membrane of nearby normal cells, which triggers the production of antiviral proteins in the cytoplasm. These antiviral proteins interfere with all protein synthesis, including viral protein synthesis. This is only temporary since you don't want to shut down protein synthesis forever...the cells would die.
2. *Active T-Cells and NK cells secrete interferons.* They are not infected by the virus. This boosts antibody production, suppresses tumor growth and activates NK cells.

The goal of interferon is to protect cells from being taken over by a virus. Synthetics have been developed to help fight leukemia, genital warts and hepatitis B.

Complement complements the action of antibodies, but can also work without antibodies. There are about thirty different plasma proteins involved.

- Some form large membrane attack complexes (MAC) that create holes in the target cell and the cell lyses.
- Others form C3b, which marks the invaders for destruction (opsonization). This enhances phagocytosis of the bad cell.
- Some stimulate the inflammatory response via chemotaxis and stimulation of histamine release from mast cells and basophils.

Inflammation (component of 2nd line of defense)

Inflammation always happens the same way. It starts with the release of chemical signals (histamines, cytokines, etc...) and results in localized pain, redness, heat and swelling. (see diagram for full pathway)

The goals of inflammation are to *clean and repair* damaged/infected tissue to *prevent further entry or spread* of pathogens...and to mobilize defenses to *destroy pathogens* (if any are present), and to *facilitate regeneration* of damaged tissue.

Each of the signs has a beneficial role and each is caused by increased blood flow and increased filtrate formation. The increased blood flow brings in more O₂ and nutrients for repair as well as more clotting and defense proteins, and leukocytes!

Redness: Alerts us to the injury. Caused by vasodilation

Pain: Caused by histamine enhancing pain perception and swelling tissue stimulating nerve fibers...tells us there's an injury so we don't move it more and re-injure.

Heat: More blood equals more heat. Speeds up phagocytic activity and slows down the bad cells...may also denature foreign proteins and interfere with bacterial enzymes.

Swelling: Increased permeability causes swelling...provides awareness of injury.

Fever (the final component of 2nd line of defense)

Fever is a global increase in body temperature. While a slight fever is beneficial, a very high fever is dangerous. Though the core body temperature is hemostatically regulated, the set-point (regulated by the hypothalamus) can be changed. Pyrogens (Interleukin-1) tell the hypothalamus to increase the set-point for body temperature. All in all, fever speeds up the metabolic rate of the immune and regenerative cells, and may hinder the activity and replication of bacteria/viruses.

The Third Line of Defense (Specific Defense)

The third line of defense involves the T and B Lymphocytes, which protect the entire body...not just at the site of infection/injury. The T-cells provide cell-mediated immunity, while the B-cells (and their antibodies) provide humoral immunity.

Characteristics
of the 3rd Line
Specificity
Diversity
Memory
Self-tolerance

Specificity: The T and B cells bind or respond to foreign molecules called antigens. An antigen is any substance that evokes an immune response. Antigens include protein or CHO components of viruses, bacteria, fungi, protozoa, parasitic worms, tumors cells, transplanted tissues and even pollen. The different recognition sites on the antigen are called epitopes or antigenic determinants. The T and B cells only bind to the cells they have receptors for...the portion they bind to is the epitope. It's a lock-and-key fit!

Specific B-cells recognize specific antigens by binding to them via antigen-binding sites on the membrane antibody (called B-Cell receptors).

Specific T-cells recognize specific antigens by binding to them via antigen-binding sites on the T-cell receptor (TCR).

Diversity: We have millions of T & B cells in our bodies...a few for each possible antigen. If we are exposed to that antigen, then the T or B-cell is activated and can then proliferate and build an army of short-lived effector cells as well as long-term memory cells that build a bigger, faster army next time around!

Memory: Cells of the non-specific immune response have no memory. However, the specific immune response does. The large number of memory cells respond to repeated exposures to the same antigen more efficiently.

The first time you are exposed to an antigen you have the PRIMARY IMMUNE RESPONSE. In this response it takes about 2 weeks to reach peak antibody concentration. It is relatively slow and only produces a limited number of antibodies. This explains why you get sick and feel cruddy....the pathogen gets a chance to produce the signs/symptoms of infection.

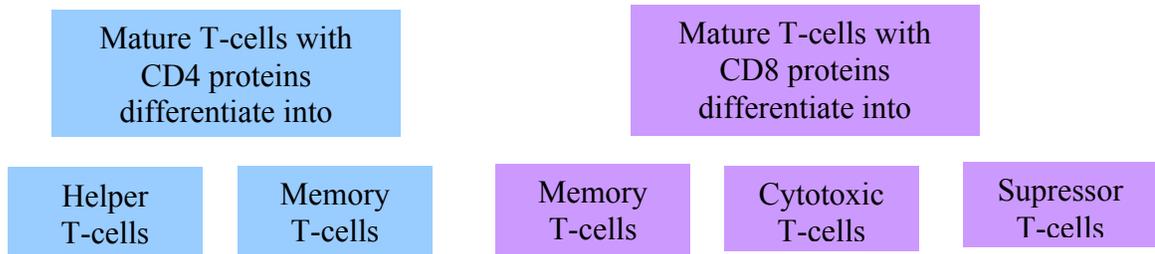
If you are exposed to the same pathogen again, you have the SECONDARY IMMUNE RESPONSE. Because of the memory B-cells created the first time around, the secondary response is faster, stronger and lasts longer! The memory Bs divide rapidly and differentiate into even more memory cells and a higher number of plasma cells (plasma cells are the effector cell), which produce greater numbers of antibodies.

The presence of memory cell is the basis for long-term, specific, acquired immunity. They can last for years up to a lifetime (like chickenpox!) Some B-cells may need to be reactivated...this is why you get a tetanus booster every ten years.

Self-tolerance: Before lymphocytes are allowed out into the immune system, they are "tested" for self-tolerance in the red bone marrow. If they react to self-cells then they are destroyed via apoptosis (programmed cell death.)

The Four Types of Effector T-Lymphocytes

Recall that T-cells are involved in cell-mediated immunity...they get in there with the hand-to-hand combat to destroy pathogens. The four types of effector T-cells are derived from those that have CD4 proteins, and those that have CD8 proteins.



Note that the cells don't differentiate into the effector cells until they are activated! This is more complicated for T-cells because they are "lazy." They won't bind to an antigen in its natural form...they wait until the cell becomes infected or until a macrophage presents it.... So, T-cells detect and respond to an antigen only when it is presented by an MHC (major histocompatibility complex) on the membrane surface of an infected body cell or Antigen Presenting Cell (APC). Note that MHC is often called HLA in a clinical setting.

Antigen Presentation

There are two classes of MHCs...Class I and Class II.

Class II MHCs present to the CD4 cells. Only a few APCs have Class II MHCs...these are macrophages, dendritic cells and sensitized B-cells. The APC internalizes the antigen and breaks it up into little pieces. Cells are always making MHCs which go onto the membrane surface as a cell-recognition tool. If there is an antigen inside, then pieces of that antigen will be put into the MHC and placed on the membrane surface. Now other cells can see it...the antigen has been "presented." If a CD4 comes along, it will recognize the MHC and interact, leading to activation and proliferation. Recall that CD4 cells become Helper Ts and Memory Ts. Note that the CD4 protein binds to the MHC, while the TCR binds to the antigen...see pic above.

Class I MHCs present to CD8 cells. Class I MHCs are found on the membrane surface of all other nucleated body cells. The infected or abnormal body cell presents antigens via its Class I MHC. These will react with CD8 (inactive Cytotoxic T-cells), resulting in their activation with help from the Helper Ts. This leads to proliferation of an army of clones which differentiate into Cytotoxic Ts, Suppressor Ts and Memory Ts.

Summary of Antigen Presentation

- Class II MHC (macrophages, dendritic cells, sensitized Bs) present to CD4 and create Helper T and Memory Ts.
- Class I MHC (all other nucleated cells) present to CD8 and

Helper T-cells are THE MOST important cells of the immune system.

create Cytotoxic Ts, Suppressor Ts and Memory Ts. (Cytokines from Helper Ts needed here!)

What do each of the T cells do?

Helper Ts are very, very important!

- Help with entire immune response by releasing cytokines (chemical messengers...Interleukins, interferon, etc...)
- They are the “central coordinator” of the immune response
- They activate cytotoxic T cells
- They activate B cells
- They attract and activate macrophages (amp up activity)
- They stimulate inflammation

Cytotoxic Ts (aka Killer T Cells)

- Secrete cytokines (interferons, Interleukins) that facilitate other immune cell activities, but not to the same extent as Helper Ts do
- Secrete cytokines that destroy infected/abnormal cells:
 - Perforin creates large holes in the cell
 - Lymphotoxin destroys DNA of cell
 - Fragmentins induce apoptosis of the cell
- Cytotoxic Ts are activated by foreign MHC proteins on donor cells of transplanted tissue/organ leading to graft rejection

Suppressor Ts

- We don't know much about these cells
- They control/moderate immune response
- They may minimize inappropriate immune response (autoimmune)
- Development is lengthy

Memory Ts

- Long-lived cells that are ready and on standby to complete differentiation and become Helper Ts and Cytotoxic Ts upon subsequent antigen exposure
- This results in a rapid, larger immune response (similar to primary and secondary of the B-cells and their antibody production)
- Provides long-term immunity

B-cells are more straightforward

In order to activate completely, B cells need help from Helper Ts. Once activated, the two daughter cells are plasma and memory cells. Plasma cells secrete antibodies for humoral immunity.

B-cells are activated when receptors on the membrane of the B-cell antibody bind to a specific antigen. When they are bound, the B-cell is now sensitized, and now has MHC displaying the antigen so the Helper T can recognize it and come along to help out. It usually needs Helper Ts for complete activation, so it will wait for the Helper T to come

along with its cytokines...then it will proliferate. If the B-cell activates with Helper T's assistance, then it creates plasma cells and memory cells. If it activates with the Helper Ts, then it just makes plasma cells...no memory cells (this is rare though)

The plasma cells produce and secrete antibodies, which form the antigen-antibody complex to eliminate the antigen in a number of ways...

- Neutralization: The antibody prevents toxins/viruses from binding to body cells
- Agglutination or precipitation: they cause the cells to clump
- Marking cell for destruction (opsonization), this enhances phagocytosis
- Activating the complement system
- Stimulating mast cells and basophils to induce inflammation

5 Classes of Antibodies (GMADE)

IgG: Largest and most diverse class

Can cross the placenta to cause passive immunity in baby

IgM: Anti-A and Anti-B antibodies, so used for ABO blood typing

Causes agglutination with incompatible blood types

IgA: Crosses epithelia, so it is found on mucosal surfaces and in glandular secretions

Can prevent antigen from entering the body

Since it gets into breast milk can cause passive immunity in baby

IgD: B-cell membrane receptor

IgE: Involved in allergies, stimulates basophils and mast cells

Memory B-cells are also long-lived, inactive cells that are activated at subsequent exposures. They are also a key component of long-term immunity. Recall that antibody production for subsequent exposures is much more potent in secondary vs primary exposures to an antigen.

Integration and Summary of the Innate and Adaptive Immune Systems

When a bacteria enters the body, the non-specific cells come into contact with it first.

Once this happens you immediately begin seeing integration between the two systems.

For the Type 1 MHC: The macrophage of the non-specific system eats the pathogen, and pieces of it end up on its cell membrane for antigen presentation. Now the T-cells can see it, they are activated and turned into helper Ts, which in turn activate the sensitized B cells with their Interleukin 1.

For the Type 2 MHC: The infected body cell presents the antigen to the T cells, which then become cytotoxic Ts and suppressor Ts. The cytotoxic Ts start destroying the infected cells. This pathway also produces Helper Ts.

Recall that Helper Ts are needed to fully activate B-cells...the Interleukin 1 enables the Bcell to proliferate and differentiate into plasma cells and memory cells. (Note that the B cells can proliferate without helper T, but they don't differentiate into memory cells...just makes plasma cells.)

So now you have the cytotoxic Ts and the antibodies from the Bs to take care of the free-floating bacteria in the ECF...Cytotoxic T will also kill infected cells that have bacteria inside then.

If it's a virus...it is engulfed by the macrophage, which then can present the antigen to CD4 cells, which differentiate into cytotoxic Ts and Helper Ts. The Helper Ts help activate the sensitized B cells which then activate, proliferate and produce antibodies.

Note that NK cells also respond to viral infections for non-specific defense.

Timeline for a bacterial infection

Neutrophils are on scene first	non-specific and abundant
NK cells are next	non-specific
Macrophages	non-specific (internalize bacteria and present it)
Cytotoxic Ts	specific
Helper Ts	specific
B cells activated and proliferate	specific
Plasma cells	specific
Antibody levels up	specific

This process takes about 2-3 weeks for peak antibody levels. As Helper Ts go up, this ramps up activity of macrophages and NK cells.

Natural vs Artificially Acquired Immunity

NATURALLY ACQUIRED	ARTIFICIALLY ACQUIRED
Active: Infected, got sick Made my own antibodies	Active: I'm given a vaccine. I make my own antibodies.
Passive: Antibodies come from mom to baby...don't have to make my own antibodies	Passive: Immune serum Antibodies are injected Don't make my own Abs

Artificially acquired passive immunization is also used to suppress involvement of own B-cell activation and thus memory cell formation. It is used to treat Rh incompatibility. It keeps mom's body from seeing the antigen and stimulating T&B cells.

Monoclonal Antibodies are made in the lab...they are clones for a specific antigen, and are used as a diagnostic tool to test for the presence of specific substances in the body fluids. So they are used to test for the presence of drugs and hCG.

Antibiotics only work on bacteria. They occur naturally, but can also be used exogenously...most exogenous ones come from plants. A particular antibiotic will not work forever, because bacteria mutate. Some antibiotics kill specific types of bacteria...and others kill a variety of bacteria "broad spectrum." Antibiotics take advantage of the differences between self cells and bacterial cells.

Bacteria have:

- Thicker cell walls
- DNA not contained in a nucleus
- Smaller ribosomes
- High rate of protein synthesis, division, growth

Penicillin blocks cell wall synthesis

Streptomycin blocks protein synthesis

Immunosuppressive Drugs

Immunosuppressive drugs are used to suppress the immune system when it is beneficial to the individual. For example, it is used in cases of uncontrolled inflammation (cortisone shot), and for generalized inflammation (prednisone in pill form.) They also suppress the body's need to reject transplanted tissues.

Inappropriate Immune Response

An inappropriate immune response takes the form of autoimmune disease or allergies. In the case of autoimmune disease, the immune system is attacking self-cells because there is a problem with self-recognition. Immunosuppressive drugs are used as a general treatment. Disease examples are rheumatoid arthritis, lupus, MS, Type I DM.

In an allergic reaction, the immune response is evoked in response to a non-threatening substance (pollen, or protein components in food are common allergies). When the skin or mucus membrane comes in contact with the allergen, it produces a localized response. This involves IgE antibodies, which attach to basophils and mast cells to stimulate histamine release...this leads to an inflammatory response causing mucus secretion, edema, and bronchoconstriction (if it's in the mucus membrane of the airway.)

If the allergen gets in contact with the blood, then you have a systemic reaction...anaphylaxis. This causes constriction of smooth muscle (so it causes bronchoconstriction and stomach cramps). It also causes global vasodilation, which leads to a sudden drop in blood pressure and edema. The drop in BP is super dangerous. If the response is severe enough, it may cause anaphylactic shock that can be fatal. It is treated with epinephrine (catecholamines get started ASAP), antihistamines and glucocorticoids.

The first time you are exposed to an allergen, there is no reaction because there are no memory cells or antibodies. However, the cells are getting sensitized and produce antibodies (IgEs that bind to mast cells and basophils)...this takes weeks so that explains why there is no initial reaction.

The second time you are exposed, the allergen will bind to the antibody (which is bound to the mast cells and basophils), which causes degranulation and the release of histamine...tada...you have your allergic reaction!

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