Chapters 20, 21. Lymphatic and Immune System
Part II. Specific Immunity

Overview
- Properties of specific immunity
- Antigen presentation and the MHC complexes
- T cell activation
- B cell activation
- Antibodies
- Primary and secondary immune response
- Clonal selection
- Diseases

Specific Defenses
- Specific resistance (immunity):
  - responds to specific antigens with coordinated action of T cells and B cells
  - Recognizes specific foreign substances
  - Acts to immobilize, neutralize, or destroy foreign substances
  - Amplifies inflammatory response and activates complement
- T Cells:
  - provide cell-mediated immunity
  - defends against abnormal cells and pathogens inside cells
- B cells:
  - provide humoral or antibody-mediated immunity
  - defends against antigens and pathogens in body fluids

Forms of Immunity
- Innate: present at birth
- Acquired: after birth
  - Naturally acquired through normal environmental exposure
    - Active: antibodies develop after exposure to antigen
    - Passive: antibodies are transferred from mother through breastfeeding
  - Artificially acquired through medical intervention
    - Active: antibodies induced through vaccines containing pathogens
    - Passive: antibodies injected into body

Forms of Acquired Immunity
- Naturally acquired
  - Active: infection; contact with pathogen
  - Passive: antibodies pass from mother to fetus via placenta or to infant in her milk
- Artificially acquired
  - Active: Vaccine; dead or attenuated pathogens
  - Passive: Injection of immune serum (gamma globulin)

Properties of Immunity
- Specificity
  - Each T or B cell: responds only to a specific antigen and ignores all others
- Versatility
  - Many subtypes of lymphocytes: each fights a different type of antigen
  - active lymphocyte clones itself to fight specific antigen
- Memory
  - memory cells stay in circulation and provide immunity against new exposure
- Tolerance
  - Immune system ignores “normal” antigens
The Immune Response

- 2 main divisions:
  - cell mediated immunity (T cells)
  - antibody mediated immunity (B cells)

- MOVIE – Cell Mediated Immunity

Antigens

- Substances that can mobilize the immune system and provoke an immune response
- The ultimate targets of all immune responses are mostly large, complex molecules not normally found in the body (nonself)

Types of T Cells

- **Cytotoxic T Cells** (Tc cells, CD8 cells)
  - Attack cells infected by viruses
  - Responsible for cell-mediated immunity
- **Helper T Cells** (Th cells, CD4 cells)
  - Stimulate function of T cells and B cells
- **Suppressor T cells** (Ts cells)
  - Inhibit function of T cells and B cells

Antigens and MHC Proteins

Antigen Recognition

- T cells only recognize antigens that are bound to glycoproteins in cell membranes → “presented”

- MOVIE: antigens and MHC proteins
"Self Antigens": MHC Proteins

- Membrane glycoproteins that differ among individuals and identify them as "self"
- Bind to and present antigens
- Class I: found in membranes of all nucleated cells
- Class II: found in membranes of professional antigen-presenting cells (APCs): B cells, dendritic cells, macrophages

MHC Proteins

- Are coded for by genes of the major histocompatibility complex (MHC) and are unique to an individual
- Each MHC molecule has a deep groove that displays a peptide, which is a normal cellular product of protein recycling
- In infected cells, MHC proteins bind to fragments of foreign antigens, which play a crucial role in mobilizing the immune system

Antigen Recognition

- T cell receptors only recognize and bind to cells whose MHC protein contains an abnormal peptide fragment, starting an immune response
  - The particular antigen occupying the MHC are recognized together.
- If the MHC contains a normal cellular protein fragment, T cells will not recognize it, no reaction will occur.
- So T cells must simultaneously recognize:
  - Nonself (the antigen)
  - Self (a MHC protein of a body cell)

MHC Proteins

- Both types of MHC proteins are important to T cell activation
- Class I MHC proteins
  - Always recognized by CD8 T cells
  - Display peptides from endogenous antigens
- Class II MHC proteins
  - Always recognized by CD4 T cells
  - Display peptides from external antigens
Class I MHC Proteins

- These MHCs pick up small peptides from inside the cell and carry them to the surface and "present" them to Tc cells
- T cells ignore normal peptides
- Abnormal peptides or viral proteins activate T cells to destroy cell

Class II MHC Proteins

- Found only on professional APCs
- These cells ingest external pathogens and processes them
  - Antigenic processing (chopping up) of pathogens brought into cells
  - Fragments bind to Class II proteins
  - MHC plus fragments are inserted into cell membrane and presented to Th cells

Antigen Presenting Cells APCs

- APCs are responsible for activating T cells against foreign cells and proteins
- Phagocytic
  - Free and fixed macrophages:
    - in connective tissues
  - Kupffer cells:
    - of the liver
  - Microglia:
    - in the CNS
- Pinocytic
  - Langerhans cells:
    - in the skin
  - Dendritic cells:
    - in lymph nodes and spleen
  - B cells

CD Markers

- Also called cluster of differentiation markers: found in T cell membranes
  - CD3 Receptor Complex – All T cells
  - CD8 - cytotoxic T cells and suppressor T cells
  - CD4 - Found on helper T cells

T Cell Activation

Step 1: antigen binding

- CD8 or CD4 binds to CD3 receptor complex and prepare cell for activation
- CD8 helps bind to MHC Class I (cell types?)
- CD4 helps bind to MHC Class II (cell types?)
- APCs produce co-stimulatory molecules that are required for Tc activation
- Mobile APCs (Langerhans' cells) can quickly alert the body to the presence of antigen by migrating to the lymph nodes and presenting antigen
**T Cell Activation**

**Step 2: Costimulation**
- For T cells to be activated, it must be costimulated by binding to a stimulating cell (APC) at second site (in addition to the TCR-MHC interaction) which confirms the first signal.
- This is antigen nonspecific and can be provided by:
  - Interaction between co-stimulatory molecules expressed on the membrane of APC and the T cell (like a second lock and key).
  - Cytokines sent from APC to T cell.
- Redundancy limits errors of inappropriate activation: without co-stimulation, T cells:
  - Become tolerant to that antigen.
  - Are unable to divide.
  - Do not secrete cytokines.

**Activated T cells**
- After antigen recognition and co-stimulation, T cells:
  - Enlarge, proliferate, and form clones.
  - Differentiate and perform functions according to their T cell class.
- Primary T cell response peaks within a week after signal exposure.
- Effector T cells then undergo apoptosis between days 7 and 30.
- The disposal of activated effector cells is a protective mechanism for the body.
- Memory T cells remain and mediate secondary responses to the same antigen.

**Actions of Cytotoxic T Cells**
- Killer T cells (Tc) seek out and immediately destroy target cells (only T cells that do hand-to-hand combat) Q: What are the targets?
  - Release perforin to lyse target cell membrane.
  - Secrete poisonous lymphotxin to destroy target cell.
  - Activate genes in target cell that cause cell to die.
- Create Memory Tc Cells which stay in circulation and immediately form cytotoxic T cells if same antigen appears again.

**2 Classes of CD8 T Cells**
- Activated by exposure to antigens on MHC proteins:
  - one responds quickly:
    - producing cytotoxic T cells and memory T cells.
  - the other responds slowly:
    - producing suppressor T cells.
- Suppressor T Cells
  - Secrete suppression factors.
  - Inhibit responses of T and B cells.
  - After initial immune response.
  - Limit immune reaction to single stimulus.
**Helper T Cells (Th)**

- Once primed by APC presentation of antigen, Activated CD4 T cells divide into:
  - effector Th cells, which secrete cytokines
  - memory Th cells, which remain in reserve
- Effectors chemically or directly stimulate proliferation of other T cells and stimulate B cells that have already become bound to antigen
- Without Th, there is no immune response

**Functions of T Cell Cytokines**

1. Stimulate T cell divisions:
   - produce memory T cells
   - accelerate cytotoxic T cell maturation
2. Attract and stimulate macrophages
3. Attract and stimulate NK cells
4. Promote activation of B cells

**Pathways of T Cell Activation**

- T cells recognize and respond only to processed fragments of antigen displayed on the surface of body cells
- T cells are best suited for cell-to-cell interactions, and target:
  - Cells infected with viruses, bacteria, or intracellular parasites
  - Abnormal or cancerous cells
  - Cells of infused or transplanted foreign tissue

**Importance of Cellular Response**
Complete immune response

Step 1: B Cell Sensitization
- Corresponding antigens in interstitial fluids bind to B cell receptors (which are antibodies)
- B cell prepares for activation, a process called sensitization
- MOVIE B cell sensitization

Step 2: B Cell Activation
- A specific Helper T cell binds to MHC Class II complex on the sensitized B cell which contains peptide fragment
- Th secretes cytokines that promote B cell activation and division
- Activated B cell divides into:
  - plasma cells: synthesize and secrete antibodies into interstitial fluid
  - memory B cells: like memory T cells remain reserve in the body to respond to next infection immediately

B Cells
- Responsible for antibody-mediated immunity
- Attack antigens by producing specific antibodies
- Millions of populations, each with different antibody molecules
- MOVIE: Antibody mediated immunity

B Cell Sensitization
- During sensitization, antigens are taken into the B cell along with surface receptor (antibody), processed, and then reappear on surface, bound to Class II MHC protein
- Remember, B Cells are one of the "the professional APCs" (any cell with MHC Class II is an APC)
- Sensitized B cell is prepared for activation but does NOT yet divide; it needs stimulation by a helper T cell that has been activated by the same antigen
Adaptive Immunity: Summary

- Two-fisted defensive system that uses lymphocytes, APCs, and specific molecules to identify and destroy nonself particles
- Its response depends upon the ability of its cells to:
  - Recognize foreign substances (antigens) by binding to them
  - Communicate with one another so that the whole system mounts a response specific to those antigens

Antibodies (Immunoglobins)

- Soluble proteins secreted by activated B cells and plasma cells in response to an antigen
- Found in body fluids
- Capable of binding specifically with that antigen
- Structure
  - 2 parallel pairs of polypeptide chains:
    - 1 pair of heavy chains
    - 1 pair of light chains
  - Each chain contains:
    - constant segments: determine the type of antibody (IgG, IgE, IgD, IgM, IgA)
    - variable segments: determine specificity of the antibody
      - Free tips of the 2 variable segments form antigen binding sites of antibody molecule

Antibody Structure

5 Classes of Antibodies

- Class is determined by constant segments
- Class has no effect on antibody specificity
  - IgG: (80%). Most important class, cross placenta providing passive immunity to fetus
  - IgE: help against worms and parasites; activate basophils and mast cells to release histamine → allergy
  - IgD: Important in B cell activation
  - IgM: Pentameric. First class to be secreted during primary response.
  - IgA: found in mucosal secretions, glands, epithelia (including breast milk)

Antibody Function

- Antibodies themselves do not destroy antigen; they inactivate and tag it for destruction
- All antibodies form an antigen-antibody (immune) complex
- Defensive mechanisms used by antibodies are neutralization, agglutination, precipitation, and complement fixation

Functions of Antigen–Antibody Complexes

- Antigen–Antibody Complex = an antibody bound to an antigen. Causes:
  - Neutralization of antigen binding sites
  - Precipitation and agglutination: formation of immune complex
  - Activation of complement (main mechanism against cellular antigens)
  - Opsonization: increasing phagocyte efficiency
  - Stimulation of inflammation
Mechanisms of Antibody Action

Antibody Function - Summary
- Antibodies produced by active plasma cells bind to target antigen and:
  - inhibit its activity
  - destroy it
  - remove it from solution
  - promote its phagocytosis by other defense cells
- Importance of humoral response:
  - Soluble antibodies are the simplest ammunition of the immune response
  - Interact in extracellular environments such as body secretions, tissue fluid, blood, and lymph

Primary and Secondary Responses to Antigen Exposure
- First exposure:
  - produces initial response
- Next exposure:
  - triggers secondary response
  - more extensive and prolonged
  - memory cells already primed

Primary and Secondary Responses
- Occur in both cell-mediated and antibody-mediated immunity

Immunological Memory
- **Primary immune response** – cellular differentiation and proliferation, which occurs on the first exposure to a specific antigen
  - Lag period: 3 to 6 days after antigen challenge
  - Peak levels of plasma antibody are achieved in 10 days
  - Antibody levels then decline
  - IgM is produced faster than IgG but is usually less effective

Immunological Memory
- **Secondary immune response** – re-exposure to the same antigen
  - Sensitized memory cells respond within hours
  - Antibody levels peak in 2 to 3 days at much higher levels than in the primary response
  - Antibodies bind with greater affinity, and their levels in the blood can remain high for weeks to months
  - Activates memory B (and T) cells at lower antigen concentrations than originally required
**Immunization**

- Immunization produces a primary response to a specific antigen under controlled conditions.
- If the same antigen appears at a later date, it triggers a powerful secondary response that is usually sufficient to prevent infection and disease.

**Fetal Immunity**

- Fetus can produce immune response or immunological competence after exposure to antigen at about 3–4 months.
- Fetal thymus cells migrate to tissues and form T cells.
- Liver and bone marrow produce B cells.
- 4-month fetus produces IgM antibodies.

**Childhood Immunity**

- Before birth maternal IgG antibodies pass through placenta, provide passive immunity to fetus.
- After birth mother's milk provides IgA antibodies (continues provision of passive immunity, which otherwise fades after birth).
- Infant begins to produce its own IgG antibodies through exposure to antigens.
- Antibody, B-cell, and T-cell levels slowly rise to adult levels by about age 12.

**Diversity**

- Immune system development involves a random process of slicing up small portions of DNA in pre-T and pre-B cells.
- This random recombination creates billions of cells with slightly different genomes.
- Each of these cells produces a slightly different receptor (antibody or T cell receptor).
- Thus, you are born with the capability to respond to all possible antigens.

**Antibody Diversity**

- Plasma cells make over a billion types of antibodies.
- However, each cell only contains 100,000 genes that code for these polypeptides.
- To code for this many antibodies, somatic recombination takes place:
  - Gene segments are shuffled and combined in different ways by each B cell as it becomes immunocompetent.
  - Information of the newly assembled genes is expressed as B cell receptors and as antibodies.
- V gene segments, called hypervariable regions, mutate and increase antibody variation.
Clonal Selection

• A selection process during development weeds out the B and T cells with antibodies that respond to your own tissues
• All the rest are present in small numbers throughout your body as naive, immunocompetent lymphocytes
• When an antigen enters, it is brought to nearby lymph tissues and your lymphocytes stream through and see if they match
• The few that do are selected (become active) and start dividing into an almost identical clone which become plasma cells and memory cells
• This is the primary response. Memory cells persist for the secondary response

Clonal Selection

• When we say someone is “born with” an immunity, this has nothing to do with being born with T or B cells that recognize a particular antigen — we ALL have that (e.g. we all have cells that will respond to avian flu).
• That has to do with which MHC proteins they have — for some reason, some present certain antigens better.

Lymphocyte Development

• Immature lymphocytes released from bone marrow are essentially identical
• Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
  – B cells mature in the bone marrow
  – T cells mature in the thymus

T Cell Selection in the Thymus

• T cells mature in the thymus under negative and positive selection pressures
  – Negative selection – eliminates T cells that are strongly anti-self
  – Positive selection – selects T cells with a weak response to self-antigens, which thus become both immunocompetent and self-tolerant
B Cells

- B cells become immunocompetent and self-tolerant in bone marrow
- Some self-reactive B cells are inactivated (anergy) while others are killed
- Other B cells undergo receptor editing in which there is a rearrangement of their receptors

Immunocompetent B or T cells

- Display a unique type of receptor that responds to a distinct antigen
- Become immunocompetent before they encounter antigens they may later attack
- Are exported to secondary lymphoid tissue where encounters with antigens occur
- Mature into fully functional antigen-activated cells upon binding with their recognized antigen
- It is genes, not antigens, that determine which foreign substances our immune system will recognize and resist

Body Responses to Bacterial Infection

- Neutrophils and NK cells begin killing bacteria
- Cytokines draw phagocytes to area
- Antigen presentation activates:
  - helper T cells
  - cytotoxic T cells
- B cells activate and differentiate
- Plasma cells increase antibody levels

Combined Responses to Bacterial Infection

- Neutrophils and NK cells begin killing bacteria
- Cytokines draw phagocytes to area
- Antigen presentation activates:
  - helper T cells
  - cytotoxic T cells
- B cells activate and differentiate
- Plasma cells increase antibody levels

Combined Responses to Viral Infection

- Similar to bacterial infection, except cytotoxic T cells and NK cells are activated by contact with virus-infected cells
Response to Bacteria vs Viruses

Viral vs Bacterial Infection
- Viruses replicate inside cells, whereas bacteria may live independently
- Antibodies (and administered antibiotics) work outside cells, so are primarily effective against bacteria rather than viruses
- Antibiotics cannot fight the common cold or flu
- T cells, NK cells, and interferons are the primary defense against viral infection

Stress and the Immune Response
- Glucocorticoids:
  - secreted to limit immune response
  - long-term secretion (chronic stress):
    - inhibits immune response
    - lowers resistance to disease
- Functions:
  - Depression of the inflammatory response
  - Reduction in abundance and activity of phagocytes
  - Inhibition of interleukin secretion

Effects of Aging on Immune Response
- Thymic hormone production:
  - greatly reduced
- T cells:
  - become less responsive to antigens
- Fewer T cells reduce responsiveness of B cells
- Immune surveillance against tumor cells declines

Immune Disorders
- 3 categories of immune response disorders:
  - an inappropriate immune response (Autoimmune disorders)
  - an insufficient immune response (Immunodeficiency disease)
  - an excessive immune response (Allergies)

Autoimmune Disorders
- A malfunction of system that recognizes and ignores "normal" antigens
- Activated B cells make autoantibodies against body cells
- Activated killer T cells attack normal body cells
- Can occur by:
  - Ineffective lymphocyte programming – self-reactive T and B cells that should have been eliminated in the thymus and bone marrow escape into the circulation
  - New self-antigens appear, generated by mutations or changes in self-antigens by hapten attachment or as a result of infectious damage
<table>
<thead>
<tr>
<th>Autoimmune Disorders</th>
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<tbody>
<tr>
<td>• Grave’s Disease – TSH receptor (activates)</td>
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<tr>
<td>• Myasthenia Gravis - AChRs</td>
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<tr>
<td>• Rheumatoid arthritis- cartilage</td>
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<tr>
<td>• Insulin-dependent diabetes mellitus – beta cells</td>
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<tr>
<td>• SLE – DNA</td>
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<tr>
<td>• MS – myelin basic protein</td>
</tr>
<tr>
<td>• Pernicious anemia – parietal cells of stomach</td>
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<tr>
<th>Allergies</th>
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<tbody>
<tr>
<td>• Inappropriate or excessive immune responses to antigens</td>
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<tr>
<td>• <strong>Allergens:</strong></td>
</tr>
<tr>
<td>– antigens that trigger allergic reactions</td>
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<tr>
<td>• Antihistamine drugs</td>
</tr>
<tr>
<td>– Block histamine released by mast cells</td>
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<tr>
<td>– Can relieve mild symptoms of immediate hypersensitivity</td>
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<td>• Anaphylaxis</td>
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<th>Immunodeficiency Diseases</th>
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<tbody>
<tr>
<td>1. Problems with embryological development of lymphoid tissues:</td>
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<td>– can result in <strong>severe combined immunodeficiency disease (SCID)</strong> = X linked “bubble boy” disease</td>
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<td>2. Viral infections such as HIV</td>
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<tr>
<td>• HIV affects CD4 T cells, limits all types of immunity</td>
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<td>3. <strong>Immunosuppressive drugs</strong> or radiation treatments:</td>
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<td>– can lead to complete immunological failure</td>
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<th>Anaphylaxis</th>
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<tr>
<td>• Can be fatal</td>
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<tr>
<td>• Affects cells throughout body</td>
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<tr>
<td>• Changes capillary permeability:</td>
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<tr>
<td>– produce swelling (hives) on skin</td>
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<tr>
<td>• Smooth muscles of respiratory system contract:</td>
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<td>– make breathing difficult</td>
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<tr>
<td>• Peripheral vasodilatation:</td>
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<tr>
<td>– can cause circulatory collapse (<strong>anaphylactic shock</strong>)</td>
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<thead>
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<th>Filariasis</th>
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<tr>
<td>• Parasitic worms block lymph nodes and vessels</td>
</tr>
<tr>
<td>• Scarring causes buildup of fluid in lymph vessels and interstitial space</td>
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<tr>
<td>• Leads to elephantiasis</td>
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<td>• Treatment?</td>
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<th>Transplants</th>
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<tr>
<td>• Require tissue matching: MHC match</td>
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<td>• <strong>Immunosupression</strong></td>
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<tr>
<td>– Drugs: Cyclosporin A, tacrolimus, others</td>
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<td>– Necessary in perpetuity after most transplants</td>
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<tr>
<td>– Patients have 100x cancer risk due to loss of immune surveillance</td>
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Summary

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• Primary and secondary immune response
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• Diseases