Ch. 11: Immune Physiology

Objectives:
1. Review immune organs & cells.
2. Two types of immunity.
3. Understand functions of immune cells (T-cells and B-cells)
4. Understand autoimmunity disorders.

1. Review Immune Organs & Cells.

Immune system = The cells and organs involved in defense against pathogens and cancer.

1) Lymph Organs:
A. Primary lymph organs
   > Bone marrow - make B lymphocytes (B-cells) & T-lymphocytes (T-cells)
   > Thymus – where T-cells mature.

B. Secondary lymph organs
   > Lymph nodes - activate lymphocytes, where B cells mature
   > Lymphatic & blood vessels - transport immune cells
   > Tonsils – first line of defense from inhaled substances
   > Brain – microglia
   > Spleen - activate lymphocytes
   > Intestines - Peyer’s patches
   > Appendix - on cecum
   > Liver - Kupffer cells
3 Lines of Defense from Pathogens!

1st Line = **External Innate Immunity (non-specific)**
- External barriers to entry for orifices of the body. **KEEP PATHOGENS OUT!**

2nd Line = **Internal Innate Immunity (non-specific)**
– If a pathogen makes it past external barriers and gets inside, a non-specific defense happens through
  - Phagocytic (patrolling) cells & Fever
  - NK cells
  - Inflammation

3rd Line = **Adaptive or Acquired Immunity (specific)**
– Slower defense based on prior exposure to a pathogen
– Specific defense (memory of a pathogen)
– Involves:
  - Lymphocytes (T-cells & B-cells)
  - Antibodies (a.k.a. immunoglobulins)

1) Innate Immunity (non-specific)

**A. External Innate Defense (barriers to keep things OUT of your body)**

- Epithelial membranes – skin blocks entrance of pathogens into body, and sweat is acidic and has lysozymes that are antimicrobial.
- Stomach acid - kills various microorganisms ingested
- Respiratory tract - mucus & alveolar macrophages
- Urinary / genital defense = pH barriers (acidic vagina, urethra)
- Eyes - Lysozyme in tears is antimicrobial
1) Innate Immunity (non-specific)

B. **Internal innate defense** *(if things get in, try & kill them without antibodies)*


- Neutrophils
- Monocytes

You’re dead suckal

WBC also secrete **endogenous pyrogens** to cause fever response.

Step 2. Natural killer (NK) cells – secrete **interferons** to kill viruses.
- **toxic granules** to kill tumor/cancer cells.

Step 3. Inflammatory response
- Mast cells – secrete **histamine** for inflammation.
- Complement proteins - antimicrobial proteins (kill bacteria) & cause inflammation

Blaargh!
You’re dead suckal

Ignore! My derp
Step 1. Phagocytic WBC response:
- In bloodstream - Neutrophils & Monocytes are phagocytes that destroy pathogens & secrete endogenous pyrogens (cause fever).

- Monocytes migrate from blood into tissues by extravasation to become Macrophages that destroy pathogens in tissue.

- Macrophages places pathogen’s antigen it cell surface – now macrophage is called an Antigen-Presenting Cell (APC). APCs will activate Helper T-cells (see later in notes).

Phagocytes then send chemical “Cries for help” = cytokines, chemokines

includes neutrophils, monocytes, & macrophages

Step 2. Natural Killer (NK) Cell response
- are activated by cries for help (cytokines, chemokines), & interferon
- release interferon to kill virus-infected cells.
- release toxic granules to kill tumor cells (abnormal cells)
Step 3. Inflammatory Response

- **Mast cells** – secrete histamine for inflammation. Causes vasodilation of blood vessels. (Allows more WBCs to enter into tissue as macrophages!)

- **Complement proteins** - kill bacteria by making holes in them (bacteria burst!) & cause inflammation.

![Activation of Internal Innate Immunity](image)

1. Neutrophil and monocytes attack pathogen in blood, secrete pyrogens (fever)
2. Pathogens and macrophages in tissue
3. Macrophages eat pathogen, become APC (will activate T-cells, & cry for help (cytokines & chemokines)
4. Mast cells release histamine (start redness & swelling)
5. Cytokines & chemokines cells of adaptive immunity to the rescue!
Review

Review of Immune Organs and Cells

Innate Immunity

External innate immunity
Internal innate immunity

Activation of Innate immunity
- Phagocytic cells
- Fever (from endogenous pyrogen)
- Natural killer (NK) cells > interferon & toxic granules for viruses and tumor cells
- Inflammation response (mast cells & histamine, edema, redness, pain, vasodilation, complement proteins)

Recap of: 1) Innate Immunity

A. External innate immune system = barriers to entry of pathogens
   - Skin keeps most pathogens from entering body. Sweat is antimicrobial.
   - Tonsils (in pharynx) = 1st line of defense from inhaled pathogens.
   - Lungs have alveolar macrophages to detect & destroy inhaled pathogens AND airways have mucus to trap pathogens (and “expectorate” them)
   - Stomach is acidic – to destroy consumed pathogens.
   - Tears are antimicrobial (protect eyes as entryway for pathogens
   - Urinary tract is acidic – to kill bacteria
   - Vaginal canal is acidic – to kill bacteria

B. Internal innate immune system = protections for once pathogens get into your body.
   - Neutrophils and monocytes (phagocytic WBCs) circulate in blood, find & destroy pathogens. Send chemical cries for help (cytokines & chemokines)
   - Monocytes can extravasate into connective tissue to become macrophages
   - Macrophages find & destroy pathogens, AND send out chemical cries for help, AND can become an APC.
   - Mast cells (in connective tissue) – secrete histamine, which causes tissue inflammation & systemic vasodilation (makes vessels “leaky”, allows WBCs to enter tissues)
   - Complement proteins – poke holes in bacteria, causing them to lyse.
   - NK cells – secrete interferon to kill viruses, and toxic granules to destroy tumor cells.
How do T-cells get “activated”? 

By Antigen-Presenting Cells (APCs) of the internal innate immunity
- APC presents antigen to Helper T-cells
- Helper T-cell then is ACTIVATED!

Activated T-cells then start a cascade of other events:
- Activate Cytotoxic T-cells (Tc)
- Activate Memory T-cells (Tm)
- Activate B-cells to make antibodies

Tissue macrophages engulf pathogen. Part of pathogen moves to outside of macrophage – now an antigen-presenting cell (APC), and APC then activates helper T-cells.
**Two types of Adaptive Immunity:**

1. **Cell-Mediated Immunity (T-cells!!)**
   - **Helper T-cells** (activated by APCs)
     Now activate **Cytotoxic T cells**, which can phagocytize pathogens.
   - **Helper T-cells** also activate formation of **memory T cells** specific to an antigen
   - **Helper T-cells** activate **B-cells** to make antibodies.

2. **Antibody-Mediated Immunity (B-cells)**
   - **B-cells** (which were activated by Helper T-cells) make **antibodies** (or immunoglobulins) specific to the pathogen.
   - Results in formation of both **Plasma B-cells & Memory B cells** that have antibodies specific to the antigen.

**Activated T-cells** stimulate **B-cells (plasma cells)** to make **antibodies** to an antigen.

![Diagram of Activated Helper T Cell stimulating B-cell to make antibodies specific to pathogen]
Plasma B-cell with antibodies (the white blob), attacks the pathogen by binding to it.

I’m hit! I’m hit! Go on without me!!!

Antibodies of B-cells stick to antigen on pathogen cells and “stick them together” – process called agglutination.

The agglutinated blob will attract macrophages, which will engulf the blob & destroy it.
3 types of T-cells

- produced in bone marrow
- mature in the thymus (childhood); then 2° lymphoid organs
- produce cytokines to activate other immune cells & directly kill infected cells

T\textsubscript{H} – helper T cells

- become activated in response to antigen from APCs (antigen-presenting cells).
- stimulate B-cells to make plasma B-cells (with antibodies).
- activate cytotoxic (killer) T-cells. and other T-cells

T\textsubscript{C} – cytotoxic T cells (a.k.a. natural killer t-cells or NKT cells)

- recognize and destroy cancerous or virus-infected cells.
  (do not confuse these with NK cells of innate immunity!!)

T\textsubscript{reg} – regulatory T cells

- inhibit T\textsubscript{C} and B cells.
- may guard against allergies and autoimmune disease.

T\textsubscript{m} – memory T-cells
Retain memory of pathogen & will attack & destroy on site
**B-Cells**

- Activated by stimulation by activated Helper T-cells.
- Produce **antibodies (immunoglobulins)** to specific antigens.

- Exposure of B-cell to its specific antigen causes:
  - Release of antibodies to bind to antigens
  - Causes clonal production of more B-cells with antibodies:
    - A) **plasma B cells** for immediate defense, and
    - B) **memory B cells** for future encounters.

- Provides **humoral (or antibody-mediated, or specific immunity)**.

**Effects of antibodies:**
- Activate complement proteins
- Agglutination reaction (antibodies sticks antigen-bearing cells together)
- Agglutination “tags” pathogenic cells so they’re recognized & destroyed by phagocytes.

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**Action of B Lymphocytes**

1. Antigen binds to antibody receptors on B-cells.

2. On contact with the antigen B-cells replicate by **cloning** to make lots and lots more B-cells.

3. **Plasma B cells** formed (for immediate action),

and

**Memory B cells** formed (kept in storage for later activation).

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**I’ll fight later … I’m ready to fight now!**
Sequence of events, from entry of pathogen into the body to the formation of antibodies:

1. Bacteria enters tissue from a break in skin.
2. Neutrophils = Phagocytic non-specific WBC in the bloodstream.
3. Monocytes = Cell that extravasates from blood vessel into tissue. (is now called an Macrophage)
4. APC = Phagocytic cell in tissue, which finds pathogen, kills it, and puts antigen on its surface.
5. Helper T cell = Cell of cell-mediated adaptive immunity, which becomes activated by interaction with the cell in #4 above.
6. Activated cell from #5 above can now activate these cells:
   A. \( T_L \) = Cell of cell-mediated adaptive immunity, which directly kills pathogen.
   B. \( T_m \) = Cell of cell-mediated adapted immunity, which keeps a memory of pathogen.
   C. B cell = Cell that is part of antibody-mediated adaptive immunity.
7. Cell from 6C above can make Antibodies (otherwise known as immunoglobulins).
8. Cell from 6C above encounters its pathogen and the following happens:
   A. cause agglutination
   B. clonal copies Plasma B cells, Memory B cells

Categories of immunity:

<table>
<thead>
<tr>
<th>Innate Immunity</th>
<th>Vs</th>
<th>Adaptive Immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(also called Non-specific immunity)</td>
<td></td>
<td>(also called Specific immunity or humoral immunity)</td>
</tr>
<tr>
<td>External</td>
<td>Non-specific immunity</td>
<td>Internal</td>
</tr>
<tr>
<td>1. Innate</td>
<td></td>
<td>2. Innate</td>
</tr>
<tr>
<td><em>Skin</em></td>
<td></td>
<td><em>WBC's (monocytes endobios)</em></td>
</tr>
<tr>
<td><em>Tonsils &amp; Macrophages</em></td>
<td></td>
<td><em>Helper T cells (Th) &amp; Plasma B cells</em></td>
</tr>
<tr>
<td><em>Stomach acid</em></td>
<td></td>
<td><em>Monocytes become Macrophage</em></td>
</tr>
<tr>
<td><em>Acidic vagina</em></td>
<td></td>
<td><em>Cytotoxic T Cells (Tc) &amp; Memory B cells</em></td>
</tr>
<tr>
<td><em>Acidic urethra</em></td>
<td></td>
<td><em>Macrophage becomes APC</em></td>
</tr>
<tr>
<td><em>Natural killer cells</em></td>
<td></td>
<td><em>Memory T cells (Tm)</em></td>
</tr>
<tr>
<td><em>Tears are anti-microbial</em></td>
<td></td>
<td><em>Cytokines &amp; Chemokines, Regulatory Cells (Treg)</em></td>
</tr>
</tbody>
</table>
Recap of: 2) Adaptive immunity

A) Cell mediated immunity (T cells)
- Helper T cell activated (by APC of internal innate immunity)
- Helper T cell activates > Cytotoxic T cells, Memory T cells, & B-cells

B) Antibody mediated immunity (B cells)
- Activated B cell makes **antibodies** (to pathogen shown by helper T cell (takes a couple weeks)
- When B cells with antibody encounters its pathogen:
  > antibodies bind to pathogen, cause clumping (**agglutination**), makes pathogen visible to phagocytic cells, which come destroy it.

  > B cells **clone themselves** into:
    - Plasma B cells (ready to fight now)
    - Memory B cells (will fight later)

Review

Adaptive Immunity
- Cell-mediated adaptive immunity
- Antibody-mediated adaptive immunity

Types of T and B Cells
- T-cell formation and activity
  - $T_H$, $T_C$, and $T_{reg}$
- B-cell formation and activity
**Vaccinations**

- Late 1700s → Edward Jenner noticed milkmaids rarely had smallpox.
- Jenner reasoned that milkmaids were immune to smallpox because they had been exposed to cowpox.
- To test his hypothesis, he inoculated a boy with cowpox pathogens and then with smallpox pathogens. As predicted, the boy did not contract smallpox.

Vaccination → $1^\circ$ immune response → memory cells

Secondary response: have lots of memory B-cells that were stored & waiting for future exposure = stronger, faster immune response!

Primary response: takes ~ 2 weeks for good production of plasma B-cells with antibodies (high antibody titer) and memory B-cells after 1st exposure.
Example of Vaccine Effectiveness:

In the United States, before measles vaccine became available in the mid-1960s was estimated over 530,000 cases with 500 deaths per year. After vaccine – has been **99.9% decrease** in incidence of the disease.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PRE-VACCINE ERA ESTIMATED ANNUAL MORBIDITY*</th>
<th>MOST RECENT REPORTS OR ESTIMATES OF U.S. CASES</th>
<th>PERCENT DECREASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>21,053</td>
<td>0†</td>
<td>100%</td>
</tr>
<tr>
<td><em>H. influenzae</em> (invasive, &lt;5 years of age)</td>
<td>20,000</td>
<td>31†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>117,333</td>
<td>2,890†</td>
<td>98%</td>
</tr>
<tr>
<td>Hepatitis B (acute)</td>
<td>66,232</td>
<td>18,800†</td>
<td>72%</td>
</tr>
<tr>
<td>Measles</td>
<td>530,217</td>
<td>187†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Mumps</td>
<td>162,344</td>
<td>584†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Pertussis</td>
<td>200,752</td>
<td>28,639†</td>
<td>86%</td>
</tr>
<tr>
<td>Pneumococcal disease (invasive, &lt;5 years of age)</td>
<td>16,069</td>
<td>1,900‡</td>
<td>88%</td>
</tr>
<tr>
<td>Polio (paralytic)</td>
<td>16,316</td>
<td>1†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Rotavirus (hospitalizations, &lt;3 years of age)</td>
<td>62,500**†</td>
<td>12,500‡</td>
<td>80%</td>
</tr>
<tr>
<td>Rubella</td>
<td>47,745</td>
<td>9†</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>Congenital Rubella Syndrome</td>
<td>152</td>
<td>1†</td>
<td>99%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>29,005</td>
<td>0†</td>
<td>100%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>580</td>
<td>26†</td>
<td>96%</td>
</tr>
<tr>
<td>Varicella</td>
<td>4,035,120</td>
<td>167,400‡</td>
<td>96%</td>
</tr>
</tbody>
</table>

**Vaccinations and Halt of Communicable Disease: THE CONTROVERSY**

**Do vaccinations cause Autism???

NO!**

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**Where did the controversy start?**

A study originally published in journal *Lancet* by Andrew Wakefield in **1995** claimed that his study of **12 children** showed that the 3 MMR (measles, mumps, rubella) vaccines taken together (1st at 1 year, then at 5-6 yrs) could alter immune systems, causing intestinal woes that then reach, and damage, the brain (autism?)

**Scientific community responded:**

- Dozens of epidemiological studies found no merit to his work
- His claims were based on a tiny sample size.
- The British Medical Journal called his research “fraudulent.”
- The British journal *Lancet* retracted his publication.
- The British medical authorities stripped him of his license.

**Problem:**

People still believe Wakefield. Groups of people began to NOT vaccinate their children.
Vaccinations and Halt of Communicable Disease:

> Nationwide, vaccination rate against diseases has stayed at 90% or higher, but % in some of the country now well below that, making those communities more vulnerable to disease outbreak.

There has been an increase in cases of Measles, Mumps is the US – especially in counties where vaccination rate below 90%.

Map of US

> Medical doctors & epidemiology experts say that vaccination rate of ~95% needed to protect a community by “herd immunity”.

**Herd immunity** = indirect protection from infectious disease when a large % of population has become immune (natural or vaccination-acquired) it reduces potential exposure of non-immune people (aren’t or can’t be vaccinated) to that disease.

Herd Immunity

The top box shows an outbreak in a community in which a few people are infected (shown in red) and the rest are healthy but unimmunized (shown in blue); the illness spreads freely through the population.

The middle box shows a population where a small number have been immunized (shown in yellow); those not immunized become infected while those immunized do not.

In the bottom box, a large proportion of the population have been immunized (yellow); this prevents the illness from spreading significantly, including to unimmunized people.
Classification of Immunity

1) Active immunity = get immunity (antibodies) that you produce from actual exposure (natural) to disease organism or from vaccination (artificial exposure).

2) Passive immunity = get immunity (antibodies) from source outside your body: Natural (breast milk) or artificial (injection of antibodies).

- Your body MAKES its own antibodies
- You are given antibodies (body does NOT have to make them)
- Natural active = You are exposed to sick person & make antibodies
- Artificial active = You are vaccinated & make antibodies
- Natural passive = Given antibodies in breast milk
- Artificial passive = Given antibodies in serum
4. Autoimmunity Disorders

Problems with the Immune Response

Autoimmunity – when immune cells attack self; can be B or T cells.

*** Abnormal T-cells from Thymus associated with most autoimmune disorders!

Ex. Of autoimmune disorders:

- **rheumatoid arthritis** – attack on connective tissue of synovial joints.
- **rheumatic heart disease** – antibodies produced from strep throat attack heart valves.
- **lupus** – nuclear proteins.
- **multiple sclerosis** – attacks myelin sheaths on neurons.
- **Grave’s disease** – attack on thyroid gland TSH receptor.
- **Crohn’s disease** – attack on cecum of large intestine.
- **diabetes** (certain forms) – destruction of beta cells in the pancreas.
- **Myasthenia gravis** – destruction of nicotinic cholinergic receptors on skeletal muscles. (muscarinic)
Review

Vaccination
  - History of vaccination
  - Action of vaccinations on immunity
  - Controversy on vaccinations
    [There shouldn’t be!!!]

Classification of Immunity

Autoimmune Disorders