Immune / Lymphatic System

Avenues of attack

- Points of entry
  - digestive system
  - respiratory system
  - urogenital tract
  - break in skin
- Routes of attack
  - circulatory system
  - lymph system

Why an immune system?

- Attack from outside
  - lots of organisms want you for lunch!
  - animals are a tasty nutrient- & vitamin-packed meal
  - cells are packages of macromolecules
  - no cell wall
  - traded mobility for susceptibility
  - animals must defend themselves against invaders
    - viruses
      - HIV, flu, cold, measles, chicken pox, SARS
    - bacteria
      - pneumonia, meningitis, tuberculosis
    - fungi
      - yeast ("Athlete’s foot")...
    - protists
      - amoeba, Lyme disease, malaria
- Attack from inside
  - defend against abnormal body cells = cancers

Lymph system

Production & transport of leukocytes
- Traps foreign invaders

Lines of defense

- 1st line: Barriers
  - broad, external defense
  - "walls & moats"
  - skin & mucus membranes
- 2nd line: Non-specific patrol
  - broad, internal defense
    - "patrolling soldiers"
  - leukocytes = phagocytic WBC
    - macrophages
- 3rd line: Immune system
  - specific, acquired immunity
    - "elite trained units"
  - lymphocytes & antibodies
    - B cells & T cells

Development of Red & White blood cells

- Lymphoid stem cells
- Myeloid stem cells
- Erythrocytes
- Leukocytes
- Platelets
- Macrophages
- Monocytes
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes

Red blood cells

Pluripotent stem cells

Inflammatory response

Bacteria & insects inherit resistance. Vertebrates acquire immunity!
1st line: External defense
- Physical & chemical defenses
  - non-specific defense
- external barrier
  - epithelial cells & mucus membranes
    - skin
    - respiratory system
    - digestive system
    - uro-genital tract
  - lining of trachea: ciliated cells & mucus secreting cells

1st line: Chemical barriers on epithelium
- Skin & mucous membrane secretions
  - sweat
    - pH 3.5
  - tears
    - washing action
  - mucus
    - traps microbes
  - saliva
    - anti-bacterial = “lick your wounds”
    - stomach acid
      - pH 2
  - anti-microbial proteins
    - lysozyme enzyme
      - digests bacterial cell walls

2nd line: Internal, broad range patrol
- Innate, general defense
  - rapid response
- Patrolling cells & proteins
  - attack invaders that penetrate body’s outer barriers
    - leukocytes
      - phagocytic white blood cells
    - complement system
    - anti-microbial proteins
    - inflammatory response

Leukocytes: Phagocytic WBCs
- Attracted by chemical signals released by damaged cells
  - enter infected tissue, engulf & ingest microbes
    - Lysosomes: digest pathogens once engulfed
- Neutrophils
  - most abundant WBC (~70%)
  - ~ 3 day lifespan
- Macrophages
  - “big eater”, long-lived
- Natural Killer Cells
  - destroy virus-infected cells & cancer cells

Phagocytes
- Yeast
- Macrophage

Destroying cells gone bad!
- Natural Killer Cells perforate cells
  - release perforin protein
  - insert into membrane of target cell
  - forms pore allowing fluid to flow into cell
  - cell ruptures (lysis)
    - apoptosis
- Natural killer cell
  - perforin
  - vesicle
  - virus-infected cell
  - cell membrane
  - perforin punctures cell membrane
  - Cell Lysis
Anti-microbial proteins

- **Complement system**
  - ~20 proteins circulating in blood plasma
  - attack bacterial & fungal cells
    - form a **membrane attack complex**
    - perforate target cell
    - **apoptosis**
      - cell lyse
    - complement proteins form cellular lesion
  - plasma membrane of invading microbe
  - extracellular fluid
  - bacterial cell

Inflammatory response

- **Damage to tissue triggers local non-specific inflammatory response**
  - release **histamines** & **prostaglandins**
  - capillaries dilate, more permeable (leaky)
    - increase blood supply
    - delivers WBCs, RBCs, platelets, clotting factors
    - fight pathogens
    - clot formation
    - accounts for swelling, redness & heat of inflammation & infection

Inflammatory response

- **Reaction to tissue damage**
  - Pin or splinter
  - Bacteria
  - Chemical alarm signals
  - Blood vessel
  - Blood clot
  - Swelling
  - Phagocytes

Fever

- **When a local response is not enough**
  - systemic response to infection
  - activated macrophages release **interleukin-1**
  - triggers hypothalamus in brain to readjust body thermostat to raise body temperature
  - higher temperature helps defense
    - inhibits bacterial growth
    - stimulates phagocytosis
    - speeds up repair of tissues
    - causes liver & spleen to store iron, reducing blood iron levels
      - bacteria need large amounts of iron to grow

3rd line: Acquired (active) Immunity

- **Specific defense**
  - **lymphocytes**
    - B lymphocytes (**B cells**)
    - T lymphocytes (**T cells**)
  - **antibodies**
    - immunoglobulins

- **Responds to...**
  - **antigens**
    - specific pathogens
    - specific toxins
    - abnormal body cells (cancer)

How are invaders recognized: antigens

- **Antigens**
  - proteins that serve as cellular name tags
    - **foreign antigens** cause response from WBCs
      - viruses, bacteria, protozoa, parasitic worms, fungi, toxins
      - non-pathogens: pollen & transplanted tissue
  - **B cells & T cells respond to different antigens**
    - B cells recognize **intact antigens**
      - pathogens in blood & lymph
    - T cells recognize **antigen fragments**
      - pathogens which have already infected cells

“**self**”  “**foreign**”
**Lymphocytes**

- **B cells**
  - mature in bone marrow
  - **humoral** response system
    - "humors" = body fluids
    - produce antibodies

- **T cells**
  - mature in thymus
  - **cellular** response system

Learn to distinguish "self" from "non-self" antigens during maturation
- If they react to "self" antigens, they are destroyed during maturation

**B cells**

- **Humoral response** = "in fluid"
  - defense against attackers circulating freely in blood & lymph
- **Specific response**
  - produce specific antibodies against specific **antigen**

- **Types of B cells**
  - **plasma cells**
    - immediate production of antibodies
    - rapid response, short term release
  - **memory cells**
    - long term immunity

**Antibodies**

- Proteins that bind to a specific antigen
  - multi-chain proteins produced by B cells
  - binding region matches molecular shape of antigen
  - each antibody is unique & specific
    - millions of antibodies respond to millions of foreign antigens
  - tagging "handcuffs"  
    - "this is foreign…gotcha!"

- Each B cell has ~100,000 antigen receptors

**How antibodies work**

- **Immunoglobulins**
  - **IgM**
    - 1st immune response
    - activate complement proteins
  - **IgG**
    - 2nd response, major antibody circulating in plasma
    - promote phagocytosis by macrophages
    - Most common, can pass placental barrier
  - **IgA**
    - in external secretions, sweat & mother’s milk
  - **IgE**
    - promotes release of histamine & lots of bodily fluids
    - evolved as reaction to parasites
    - triggers allergic reaction
  - **IgD**
    - receptors of B cells?? Function unclear—found in blood

**Structure of antibodies**

- antigen-binding site
  - variable region
  - light chain
  - heavy chain

**Classes of antibodies**

- **Immunoglobulins**
  - **IgM**
    - activates complement proteins
  - **IgG**
    - promote phagocytosis by macrophages
  - **IgA**
    - in external secretions, sweat & mother's milk
  - **IgE**
    - promotes release of histamine & lots of bodily fluids
  - **IgD**
    - receptors of B cells?? Function unclear—found in blood
B cell immune response tested by B cells (in blood & lymph) 10 to 17 days for full response

Invader (foreign antigen) B cells + antibodies Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y recycled Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y clone Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y Memory cells reserves

Plasma cells release antibodies A

How do vertebrates produce millions of antibody proteins, if they only have a few hundred genes coding for those proteins?

By DNA rearrangement & somatic mutation vertebrates can produce millions of B & T cells

Immune system exposed to harmless or weakened version of pathogen

- triggers active immunity
- stimulates immune system to produce antibodies to invader
- rapid response if future exposure

Most successful against viral diseases

Vaccinations

Jonas Salk
1914 – 1995
        April 12, 1955

- Developed first vaccine
  - against polio
  - attacks motor neurons

Albert Sabin
1962
oral vaccine

Polio epidemics

1944:
America is polio free
Passive immunity
- Obtaining antibodies from another individual
- Maternal immunity
  - antibodies pass from mother to baby across placenta or in mother’s milk
  - critical role of breastfeeding in infant health
    - mother is creating antibodies against pathogens baby is being exposed to
- Injection
  - injection of antibodies
  - short-term immunity

What if the attacker gets past the B cells in the blood & actually infects some of your cells?
You need trained assassins to kill off these infected cells!

T cells
- Cell-mediated response
  - immune response to infected cells
    - viruses, bacteria & parasites (pathogens) within cells
    - defense against “non-self” cells
    - cancer & transplant cells
- Types of T cells
  - helper T cells
    - alerts immune system
  - killer (cytotoxic) T cells
    - attack infected body cells

How are cells tagged with antigens
- Major histocompatibility (MHC) proteins
  - antigen glycoproteins
  - MHC proteins constantly carry bits of cellular material from the cytosol to the cell surface
    - “snapshot” of what is going on inside cell
    - give the surface of cells a unique label or “fingerprint”

How do T cells know a cell is infected
- Infected cells digest pathogens & MHC proteins bind & carry pieces to cell surface
  - antigen presenting cells (APC)
  - alerts Helper T cells

T cell response
- infected cell
  - activated macrophage
  - helper T cell
  - interleukin 1
  - interleukin 2
  - B cells & antibodies
  - stimulate killer T cells

- infected cell
  - MHC proteins displaying foreign antigens
  - T cell antigen receptors
  - T cell
  - helper T cell
  - interleukin 1
  - interleukin 2
  - activate killer T cells
**Attack of the Killer T cells**
- Destroys infected body cells
  - binds to target cell
  - secretes **perforin** protein
    - punctures cell membrane of infected cell

**Blood type**

<table>
<thead>
<tr>
<th>Blood type</th>
<th>Antigen on RBC</th>
<th>Antibodies in blood</th>
<th>Donation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anti-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Anti-A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>Anti-A, Anti-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Anti-A, Anti-B</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Matching compatible blood groups is critical for blood transfusions. A person produces antibodies against foreign blood antigens.

**Blood donation**

<table>
<thead>
<tr>
<th>(a) Phenotype (blood group)</th>
<th>(b) Genotypes</th>
<th>(c) Antibodies present in blood serum</th>
<th>(d) Results from adding red blood cells from groups below to serum from groups at left</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>( a^+ ) or ( \bar{a}^+ )</td>
<td>Anti-B</td>
<td>A B AB O</td>
</tr>
<tr>
<td>B</td>
<td>( b^+ ) or ( \bar{b}^+ )</td>
<td>Anti-A</td>
<td>A B AB O</td>
</tr>
<tr>
<td>AB</td>
<td>( a^+ ) or ( \bar{a}^+ )</td>
<td>Anti-A, Anti-B</td>
<td>A B AB O</td>
</tr>
<tr>
<td>O</td>
<td>( \bar{a}^+ )</td>
<td>Anti-A, Anti-B</td>
<td>A B AB O</td>
</tr>
</tbody>
</table>

**HIV & AIDS**

- **Human Immunodeficiency Virus**
  - virus infects **helper T cells**
  - helper T cells don’t activate rest of immune system: T cells & B cells
    - also destroy T cells
- **Acquired ImmunoDeficiency Syndrome**
  - infections by opportunistic diseases
  - death usually from other infections
    - pneumonia, cancer

**Immune system malfunctions**

- **Auto-immune diseases**
  - immune system attacks own molecules & cells
    - lupus
    - antibodies against many molecules released by normal breakdown of cells
    - rheumatoid arthritis
    - antibodies causing damage to cartilage & bone
    - diabetes
    - beta-islet cells of pancreas attacked & destroyed
    - multiple sclerosis
    - T cells attack myelin sheath of brain & spinal cord nerves
- **Allergies**
  - over-reaction to environmental antigens
    - allergens = proteins on pollen, dust mites, in animal saliva
    - stimulates release of histamine
Key attributes of immune system

- 4 attributes that characterize the immune system as a whole
  - **specificity**
    - antigen-antibody specificity
  - **diversity**
    - react to millions of antigens
  - **memory**
    - rapid 2° response
  - **ability to distinguish self vs. non-self**
    - maturation & training process to reduce auto-immune disease