The Immune System

1. Viral nucleic acid enters the host cell.
2. Interferon genes are turned on.
3. Interferon molecules are produced.
4. Host cell 1 makes interferon and is killed by the virus.
5. Interferon stimulates cell 2 to turn on genes for antiviral proteins.
   - New viruses are produced, but they are blocked by antiviral proteins.

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Bacteria
INNATE DEFENSES AGAINST INFECTION

• first line of defense against bacteria, virus, pathogens
• present and effective long before actual exposure to pathogens
• skin and mucous membranes, phagocytic cells, stomach acid, lysozymes, hair and cilia in respiratory tract, and antimicrobial proteins
• non-specific response (response is same regardless of pathogen)
Innate Defenses:  Who Are They?

Microbe entering skin through cut – triggers innate defenses

A) microbes met by innate defense cells
   ex) phagocytic WBC’s (neutrophils, macrophages)

B) natural killer cells (not phagocytic) – release chemicals causing apoptosis in viral infected and cancerous cells

C) interferons – proteins made in viral infected cells to slow down viral infection of other cells

D) Complement System – about 30 proteins in plasma activated when microbe is present. Cause microbe lysis and trigger the inflammatory response
- Help other cells resist viral infection

1. virus infects cell
2. interferon genes activated
3. interferon made and released to neighbor cells before infection
4. host cell death
5. neighbor cells stimulated to make antiviral replication proteins

***Good example of a non-specific response. ie; the interferon works for all types of viruses.***
The Complement System and the Inflammatory Response

The Complement System - about 30 proteins activated when microbes are present, cause microbe lysis and the inflammatory response.

Inflammatory response: triggered by physical damage or microbe presence

"inflamed" = set on fire (red, swollen, warm)

eample response: pin prick to the skin

damaged cells release histamines

histamine release causes:

- nearby blood vessels to dilate and leak plasma into tissue
- increased blood flow to area
- other chemicals of complement system attract phagocytes to injury site
- phagocytes leak out of plasma → into infected tissue

Result? Increased blood flow, plasma, and phagocytes in tissue area → inflammation (red, swollen, warm)
Why is inflamed tissue a good thing?

1. Phagocytes can disinfect and clean injured tissue
   • ex: WBC's engulf bacteria and any dead body cells. Many WBC's die in process, engulfed by other WBC's. pus = dead WBC's and plasma

2. Prevent spread of infection
   • ex: platelets at injury site release clotting proteins into tissue fluid. Proteins form clot to seal off injury site and help healing process
   • * If microbe is in blood, inflammatory response is systemic. Response?
     a. release more WBC's into blood
     b. fever to increase phagocytosis and microbe death
   • **Dangerous reaction = septic shock
     • - very high fever and very low blood pressure
     ***can be fatal
The Lymphatic System: fights infection and returns fluid to circulation

- needed in BOTH innate and acquired immunity
- a branching network of vessels, lymph nodes, tonsils, adenoids, appendix, spleen, bone marrow, thymus
- vessels carry lymph fluid
- leaked plasma at injury site is returned to circulation through lymph vessels
- lymph also carries microbes from injury site to organs of lymph system

- once microbes are inside lymph organs, they are destroyed by macrophages
- fighting an infection? lymph nodes are swollen with extra macrophages and lymphocytes
When innate responses fail = Acquired Immunity

- a highly specific response for a specific microbe
- develops AFTER exposure to the pathogen
- response must be signaled by specific antigens on microbe surface (ANTIbody GENERating)
  - ex: pollen, mold, viral proteins, cell wall of bacteria
- when antigens are detected, cells respond by making antibodies (defensive proteins)
- antibodies stick to antigens on pathogen
- immune system can “remember” antigens from previous infections. Will now make new batch of antibodies quickly and prevent second infection.
  - ex: chicken pox initial exposure generates antibodies which can be re-made many years later
- immune response is quicker with each exposure
- “immunity” = resistance to a specific invader
Immunity to Pathogens Gained Actively or Passively

- Vaccination (immunization) = portion of the microbe or a harmless mutant

- stimulates immune system to make antibodies which will work when “real” pathogen is present (ex: polio, mumps, measles)

- Small Pox vaccine: the only viral disease eliminated from human system by 1977. Massive, world-wide vaccination program. EVERYONE was vaccinated

Active Immunity vs. Passive Immunity:

**Active:** through production of antibodies from natural exposure or from vaccine, long lasting effect

**Passive:** through receiving pre-made antibodies, temporary effect

ex) maternal antibodies passing thru placenta to fetus

ex) maternal antibodies passed in breast milk to baby

ex) precautionary antibodies given before travel

ex) antivenin for snake bites: antibodies derived from animals exposed to venom.
Lymphocytes: B cells and T cells boost immune system functions

Lymphocytes: WBC’s in lymph system, made in bone marrow

• if remain in bone marrow to mature → B-cell lymphocytes
• if travel and mature in thymus → T-cell lymphocytes
• after maturing, both B’s and T’s travel to lymph nodes, spleen, other organs of lymphatic system

B-Cell Lymphocytes: give humoral immunity (humor = fluid)

* secrete antibodies which circulate in plasma and lymph
* antibodies attach to foreign antigens and flag microbes for phagocytosis
* our primary defense against microbes in body fluids
* antibodies can be transferred to non-immune person

T-Cell Lymphocytes: give cell-mediated immunity and humoral immunity

* circulate in plasma and lymph and attack microbe infected cells
* stimulate B cells to make more antibodies
* signal more WBC’s to do more phagocytosis of microbes
B and T cells have specific antigen receptor proteins
- receptor proteins are on cell membrane of B and T cells
- receptors can bind to only one type of antigen
- each B or T cell has approx. 100,000 receptors - all identical to one antigen

ex: one cell can recognize antigen on mumps virus while another cell can recognize antigen on tetanus bacteria

- Any microbe which enters body, will be taken by lymph vessels to lymph organs (nodes, spleen, etc) and destroyed
- Estimated that one person has millions of different B and T cells waiting for their specific target microbe.

- “like an army of soldiers, each made to respond to one specific kind of invader”
Antigens and Antibodies:

- **Antigens:**
  - protein or polysaccharide on surface of microbes
  - ex: viral protein coat, polysaccharide on cell wall of bacteria, foreign cell surface proteins and carbs, toxins
  - have specific regions called "antigenic determinants" or "epitopes" where antibodies bind

- **Antibodies:**
  * have antigen binding sites with complimentary shape to epitopes on antigen (lock and key / puzzle piece)
How do we make antibodies? Clonal Selection

- foreign antigen interacts with the few B or T cells possessing correct receptors

- these few cells do rapid mitosis (cloning) to make many cells which now possess the specific receptors

- clonal selection = “antigen-driven cloning of lymphocytes”

- rapid mitosis produces 2 genetically identical but physically different cells:
  
  a) effector cells (B cells in plasma) (aka: plasma B cells)
     - make and secrete many antibodies specific to antigen
     - about 2000/sec
     - lots of ER in these cells
     - antibodies circulate in blood and lymph aiding humoral immunity
     - highly effective for first exposure but short lived effect (5 days)

  b) memory cells (B cells remaining in lymph nodes)
     - different appearance and function than effectors
     - last for decades
     - remain in lymph nodes for 2\textsuperscript{nd} exposure
     - some memory cells give lifetime immunity
       (ex: chicken pox, mumps, polio)
Clonal Selection in Pictures:

Process:

1. antigen in body → transported to lymph nodes
2. few B or T cells with correct shape of epitope bind to foreign antigen
3. rapid mitosis (cloning) of these few cells to make:
   4.) effector cells - make and secrete many antibodies into plasma and lymph
   5.) memory cells - stay in nodes, ready for second exposure.

** 2nd exposure’s clonal selection is faster, stronger, and produces more antibodies than 1st response
Primary vs. Secondary Immune Response

**clonal selection after second exposure: faster, stronger, and produces more antibodies than 1st response**
Antibody Structure:

- the weapons of humoral immunity
- secreted by plasma (effector) B cells during clonal selection

**Antibody Structure:**

- 4 polypeptide chains: 2 (heavy/long) and 2 (light/short)
- each chain has a “c” (constant) and “v” (variable) region
- “Y” shape overall structure
- at tip of each arm, a pair of “v’s” form an antigen binding site – where antibody will recognize and bind to the antigen
- large variety in binding site shapes
- “c” chains at bottom help to dispose of bound antigen
- 5 classes of antibodies based on the “c” chain: ex) IgA, IgD, IgE, IgG, and IgM
  “I”= immunoglobulin (antibody)
Antibody Function Mechanisms:

- recognize and bind to foreign antigen
- aid in the destruction of antigen

How?:
- antibody “marks” or attaches to antigen on invader
- creates an “antibody-antigen” complex
- this starts mechanisms to destroy the invader and its antigen

Four mechanisms:
Neutralization, Agglutination, Precipitation, Complement System Activation

1. Neutralization -
   ex: antibodies bind to viral proteins, block new host cell infection
   ex: antibodies bind to cell wall of bacteria, promotes phagocytosis

2. Microbe agglutination - antibodies on surface of pathogen clump invaders together → efficient phagocytosis
Antibody Mechanisms Continued:

3. Precipitation: similar to agglutination
   ex) antibodies link antigens together - allows antigens to precipitate out of solution as solids → phagocyte capture

4. Activation of Complement System:
   special proteins poke holes into foreign cell → lysis of invader
To Sum it All Up:

All effector mechanisms show specific recognition/attack phase → followed by a non-specific destruction phase.

A COMPLETE Immune system Needs:

1) the antibodies of humoral immunity (which ID and bind to specific antigens)

2) the innate defenses (the phagocytes and complement system)
Monoclonal Antibodies

- powerful tools in the lab and clinic
- produced by fusing B cells specific for a single antigenic determinant with easy to grow tumor cells
- result: immortal hybrid cells making huge amounts of a specific antibody
- applications:
  a) clinical lab tests to ID a particular protein (ex: home pregnancy test)
     test strip is loaded with antibodies for HCG protein. If present in urine, the protein will bind to antibodies on strip - color change indicates presence
  b) disease treatment (ex: breast cancer)
     MC antibody called “Herceptin” will bind to growth factor receptors on cancer cells and block binding of any growth hormone.
  c) chemotherapy (ex: toxin targeted cells)
     antibodies linked to toxins will seek out and bind specific antigens on tumor cells and destroy them. A targeted “smart bomb” that only destroys cancer cells, not normal ones
How do we fight microbes already present in our cells?

- **answer:** T cells and their cell-mediated immunity
- T cells respond to antigens present on cell surface of infected WBC’s
- 2 types of T cells:
  a) **cytotoxic T Cells:** attack and destroy infected WBC’s
  b) **helper T Cells:** HELP to activate cytotoxic T cells and to stimulate B cell antibody production
The Scenario:

1. macrophage ingests microbe → digests it into antigens
2. self proteins on cell membrane join with foreign (non-self) antigen
3. Helper T's recognize the self/non-self complex and bind to complex.
4. This binding activates the Helper T cell. Other ways to activate Helper T's:
   a) Interleukin-1 (IL-1) protein secreted by infected cell
5. Activated Helper T's promote the immune response:
   a) secrete IL-2 protein → stimulates cell division of Helper T's (“+” feedback)
   b) IL-2 activates more B cells → stimulates humoral immunity
   c) Helper T's stimulate cytotoxic T cells to go kill infected cells
HIV Virus: Destroys the Helper T cells

- severely impairs the immune system causing the disease known as AIDS (acquired immune deficiency syndrome)
- HIV virus transmitted in body fluids, blood in skin wound, infected needles
- virus infects and destroys Helper T cells → shuts down both humoral and cell-mediated immunity
- once inside a T cell, HIV’s reverse transcriptase kicks in → viral DNA now incorporates itself into host genome.
- about 10 years for full effects of this immune disease
- patients succumb to (die of) “opportunistic infections” and/or cancers ex) fungal infections (P. carinii) ex) Kaposi’s sarcoma in skin
- current drugs can slow HIV replication
- a “cocktail” combination of several drugs is prescribed
Cytotoxic T Cells: the only ones to destroy infected cells

- Once activated, Cytotoxic T’s recognize foreign antigens on infected cells and bind to them using their receptors.

- This binding causes Cytotoxic T cell to make new proteins (ex: perforin and hydrolytic enzymes).

- Perforin released from cyto-T → creates a hole in infected cell.

- Now, hydrolytic enzymes from cyto-T enter infected cell thru hole → triggers apoptosis and cell death of infected cell.
Cytotoxic T Cells may help fight cancer

- Genetic mutations that lead to cancer cell growth may result in abnormal protein production.
- Some of these proteins (tumor antigens) will appear on the cell surface of tumor cells.
- May be identified by cytotoxic T cells and destroyed.

Cytotoxic T cells (blue) attacking a tumor cell (gold).
The immune system depends on our molecular fingerprints

- The immune system normally reacts only against non-self substances, not against self.

- May reject transplanted organs because these cells lack the unique “fingerprint” of the recipient’s self proteins.

- Everyone has a unique protein collection or “molecular fingerprint” on cell membrane.

- Results from a group of genes called “Major Histocompatibility Complex” (MHC).

- Hundreds of alleles for each MHC gene → virtually impossible for any 2 people to have completely matching sets of self proteins (exception for identical twins).

- Must do a “tissue typing” for all potential organ transplants.

- Organ recipients receive major immunosuppressive medications during recovery.

- A “rejection” means that the immune system of recipient identified the foreign proteins on donated cells and is actively attacking them → leads to organ breakdown/failure.
Disorders/Malfunctions of the Immune System (3)

Autoimmune diseases, Immunodeficiency diseases, Stress (physical/emotional)

A: Autoimmune Diseases:

“self” is recognized as “non-self” → attacked

ex: lupus - B cells make antibodies against own self proteins. results in: skin rashes, fevers, arthritis, kidney malfunctions

ex: rheumatoid arthritis (RA) - antibodies made and attack own bone and cartilage cells in joints (pain and swelling)

ex: insulin dependent diabetes: Cytotoxic T’s target insulin producing cells in pancreas

ex: Multiple Sclerosis (MS): Cytotoxic T’s attack myelin sheath → neurological issues

** medications to treat auto-immune diseases work by suppressing immune function → may lead to inability to fight other infections
Disorders/Malfunctions of the Immune System

- **B: Immunodeficiency Diseases**: lack some components of the immune system. Results in frequent infections and potential cancers.
  
  - **ex) SCID (Severe Combined Immunodeficiency)**:
    - either inactive or absence of B and T cells.
    - Patients are extremely susceptible to even minor infections.
    - Bone marrow transplant may help
  
  - **ex) Hodgkin’s Lymphoma**: cancer of the lymphocytes.
    - lymphocytes do not function correctly
  
  - **ex) AIDS via HIV infection**: destruction of Helper T cells

- **C: Abnormal Physical and Emotional Stress**:
  
  - hormones released by adrenal glands can lower WBC count and affect immune responses.
  
  - certain neurotransmitters may affect interferon production
Allergies: Overreactions to Environmental Antigens

• Allergies: abnormal sensitivities to antigens (allergens) in the surroundings

• ex: proteins on pollen capsule, fecal material of mites, animal dandruff (dander), saliva of cats/dogs

• reactions on skin, nasal passages, bronchial tubes
  - sneezing, runny nose, cough, itching, rash, wheezing

• Allergic reaction: A 2 stage sequence

• Stage 1: Sensitization at first exposure to allergen
  - allergen in blood stream → binds to B cells
  - B cells proliferate thru clonal selection, secrete large amounts of antibodies to specific allergen
  - some antibodies attach to receptor proteins on Mast cells (histamine producers)
The two stages of an allergic reaction

Stage 2: Secondary Exposure
- allergen enters body again and now binds to antibody receptors on MAST cells
- binding triggers mast cells to create histamine → get allergic reaction
- histamines cause blood vessel dilation and leaking of fluid
  → nasal irritation, runny nose, itchy skin, tears
- antihistamines (Claritin, Nasonex, etc) are drugs that interfere with histamine function - relieve allergy symptoms
Worst Allergic Response: Anaphylactic Shock

• Overproduction and quick release of histamines → rapid inflammatory response

• can lead to dangerous drop in blood pressure, swelling and blocking of trachea

• an Epipen (with epinephrine) can quickly reverse the swelling reaction

• seen with bee venom, oils of certain nuts, shellfish proteins, penicillin