Genetics of Immunity

Chapter 17
What is Immunity?

• Process by which our bodies protect themselves against:
  – Pathogens
  – Cancer
  – Foreign Objects
  – Infectious Agents

• Cell surfaces are covered with messages that tell the body what is “self” and what is “foreign”
Antigens

• Any “foreign” signal that induces an immune response
• Usually refers to the molecules on the cell surface that are recognized by immune system as foreign
• Usually made of:
  – Carbohydrates
  – Proteins
Antibodies

• **Proteins** that recognize antigens and signal the “attack” against them
• Controlled by immune system
• Bind to specific antigens
• Part of the immune system that allows body to “remember” a previous foreign pathogen
Antigens and Antibodies

Antigen

Antibody

Foreign Cell
Pathogens

Organisms or infectious agents that cause disease

• Bacteria:
  – Single celled prokaryotic organisms
  – Can be treated with Antibiotics

• Viruses:
  – RNA or DNA wrapped in proteins
  – Cannot be “cured” once infected
  – Can be vaccinated against
How are genes involved?

Any ideas?

• Developing Antibodies and other defense mechanisms
• Genes determine Antigen that is present

What would happen if genes aren’t functioning properly?

• Autoimmune disorders
• Allergies
• Inherited immune deficiencies
Blood Types – ABO

What is different between blood types?

• Different antigens on red blood cells
• Antigens are complex sugars
• Two different types of antigens:
  – A or B
  – O means RBC have no sugars
  – AB RBC have both sugars
• Your antibodies are only against the antigens that you DO NOT have
ABO Blood Types

Type A

Type B

Type AB

Type O
Blood Types – ABO

• Individual is Type A:
  – What antibodies do they carry?
  – What blood can they receive?
  – What blood types can accept Type A blood?

• Individual is Type O

• Type AB

• When you receive a blood transfusion your body will only recognize foreign antigens based on the antibodies it has and reject
Blood Types – Rh Factor

• Blood is also either positive or negative
• This is referring to whether or not individual carries a second antigen known as “Rh”
• Positive – have Rh factor
• Negative – do not have Rh factor
• Blood types have to be matched for this, and other antigens, before transfusion
Blood Types – Rh Factor

Problem: Mother is Rh- and Father is Rh+
  • Baby may be Rh+
  • Rh- mother may reject baby’s tissue as foreign:
    – Baby’s blood supply is attacked
  • Seems to get worse after one pregnancy with Rh+ baby
  • Why is that??
HLA genes

- Human Leukocyte Antigens (HLA)
  - Leukocyte = white blood cells
  - WBC are protective part of blood
- All cells with a nucleus have HLA antigens attached to their cell surface
- This recognizes cells as “self” within body
- HLA encodes many genes all with many alleles – therefore many combinations of antigens
HLA genes

• About 50% of the genetic control of immunity is within the HLA genes
• On Chromosome 6
• Therefore this region has been linked to autoimmune disorders:
  – Asthma
  – Diabetes
  – Multiple Sclerosis (MS)
  – Arthritis and many others
Immune Response

Three levels of protection:

1. Physical Barriers:
   - Skin, mucous membranes, tears, saliva, etc

2. Innate (nonspecific) immunity
   - Phagocytosis, Antimicrobial proteins, fever

3. Adaptive (specific) immunity
   - B cells and T cells
   - Antibodies, Cytokines, etc
First Line of Defense

- Unbroken skin
- Mucous membranes
- Earwax
- Cilia in respiratory tract
- Stomach acid
- Infection fighting chemicals in tears and saliva
Second Line – Innate

• Innate because these are general defenses we are born with
• Non-specific
• Inflammation:
  – Creating a hostile environment
• Fever
• Phagocytosis:
  – WBC that ingest foreign particles whole
Second Line – Innate

Three major classes of proteins:

1. Collectins:
   - Recognize foreign antigens and recruit others

2. Complement:
   - Puncture or burst cells, release histamine
   - Histamine – induces inflammation at site

3. Cytokines:
   - Interferon, Interleukins, and TNF
Cytokines

Small secreted proteins that induce gene expression to trigger immune responses

- Interferons – alert immune response to viruses
  - Stimulate macrophages and antibodies
- Interleukins – induce fever
  - Fever makes environment hostile
- Tumor Necrosis Factor (TNF)
  - Destroys toxins and certain cancer cells
Third Line – Adaptive

Highly specific to antigens and foreign agents that are attacking.
• Takes much longer than innate response
• But works better and without such severe side effects
• B cells
  – Produce antibodies
• T cells
  – Produce Cytokines
Third Line – Adaptive

Three basic characteristics:

1. Diverse:
   - Can handle many different types of pathogens

2. Specific:
   - Distinguishes with great specificity between harmful and non-harmful antigens

3. Remembers:
   - Builds and keeps antibodies for a second attack
B cells

• T cell stimulates B cells into action
• B cells “try on” the antigen until it finds one cell type that “matches” that antigen
• That specific B cell type then:
  – Makes tons of antibody against antigen
  – Antibody speeds destruction of pathogen
  – Also, makes a “memory cell”
  – Appropriate antibody will be ready for a secondary immune response
B cells

- B cells
- Antigen
- Proliferation
- Memory cell
- Plasma cells
Antibodies

- Constructed of several polypeptides:
Antibodies

• Antigen Binding Sites – specifically binding up antigens

• Mechanism of action:
  – Kill pathogen directly
  – Neutralize toxin pathogen is producing
  – Clump pathogens together to be removed by macrophages (phagocytosis)
  – Activate complement proteins
T cells

• Both B and T cells are made in bone marrow
• T cells then move to Thymus gland
• Where do B cells act?
• As T cells move through body those that attack “self” antigens are killed off
• Therefore the T cells that reach the Thymus are selected for and remain
T cells

Several types of T cells exist:

• Helper T cells:
  – Stimulate B cells and cytokines to action

• Cytotoxic T cells:
  – Directly bind and kill pathogens
  – Or cancerous cells

• Also suppress immune system when response is finished or out of control
# Immune System Cells

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Function</th>
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| Macrophage  | Presents antigens  
              | Performs phagocytosis  |
| Mast cell   | Releases histamine in inflammation  
              | Releases allergy mediators  |
| B cell      | Matures into antibody-producing plasma cell or into memory cell  |
| T cells     | Recognizes nonself antigens presented on macrophages  
              | Stimulates B cells to produce antibodies  
              | Secretes cytokines  
              | Activates cytotoxic T cells  |
| Helper      | Attacks cancer cells and cells infected with viruses  |
| Cytotoxic   |          |
Abnormal Immunity

• Inherited Immune Deficiencies:
  – Very rare

• Acquired Immune Deficiency Syndrome:
  – HIV virus induces AIDS

• Autoimmune Disorders:
  – Very common – especially now
  – Diabetes, Arthritis, MS, Asthma

• Allergies
Inherited Immune Deficiency

• Can affect either Innate or Adaptive Immunity
• Genetically inherited disorders
• Usually rare Mendelian disorders

What genes could be involved?
• Treated with bone marrow transplants

Why does that work?
• Think of the “Bubble Boy”
AIDS

• Caused by the HIV virus
  – Human Immunodeficiency Virus

• All viruses have two choices:

• **Lysis** – to immediately kill host cell after copying selves (by bursting)

• **Lysogeny** – to insert their viral RNA into the host DNA
  – Force Host cell to copy their DNA
  – While also **Lysing** majority of cells (same time)
Viruses:

- Infectious agents that attack cells
- Can reproduce and mutate
- Cannot replicate on their own, they need the host cell’s proteins (machinery)
Choice:

Uninfected Cell → Virus Attacking and Inserting RNA → Viral RNA Integrated Into Cellular DNA → Lysogenic Cycle

Lytic Cycle

Virus Replicates Itself Until Cell Bursts

A fraction of cells integrate, while most lysis at same time.
HIV

• HIV choose **Lysogenic Cycle**
• Insert’s viral RNA into host cell’s DNA through a protein called:
  • **Reverse Transcriptase (RT)**
How do you imagine RT works?
• Reverse’s transcription by transcribing **DNA from RNA**
• Now host cell produces HIV for the virus
HIV

1. Virus binds receptors on plasma membrane and enters cell. Enzymes remove proteins around viral RNA.
2. RT catalyzes formation of DNA complementary to viral RNA.
3. New DNA strand serves as a template for complementary DNA strand.
4. Double-stranded DNA is incorporated into host cell's genome.
5. Viral genes transcribed into mRNA.
6. mRNA translated into HIV proteins in cytoplasm.
7. Capsids surround new viral RNA genomes.
8. New viruses bud from host cell.
HIV

• What would the body’s normal response to the HIV virus be?
• Attack with:
  – Fever, phagocytosis
  – Cytokines – especially Interferons
  – T cells and B cells
• HIV is an incredibly well adapted virus because it uses T cells as it’s host cells
AIDS

• As virus is being replicated by host cell
• It is also killing off T cells
• The very cells that are needed to activate the immune response
• Body cannot fight off HIV virus
• Also cannot fight off any infections
• Eventually, will develop into AIDS – Acquired Immune Deficiency Syndrome
Autoimmune Disorders

When the immune system attacks body’s own cells

• Cells that are marked with “self”
• Produce Autoantibodies – Antibodies against your own cells

Q: How does it develop?
A: We don’t really know yet:
   – Self attacking T cells aren’t selected off
   – Self antigen looks very similar to foreign?
Autoimmune Disorders

- Multiple Sclerosis (MS)
  - Body attacks CNS
- Colitis or Crohn’s Disease
  - Body attacks colon or digestive track
- Arthritis
  - Body attacks collagen
- Diabetes
  - Body attacks beta-Islet cells
Allergies

Immune system is responding to a harmless particle

• Allergen
• B cells produce antibodies against allergen
• Mast cells release histamine
• Asthma
  – Contraction of airways because of inflammation – in response to allergens
  – Can also be autoimmune
Allergies

**Initial exposure**
- Allergen

- B cell is activated
- Antibody-secreting plasma cell
- Antibodies attach to mast cell

**Subsequent exposure**
- Allergens combine with mast cell
- Mast cell releases allergy mediators

- Histamine and other chemicals cause allergic reaction
Altering Immune Function

1. Vaccines
2. Immunotherapy
   - Either amplify or redirect the immune response
3. Attacking cancer cells
4. Weakening autoimmune attacks
5. Decreasing immune response for transplantation
6. Bioterrorism
Vaccines

Inactive, or partial form of a pathogen, that stimulates B cells to develop antibodies against that pathogen

• Protection of having a previous attack without actually having the risk

• Once some diseases have been removed with vaccines there is no longer any need to administer them:
  – Polio, Smallpox
Immunotherapy

Amplifying or redirecting the immune response:

• Monoclonal antibody (MAb) treatment:
  – Producing and administering antibodies
  – Some cancer treatments, to target drugs

• Administering Cytokines:
  – Various types of cancer treatments
  – Interferon administered to prevent MS attacks
  – Why would that work?
Transplantation

Replacing a damaged organ (or tissue or blood) with one from a donor

- Immune system usually recognizes replacement as foreign (non-self)
- Attempts to destroy it
- Closely match HLA types and blood type
  - Better chance of acceptance
- Immunosuppressive drugs
  - Inhibit T cells or production of antibodies
Bioweapons

Biological weapons – use pathogens to intentionally harm individuals

• Medieval times – catapulted plague ridden bodies over city walls
• Modern times – weaponize a pathogen
  – Genetically manipulate pathogen
  – Make it stronger, more effective, concentrated
• What are your opinions about their use?
Summary

- Antigen and Antibody
- Three levels of protection
- Innate vs. Adaptive Response and all the players
- Abnormal Immunity
  - Too little or too much
- Altering Immunity
  - Vaccines, immunotherapy, transplants
Next Class:

• Read Chapter Eighteen

• Homework – Chapter Seventeen Problems;
  – Review: 1, 2, 4, 5, 7, 9
  – Applied: 1, 2, 5, 13, 15