BIOL 1030
Introduction to Biology: Organismal Biology. Spring 2011
Section A
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Keeping the bad guys at bay — immunology

The vertebrate immune system has two major components — innate immunity and adaptive immunity — they both work together to attack any and all invading pathogens (and sometimes they mess up and attack our own cells).
Immune system...

* Potential pathogens (organisms that cause disease) are everywhere in our environment.
* Yet we aren’t constantly sick.
* The vertebrate immune system allows the body to recognize its own cells, and to destroy any cell, or other structure, perceived as ‘not self.’
* It consists of a network of cells, defensive chemicals, and fluids that permeate the entire body.
Many of the organs we’ve already discussed are also a part of the immune system.
It's composed of two major tissue types.

<table>
<thead>
<tr>
<th>Main tissue types</th>
<th>Examples of Locations/Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>Thymus, spleen, and tonsils consist partly of epithelial tissue; lines lymphatic and blood vessels; lymphoid tissue lies beneath epithelial tissues of the digestive, respiratory, and urinary tracts, guarding potential points of entry for pathogens</td>
</tr>
<tr>
<td>Connective</td>
<td>Lymphocytes, antibodies, and other immune system chemicals circulate in blood and lymph, which are connective tissues; bone marrow is connective tissue that produces lymphocytes; thymus, spleen, and lymph nodes consist partly of connective tissue</td>
</tr>
</tbody>
</table>
Stem cells in red bone marrow give rise to white blood cells (WBCs).

- There are five different types of WBCs:
  1) Basophils, the least abundant of them, release chemicals that trigger inflammation.
  2) Neutrophils and . . .
  3) Eosinophils function as phagocytes (they eat foreign cells).
  4) Monocytes leave the bloodstream to become phagocytic macrophages in the body's tissues.
  5) Lymphocytes are B and T cells, which also migrate throughout the body's tissues.
Here's what they look like in humans.

White blood cells

<table>
<thead>
<tr>
<th>Neutrophil</th>
<th>Eosinophil</th>
<th>Monocyte</th>
<th>Lymphocyte</th>
<th>Basophil</th>
</tr>
</thead>
</table>

a. Phagocytes (cells that engulf bacteria and debris)

- Develops into macrophage, a type of phagocyte
- Develops into B cells or T cells
- Triggers inflammation

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Here’s what a macrophage looks like in action.
Lymphocytes deserve special mention.

- The B cells . . .
- Mature in bone marrow and then . . .
- Migrate to lymphoid tissues and throughout the blood.

- T cells also . . .
- Originate in bone marrow, but then . . .
- Mature in the thymus. From there they . . .
- Migrate throughout body. Together they . . .
- Coordinate the body’s specific immune response.
The fates of lymphocytes

1. Stem cells are formed in bone marrow.
2. Stem cells mature into B cells in bone marrow and T cells in the thymus.
3. B and T cells migrate into the blood and to lymphoid organs.
Remember the lymphatic system.

* It has multiple roles:
  * It helps to regulate tissue (interstitial) fluid;
  * It absorbs fat in the small intestine (microvilli);
  * And it works with the immune system to help defend the body against invaders.

* Its components include:
  * Lymph – the colorless fluid in the lymphatic system that originates as blood plasma.
  * Thymus – as mentioned, where T cells mature.
  * Spleen – the largest lymphoid organ and analogous to one huge lymph node in many respects.
  * Lymph nodes cleanse lymph, and may swell in an infection.
Swollen lymph nodes; tonsils and adenoids are also involved.
The body’s innate defenses . . .

* Are nonspecific and provide for a rapid, broad-spectrum defense against any infectious agent.
* They are always present and ready for action.
* Some elements can distinguish invading cells from ‘self,’ but there is no ‘memory’ to aid in future responses. However, . . .
* Physical barriers are the first line of innate defense, e.g. . . .
* Skin, mucus, tears, respiratory cilia, and stomach acid. And don’t forget the all important . . .
* Normal microflora on the skin and in the gut.
Inflammation is the . . .

* Body’s immediate, localized reaction to an injury or any pathogen that breaches the body’s physical barriers. It . . .
* Recruits immune components, helps clear debris, and creates a hostile environment for invaders.
* Basophils and mast cells trigger inflammation.
* Histamine dilates blood vessels.
* Pus may accumulate, which is – white blood cells, bacteria, and debris from the inflammation.
* Aspirin and ibuprofen (NSAIDs) reduce pain and swelling by blocking the enzymes required for inflammation.
The inflammatory response...

1. After a splinter penetrates the skin, damaged cells trigger mast cells and basophils to release histamine and other chemical signals.

2. Histamine causes blood vessels to dilate and become more permeable, causing swelling. White blood cells move into the damaged area by squeezing between the cells in the capillary walls.

3. White blood cells engulf and destroy bacteria and damaged cells.

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Innate chemicals...

* Are released as inflammation begins.
* Complement proteins (about 25 different types) recognize and punch holes in bacteria, cause mast cells to release histamine, and attract phagocytes.
* Interferons – are cytokines (cell regulators) released by cells infected with viral invaders.
* Interleukins – are cytokines released by white blood cells – some of them activate B and T cells.
* Cytokines travel to the hypothalamus and induce fever, which actually helps the fight.
The complement attack . . .

1 Activation. Complement proteins bind directly to surface of bacterium or to bound antibodies.

2 Cascade reactions. Bound complement triggers rapid activation of many other complement proteins.

3 Attack complexes formed. Complement proteins join, forming attack complexes that dot bacterial surface.

4 Lysis. Cell contents leak out of many attack complexes, killing bacterial cell.
And how interferon works . . .

http://www.valdosta.edu/~stthompson/animations/Chapter36/Antiviral_activity_of_interferon.swf
Adaptive immunity, on the other hand...

- Recognizes and remembers specific pathogens.
- It works with innate defenses.
- Antigen – any molecule that stimulates a response from B and T cells.
- Each B or T cell responds to only one specific antigen. Really!
- Antibodies are Y-shaped molecules made by B cells in response to antigens.
The two systems work together to provide multiple levels of defense.
So how's that specificity thing work?

- All of an individual's lymphocytes produce a billion or so different specific antibodies and antigen receptors over a lifetime.
- Yet fewer than 250 genes encode antigen binding precursors, because different segments of these genes are rearranged in thousands of different ways in newly developing lymphocytes.
- An analogy is there are only so many words in a language, but all sorts of different stories can be told.
- This huge diversity in antigens that can be recognized is generated through genetic recombination.
- Countless lineages produce a unique antigen receptor and antibody (B cells), many of which will never encounter a pathogen, but many will!
Here’s a schematic of the process. This ‘shuffling,’ like much in biology, is a random phenomenon.
And one more time in animation.

Human cells do not have enough DNA to have separate genes for each antibody molecule. Instead, different segments of DNA can be mixed and matched to form different antibodies.

http://www.valdosta.edu/~stthompson/animations/Chapter36/Antibody_diversity.swf
Clonal deletion . . .

* In this huge diversity of generated antibodies, some may respond (badly) to your body’s own cells.

  This would not be good! Therefore, . . .

* All of them are tested against your body’s cell surface proteins, and those that match ‘self’ are destined for . . .

* Apoptosis (remember, programmed cell death), and this weeds out lymphocytes that react to the body’s own tissues.

* All of this begins well before birth.
Clonal deletion of the 'problem children'...

Gene recombination

Receptors

Self

Eliminated clones

Self
Macrophages . . .

* The macrophages are one of the first cells to respond to attack. They both . . .
* Participate in innate defenses, and . . .
* Trigger adaptive immunity.
* They engulf the pathogen, then dismantle it, and then link its antigens to self-proteins on the macrophage surface. Thus they become the . . .
* “Antigen-presenting cells” of the immune system.
* Then they travel to the lymph nodes.
This diagram depicts a macrophage displaying but one of the many antigens that any pathogen would have in reality.

1. Phagocytosis of the microbial invader

2. Antigens from the dismantled invader are attached to self proteins.

3. Self proteins and their attached antigens are displayed on macrophage surface.

4. Antigen-presenting macrophage travels in lymph to lymph node.

5. At the lymph node helper T cells recognize antigens and self proteins and bind to the macrophage, initiating a series of immune events.
Here’s what the complex looks like for real.
And here's what happens at that macrophage/helper T cell interaction.

Proteins generally require the cooperation of T-helper cells (Th2) to stimulate B cells into becoming antibody-producing cells and memory cells. Such antigens are therefore said to be T-cell dependent.

http://www.valdosta.edu/~stthompson/animations/Chapter36/t_cell_dependent_antigens.swf
**Helper T cells are the . . .**

* ‘Master cells’ of the immune system.
* Antigen-presenting macrophages meet Helper T cells specific to the antigen being displayed, and . . .
* The two cells bind. This initiates both . . .
* Cell-mediated immunity, where . . .
* Cytotoxic T cells kill invaders by direct cell-to-cell contact. And it also initiates . . .
* Humoral immunity, where . . .
* B plasma cells make antibodies that circulate in the blood, and B memory cells ‘remember’ the antigen.
There's a lot going on with these T and B cells.

**T**: Cell-mediated

**B**: Humoral

**Cell-mediated immunity**: Cytotoxic T cells attack infected cells.

**Humoral immunity**: B cells secrete circulating antibodies.
Here's an animation of the interaction between an infected cell and the cytotoxic T cell.

http://www.valdosta.edu/~stthompson/animations/Chapter36/cytotoxic_t_cells.swf
Lots of parts to the adaptive immune system...

Bone marrow:
- T cells, B cells, and macrophages originate in the bone marrow and migrate into the blood.

T cells mature in the thymus gland, in the small intestine, and in the skin.

Mature T cells
- Interleukins
  - Helper T cells initiate cell-mediated and humoral immunity.

Helper T cells
- Cytotoxic T cells
  - Cell-mediated immunity: Cytotoxic T cells attack cells directly

Mature B cells
- B cells are released from lymphoid tissue and secrete antibodies.
  - Humoral immunity: Antibodies

B cells mature in bone marrow and travel to lymphoid tissues, such as the spleen and lymph nodes.

Macrophages
- Macrophages engulf bacteria and stimulate helper T cells to proliferate and activate B cells.
More on T cells . . .

- Cytotoxic T cell are also called killer T cells. And as I just said . . .
- They provide cell-mediated immunity, because specific . . .
- Surface receptors bind to specific antigens on the attacker.
- They release biochemicals that cut holes in the invader’s cell membrane. This kills the invading cells.
- They also recognize and kill:
  - ‘Self-cells’ infected with viruses; . . .
  - Transplanted tissues; and . . .
  - Cancer cells.
- Memory T cells help ‘remember’ the specific triggering antigen, such that . . .
- Next time the response is faster and stronger.
Here's a cytotoxic T cell killing a cancer cell.

1. Cytotoxic T cell binds to cancer cell.
2. Toxic chemicals from cytotoxic T cell break cancer cell apart.
3. Cytotoxic T cell has lysed cancer cell.
And the real thing in action.
Here's a video of cytotoxic T cells.

http://www.valdosta.edu/~stthompson/videos/Chapter36/FleshEatingCells.mov
What about those B cells?

* They direct the humoral response.
* Each B cell makes a specific different antibody.
* In passive immunity antibodies are received from some external source, like when . . .
* Infants get antibodies in breast milk.
* In active immunity the body makes its own antibodies.
The humoral immune response can be launched in two ways.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Passive immunity| Individual acquires antibodies from another individual | • Fetus acquires antibodies from mother via placenta or milk
                                                                  • Dog bite victim receives injections of antibodies to rabies virus |
| Active immunity | Individual produces antibodies to an antigen      | • Having chickenpox confers future immunity to that disease ("natural" active immunity)
                                                                  • Influenza vaccine triggers production of memory cells specific to antigens in the vaccine ("artificial" active immunity) |
Let's return to antibodies (a.k.a. immunoglobulins)

- They circulate freely in blood, lymph, and interstitial fluids. They are composed of a...
- Constant region – similar in all antibody molecules, and a...
- Variable region – which determines the specific target antigen interacted with.
- Binding to antigens can inactivate microbes, neutralize toxins, cause clumping of microbes making them attract macrophages, coat viruses, and activate complement proteins!
The simplest and most dominant form of them has a classic Y-shape. Here’s a schematic, and a model, and the ‘real’ thing: http://molbio.info.nih.gov/v/cgi-bin/moldraw?1IGT
Clonal selection . . .

- Each B cell has a version of the antibody that it is programmed to make. However, each . . .
- B cell is dormant until it is activated by the specific antigen that it recognizes.
- Helper T cells help complete the activation.
- Then the B cells clonally and rapidly divide to form:
  - Memory cells – which do not make antibodies, last a long time, and wait for the next time that that specific antigen enters the body to react faster and stronger. And . . .
  - Plasma cells – which make antibodies, but do not last very long.
Here's a diagram of clonal selection. Only the B cell that binds the antigen proliferates.
But all pathogens have many different antigens; therefore, many different B cells participate in the humoral response.
And an overview of the entire process.

http://www.valdosta.edu/~stthompson/_animations/Chapter36/immResponse.swf

* Activation of the immune response typically begins when a pathogen enters the body. Macrophages that encounter the pathogen ingest, process and display the antigen fragments on their cell surfaces.
However, . . .  

* Turning off the immune system is as important as turning it on.  
* Otherwise the system could start attacking our own bodies.  
* Therefore, negative feedback loops turn off the immune system.  
* A key element is suppressor T cells begin to reduce the number of dividing B and T cells, until mainly memory cells remain.
As mentioned, this is controlled by yet another negative feedback loop.

- Antigen present
  - Lymphocytes stimulated to divide
  - Number of B cells and T cells increases
  - Number of B and T cells decreases

- Immune system activation
  - Immune system “backs down”
  - Cytotoxic T cells kill proliferating B and T cells

- Antigen absent (or diminished by immune system action)
These memory cells are important!

- The primary immune response is...
- The first reaction to an antigen.
- It takes days or even weeks to reach effective levels of circulating antibodies.
- However, the memory B and T cells ‘remember’.
- Such that during a secondary immune response to the same antigen the...
- Memory cells respond much faster and much stronger.
- Vaccines create this same effect without risking an actual infection.
Here are the responses graphically.

- Primary response
- Secondary response

Antibody concentration

First exposure to antigen

Second exposure to antigen

Time
Which brings up vaccines.

Table 36.A  *Types of Vaccines*

<table>
<thead>
<tr>
<th>Vaccine Formulation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live, weakened (attenuated) pathogen</td>
<td>Polio (oral vaccine), measles, mumps, rubella, chickenpox</td>
</tr>
<tr>
<td>Inactivated (killed) pathogen</td>
<td>Polio (injectable vaccine), influenza, hepatitis A</td>
</tr>
<tr>
<td>Inactivated toxins</td>
<td>Tetanus, diphtheria</td>
</tr>
<tr>
<td>Parts of killed pathogens</td>
<td>Cholera, whooping cough</td>
</tr>
<tr>
<td>Recombinant vaccines; component vaccines</td>
<td>Lyme disease, hepatitis B, human papillomavirus</td>
</tr>
</tbody>
</table>
And how they’re built.

Vaccines present antigens from a pathogen to stimulate immunity. Antigens are parts of a pathogen that the immune system can recognize, such as a surface protein.

* [http://www.valdosta.edu/~stthompson/animations/Chapter36/constructing_vaccines.swf](http://www.valdosta.edu/~stthompson/animations/Chapter36/constructing_vaccines.swf)
But the system can mess up — immune disorders

* A weakened immune system leaves a person open to opportunistic infection. These are caused by pathogens that do not normally infect people with healthy immune systems.
* Human immunodeficiency virus (HIV) does this by . . .
  * Causing acquired immune deficiency syndrome (AIDS).
  * HIV targets helper T cells, and can remain latent for years.
  * Symptoms appear when helper T cell count falls.
* Severe combined immune deficiency (SCID) is an . . .
  * Inherited condition in which neither B or T cells function.
  * (The bubble boy) Now patients can receive gene therapy.
* Immune systems are intentionally crippled by drugs after transplant operations so that tissues are not rejected. These people need to stay on immunosuppressants the rest of their lives.
This is Karposi Sarcoma, an AIDS related cancer.
Another type of immune disorder is autoimmunity.

* In these the immune system attacks the body’s own “self antigens.” Examples include . . .
  * Juvenile (Type I) diabetes – the pancreatic beta cells are attacked. This stops insulin production (often in children) for the life of the patient.
  * Rheumatoid arthritis – (as seen earlier in the course) the cells lining the joints are destroyed.
  * Systemic lupus – DNA, neurons, and blood cells are all attacked.
  * We do not understand autoimmunity well at all!
**Here are those and some others.**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Symptoms</th>
<th>Targets of Antibody Attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>Lower back pain, kidney damage</td>
<td>Kidney cell antigens that resemble <em>Streptococcus</em> antigens</td>
</tr>
<tr>
<td>Graves disease</td>
<td>Restlessness, weight loss, irritability,</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td></td>
<td>increased heart rate and blood pressure</td>
<td></td>
</tr>
<tr>
<td>Juvenile (Type I) diabetes</td>
<td>Thirst, hunger, weakness, emaciation</td>
<td>Pancreatic beta cells</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Muscle weakness</td>
<td>Nerve message receptors on skeletal muscle cells</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>Weakness, shortness of breath</td>
<td>Heart valve cell antigens that resemble <em>Streptococcus</em> antigens</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Joint pain and deformity</td>
<td>Cells lining joints</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Thick, hard, pigmented skin patches</td>
<td>Connective tissue cells</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Red rash on face, prolonged fever,</td>
<td>DNA, neurons, blood cells</td>
</tr>
<tr>
<td></td>
<td>weakness, kidney damage</td>
<td></td>
</tr>
</tbody>
</table>
Allergies are also an immune system problem.

* An overly sensitive immune system reacts to normally harmless substances. These are...

* Allergens – the antigen triggering an allergy – can include plant pollens, pet dander or fur, dust mites, various foods, plant oils, antibiotics, toxins, etc.

* In all cases the allergen activates B cells to produce antibodies. Subsequent exposures cause mast cells to release histamines and other immune biochemicals. This causes the symptoms.

* The severity depends on dose and site in the body.

* Anaphylactic shock can be life-threatening.

* The “hygiene hypothesis” suggests that we work too hard to keep our environment ultra-sterile!
An allergic reaction...

First exposure to antigen

Pollen

Allergen

B cell

B cell is activated

Plasma cell

Antibody-secreting plasma cell

Mast cell

Antibodies attach to mast cell

Subsequent exposure to antigen

Allergens combine with mast cell

Mast cell releases allergy mediators

Histamine and other chemicals cause allergic reaction

Mast cell bursting

(top) © David Scharf/Peter Arnold, Inc., (bottom) © Phil Harrington/Peter Arnold, Inc.
In general, a female’s immune system dampens during pregnancy.

- So that a woman's immune system doesn’t attack her fetus. However, the . . .

- Immune system of an Rh⁻ woman (she lacks the RH antigen on her red blood cells) can destroy the blood of her Rh⁺ fetus.

- Therefore, blood tests are always given to identify this potential problem, and . . .

- Drugs can be administered to inactivate the woman’s anti-RH⁺ antibodies.
Here's the scenario.

First pregnancy with Rh\(^+\) fetus

If an Rh\(^-\) woman is carrying an Rh\(^+\) fetus,

Rh\(^+\) cells enter her bloodstream during childbirth.

She produces anti-Rh\(^+\) antibodies.

Generally this is no problem for this fetus and it has a normal birth.
But during subsequent pregnancies (if anti-Rh+ antibody drugs aren’t used)...

This can kill the fetus!
That’s it for immunology.

* Next time we’ll cover animal reproduction, embryology, and development.

* And then the class session after that is the exam covering all of animal physiology!

* Remember – with this much material you will only be tested on the very most important general concepts. I’ve mentioned these as I’ve gone through the lectures. It’s your responsibility to have been paying enough attention to know what they are.