**Microbiology 204: Cellular and Molecular Immunology**

Class meets MWF 1:00-2:30PM  
(*exceptions: no class Fri Oct 11; Wed Nov 27 will be moved to 11/25)

Lectures are open to auditors

Discussions are restricted to those enrolled in class (or by permission)

Problem sets and review sessions every other week by our TA: Mark Noviski ([Mark.Noviski@ucsf.edu](mailto:Mark.Noviski@ucsf.edu))

Course web site: http://immunology.ucsf.edu/courses  
Recommended textbook: Janeway’s Immunobiology;  
OR Abbas and Lichtman Cellular and Molecular Immunology;  
OR DeFranco, Robertson, and Locksley Immunity

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**Microbiology 204: Cellular and Molecular Immunology**

Grades: 2/3 take-home final and 1/3 participation in discussions

My office hours: Mondays 3-4PM HSE1001E or by arrangement (anthony.defranco@ucsf.edu)
What does the immune system do?

• It protects us from infections with:
  – 208 viruses
  – 538 bacteria
  – 317 fungi
  – 287 worms
  – 57 parasitic protozoa (CDC numbers)
• It promotes normal functioning of the body (tissue cleanup, wound repair)
• It removes abnormal cells including malignant ones
• But the immune system can also cause disease when it is not doing the right thing (allergies, autoimmunity, transplant rejection, etc.)

The players

• Sentinel cells in tissues
  – Dendritic cells, macrophages, mast cells
• Circulating phagocytes and granulocytes
  – Neutrophils, monocytes, eosinophils, basophils
• Lymphocytes: cells which can recognize particular pathogens (but also can cause allergies and autoimmune diseases)
  – B lymphocytes: antibodies
  – T lymphocytes: cell-mediated immunity
  – (also innate lymphoid cells, NK cells, etc.)
• Tissue cells (epithelial cells, endothelial cells, etc.)
Immune sentinel cells in the tissues: dendritic cells

**Langerhans cells (epidermal dendritic cells) in the skin**

### Response to Infection I: Inflammation

- Dendritic cells in tissue recognize characteristic features of infectious agent or tissue damage
- They secrete proteins ("**cytokines**") that act on neighboring cells/blood vessel cells
- Blood vessel cells put adhesion molecules on their surface → circulating immune cells adhere and move into infected tissue
- Blood vessels also allow fluid from blood to enter into the infected site providing soluble components such as antibodies
- We call this response **inflammation**. In the context of infection it is good, but if inflammation is prolonged or chronic then tissue damage can result
Leukocyte recruitment to sites of inflammation

The neutrophil is the immune system’s first responder

- Neutrophils are typically the first white blood cells to come into a site of acute inflammation
- Neutrophils make nasty chemicals and are very good at killing microbes, but also can damage tissue (pus is mostly dead neutrophils)
- Neutrophils are usually short-lived cells and must be replenished continuously by the bone marrow (impaired by many chemotherapies for cancer treatment)
- Next in are the monocytes, which can either continue the fight or can clean up the mess (directed by cytokines)
Killing of microbes by phagocytes

- Neutrophils and monocytes can directly recognize characteristic features of the cell surface of many microbes ("innate immunity") to allow them to "eat" the bugs ("phagocytosis") and then kill them once inside.
- Soluble immune components (innate components and antibodies) can bind to microbes and allow phagocytes to eat them voraciously.
- Microbes that cause illness in healthy people either resist phagocytosis or resist killing inside phagocytes (mostly).

Adaptive immunity: our most powerful defense

- Innate immunity utilizes evolved recognition mechanisms and is surprisingly effective, but changes little based on life experience.
- **Adaptive immunity** learns from previous experience and hence can protect better upon a second infection by the same agent.
- In innate immunity, many cells use the same "receptors" to recognize conserved molecules of microbes, viruses, worms, etc.
- In adaptive immunity "antigen receptors" of T and B lymphocytes are generated by DNA rearrangements in each developing cell, they are each a little bit different and what they recognize is based on chance, the system must then decide which are useful, and which are potentially harmful.
Many different antibodies are created by combinations of gene segments

Adaptive Immunity: Antibodies I

- We can make millions or billions of different antibodies, each highly specific for a single molecule (ideally a pathogen molecule)
- As it develops, each B lymphocyte alters its DNA so it makes ONE antibody; each B lymphocyte is an individual, its antibody is unique
- A molecule that induces the production of an antibody is called an “antigen”
- In a normal immune response, several B cells that make antibodies that recognize the infectious agent become activated, each multiply to form a “clone”. These progeny then become antibody-secreting factories.
The Clonal Selection Hypothesis

Generation of lymphocytes of many specificities

Clonal deletion to remove self-reactive lymphocytes

Clonal selection to expand pathogen-reactive lymphocytes during an immune response

Specificity and memory in adaptive immunity, illustrated by primary and secondary immune responses.
Adaptive Immunity: Antibodies II

- Often, B cells are “helped” by T lymphocytes which also recognize the pathogen, these B cells take longer to make antibodies, but make higher quality antibodies (bind more strongly). Some of these high quality-producing B cells turn into antibody-secreting factories that go to the bone marrow and last a very long time (years). The antibody they produce can protect us immediately when that infectious agent returns and prevent noticeable illness.
- This type of high quality/long lasting immune response ("germinal center response") is the mechanism behind almost all successful vaccines; understanding this principle was used to greatly improve a class of vaccines against bacterial pathogens, resulting in the "conjugate vaccines" (starting in the 1990s).

Antibodies bind antigens

Two protein components: heavy chain and light chain; can come in 5 varieties of heavy chains: IgM, IgG, IgA, IgE, IgD.
Antibodies can be directly protective or can promote immune protective mechanisms via other cells or molecules

Adaptive Immunity:  Antibodies III

- Vaccines produce “active immunity”, which is the best kind but takes 1-2 weeks to become effective
- Antibodies can be transferred to an individual needing them, in which case they take effect almost immediately. Examples: protection against tetanus (in an exposed person not previously vaccinated), hepatitis A, protection against snake venoms, therapeutic antibodies, etc. (“passive immunity”)
- Antibodies taken from a person or an animal are “polyclonal antibodies” because they are the products of multiple B cells. We can take a single B cell that makes a desired antibody, immortalize it, and use this antibody as a therapeutic. This is called a “monoclonal antibody” because it all derives from one original B cell (or clone of B cells). Monoclonal antibodies are all identical and hence a more standardized therapeutic or diagnostic.
- In the last 10 years, several novel monoclonal antibody therapies have been introduced each year. The breakthrough was to make these antibodies be as similar to human antibodies as possible, so that our own immune system doesn’t react to them. Most of these are used for treating cancers or for suppressing immune responses
Monoclonal antibodies used in medicine

Standardized, unlimited reagents for diagnosis or therapy

<table>
<thead>
<tr>
<th>Monoclonal Antibodies Used in Therapies</th>
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<tbody>
<tr>
<td>monoclonal antibody</td>
</tr>
<tr>
<td>trastuzumab</td>
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<td>infliximab</td>
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From Immunity: The Immune Response in Infectious and Inflammatory Disease ©2007 New Science Press Ltd by DeFranco, Locksley and Robertson

Some representative examples. This list is rapidly expanding in recent years

CD Nomenclature

- Structurally defined leukocyte surface molecule that is expressed on cells of a particular lineage (“differentiation”) and recognized by a group (“cluster”) of monoclonal antibodies is called a member of a cluster of differentiation (CD)

- CD molecules (CD antigens, CD markers) are:
  - Identified by numbers
  - Used to classify leukocytes into functionally distinct subpopulations, e.g. helper T cells are CD4+CD8-, CTLs are CD8+CD4-
  - Often involved in leukocyte functions

- Antibodies against various CD molecules are used to:
  - Identify and isolate leukocyte subpopulations
  - Study functions of leukocytes
  - Eliminate particular cell populations
Adaptive Immunity: Cell-mediated immunity I

- T lymphocytes recognize small pieces of proteins ("peptides") associated with our own cells.
- They do this with the "T cell antigen receptor" or TCR which is like an antibody, but always on the surface of the T cell, never secreted.
- Therefore the T cell only functions locally next to cells that have its antigen.
- As with B cells, T cells alter their DNA such that each T cell makes a unique TCR and different T cells recognize different antigens.
- There are two types of T cells: helper T cells and killer (or cytotoxic) T cells.
- Helper T cells express a molecule called CD4 and are the cells that are infected by HIV-1; their depletion leads to the immunodeficiency of AIDS.
- Cytotoxic T cells express a similar molecule called CD8.

Peptides are bound to MHC molecules and presented to T cells

\[ \text{MHC} = \text{major histocompatibility complex, HLA = human leukocyte antigen} \]
T cells can directly kill virus-infected cells or can promote the immune defense capabilities of other cells.

Adaptive Immunity: Anatomy of the response

- Naïve T cells and B cells recirculate between lymph nodes, spleen, and the blood.
- Antigen is taken from site of infection to the lymph node either by the flow of lymph or is carried by a maturing dendritic cell that migrates along the lymphatics.
- The dendritic cell presents antigen to naïve T cells in the lymph node to initiate the T cell immune response.
- Activated T cells, after they have expanded in number, leave the lymph node and go via the blood to sites of inflammation, where they look for their antigen to mediate cell-mediated immunity.
Immune responses are tailored to the type of infection

- **Defense against most microbes:** Antibodies and phagocytes; neutrophil-rich inflammation can be prolonged by helper T cells ("Th17")
- **Defense against microbes that survive and replicate inside phagocytes (macrophages and monocytes):** "**type 1 immunity**" with helper T cells which can detect infected cells and promote killing of the microbes inside macrophages
- **Defense against viruses:**
  - Early defense: innate mechanisms that restrict virus replication (interferon, etc.)
  - Adaptive immune defense: antibodies which block virus infection of cells ("neutralizing antibodies") plus **cytotoxic T cells**, which can detect infected cells and kill them
- **Defense against worms and biting insects:** "**type 2 immunity**", specialized helper T cells promote IgE antibody formation, which works with mast cells (tissue) and basophils (blood) to strengthen epithelial barriers and to bring in eosinophils which can attack worms. Manifestations include: sneezing, coughing, itching, diarrhea, tears, etc. (allergies and asthma mostly involve this type of immune response)

Innate Lymphoid Cells: Parallels to T cell subsets


IL-5
B cells and T cells: how do they know what is an infection?

- Many (but not all) B cells and T cells that react to self components are removed during their development.
- Innate immune recognition leads dendritic cells to express molecules that promote T cell activation ("costimulation"; new therapeutic that blocks this).
- Some T cells of the CD4 type secrete cytokines that inhibit immune responses instead of stimulate them ("regulatory T cells"). Mostly these are generated during the development of T cells if they see self-antigen during their maturation. Some are generated in the periphery during immune responses to foreign antigens.
- Individuals who have a genetic defect in making regulatory T cells experience severe inflammatory disease of many organs starting at the time of birth, demonstrating a critical role of these cells in preventing autoimmune and inflammatory disease at body surfaces in most of us.

Immune system and chronic inflammation

- **Sterile inflammation** (tissue injury but no infectious agent present): innate recognition of tissue damage
- **Chronic inflammation**: if antigen persists, antigen-reactive T cells can drive continued inflammation, which can cause tissue damage (autoimmune diseases and inflammatory diseases)
- Likely important role of inflammation in pathogenesis of chronic diseases: atherosclerosis, type 2 diabetes, probably Alzheimer’s disease, cancer (can be positive or negative)
Immune surveillance and cancer

- There is good evidence that the immune system removes early cancerous cells in many cases (reduces cancer incidence)
- Monoclonal antibody therapeutics for several types of cancer (trastuzimab, rituximab)
- The immune system cures leukemias after using chemotherapy to kill most of the cancer cells and bone marrow transplantation ("graft vs. leukemia effect")
- Ongoing efforts to boost a patient’s own T cells to reject their cancer (anti-CTLA4 recently approved for treatment of malignant melanoma, “Ipilimumab”)

Anti-inflammatory therapies

- Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen): inhibit inflammation as well as pain but mostly useful for relatively mild inflammation
- Glucocorticoid steroids (cortisone, etc.): very potent anti-inflammatory and immunosuppressive drugs but very significant side effects of long-term use
- Newer biologics (monoclonal antibodies and related molecules) block inflammatory cytokines for nasty autoimmune and inflammatory diseases
Keeping your immune system in good working order

- Topic for conversation with friends and family at Christmas time!
- Nutrition and the immune system
  - Malnutrition impairs immune function (macronutrients and also some micronutrients)
- Stress and the immune system
  - Chronic stress has detrimental effects on immune function but this is complex
- Mind over matter?
  - The vagus nerve regulates immune responsiveness to some extent
  - Placebo effects tend to be significant for diseases in which immune system contributes
- Ageing and the immune system
- Vaccination

Keeping your immune system in good working order: Vaccination

- We have many vaccines that are highly effective, some that are marginally effective; we have a need to develop new vaccines against HIV, TB and malaria, etc.
- Childhood vaccinations: Yes, do it; don’t believe the fears spread on the internet
  - A British physician claimed that mercury preservative in vaccines caused autism. This has been completely discredited
  - DPT vaccine for infants protects against diphtheria, tetanus and pertussis (whooping cough). The formulation used prior to 2002 did have high fever as an infrequent but significant side effect. This has been replaced in the US with a safer formulation (DaPT) in which the pertussis component is more purified.
  - Whooping cough has made a very significant comeback among unvaccinated young children and is a severe disease. Now seeing that the DaPT vaccine only gives protection for about 10 years.
Keeping your immune system in good working order: Vaccination II

Vaccines aren’t just for children!

• Tetanus booster: every 10 years!
• Flu vaccine: Yes, for most people. Influenza can be life-threatening, especially in older people (generally needed every year due to changes in the virus coat)
• Traveling to foreign countries: vaccination may be helpful. Plan ahead. City of San Francisco’s Adult Immunization and Travel Clinic, also see CDC web site
• As we (or your parents) get older: Shingles vaccine and/or Pneumovax? ask your doctor