MCB55 **Innate Immunity Handout**

The PURPOSE OF THE IMMUNE SYSTEM is to protect us from pathogens. However, this is no easy task, in part because the pathogens that infect us are incredibly diverse, and have so many different ways to infect us, replicate within us, and spread to new hosts. Here we describe the basic architecture of the immune system and how it copes with such diversity.

THE IMMUNE SYSTEM

1. Immune responses

The immune system is responsible for the recognition and elimination of pathogens. It acts continuously to protect us from the microbes that we eat and breathe every single day. Microbes that are harmless to us would be lethal to us if we didn't have an immune system (e.g., the 'Bubble Boy').

Inflammation. Inflammation is a coordinated physiological immune response (familiar to all of us) characterized by redness, pain, heat and swelling. Inflammation is caused by the influx of cells and fluid, and tissue destruction often associated with immune responses. The goal of inflammation is to eliminate infection and return tissue to normal. However, excessive acute inflammation can lead to severe disease. Also, chronic inflammation is part of many diseases including autoimmunity, cancer, heart disease or Alzheimer's.

Thus, inflammation is an example of an immune response that is 'double-edged': these immune responses are essential to protect us from infection but can also cause us harm if not properly regulated.

2. Adaptive vs Innate Immunity

The immune system of mammals is divided into two (connected) parts: innate and adaptive immunity. Note that many if not most animals (flies, worms, lobsters, etc.) only have innate immunity.

Innate Immunity. 1. Initial recognition of the pathogen (sensing): the immune system must determine that it has become infected. 2. Initial innate non-specific responses are made rapidly, and are intended to hold the pathogen in check, e.g., fever and inflammation. These initial rapid but relatively non-specific innate responses also trigger slower, but more specific, adaptive responses.

Adaptive Immunity. 3. The specific adaptive responses occur later and are often required to effectively eliminate the pathogen. Production of ANTIBODIES is an example of an adaptive immune response. ANTIBODIES are proteins that bind very specifically to a particular pathogen and neutralize it. The immune cells critical for adaptive immunity are B and T cells (see next lecture).

3. Fundamental architecture of the immune system. The organs of the immune system include the spleen, lymph node, bone marrow and thymus. Blood provides an important circulation for immune cells. Blood is composed of 1. red blood cells (RBC) – carry oxygen to tissues; no immune function. 2. white blood cells (WBC) – many different types; all involved in immunity and 3. plasma – the fluid in blood that contains numerous proteins. Plasma diffuses into tissues throughout the body and is collected by another system of vessels called the lymphatic system. The lymph fluid drains into lymph nodes, which are present throughout the body. Lymph nodes also contain lots of white blood cells, which are waiting for signs of infection. For the most part, the immune system is providing a targeted and balanced immune response to pathogens without harming the host in the process. However, sometimes the immune system can respond too vigorously causing pathogenesis which often leads to symptoms of disease.

This is different from an autoimmune disease that occurs when the body's immune system attacks itself.

(Non-blood components of the innate immune system. The immune system can also be considered to include the innate barriers to infection such as the skin, mucociliary clearance in the trachea, stomach acidity, lysozyme in tears.)

4. Cells of the innate immune system. All cells of the innate immune system are white blood cells.

Phagocytes: cells that eat bacteria, cellular debris, dying cells, etc. Basically, sorting through garbage in the blood looking for signs of infection. Phagocytes have many receptors that detect pathogens for phagocytosis (basically engulfing pathogens) or can be activated to release molecules to kill pathogens. When phagocytic cells sense or engulf pathogens, they become activated to produce proteins called cytokines that bind to other cells in the immune system.

1. Macrophages–phagocytes that specialize in engulfing and killing bacteria and important producers of cytokines.
2. Dendritic Cells (DCs)–Like macrophages, dendritic cells are phagocytic. Reside in tissues, and upon detecting PAMPs, migrate to lymph nodes and activate T cells of the adaptive immune system.
3. Neutrophils are abundant phagocytes for killing bacteria

INNATE IMMUNITY

5. How does the innate immune system sense that a host has become infected?

A primary job of the innate immune system is to detect when a microbe is pathogenic, but it is a conceptually difficult problem, given the following considerations:

1. Pathogens are diverse: there is nothing structurally similar about all pathogens, i.e., no defining characteristic that makes a pathogen a pathogen
2. Non pathogens are also diverse – i.e., there is a complex background "noise"
3. Our bodies are already filled and covered with many non-pathogenic bacteria, e.g., *Staphylococcus* on the skin, *Streptococcus* in the respiratory tract, *E.coli* in the intestines.
4. Pathogenic and non-pathogenic bacteria can be highly similar (acquisition of only a few genes can transform a nonpathogen into a pathogen).
5. Pathogens evolve rapidly–they are a moving target. They replicate and evolve much faster than we possibly can!

6. Strategies for Self-Nonself discrimination by the innate immune system

The innate immune system detects specific molecular structures present on microbes called **Pathogen Associated Molecular Patterns or PAMPs. PAMPs** are: 1. conserved among many pathogens
2. difficult for the pathogen to alter

Known examples of PAMPS:

1. Lipopolysaccharide (LPS)–critical constituent of the outer membrane of gram-negative bacteria
2. Peptidoglycan–critical component of bacterial cell walls (both gram+ and gram- bacteria have peptidoglycan)
3. Flagellin–primary protein constituent of the flagellum
4. Bacterial DNA–in bacteria the sequence CG in DNA is not usually methylated, whereas in mammalian DNA it usually is (the methylation obscures recognition of self DNA)
5. Double-stranded RNA–most RNA produced by human cells is single stranded messenger RNA. Many viruses, by contrast, produce double stranded RNA.
6. Bacterial lipoproteins–lipoproteins are proteins that have a lipid attached to them; the lipid anchors the protein in the membrane of the cell; certain lipoproteins are unique to bacteria and essential for the bacteria.

Puzzling point: all the above "PAMPs" are also found on non-pathogenic bacteria! So how does the immune system figure out that it has been infected with a pathogen? Still an interesting question, the answer is not entirely clear.

- Immunologists have discovered that certain cells in the immune system have specific **receptors** that recognize these PAMPS. A receptor is a protein that binds specifically to something, and upon such binding, transmits a biochemical signal that alerts the cell. The generic term for something that binds to a receptor is a **ligand** (e.g., PAMPs are ligands that bind to certain immune receptors).
- The receptors that recognize PAMPs tend to be evolutionarily ancient. One example is a family of receptors called Toll-like receptors (abbreviated as TLR). In humans there are several different Toll-like receptors:
- Once a Toll-like receptor binds to its ligands (PAMPs), then it transmits a biochemical signal to the cell that alerts it to the presence of the pathogen. The cell is then stimulated to produce secreted alarm signals called cytokines.

7. Cytokines: How cells of the innate immune system alert the adaptive immune system of a threat

– When cells of the innate immune system detect a pathogen, they send alarm signals to the rest of the immune system particularly the adaptive immune system. The signals take the form of secreted 'messenger' proteins called cytokines.
– These proteins are released at the site of infection where they bind to receptors on other blood cells and thereby transmit signals that can increase the immune response.
– Too much cytokine can activate too many immune cells all at once and can lead to 'shock' or even death
– An example of a cytokine is Tumor Necrosis Factor (TNF). TNF is critical for defense against infection, but too much TNF is known to contribute to autoimmune disease. In fact, people with Crohn's Disease or Rheumatoid Arthritis are often treated with antibodies that neutralize TNF.
– Therefore, **a key concept is that successful immune responses have to strike a balance** between failing to respond strongly enough (which would be bad because then the pathogen could replicate unchecked) and responding too strongly (which is bad because the immune response itself can be harmful).