

Biomedical Engineering for Global Health

Pathogens and the immune system Lecture 8

Review of lecture 7

- Science
 - "Science is the human activity of seeking natural explanations for what we observe in the world around us."
- Engineering
 - Systematic design, production and operation of technical systems to meet practical human needs under specified constraints
 - Six steps of the engineering design method

How can technology help?

Science

1. Understanding biology: pathogens & disease immune system

Engineering

2. Developing vaccines: from idea to product
 - vaccine design
 - production
 - testing safety & effectiveness
3. Addressing challenges for vaccine development:
 - Developed vs. developing countries
 - The AIDS vaccine challenge

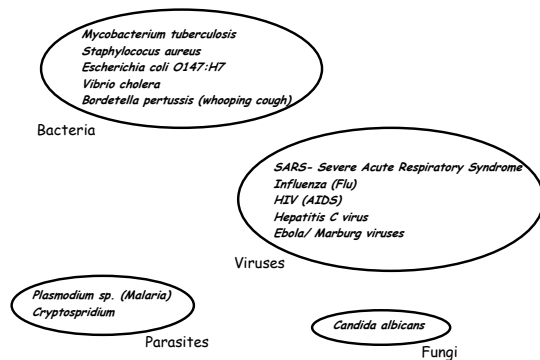
Lecture map

1. The players: Types of pathogens
Cells of the Immune system
2. Types of Immunity
 - 2A. Physical barriers
 - 2B. Innate Immunity
 - Macrophages
 - Neutrophils
 - Complement proteins
 - Splinter example
 - 2C. Adaptive Immunity
 - B-lymphocytes: ANTIBODIES
 - T-lymphocytes: Cell-mediated
 - Immunologic MEMORY

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Types of pathogens

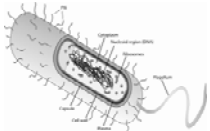


Bacteria

- Cells with membrane and cell wall (usually)
- Can survive & reproduce outside host
- Can be killed or inhibited by antibiotics
- Responsible for >90% of hospital infections

How do bacteria cause disease?

- Invade host
- Reproduce
- Produce toxins which disturb function of normal cells

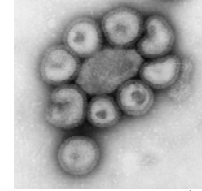
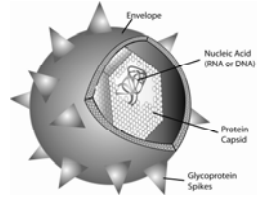


Size ~ 1 μm

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Viruses

- Nucleic acid core surrounded by protein capsid, and for some viruses an envelope
- Use host intracellular machinery to reproduce
- They cannot be killed with antibiotics, but antivirals may inhibit different stages of their life cycle in the host
- >50 viruses that can infect humans



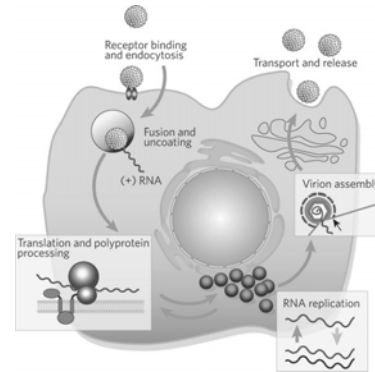
Size ~ 0.1 μm = 100nm

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How do viruses cause disease?

1. Virus invades host cell
 - Binds to cell membrane receptors
 - Endocytosis brings virus into cell
2. Virus takes over cell
 - Use viral nucleic acid and host cell resources to make new viral nucleic acid and proteins
3. More virus is released from host cell
 - Virus causes host cell to lyse OR
 - Viral particles bud from host cell surface

How do viruses cause disease?

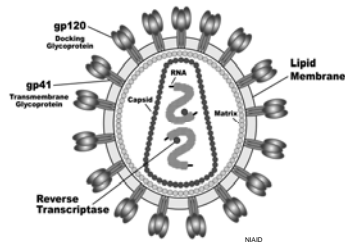


Lindenberg Charles M. Ross. Unravelling hepatitis C virus replication from genome to function. Nature Publishing Group, 2005. 4367053; 0333-038

The Human Immunodeficiency virus (HIV)

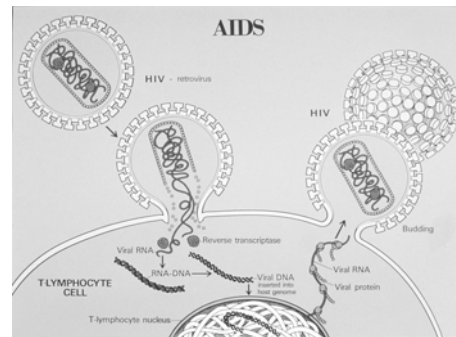
Viral components:

- nucleic acid core (DNA/RNA)
- protein capsid
- envelope
- Glycoproteins



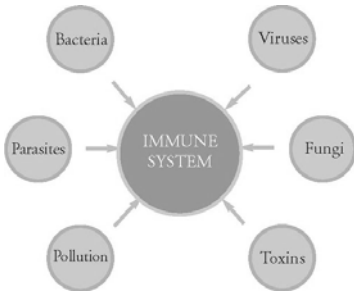
NIAID

The Human Immunodeficiency virus (HIV)



NCI/Trudy Nicholson

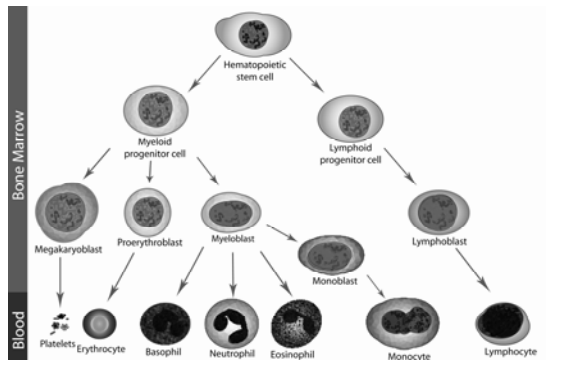
How are we protected against pathogens?



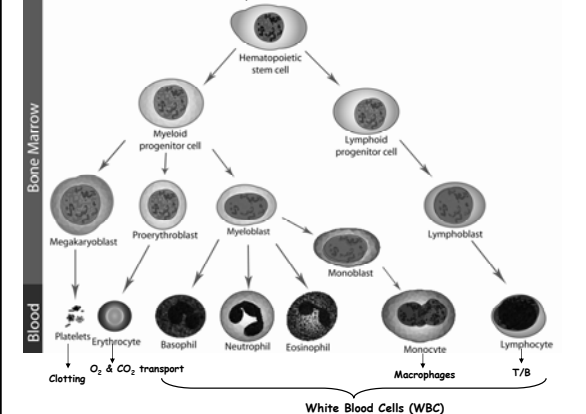
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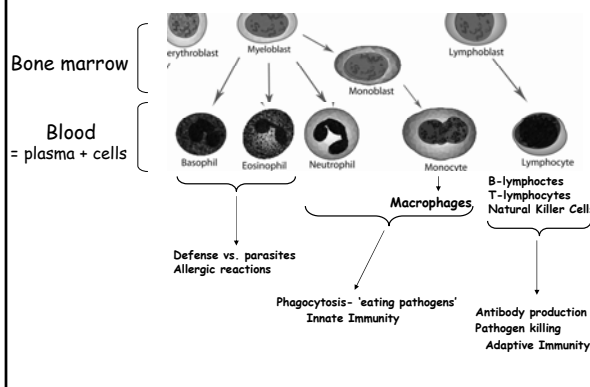
Cells of the immune system



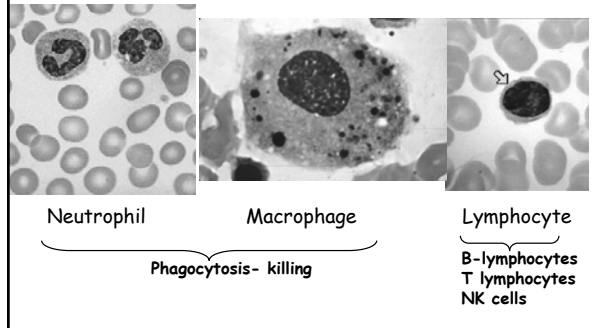
Cells of the immune system



Cells of the immune system



Cells of the immune system



Question:

- Based on your understanding of the characteristics of bacteria, viruses, and blood cells, identify which item best represents a bacterium, a virus and a blood cell and be able to explain why you chose each.

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Types of Immunity

Physical Barriers

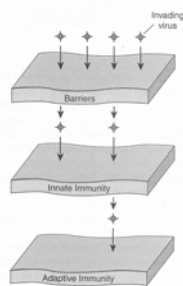
- skin (2 square meters)
- mucose membranes (400 square meters)

Innate Immune System

- General inflammatory response against pathogens outside of the cell

Adaptive Immune System

- Can adapt to defend against any specific invader inside or outside of the cell
- Important when innate immunity cannot defend against the attack
- Provides 'Immune Memory'



What happens when you get a splinter?

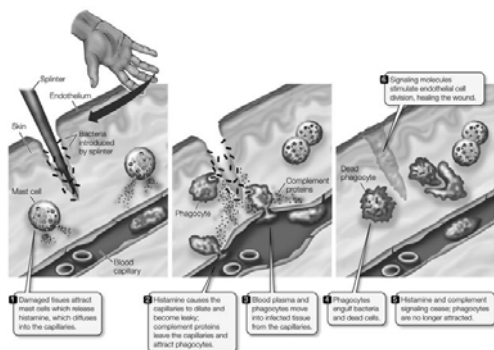
What happens when you get a splinter?

- Pathogen makes it past a physical barrier
- Symptoms?
 - Red, swollen, hot, pus
- What causes these symptoms?
 - The Innate immune system is kicking into gear!
- Usually innate immune system can take care of it

The Innate Immune System: 3 main weapons

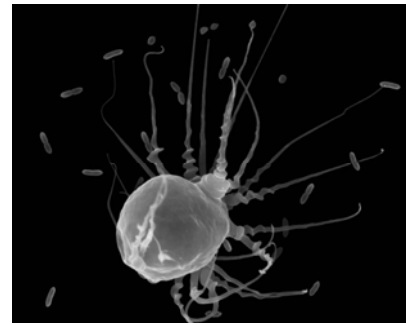
- Activated Macrophages**
 - Phagocyte ('eat') invading pathogens
 - Produce chemicals that:
 - increase blood flow (redness & heat)
 - cause 'fluid leaking' (swelling)
 - recruit **neutrophils** (pus)
 - Present antigen to adaptive immune system
- Complement proteins**
 - Present in tissue and blood
 - Attach to surface of bacteria and viruses targeting them for phagocytosis
 - Recruit other immune cells from blood

What happens when you get a splinter?



LIFE 6e, Figure 18.4

LIFE: THE SCIENCE OF BIOLOGY, Seventh Edition, © 2004 Sinauer Associates, Inc. and W. H. Freeman & Co.



Macrophage attacking *E. coli* ©David Kunkel

Question:

- Based on your understanding of the innate immune system, represent a macrophage during phagocytosis

Lecture map

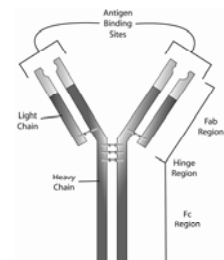
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The Adaptive Immune System

- Recognizes antigens (molecular signatures) specific for each pathogen
- Effective against both intra- and extracellular pathogens
- Two main components:
 - Humoral immunity
 - Relies on Antibodies produced by B-lymphocytes
 - Fights pathogens outside of cells
 - Cell-mediated Immunity
 - Relies on specific receptors on the surface of T-lymphocytes
 - Fights pathogens inside of cells

What is an antibody?

- Bridge between:
 - Pathogen
 - Tool to kill it
- Antibodies have two important regions:
 - Fab region:
 - Binds antigen
 - Binds surface of virus infected cell
 - Fc region:
 - Binds macrophages and neutrophils, induces phagocytosis
 - Binds natural killer cell, induces killing

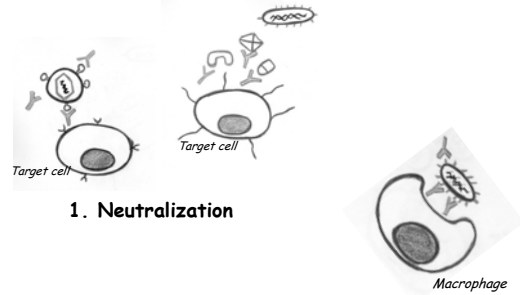


The Adaptive Immune response: humoral immunity

How do antibodies work?

- 1. Neutralization:** Blocking the biological activity of toxin or pathogen *ie. Blocking access*
- 2. Bridge:** Bringing together pathogens and phagocytes

The Adaptive Immune response: humoral immunity



1. Neutralization

2. Bridge: pathogen-phagocyte

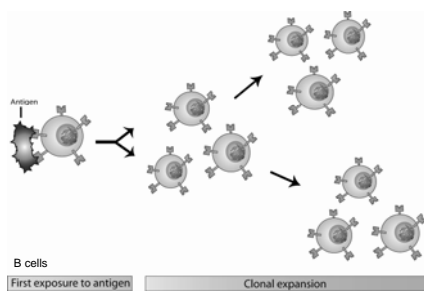
Question:

- Which components of your kit are most like antibodies?
- Arrange the components of the kit to demonstrate how these antibodies “bridge” a pathogen and the tool to kill it?

The Adaptive Immune response: humoral immunity

- How are antibodies made?
 - B cells
 - Lymphocytes that make antibodies
 - Have B cell receptors on surface
 - 100 million different types of B cells, each with different surface receptors
 - B cell receptors are so diverse they can recognize every organic molecule
 - When a B cell binds antigen:
 - Proliferates - In one week, clone of 20,000 identical B cells
 - Secretes antibody

Clonal selection and proliferation



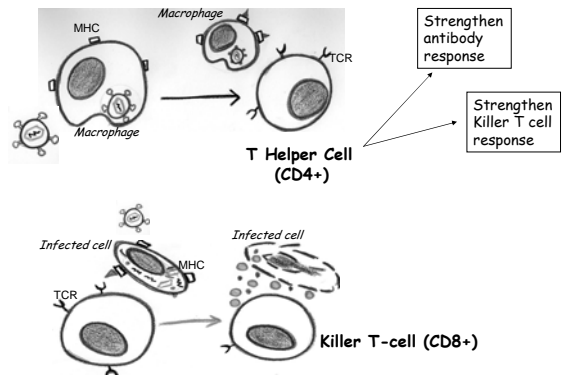
The Adaptive Immune response: cell-mediated immunity

- How do we kill virus once inside the cell?
 - Antibodies cannot get to it
 - Need T cells
- T Cells
 - Recognize protein antigens
 - When bind antigen, undergo clonal selection
 - Three types of T Cells:
 - Killer T Cells (Cytotoxic T Lymphocytes - CTLs)
 - Helper T Cells (orchestrate adaptive immune response)
 - Regulatory T Cells

How do T Cells recognize Virus-Infected Cells?

- All cells have **Major Histocompatibility Complex (MHC)** molecules on surface
- T Cells inspect MHC proteins and use this as a signal to identify infected cells
- Antigens (bits of pathogens) get loaded into MHC molecules:
 - When virus invades target cell, fragments of viral protein are loaded onto MHC proteins
 - 'Professional' Antigen Presentation Cells (APCs= phagocytes of innate immunity)

Antigen presentation and cellular immunity



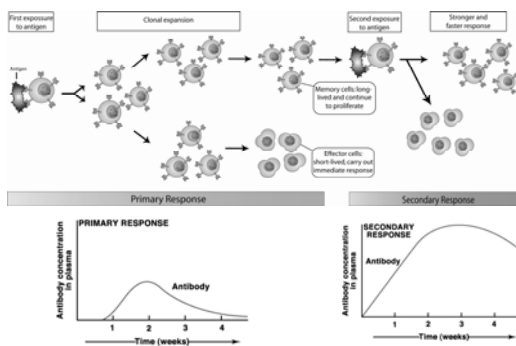
Question:

- Demonstrate how the T cell can identify a virus infected cell: antigen presentation
- Why is this component of the adaptive immune system a significant advance over the innate immune system?

Immunologic Memory

- **First time** adaptive immune system is activated by an antigen:
 - Build up a clone of B cells and T cells
 - Takes about a week
 - After infection is over, most die off
 - Some remain - memory cells
- **Second time** adaptive immune system is activated by that antigen:
 - Memory cells are easier to activate
 - Response is much faster - no symptoms

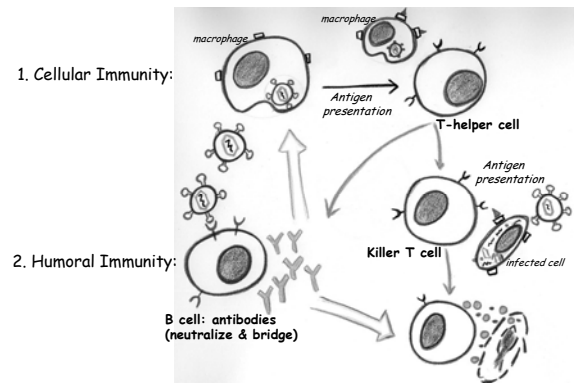
Immunologic Memory



The adaptive Immune Response

Putting it together...

The Adaptive immune response



Summary of lecture 8

- Pathogens: Bacteria and Virus
- Levels of Immunity:
 - Barriers → First line of defense
 - Innate → Inflammation
 - Phagocytes
 - Complement
 - Adaptive → Immunologic memory
 - Antibody mediated immunity
 - Cell mediated immunity → Pathogens within cells
 - Diversity to recognize 100 million antigens

Next time

- How do vaccines work?
- Vaccine development:
 - Design
 - Production
 - Testing safety & efficacy
- Challenges of vaccine development