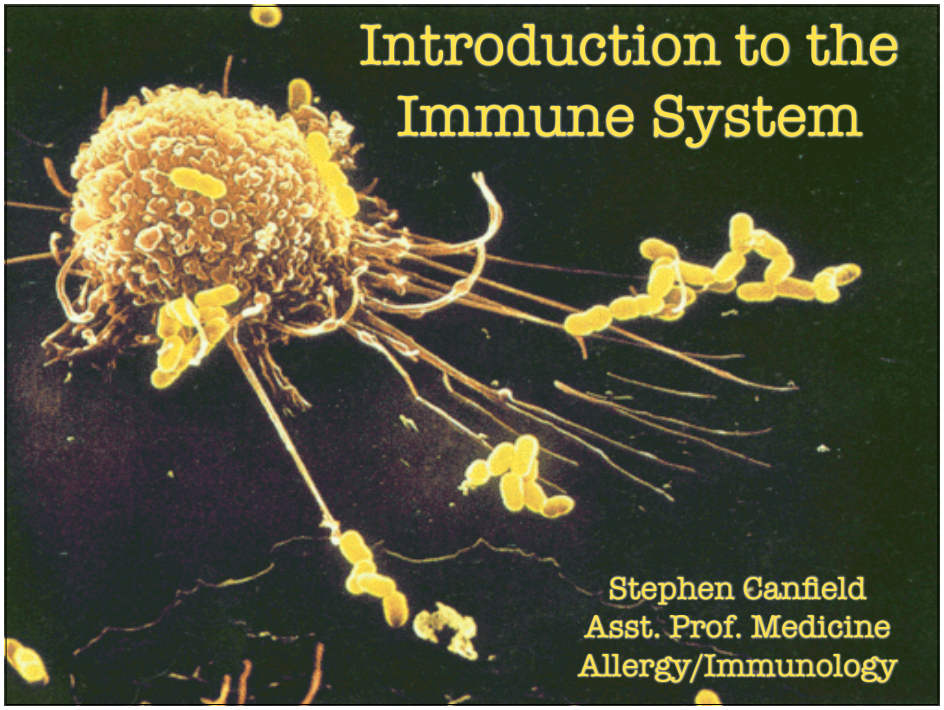


Prologue:
The Immune System in Health

- Defense against invading organisms
- Surveillance against malignancy
- Orchestrator of tissue repair
- Patrol against senescence
- Interface with metabolic processes
  - Body temperature
  - Fe^{3+} balance
  - Body mass

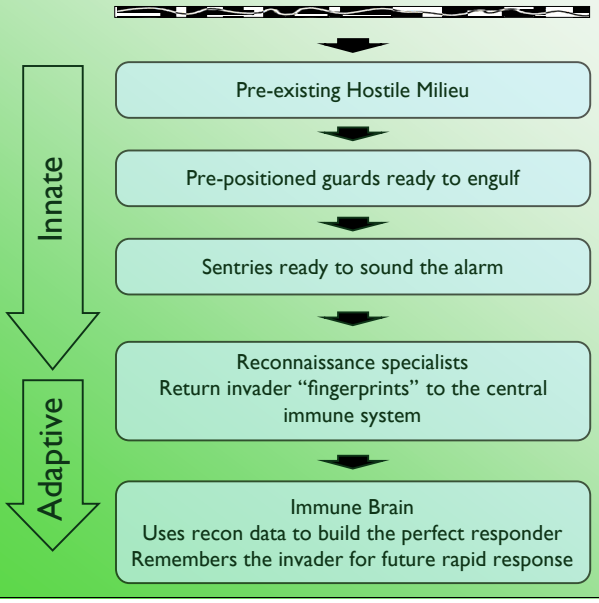
Prologue: The Immune System in Disease

- Too little - immune deficiency
- Too much - attack on self
- Too long - tissue remodeling
- Too vigilent - hypersensitivity
- Too effective - graft rejection

Prologue: Tips on Challenges You Will Face

- Details, details, details - new vocabulary
- "Rules" are built on experimental observation
  - Every rule has an exception
- The "system" is a network of many players
  - Zoom in to study a player, but remember...
  - Pan around to see how it fits in big picture
  - The elegance is in the orchestra, not one player
- Understanding is evolving
  - New concepts and new players added every year

Plight of the Hapless Pathogen



Epidermis, Mucous Membranes

Serum, Lymph

Dermal and submucosal tissues

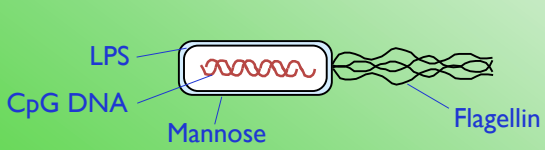
Peripheral tissues → 2° *Lymphoid Organs*

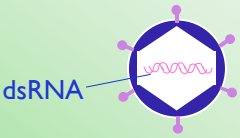
2° Lymphoid Organs: LN, Spleen Mucosa-Associated Lymphoid Tissue

Innate Immune System

Soluble	Cellular
Complement Cascade	*Phagocytes*
	Natural Killers

- Array of sensors for "danger"
  - Recognize pathogen-associated molecular patterns (*PAMP's*) - shared by many pathogens

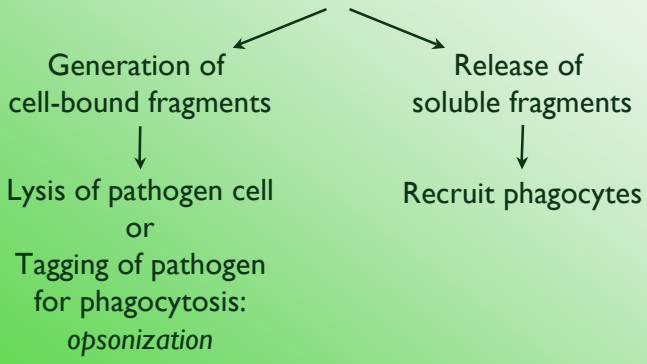




- Rapid activation - no prior contact needed

The Complement System

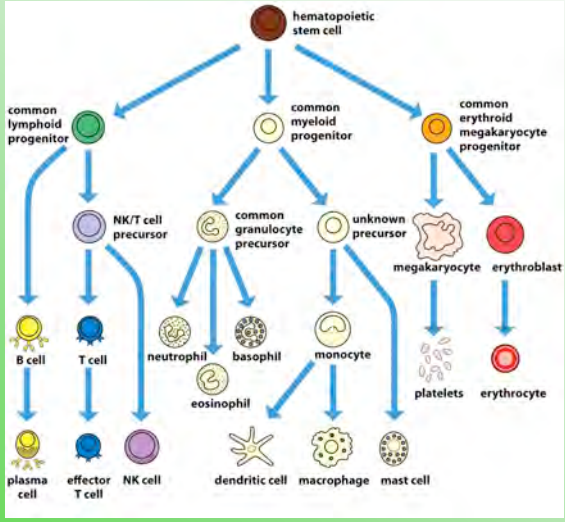
- The pre-existing hostile milieu
  - Set of ~25 highly abundant serum proteins
  - Forms a proteolytic cascade at the cell surface



Cells of the Innate System

- Phagocytes
  - Macrophages
  - Neutrophils (aka: polymorphonuclear leukocytes)
  - Dendritic Cells
- Natural Killers (NK) Cells

Hematopoietic Lineage



Macrophages

Tissue-resident sentinels
& refuse collectors

Arrayed with "sensors":
- PAMP receptors
- Complement R's
- Antibody R's

Reorganize cytoskeleton
in response to these inputs:
Seek & Engulf

MΦ as Refuse Manager

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Neutrophils

Most abundant blood leukocyte
- 3 million/day exit bone marrow
- production ↑↑ with infection

Exit blood ➟ tissue when called

Chemotax along gradients:
- pathogen components
- complement fragments
- macrophage signals

Engulf and kill

Survive hours to days - major component of pus

Lichtman, et al: Review of Immunology, Copyright © 2005 by Elsevier, Inc.

Neutrophil Chemotaxis

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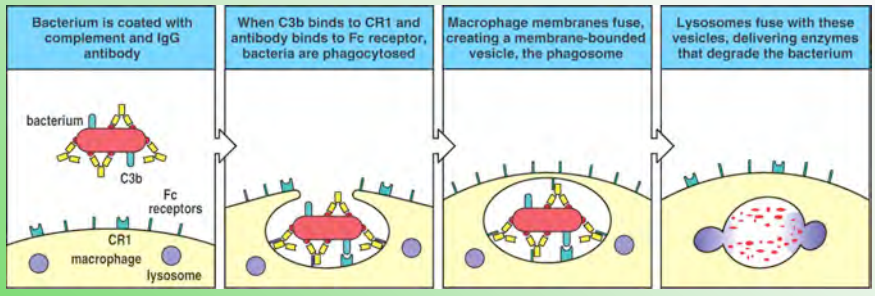
Macrophage/Neutrophil Killing



- Phago-lysosome contents
  - Phagocyte Oxidase ➟ oxygen radicals
  - Inducible NO Synthase ➟ nitric oxide
  - Acid pH
  - Proteases

Janeway, et al: Immunobiology, 6th Edition. Copyright © 2005 by Garland Science.

Dendritic Cells

- Phagocyte with a dual career - reconnaissance specialist
  - Starts out a tissue-resident sentinel
    - Constant *pinocytosis* - "small bites" sampling surroundings
  - Pathogen contact ➟ career change
    - Picks up stakes - migrates from tissue to local lymph node
    - Literally "presents" pathogen fragments to cells of the adaptive system
    - Bridge between the innate and adaptive responses

Soluble Intercellular Signals

- *Cytokines* - secretory proteins that mediate immune cell development & inflammatory reactions
  - Bind to specific receptors on signal-receiving cells
  - Influence the state of activation, effector functions, or lineage of the recipient cell
- *Interleukins* - cytokines that generally function to communicate between leukocytes
- *Chemokines* - small cytokines that function in leukocyte chemotaxis: hence "chemo-" + "-kine"

Innate Call for Help

- PAMP recognition ➟ MΦ activation ➟ ALARM
  - ➟ Secrete interleukin-1 (IL-1)
  - ➟ Secrete tumor necrosis factor (TNF-α)
- Two critical "innate" immune system cytokines:
  - Activate nearby neutrophils
  - Alter local vascular endothelium
    ➟ recruit more neutrophils
  - Signal DC's to "mature" - initiate migration
  - Signal hypothalamus to ↑ body temperature

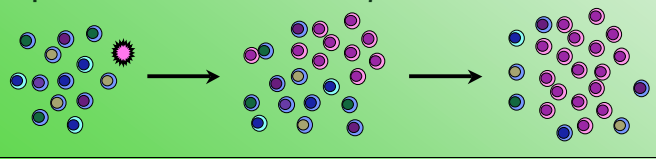
Is that all there is?

- Yes, for 99% of the animal kingdom
- But if you're a jawed vertebrate... there's more!

  Adaptive Immune System: B & T Lymphocytes
  - Learn from pathogen contact: ↑ effectiveness
  - Discern fine molecular differences:
    - Addition of a phosphate group to an amino acid side chain in a polypeptide
  - The target of these lymphocytes is termed an *antigen* (abbreviated Ag)

How the Adaptive System Learns

- Each cell develops with a *unique* Ag receptor
  - Generated randomly
  - Gen. by genomic DNA rearrangement
  - Extremely diverse: ~100 billion possible R's
- *Naive* lymphocytes patrol 2° lymphoid organs
  - Most never find Ag ➟ survive ~3 weeks
  - Lucky few: Ag encounter ➟ activation and proliferation ➟ *clonal expansion*

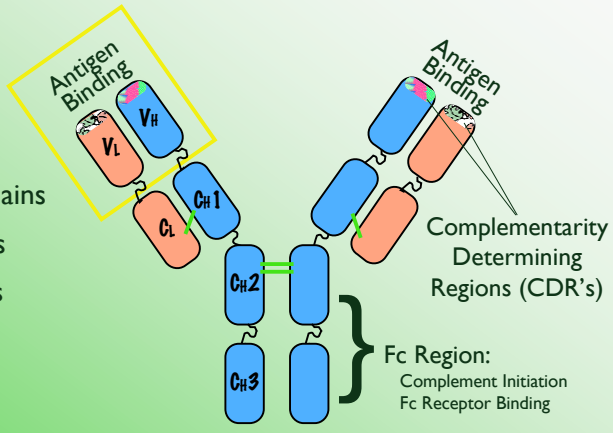


B Lymphocytes

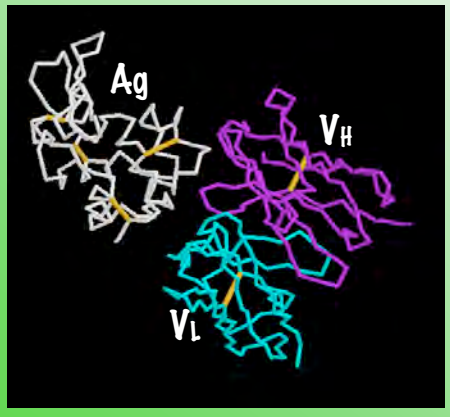
- Develop in the bone marrow
- Each new B cell makes a <u>unique</u> antigen receptor (BCR)
  - This BCR is also called surface *immunoglobulin* (Ig), or antibody
    - Ag binding by BCR ➟ clonal expansion
      - Some daughter cells become *plasma cells*: immunoglobulin secreting factories
      - Others become *memory B cells*: long-lived, capable of rapid response on re-encounter of antigen

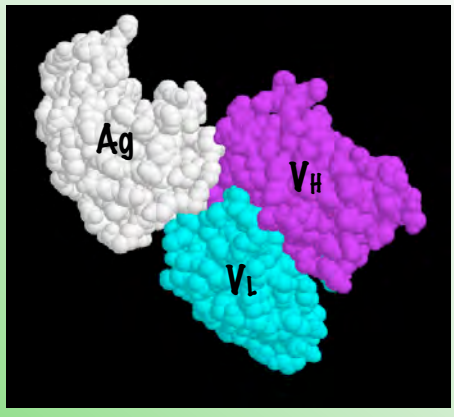
Immunoglobulins

- Tetramer
  - 2 H chains + 2 L chains
  - Interchain disulfides
- Variable End - CDR's
- Huge diversity
- Constant End
  - Determines Ig Class:
    IgM, IgD, IgG, IgA, IgE
    and effector functions



Immunoglobulin-Antigen Binding





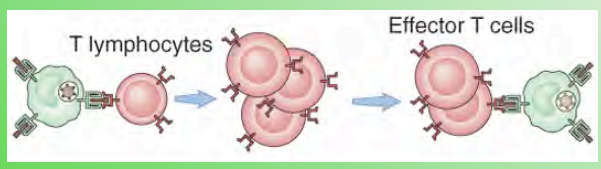
T Lymphocytes

- Hematopoietic origin (marrow) but most of their development occurs in the *thymus*
- Like B cells, T cells:
  - Utilize a surface Ag receptor (TCR)
  - Extreme diversity of Ag binding
  - Ag receptor triggering is required to initiate clonal expansion
  - Ag "experienced" cells produce a long-lived memory population

T Lymphocytes

- Unlike B cells, T cells:
  - Never secrete their Ag receptor
  - Cannot bind free antigen molecules - only peptides of 8-25 amino acids
  - Require that Ag be *presented* to them on a special "billboard":

    Major Histocompatibility Molecule

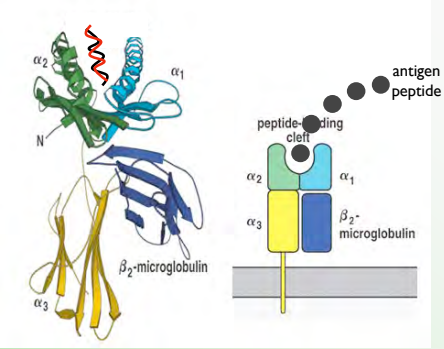


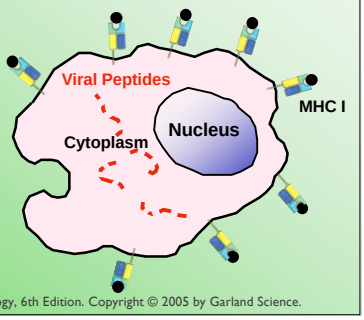
Major Histocompatibility Molecules

- Two Classes: I and II
- Highly *polymorphic*
  - Vary greatly from one individual to the next
- Identified as the basis for organ rejection between genetically non-identical individuals
- Also termed "Human Leukocyte Antigens" (HLA)

MHC Class I

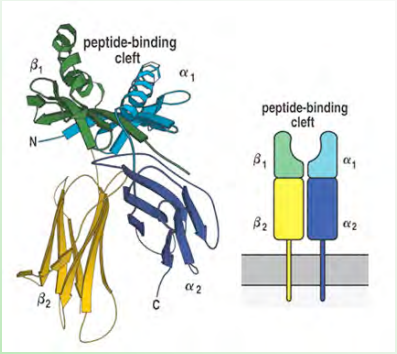
- Expression:
  - All nucleated cells
- Structure:
  - α-chain + β_2 microglobulin
- Antigenic peptides:
  - Derived from cell's cytoplasm (generally from proteins made within the cell)

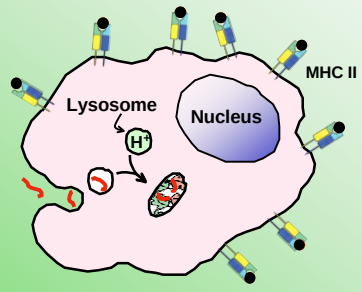




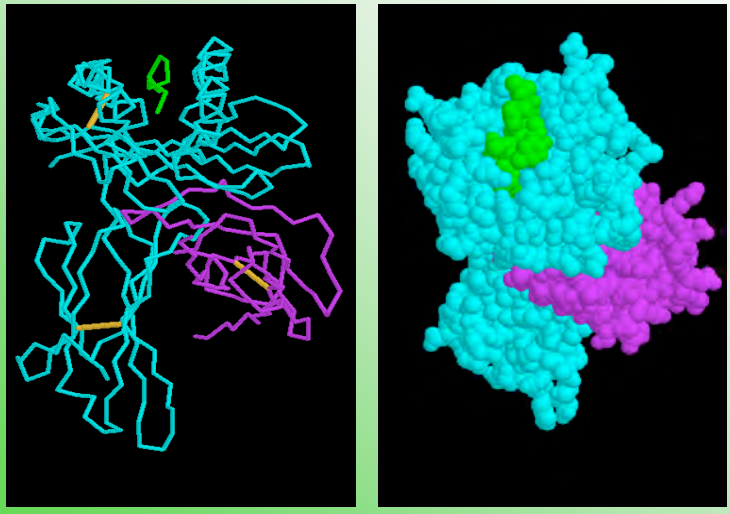
MHC Class II

- Expression:
  - *Antigen presenting cells* (APC's)
  - Examples - macrophages, dendritic cells, B cells
- Structure
  - α and β chains
- Antigenic peptides
  - Derived from the cell's endocytic compartment (generally from proteins external to the cell)



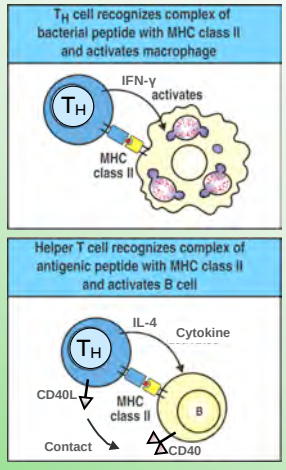


Peptide/MHC Class I



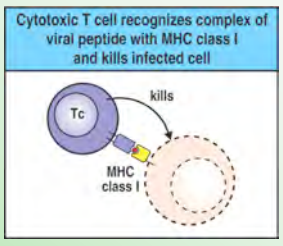
T Cell Career Paths

- $CD4^+$ T cells
  - Most commonly termed "helper T cells" (T_H's)
  - Recognize Ag peptide presented by MHC Class II
  - Provide <u>essential</u> activation signals to B Cells, $CD8^+$ T cells, and phagocytes
    - soluble - cytokines
    - surface molecules - *CD40L*



T Cell Career Paths

- $CD8^+$ T cells
  - Most commonly termed "cytotoxic T cells" (CTL's)
  - Recognize Ag peptide presented by MHC Class I
  - Kill target cells expressing abnormal cytoplasmic proteins
    - Infected by intracellular pathogen - eg, virus
    - Tumor cells



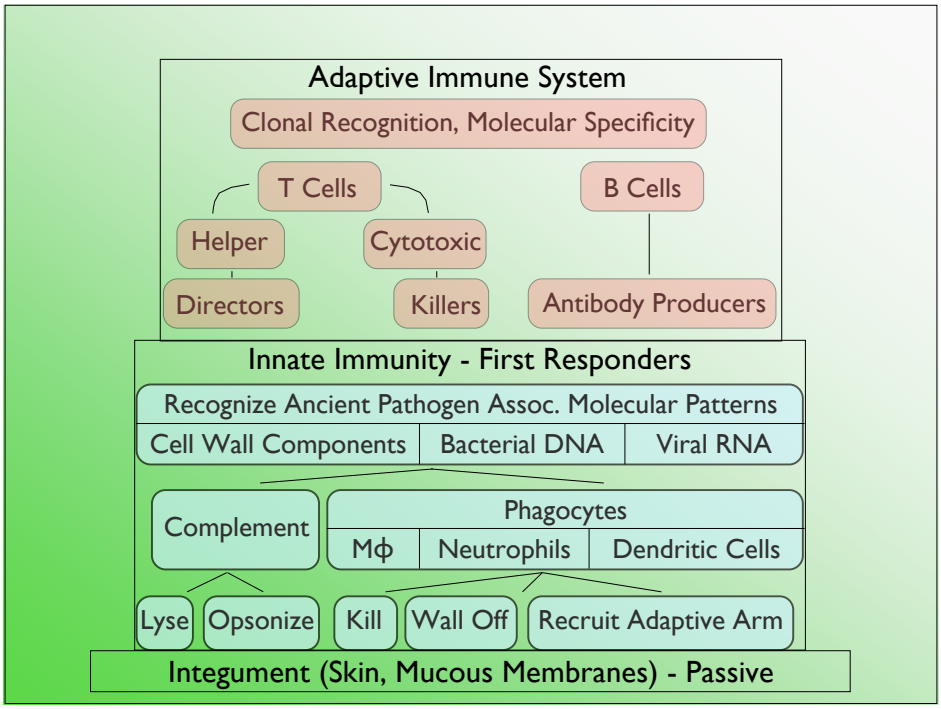
- Killing
  - puncture cell membrane
  - Induce programmed cell death or *apoptosis*

Natural Killer (NK) Cells

- Lymphocyte without BCR or TCR - "innate" like
- Don't require prior contact or clonal expansion
- Receptors recognize distressed cells:
  - Virally infected
  - DNA damaged
  - Transformed (malignant)
- Also recognize cells opsonized by Ig
- Kill, using a mechanism similar to CTL's

Innate vs. Adaptive Immunity

	Innate	Adaptive
On first contact	Immediate response	5-10 days for clonal expansion
Receptor Specificity	Broad classes of molecules	Highly specific for a single structure
Ligands	Microbial origin	Potentially any protein, lipid, or carbo
Memory	None	Long-lived
Recurrent contact	Same response as previously	Rapid response tailored to pathogen



Summary

1. We are protected from dissolution at the hands of microbes by an army of specialists each of which provides an essential piece of a complex defense.
2. The innate arm, the most ancient, is the first to respond. It's cells utilize evolutionarily conserved pathogen characteristics to recognize "danger" and act rapidly to tag, engulf, lyse, or wall off the invader.
3. The innate system recruits the more highly evolved adaptive system through specialized reconnaissance experts termed dendritic cells (DC's). These cells engulf bacteria and virally infected cells, digest the pathogen proteins, and present peptides from these proteins to naive CD4+ T cells, resulting in their activation and clonal expansion.
4. The adaptive system utilizes a unique gene rearrangement technique to generate awesome diversity and subtlety in antigen recognition: the lymphocyte repertoire.
5. a) $CD4^+$ T cells provide cytokine and contact-dependent help to B cells, resulting in a highly specific, high-affinity antibody response.

   b) $CD4^+$ T cell help and immunoglobulins in turn provide signals to the innate system, greatly facilitating phagocytosis and killing.
6. T cell direction, required for the optimal immune response, is completely dependent on the peptides presented. Highly polymorphic MHC genes, and co-dominant expression of multiple MHC molecules helps ensure that every individual can make a response to some part of every pathogen.