The Immune System: An Overview

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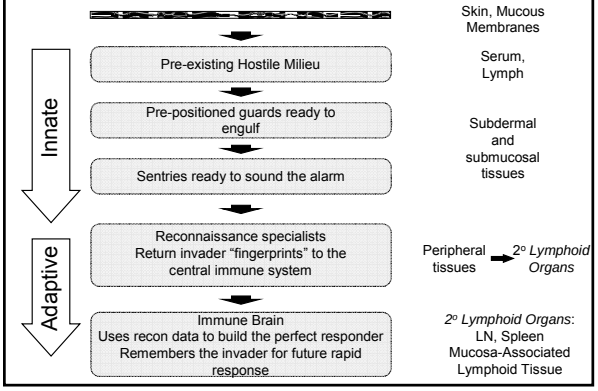
Tips on Challenges You Will Face

- 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...
  - Zoom back out 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

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

Plight of the Hapless Pathogen



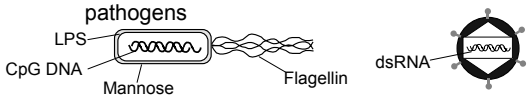
The Immune System in Disease

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

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

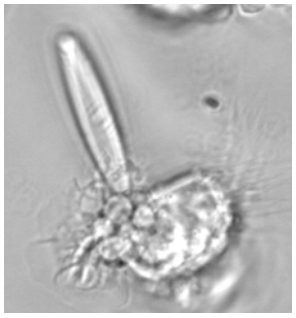
The Complement System

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

Generation of cell-bound fragments → Lysis of pathogen cell or Tagging of pathogen for phagocytosis: *opsonization*

Release of soluble fragments → Recruit phagocytes

MΦ as Refuse Manager



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Cells of the Innate System

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

Neutrophils

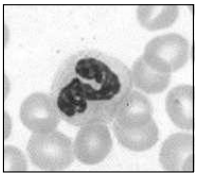
Most abundant blood leukocyte
- 3 million/day exit bone marrow
- production ↑↑ with infection

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

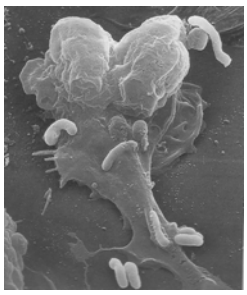


Lichtman, et al: Review of Immunology, Copyright © 2005 by Elsevier, Inc.

Macrophages

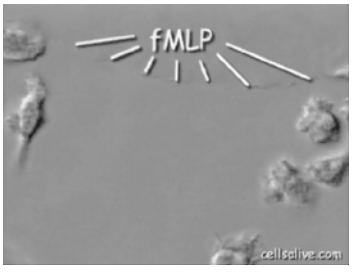
Tissue-resident sentinels & refuse collectors
Arrayed with "sensors":
- PAMP receptors
- Complement R's
- Antibody R's

Reorganize cytoskeleton in response to these inputs:
Seek & Engulf



Sompayrac: How the Immune System Works, 3rd Edition. Copyright © 2008 by Blackwell Publishing, Inc.

Neutrophil Chemotaxis



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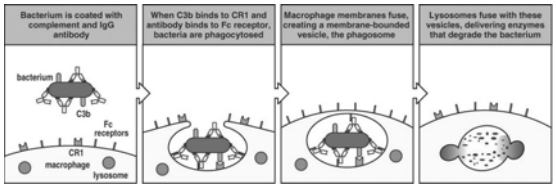
Macrophage/Neutrophil Killing



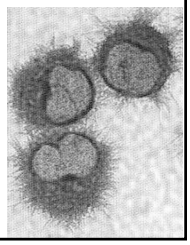
- Phago-lysosome contents
  - Phagocyte Oxidase ➟ oxygen radicals
  - Inducible NO Synthase ➟ nitric oxide
  - Acid pH
  - Proteases

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 to recruit more neutrophils
  - Signal DC's to "mature" - initiate migration
  - Signal hypothalamus to thank temperature

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



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:
  - Single amino acid substitution in a peptide chain
  - Even addition of a phosphate group to an amino acid side chain

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"

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 2º lymphoid organs
  - Most never find Ag ➟ survive ~3 weeks
  - Lucky few: Ag encounter ➟ activation and proliferation ➟ *clonal expansion*

B Lymphocytes

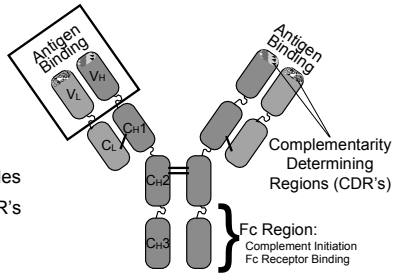
- Develop in the bone marrow
- Each new B cell makes a <u>unique</u> antigen receptor (BCR)
  - This BCR is an *immunoglobulin* (Ig), aka, antibody
    - Ag binding by BCR → clonal expansion
      - Some daughter cells become *plasma cells*: immunoglobulin secreting factories
      - Others become *memory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

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

Immunoglobulins

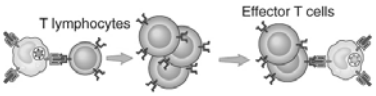
- Tetramer
  - 2 H chains + 2 L chains
  - Interchain disulfides
- Variable End - CDR's
- Huge diversity
- Constant End
  - Determines Ig Class: IgM, IgD, IgG, IgA, IgE



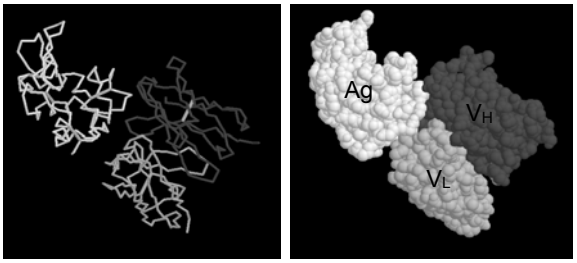
T Lymphocytes

- 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



Immunoglobulin-Antigen Binding

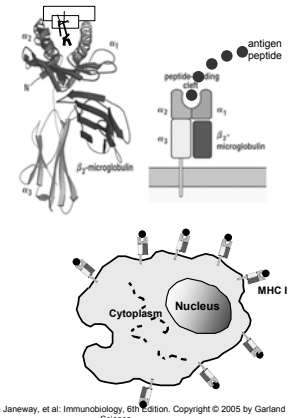


Major Histocompatibility Molecules

- 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)

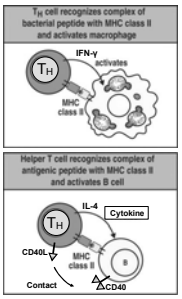
MHC Class I

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



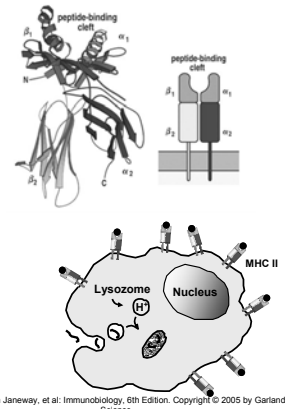
T Cell Career Paths

- $CD4^+$ 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 -



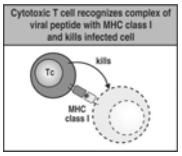
MHC Class II

- Expression:
  - A*ntigen 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)



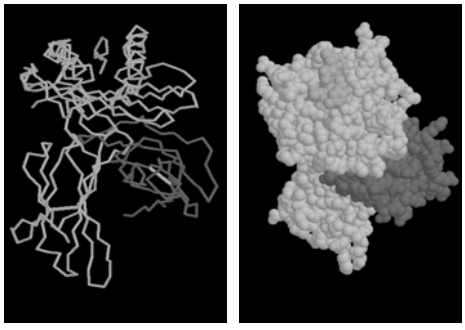
T Cell Career Paths

- $CD8^+$ 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



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

Peptide/MHC Class I



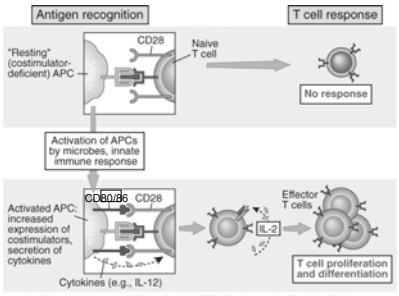
Natural Killer (NK) Cells

- 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

T Cell Activation: Under Innate Cell Control

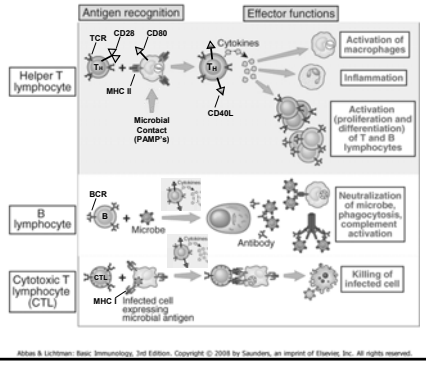


Autoimmunity:

Distinguishing native tissue from foreign pathogen

- Innate System - inherent in the receptors
  - Directed at microbial molecules (PAMP's)
- Adaptive System - <u>not</u> inherent in the receptors
  - Able to bind anything - protein, carbohydrate, lipid
  - Need safeguards to ensure non-reactivity with native (self) molecules - that is, to maintain *tolerance*

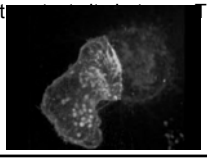
Lymphocyte Effector Functions



One Layer of Safeguard:

T Cell Activation requires Innate/Adaptive Cooperation

- Naive T cells require two discreet activation signals
  - *Signal I*: TCR binding to peptide/MHC
  - *Signal II*: *Co-stimulation* provided by the APC
    - Involves binding of T cell CD28 to APC CD80 & 86
    - Occurs at [illegible] T cell and APC



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 simultaneously provides pathogen-specific information (in the form of MHC/peptides) and essential activation signals (in the form of CD80 and CD86) to the adaptive system resulting in helper T cell activation and differentiation.
4. 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 provide reciprocal signals to the innate system, greatly facilitating phagocytosis and killing.

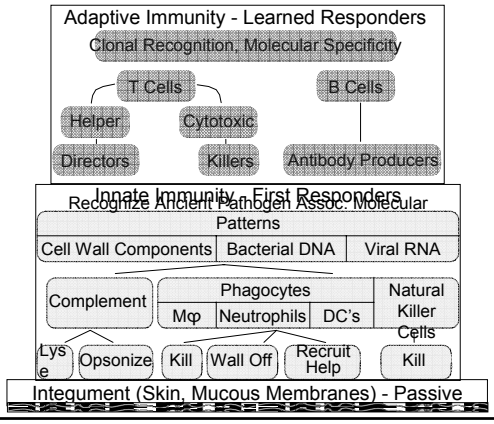
5. The adaptive system utilizes a unique gene rearrangement technique to generate awesome diversity and subtlety in antigen recognition: the lymphocyte repertoire.
6. T cell direction, required for the optimal immune response, is completely dependent on the peptides presented. Highly polymorphic MHC genes, and co-dominant expression of multiple MHC molecules helps ensure that every individual can make a response to some part of every pathogen. However, not all

Helpful Hints

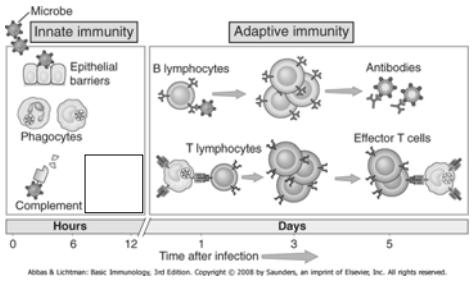
- Read Sompayrac in full early
  - Easy read, great for framework
- Good glossary at the back of Abbas
- List of surface molecules, Abbas Appendix II
- Searchable Janeway on line

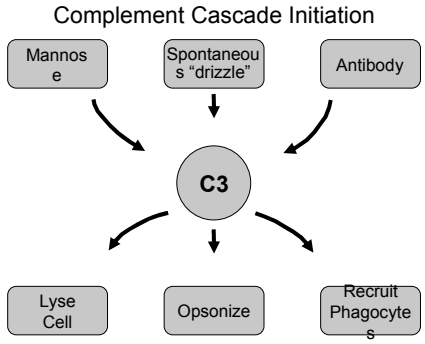
(http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=imm.TOC&depth=2)

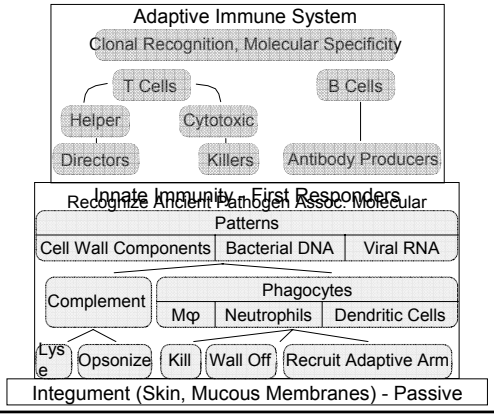
- Recent journal reviews listed on Courseworks for a different perspective



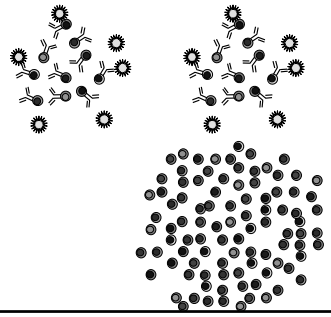
Adaptive Immune Cells: B & T Lymphocytes







MΦ as Cop: C. albicans (yeast)



Compare and Contrast: Innate and Adaptive Immunity

- Innate system receptors -
  - Recognize broad motifs, not organism-specific
- Adaptive system receptors -
  - Distinguish *fine* molecular differences
    - addition of a phosphate group to a peptide
    - single sugar substitution in a long polysaccharide
    - UV-induced conformational change in a protein
  - Target bound is termed the *antigen*

Complement System

- Set of 25 highly abundant serum proteins
  - Form a proteolytic cascade (not unlike the clotting cascade) on cell surfaces
- Function: Lyse pathogen; tag pathogen for killing by phagocyte; summon phagocytes
- Three routes of initiation:
  - Spontaneous - continuous "drizzle" of complement components depositing on all cells (host cells have "umbrellas")
  - PAMP's - mannose residues on bacterial cell surfaces can initiate the cascade
  - Antibodies - feedback from the adaptive system

Adaptive Immune Cells

- Only two cells:
  - B lymphocyte
    - 1st identified in the bursa (B) of the chicken
    - Antigen (Ag) receptor: B cell receptor (BCR)
  - T lymphocyte
    - Develops in the thymus (T) of chicken (and us)
    - Ag receptor: T cell receptor (TCR)

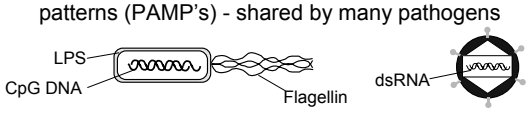
Top 10 Challenges to Getting It

1. Distracting good looks of the presenters
2. Details, details, details!
3. Doesn't come in a sleek Apple/MacIntosh-style package
4. So many players to get to know
5. (something about what do we have to know for exam?)
6. Greek characters set you on edge
7. Best friend won't stop IM'ing you
8. Difficult NYT crossword
9. Not a morning person
10. "I should have been lawyer"

The Immune System:
An Overview

Innate Immune System

- Array of sensors for “danger”
  - Recognize pathogen-associated molecular patterns (PAMP’s) - shared by many pathogens



  - Pathogen contact produces rapid activation
    - No requirement for prior contact
  - Innate Effectors: Both Soluble (serum) and Cellular
    - Soluble (serum) - Complement System
    - Cellular (blood and tissues) - Phagocytes, natural killer