Innate Immunity (part 1)
BIOS 486A/586A

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Topic Outline

- Define innate vs. adaptive immunity
- Identify innate immune cells & molecules
- Describe functions of phagocytic cells
  - Detection of microbes (pattern recognition receptors)
  - Phagocytosis & microbicidal mechanisms
  - Secretion of pro-inflammatory proteins (Cytokines)
  - directed migration (Chemotaxis)
- Describe inflammation/leukocyte adhesion
- Describe other innate cells/factors

Immune Mechanisms

- INNATE
  - Present at birth
  - Self-discrimination
  - Limited diversity
  - Nonspecific defense
  - No memory
  - Examples: skin, cough, gastric pH, fever, inflammation (phagocytic cells)
- ACQUIRED
  - Appears after contact with antigen
  - Self-discrimination
  - Vast diversity
  - Specific defense
  - Memory responses
  - Examples: antibody, cytotoxic lymphocytes

Innate Immunity

- **Present at birth**
- **Nonspecific**
  - **Response does not target one specific immunogen**
- **Limited diversity**
  - **Fixed, repeating, broad responses to a limited number of foreign substances**
- **No memory**
  - **primary and secondary responses are identical**

Components of Innate Immunity

- **Physical/mechanical barriers**
  - **Intact skin, epithelial layers, cough, fever**
- **Nonspecific chemical factors**
  - **Antimicrobial peptides & fatty acids, gastric pH, lysozyme**
- **Inflammation**
  - Phagocytes **(engulf and digest microbes)**
  - **Proinflammatory factors (**cytokines, complement proteins**)**
- **Natural killer cells (nonspecific cytotoxic cells)**
- **Interferon (produced by virus-infected cells and induces antiviral state in neighboring uninfected cells)**

Intrinsic epithelial barriers to infection	
Mechanical	Epithelial cells joined by tight junctions Longitudinal flow of air or fluid across epithelium Movement of mucus by cilia
Chemical	Fatty acids (skin) Enzymes: lysozyme (saliva, sweat, tears), pepsin (gut) Low pH (stomach) Antibacterial peptides; defensins (skin, gut), cryptidins (intestine)
Microbiological	Normal flora compete for nutrients and attachment to epithelium and can produce antibacterial substances

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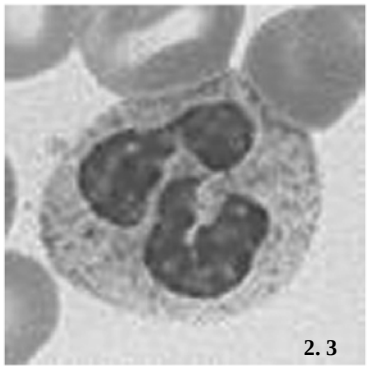
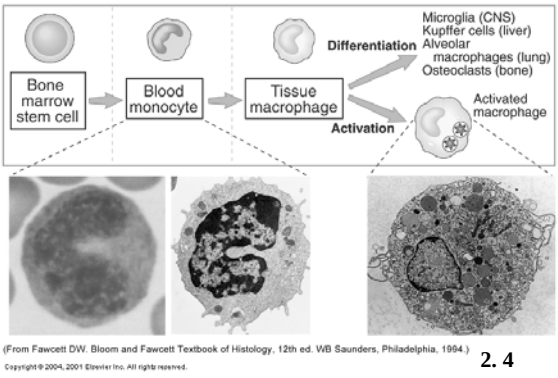


2. 3

Neutrophil (neutrophilic polymorphonuclear leukocyte) in stained blood smear. Neutrophils (PMN) are professional phagocytes



(From Fawcett DW. Bloom and Fawcett Textbook of Histology, 12th ed. WB Saunders, Philadelphia, 1994.)

2. 4

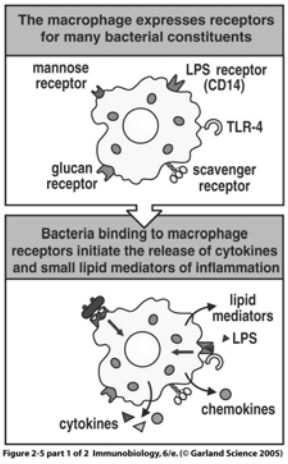
Mononuclear phagocytes (monocytes & macrophages)

Phagocyte Functions

- **Recognition of microbes (pattern recognition)**
- **Synthesis and secretion of cytokines/chemokines**
- **Phagocytosis (binding and engulfment of particles)**
- **Intralysosomal digestion and killing of ingested material.**
  - **Antigen presentation to lymphocytes**
- **Chemotaxis (migration toward a chemoattractive signal)**

Innate recognition of Microbes by Phagocytes

- Phagocytes recognize **pathogen-associated molecular patterns** (PAMP) via pattern recognition receptors such as **CD14/Toll receptors** and produce proinflammatory cytokines and chemokines.
- Microbial substances (LPS,LTA,PPG) may directly activate plasma **complement** proteins stimulating inflammation



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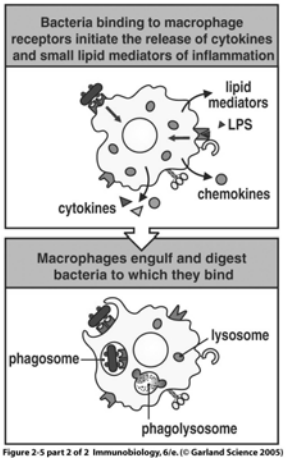
Pattern Recognition Receptors on macrophages bind foreign molecules common to many microbes. Binding stimulates phagocytes to release mediators of inflammation.



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Phagocyte binding to the microbe surface can stimulate phagocytic ingestion of the microbial particle with possible subsequent digestion and killing of the ingested microbe.

Innate immune recognition by Toll-like receptors	
Toll-like receptor	**Ligand**
TLR-1 dimer	Peptidoglycan Lipoproteins Lipoarabinomannan (mycobacteria) GPI (*T. cruzi*) Zymosan (yeast)
TLR-2/TLR-6 dimer	
TLR-3	dsRNA
TLR-4 dimer (plus CD14)	LPS (Gram-negative bacteria)
TLR-5	Flagellin
TLR-9	Unmethylated CpG DNA

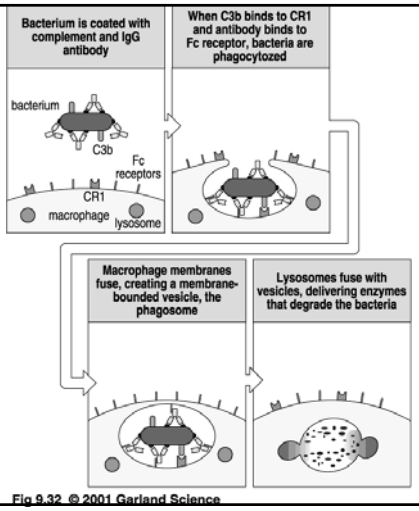
Figure 2-12 Immunobiology, 6/e. (© Garland Science 2005)

Toll-like receptors (TLR) are pattern recognition receptors that bind molecular patterns common to multiple infectious microorganisms. Phagocytes use these receptors to distinguish self from inflammatory non-self material.

Phagocytosis (cellular ingestion of particles)

- Non-opsonic
  - Direct engulfment via innate pattern recognition receptors. Slow, limited, inefficient
- Opsonic
  - Engulfment of complement-coated or antibody-coated microbes via complement receptors (CR) or antibody receptors (FcR). Rapid, very efficient

FIG. 9.32.
Opsonic phagocytosis



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Phagocyte Killing Mechanisms

- **OXYGEN INDEPENDENT**
  - **lysosomal hydrolases, lysozyme, lactoferrin, defensins, acid pH**
- **OXYGEN-DEPENDENT (Reactive oxygen and reactive nitrogen intermediates)**
  - **Hydrogen peroxide, superoxide anion, hydroxyl radical, hypochlorite**
  - **Reactive Nitrogen Intermediates (RNI)**
    - **Nitric oxide, peroxynitrite**

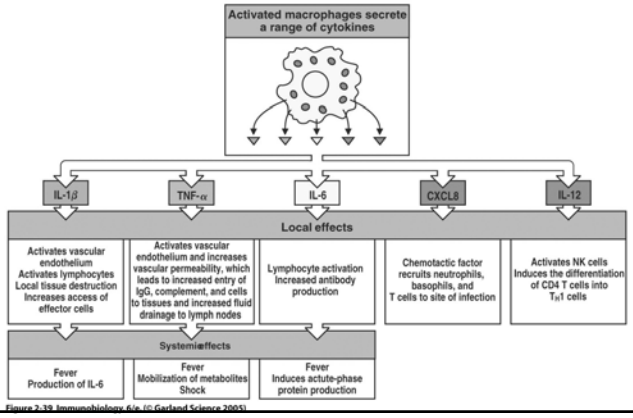
Inflammation

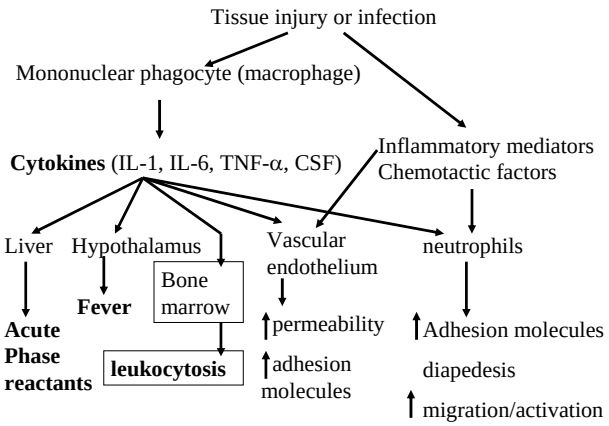
- Definition
  - local accumulation of fluid, plasma proteins, and WBC that is initiated by physical injury, infection , or a local immune response.

Proinflammatory cytokines

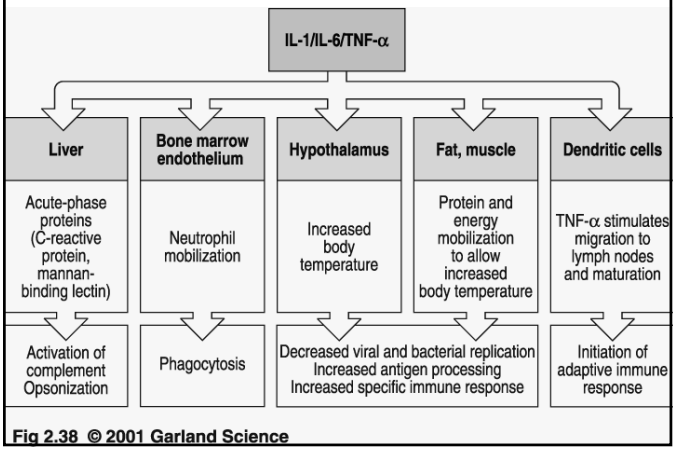
- **Cellular sources: <u>macrophages</u>, infected cells, injured cells**
- **Factors:[interleukin = IL]**
  - **<u>CYTOKINES</u>: IL-1, IL-6,TNF-α, IL-12**
    - **Induce fever,acute phase protein synthesis, leukocyte adhesion**
  - **<u>CHEMOKINES</u>: IL-8**
    - **Attracts and recruits neutrophils**

Proinflammatory cytokines secreted by macrophages stimulated by bacterial products via TLR





Functions of pro-inflammatory cytokines



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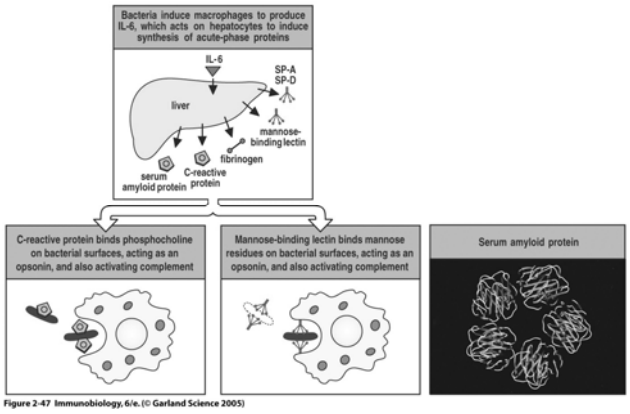
Function of Acute Phase Proteins induced by cytokines



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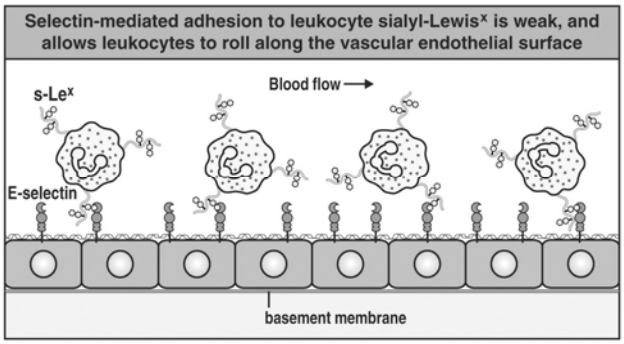
CHEMOTAXIS (directed migration)

- **Dependence on:**
  - **ADHESION MOLECULES (induced by cytokines)**
    - **β2-integrins on leukocyte**
    - **E-selectins on vascular endothelium**
  - **RECEPTORS for Chemoattractants**
  - **CHEMOATTRACTANTS**
    - **Leukotriene B4, Complement C5a, bacterial formyl-methionyl peptides, chemokines (interleukin-8, etc.)**

Factors which activate and recruit inflammatory phagocytes

- **Cytokines (released locally) stimulate phagocyte adhesion to vascular endothelium and extravasation (diapedesis)**
- **Chemoattractant compounds direct phagocytes to the site of infection.**
- **"Acute phase" and complement proteins enhance phagocytosis and killing of microbes by recruited "inflammatory" phagocytes**

Leukocyte adhesion and diapedesis. Cytokine-induced adhesion molecules and locally-released chemokines promote binding of circulating phagocytes to the vascular endothelium and cause a directed migration to sites of tissue injury or infection. (slide 1)



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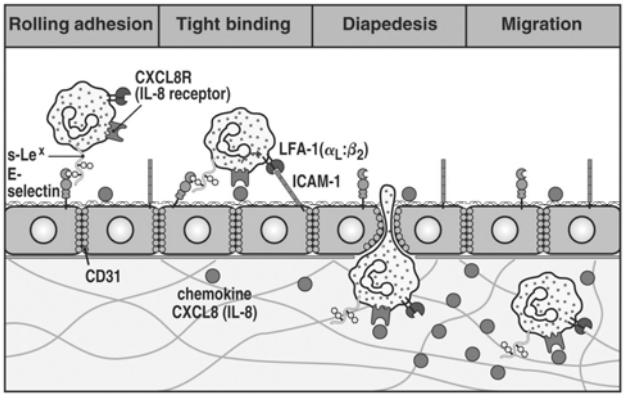
Leukocyte adhesion and diapedesis (slide 2)



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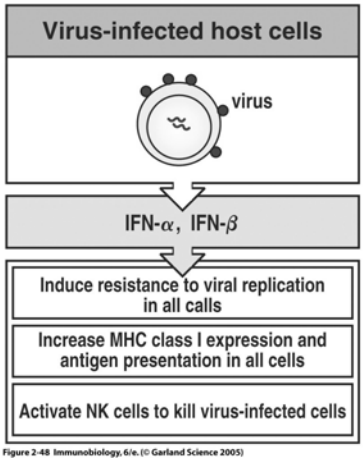

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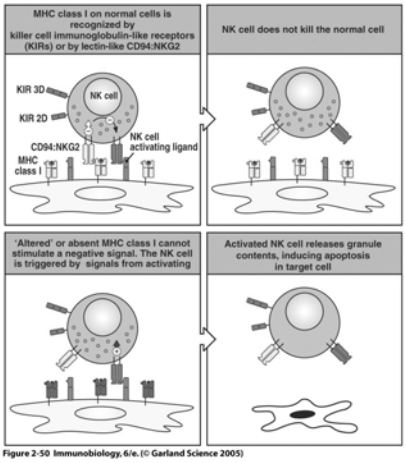
Innate immune functions of interferons



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Natural killer cells exhibit cytotoxicity toward cells that downregulate MHC molecules that are present on normal cells.

Innate-like lymphocytes		
B-1 cells	**Epithelial γ:δ cells**	**NK T cells**
Make natural antibody, protect against infection with *Streptococcus*	Produce cytokines rapidly	Produce cytokines rapidly
Ligands not MHC associated	Ligands are MHC class IB associated	Ligands are lipids bound to CD1d
Cannot be boosted	Cannot be boosted	Cannot be boosted

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