MIMG 185A/Spring 2026

Lecture 5

Innate Immunity

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Innate Immune System

- Initial Response to Infection (immediate vs. days)
- Frequently is sufficient to eliminate the infection
  - thus, adaptive immune response not needed
- Innate immunity stimulates adaptive immune response and
  ** **influences the nature of the adaptive response****

(nature of cytokines released will skew response → Th1 vs Th2, Ab isotype)

- Effector mechanisms of innate immunity are often shared with the adaptive immune response (ex: FcR and complement)

Functions of Innate Immune Response

- Barrier to infection
- Recognize pathogen
- Trigger inflammation
- Attract effector cells
- Induce effector molecules
- Activate and influence the nature of the adaptive immune response

Innate Immune Response

There are multiple barriers to infection:

1. **Mechanical**: Tight junctions of epithelial cells form a physical barrier.

2. **(Bio)Chemical**: Antibacterial peptides (defensins), enzymes (lysozyme, pepsin), and low pH environment.

3. **Cellular**: Mast cells, Natural Killer T cells , B-1 B cells, Phagocytes, and NK cells.

Skin and other epithelial barriers to infection

Organ or tissue	Innate mechanisms protecting skin/epithelium
Skin	Antimicrobial peptides, fatty acids in sebum
Mouth and upper alimentary canal	Enzymes, antimicrobial peptides, and sweeping of surface by directional flow of fluid toward stomach
Stomach	Low pH, digestive enzymes, antimicrobial peptides, fluid flow toward intestine
Small intestine	Digestive enzymes, antimicrobial peptides, fluid flow to large intestine
Large intestine	Normal intestinal flora compete with invading microbes, fluid/feces expelled from rectum
Airway and lungs	Cilia sweep mucus outward, coughing, sneezing expel mucus, macrophages in alveoli of lungs
Urogenital tract	Flushing by urine, aggregation by urinary mucins; low pH, anti-microbial peptides, proteins in vaginal secretions
Salivary, lacrimal, and mammary glands	Flushing by secretions; anti-microbial peptides and proteins in vaginal secretions

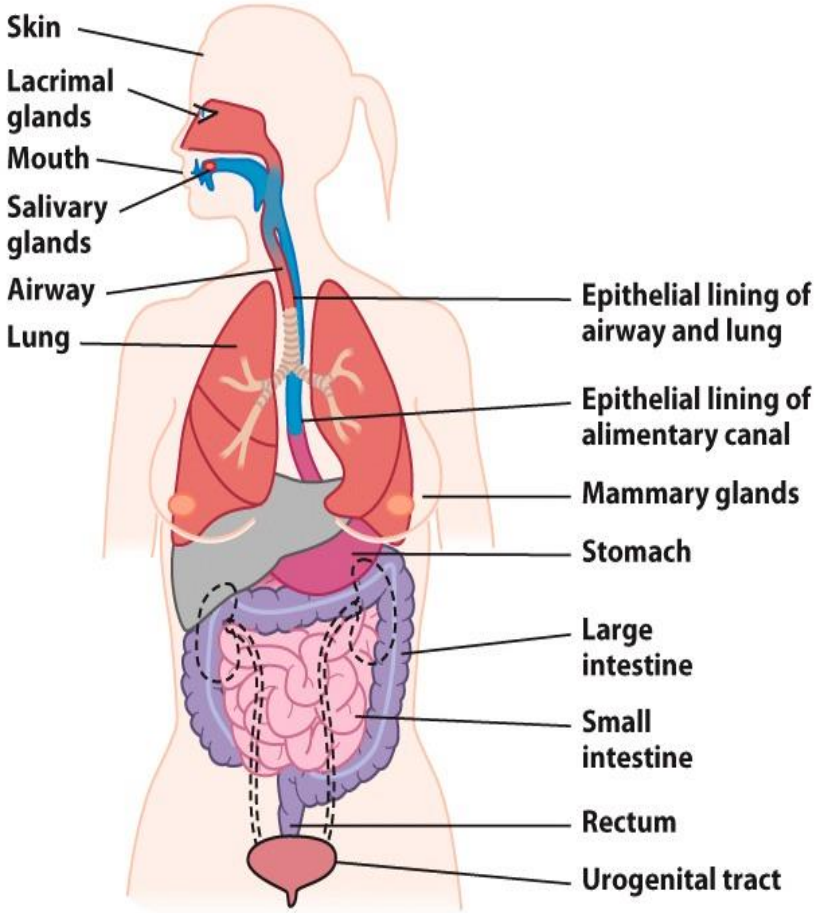


Figure 5-2
Kuby Immunology, Seventh Edition

Mucus

- Epithelial cells of the respiratory, digestive, and urogenital systems produce mucus.
- **Mucus** is a sticky, viscous, proteinaceous fluid that can trap invading microbes.
- In the respiratory system, **cilia** work along with mucus to expel trapped pathogens.
- Mucus can protect against infection, dehydration, and injury.
- Mucus protects the stomach lining from extremely acidic conditions.
- The organization of the mucus layer varies according to its location.

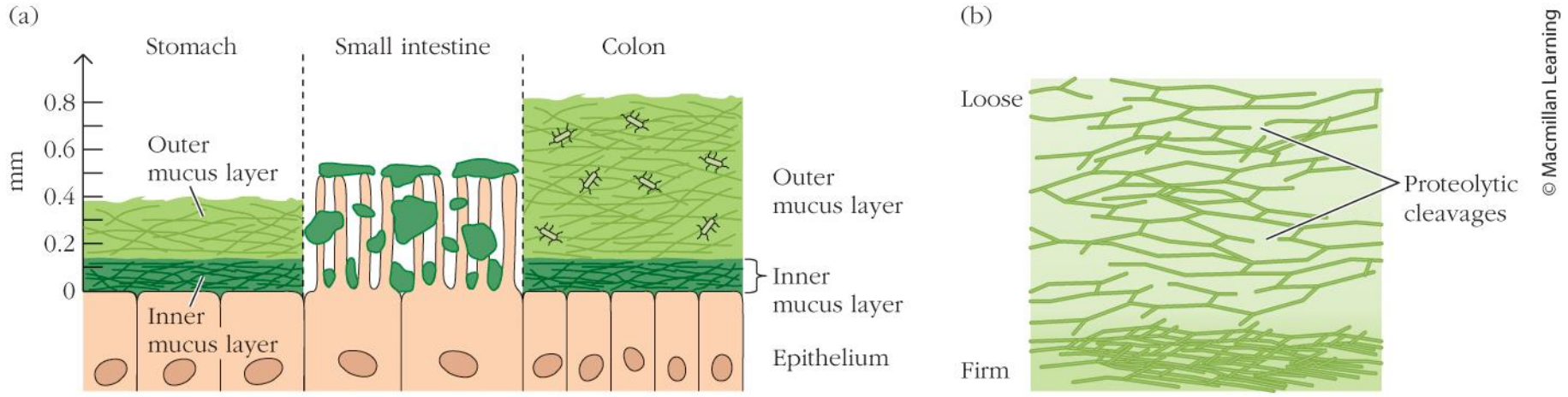


Figure 4-2. Kuby Immunology 8th edition

Antimicrobial proteins and peptides (AMPs).

- Epithelial layers produce hundreds of protective AMPs.
- One AMP, lysozyme, was discovered in 1922 by Sir Alexander Fleming.

  Lysozyme cleaves bonds between sugars in the cell wall of bacteria, leading to bacterial death.

- More than 3,000 AMPs have been identified across various organisms.
- AMPs are found in tears, saliva, milk, intestinal epithelia, and the skin.
- AMPs have broad antimicrobial activity, including:
  - finding and sequestering iron to prevent bacterial growth,
  - disrupting microbial membranes, leading to cell death,
  - preventing bacterial binding,
  - antifungal action, and
  - antiviral action.

  AMPs can be derived from commensal bacteria.

Cellular barriers to infection

Phagocytes (Neutrophils and Macrophages):

Trap, engulf and destruct microorganisms by phagocytosis.
Activation of adaptive immune response (macrophages).

Mast cells:

Secrete substances that stimulate inflammation.

Natural killer (NK) cells:

Kill target cells.

Natural killer T (NKT) cells :

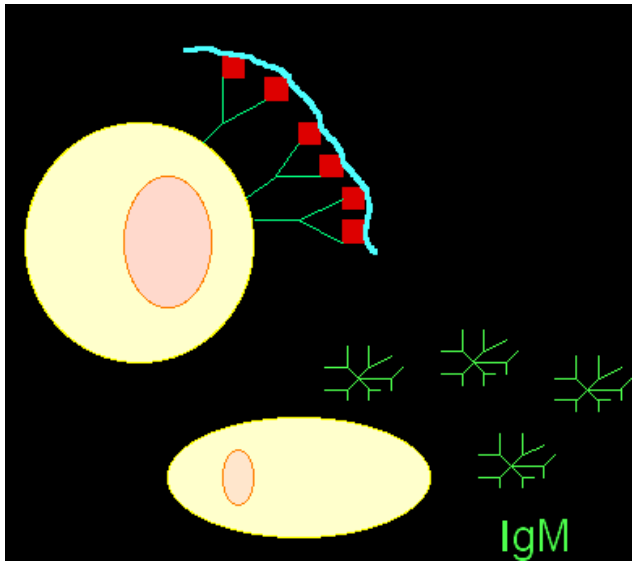
Express semi-invariant TCR that recognizes glycolipids presented by non-polymorphic CD1d molecule.
Upon activation produce IL-4 and IFN-γ.

B-1 B cells:

Make rapid antibody response to polysaccharide antigens.

B1 B cells

- *Distinct subset of B-cells that function in innate system*



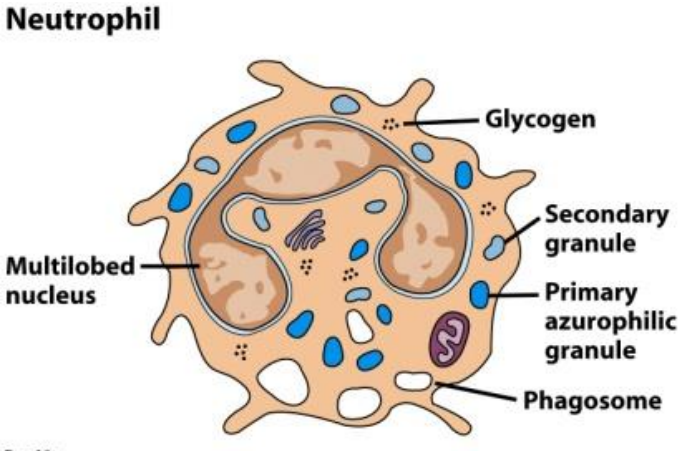
- Ab responses mainly to polysaccharide Ags/limited Ab repertoire
- Response appears within 48 hrs of Ag exposure so it can provide immediate protection before T cell-mediated response
- Do not depend on T cells help
- Do not exhibit memory
- Produce IgM Ab that effectively activates complement for removal of bacteria.

Phagocytes:

1. Neutrophils

a. Produced and lost in large number every day
b. Abundant in blood (50-60% of circulating white blood cells)
c. Not present in healthy tissue, but recruited to site of infection
   - pus contains dead & dying neutrophils
d. Short-lived
e. Contain granules with α-bacterial proteins and peptides
   - lysozyme
   - collagenase
   - elastase
f. Can eliminate pathogens by phagocytosis
   (*recall*: express Fc and complement receptors)

Effector fxns to clear pathogen



Phagocytes:

2. Macrophages

a. Circulating precursors are called monocytes
b. Can divide at site of infection
c. Longer lived than neutrophils
d. Express FcRs and complement receptors for phagocytosis of Ab and complement coated pathogens

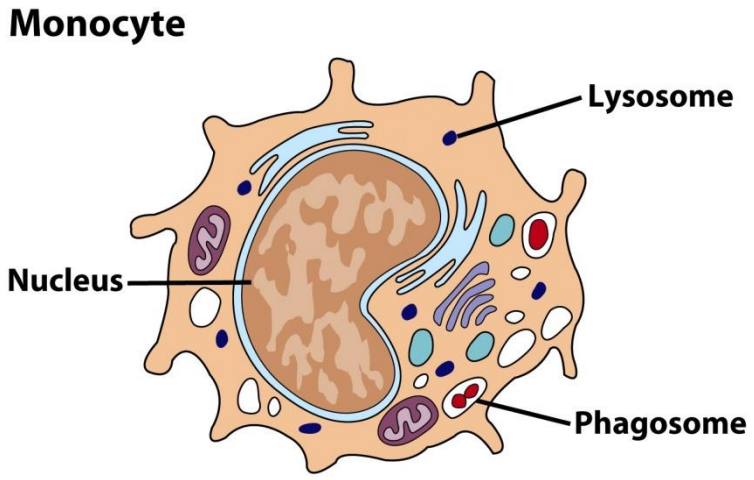


Figure 2-7a
Kuby IMMUNOLOGY, Sixth Edition

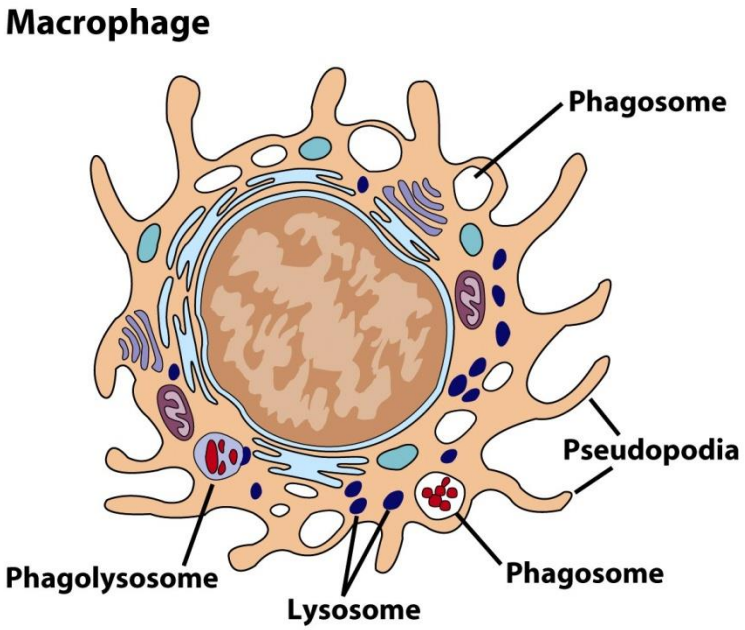


Figure 2-7b
Kuby IMMUNOLOGY, Sixth Edition

Natural Killer Cells:

Function against intracellular pathogens such as viruses

Also, role in tumor immunity

Activated by IFNγ, IFNβ or IL-12

Must be able to distinguish infected from uninfected cells!

-Multiple activating and inhibitory receptors involved in recognition of target cell, NK activation state is based on the sum of these interactions.

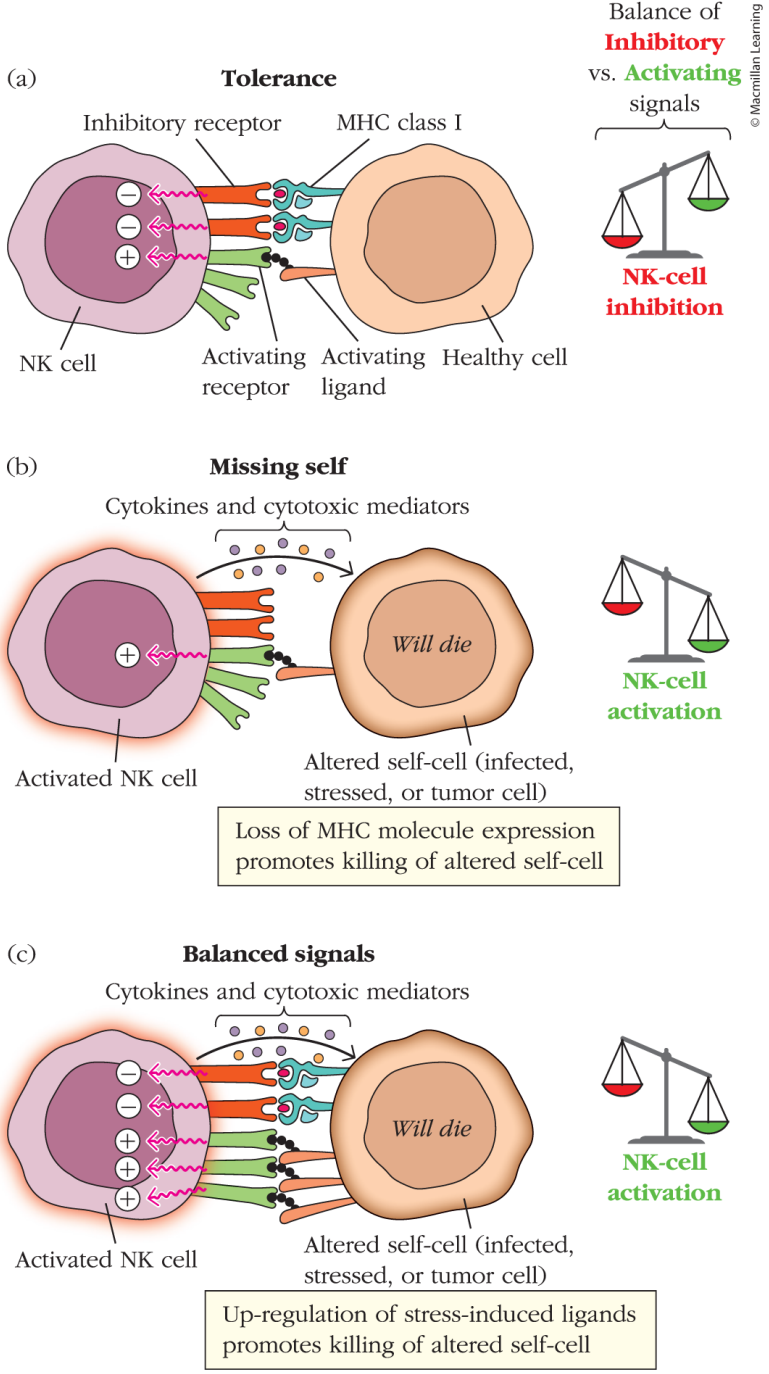


Figure 12-15. Kuby Immunology 8th edition

How does the innate system recognize foreign pathogen?

Receptors for opsonins

-binding mediated by Abs and complement

-recognize microorganisms ***indirectly*** & stimulate phagocytosis and killing.

1. **FcγRs** → FcγRI & FcγRIIA on Macrophages and Neutrophils
   FcγRIIIA on Macrophages and NK cells
   FcγRIIIB on Neutrophils

2. **Complement Receptors** → CR1, 3, & 4
   (recognize cleavage products of **C3 & C5**)

Triggering these receptors stimulates phagocytosis and activates phagocytes → induces adaptive response

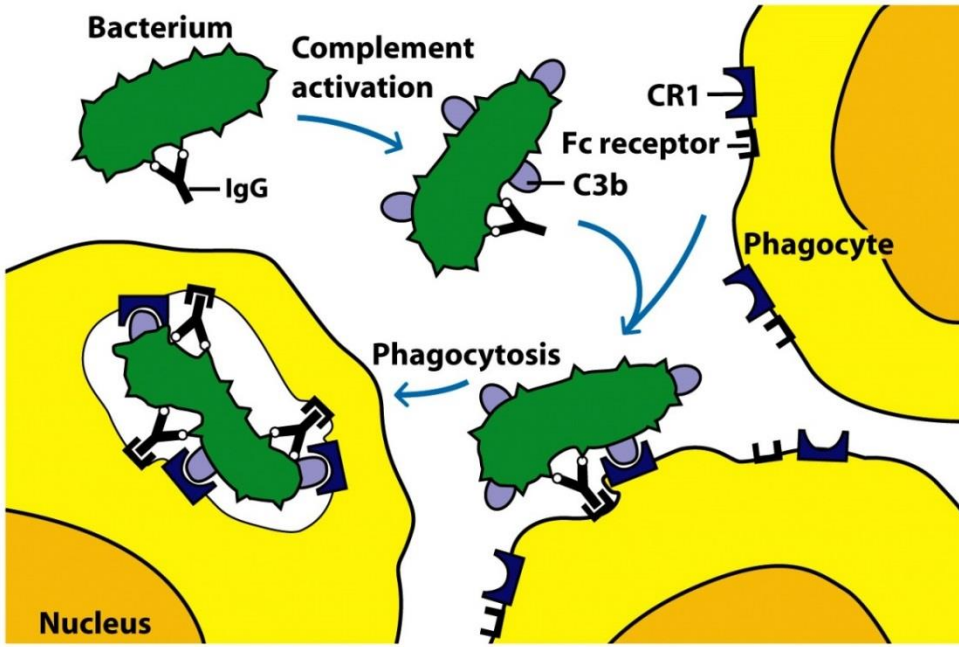


Figure 7-13a
Kuby IMMUNOLOGY, Sixth Edition

How does the innate system recognize foreign pathogen?

Pattern-Recognition Receptors (PRR)

Receptors of the innate system recognize distinct PAMPs (pathogen associated molecular patterns), such as:

a. Nucleic acids unique to microbes
   (ex: double stranded RNA or unmethylated CpG DNA)
b. Features of proteins found in microbes (N-formylmethionine)
c. Complex lipids & carbohydrates synthesized by microbes, but not by mammalian cells. Examples:
   - LPS in gram-negative bacteria or Teichoic acids in gram-positive bacteria
   - Mannose-rich oligosaccharides found in microbial glycoproteins

IMPORTANT:

This system has evolved to recognize microbial components that are often essential for microbe survival!

Pattern-Recognition Receptors (PRR)

1. Specificity inherited in genome (vs. T- and B- C.R.s)

2. Expressed by all cells of a particular type & not clonally distributed

   (T & B contain heterogeneous clonal populations vs. homogeneous Mϕ populations)

3. Trigger immediate response (vs. adaptive)

4. Recognize a broad class of pathogens (vs. a single specific target)

Pattern-Recognition Receptors (PRR)

Recognize microbes ***directly*** & stimulate phagocytosis and killing.

1. **Mannose receptors** – binds terminal mannose and fucose residues found on microbial cell walls

2. **Scavenger receptors** – binds anionic polymers and acetylated LDLs

3. **Toll-like Receptors** –TLRs recognize PAMPs and are expressed on a number of different cells including macrophages, neutrophils, B cells, dendritic cells, & mucosal epithelial and endothelial cells.
   - **TLR-2**: zymosan from yeast, bacterial lipoproteins & lipoteichoic acid & peptidoglycans on gram (+) bacteria
   - **TLR-3**: double stranded RNA
   - **TLR-4**: LPS on gram (-) bacteria; viral proteins
   - **TLR-5**: flagellin
   - **TLR-9**: unmethylated CpG

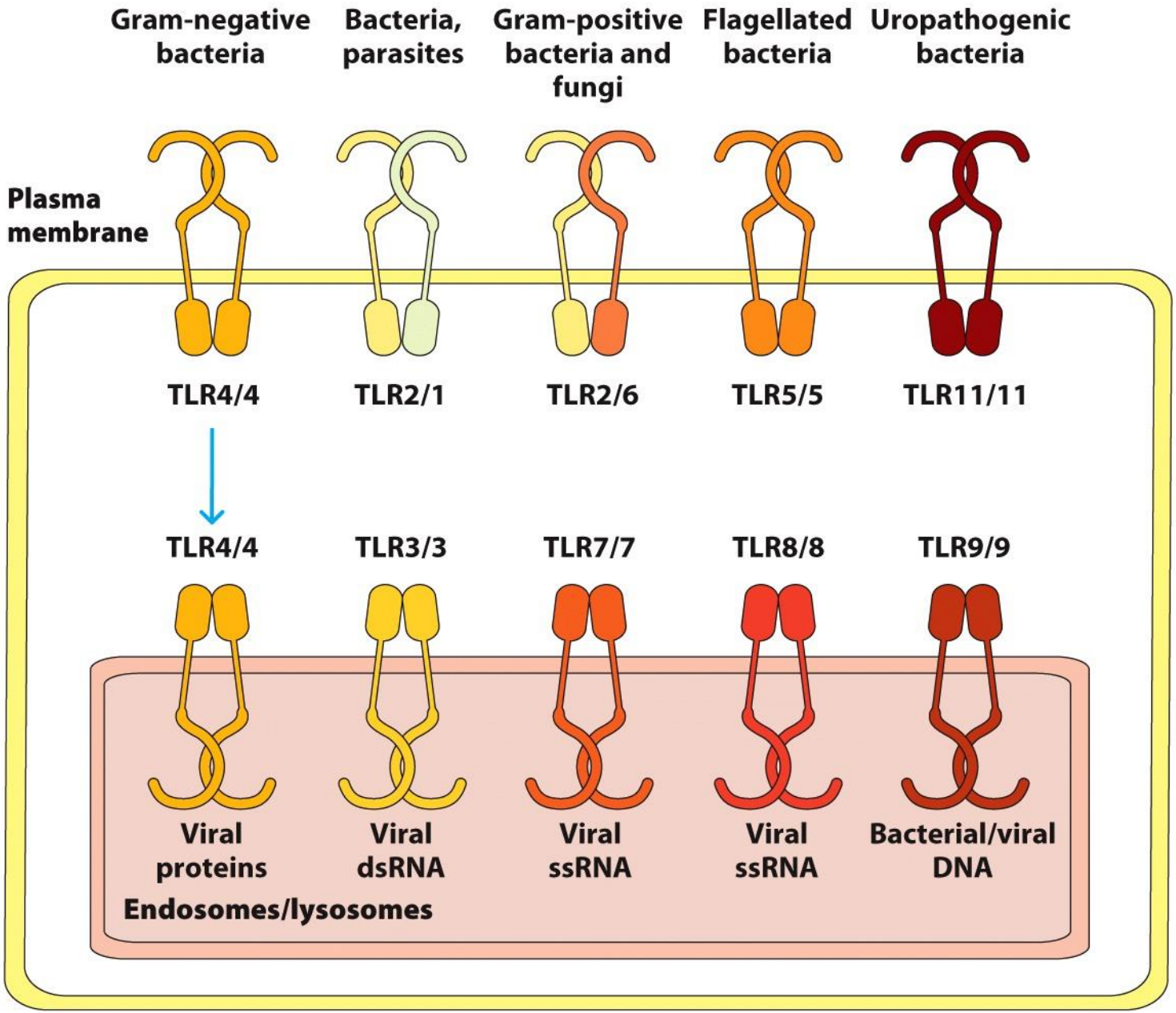


Figure 5-12
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Cellular location and specificity of TLRs

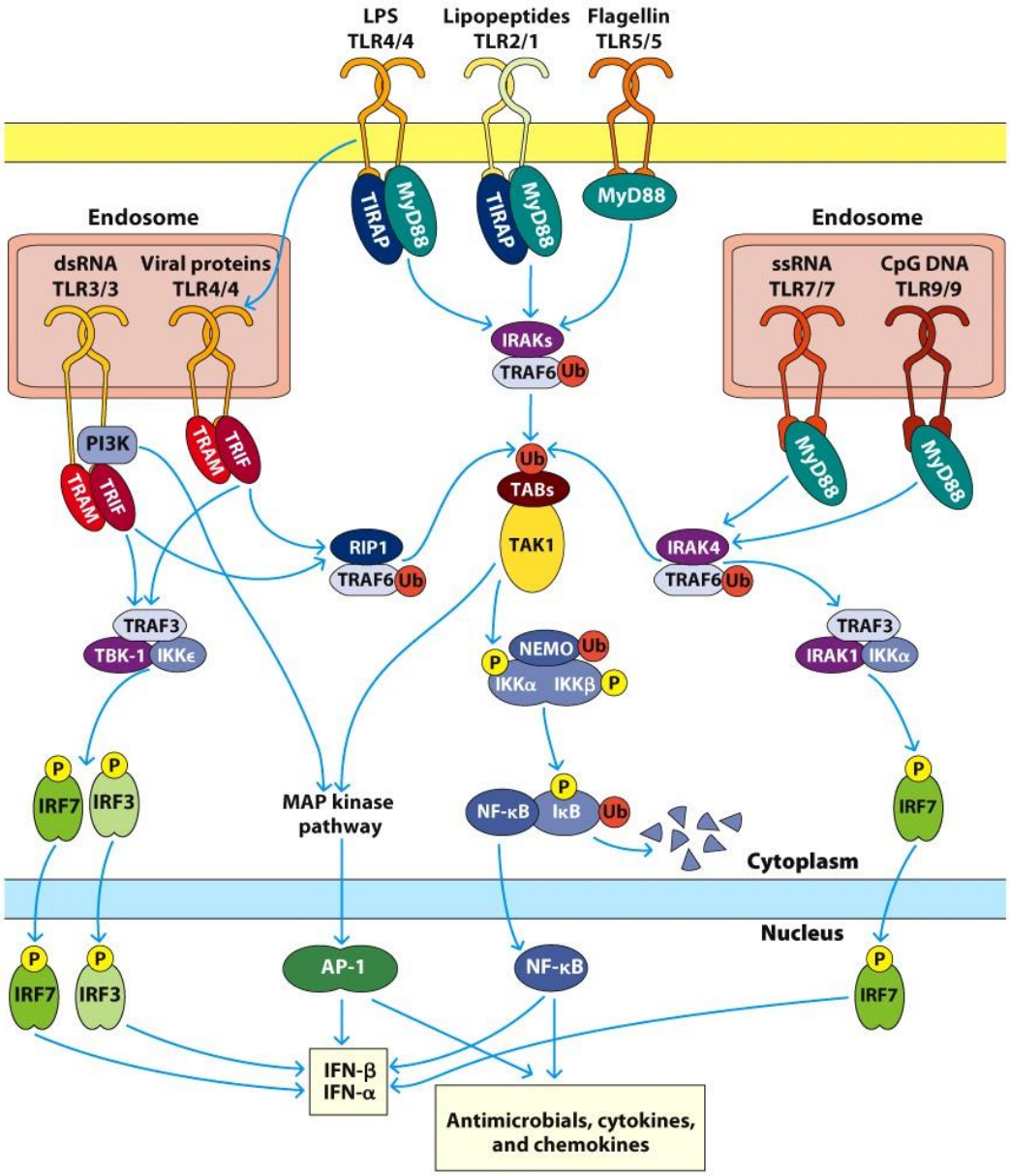

Figure 5-13
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Activation through TLRs triggers cytokine production & expression of co-stimulatory molecules (→ interface with activation of adaptive response)

Interferon response

- Viral infections cause production of Type I IFN (α and β) by infected cells
- Function to inhibit protein synthesis and DNA replication in infected cells
- Increase in MHC I expression and Ag presentation in all cells
- Activate NK cells to kill virally infected cells

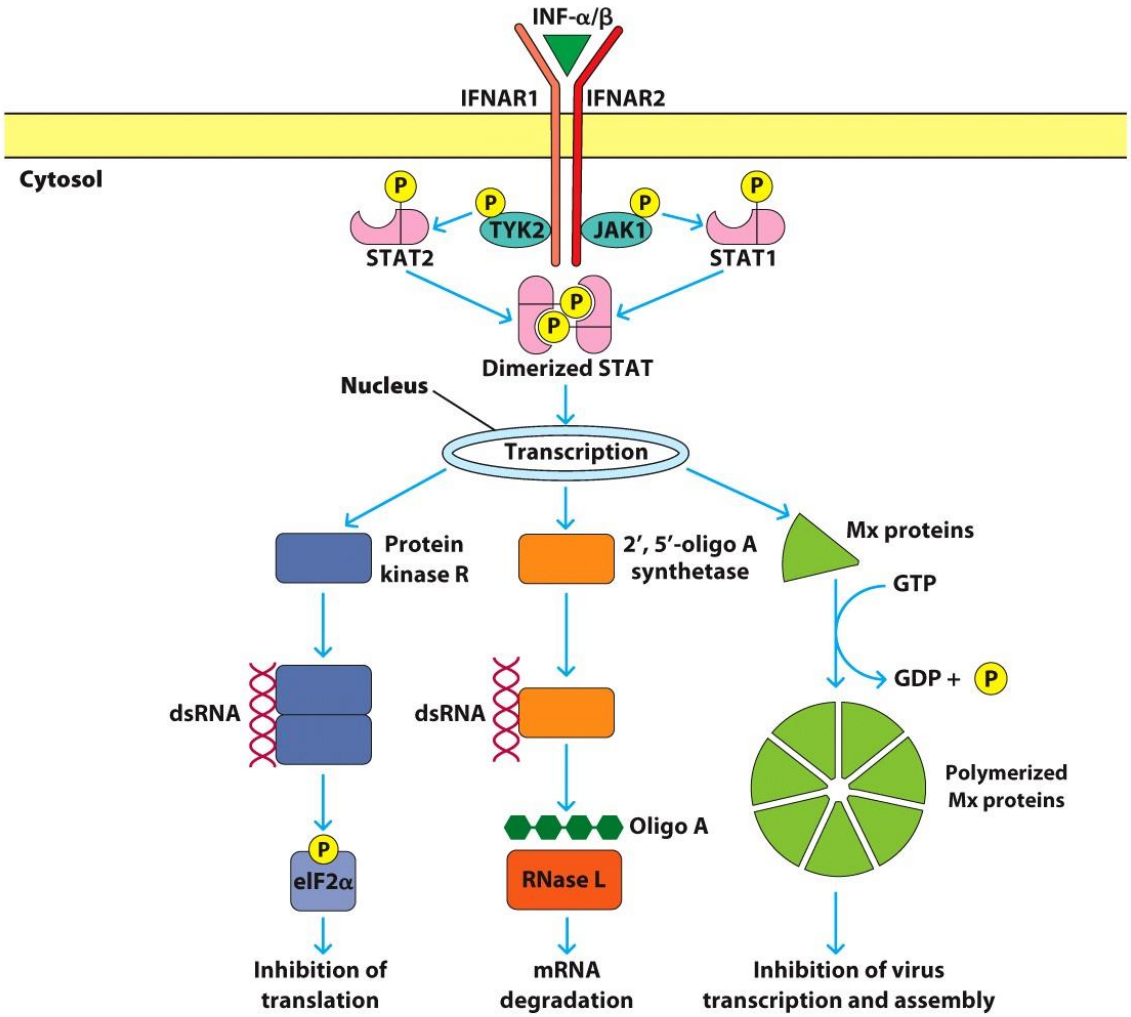

Figure 5-16
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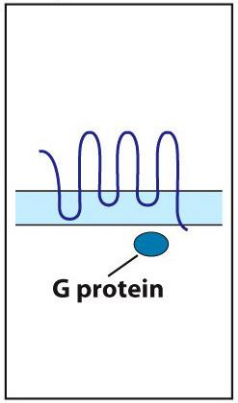
Chemokine and cytokine receptors

-recognize chemokines, cytokines & microbial products

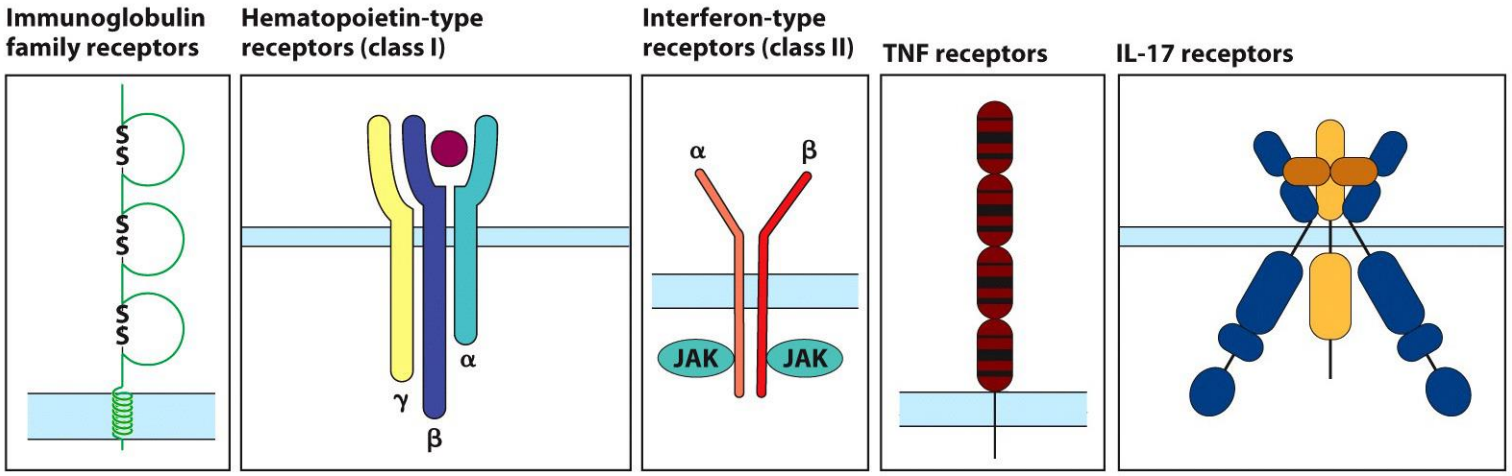
1. **Seven transmembrane α-helical (G-protein-coupled receptors):**

Activation induced migration of cells from blood through endothelium & production of microbicidal substances



Receptors of this class recognize: bacterial peptides containing N-formylmethionine residues, **Chemokines**, C5a, and lipid mediators of inflammation (platelet activating factor, prostaglandin E, & leukotriene B_4).

2. **Cytokine Receptors → Interleukins, Interferons, Inflamatory cytokines**



Initiation of a local inflammatory response

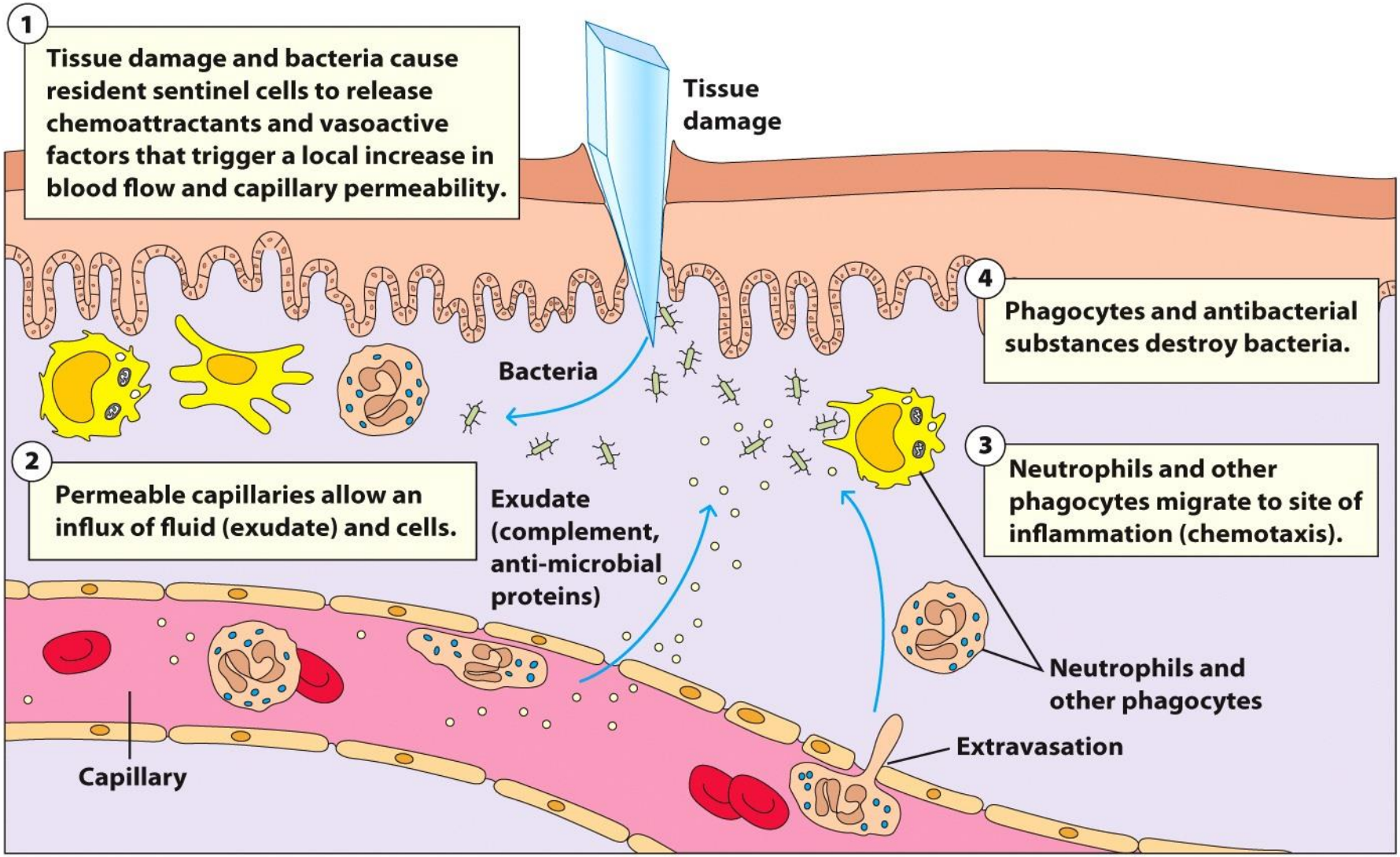


Figure 5-17
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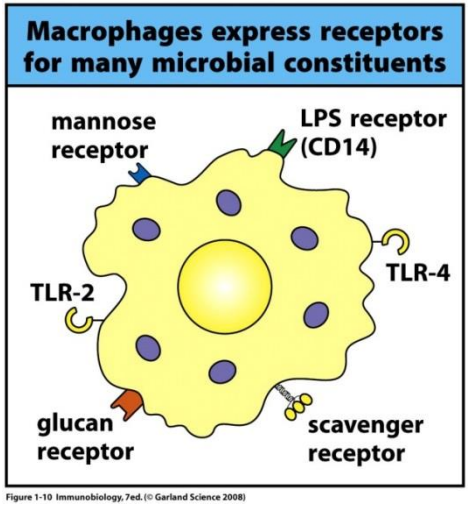
Innate Immune Response: The Cellular Response



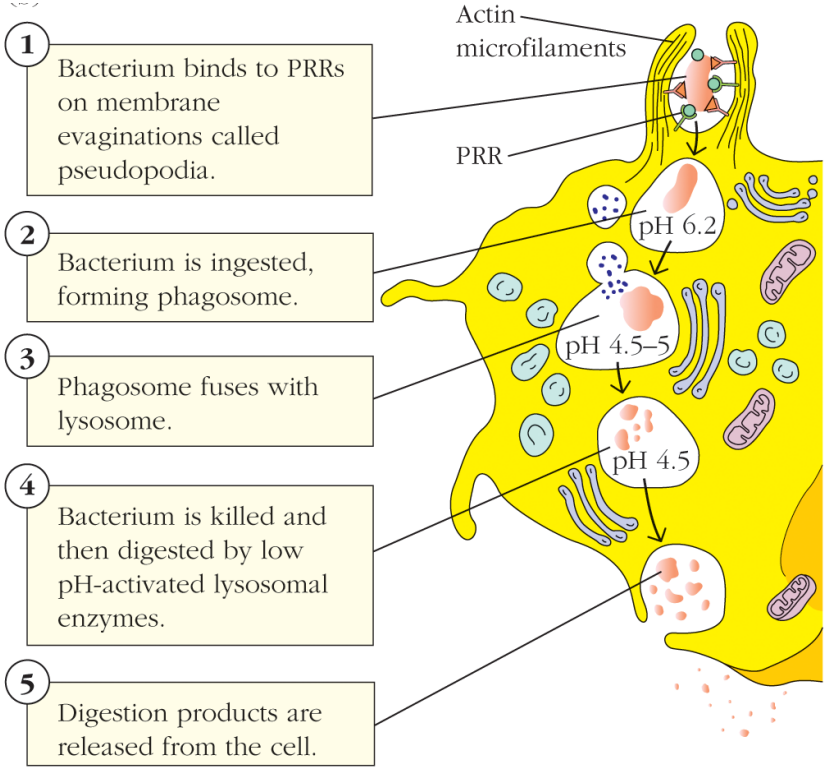


Figure 4-18. Kuby Immunology 8th edition

- Pathogens that cross the epithelial barrier are recognized by phagocytes in the subepithelial connective tissues.

-Bound pathogen is surrounded by a membrane forming a phagosome which becomes acidified.

-Lysosomes containing enzymes, proteins and peptides fuse with phagosome to form the phagolysosome in which the pathogen is digested. Products toxic to bacteria such as H_2O_2, superoxide anion and nitric oxide are produced.

- These initial events lead to……

Macrophage activation

Innate Immune Response: The Cellular Response

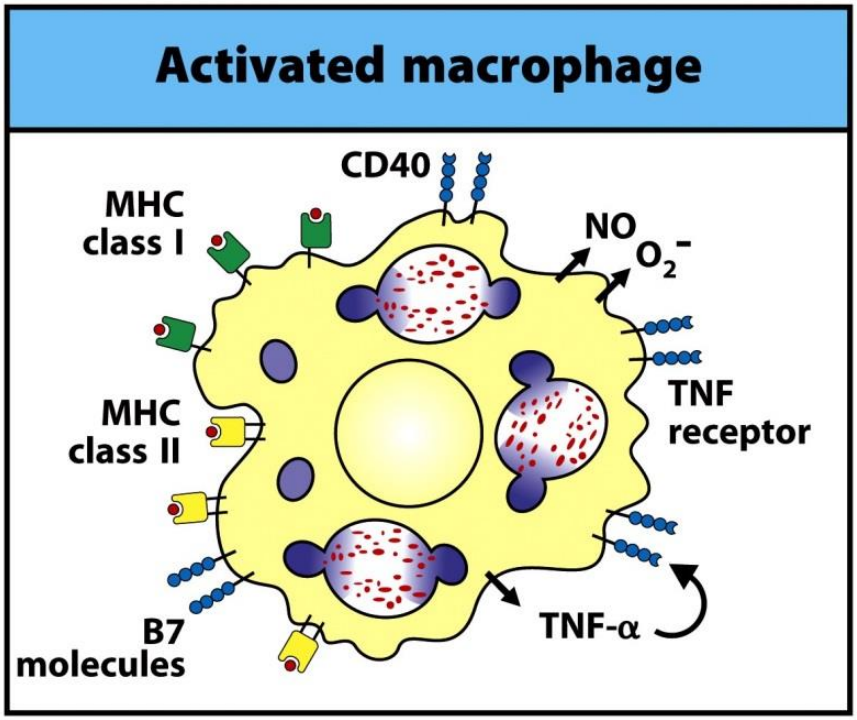


Figure 8-42 Immunobiology, 7ed. (© Garland Science 2008)

Activation leads to:

- **Cytokine secretion**

- **Induction of co-stimulatory molecules**

-Antigen processing and presentation (MHCII)

….hence….

Adaptive response can be activated too!

Macrophages → What are the Cytokines Released?

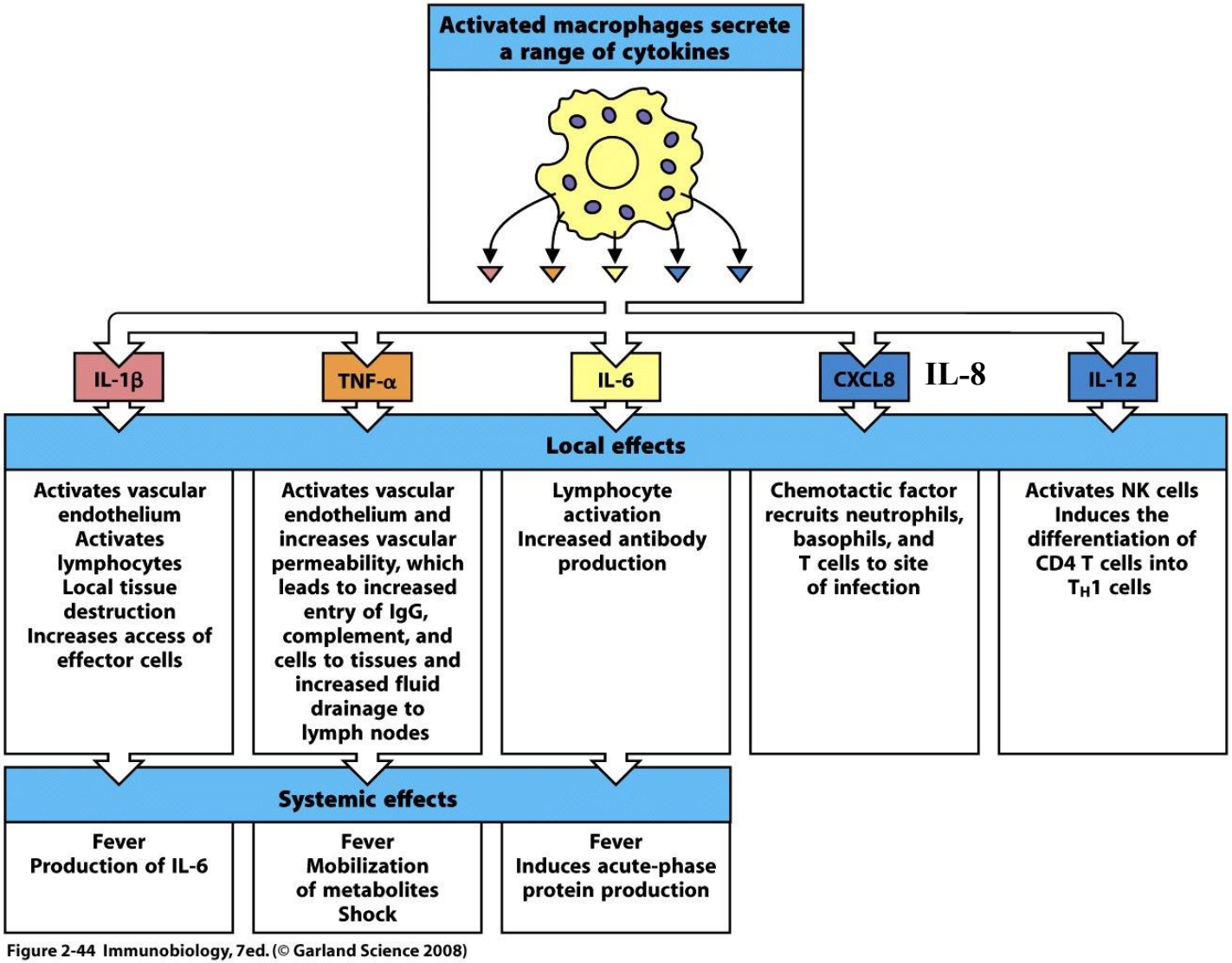


Figure 2-44 Immunobiology, 7ed. (© Garland Science 2008)

Other Mϕ products: Nitrous Oxide (NO), leukotrines & platelet-activating factor (PAF) contribute to inflammation.

Certain cytokines activate the Acute-Phase Response:

Examples are TNFα, IL-1, and IL-6
- "endogenous pyrogens"

Elicit production of acute-phase proteins
such as: C-reactive protein
& mannose-binding lectin
by hepatocytes, not immune cells!

Important in innate immune response –
act as opsonin & activate
complement pathway
(*recall Lectin pathway*)

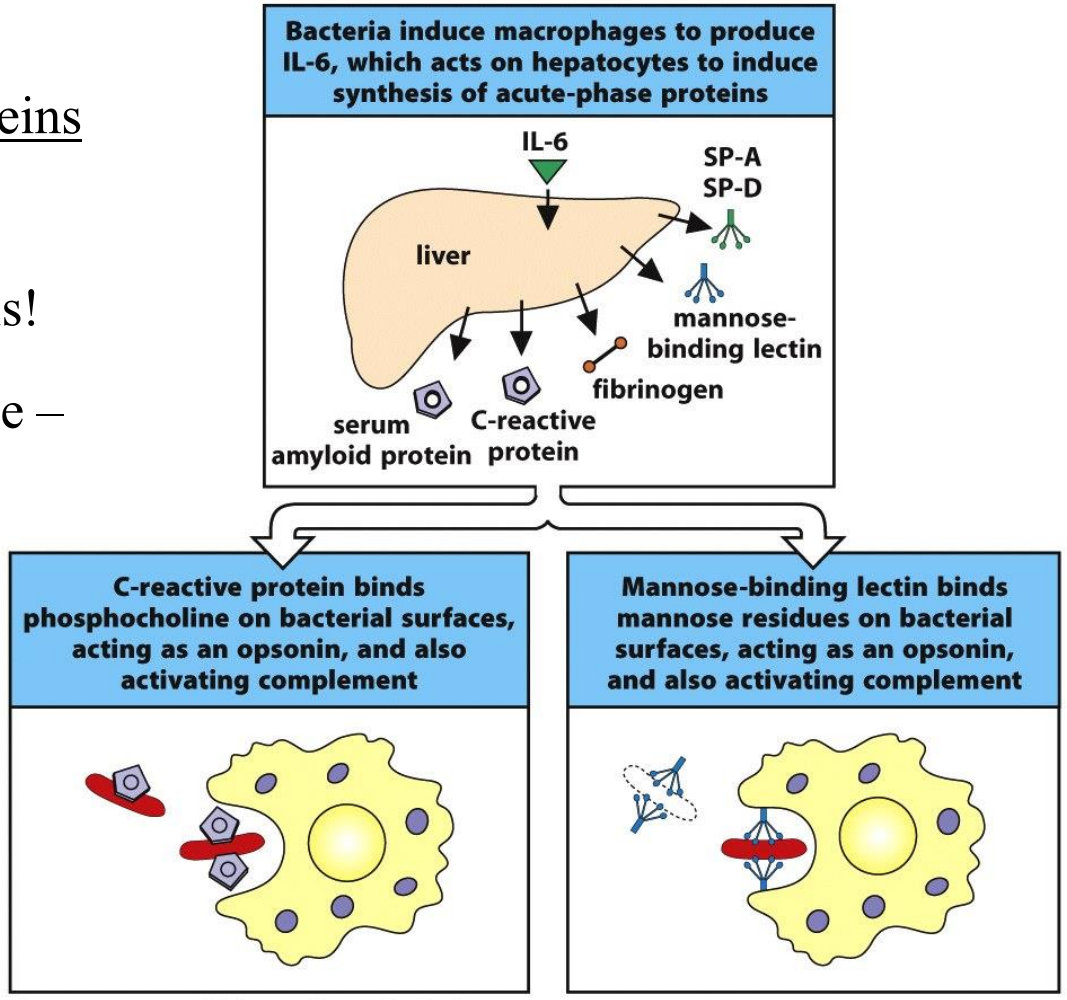


Figure 2-52 Immunobiology, 7ed. (© Garland Science 2008)

What is the role of inflammation in combating infection?

Delivers additional effector molecules & cells to site of infection

1. Increase in vascular diameter, so increase in blood volume
2. Decreased blood flow (heat & redness)
3. Increase in vascular permeability
4. Induced expression of adhesion molecules on endothelium
5. Directional migration of leukocytes through tissue

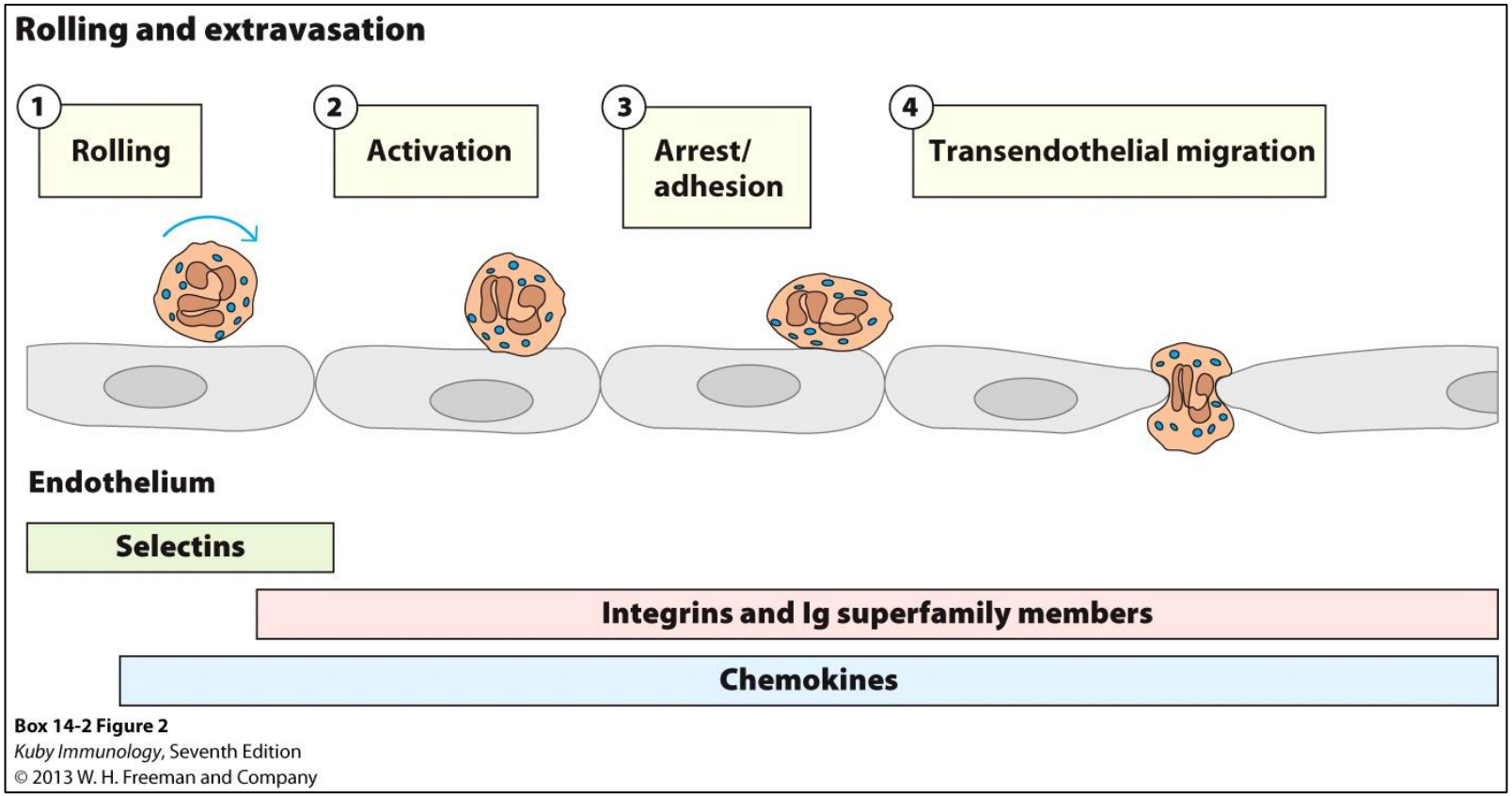
Provides a physical barrier to prevent spread of infection
(blood clots, formation of granulomas to localize infection)

Promotes repair of injured tissues

Innate Immune Response: The Cellular Response

Neutrophils and Macrophages (and other leukocytes) are recruited *from* the blood *to* sites of infection.

Resident tissue macrophages that recognize microbes secrete cytokines & chemokines that act on endothelial cells to produce adhesion molecules & attract circulating neutrophils & macrophages



Box 14-2 Figure 2
Kuby Immunology, Seventh Edition

Q. What is the role of inflammation in combating infection?

2. Decreased blood flow allows leukocytes to better interact with the vascular endothelium. Why is this important?
   - Extravasation!

   Selectins recognize certain leukocyte glycoproteins causing lymphocytes to roll
   ICAM-1 on endothelium interacts with…..
   LFA-1 (aka: CD11a: CD18) so that leukocytes attach firmly to the endothelium to cross the vascular endothelial wall & enter the site of infection

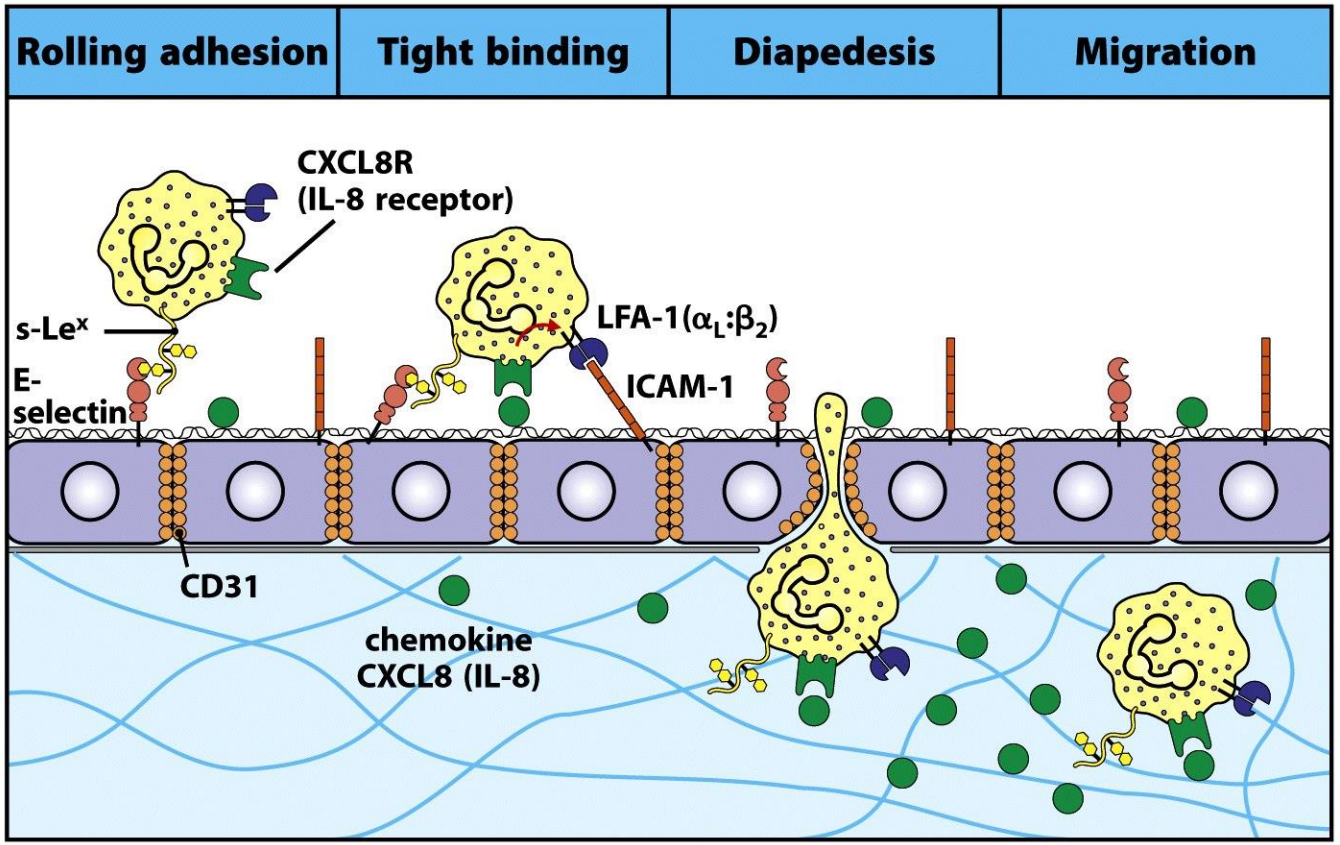


Figure 2-49 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

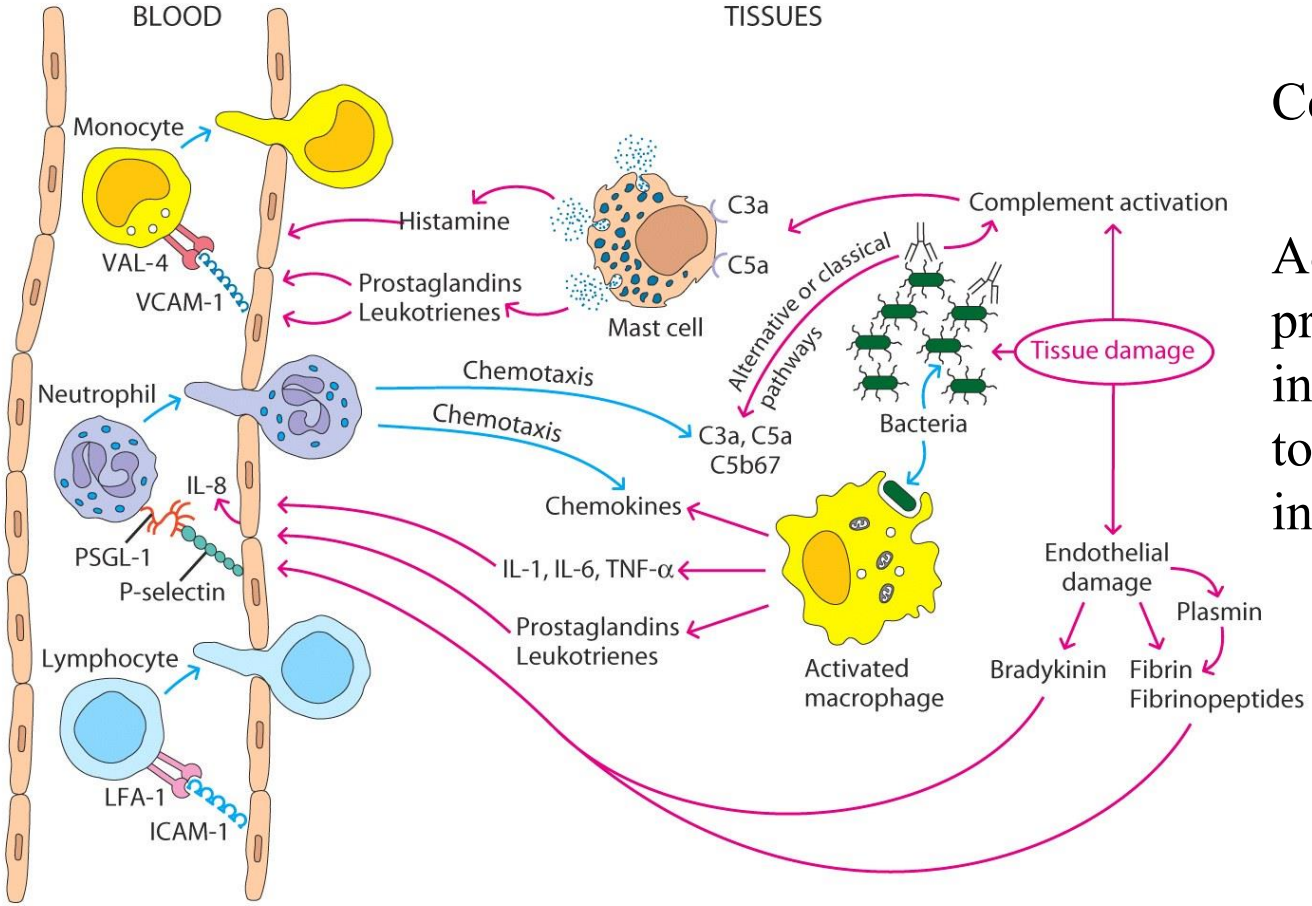
Trafficking is controlled by:

Appearance/disappearance of adhesion molecules on endothelial cells (EC)
Appearance/disappearance of their ligands on lymphocytes

At the site of inflammation, pro-adhesion molecules induced on EC

Ligands on white blood cells bind, cell slows down and rolls

This induces expression of true adhesion molecules on white blood cells (also EC)



Cell extravasates

Additional signals provided by chemokines induce cells to move towards the site of inflammation

Q. What is the role of inflammation in combating infection?

3. Increase in vascular permeability leads to local accumulation of fluid → swelling, (edema) & pain…but also, accumulation of Igs, complement, & other blood proteins in the tissue.

4. Mediators induce expression of adhesion molecules on the endothelium; neutrophils & monocytes are recruited to the site

5. Directional migration of leukocytes through tissues under the influence of chemoattractant molecules
   - Direct migration along a gradient of chemokines that increase as move nearer to the site of infection
   - Leukocytes recognize chemokines via chemokine receptors

- Entry of fluid *back* into blood at site of infection is prevented as local clots in small vessels are produced, therefore….
- Fluid in tissue carries pathogen, either directly or within a phagocytic cell, **via lymph** to regional lymph nodes where an adaptive immune response is elicited

Sepsis: Infection spreads to the blood stream (commonly bacterial)

Overwhelming release of cytokines (and other biological mediators), especially TNFa

Vasodilation occurs with increased vascular permeability leading to shock

- Septic shock requires signaling through TLR-4 (recognizes endotoxin -LPS)
- Mice defective in TLR-4 do not experience septic shock
- Mice defective in TLR-4 are highly sensitive to LPS containing pathogens

Functional Overview of Innate Immune Response: Summary

1. Triggered by ***germline encoded*** receptors of limited diversity
2. No lasting immune memory
3. Elicit cytokine release by phagocytes
4. Induce production of acute-phase proteins
5. Elevate body temperature
6. Induce inflammation
7. NK T cells:
    a. have TCRs of limited diversity & recognize some pathogens
    b. are able to recognize infected or altered cells
8. B-1 B cells can rapidly provide pathogen specific Abs
    of limited diversity in the absence of T cell help

TABLE 5-1 Innate and adaptive immunity

Attribute	Innate immunity	Adaptive immunity
Response time	Minutes/hours	Days
Specificity	Specific for molecules and molecular patterns associated with pathogens and molecules produced by dead/damaged cells	Highly specific; discriminates between even minor differences in molecular structure of microbial or nonmicrobial molecules
Diversity	A limited number of conserved, germ line–encoded receptors	Highly diverse; a very large number of receptors arising from genetic recombination of receptor genes in each individual
Memory responses	Some (observed in invertebrate innate responses and mouse/human NK cells)	Persistent memory, with faster response of greater magnitude on subsequent exposure
Self/nonself discrimination	Perfect; no microbe-specific self/nonself patterns in host	Very good; occasional failures of discrimination result in autoimmune disease
Soluble components of blood	Many antimicrobial peptides, proteins, and other mediators	Antibodies and cytokines
Major cell types	Phagocytes (monocytes, macrophages, neutrophils), natural killer (NK) cells, other leukocytes, epithelial and endothelial cells	T cells, B cells, antigen-presenting cells

Table 5-1
Kuby Immunology, Seventh Edition