Kindt • Goldsby • Osborne

Kuby IMMUNOLOGY

Sixth Edition

Chapter 3

Innate Immunity

Know Differences and Provide Examples

TABLE 3-1 Innate and adaptive immunity

Attribute	Innate immunity	Adaptive immunity
Response time	Minutes/hours	Days
Specificity	Specific for molecules and molecular patterns associated with pathogens	Highly specific; discriminates even minor differences in molecular structure; details of microbial or nonmicrobial structure recognized with high specificity
Diversity	A limited number of germ line–encoded receptors	Highly diverse; a very large number of receptors arising from genetic recombination of receptor genes
Memory responses	None	Persistent memory, with faster response of greater magnitude on subsequent infection
Self/nonself discrimination	Perfect; no microbe-specific patterns in host	Very good; occasional failures of self/nonself discrimination result in autoimmune disease
Soluble components of blood or tissue fluids	Many antimicrobial peptides and proteins	Antibodies
Major cell types	Phagocytes (monocytes, macrophages, neutrophils), natural killer (NK) cells, dendritic cells	T cells, B cells, antigen-presenting cells

Table 3-1
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Skin and Epithelial Barriers

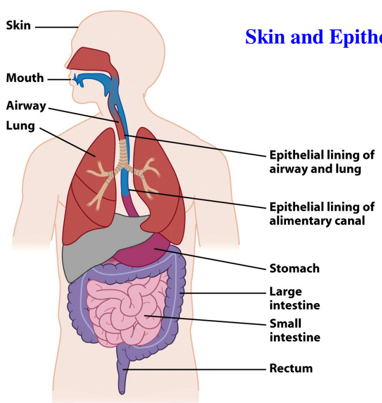

Figure 3-1 part 2
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Organ or tissue	Innate mechanisms protecting skin/epithelium
Skin	Antimicrobial peptides, fatty acids in sebum
Mouth and upper alimentary canal	Enzymes, antimicrobial peptides, and sweeping of surface by directional flow of fluid 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

Figure 3-1 part 1
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Antimicrobial peptide – psoriasin

-Activity against Gram (-) *E. coli*

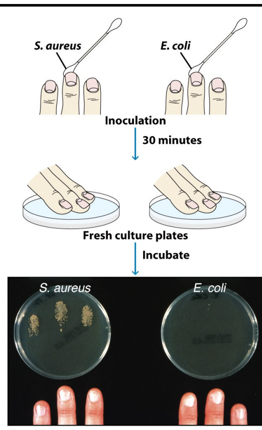

Figure 3-2
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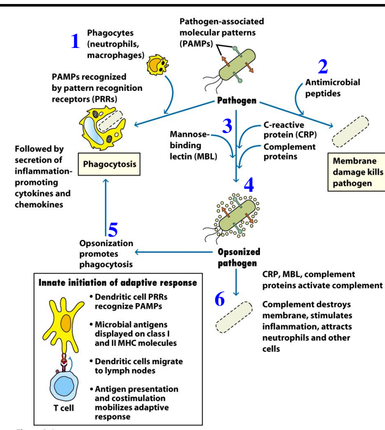

Figure 3-4
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PRRs – Pattern Recognition Receptors → on **HOST CELLS**

PAMPs – Pathogen-Associated Molecular Patterns → on **MICROBES**

INFLAMMATION

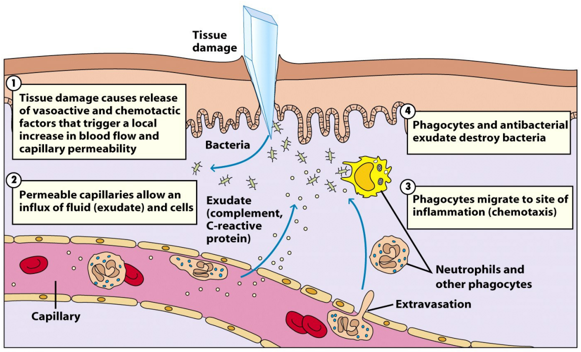

Figure 3-5
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Inflammation

Tissue damage

- 1) **Release of Vasoactive and chemotactic Mediators →** histamine, serotonin, etc
- 2) **Vasodilation**: ↑diameter of capillaries, ↑blood flow
- 3) **Increased Vascular Permeability**: ↑ Leakiness from blood vessels → ↑ recruitment of cells and fluid → edema
- 4) **Extravasation of Phagocytes** – recruitment of leukocytes → Chemotaxis (chemokines; C3a/C5a, N-formyl peptides)
- 5) **Action on Blood Vessels** → ↑ intercellular adhesion molecule (ICAM)
- 5) **Tissue Repair** – fibrin (clotting) and fibroblasts

4 Steps in Cell Recruitment from Blood Vessels

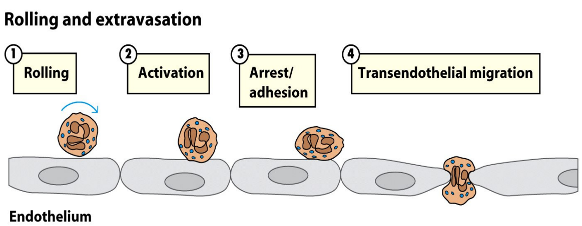

Figure 3-7a
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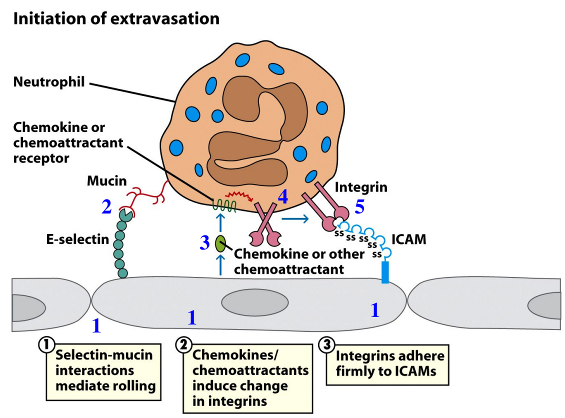

Figure 3-7b
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Soluble Molecules and Membrane-Associated Receptors

- 1) **Antimicrobial Peptides** – defensins, interferons
  - **Defensins** – α-Defensins, β-Defensins
    - Cationic (+) peptides
    - Antibacterial
    - Disrupt microbial membranes and synthesis of RNA, DNA, and proteins
    - Produced among others by neutrophils, epithelial cells
  - **Interferons** – IFN-α and IFN-β
    - Block viral replication (RNA viruses)

Soluble Molecules and Membrane-Associated Receptors

2) **Acute Phase Response Proteins**

- C Reactive Proteins (CRP), Mannose Binding Protein (MBP)
  - Increased in blood after tissue injury
  - Synthesized by liver and Macrophages
  - Phagocytosis → IL-1β, IL-6, TNF-α → Liver
  - **CRP** – binds polysaccharides and phosphorylcholine on microbial membranes → ↑ phagocytosis
  - **MBL -** binds mannose residues on molecules found on microbial membranes → Activates complement

TABLE 3-2 Some antimicrobial peptides

Peptide	Typical producer species*	Typical microbial activity*
Defensin family α-Defensins	Human (found in paneth cells of intestine and in cytoplasmic granules of neutrophils)	Antibacterial
β-Defensins	Human (found in epithelia and other tissues)	Antibacterial
Cathelicidins	Human, bovine	Antibacterial
Magainins	Frog	Antibacterial; antifungal
Cercropins	Silk moth	Antibacterial
Drosomycin	Fruit fly	Antifungal
Spinigerin	Termite	Antibacterial; antifungal

*In many cases, production of the indicated antimicrobial peptide or family is not limited to the typical producer but is produced by many different species. Also, some members of the indicated peptide or family may have broader antimicrobial activity than the typical one indicated.

Table 3-2
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TABLE 3-3 Receptors of the innate immune system

Receptor (location)		Target (source)	Effect of recognition
Complement (bloodstream, tissue fluids)	S	Microbial cell wall components	Complement activation, opsonization, lysis
Mannose-binding lectin (MBL) (bloodstream, tissue fluids)	S	Mannose-containing microbial carbohydrates (cell walls)	Complement activation, opsonization
C-reactive protein (CRP) (bloodstream, tissue fluids)	S	Phosphatidylcholine, pneumococcal polysaccharide (microbial membranes)	Complement activation, opsonization
Lipopolysaccharide (LPS) receptor;* LPS-binding protein (LBP) (bloodstream, tissue fluids)	S	Bacterial lipopolysaccharide (gram-negative bacterial cell walls)	Delivery to cell membrane
Toll-like receptors (cell surface or internal compartments)		Microbial components not found in hosts	Induces innate responses
NOD† family receptors (intracellular)		Bacterial cell wall components	Induces innate responses
Scavenger receptors (SRs) (cell membrane)		Many targets; gram-positive and gram-negative bacteria, apoptotic host cells	Induces phagocytosis or endocytosis

* LPS is bound at the cell membrane by a complex of proteins that includes CD14, MD-2, and a TLR (usually TLR4).
† *N*ucleotide-binding *o*ligomerization *d*omain.

Table 3-3
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Soluble Molecules and Membrane-Associated Receptors

NOD – Nucleotide-Binding Oligomerization Domain

- Cytosolic receptors
- Two types: NOD1 and NOD2
- Recognize products derived from peptidoglycan

Pattern-Recognition Receptors

- Receptors of the innate immune system
- Recognize unique antigens (motifs) in micro-organisms (Danger Signals!!!)
- These antigens are absent in the host (non-self)
- Several Patter-Recognition Receptors (PRRs) identified
- BIO401: Toll-like receptors (TLRs)

Soluble Molecules and Membrane-Associated Receptors

TLRs – Toll-Like Receptors

- 11 found in humans and 12 in mice
- Structure: Exterior – Leucine-rich repeats; Interior – TIR (Toll-IL-1 Receptor) domain
- Can form (HETERO)DIMERS → affect their binding specificity
- Membrane and cytoplasmic localization

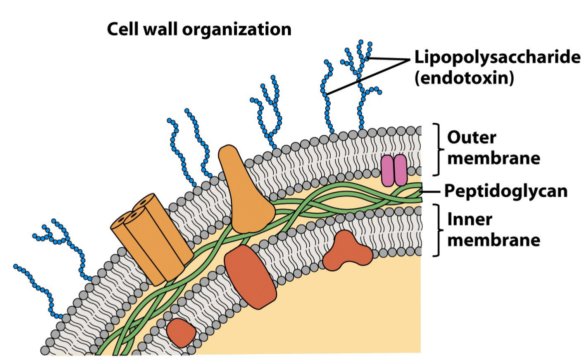

Figure 3-9 part 2
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Type of bacterium?

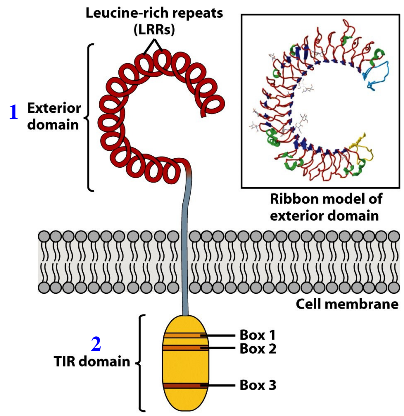

Figure 3-10
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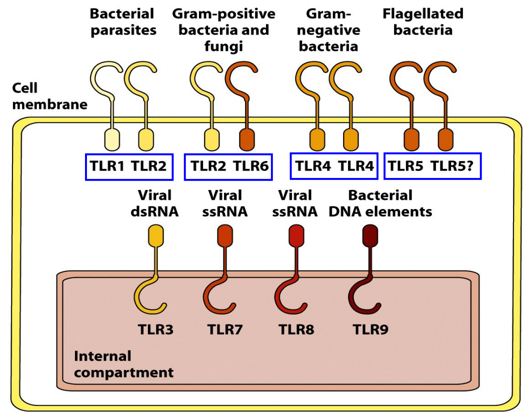

Figure 3-11 part 1
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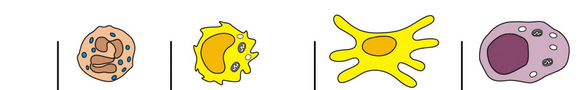
Cell Types of Innate Immunity



Cell type	Neutrophils	Macrophages	Dendritic cells	Natural killer cells
Function	Phagocytosis Reactive oxygen and nitrogen species Antimicrobial peptides	Phagocytosis Inflammatory mediators Antigen presentation Reactive oxygen and nitrogen species Cytokines Complement proteins	Antigen presentation Costimulatory signals Reactive oxygen species Interferon Cytokines	Lysis of viral-infected cells Interferon Macrophage activation

Figure 3-12
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Neutrophils

- Phagocytosis
- Express PRRs on surface (TLRs, Complement, Antibodies, etc)
- Oxidative and Non-oxidative Killing
- Oxidative: ROS (reactive oxygen species) and RNS (reactive nitrogen species) → triggered by NADPH Phagosome Oxidase (phox)
- Respiratory Burst → ↑ oxygen uptake
- Non-oxidative Killing – lysozyme, acidic cathepsins, proteases, defensins, etc

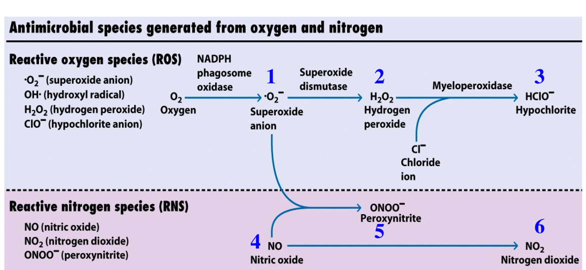

Figure 3-13
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Activated Macrophages

- TLRs, Cytokines
  - ↑ phagocytic activity
  - ↑ killing activity
  - ↑ MHC-II expression
  - ↑ cytokine production
  - ↑ APR proteins and complement synthesis
  - ↑ iNOS (inducible nitric oxide synthase)
    - L-arginine + O_2 + NADPH → **NO** + L-citruline + NADP

NK Cells

- Protect against viral infections
- Produce cytokines: IFN-γ and TNF-α
- These cytokines → activate Macrophages, and differentiation of Th cells

Dendritic Cells

- Immature
- Interact with both Th and Tc cells
- Activation → TLRs leads to ↑ MHC-II and co-stimulatory molecules
- Produce cytokines
- Killing by oxygen-dependent mechanisms

TLR Signaling

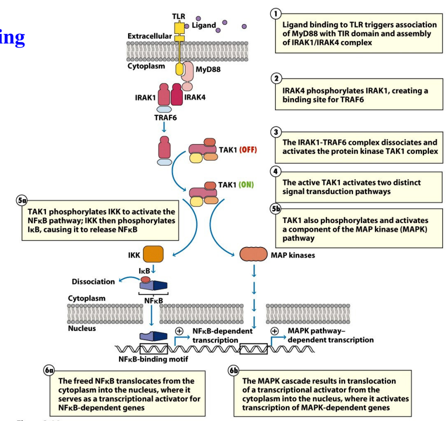

Figure 3-14
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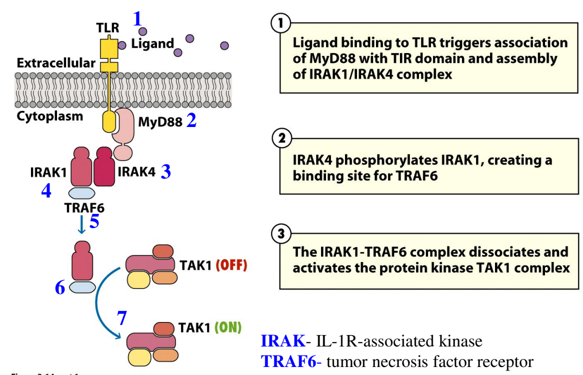

Figure 3-14 part 1
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IRAK- IL-1R-associated kinase
TRAF6- tumor necrosis factor receptor associated factor 6
TAK1- Transforming growth factor β-activated kinase

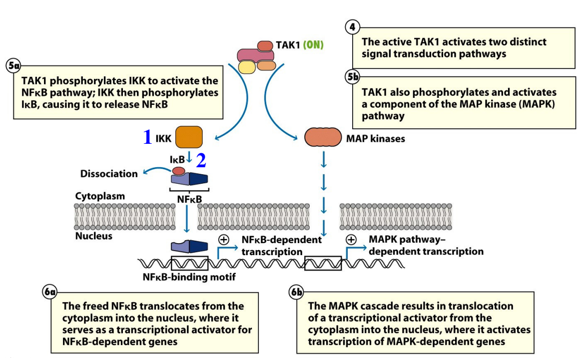

Figure 3-14 part 2
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IKK – IκB Kinase
MAP – mitogen activated protein

TABLE 3-4 Immunity in multicellular organisms

Taxonomic group	Innate immunity (nonspecific)	Adaptive immunity (specific)	Invasion-induced protective enzymes and enzyme cascades	Phagocytosis	Anti-microbial peptides	Pattern recognition receptors	Graft rejection	T and B cells	Anti-bodies
Higher plants	+	−	+	−	+	+	−	−	−
Invertebrate animals									
Porifera (sponges)	+	−	?	+	?	?	+	−	−
Annelids (earthworms)	+	−	?	+	?	?	+	−	−
Arthropods (insects, crustaceans)	+	−	+	+	+	+	?	−	−
Vertebrate animals									
Elasmobranchs (cartilaginous fish; e.g., sharks, rays)	+	+	+	+	Equivalent agents	+	+	+	+
Teleost fish and bony fish (e.g., salmon, tuna)	+	+	+	+	Probable	+	+	+	+
Amphibians	+	+	+	+	+	+	+	+	+
Reptiles	+	+	+	+	?	+	+	+	+
Birds	+	+	+	+	?	+	+	+	+
Mammals	+	+	+	+	+	+	+	+	+

KEY: + = definitive demonstration; − = failure to demonstrate thus far; ? = presence or absence remains to be established.

SOURCES: M. J. Flajnik, K. Miller, and L. Du Pasquier, 2003, "Origin and Evolution of the Vertebrate Immune System," in *Fundamental Immunology*, 5th ed., W. E. Paul (ed.), Lippincott, Philadelphia; M. J. Flajnik and L. Du Pasquier, 2004, *Trends in Immunology* **25**:640.

Table 3-4
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