

Chapter 3

Innate Immunity

Know Differences and Provide Examples

| 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 structures; 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 macrobe-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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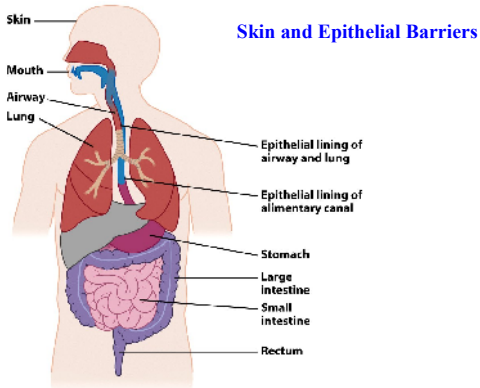


Figure 3-1 part 2
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Organ or tissue Innate mechanisms protecting skin/epithelium

| | |
|---|--|
| 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

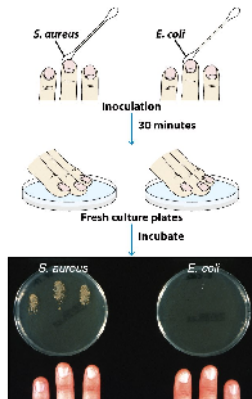
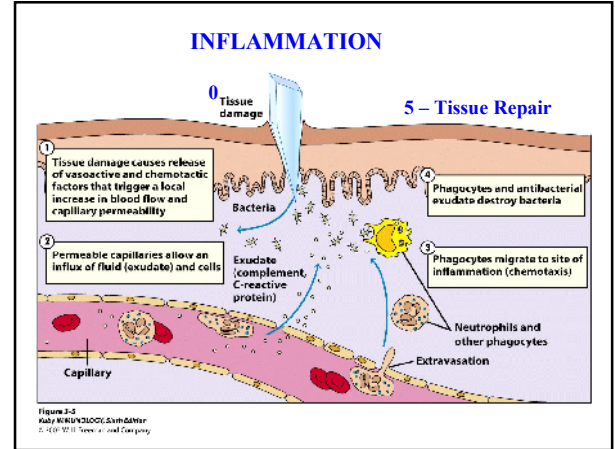
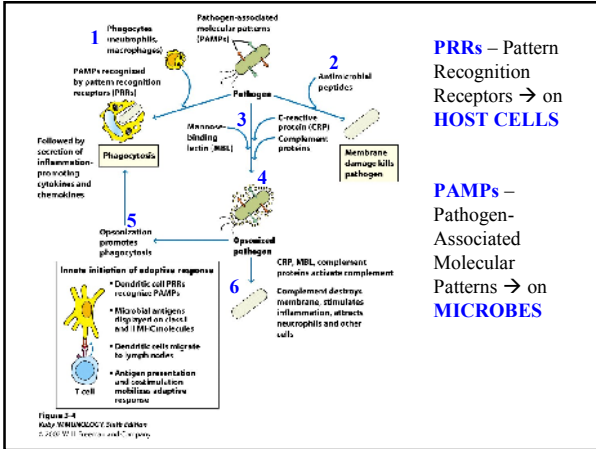
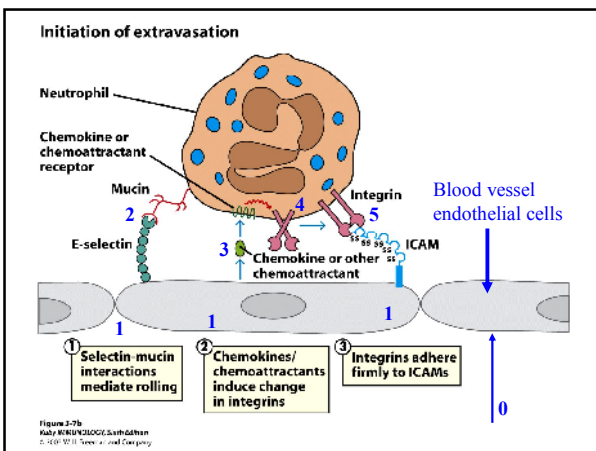
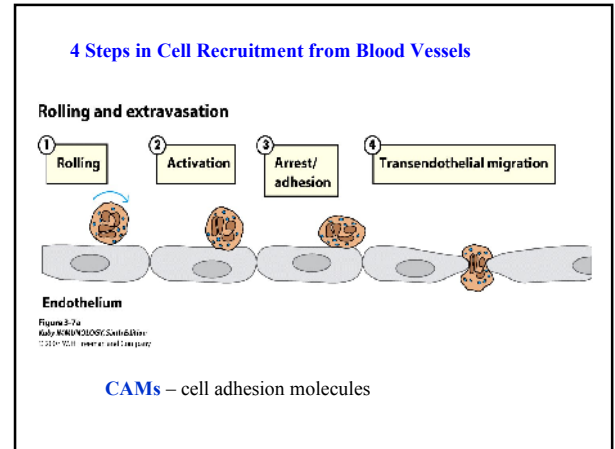


Figure 3-2
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Connection Between Innate and Adaptive Immunity



- ## Inflammation
- Tissue damage → Acute**
- 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** → ↑ cell adhesion molecules (CAMs)
 - 6) **Tissue Repair** – fibrin clotting and fibroblasts



- ## Soluble Molecules and Membrane-Associated Receptors
- 1) **Antimicrobial Peptides** – defensins, interferons
 - **Defensins** – α-Defensins, β-Defensins
 - Cationic (+) peptides (29-35 aa)
 - Antibacterial and anti-fungal
 - Disrupt microbial membranes and synthesis of RNA, DNA, and proteins
 - Produced among others by neutrophils and 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-1 β , IL-6, TNF- α → Liver
- **CRP** – binds polysaccharides and phosphorylcholine on microbial membranes → ↑ phagocytosis and complement activation
- **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 granule cells of neutrophils and in cytoplasmic granules of neutrophils) | Antibacterial |
| β -Defensins | Human (found in epithelia and other tissues) | Antibacterial |
| Cathelicidins | Human, bovine | Antibacterial |
| Alagunins | Frog | Antibacterial; antifungal |
| Cecropins | Silk moth | Antibacterial |
| Drosomycin | Fruit fly | Antifungal |
| Spinigalins | 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.

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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 ^a (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) | M Microbial components not found in hosts | Induces innate responses |
| NOD ^b family receptors (intracellular) | Bacterial cell wall components | Induces innate responses |
| Scavenger receptors (SRs) (cell membrane) | M 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 include CD14, MD-2, and a TLR (usually TLR4).
^b Cytosolic binding/oligomerization domain.

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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 degradation.

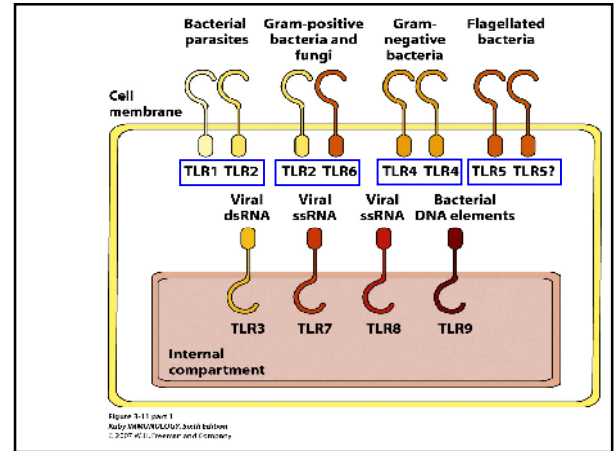
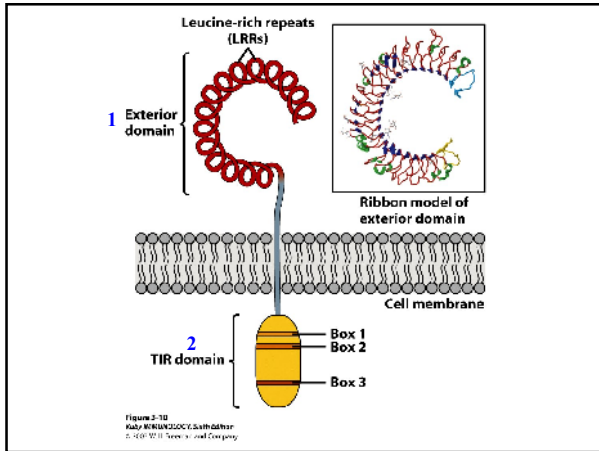
Pattern-Recognition Receptors

- Receptors of the **innate immune system**
- Recognize unique antigens (motifs) in microorganisms (**Danger Signals!!!**)
- These antigens are absent in the host (non-self)
- Several Pattern-Recognition Receptors (**PRRs**) identified

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 or HOMO)**DIMERS** → affect their binding specificity
- Membrane and cytoplasmic localization



| PAMP | PRR | Biological Consequence of Interaction |
|--------------------------------------|------------------------------|--|
| Microbial cell wall components | Complement | Opsonization; Complement activation |
| Mannose-containing carbohydrates | Mannose-binding protein | Opsonization; Complement activation |
| Polyanions | Scavenger receptors | Phagocytosis |
| Lipoproteins of <i>Mycobacterium</i> | TLR-1 (Toll-like receptor 1) | Macrophage recruitment & activation; Secretion of inflammatory cytokines |

| PAMP | PRR | Biological Consequence of Interaction |
|---|------------------------------|--|
| Lipoteichoic acid of Gram + bacteria | TLR-2 (Toll-like receptor 2) | Macrophage recruitment & activation; Secretion of inflammatory cytokines |
| Yeast cell wall components | | |
| Double stranded RNA | TLR-3 | Production of interferon (antiviral) |
| LPS (lipopolysaccharide of Gram - bacteria) | TLR-4 | Macrophage recruitment & activation; Secretion of inflammatory cytokines |
| Viral proteins | | |

| PAMP | PRR | Biological Consequence of Interaction |
|--------------------------------|-------|--|
| Flagellin (bacterial flagella) | TLR-5 | Macrophage recruitment & activation; Secretion of inflammatory cytokines |
| Lipopeptides | TLR-6 | Macrophage recruitment & activation; Secretion of inflammatory cytokines |
| Zymosan (yeast) | | |
| ssRNA viruses | TLR-7 | Type I interferons |

| PAMP | PRR | Biological Consequence of Interaction |
|---|--------|--|
| ssRNA | TLR-8 | Type I IFNs |
| CpG unmethylated dinucleotides | TLR-9 | Macrophage recruitment & activation; Secretion of inflammatory cytokines |
| | TLR-10 | Unknown |
| <i>Toxoplasma</i> profilin; uropathogenic bacteria components | TLR-11 | Unknown |

NF- κ B – IL-12, IL-1 β , IL-6, TNF- α / \uparrow Tc cells (MyD88)
 MAPK – Type I IFNs / \uparrow Tc cells (TRIF)

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 |

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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

Antimicrobial species generated from oxygen and nitrogen

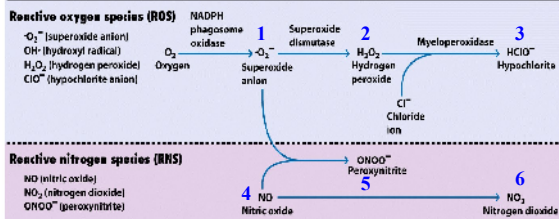


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Activated Macrophages

- **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-citrulline + 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 → Antigen → Mature
- Interact with both Th and Tc cells
- Activation → TLRs leads to ↑ MHC-II and co-stimulatory molecules
- Produce cytokines: type I IFNs and IL-12, TNF- α , IL-6.
- Killing by oxygen-dependent mechanisms

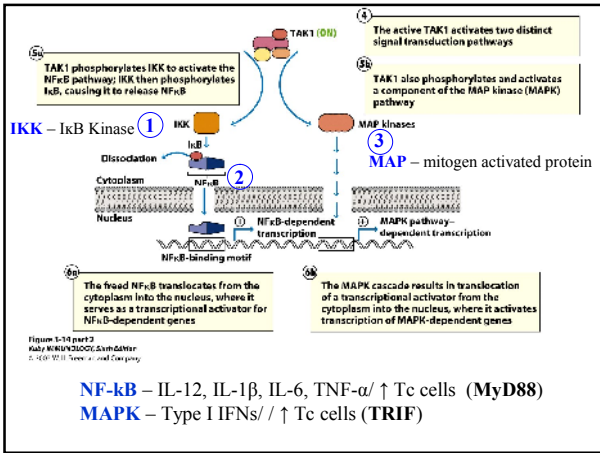
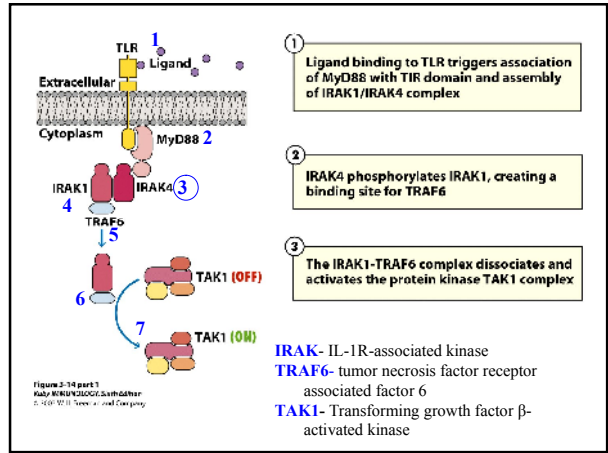
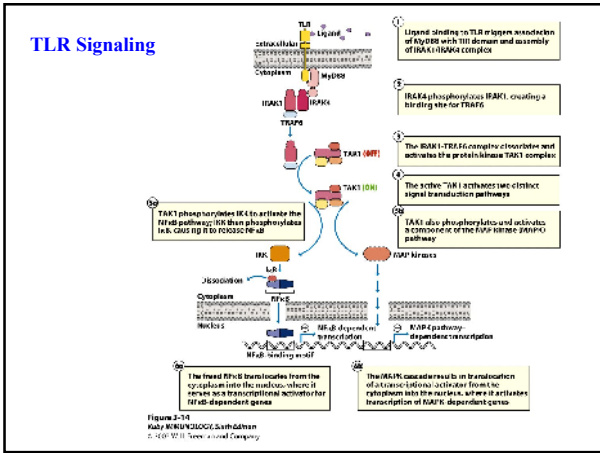


TABLE 3-4 Immunity in multicellular organisms

| Taxonomic group | Innate immunity (nonspecific) | Adaptive immunity (specific) | Invasion-induced protective response and antibody cascade | Phagocytosis | Anti-microbial peptides | Pattern recognition receptors | Granulocytes | T and B cells | Antibodies |
|---|-------------------------------|------------------------------|---|--------------|-------------------------|-------------------------------|--------------|---------------|------------|
| Higher plants: | + | - | + | + | + | + | - | - | - |
| Invertebrate animals: | | | | | | | | | |
| Porifera | + | - | ? | + | ? | ? | - | - | - |
| Spongestia | + | - | ? | + | ? | ? | - | - | - |
| Amoebids | + | - | ? | + | ? | ? | - | - | - |
| Inarthropods (insects, crustaceans) | + | - | + | + | + | + | ? | - | - |
| Vertebrate animals: | | | | | | | | | |
| Echinoderms (echinoderms, tunicates) | + | - | + | + | Equivalent agents | + | + | + | - |
| Fish (e.g., sharks, rays) | + | - | + | + | Probable | + | + | + | - |
| Tetrapod fish and lung fish (e.g., salmon, trout) | + | - | + | + | + | + | + | + | - |
| Amphibians | + | - | + | + | + | + | + | + | - |
| Reptiles | + | - | + | + | ? | + | + | + | - |
| Birds | + | - | + | + | ? | + | + | + | - |
| Mammals | + | - | + | + | + | + | + | + | - |

ICV = definitive demonstration; ? = failure to demonstrate that the ? = presence or absence remains to be established.

SOURCES: W. L. Flajali, K. M. Brown, and L. Du Pasquier, 2001, "Origin and Evolution of the Vertebrate Immune System," in *Immunological Evolution: The Role of Innate Immunity*, ed. L. Du Pasquier, 2001, Trends in Immunology 25:64.

Table 3-4
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