Kuby Immunology, 7e: Chapter 5

Innate Immunity

Anatomical barriers to infection

- Several barriers, both physical and chemical, exist to prevent pathogens from gaining access to deep tissues
  - Should those barriers be breached, innate immune system receptors recognize the threat
    - Conserved pathogen-associated molecular patterns (PAMPs) found on microbes
  - Aging, dead, or damaged self structures can also be recognized
    - Damage-associated molecular patterns (DAMPs)
  - Pattern recognition receptors (PRRs) recognize these structures and target them for clearance

Anatomical barriers to infection

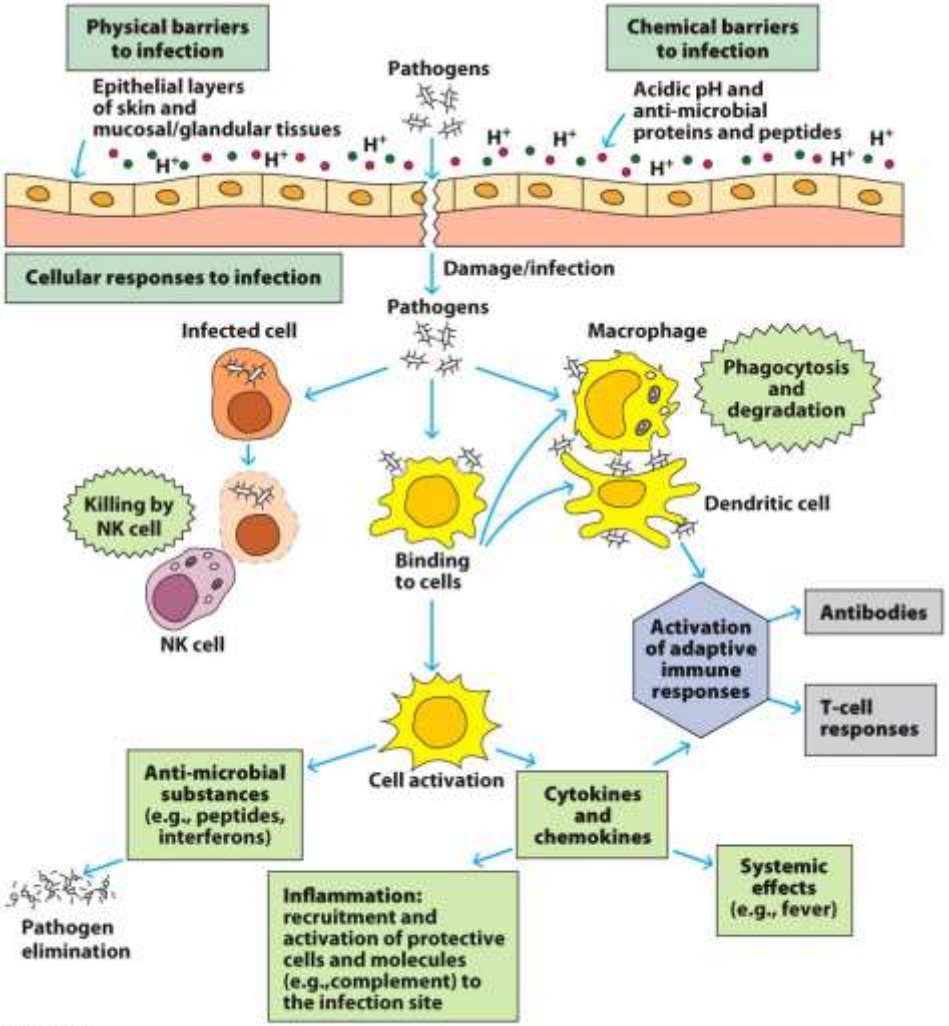

Figure 5-1
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Anatomical barriers to infection

- Barriers are just one difference between innate and adaptive immune responses

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
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Anatomical barriers to infection

- Epithelial barriers prevent pathogen entry into the body's interior
  - Skin
  - Mucosal membranes

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

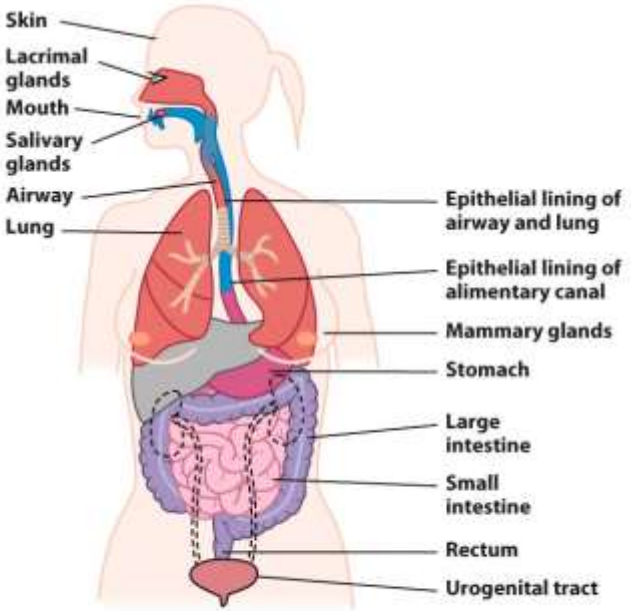

Figure 5-2
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Anatomical barriers to infection

- Epithelial layers produce protective substances
  - Acidic pH
  - Enzymes and binding proteins
  - Antimicrobial peptides

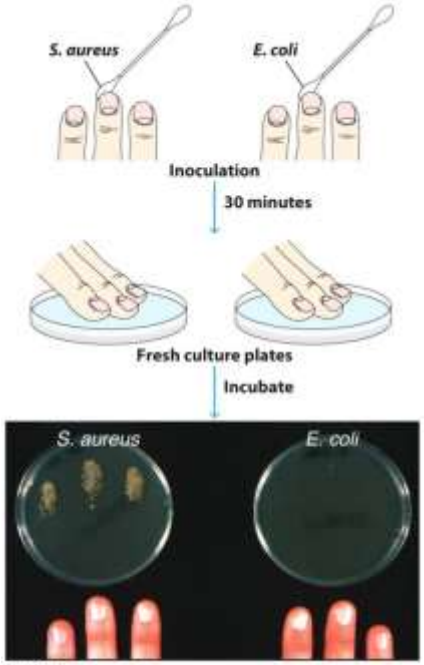

Figure 5-4
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TABLE 5-2 Some human antimicrobial proteins and peptides at epithelial surfaces

Proteins and peptides*	Location	Antimicrobial activities
Lysozyme	Mucosal/glandular secretions (e.g., tears, saliva, respiratory tract)	Cleaves glycosidic bonds of peptidoglycans in cell walls of bacteria, leading to lysis
Lactoferrin	Mucosal/glandular secretions (e.g., milk, intestine mucus, nasal/respiratory and urogenital tracts)	Binds and sequesters iron, limiting growth of bacteria and fungi; disrupts microbial membranes; limits infectivity of some viruses
Secretory leukocyte protease inhibitor	Skin, mucosal/glandular secretions (e.g., intestines, respiratory, and urogenital tracts, milk)	Blocks epithelial infection by bacteria, fungi, viruses; antimicrobial
S100 proteins, e.g.: - psoriasin - calprotectin	Skin, mucosal/glandular secretions (e.g., tears, saliva/tongue, intestine, nasal/respiratory and urogenital tracts)	- Disrupts membranes, killing cells - Binds and sequesters divalent cations (e.g., manganese and zinc), limiting growth of bacteria and fungi
Defensins (α and β)	Skin, mucosal epithelia (e.g., mouth, intestine, nasal/respiratory tract, urogenital tract)	Disrupt membranes of bacteria, fungi, protozoan parasites, and viruses; additional toxic effects intracellularly; kill cells and disable viruses
Cathelicidin (LL37)**	Mucosal epithelia (e.g., respiratory tract, urogenital tract)	Disrupts membranes of bacteria; additional toxic effects intracellularly; kills cells.
Surfactant proteins SP-A, SP-D	Secretions of respiratory tract, other mucosal epithelia	Block bacterial surface components; promotes phagocytosis

*Examples listed in this table are all produced by cells in the epithelia of mucosal and glandular tissues; examples of prominent epithelial sites are listed. Most proteins and peptides are produced constitutively at these sites, but their production can also be increased by microbial or inflammatory stimuli. Many are also produced constitutively in neutrophils and stored in granules. In addition, synthesis and secretion of many of these molecules may be induced by microbial components during innate immune responses by various myeloid leukocyte populations (monocytes, macrophages, dendritic cells, and mast cells).

**While some mammals have multiple cathelicidins, humans have only one.

Table 5-2
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Phagocytosis

- Defined as engulfment and internalization of materials such as microbes for their clearance and destruction

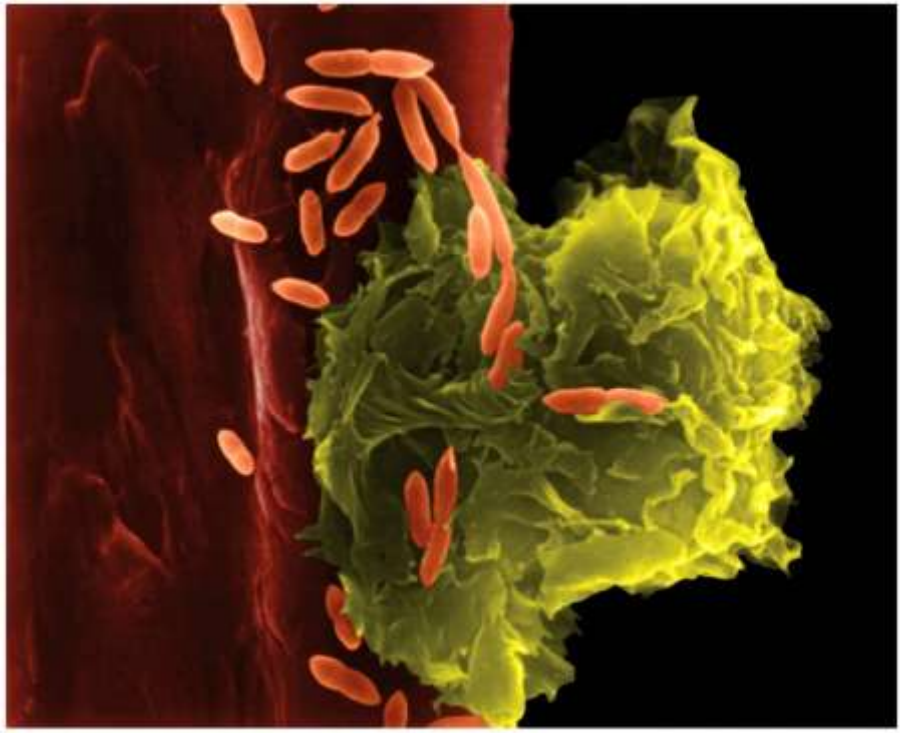

Figure 5-5a
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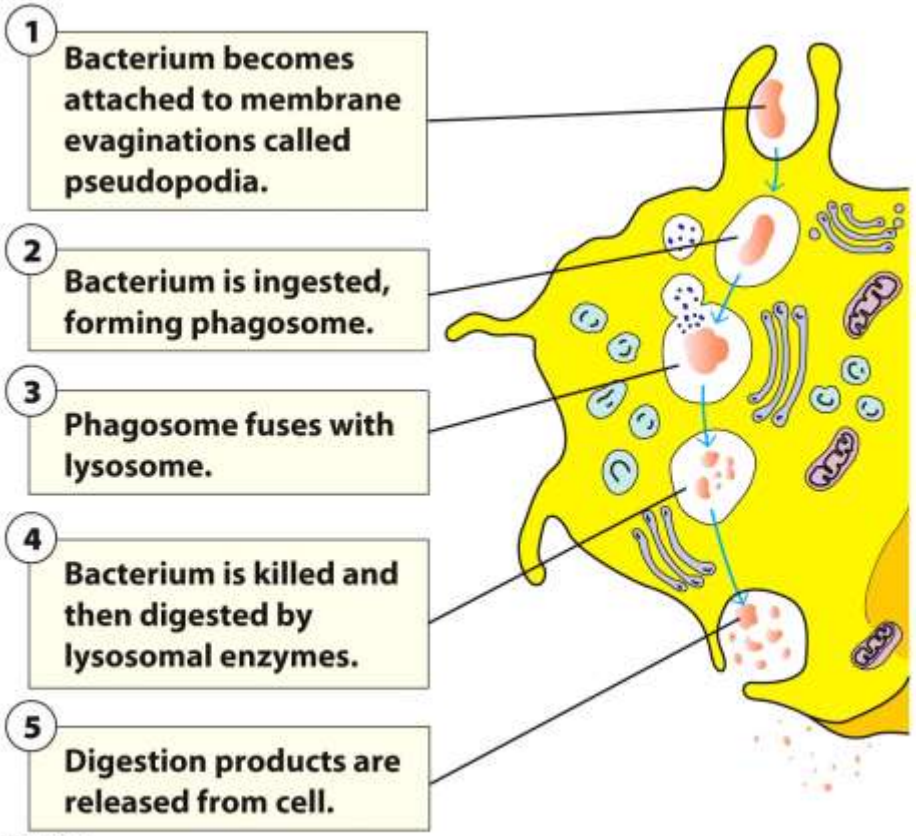

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Microbes are recognized by receptors on phagocytes

May recognize
PAMPs directly

May recognize soluble
opsonin protein
bound to microbes

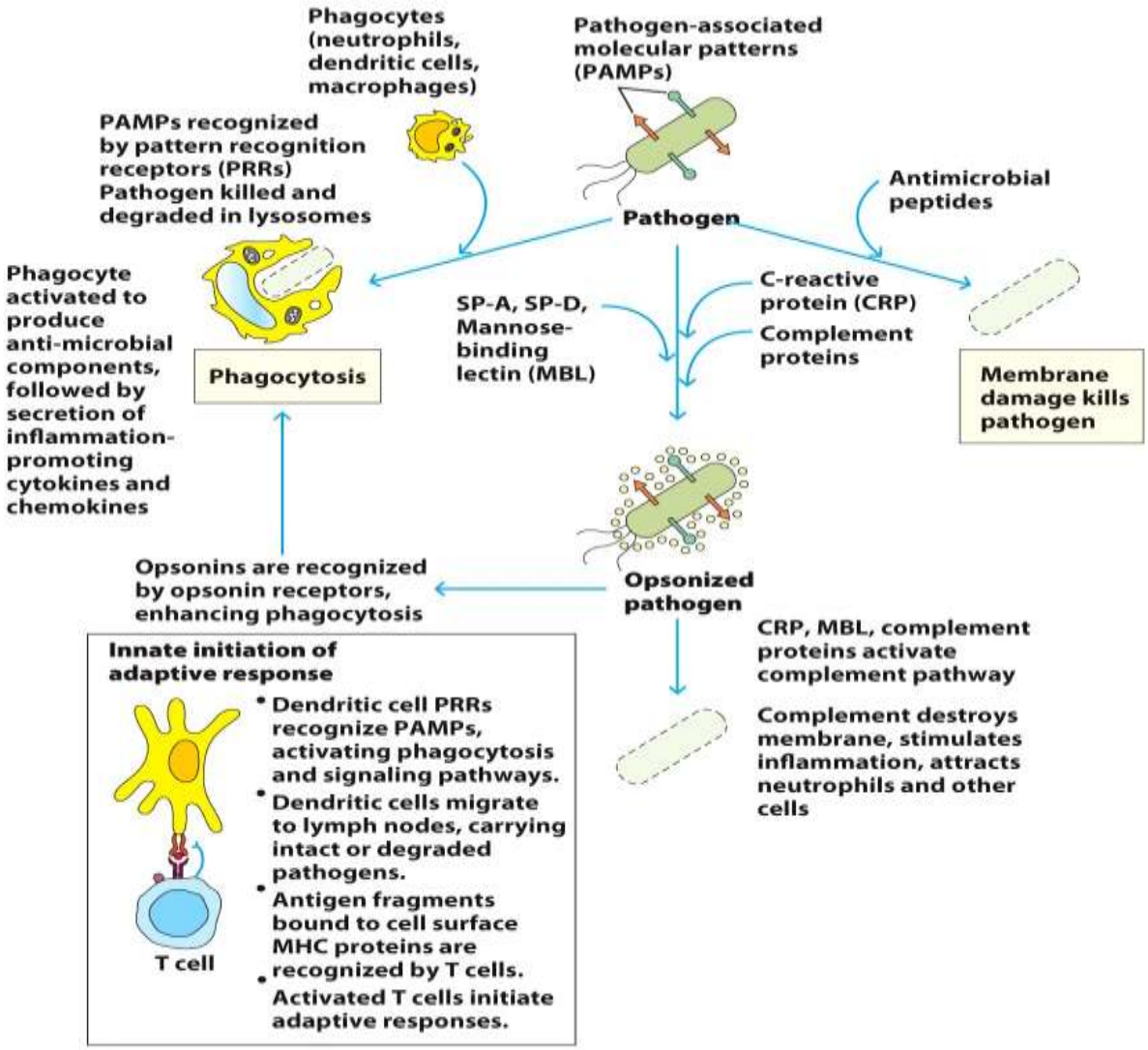

Figure 5-6
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Phagocytosed microbed killed by multiple mechanisms

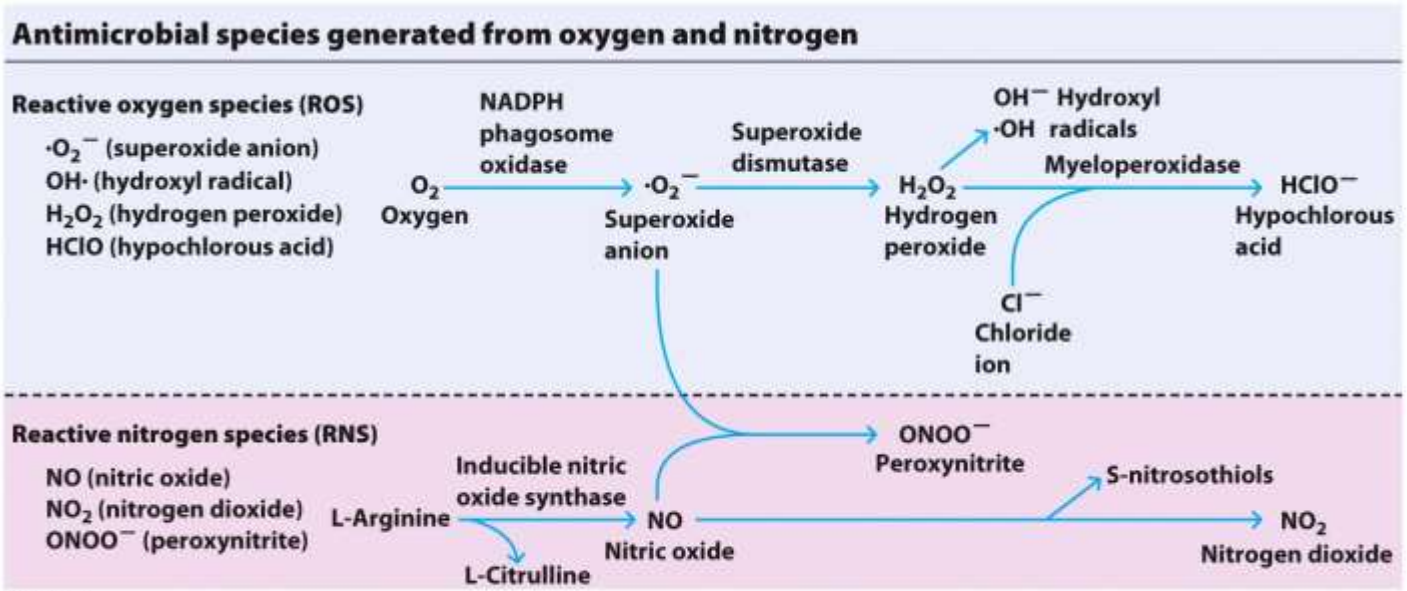

Figure 5-8
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- Ingested materials are taken into phagosomes
  - Phagosomes are fused with lysosomes or granules
    - Destruction occurs through enzyme degradation, antimicrobial proteins, and toxic effects of reactive oxygen and reactive nitrogen species (ROS and RNS)

Induced cellular innate responses

- Families of PRRs recognize a wide variety of PAMP ligands
  - TLRs
  - CLRs
  - RLRs
  - NLRs
- Signaling pathways are activated, contributing to innate/inflammatory responses

Induced cellular innate responses

- Toll-like receptors (TLRs) recognize many types of pathogen molecules
  - Homologous to fruit fly Toll receptor
  - Dimers with extracellular leucine-rich (LRR) domains that bind PAMPs and DAMPs

Figure 5-9
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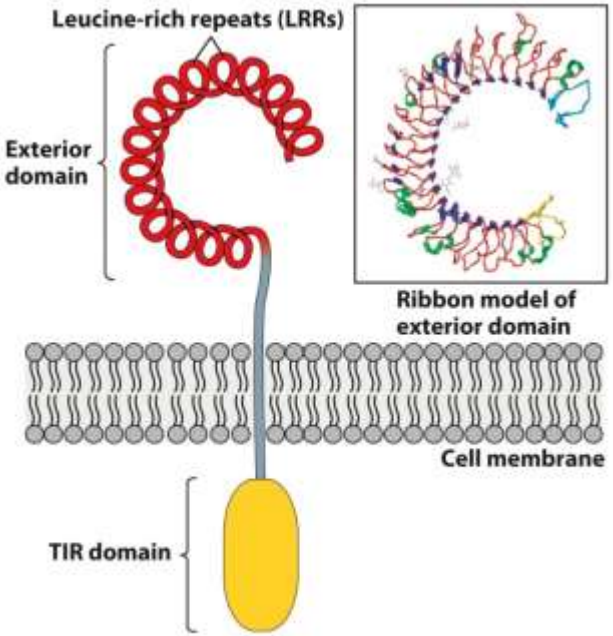

Figure 5-11a
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Induced cellular innate responses

- Of 13 TLRs in mice and humans, some are in lysosomes and some are surface bound
- Location helps determine what each binds

- TLR binding of PAMPs activates signaling pathways
  - Different TLRs recruit different adapter proteins to the TIR domain
    - Different adapter proteins lead to different events
    - Pathways include:
      - NF-κB transcription factor activation
      - Interferon regulating factor (IRF) pathways
      - MAP kinase pathway downstream transcription factors such as AP-1

TLR Signaling Pathways

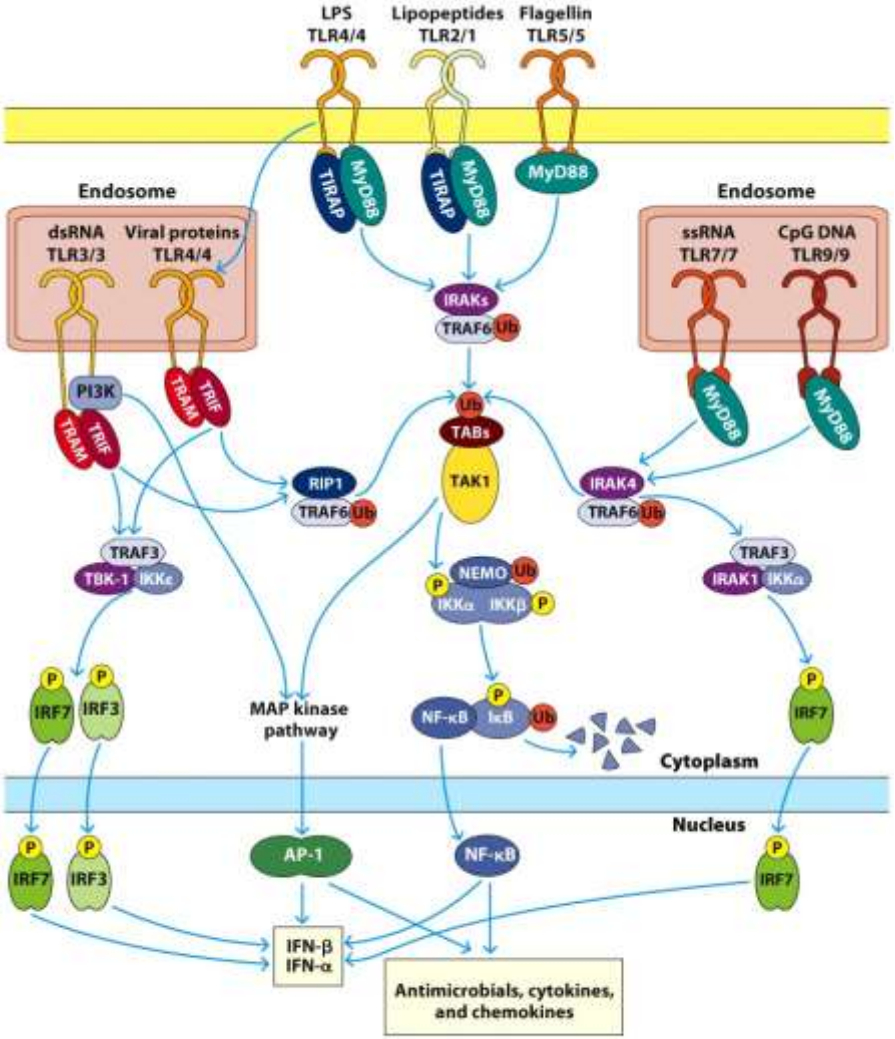

Figure 5-13
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C-type lectin receptors (CLRs)

- Heterogeneous population of surface PRRs
- Recognize cell wall components
  - Sugars/polysaccharides of bacteria/fungi
- Trigger a variety of pathways
  - Some similar to those activated by TLRs

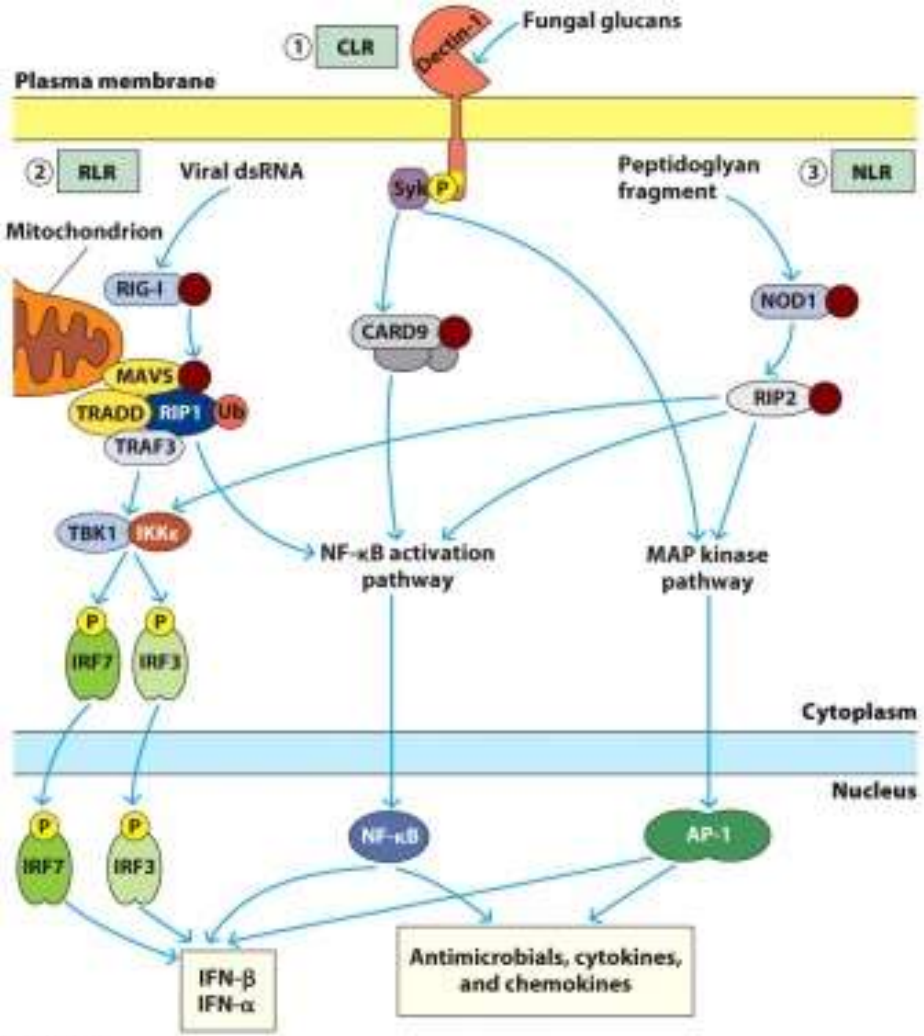

Figure 5-14
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Induced cellular innate responses

- NOD-like receptors (NLRs)
  - Large family of cytosolic PRRs
  - Activated by intracellular PAMPs
  - Can also sense changes in intracellular environment
    - Activates caspase-1 protease
    - Caspase-1 cleaves IL-1/IL-18 into active forms for release
- RIG-I-like receptors (RLRs)
  - RNA helicases
  - Function as cytosolic PRRs
  - Recognize viral double-stranded RNAs
  - Trigger signaling pathways that activate:
    - IRFs to trigger antiviral interferon responses
    - NF-κB transcription factor

PRR signaling pathways activate expression of a large variety of genes

- Antimicrobial peptides
- Type I interferons (potent antiviral activity)
- Cytokines (inflammatory IL-1, TNF-α, and IL-6)
- Chemokines
- Enzymes: iNOS and COX2

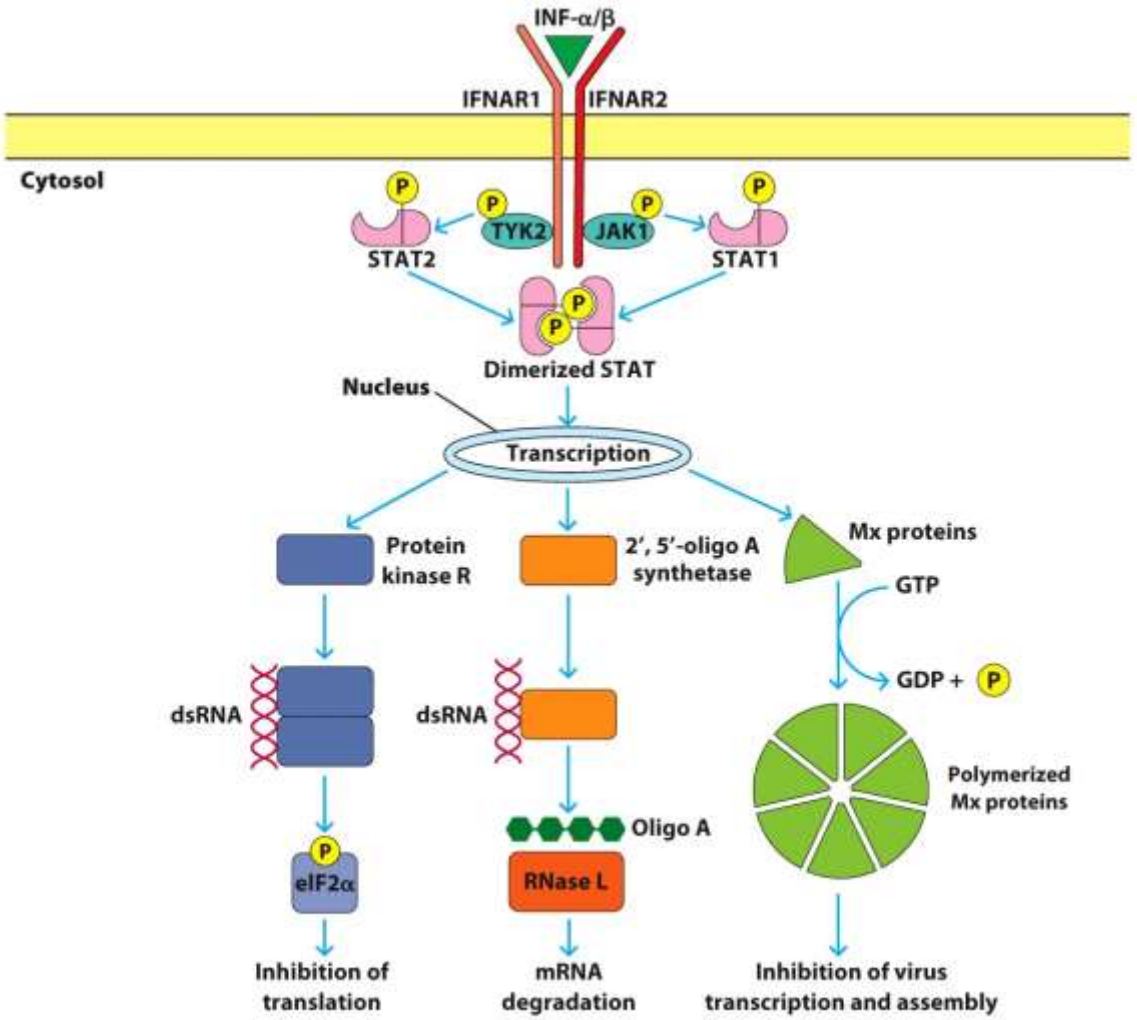

Figure 5-16
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Inflammatory responses

- Proinflammatory cytokines and chemokines triggered by innate responses to infection, damage, or harmful substances
- **Early components of inflammation include:**
  - Increased vascular permeability
  - Recruitment of neutrophils and other leukocytes from the blood to the site of damage/infection
- Later stages of inflammation are the acute phase responses (APRs)
  - Induced by proinflammatory cytokines (IL-1, TNF-α, and IL-6)
  - APR involves:Increased synthesis/secretion of antimicrobial proteins from the liver (MBL,CRP,Complement components)
    - Liver acute phase proteins activate other processes that help eliminate pathogens

Inflammatory responses

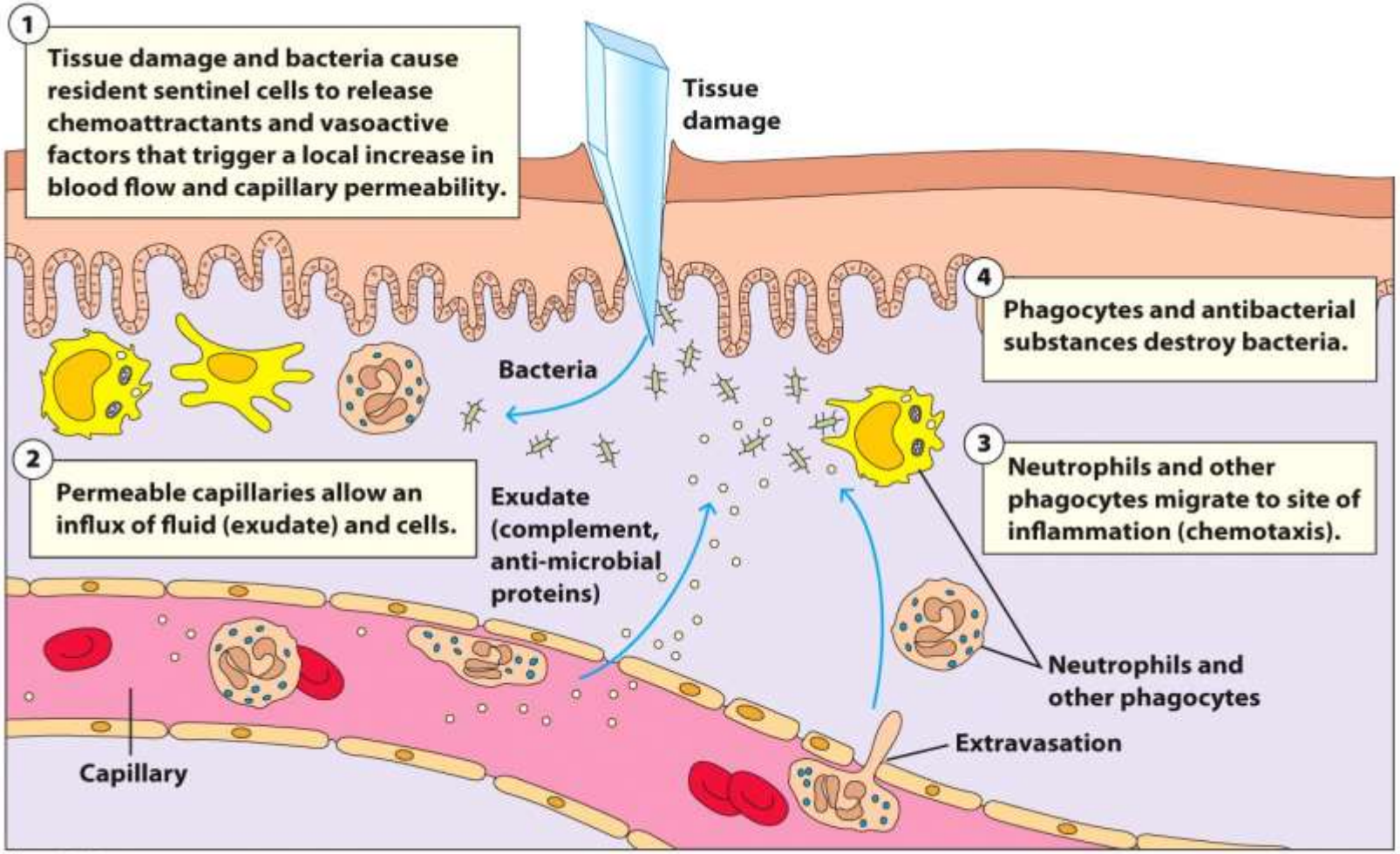

Figure 5-17
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Natural killer (NK) cells

- NK cells are lymphocytes with innate immune functions
  - Express a set of receptors for self proteins induced by:
    - Infections
    - Malignant transformations
    - Other stresses
  - Activated NK cells perform one of two functions:
    - Kill the altered self cell
    - Produce cytokines that induce adaptive responses against the altered self cell

Regulation and evasion of innate and inflammatory responses

- Regulation and control of these responses are important
  - Defects in PRRs and signaling pathways increase susceptibility to infections
  - Defects that allow the systems to remain abnormally “turned on” contribute to inflammatory disorders
    - These can be cases where more and more of a good thing ends up being unhealthy and damaging
  - Regulation includes both
    - Positive feedback mechanisms
    - Negative feedback mechanisms

Regulation and evasion of innate and inflammatory responses

- Pathogens have evolved strategies to block, evade, and escape these responses

TABLE 5-6 Pathogen evasion of innate and inflammatory responses

Type of evasion	Examples
Avoid detection by PRRs	*Proteobacteria* flagellin has a mutation that prevents it from being recognized by TLR5.
	Helicobacter, Coxiella, and Legionella bacteria have altered LPS that is not recognized by TLR4.
	HTLV-1 virus p30 protein inhibits transcription and expression of TLR4.
	Several viruses (Ebola, influenza, Vaccinia) encode proteins that bind cytosolic viral dsRNA and prevent it from binding and activating RLR.
Block PRR signaling pathways, preventing activation of responses	Vaccinia virus protein A46R and several bacterial proteins have TIR domains that block MyD88 and TRIF from binding to TLRs.
	Several viruses block TBK1/IKK-activation of IRF3 and IRF7, required for IFN production.
	West Nile Virus NS1 protein inhibits NF-κB and IRF transport into the nucleus.
	Yersinia bacteria produce Yop proteins that inhibit inflammasome activity; the YopP protein inhibits transcription of the IL-1 gene.
Prevent killing or replication inhibition	*Salmonella* and *Listeria* bacteria rupture the phagosome membrane and escape to the cytosol.
	Mycobacteria tuberculosis blocks phagosome fusion with lysosomes.
	Vaccinia virus encodes a protein that binds to Type I IFNs and prevents them from binding to the IFN receptor.
	Hepatitis C virus protein NS3-4A and Vaccinia virus protein E3L bind protein kinase R and block IFN-mediated inhibition of protein synthesis.

Table 5-6
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Interactions between the innate and adaptive immune systems

- A constant interplay between the two systems exists
  - Several innate systems have been co-opted by adaptive immunity to contribute to antibody-mediated pathogen elimination
    - Opsonization
    - Complement activation
  - Some lymphocytes express TLRs, but use them as costimulatory receptors

Dendritic cells are a key bridge

- They bring antigens from the site of infection and present them to T cells in lymph nodes
- This activates the T cells, allowing them to differentiate into particular pathogen-specific subsets for the best antigen clearance: T_H cell subsets, T_C cells

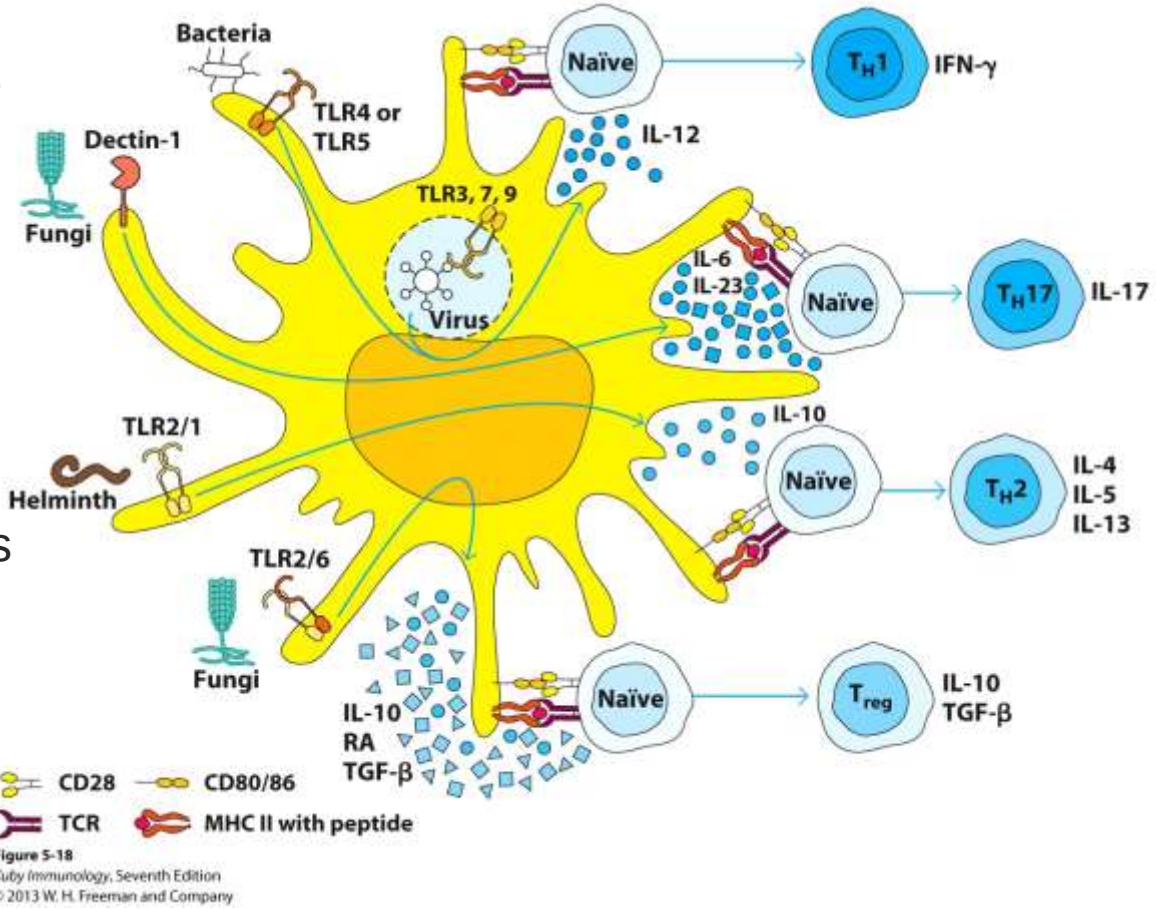

Figure 5-18
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