INNATE IMMUNITY

- Key elements of innate immunity include the physical and chemical barriers that prevent infection, provided by the epithelial cell layers of the skin, mucosal tissues (e.g., gastrointestinal, respiratory, and urogenital tracts), and glandular tissues (e.g., salivary, lacrimal, and mammary glands). Once pathogens enter the body, such as through a breach in an epithelial layer, they are confronted by an array of cells with cell surface and intracellular receptors that recognize pathogen components and trigger a variety of cellular responses. Pathogen recognition by these receptors activates some cells to phagocytose and degrade the pathogen, and many cells are activated through their receptors to produce a variety of antimicrobial substances that kill pathogens, as well as cytokine and chemokine proteins that recruit cells, molecules, and fluid to the site of infection, leading to swelling and other symptoms collectively known as inflammation.

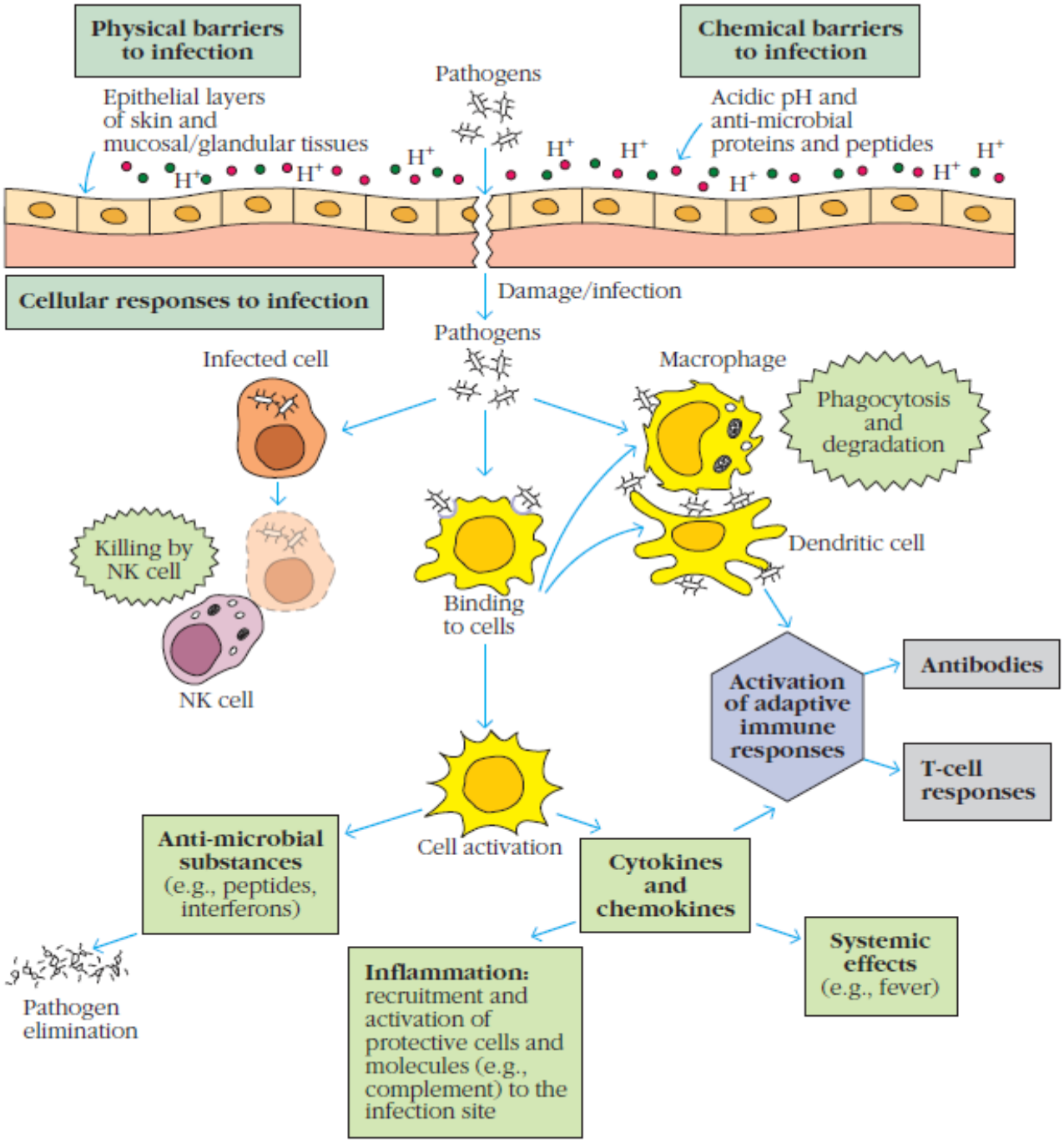

Physical barriers to infection
Chemical barriers to infection
Pathogens
Epithelial layers of skin and mucosal/glandular tissues
Acidic pH and anti-microbial proteins and peptides
H+
Cellular responses to infection
Damage/infection
Pathogens
Infected cell
Macrophage
Phagocytosis and degradation
Killing by NK cell
Dendritic cell
Binding to cells
NK cell
Activation of adaptive immune responses
Antibodies
T-cell responses
Cell activation
Anti-microbial substances (e.g., peptides, interferons)
Cytokines and chemokines
Systemic effects (e.g., fever)
Pathogen elimination
Inflammation: recruitment and activation of protective cells and molecules (e.g., complement) to the infection site

TABLE 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

- **Anatomical Barriers to Infection**
- The most obvious components of innate immunity are the external barriers to microbial invasion: the epithelial layers that insulate the body's interior from the pathogens of the exterior world. These epithelial barriers include the skin and the tissue surfaces connected to the body's openings: the mucous epithelial layers that line the respiratory, gastrointestinal, and urogenital tracts and the ducts of secretory glands such as the salivary, lacrimal, and mammary glands (which produce saliva, tears, and milk, respectively). They contribute to physical and mechanical processes that help the body shed pathogens and also generate active chemical and biochemical defenses by synthesizing and deploying molecules, including peptides and proteins, that have or induce antimicrobial activity.

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

- **Antimicrobial Proteins and Peptides Kill Would-be Invaders:**

To provide strong defense at these barrier layers, epithelial cells secrete a broad spectrum of proteins and peptides that provide protection against pathogens. The capacity of skin and other epithelia to produce a wide variety of antimicrobial agents on an ongoing basis is important for controlling the microbial populations on these surfaces, as breaks in these physical barriers from wounds provide routes of infection that would be readily exploited by pathogenic microbes if not defended by biochemical means.

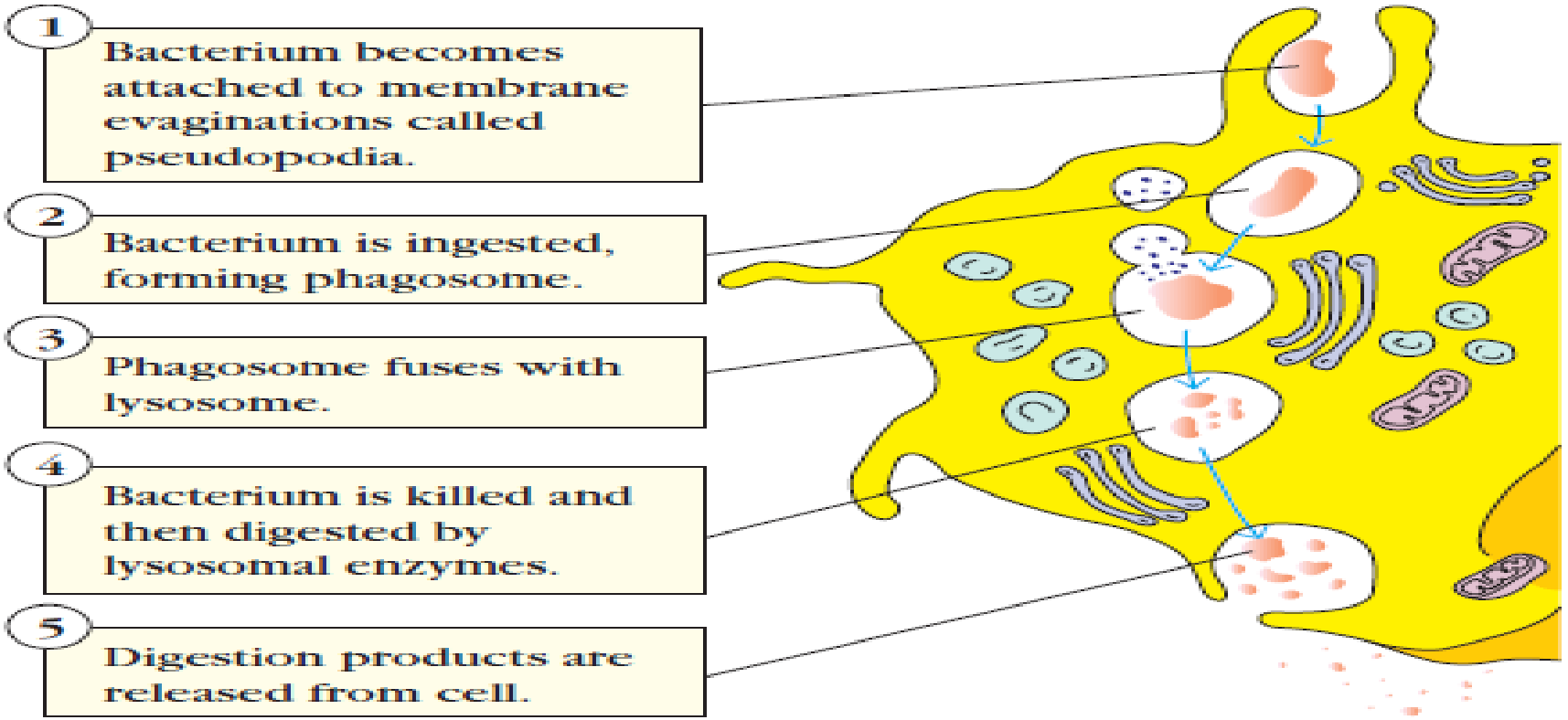
TABLE Some human antimicrobial proteins and peptides at epithelial surfaces

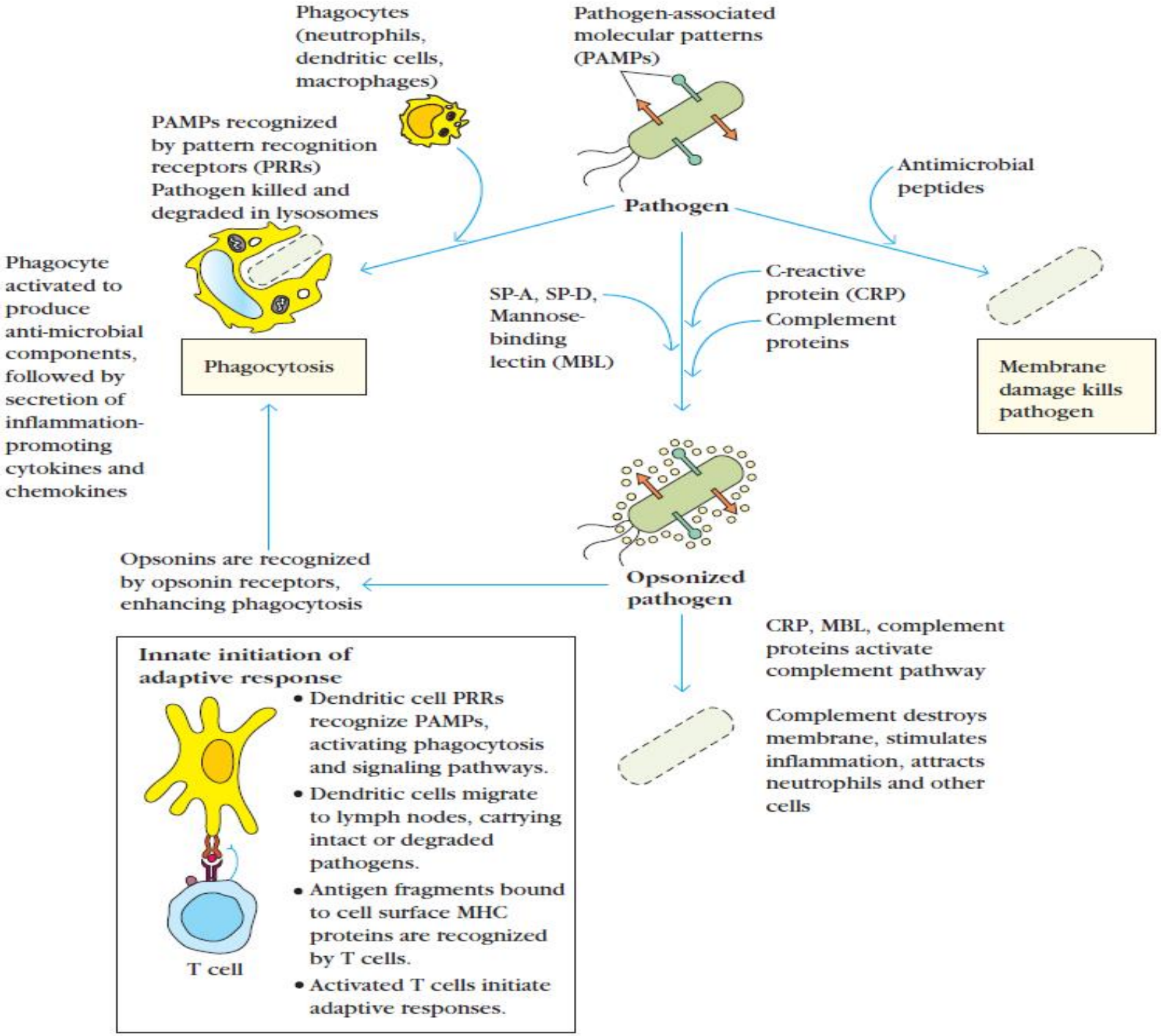
Proteins and peptides*	Location	Antimicrobial activities
Lysozyme	Mucosal/glandular secretions (e.g., tears, saliva, respiratory tract)	Cleaves glycosidic bonds of peptidoglycans in cell walls of bacteria, leading to lysis
Lactoferrin	Mucosal/glandular secretions (e.g., milk, intestine mucus, nasal/respiratory 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

- Phagocytosis

Despite the strong defenses of our protective epithelial layers, some pathogens have evolved strategies to penetrate these defenses, and epithelia may be disrupted by wounds, abrasions, and insect bites that may transmit pathogens. Once pathogens penetrate through the epithelial barrier layers into the tissue spaces of the body, an array of cellular membrane receptors and soluble proteins that recognize microbial components play the essential roles of detecting the pathogen and triggering effective defenses against it. Phagocytic cells make up the next line of defense against pathogens that have penetrated the epithelial cell barriers. Macrophages, neutrophils, and dendritic cells in tissues and monocytes in the blood are the main cell types that carry out phagocytosis—the cellular uptake (eating) of particulate materials such as bacteria—a key mechanism for eliminating pathogens.

- Through various cell surface receptors they recognize microbes such as bacteria, extend their plasma membrane to engulf them, and internalize them in phagosomes (endosomes resulting from phagocytosis . Lysosomes then fuse with the phagosomes, delivering agents that kill and degrade the microbes. Neutrophils are a second major type of phagocyte, usually recruited to sites of infection. Finally, dendritic cells also can bind and phagocytose microbes.




Phagocytes (neutrophils, dendritic cells, macrophages)
Pathogen-associated molecular patterns (PAMPs)
PAMPs recognized by pattern recognition receptors (PRRs)
Pathogen killed and degraded in lysosomes
Pathogen
Antimicrobial peptides
Phagocyte activated to produce anti-microbial components, followed by secretion of inflammation-promoting cytokines and chemokines
Phagocytosis
SP-A, SP-D, Mannose-binding lectin (MBL)
C-reactive protein (CRP)
Complement proteins
Membrane damage kills pathogen
Opsonins are recognized by opsonin receptors, enhancing phagocytosis
Opsonized pathogen
CRP, MBL, complement proteins activate complement pathway
Complement destroys membrane, stimulates inflammation, attracts neutrophils and other cells
Innate initiation of adaptive response
• Dendritic cell PRRs recognize PAMPs, activating phagocytosis and signaling pathways.
• Dendritic cells migrate to lymph nodes, carrying intact or degraded pathogens.
• Antigen fragments bound to cell surface MHC proteins are recognized by T cells.
• Activated T cells initiate adaptive responses.
T cell

Cellular Pattern Recognition Receptors Activate :

Several families of cellular PRRs contribute to the activation of innate immune responses that combat infections. Some of these PRRs are expressed on the plasma membrane, while others are actually found *inside* our cells. Many cell types in the body express these PRRs, including all types of myeloid white blood cells (monocytes, macrophages, neutrophils, eosinophils, mast cells, basophils, dendritic cells) and subsets of the three types of lymphocytes (B cells, T cells, and NK cells). PRRs are also expressed by some other cell types, especially those commonly exposed to infectious agents; examples include the skin, mucosal and glandular epithelial cells, vascular endothelial cells that line the blood vessels, and fibroblasts and stromal support cells in various tissues.

Toll-Like Receptors Recognize Many Types of Pathogen Molecules

Toll-like receptors (TLRs) were the first family of PRRs to be discovered and are still the best-characterized in terms of their structure.

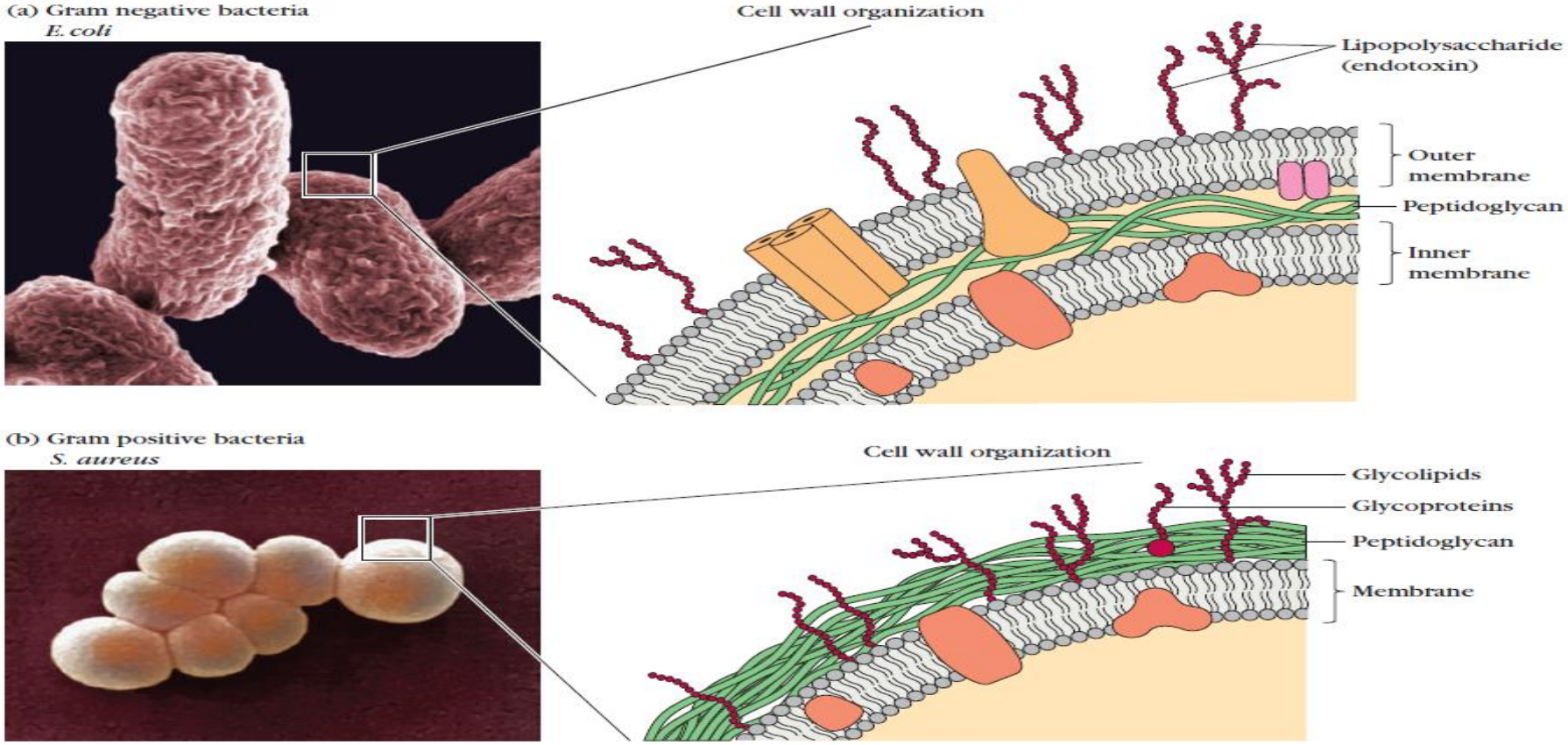


TABLE TLRs and their microbial ligands

TLRs*	Ligands	Microbes
TLR1	Triacyl lipopeptides	Mycobacteria and Gram-negative bacteria
TLR2	Peptidoglycans	Gram-positive bacteria
	GPI-linked proteins	Trypanosomes
	Lipoproteins	Mycobacteria and other bacteria
	Zymosan	Yeasts and other fungi
	Phosphatidlyserine	Schistosomes
TLR3	Double-stranded RNA (dsRNA)	Viruses
TLR4	LPS	Gram-negative bacteria
	F-protein	Respiratory syncytial virus (RSV)
	Mannans	Fungi
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipopolypeptides	Mycobacteria and Gram-positive bacteria
	Zymosan	Yeasts and other fungi
TLR7	Single-stranded RNA (ssRNA)	Viruses
TLR8	Single-stranded RNA (ssRNA)	Viruses
TLR9	CpG unmethylated dinucleotides	Bacterial DNA
	Dinucleotides	
	Herpes virus components	Some herpesviruses
	Hemozoin	Malaria parasite heme byproduct
TLR10	Unknown	Unknown
TLR11	Unknown	Uropathogenic bacteria
	Profilin	Toxoplasma
TLR12	Unknown	Unknown
TLR13	Unknown	Vesicular stomatitis virus

2- THE COMPLEMENT SYSTEM

The complement system is another important component of innate immunity. The system consists of 30 proteins found in serum or on the surface of certain cells . Activation of the complement system results in a cascade of biochemical reactions that ultimately ends in lysis and disruption of foreign or effete cells. Without activation, the components of the complement system exist as pro-enzymes in body fluids. As a by-product of the activation of the cascade, a number of biologically reactive complement fragments are generated. The complement fragments can modulate other parts of the immune system by binding directly to T lymphocytes and bone marrow–derived lymphocytes (B lymphocytes) of the adaptive immune system and also stimulate the synthesis and release of cytokines.

There are three activation pathways for the complement system. Although the activation pathways are different, they all act at the microbial surface to assemble an enzyme convertase that cleaves C3 to form C3b that binds to a microbial surface where it activates C5 and the other components of the cascade. The three pathways are the classical, mannan-binding lectin (MBL), and the alternative. Each of the pathways has its own recognition mechanism and is activated through different mechanisms, but all result in the formation of a membrane attack complex (MAC) and lysis of a target cell.

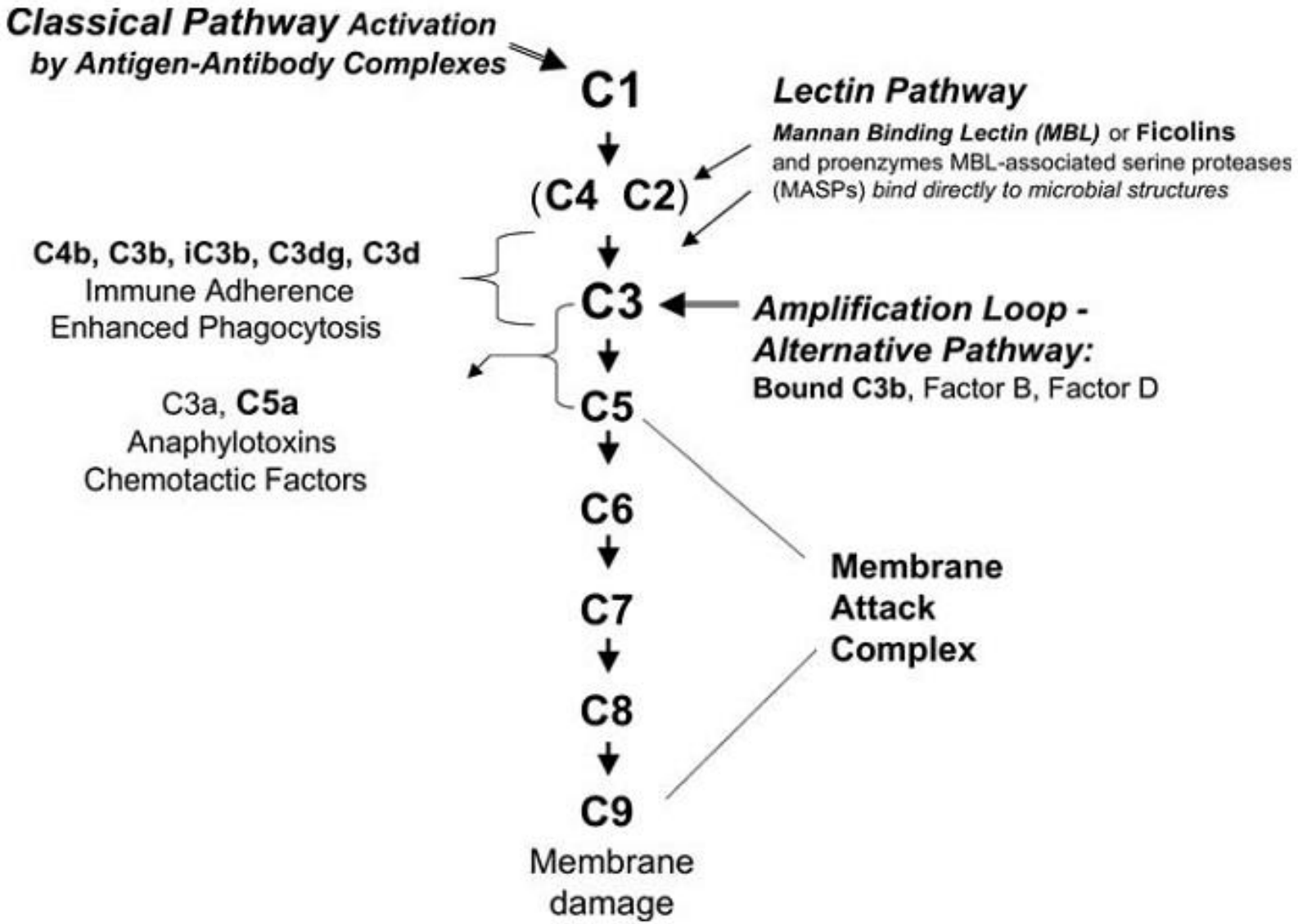


FIGURE The sequence of complement activation pathways.

CLASSICAL COMPLEMENT PATHWAY
Activation of the Classical Complement Pathway

- Immunoglobulins and native complement components are normally found in the serum and in the lymph, but these molecules do not interact with each other until the antibodies interact with their corresponding antigens and undergo the necessary secondary and tertiary conformational changes. These immunoglobulin conformational changes are the basis for specific activation of the very powerful classical complement pathway.

***Classical Pathway** Activation*
by Antigen-Antibody Complexes

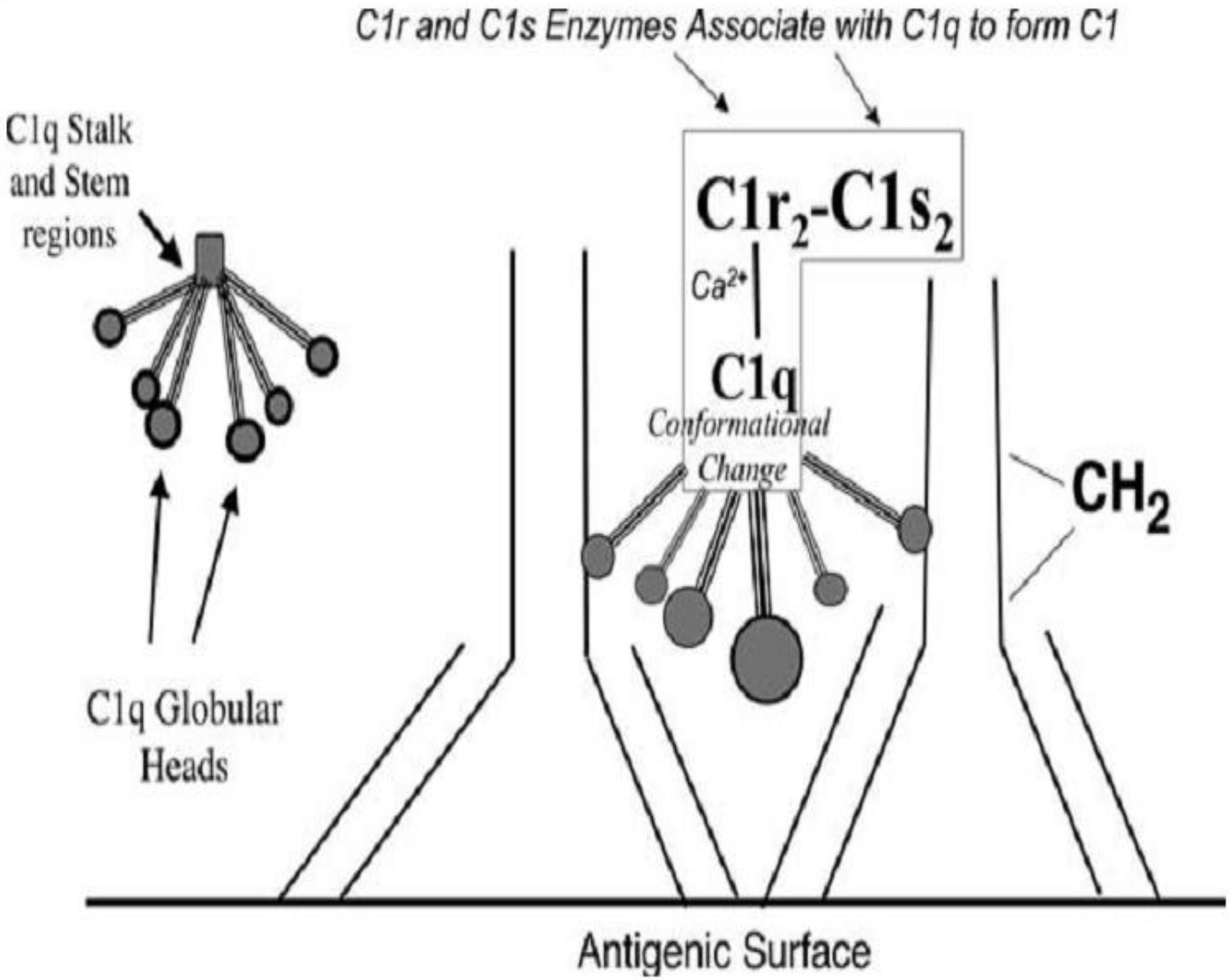


FIGURE C1 activation by an antibody duplet formed by binding to the corresponding antigen.

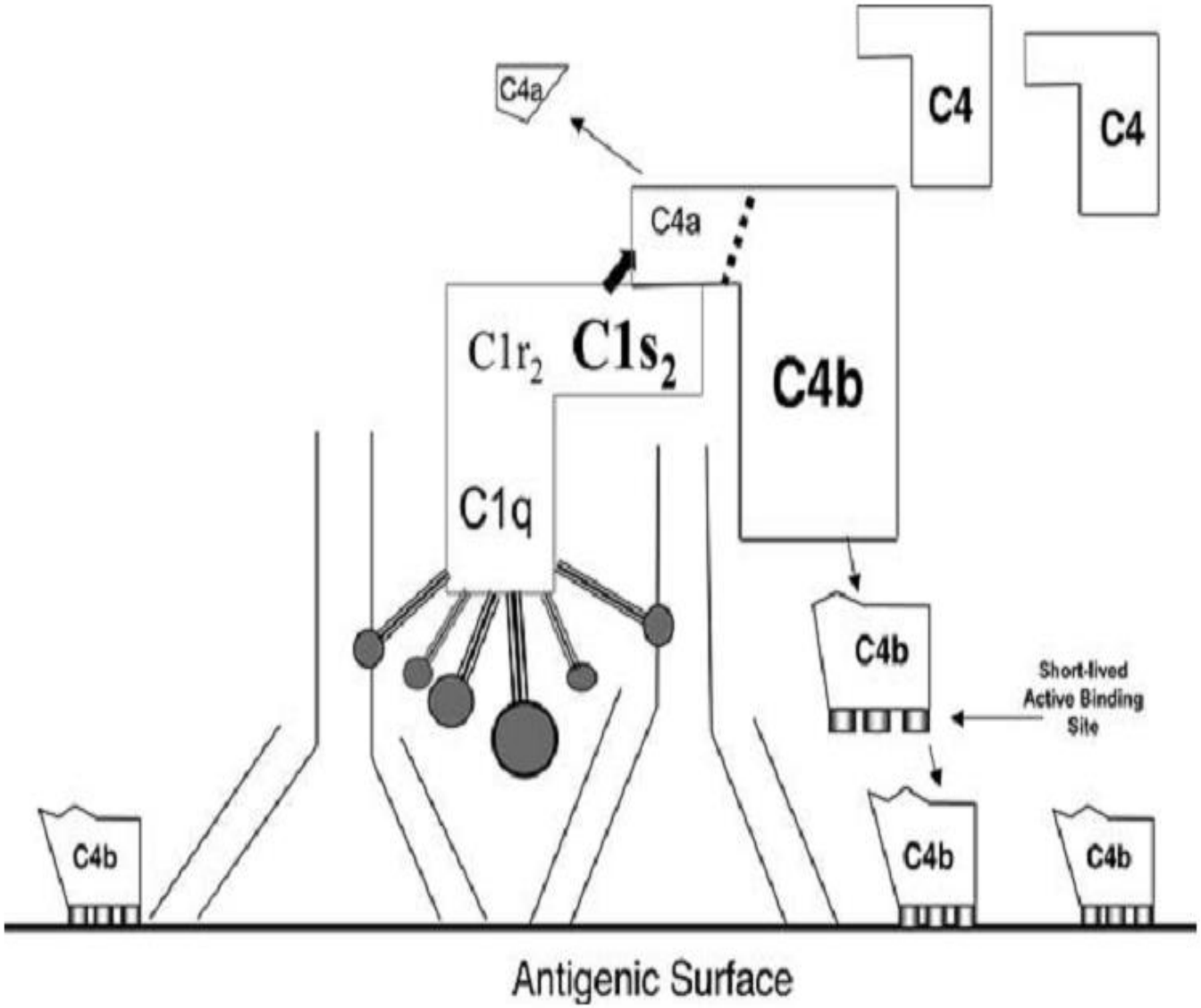


FIGURE Conversion of C4 followed by covalent deposition of C4b on the antigenic surface.

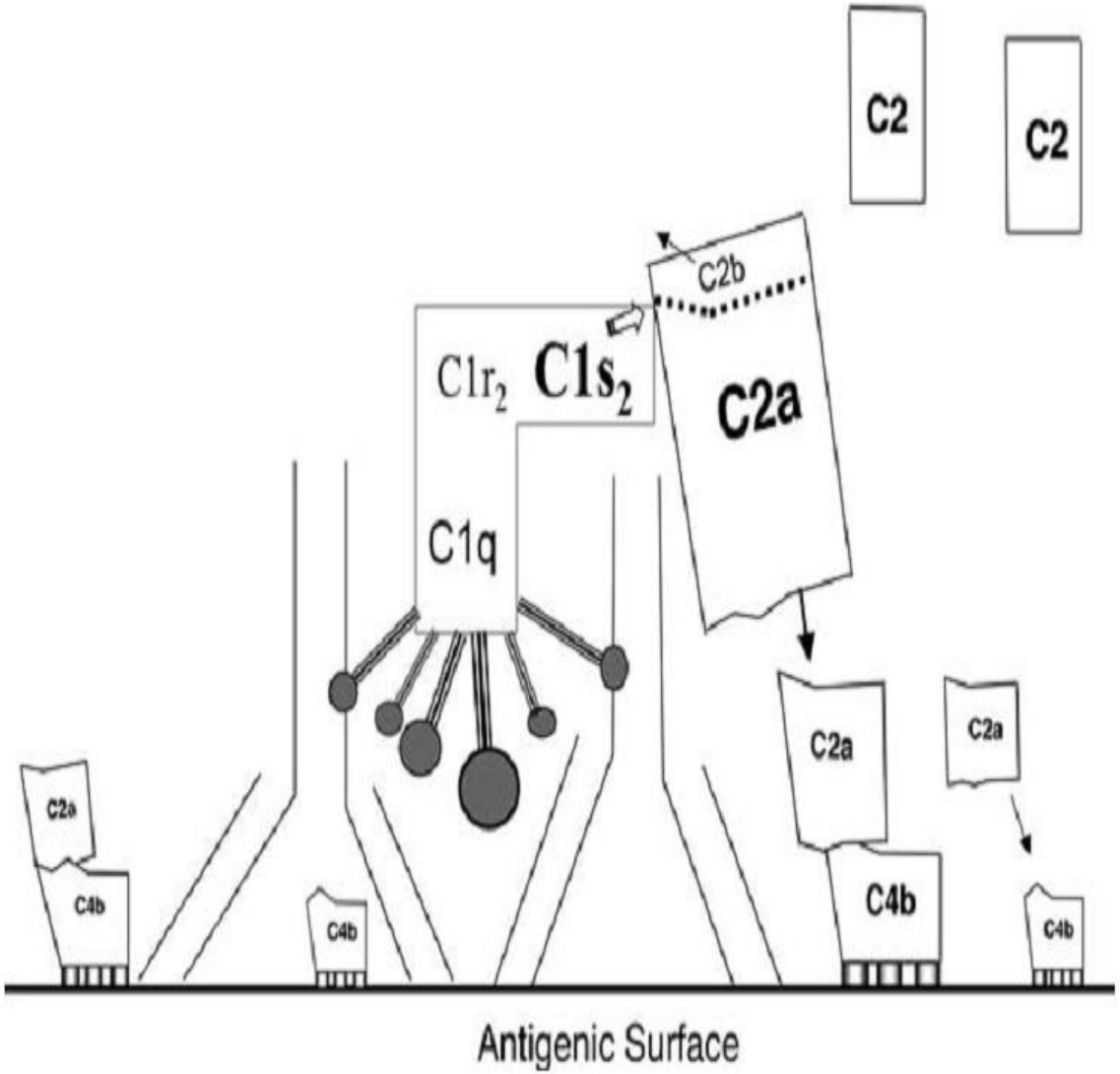


FIGURE Formation of C4b2a complex (C3 convertase) on the antigenic surface. Although activated C1s (within the macromolecular C1 complex) can activate any C2 molecule that it contacts, the cleavage of C2 adjacent to a membrane-bound C4b increases the probability of generating bound-C4b2a complexes on that foreign membrane.

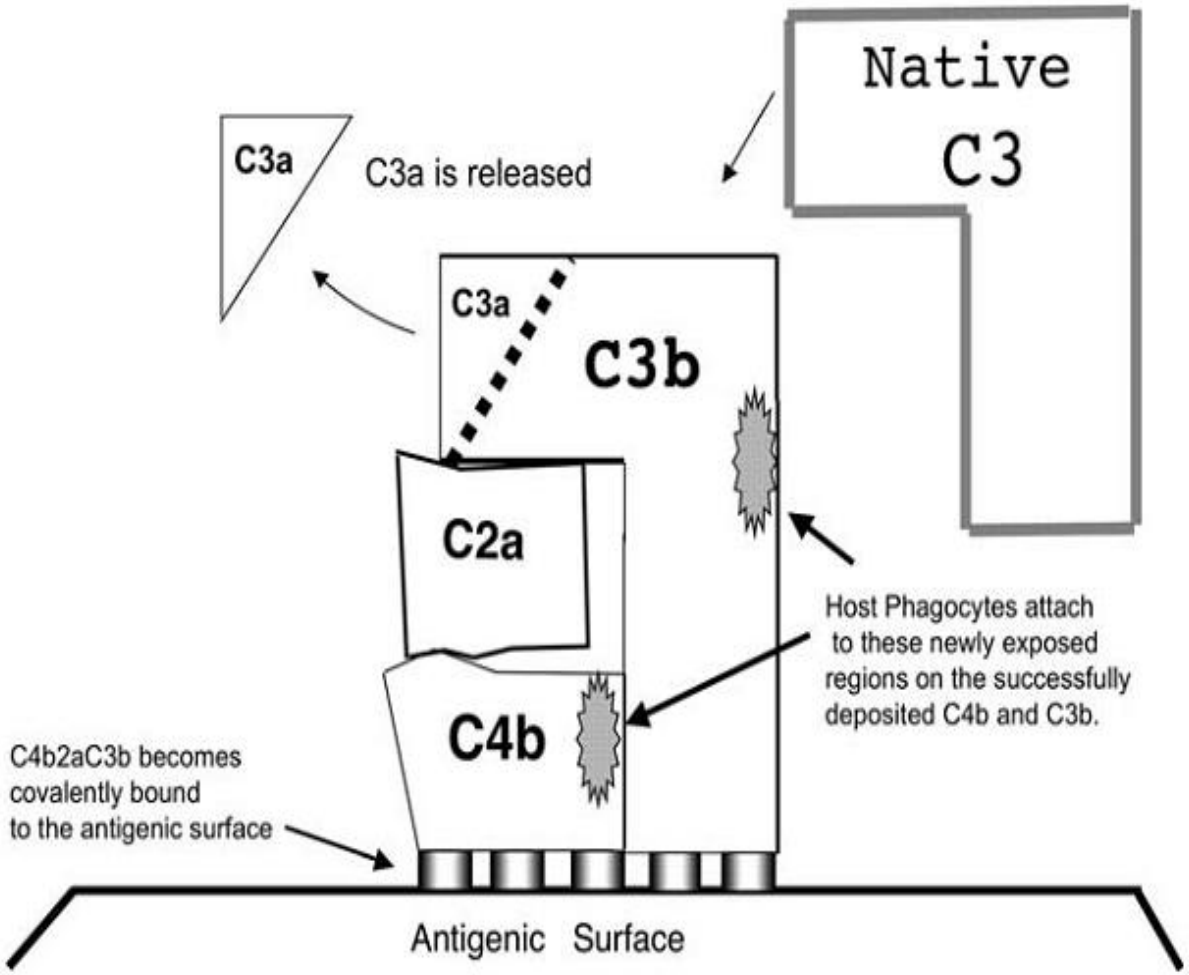


FIGURE C3 activation by C4b2a enzyme complex (C3 convertase) results in the split of C3 into two fragments. While C3b remains associated with C4b2a, C3a is released into the fluid phase. Sites on the deposited C4b and C3b are now exposed and recognized by phagocytic cell receptors.

Biologically Important Active Fragments: Fifth and Third Complement Component "a" (Anaphylatoxins and Chemotactic factors) :

1. The small complement fragments, C5a and C3a released into the fluid phase are recognized by neutrophils and cause these phagocytes to migrate in the direction from which they originated. The term for this chemical attraction is chemotaxis, and its main biological function is to attract phagocytes into a tissue in which complement-activating antigen-antibody reactions are taking place.
2. Besides their role as chemokines, C5a and C3a activate the phagocytic cells that carry C5a and C3a receptors.
3. In the case of neutrophils, such activation leads to the expression of cell adhesion molecules (CAMs) and facilitates extravascular migration.
4. In the case of circulating basophils and of mast cells associated with the epithelial and mucosal tissues, C5a and C3a stimulate the release of biologically active mediators such as heparin and vasoactive amines (e.g., histamine). Histamine, when released into the tissues results in increased capillary permeability and in smooth muscle contraction. Fluid is released into the tissue, causing edema and swelling.

ALTERNATIVE COMPLEMENT PATHWAY

Another group of activators of the complement system includes many types of foreign substances, aggregated (hydrophobic) proteins, artificially aggregated immunoglobulins of all classes and subclasses (including IgG4, IgA, and IgE), and microbial membranes and cell walls (Table 1). These activators affect the complement sequence via a mechanism termed the "alternative pathway." The alternative pathway received this designation because its activation does not absolutely require antibody and can proceed in the absence of C1, C4, and C2—all essential for the classical pathway of complement activation.

TABLE 1 Activators of the Alternative Pathway

Bacterial membranes (endotoxic lipopolysaccharides) and viral envelopes
Bacterial and yeast cell walls
Classical pathway (via C3b generation)
Proteases (i.e., via enhanced C3b generation), released by:
Polymorphonuclear leukocytes
Bacteria
Organ failure (pancreatitis)
Damaged tissue (burns, necrosis, trauma)
Fibrinolytic system (plasmin)
Aggregated immunoglobulins (including IgA, IgG4, and IgE)
Virus-transformed host cells (limited effects)

Abbreviations: C, complement component; Ig, immunoglobulin.

- Some of the most significant activators of the alternative pathway are the bacterial membrane lipopolysaccharides characteristic of gram-negative bacteria and the peptidoglycans and teichoic acids from the cell walls of certain gram-positive bacteria.
- The biological significance of the alternative pathway can be understood if we consider, as an example, an infection with a hypothetical bacterium. Since all normal individuals have low levels of antibody to most bacteria, some limited classical pathway activation occurs. Theoretically, in the presence of large numbers of bacteria, the relatively low levels of specific antibody may be effectively absorbed by antigens present on the proliferating bacteria, allowing uncoated bacteria to escape destruction by the more effective classical pathway.
- In summary, the alternative pathway of complement activation is important especially during the early phase of the infection, when the concentrations of specific antibody are very low. After the antibody response is fully developed, the classical and alternative pathways work synergistically, with the alternative pathway functioning as an amplification loop of the classical pathway.

Lectin Pathway of Complement Activation

The newest discovered pathway for activating the second, fourth, and third complement components is the lectin complement pathway, which involves a serum MBL and other serum lectins called ficolins. Mannan, a constituent of the polysaccharide capsules of many pathogenic fungi and yeasts (e.g., Cryptococcus neoformans and Candida albicans), is one of the several polysaccharide substances to which human MBL binds via Ca2þ-dependant interactions, while bacterial lipoteichoic acid and peptidoglycan associate with serum ficolins. In addition to carbohydrate motifs of microorganisms, MBL can bind to glycoproteins on the envelope of several types of viruses.

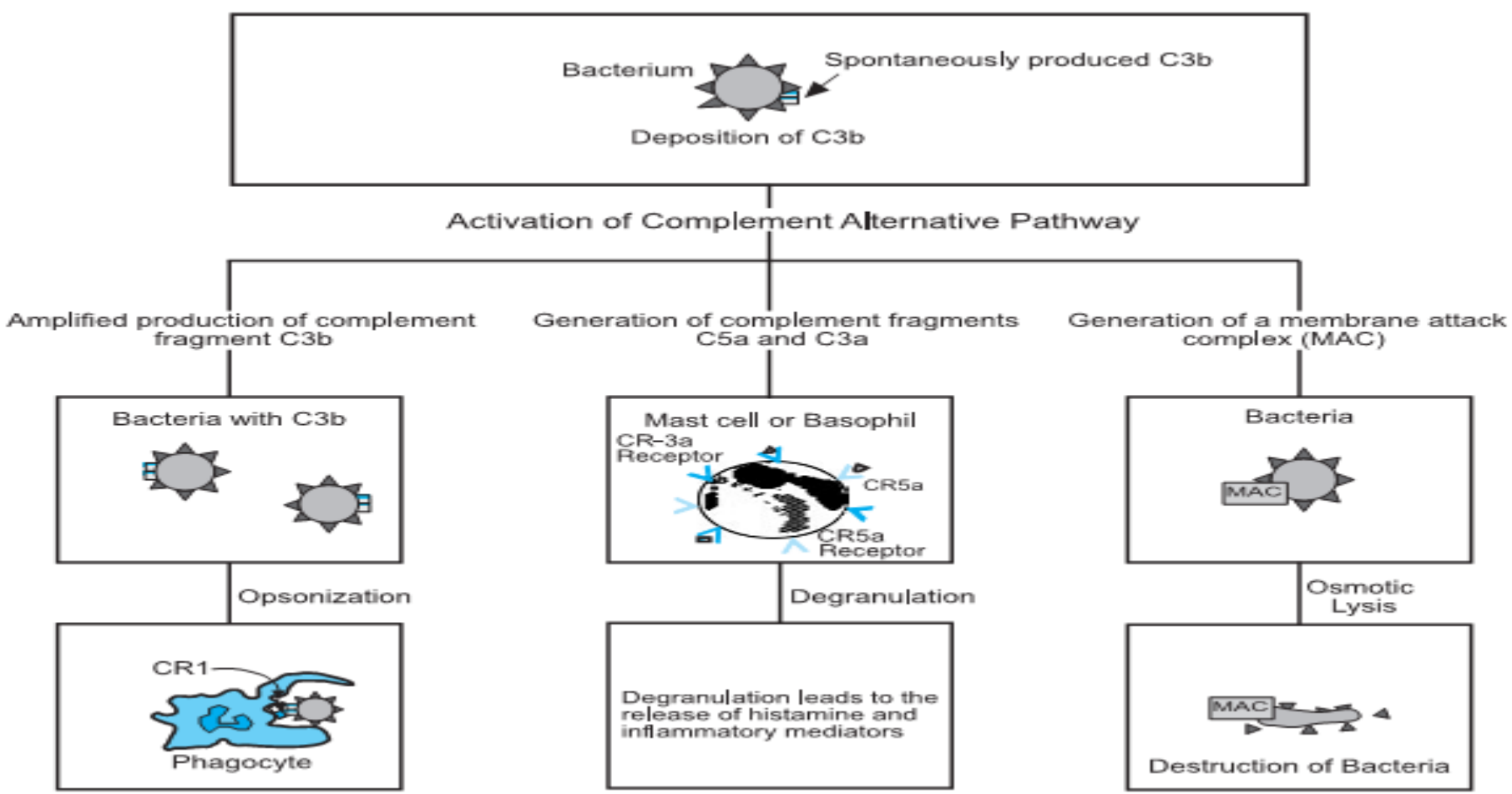


Fig. Activation of the alternative pathway of complement enhances innate immunity. The deposition of a spontaneously generated fragment, (C3b), of serum complement proteins onto a microbial membrane triggers activation of the complement cascade. Various protein fragments with distinct biological activities are generated that enhance innate immunity.