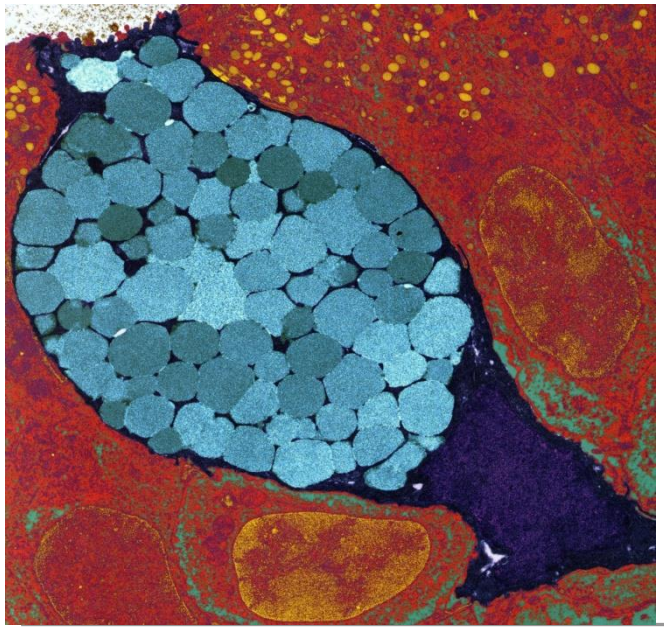


Goblet cellsl secrete the mucus that protects epithelial surfaces from invasion by microorganisms.

Chapter 2

Innate Immunity

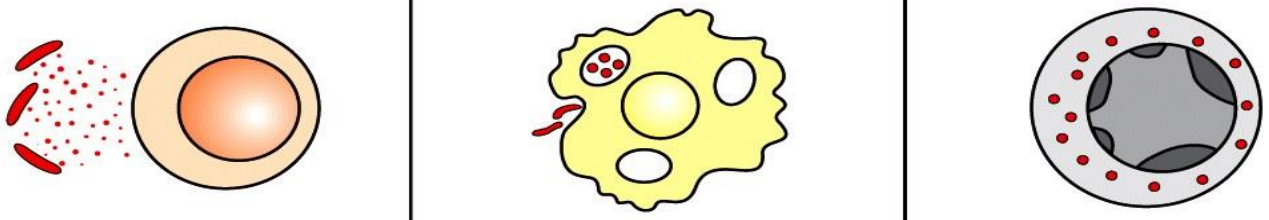
	Mechanisms of tissue damage by pathogens		
	Exotoxin release	**Endotoxin release**	**Direct cytopathic effect**
Pathogenic mechanism			
Infectious agent	***Vibrio cholerae***	***Yersinia pestis***	**Influenza virus**
Disease	**Cholera**	**Plague**	**Influenza**

Figure 2.1 Pathogens damage tissues in different ways. Pathogens can kill cells and damage tissues in three ways. Exotoxins released by microorganisms act at the surfaces of host cells, usually via a cell-surface receptor (first column). When phagocytes degrade certain microorganisms, endotoxins are released that induce the phagocytes to secrete cytokines, causing local or systemic symptoms (second column). Cells infected by pathogens are usually killed or damaged in the process (third column).

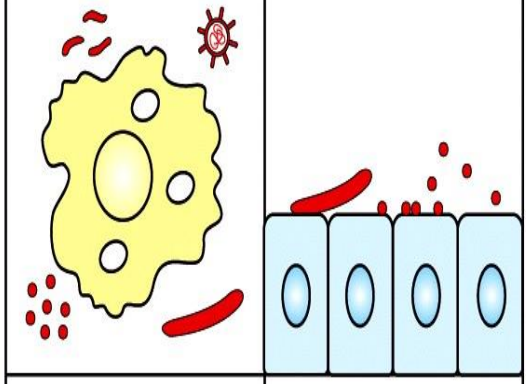
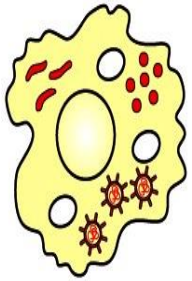
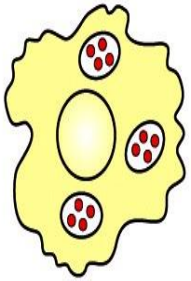
	Extracellular		Intracellular	
	Interstitial spaces, blood, lymph	Epithelial surfaces	Cytoplasmic	Vesicular
Site of infection				
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Candida albicans* Worms	Viruses *Listeria* Protozoa	Mycobacteria Trypanosomes *Cryptococcus neoformans*
Defense mechanism	Complement Macrophages Neutrophils	Antimicrobial peptides	NK cells	Activated macrophages

Figure 2.2 Pathogens exploit different compartments of the body that are defended in different ways by innate immunity. Virtually all pathogens have an extracellular stage in their life cycle. For the other compartments, a representative example of each type of pathogen that exploits the compartment is given. For some pathogens, all stages of their life cycle are extracellular, whereas others exploit intracellular sites as places to grow and replicate. Different components of the immune system contribute to defense against different types of microorganism in different locations. NK cells, natural killer cells.

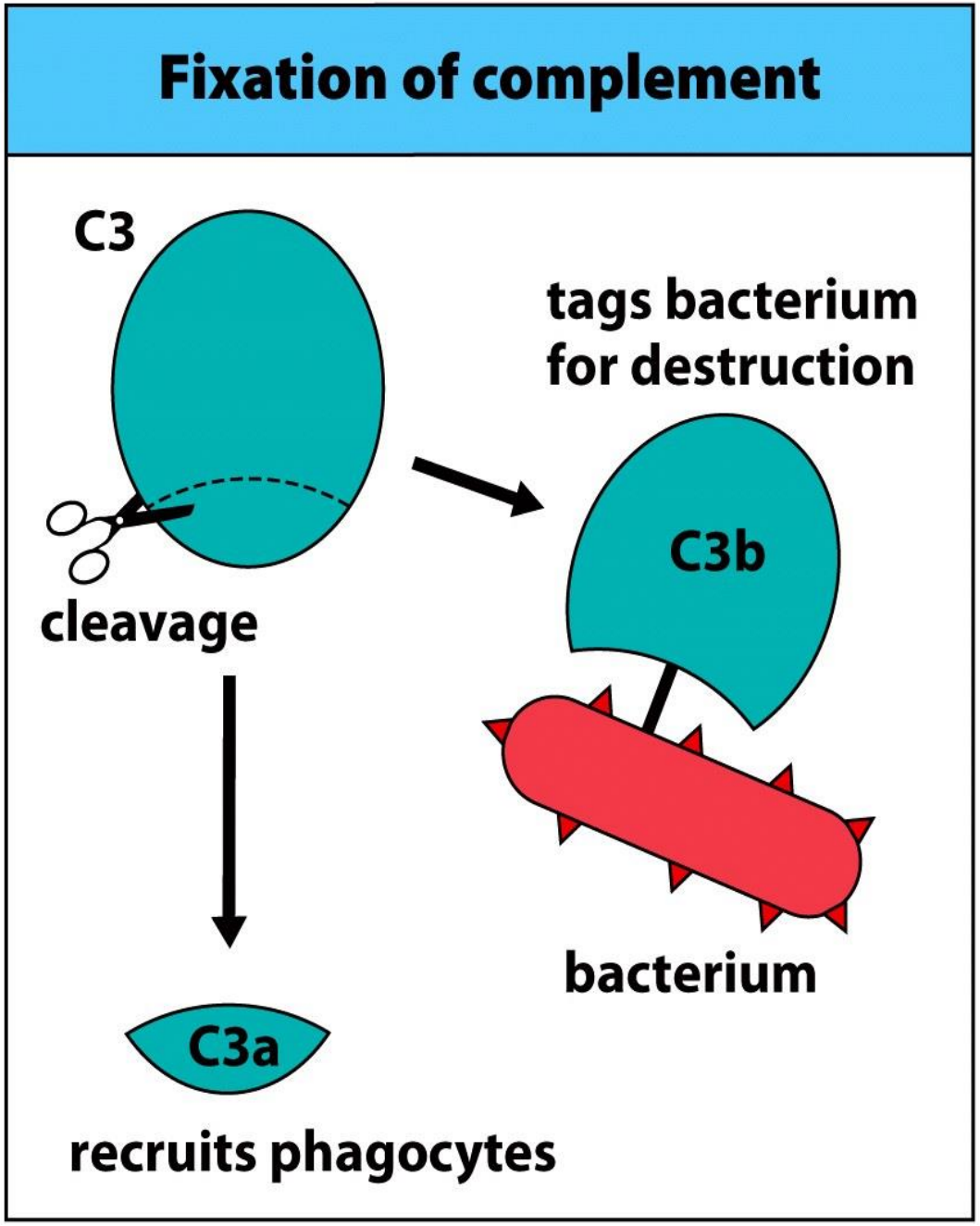


Figure 2.3 Complement activation achieves covalent attachment of C3b to a pathogen's surface. The key event in complement activation by a pathogen is the proteolytic cleavage of complement fragment C3. This cleavage produces a large C3b fragment and a small C3a fragment. C3b is chemically reactive and becomes covalently attached, or fixed, to the pathogen's surface, thereby marking the pathogen as dangerous. C3a recruits phagocytic cells to the site of infection.

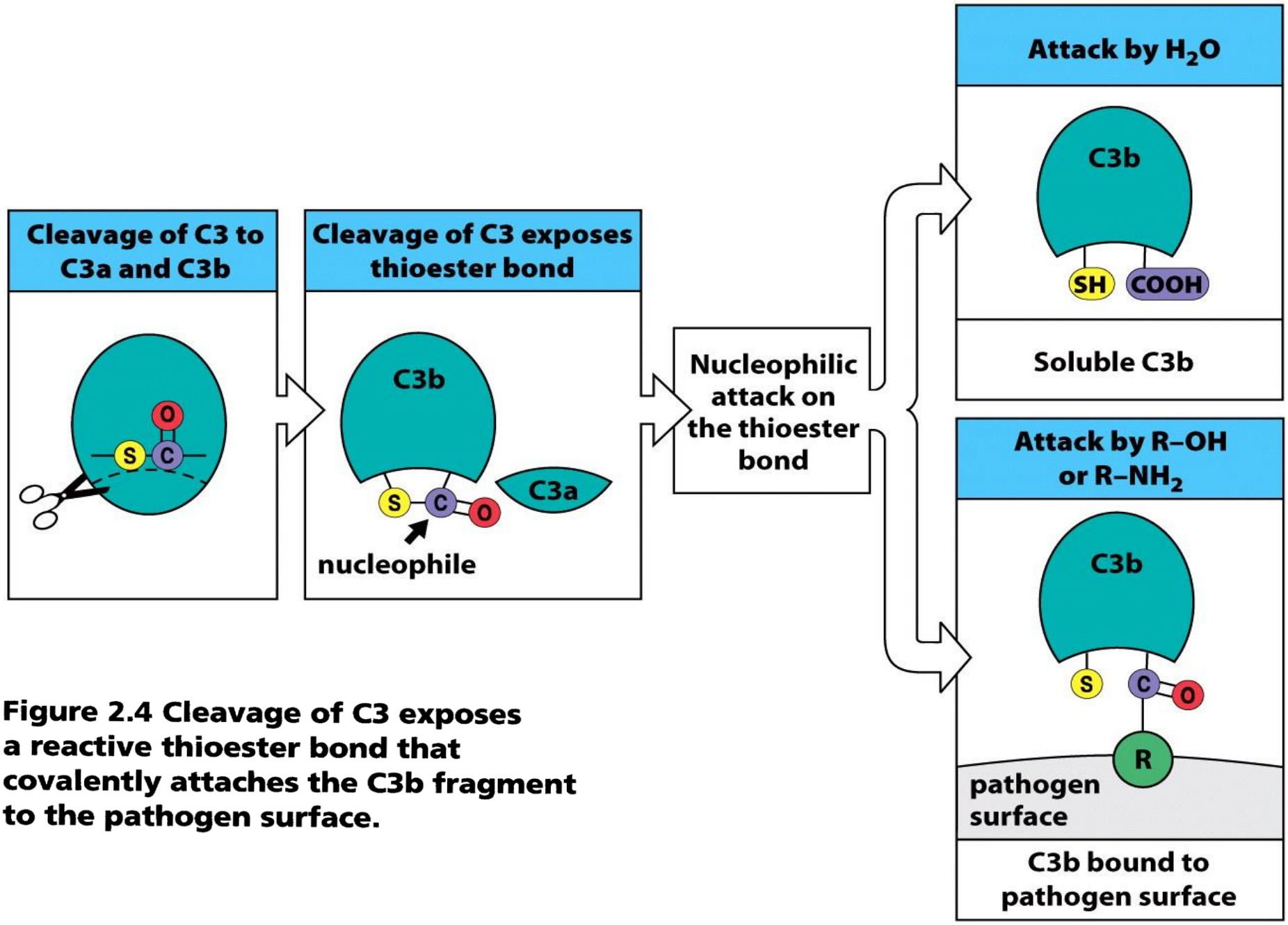


Figure 2.4 Cleavage of C3 exposes a reactive thioester bond that covalently attaches the C3b fragment to the pathogen surface.

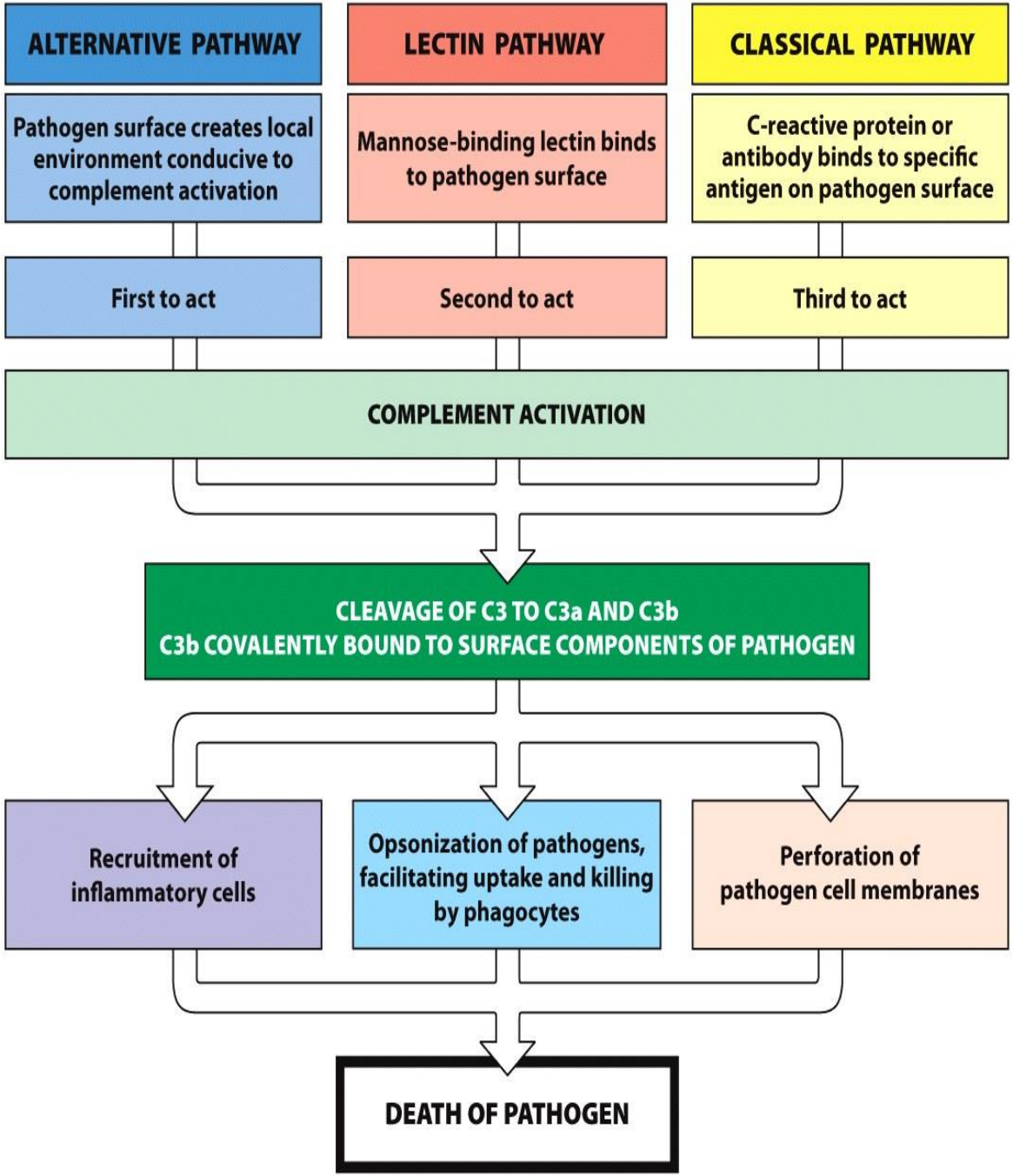


Figure 2.5 The three pathways of complement activation. The alternative pathway of complement activation is triggered by changes in the local physicochemical environment that are caused by the constituents of some bacterial surfaces. The alternative pathway acts at the earliest times during infection. The lectin-mediated pathway is initiated by the mannose-binding lectin of plasma, which binds to carbohydrates found on bacterial cells and other pathogens. The lectin-mediated pathway is induced by infection and contributes to innate immunity. The classical pathway is initiated in the innate immune response by the binding of C-reactive protein to bacterial surfaces, and in the adaptive immune response by the binding of antibodies to pathogen surfaces.

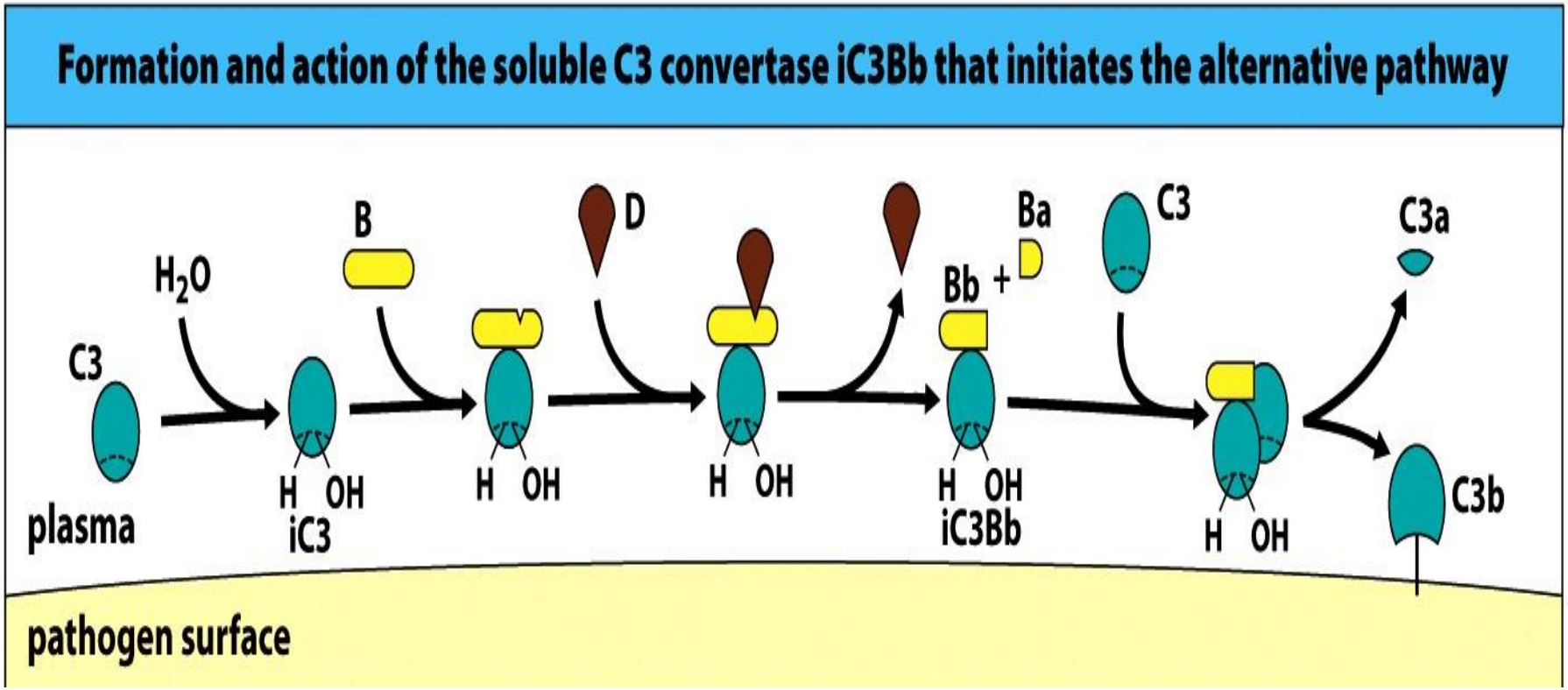


Figure 2.6 Formation and action of the soluble C3 convertase that initiates the alternative pathway of complement activation. In the plasma close to a microbial surface the thioester bond of C3 spontaneously hydrolyzes at low frequency. This activates the C3, which then binds factor B. Cleavage of B by the serine protease factor D produces a soluble C3 convertase, called iC3Bb, which then activates C3 molecules by cleavage into C3b and C3a. Some of the C3b fragments become covalently attached to the microbial surface.

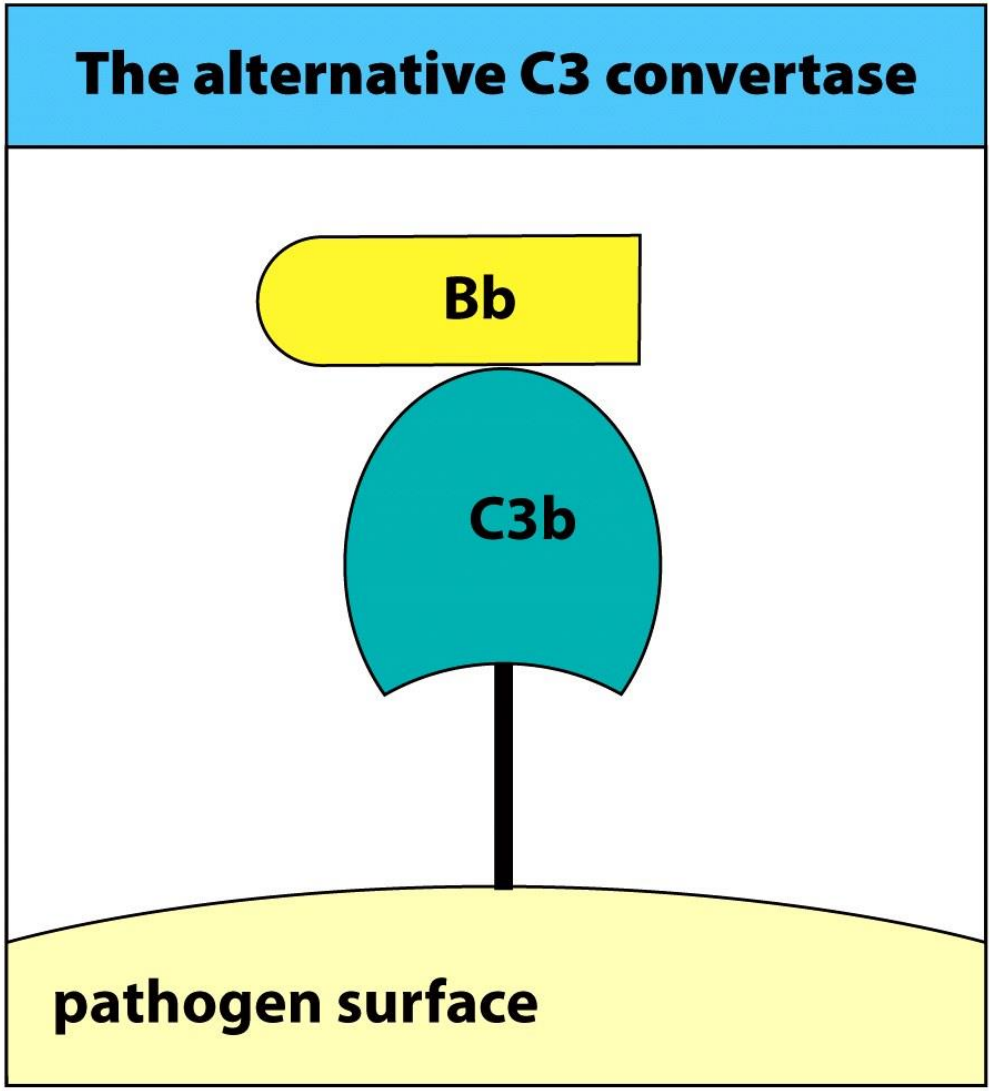


Figure 2.7 The C3 convertase of the alternative pathway is a complex of C3b and Bb. In this complex the Bb fragment of factor B provides the protease activity to cleave C3, and the C3b fragment of C3 locates the enzyme to the pathogen's surface.

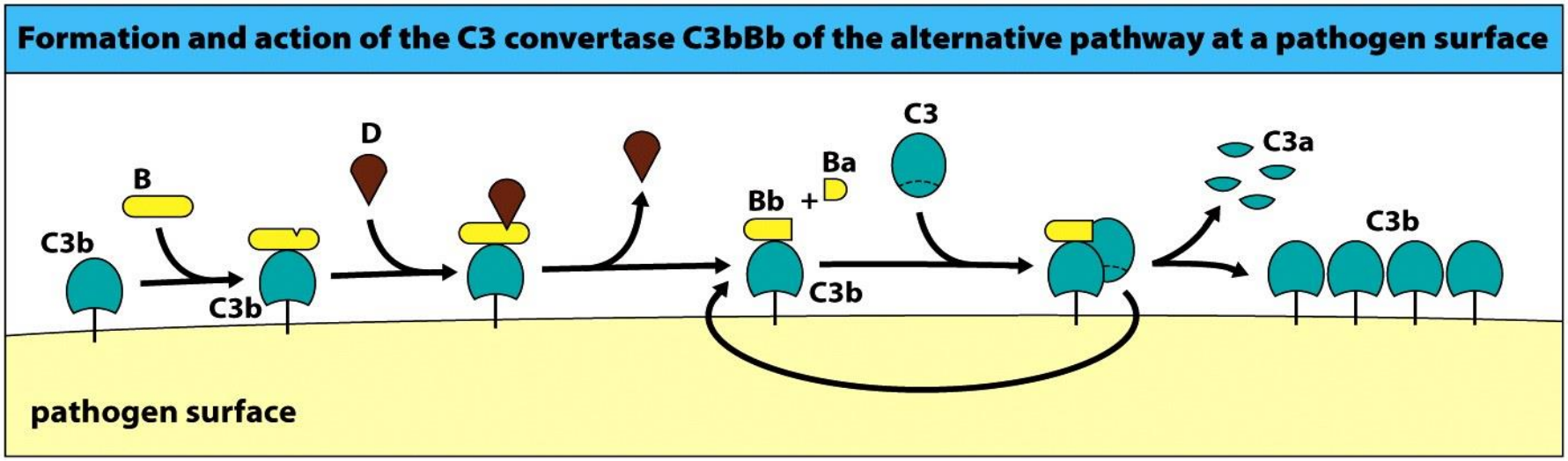


Figure 2.8 Formation and action of the C3 convertase, C3bBb, of the alternative pathway at a microbial surface. Through the action of the soluble C3 convertase, iC3Bb, C3b fragments are bound to the microbial surface (see Figure 2.6). These bind factor B, which is then cleaved by factor D to produce C3bBb, the surface-bound convertase of the alternative pathway. This enzyme cleaves C3 to produce further C3b fragments bound to the microbe and small soluble C3a fragments. The C3b fragments can be used either to make more C3 convertase, which amplifies the activation of C3, or to provide ligands for the receptors of phagocytic cells. The small, soluble C3a fragments attract phagocytes to sites of complement fixation.

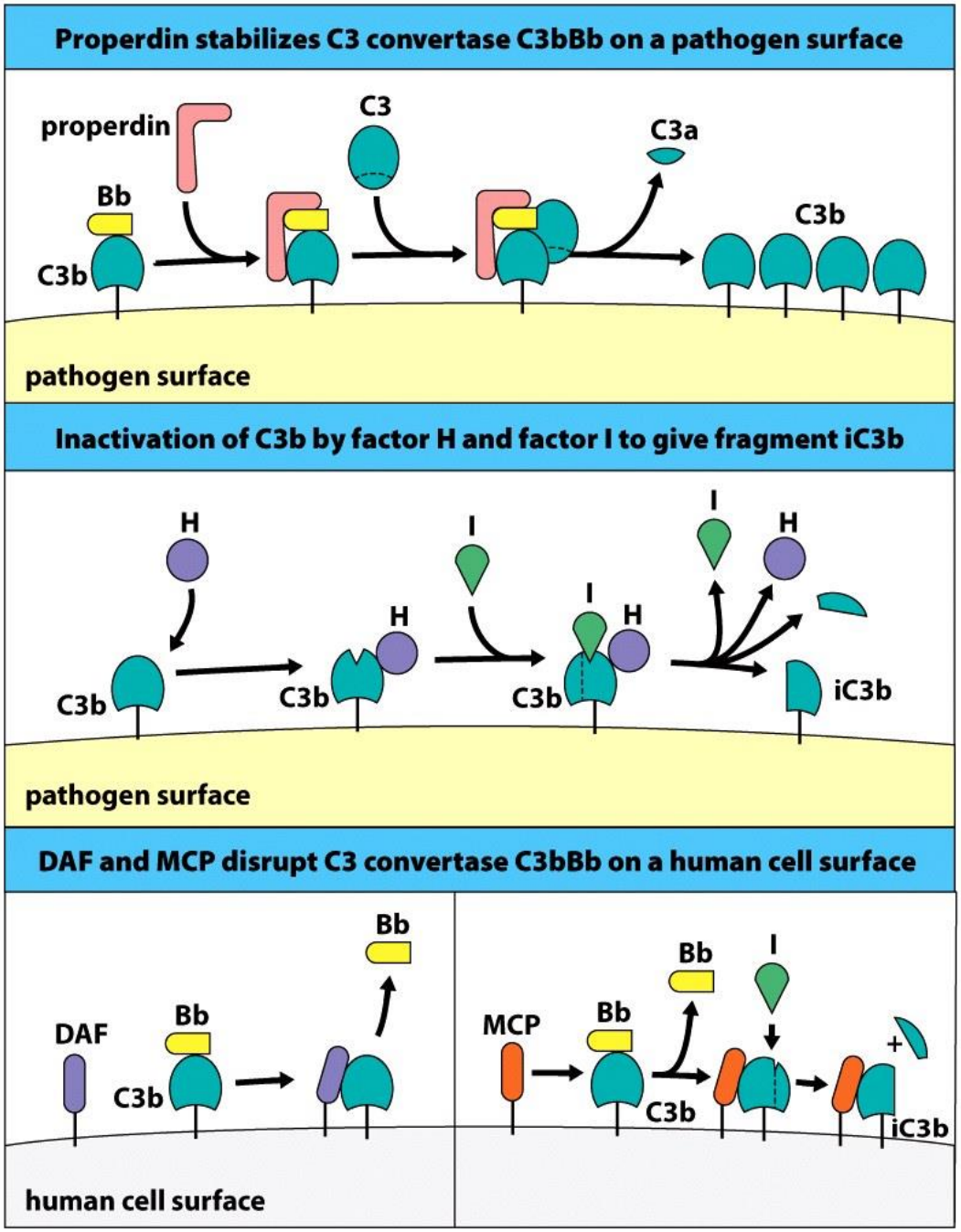


Figure 2.9 Formation and stability of the alternative C3 convertase on cell surfaces is determined by complement control proteins. Upper panel: the soluble protein properdin (factor P) binds to C3bBb and extends its lifetime on the microbial surface. Middle panel: factor H binds to C3b and changes its conformation to one that is susceptible to cleavage by factor I. The product of this cleavage is the iC3b fragment of C3, which remains attached to the pathogen surface but cannot form a C3 convertase. Lower panel: when C3bBb is formed on a human cell surface it is rapidly disrupted by the action of one of two membrane proteins: decay-accelerating factor (DAF) or membrane cofactor protein (MCP). In combination, these regulatory proteins ensure that much complement is fixed to pathogen surfaces and little is fixed to human cell surfaces.

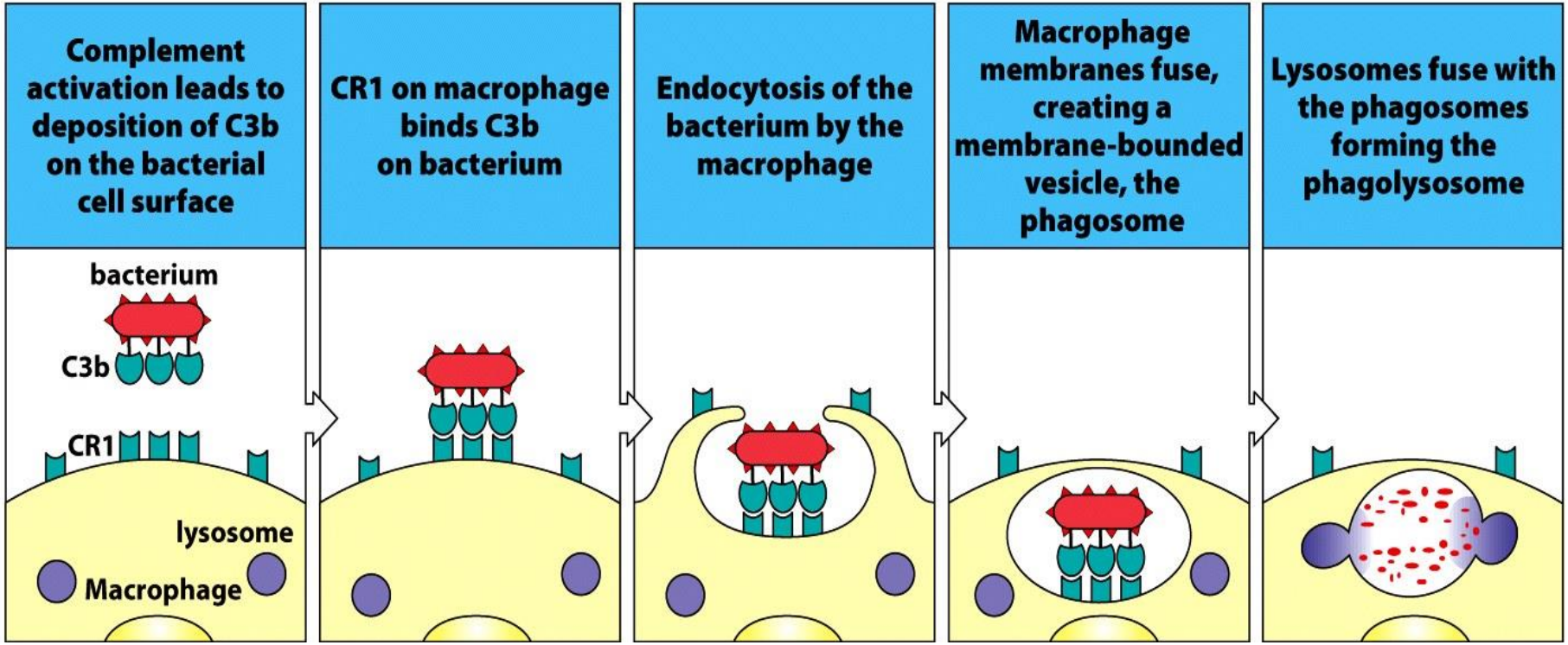


Figure 2.10 Complement receptors on phagocytes trigger the uptake and breakdown of C3b-coated pathogens. Covalently attached C3b fragments coat the pathogen surface, here a bacterium, and bind to complement receptor 1 (CR1) molecules on the phagocyte surface, thereby tethering the bacterium to the phagocyte. Intracellular signals generated by CR1 enhance the phagocytosis of the bacterium and the fusion of lysosomes containing degradative enzymes and toxic molecules with the phagosome. Ultimately, the bacterium is killed.

The terminal complement components that form the membrane-attack complex		
Protein	**Concentration in serum (μg/ml)**	**Function**
C5	85	On activation the soluble C4b fragment initiates assembly of the membrane-attack complex in solution
C6	60	Binds to and stabilizes C5b. Forms a binding site for C7
C7	55	Binds to C5b6 and exposes a hydrophobic region that permits attachment to the cell membrane
C8	55	Binds to C5b67 and exposes a hydrophobic region that inserts into the cell membrane
C9	60	Polymerization on the C5b678 complex to form a membrane-spanning channel that disrupts the cell's integrity and can result in cell death

Figure 2.11 The terminal components of the complement pathway.

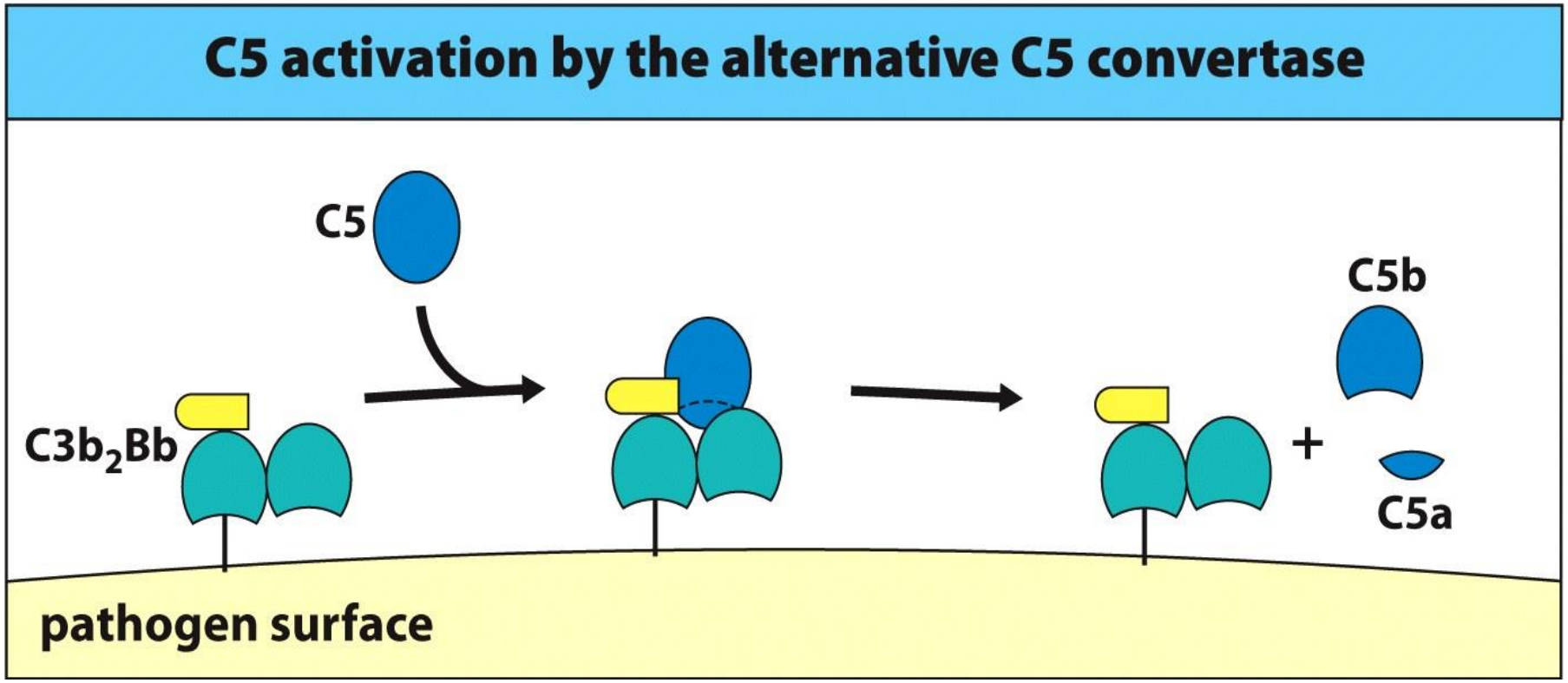
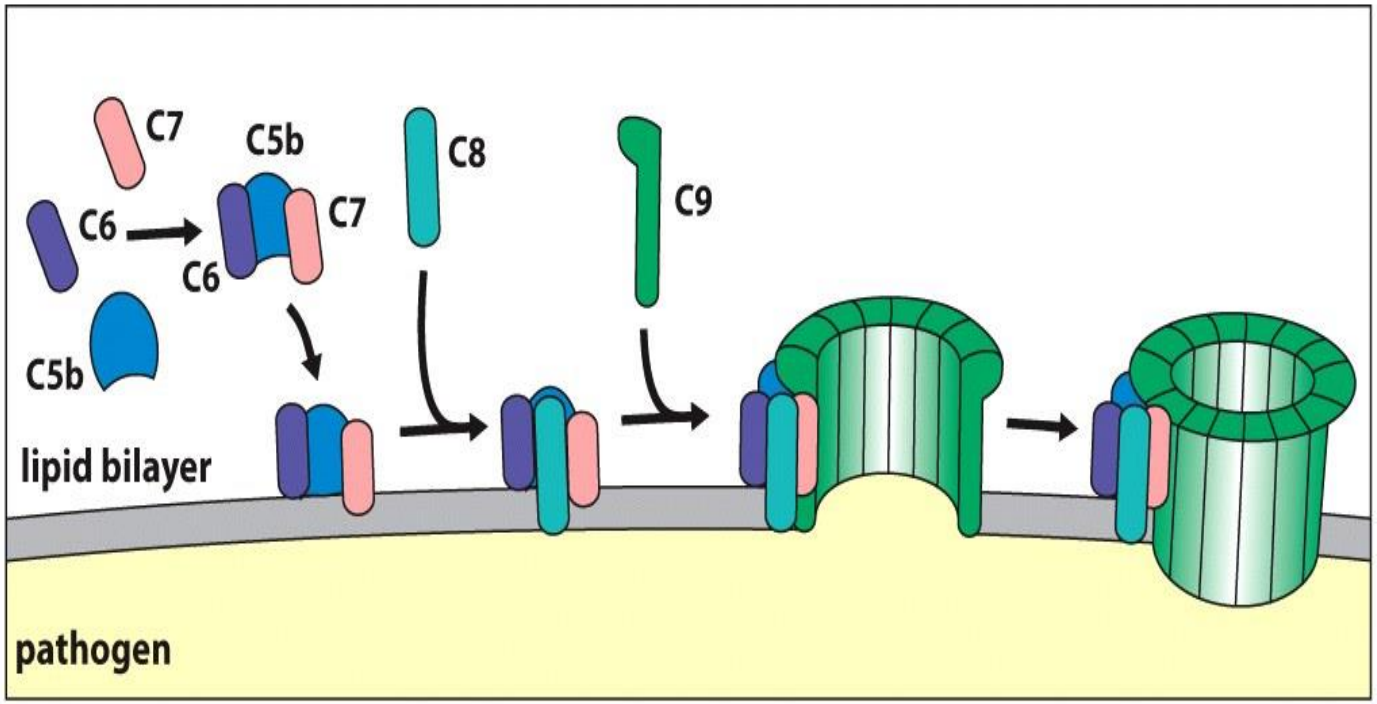


Figure 2.12 Complement component C5 is cleaved by C5 convertase to give a soluble active C5b fragment. The C5 convertase of the alternative pathway consists of two molecules of C3b and one of Bb ($C3b_2Bb$). C5 binds to the C3b component of the convertase and is cleaved into fragments C5a and C5b, of which C5b initiates the assembly of the terminal complement components to form the membrane-attack complex.



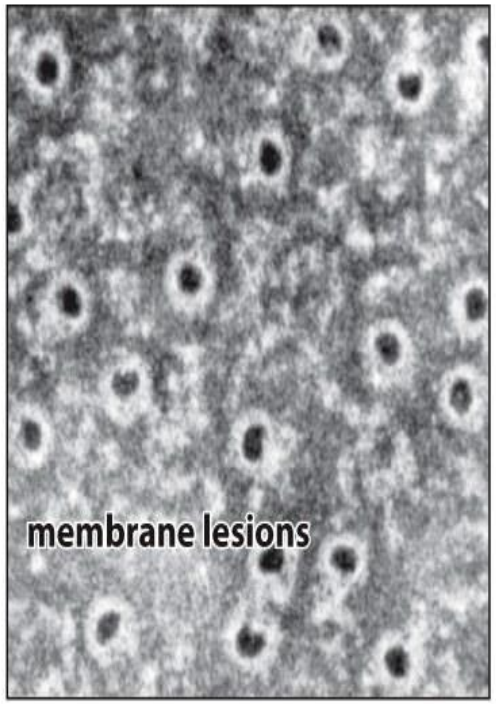


Figure 2.13 The membrane-attack complex assembles to generate a pore in the lipid bilayer membrane. The sequence of steps and their approximate appearance is shown here in schematic form. C5b is generated by the cleavage of C5 by the alternative C5 convertase $C3b_2Bb$. C5b then forms a complex by the successive binding of one molecule each of C6, C7, and C8. In forming the complex, C7 and C8 undergo a conformational change that exposes hydrophobic sites, which insert into the membrane. This complex causes some membrane damage and also induces the polymerization of C9. As each molecule of C9 is added to the polymer, it exposes a hydrophobic site and inserts into the membrane. Up to 16 molecules of C9 can be added to generate a transmembrane channel 100 Å in diameter. The channel disrupts the bacterial outer membrane, killing the bacterium. In the laboratory, the erythrocyte is a convenient cell with which to measure complement-mediated lysis. The electron micrograph shows erythrocyte membranes with membrane-attack complexes seen end on. Photograph courtesy of S. Bhakdi and J. Tranum-Jensen.

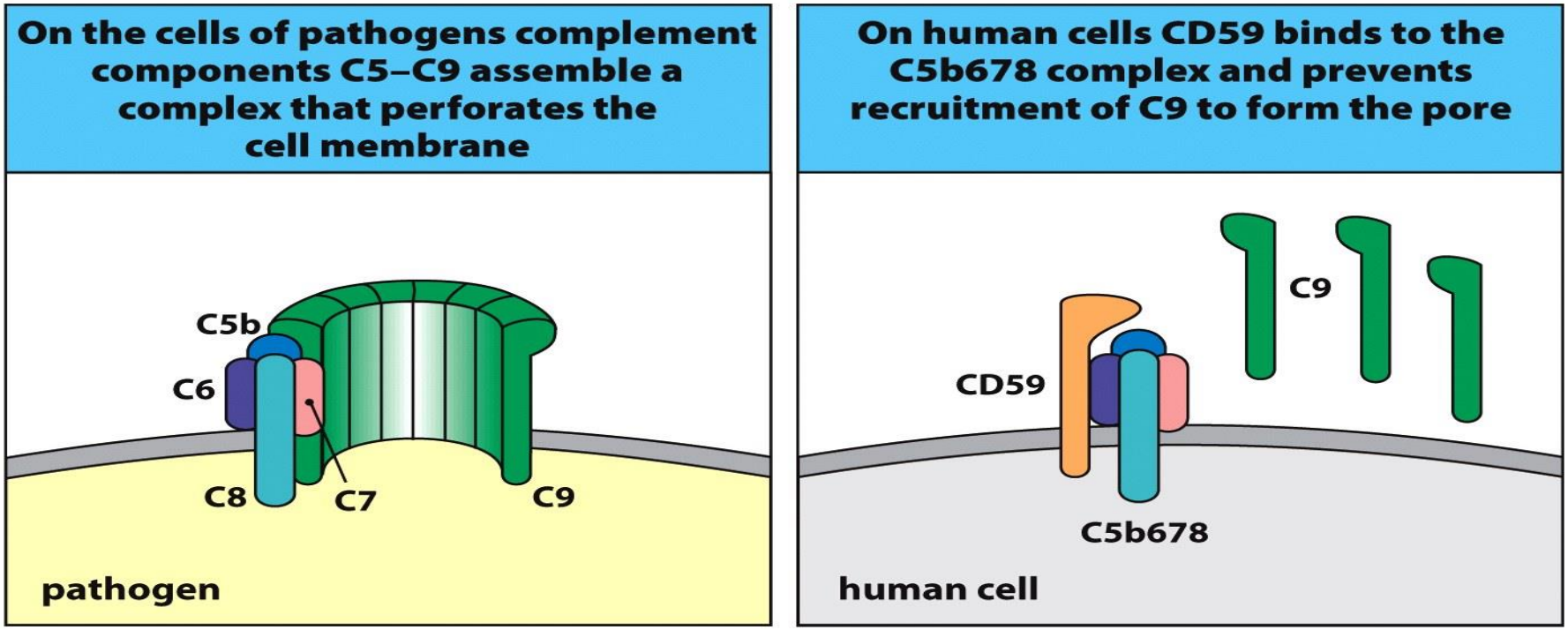


Figure 2.14 CD59 prevents assembly of the membrane attack complex on human cells. Left panel: the formation of a pore by the membrane attack complex (MAC) on a pathogenic microorganism. Right panel: how the human cell-surface protein CD59 prevents pore formation on human cells. By binding to the C5b678 complex, CD59 prevents the polymerization of C9 in the membrane to form a pore. Homologous restriction factor (HRF, not shown) works in the same way.

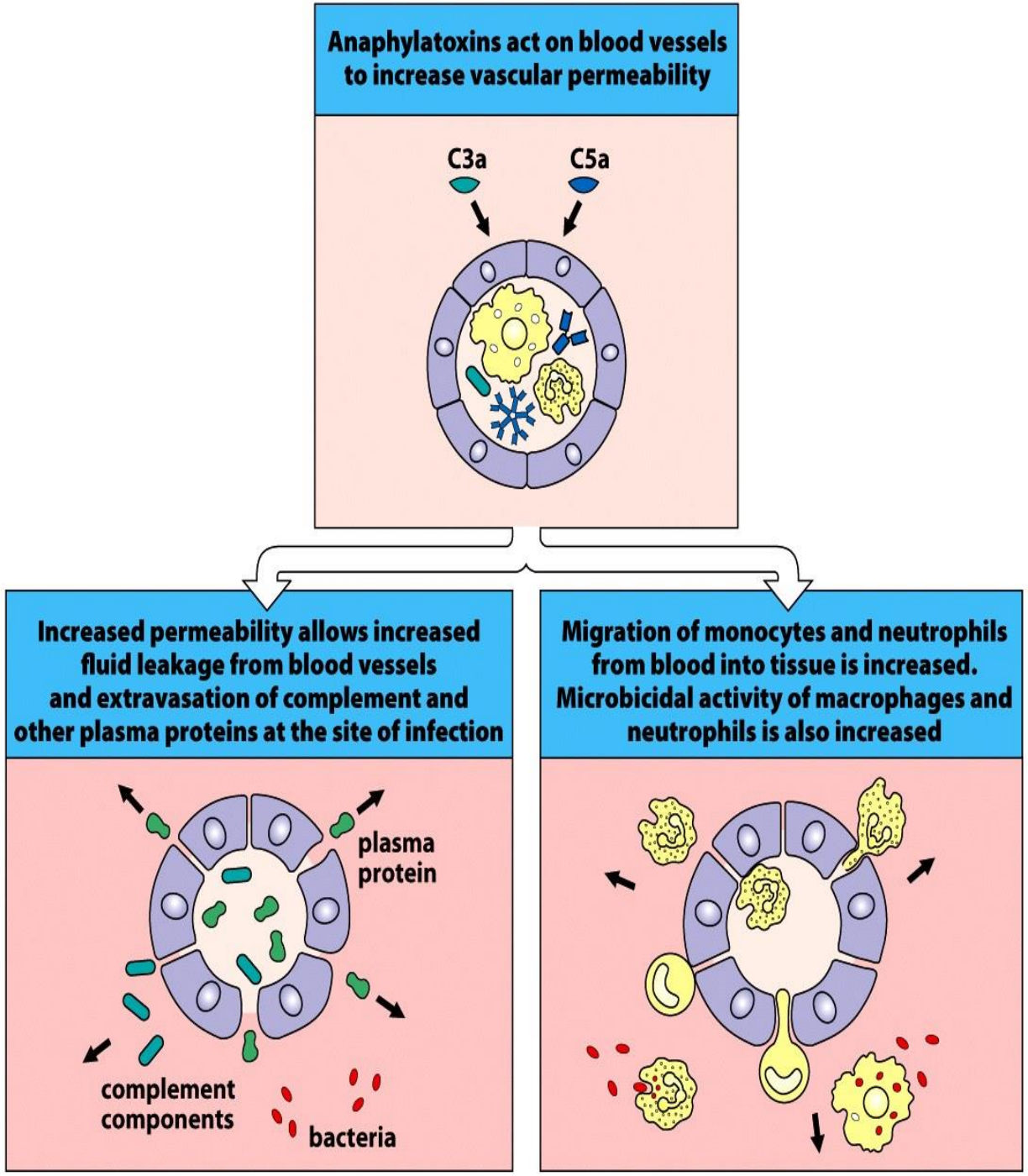


Figure 2.15 Local inflammatory responses can be induced by the small complement fragments C3a and C5a. These small anaphylatoxic peptides are produced by complement cleavage at the site of infection and cause local inflammatory responses by acting on local blood vessels. They cause increased blood flow, increased binding of phagocytes to endothelial cells, and increased vascular permeability, leading to the accumulation of fluid, plasma proteins, and cells in the local tissues. The complement and cells recruited by this inflammatory stimulus remove pathogen by enhancing the activity of phagocytes, which are themselves also directly stimulated by the anaphylatoxins. C5a is more potent than C3a.

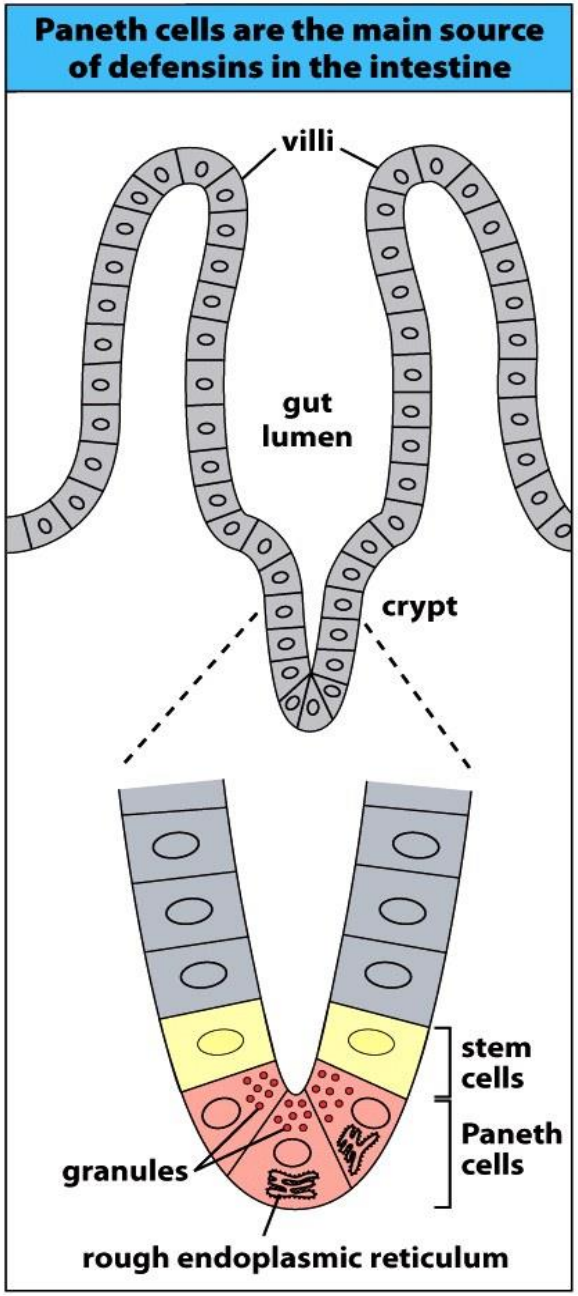


Figure 2.17 Paneth cells are located in the crypts of the small intestine. The α-defensins HD5 and HD6, also known as cryptdins, are made only by Paneth cells. The upper part of the diagram shows the location of a crypt between two villi in the distal part of the small intestine (ileum). The lower part of the diagram shows the Paneth cells at the base of the crypt and the epithelial stem cells that give rise to them. Paneth cells also secrete other antimicrobial factors, including lysozyme and phospholipase A2. Although they are of epithelial, not hematopoietic, origin, Paneth cells can be considered cells of the immune system.

Defensin		Site of synthesis	Tissues defended	Regulation of synthesis
Class	Name			
α	HNP1	Neutrophils > monocytes, macrophages, NK cells, B cells, and some T cells	Intestinal epithelium, placenta, and cervical mucus plug	Constitutive
α	HNP2			
α	HNP3			
α	HNP4	Neutrophils	Not determined	Constitutive
α	HD5	Paneth cells > vaginal epithelial cells	Salivary glands, gastrointestinal tract, eyes, female genital tract, and breast milk	Constitutive and induced by sexually transmitted infection
α	HD6	Paneth cells	Salivary glands, gastrointestinal tract, eyes, and breast milk	
β	HBD1	Epithelial cells > monocytes, macrophages, dendritic cells, and keratinocytes	Gastrointestinal tract, respiratory tract, urogenital tract, skin, eyes, salivary glands, kidneys, and blood plasma	Constitutive and induced by infection
β	HBD2			
β	HBD3			
β	HBD4	Epithelial cells	Stomach (gastric antrum) and testes	

Figure 2.18 Human defensins are variable antimicrobial peptides. Defensins are small antimicrobial peptides that are found at epithelial surfaces and in the granules of neutrophils. They form two families: the α-defensins and the β-defensins. HNP, human neutrophil protein; HD, human defensin; HBD, human β-defensin. The gastric antrum is that part of the stomach nearer the outlet and does not secrete acid.

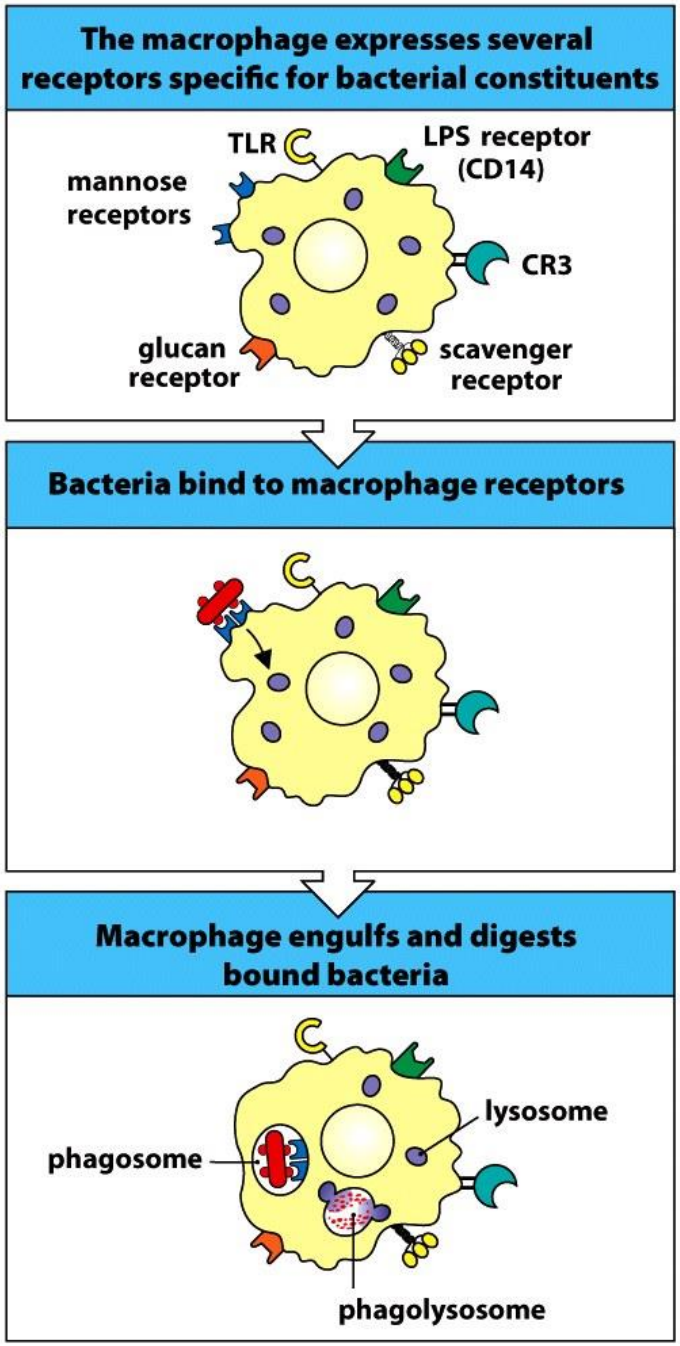


Figure 2.19 Macrophages have many different cell-surface receptors by which they recognize pathogens. The mannose, glucan, and scavenger receptors are phagocytic receptors that bind microbial consitutents not found in human cells. Binding to such receptors results in the internalization of the pathogen by phagocytosis and its destruction in a phagolysosome. The Toll-like receptor (TLR) represents a class of signaling receptors that detect the presence of a wide variety of microbial components. CD14 is a lectin that binds the lipopolysaccharide of Gram-negative bacteria and becomes associated with one of the TLRs. CR3 is a receptor for the complement component iC3b.

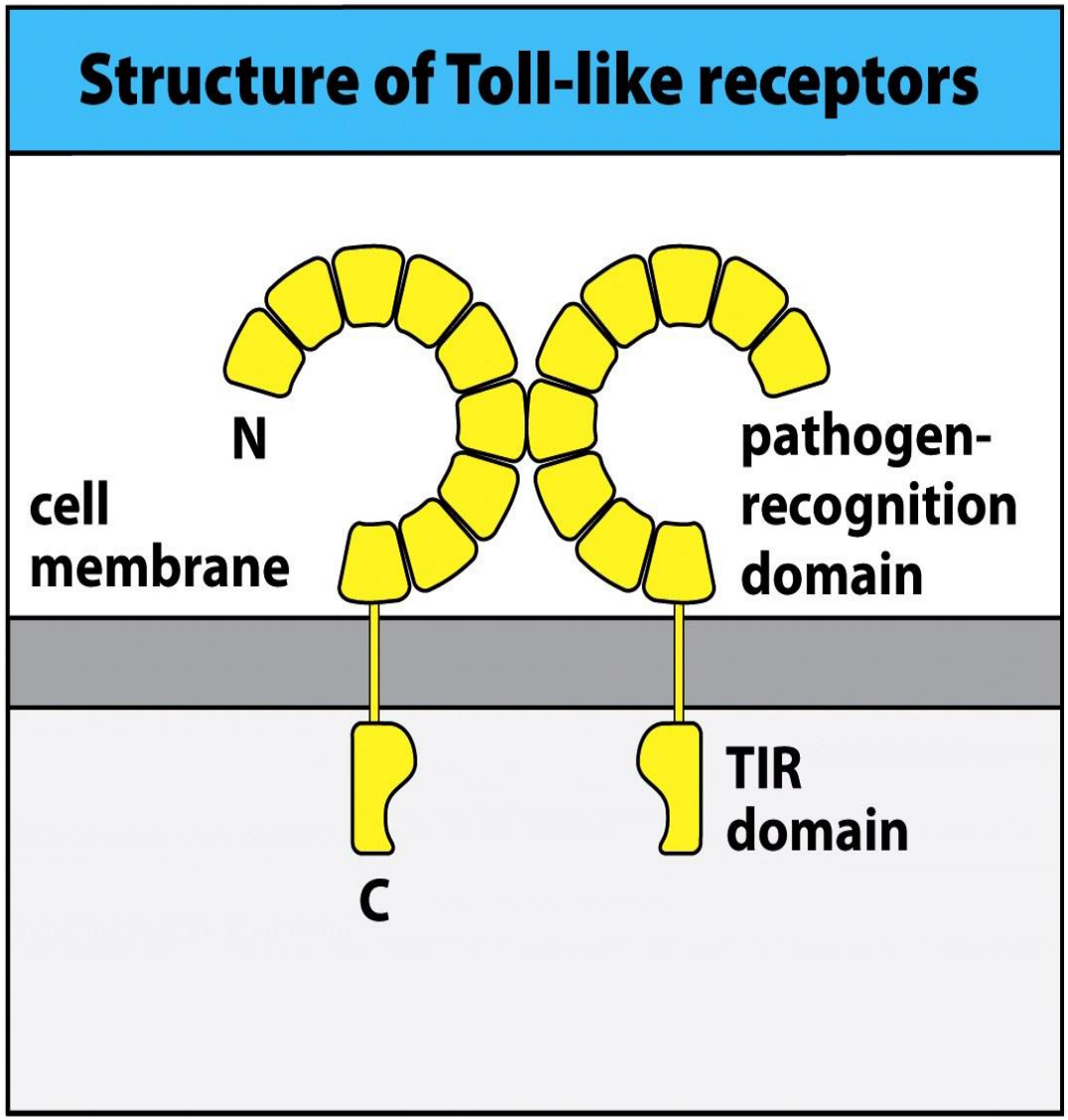


Figure 2.20 Toll-like receptors sense infection with a horseshoe-shaped structure. A Toll-like receptor (TLR) protein is a transmembrane polypeptide with a Toll–interleukin receptor (TIR) signaling domain on the cytoplasmic side of the membrane and a horseshoe-shaped sensor domain on the other side. Functional receptors can be homodimers (as shown here) or heterodimers of TLR polypeptides.

Recognition of microbial products through Toll-like receptors				
Receptor	**Ligands**	**Microorganisms recognized**	**Cells carrying receptor**	**Cellular location of receptor**
TLR1:TLR2 heterodimer	Lipopeptides GPI	Bacteria Parasites e.g., trypanosomes	Monocytes, dendritic cells, eosinophils, basophils, mast cells	Plasma membrane
TLR2:TLR6 heterodimer	Lipoteichoic acid Zymosan	Gram-positive bacteria Yeasts (fungi)		Plasma membrane
TLR3	Double-stranded viral RNA	Viruses e.g., West Nile virus	NK cells	Endosomes
TLR4:TLR4 homodimer	Lipopolysaccharide	Gram-negative bacteria	Macrophages, dendritic cells, mast cells, eosinophils	Plasma membrane
TLR5	Flagellin	Motile bacteria having a flagellum	Intestinal epithelium	Plasma membrane
TLR7	Single-stranded viral RNAs	Viruses e.g., human immunodeficiency virus (HIV)	Plasmacytoid dendritic cells, NK cells, eosinophils, B cells	Endosomes
TLR8	Single-stranded viral RNAs	Viruses e.g., influenza	NK cells	Endosomes
TLR9	Unmethylated CpG-rich DNA	Bacteria Viruses e.g., herpes viruses	Plasmacytoid dendritic cells, B cells, eosinophils, basophils	Endosomes
TLR10 homodimer and heterodimers with TLR1 and 2	Unknown		Plasmacytoid dendritic cells, basophils, eosinophils, B cells	Unknown

Figure 2.21 The human Toll-like receptors allow the detection of many different types of infection. Each of the known Toll-like receptors (TLRs) seems to recognize one or more characteristic features of microbial macromolecules, but TLR5 is the only TLR so far for which a direct interaction with a microbial product, the bacterial protein flagellin, has been demonstrated. There are 10 TLR genes in humans, each encoding a distinct TLR polypeptide. Some TLRs are known to be heterodimers of these polypeptides; some, such as TLR4, are known to act only as homodimers. The Toll-like receptors take their name from their structural similarities to a receptor called Toll in the fruitfly *Drosophila melanogaster*, which is involved in the adult fly's defense against infection.

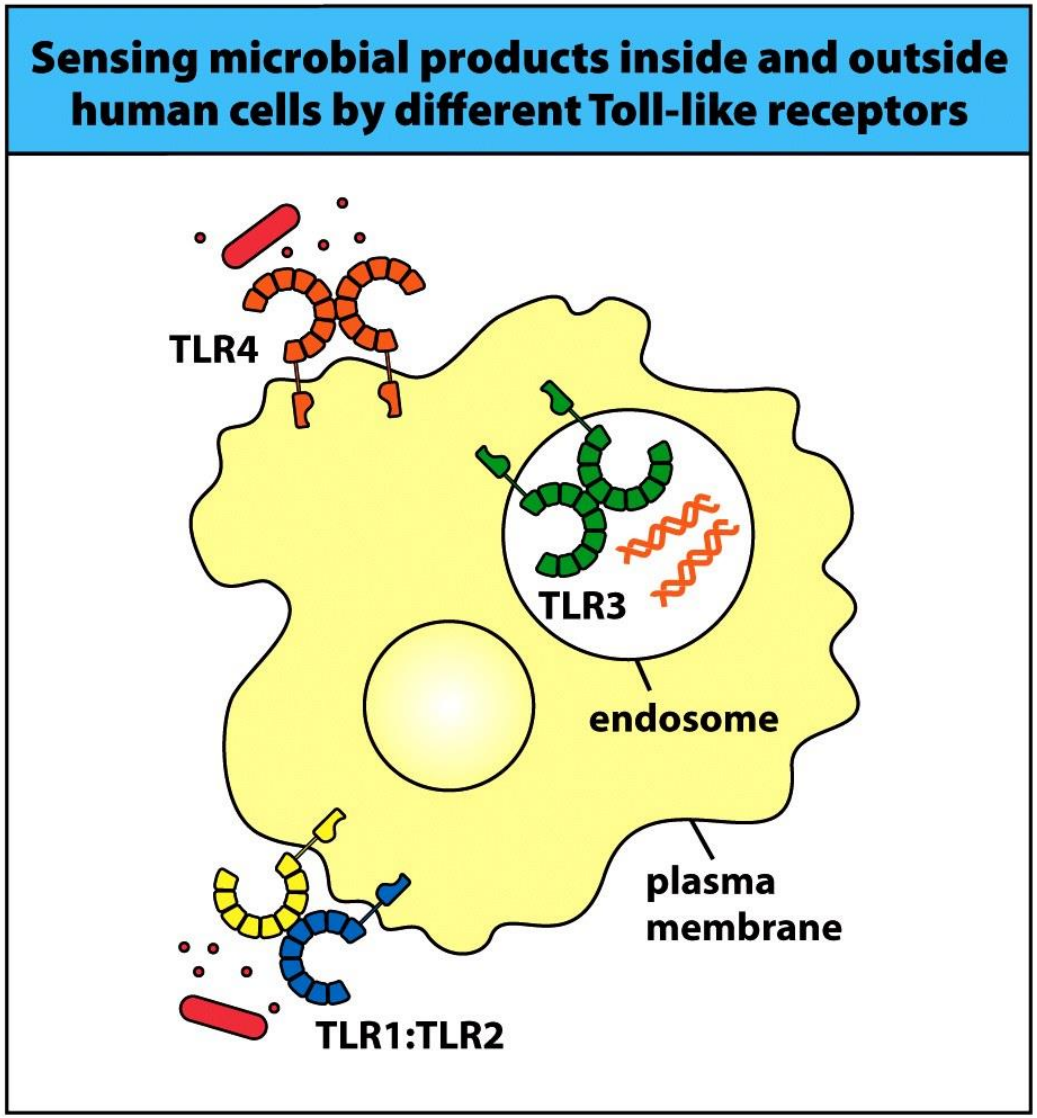


Figure 2.22 Different Toll-like receptors sense bacterial infection outside the cell and viral infection inside the cell. The TLR4 homodimer and the TLR1:TLR2 heterodimer at the cell surface are shown sensing a bacterial infection, and the homodimer of TLR3 in an endosomal vesicle is detecting a viral infection.

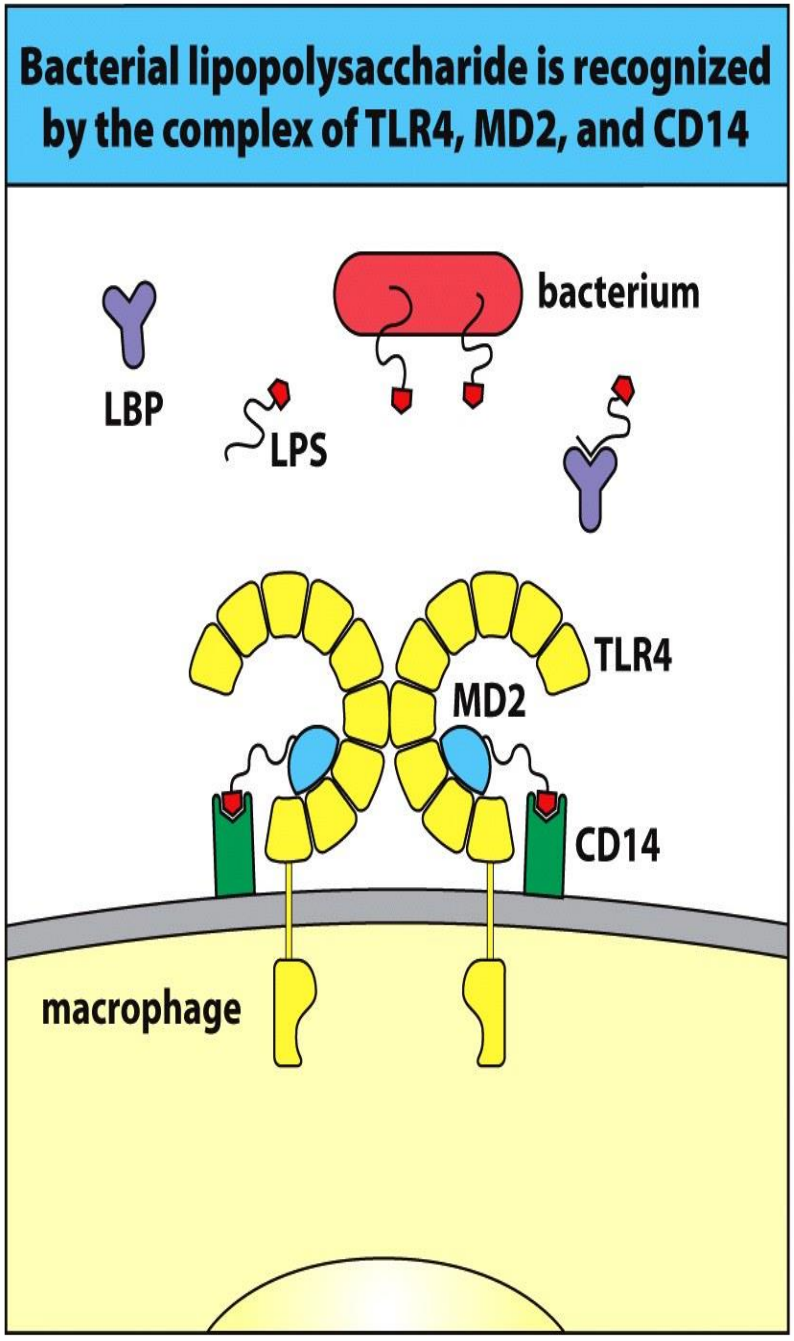


Figure 2.23 TLR4 recognizes bacterial lipopolysaccharide with help from other proteins. Bacterial lipopolysaccharide (LPS) is recognized by a complex of the TLR4, MD2, and CD14 proteins at the cell surface. MD2 is a soluble protein that associates with the extracellular domains of TLR4, but not with other TLR family members, and confers sensitivity to LPS. The soluble lipopolysaccharide-binding protein (LBP) can also deliver LPS to this cell-surface complex.

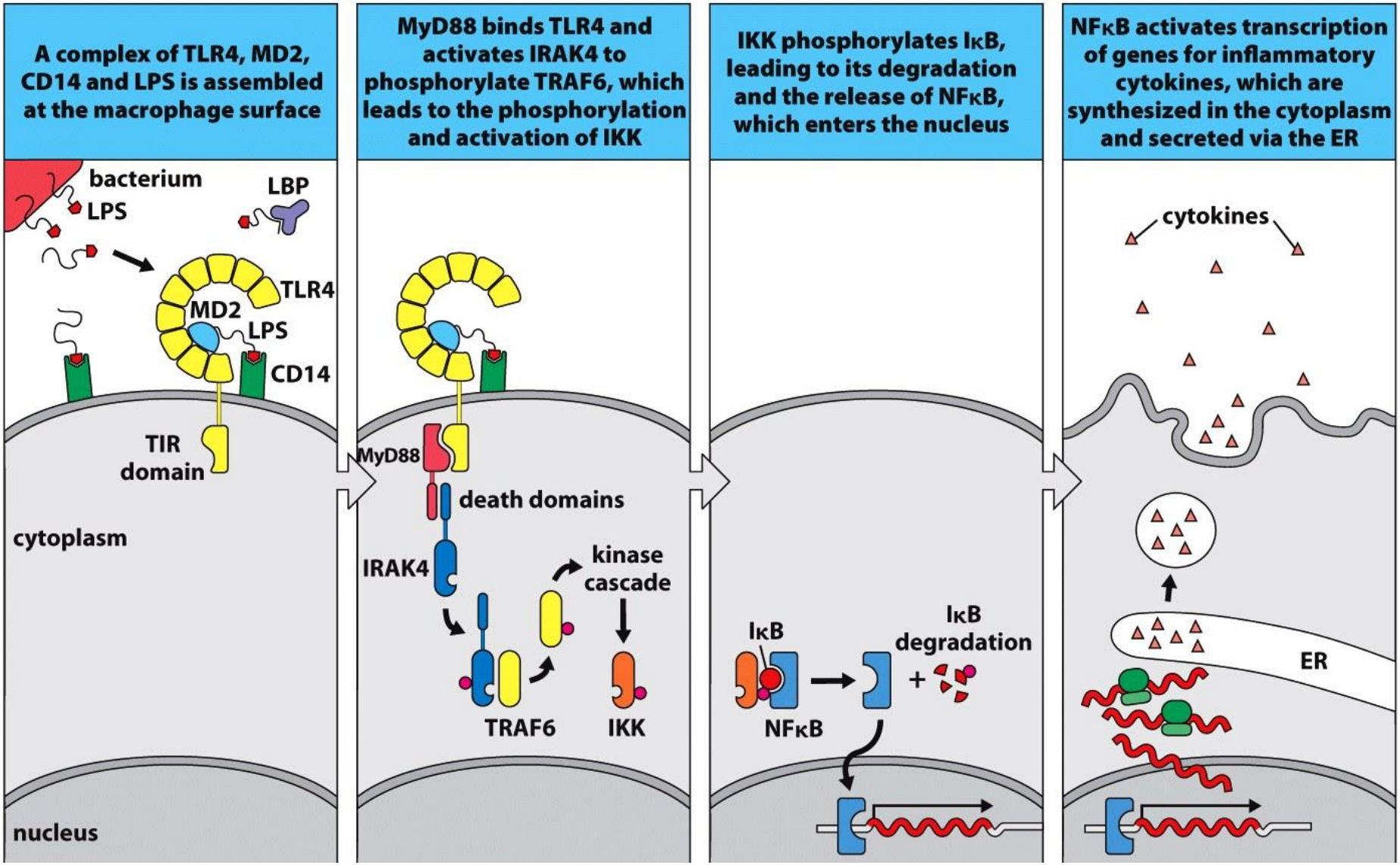


Figure 2.24 Sensing of LPS by TLR4 on macrophages leads to activation of the transcription factor NFκB and the synthesis of inflammatory cytokines.

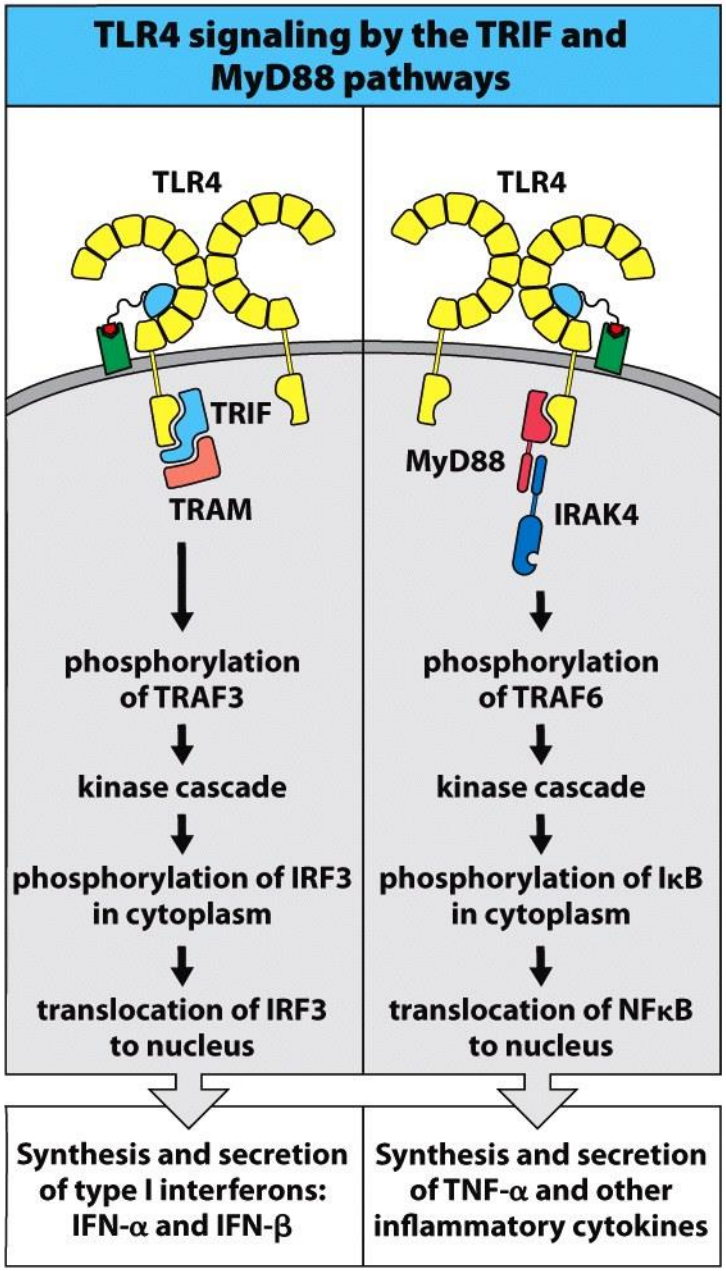
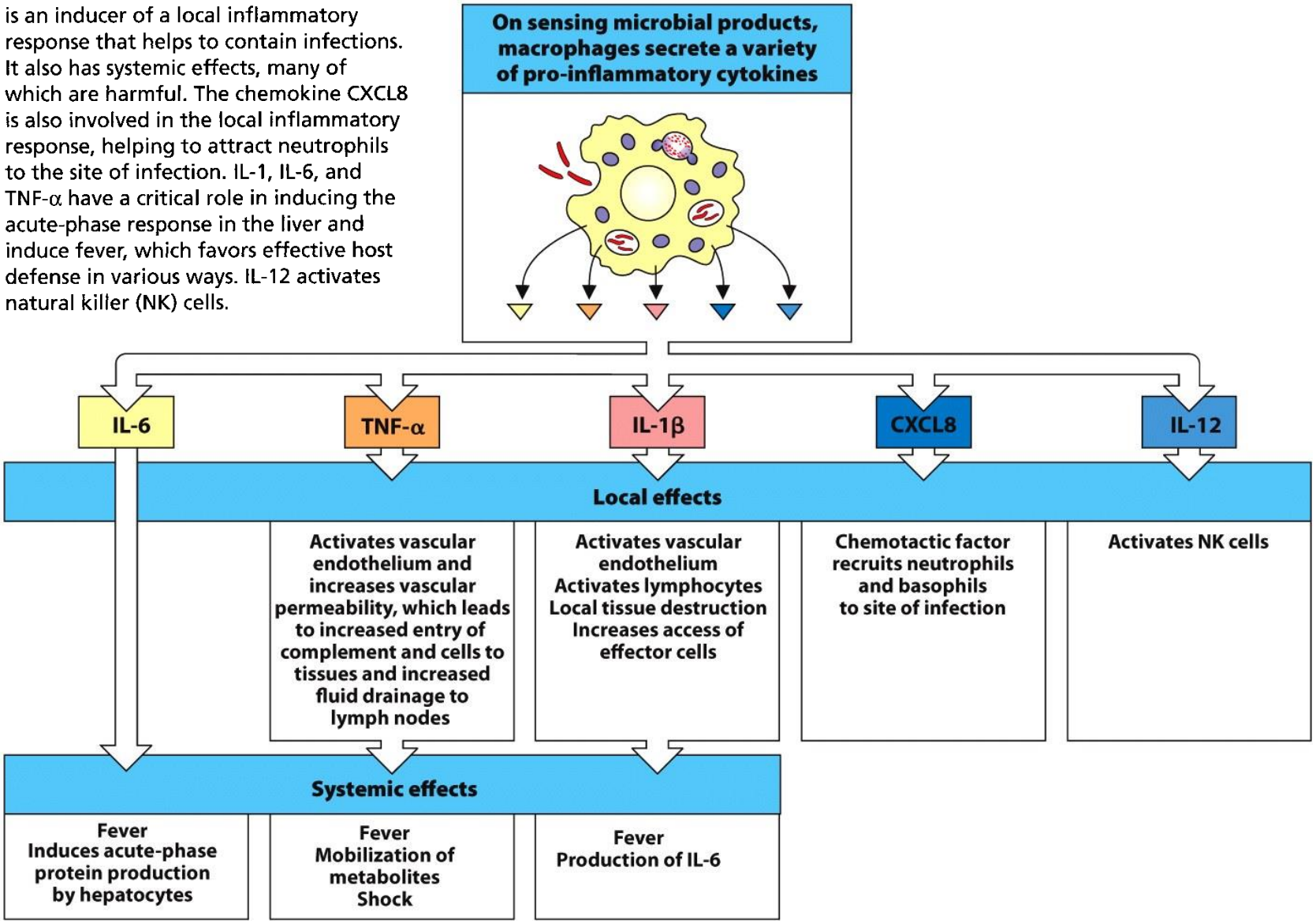


Figure 2.26 TLR4 activation can lead to the production of either inflammatory cytokines or antiviral type I interferons. TLR4 can stimulate two different intracellular signaling pathways, depending on whether the adaptor protein MyD88 or TRIF is recruited to the activated receptor. TLR4 signaling through TRIF leads to activation of the transcription factor interferon response factor 3 (IRF3) and the production of type I interferons. Signaling through MyD88 leads to activation of the transcription factor NFκB and the production of inflammatory cytokines such as IL-6 and TNF-α. TLR3 also uses the TRIF pathway.

Figure 2.27 Important cytokines secreted by macrophages in response to bacterial products include IL-1, TNF-α, IL-6, CXCL8, and IL-12. TNF-α is an inducer of a local inflammatory response that helps to contain infections. It also has systemic effects, many of which are harmful. The chemokine CXCL8 is also involved in the local inflammatory response, helping to attract neutrophils to the site of infection. IL-1, IL-6, and TNF-α have a critical role in inducing the acute-phase response in the liver and induce fever, which favors effective host defense in various ways. IL-12 activates natural killer (NK) cells.



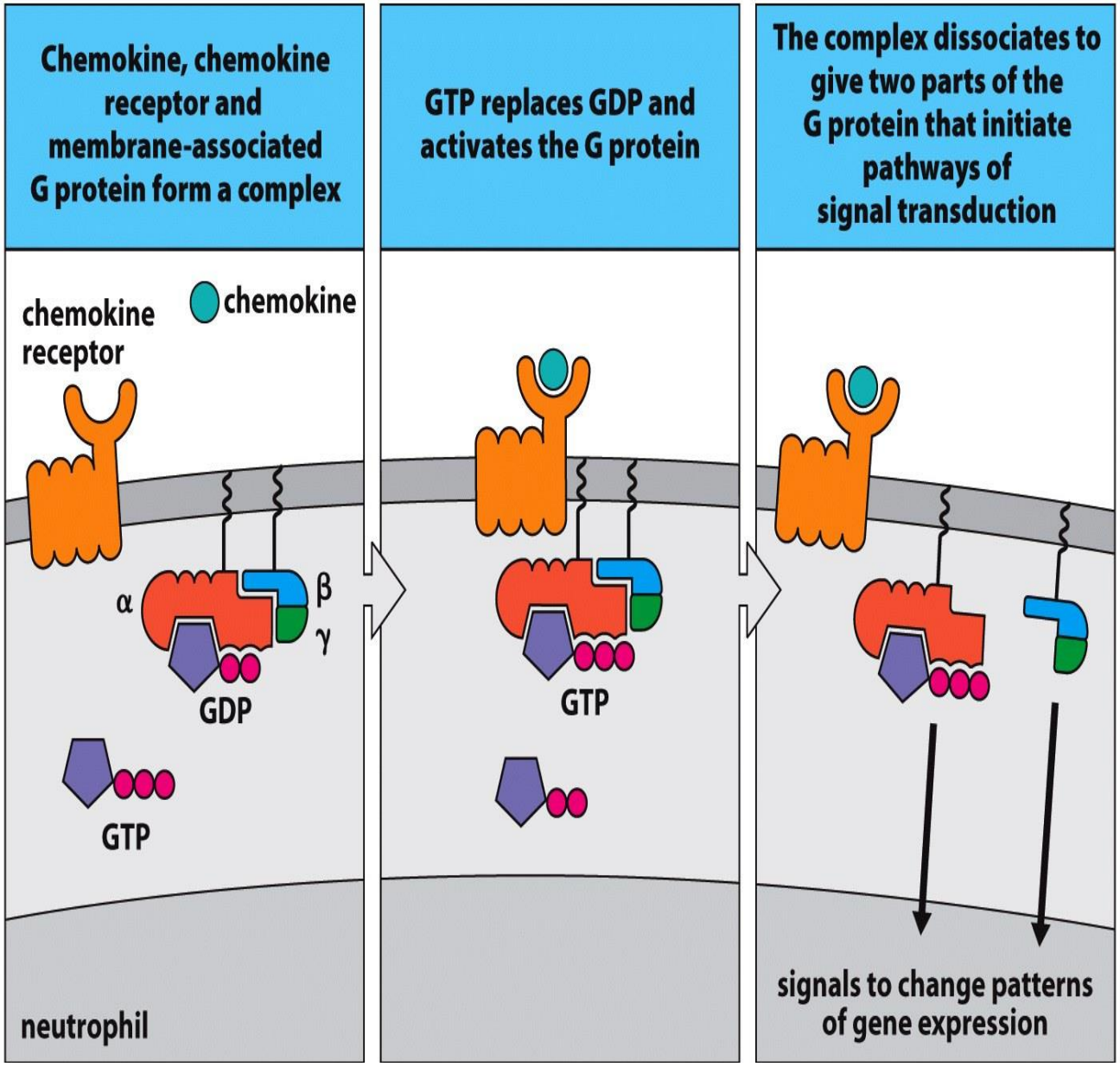


Figure 2.28 Chemokines bind to chemokine receptors that are G-protein-coupled receptors. Chemokine receptors are a family of seven-span receptors that have seven transmembrane helices. When a chemokine such as CXCL8 binds to its receptor, the receptor associates with an intracellular GTP-binding (G) protein, which in its inactive state consists of three polypeptides (α, β, and γ) and has GDP bound. On association with the chemokine receptor GDP is replaced by GTP which leads to dissociation of the α chain of the G protein from the β and γ chain. The α chain, and to a lesser extent the β and γ chain, bind to other cellular proteins that generate signals which change the cell's pattern of gene expression.

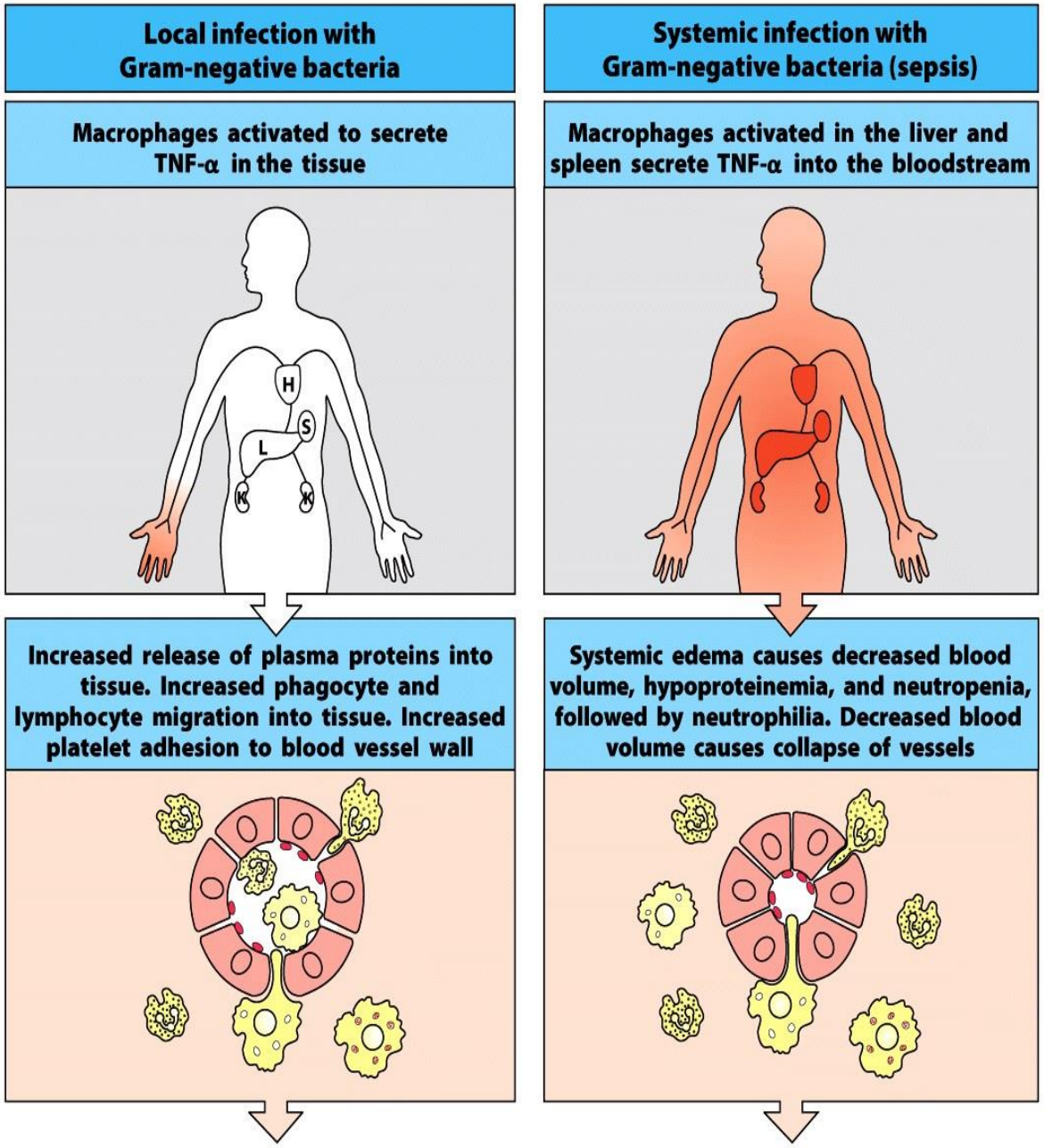


Figure 2.29 TNF-α released by macrophages induces protection at the local level but can lead to catastrophe when released systemically. The panels on the left describe the causes and consequences of the release of TNF-α within a local area of infection. In contrast, the panels on the right describe the causes and consequences of the release of TNF-α throughout the body. The initial effects of TNF-α are on the endothelium of blood vessels, especially venules. It causes increased blood flow, vascular permeability, and endothelial adhesiveness for white blood cells and platelets. These events cause the blood in the venules to clot, preventing the spread of infection and directing extracellular fluid to the lymphatics and lymph nodes, where the adaptive immune response is activated. When an infection develops in the blood, the systemic release of TNF-α and the effect it has on the venules in all tissues simultaneously induce a state of shock that can lead to organ failure and death. H, heart; K, kidney; L, liver; S, spleen.

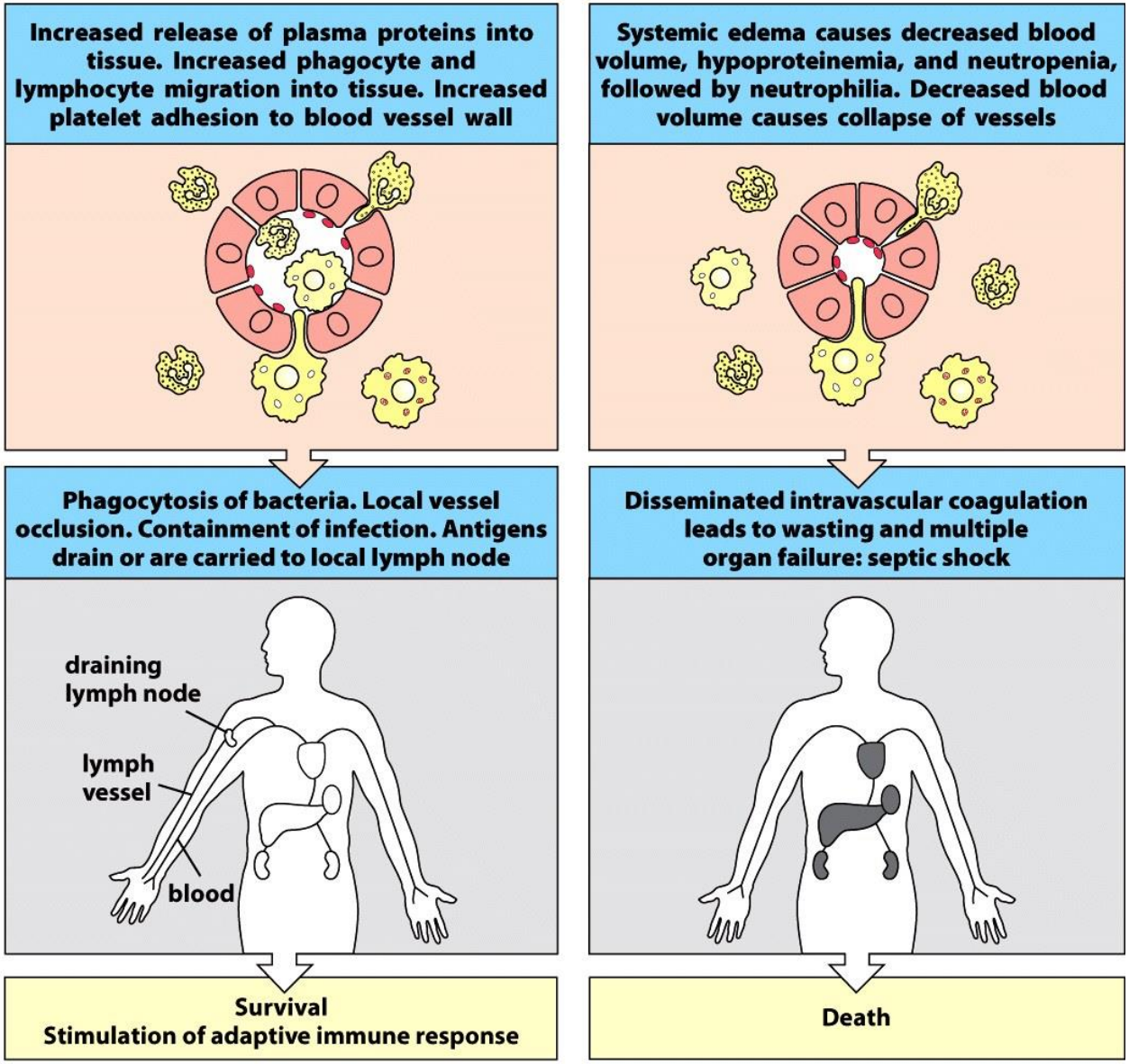


Figure 2.29 TNF-α released by macrophages induces protection at the local level but can lead to catastrophe when released systemically. The panels on the left describe the causes and consequences of the release of TNF-α within a local area of infection. In contrast, the panels on the right describe the causes and consequences of the release of TNF-α throughout the body. The initial effects of TNF-α are on the endothelium of blood vessels, especially venules. It causes increased blood flow, vascular permeability, and endothelial adhesiveness for white blood cells and platelets. These events cause the blood in the venules to clot, preventing the spread of infection and directing extracellular fluid to the lymphatics and lymph nodes, where the adaptive immune response is activated. When an infection develops in the blood, the systemic release of TNF-α and the effect it has on the venules in all tissues simultaneously induce a state of shock that can lead to organ failure and death. H, heart; K, kidney; L, liver; S, spleen.

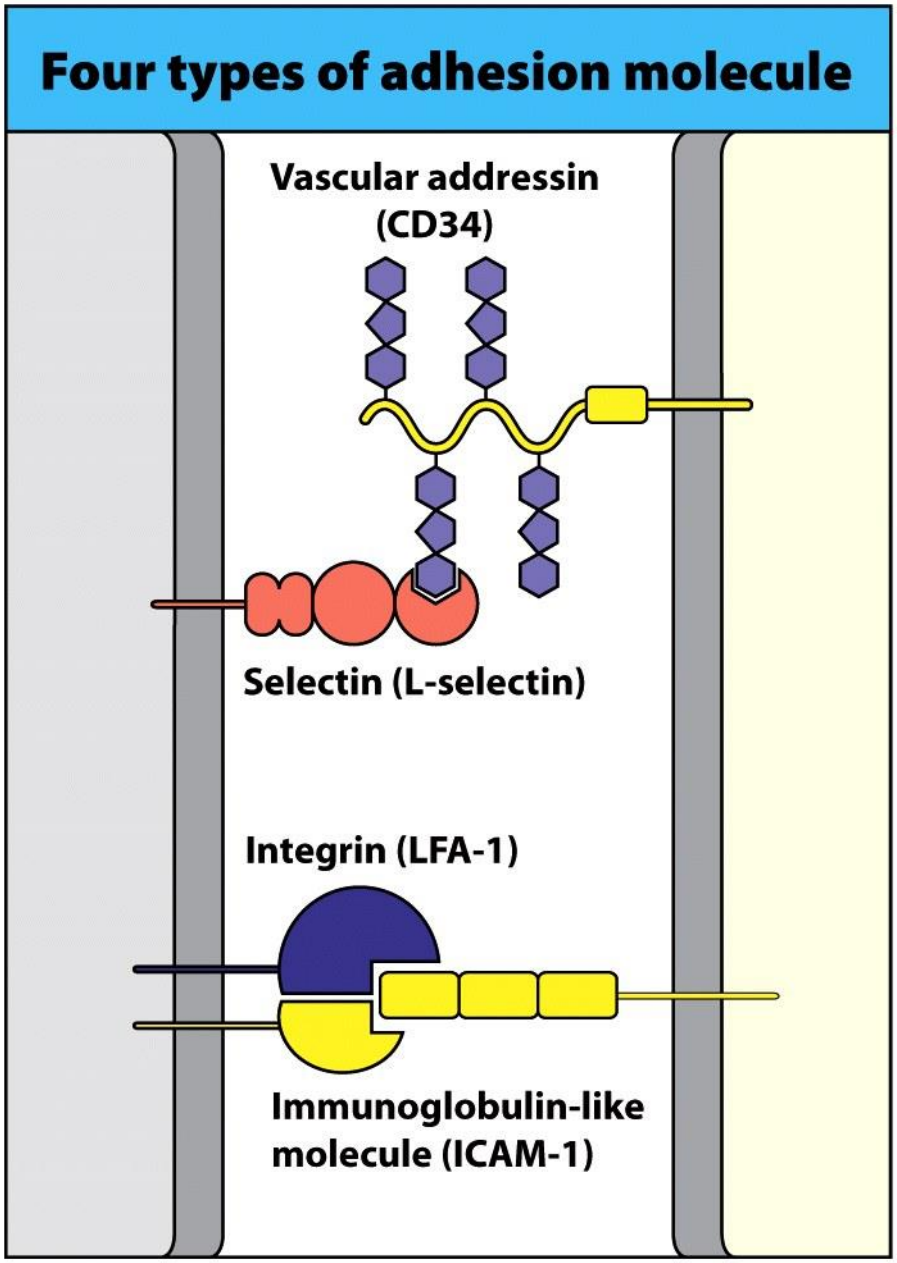
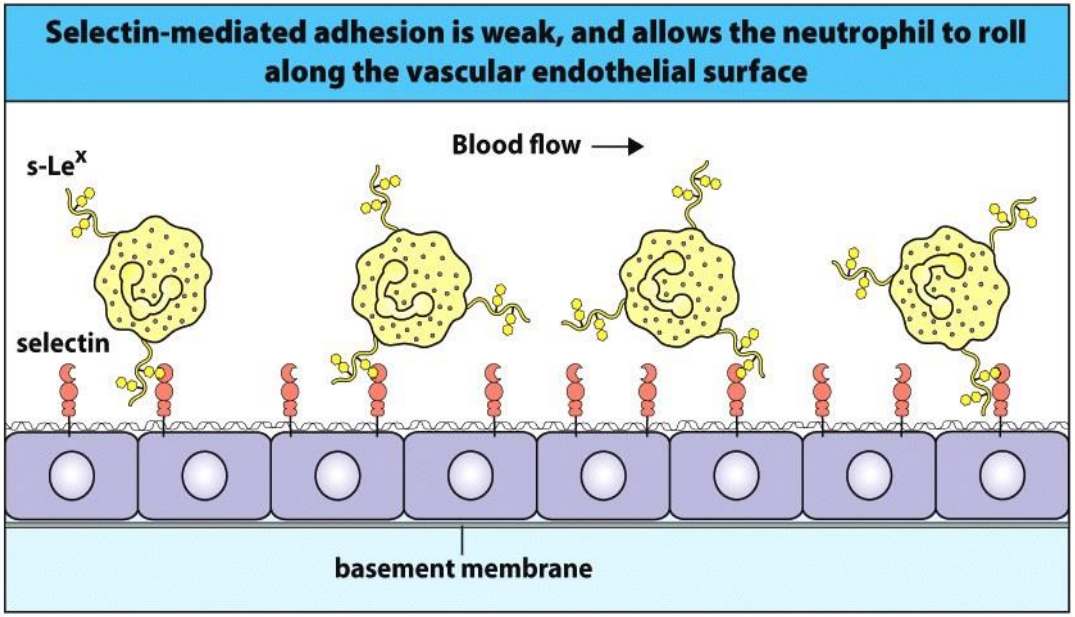
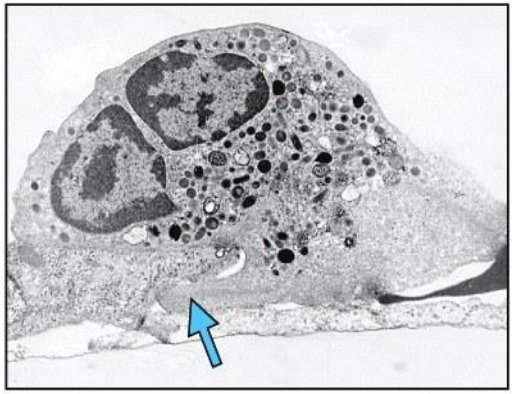


Figure 2.30 Adhesion of leukocytes to vascular endothelium involves interactions between adhesion molecules of four structurally different types. These are the vascular addressins, the selectins, the integrins, and proteins containing immunoglobulin-like domains.





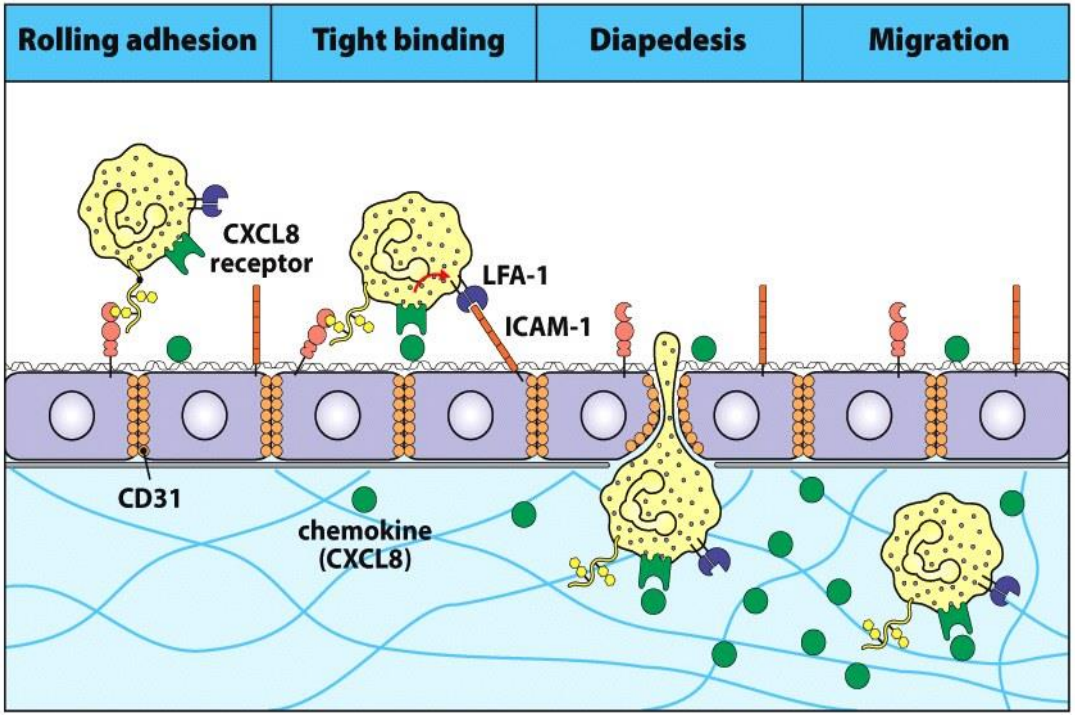


Figure 2.31 Neutrophils are directed to sites of infection through interactions between adhesion molecules.

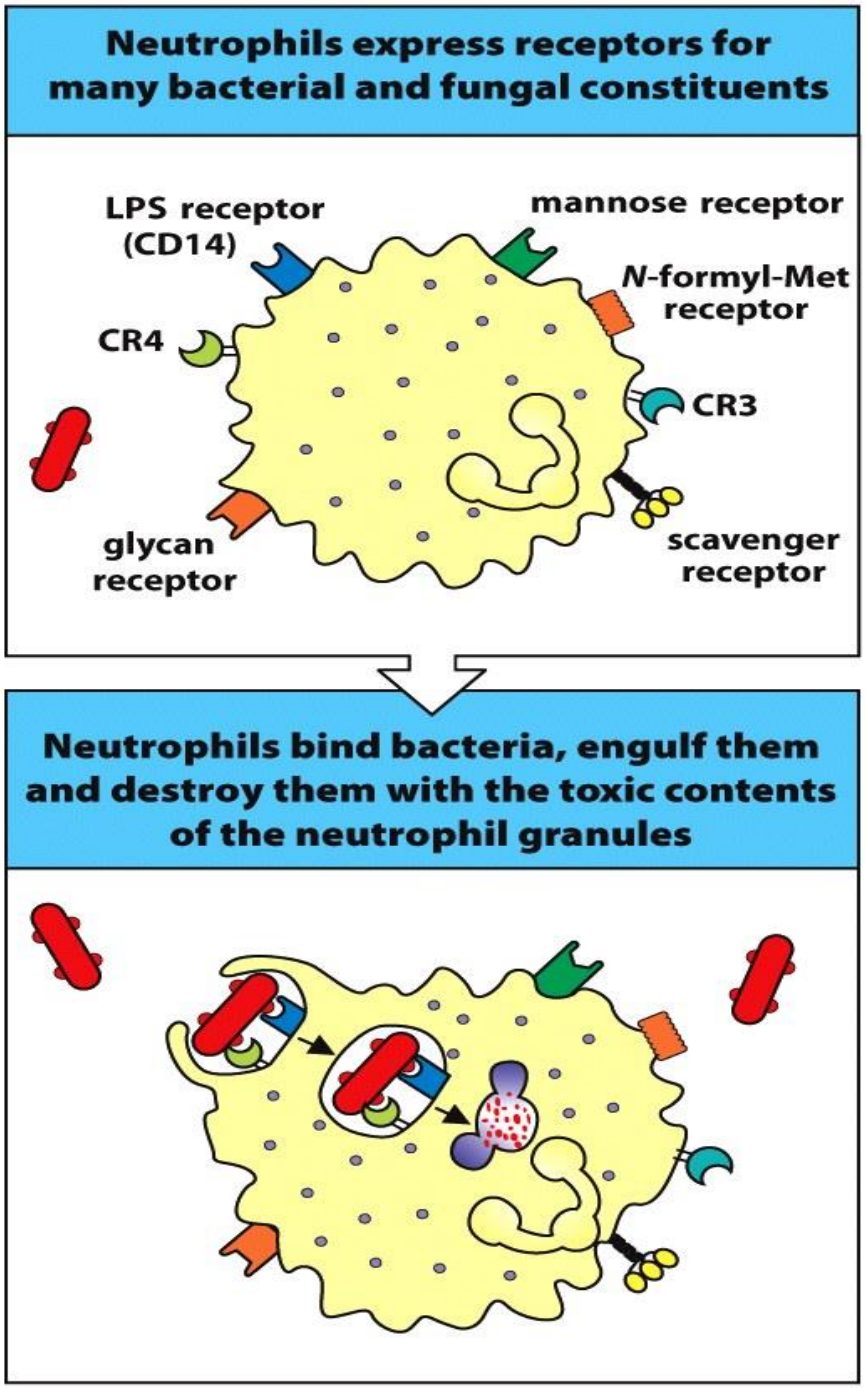


Figure 2.32 Bacteria binding to neutrophil receptors induce phagocytosis and microbial killing. Upper panel: the neutrophil has several different receptors for microbial products. Lower panel: the mechanism of phagocytosis for two such receptors, CD14 and CR4, which are specific for bacterial lipopolysaccharide (LPS). A bacterium binding to these receptors stimulates its phagocytosis and degradation.

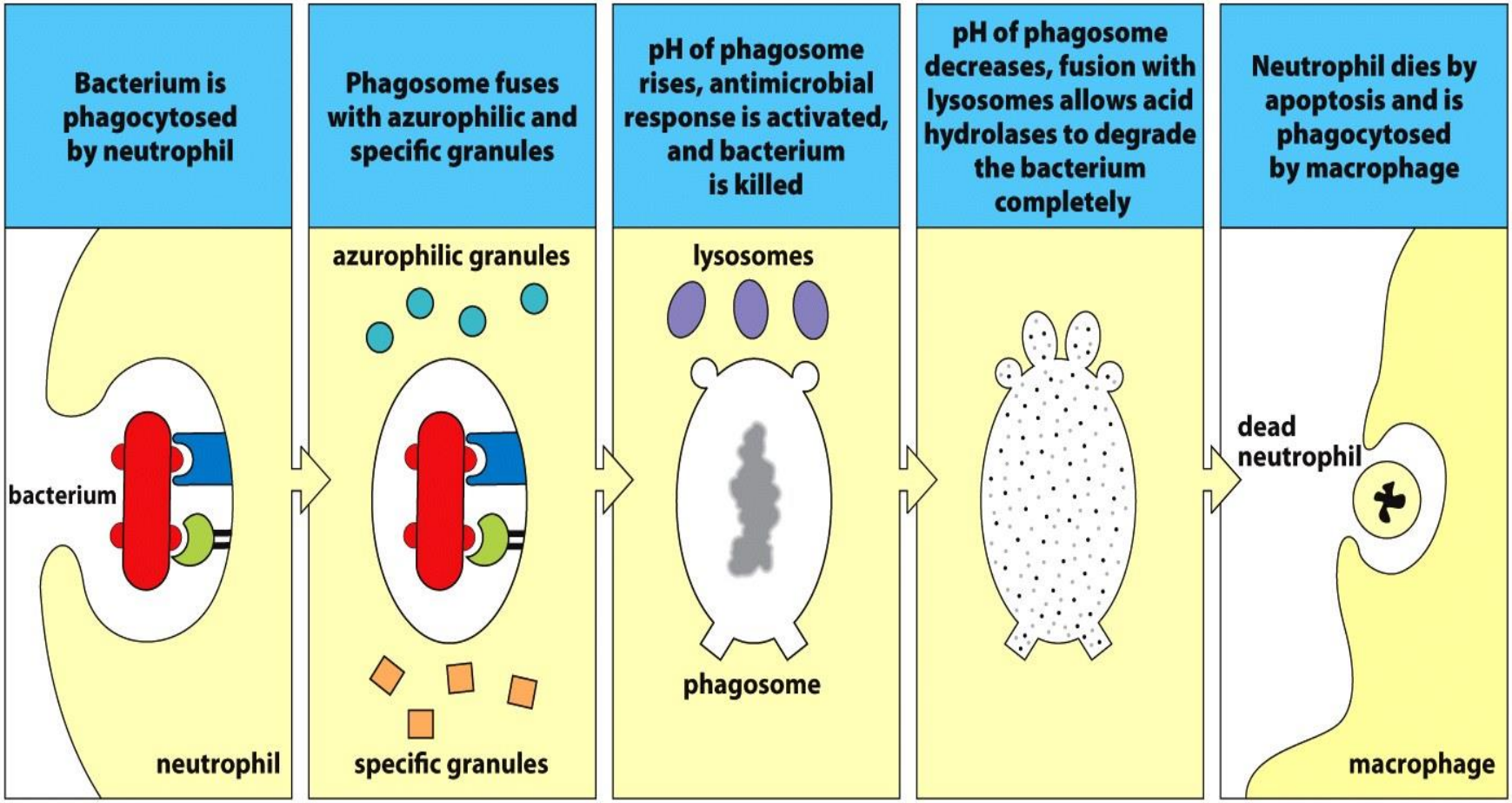


Figure 2.33 Killing of bacteria by neutrophils involves the fusion of two types of granule and lysosomes with the phagosome. After phagocytosis (first panel), the bacterium is held in a phagosome inside the neutrophil. The neutrophil's azurophilic granules and specific granules fuse with the phagosome, releasing their contents of antimicrobial proteins and peptides (second panel). NAPDH oxidase components contributed by the specific granules enable the respiratory burst to occur, which raises the pH of the phagosome. Antimicrobial proteins and peptides are activated and the bacterium is damaged and killed. A subsequent decrease in pH and the fusion of the phagosome with lysosomes containing acid hydrolases results in complete degradation of the bacterium. The neutrophil dies and is phagocytosed by a macrophage.

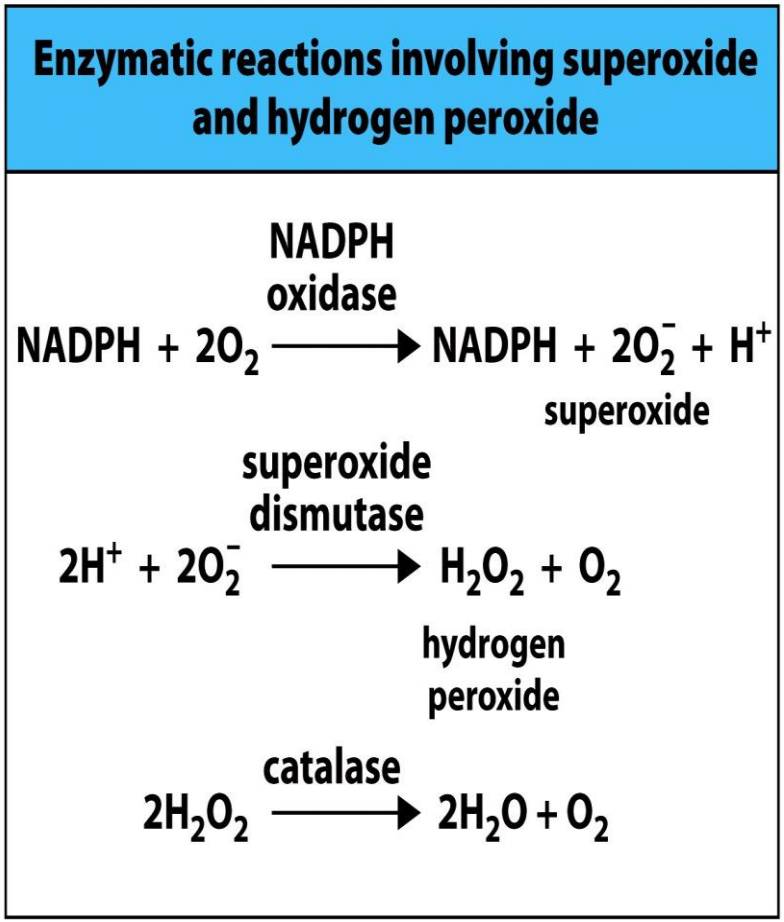


Figure 2.34 Killing of bacteria by neutrophils is dependent on a respiratory burst. In the absence of infection the antimicrobial proteins and peptides in neutrophil granules are kept inactive at low pH. After the granules fuse with the phagosome the pH within the phagosome is raised through the first two reactions, involving the enzymes NADPH oxidase and superoxide dismutase. Each round of these reactions eliminates a hydrogen ion, thereby reducing the acidity of the phagosome. A product of the two reactions is hydrogen peroxide, which has the potential to damage human cells. (In hair salons and the manufacture of paper it is used as a powerful bleach.) The third reaction, involving catalase, the most efficient of all enzymes, promptly gets rid of the hydrogen peroxide produced during the neutrophil's respiratory burst, raising the pH of the phagosome and enabling activation of the antimicrobial peptides and proteins.

Fungus
Aspergillus fumigatus
Bacteria
Staphylococcus aureus
Chromobacterium violaceum
Burkholderia cepacia
Nocardia asteroides
Salmonella typhimurium
Serratia marcescens
Mycobacterium fortuitum
Several species of *Klebsiella*
Escherichia coli
Several species of *Actinomyces*
Legionella bosmanii
Clostridium difficile

Figure 2.35 The species of fungi and bacteria most commonly responsible for infections in chronic granulomatous disease.

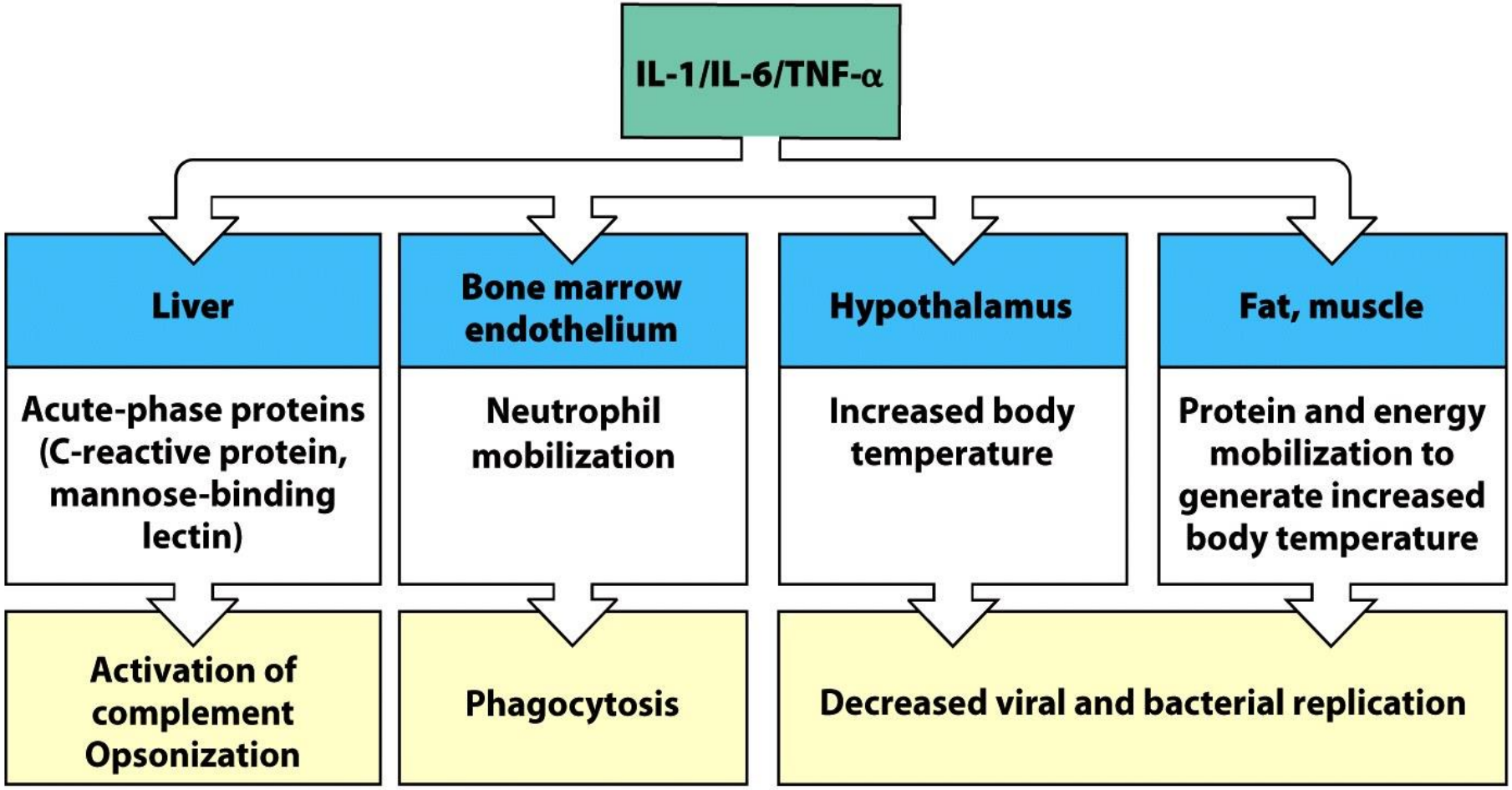


Figure 2.36 The macrophage-produced cytokines TNF-α, IL-1, and IL-6 have a spectrum of biological activity.

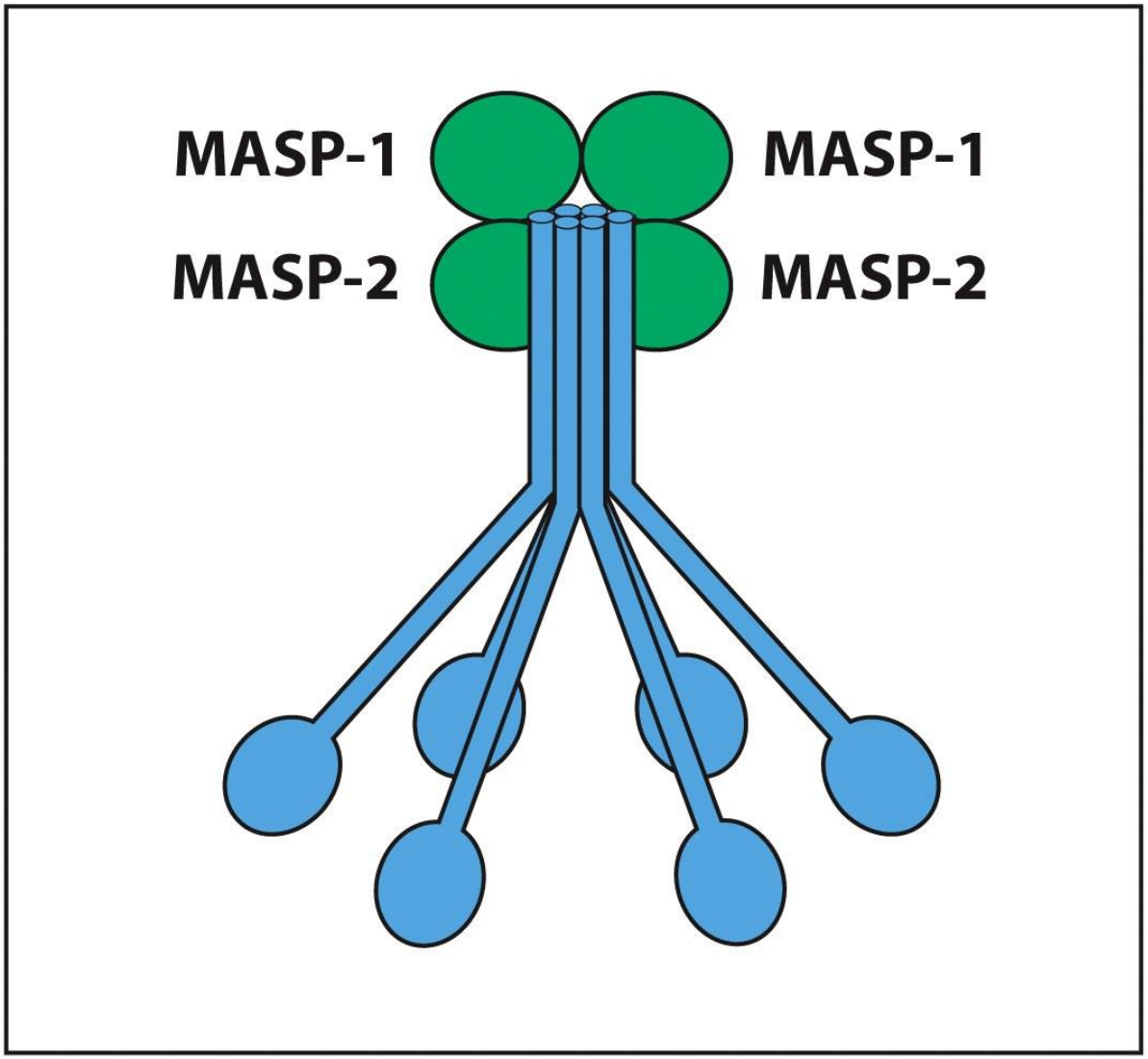


Figure 2.37 Structure of mannose-binding lectin. It resembles a bunch of flowers, with each flower composed of three identical polypeptides. The stalks are rigid triple helices like collagen, with a single bend; each flower comprises three carbohydrate-binding domains. Associated with the mannose-binding lectin (blue) are the mannose-binding lectin associated serine proteases (MASP) 1 and 2.

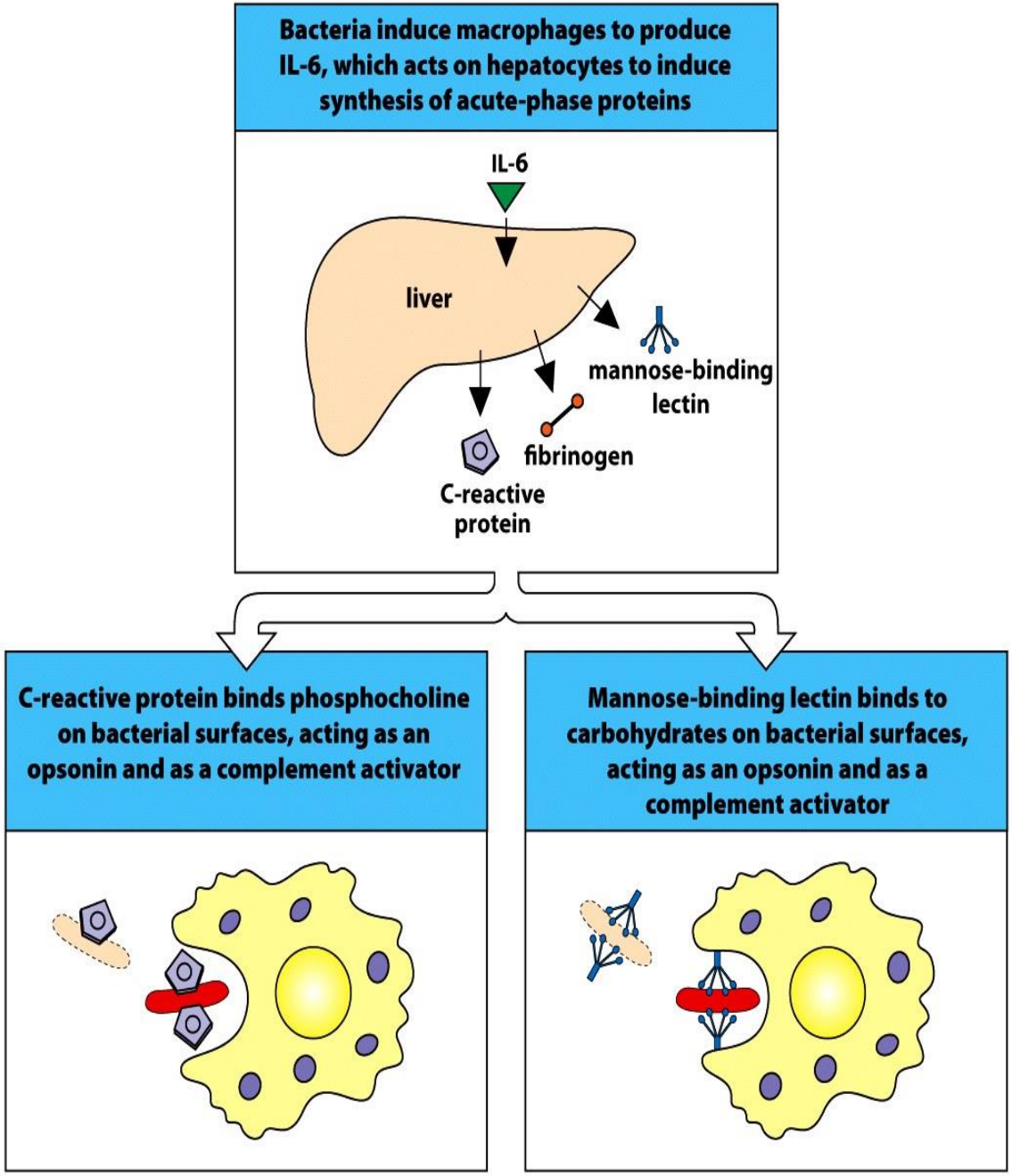


Figure 2.38 The acute-phase response increases the supply of the recognition molecules of innate immunity. Acute-phase proteins are produced by liver cells in response to the cytokines released by phagocytes in the presence of bacteria. In humans they include C-reactive protein, fibrinogen, and mannose-binding lectin. Both C-reactive protein and mannose-binding lectin bind to structural features of bacterial cell surfaces that are not found on human cells. On binding to bacteria, they act as opsonins and also activate complement, facilitating phagocytosis and also direct lysis (dashed lines) of the bacteria by the terminal complement components (not shown).

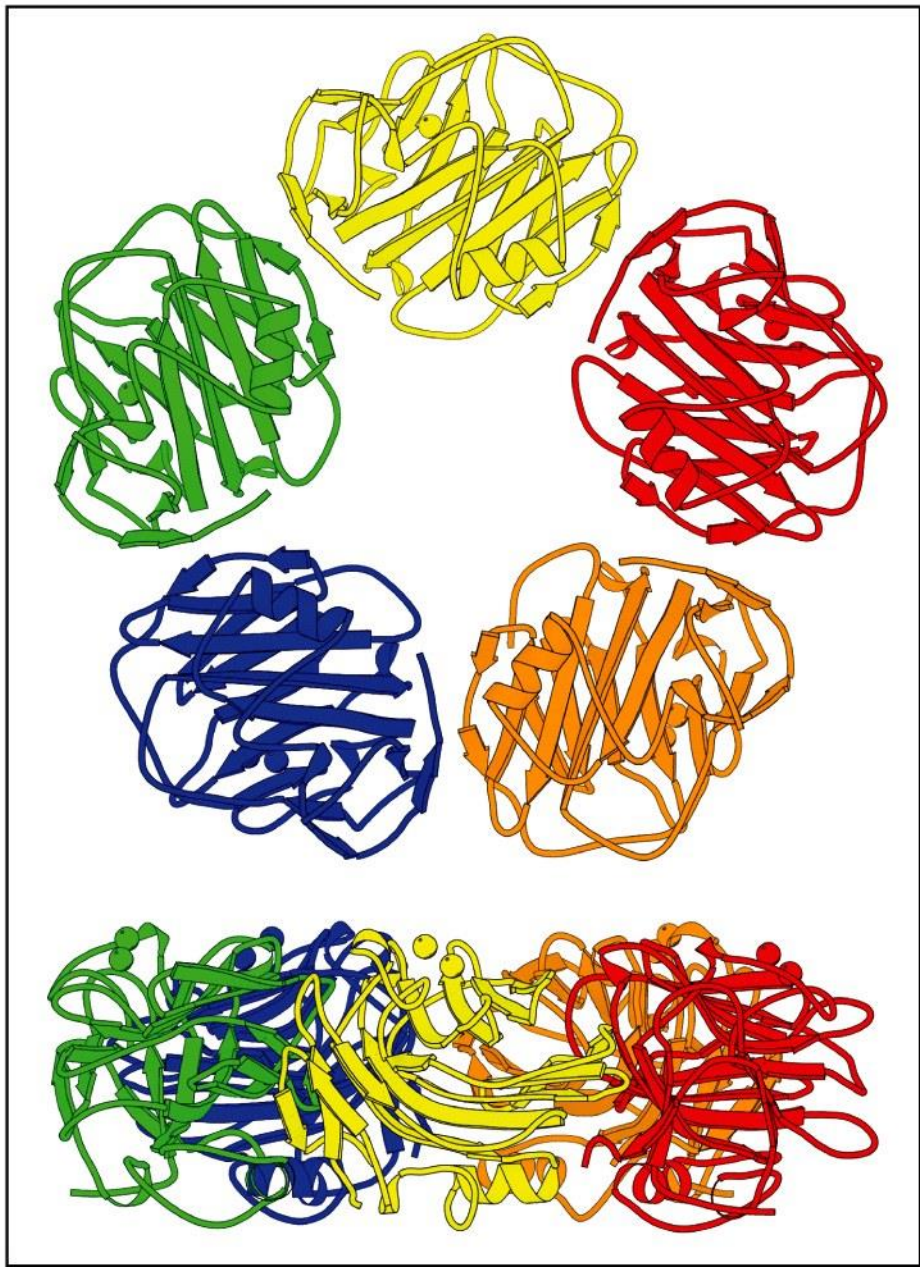


Figure 2.39 The structure of C-reactive protein. C-reactive protein belongs to the pentraxin family, so called because these proteins are composed of five identical subunits. The polypeptide backbones of the five subunits are traced by ribbons of different color. Overall, C-reactive protein resembles a pentagonal slab with a hole in the middle, as is seen by comparing a view from above (upper image) with one from the side (lower image). Images courtesy of Annette Shrive and Trevor Greenhough.

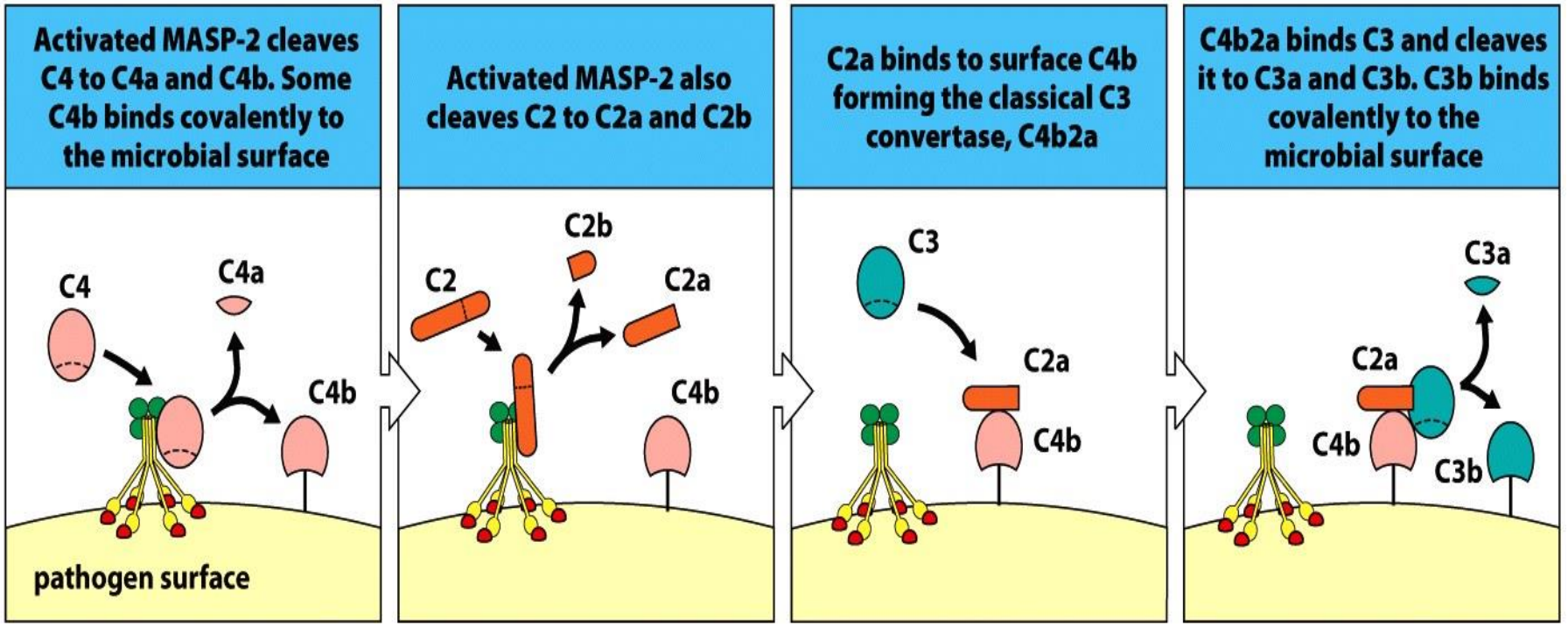


Figure 2.40 The activated MBL complex cleaves C4 and C2 to produce C4b and C2a, which associate to form the classical C3 convertase. First panel: a complex of MBL and MASP-1 and MASP-2 binds to the pathogen surface. This activates MASP-2, which binds and cleaves C4 to reveal the thioester bond of the C4b fragment. C4b becomes covalently bound to the microbial surface. Second panel: C2 binds to the MBL complex and is cleaved by activated MASP-2. Third panel: the C2a fragment binds to C4b to form the classical C3 convertase, C4bC2a. Fourth panel: C3 is bound and cleaved by C4bC2a. The thioester bond of the C3b fragment is exposed and C3b becomes covalently bound to the microbial surface.

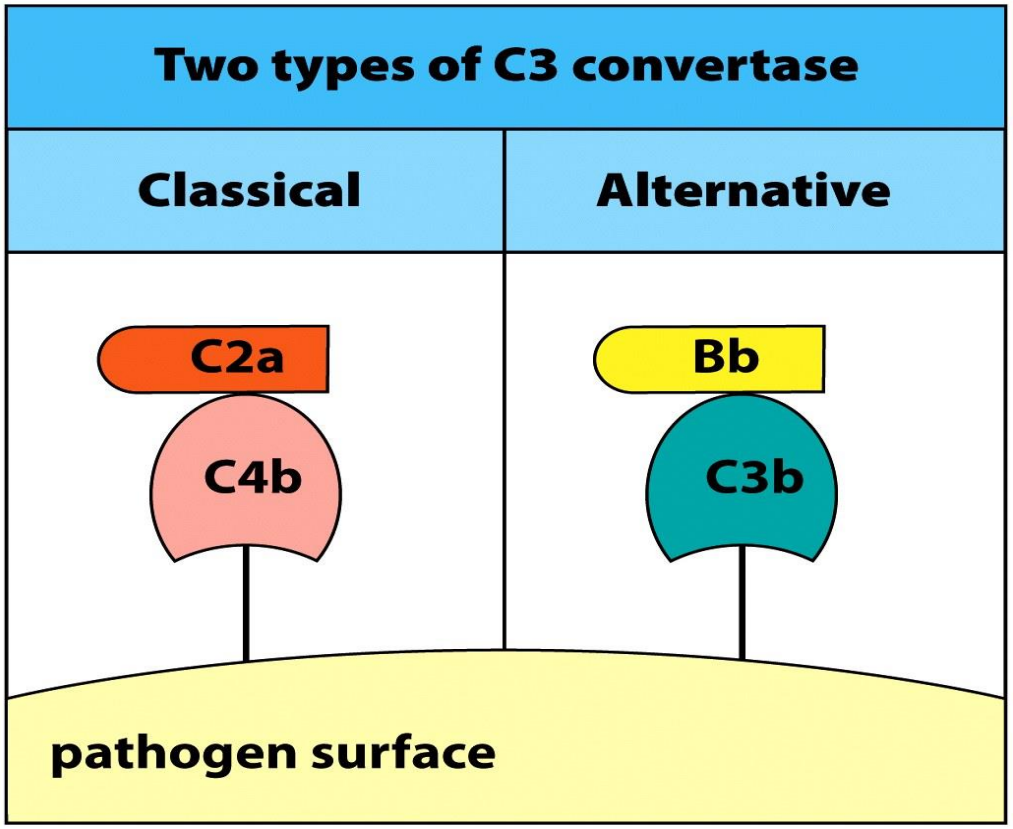


Figure 2.41 The two types of C3 convertase have similar structures and functions. In the C3 convertase produced by the classical pathway, C4bC2a, the activated protease C2a cleaves C3 to C3b and C3a (not shown). In the analogous C3 convertase of the alternative pathway, C3bBb, the activated protease Bb carries out exactly the same reaction.

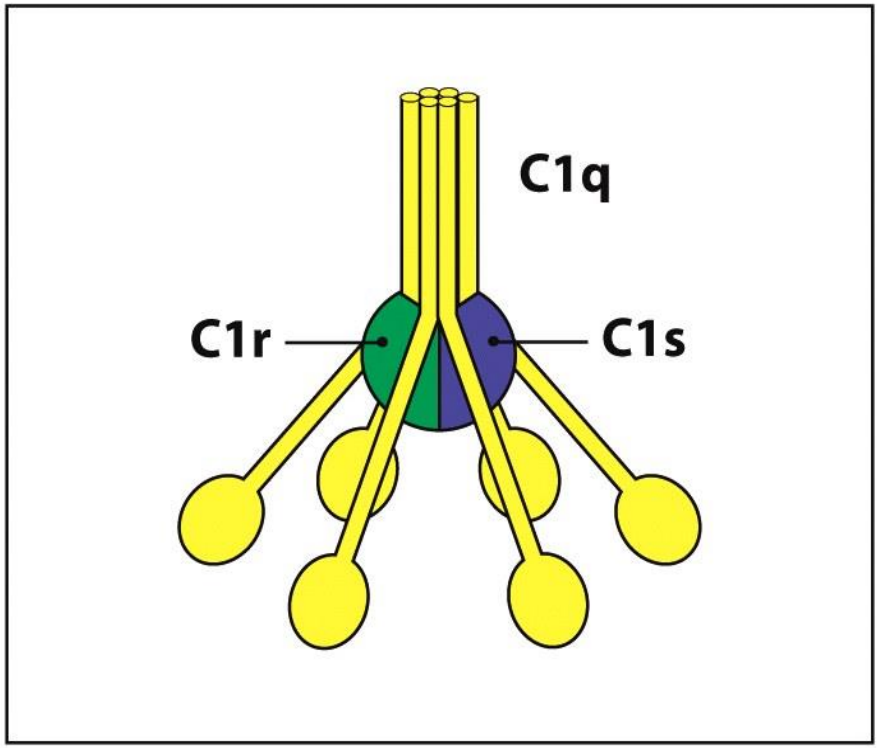


Figure 2.42 The complement component C1. The C1 molecule consists of a complex of C1q, C1r, and C1s. The C1q component consists of six identical subunits, each with one binding site for the Fc region of IgM or IgG and extended amino-terminal stalk regions that interact with each other and with two molecules each of the proteases C1r and C1s. The electron micrograph on the right contains images of three C1q molecules. Photograph courtesy of K.B.M. Reid.

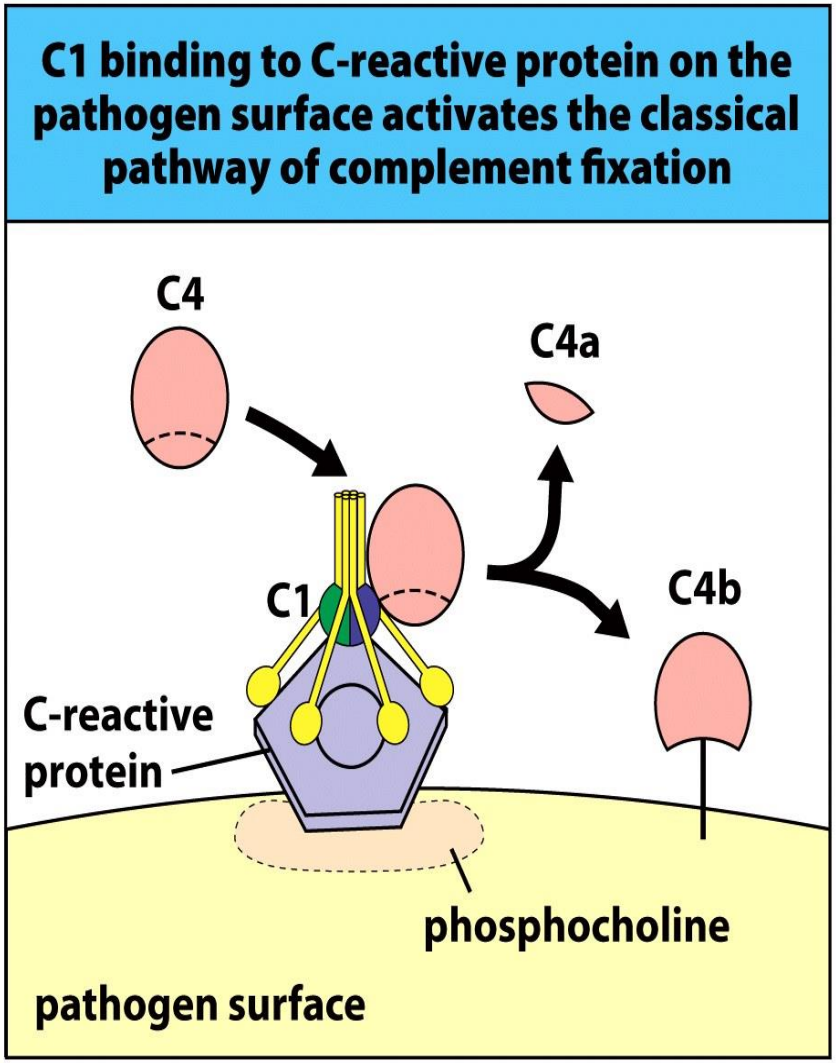


Figure 2.43 C-reactive protein can initiate the classical pathway of complement activation. C-reactive protein bound to phosphocholine on bacterial cell surfaces binds complement component C1, resulting in the cleavage of C4 and opsonization of the bacterial surface with C4b.

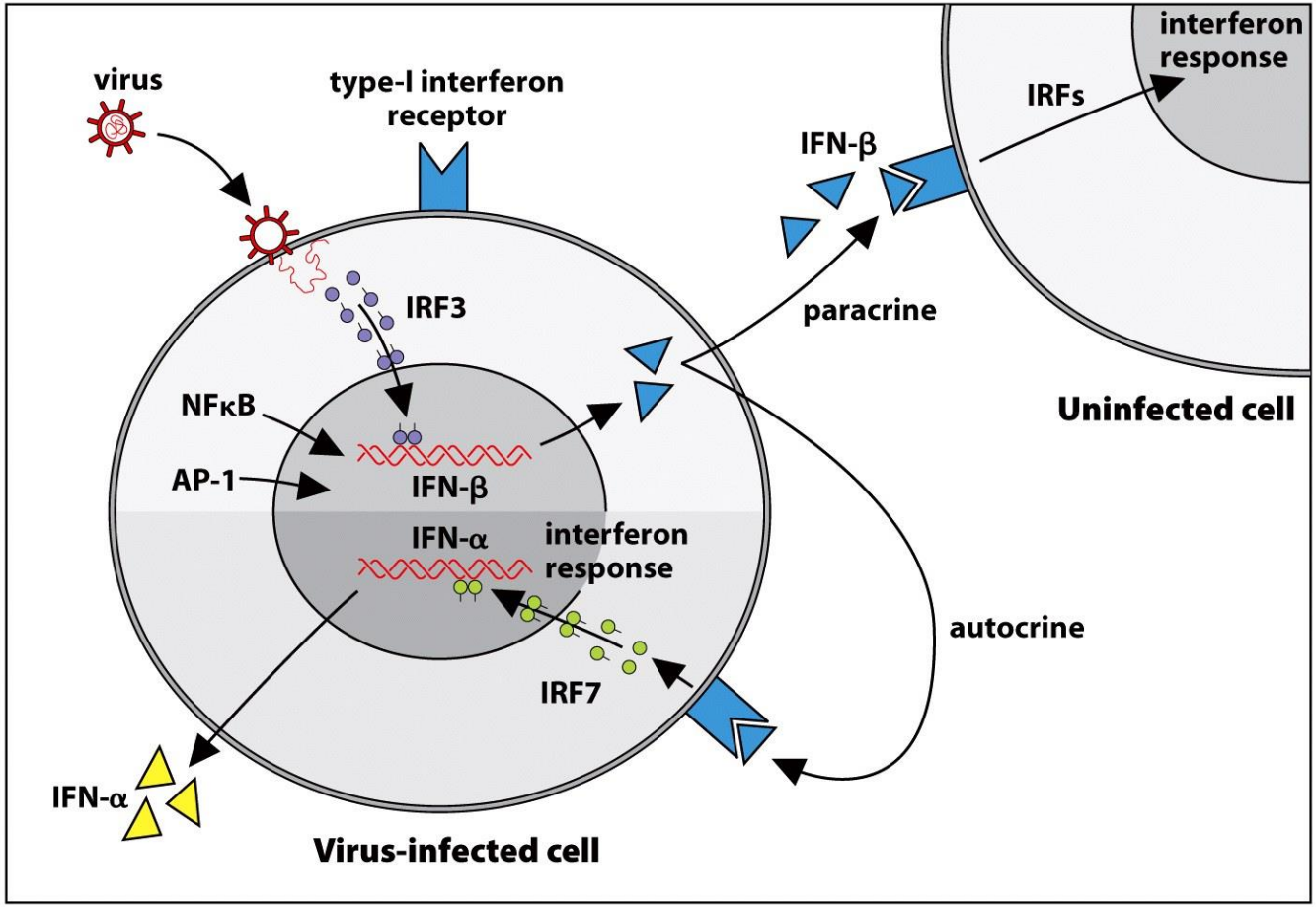


Figure 2.44 Virus-infected cells are stimulated to produce type I interferons. The cell on the left is infected with a virus that triggers signals that lead to the phosphorylation, dimerization, and passage to the nucleus of the transcription factor interferon-response factor 3 (IRF3). Transcription factors NFκB and AP-1 are also mobilized and coordinate with IRF3 to turn on transcription of the interferon (IFN)-β gene. These events are depicted in the upper half of the cell. Secreted IFN-β binds to the interferon receptor on the infected cell surface, acting in an autocrine fashion to mobilize other interferon-response factors and change patterns of gene expression to give the interferon response. These events are depicted in the lower half of the cell, being exemplified by IRF7 turning on transcription of the IFN-α gene, which it does without the need for AP-1 or NFκB. Secreted IFN-β will also bind to the interferon receptor expressed by nearby cells that are not infected by the virus, acting in a paracrine fashion to induce the interferon response that helps these cells to resist infection.

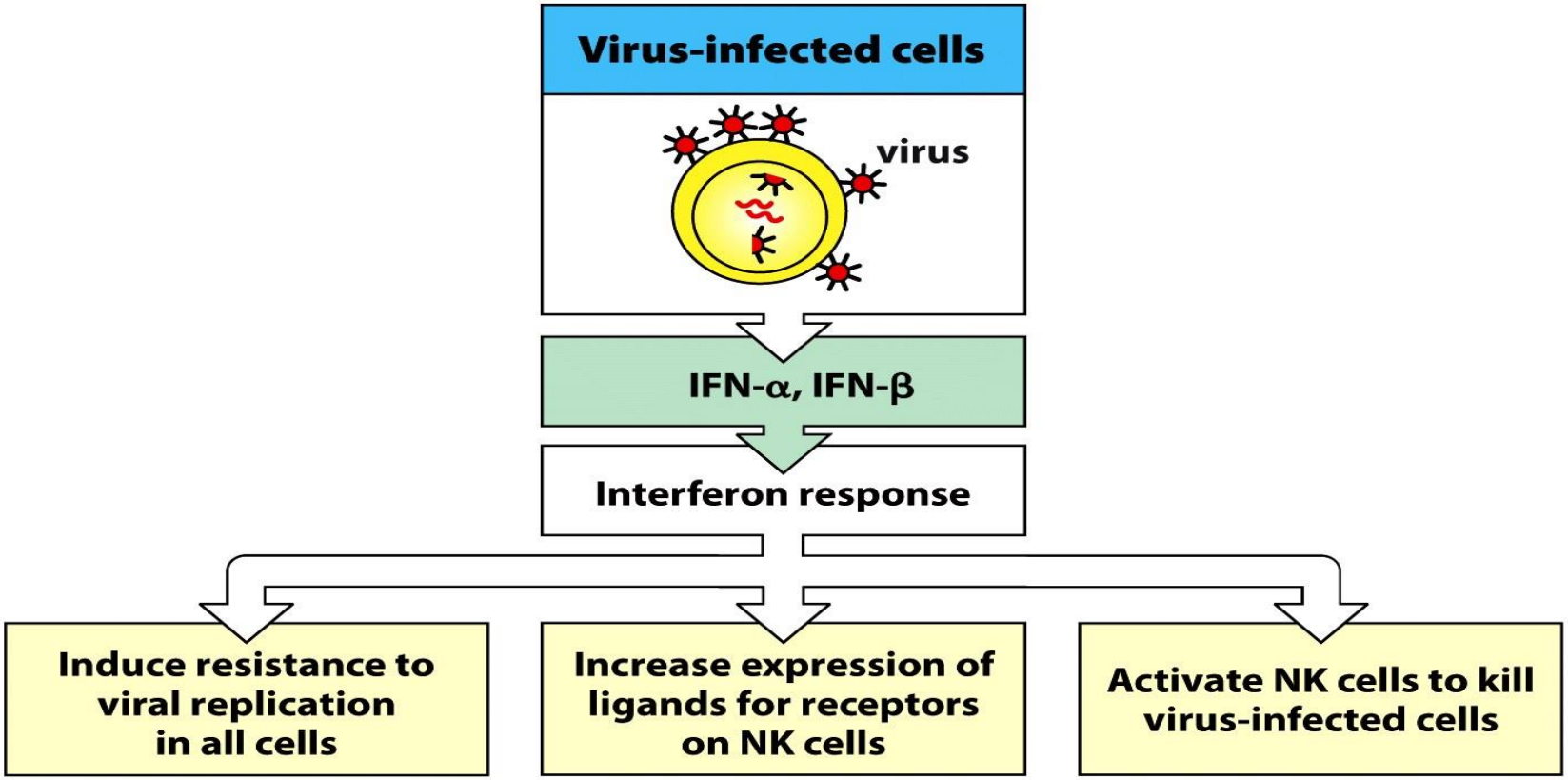


Figure 2.45 Major functions of the type I interferons. Interferon-α and interferon-β (IFN-α and IFN-β) have three major functions. First, they induce resistance to viral replication by activating cellular genes that destroy viral mRNA and inhibit the translation of viral proteins. Second, they increase the expression of ligands for NK cell receptors on virus-infected cells. Third, they activate NK cells to kill virus-infected cells.

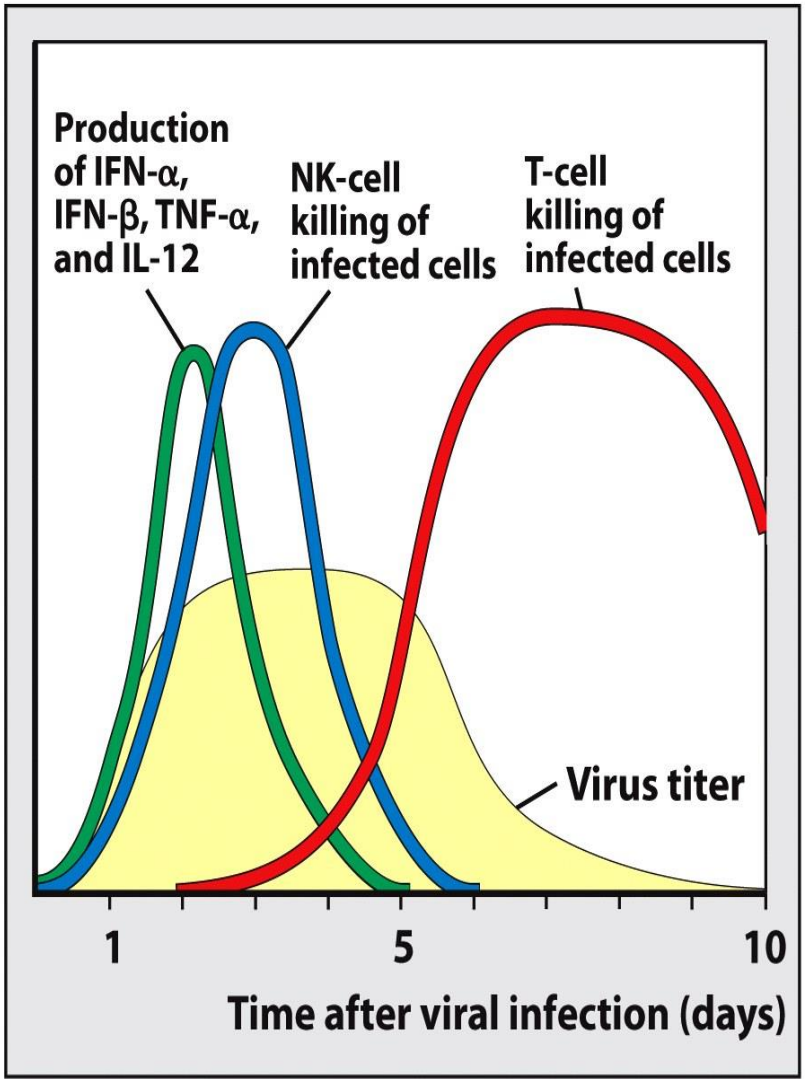


Figure 2.47 NK cells provide an early response to virus infection. The kinetics of the immune response to an experimental virus infection of mice are shown. As a result of infection, a burst of cytokines is secreted, including IFN-α, IFN-β, TNF-α, and IL-12 (green curve). These induce the proliferation and activation of NK cells (blue curve), which are seen as a wave emerging after cytokine production. NK cells control virus replication and the spread of infection while effector killer T cells (red curve) are developing. The level of virus (the virus titer) is given by the curve described by the yellow shading.

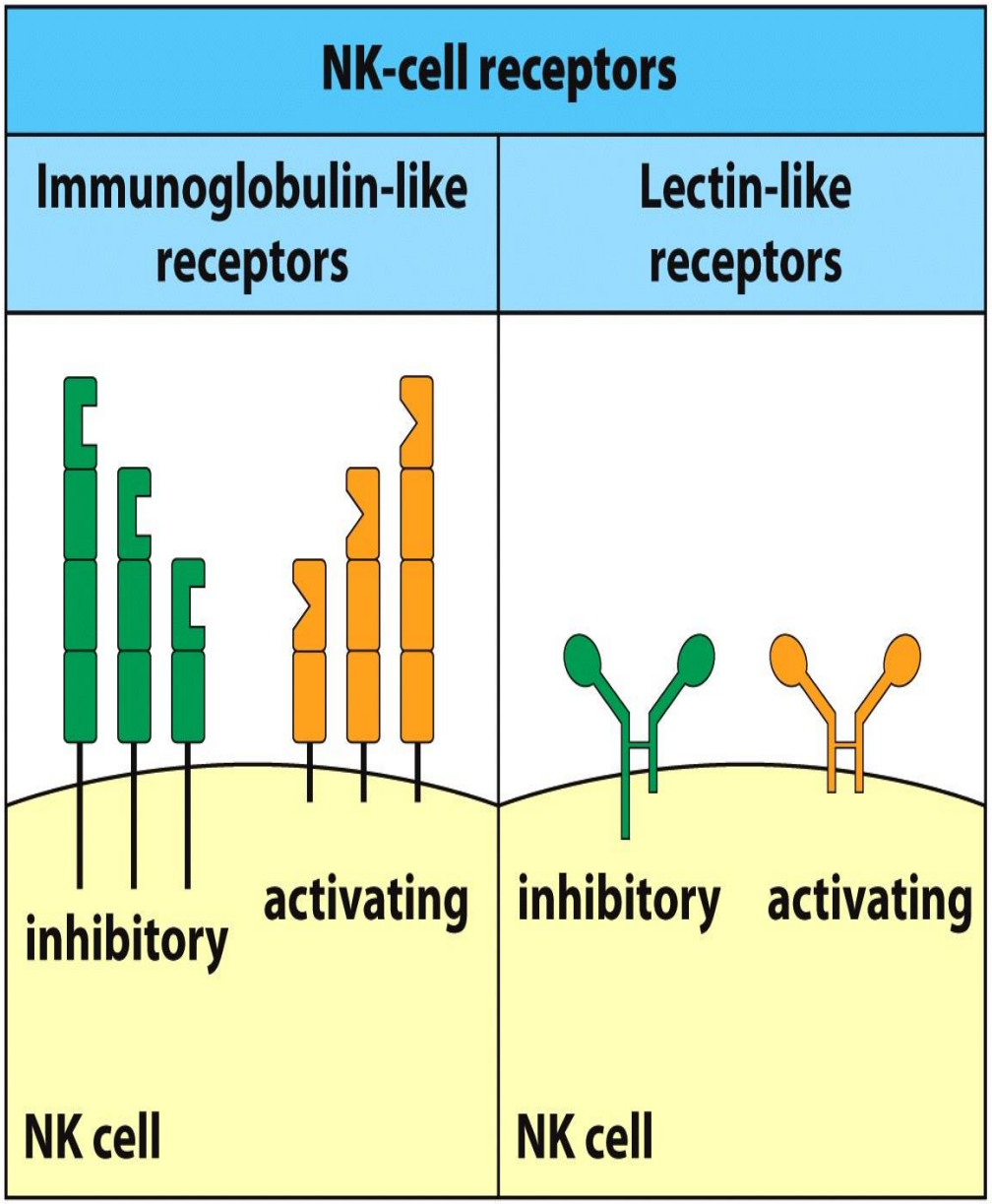


Figure 2.48 Immunoglobulin-like and lectin-like NK-cell receptors. Most NK-cell receptors have extracellular ligand-binding regions that are made up of immunoglobulin domains (left panel) or lectin-like domains resembling that of mannose-binding lectin (right panel). Activating receptors have short cytoplasmic tails and charged amino acid residues in the transmembrane domain that facilitate interaction with intracellular signaling proteins. Inhibitory receptors have long cytoplasmic tails that contain a short amino acid sequence motif called an immunoreceptor tyrosine-based inhibitory motif (ITIM), which binds protein phosphatases that act to inhibit the activating pathways.

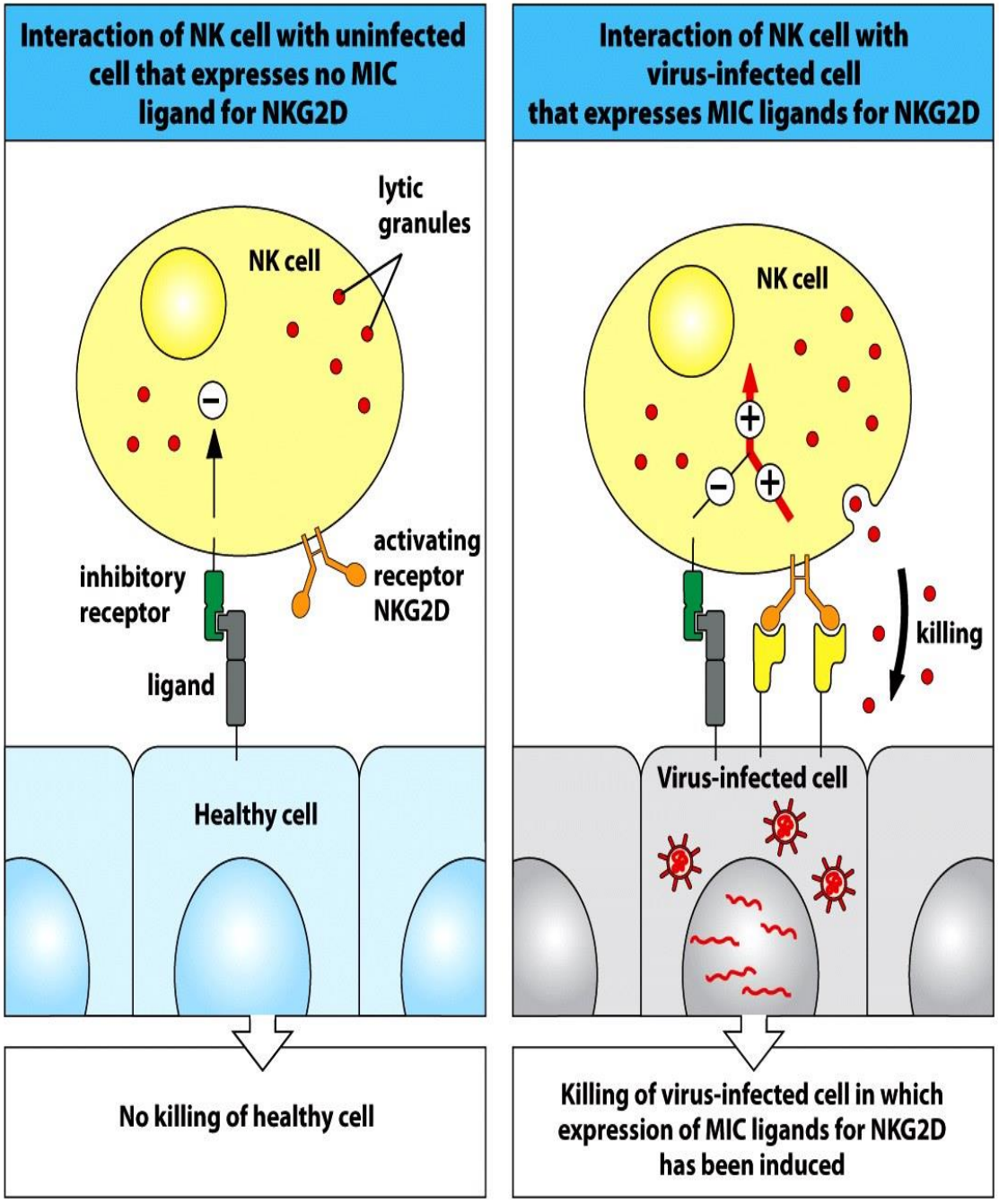


Figure 2.49 NK cell receptors distinguish unhealthy cells from healthy cells. NK cells have activating and inhibitory cell-surface receptors. The ligands for NKG2D, an activating receptor present on all human NK cells, are MIC-A and MIC-B, proteins that are not expressed by healthy cells but are expressed by cells stressed by virus infection or other trauma. Healthy cells resist attack by NK cells because signals generated from inhibitory receptors dominate those generated from activating receptors (left panel). NK cells attack the virus-infected cell because the signal generated by NKG2D interacting with MIC proteins tips the balance from inhibition to activation.