

# Innate Immunity

GSK Immunology

(Graphics from Janeway's Immunobiology)

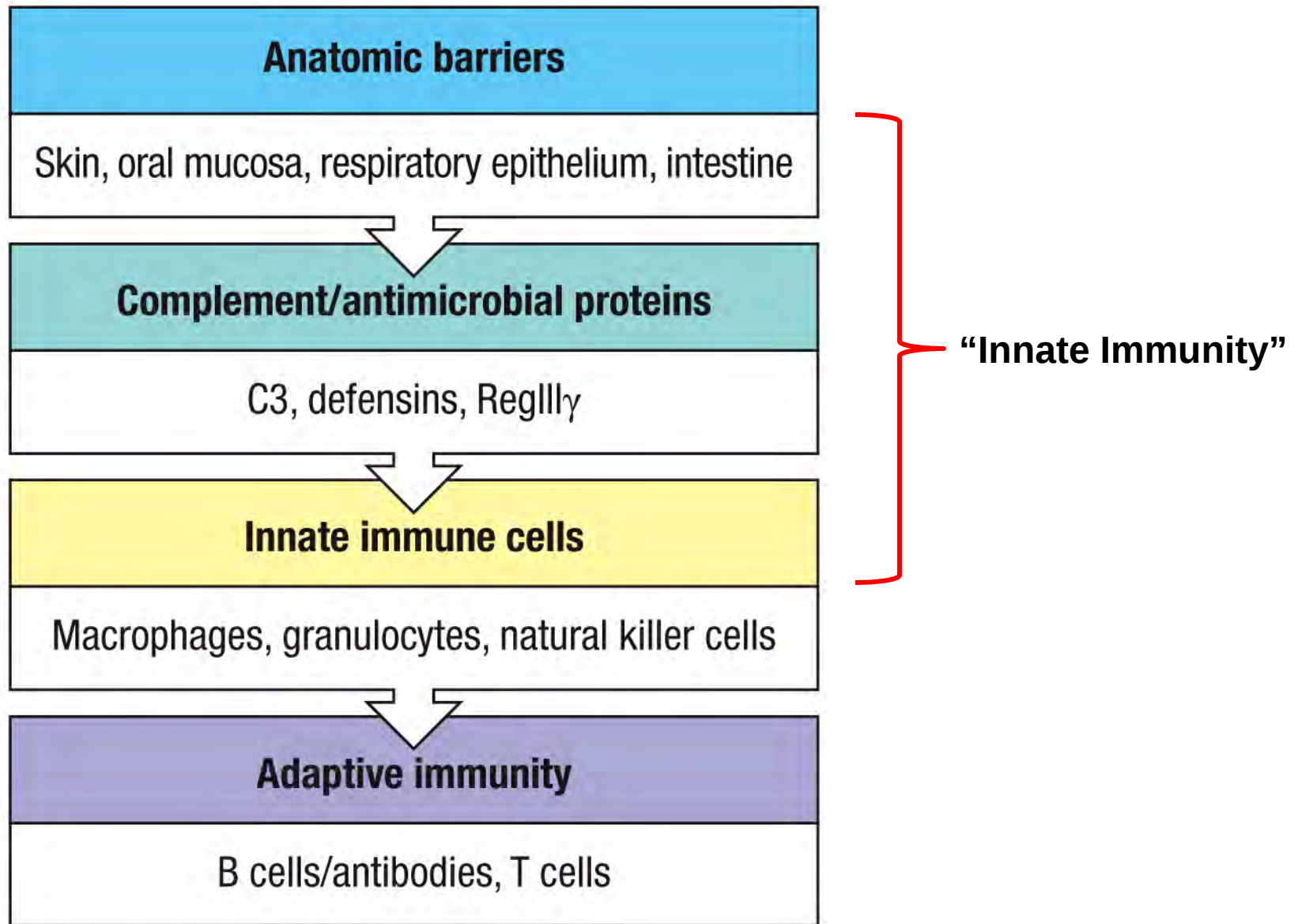


Figure 1.5 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

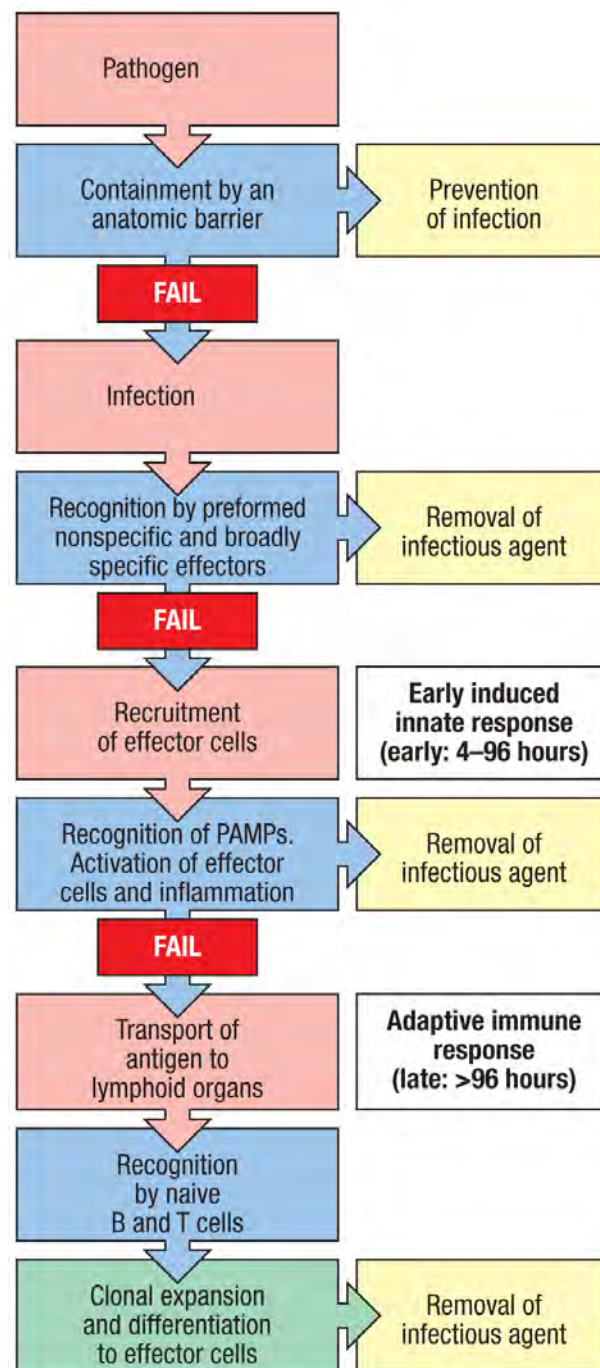


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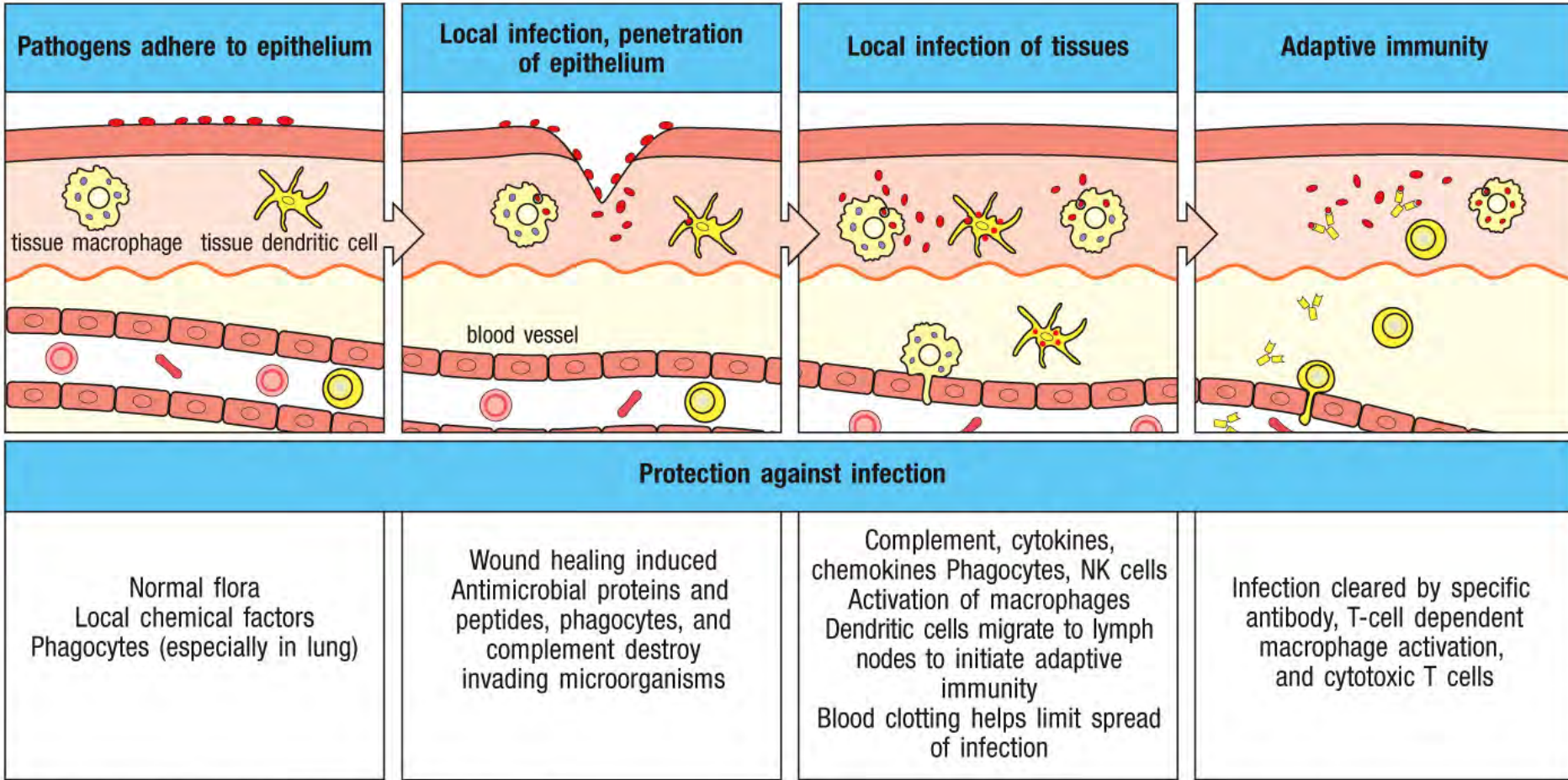


Figure 2.8 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| Phases of the immune response |                                                                                                                                                                                 |                                                   |                      |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------|
| Response                      |                                                                                                                                                                                 | Typical time after infection to start of response | Duration of response |
| Innate immune response        | Inflammation, complement activation, phagocytosis, and destruction of pathogen                                                                                                  | Minutes                                           | Days                 |
| Adaptive immune response      | Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation | Hours                                             | Days                 |
|                               | Activation of antigen-specific B cells                                                                                                                                          | Hours                                             | Days                 |
|                               | Formation of effector and memory T cells                                                                                                                                        | Days                                              | Weeks                |
|                               | Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody                     | Days                                              | Weeks                |
|                               | Emigration of effector lymphocytes from peripheral lymphoid organs                                                                                                              | A few days                                        | Weeks                |
|                               | Elimination of pathogen by effector cells and antibody                                                                                                                          | A few days                                        | Weeks                |
| Immunological memory          | Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection                                                             | Days to weeks                                     | Can be lifelong      |

Figure 1.7 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

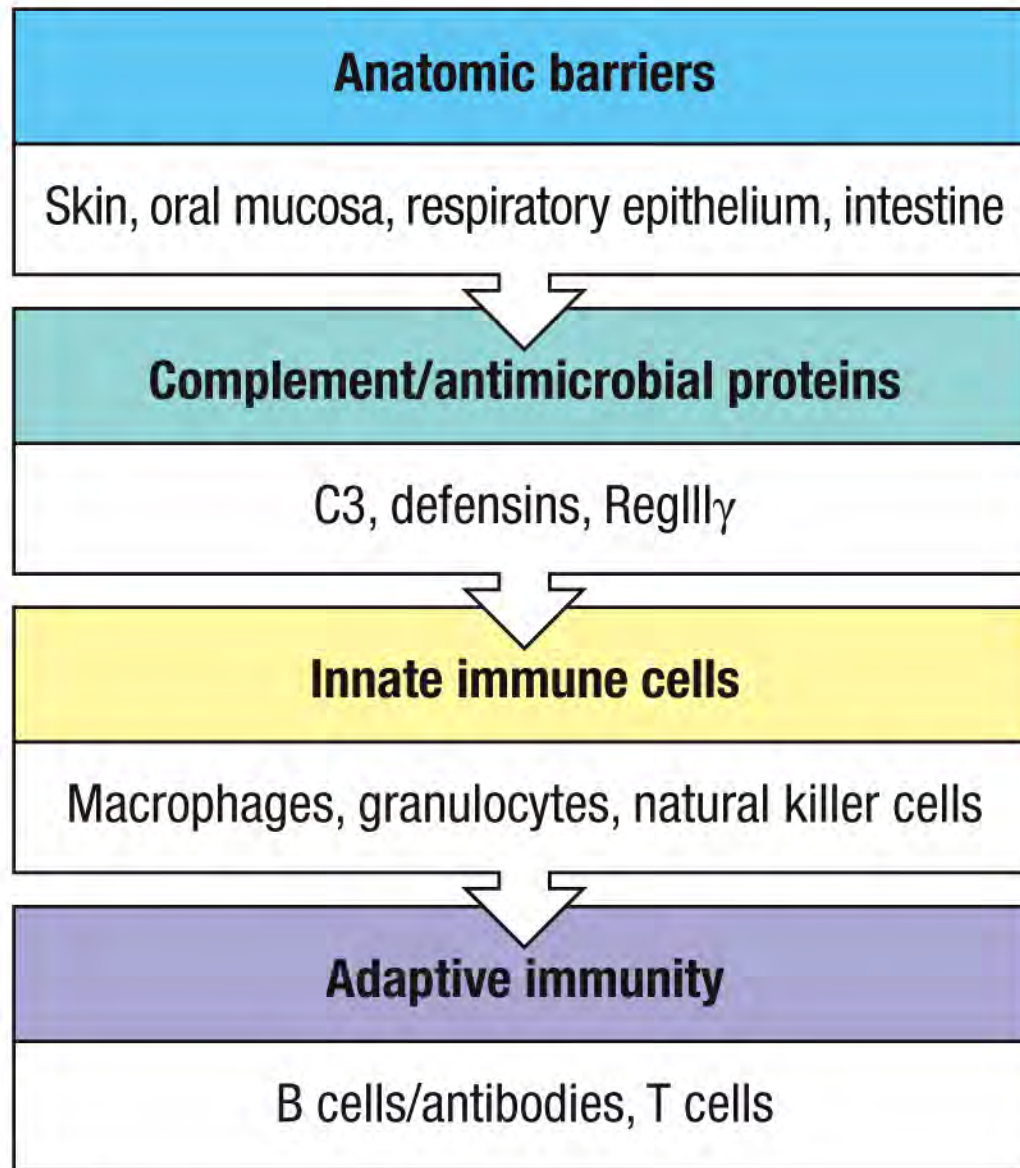
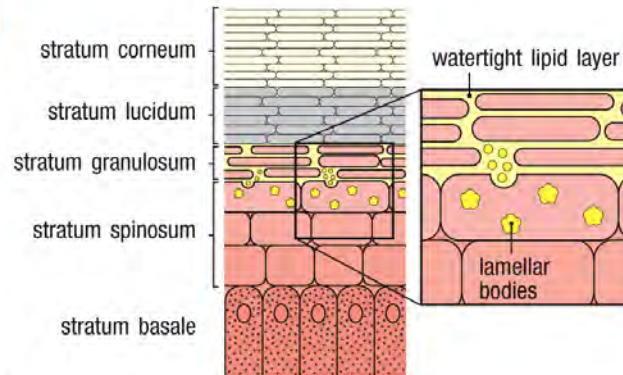
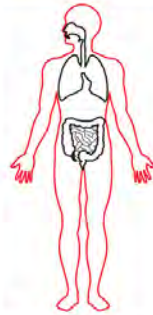


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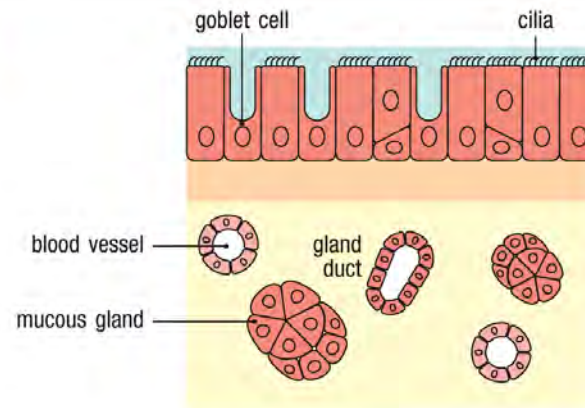
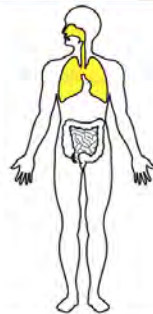
|                 | Skin                                                  | Gut                                                                     | Lungs                               | Eyes/nose/oral cavity                  |
|-----------------|-------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------|----------------------------------------|
| Mechanical      | Epithelial cells joined by tight junctions            |                                                                         |                                     |                                        |
|                 | Longitudinal flow of air or fluid                     | Longitudinal flow of air or fluid                                       | Movement of mucus by cilia          | Tears<br>Nasal cilia                   |
| Chemical        | Fatty acids                                           | Low pH                                                                  | Pulmonary surfactant                | Enzymes in tears and saliva (lysozyme) |
|                 |                                                       | Enzymes (pepsin)                                                        |                                     |                                        |
|                 | $\beta$ -defensins<br>Lamellar bodies<br>Cathelicidin | $\alpha$ -defensins (cryptdins)<br>RegIII (lecticidins)<br>Cathelicidin | $\alpha$ -defensins<br>Cathelicidin | Histatins<br>$\beta$ -defensins        |
| Microbiological | Normal microbiota                                     |                                                                         |                                     |                                        |

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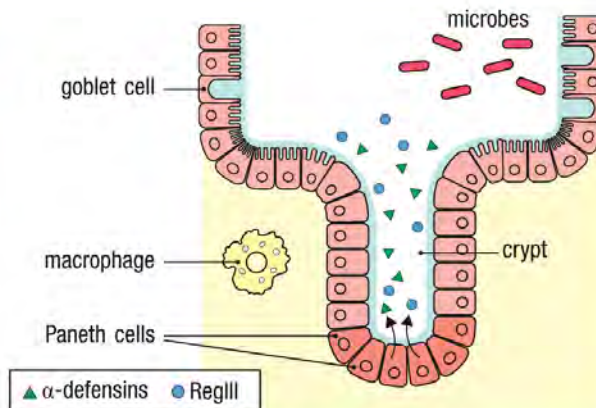
### Epidermis of skin



### Bronchial ciliated epithelium



### Gut epithelium



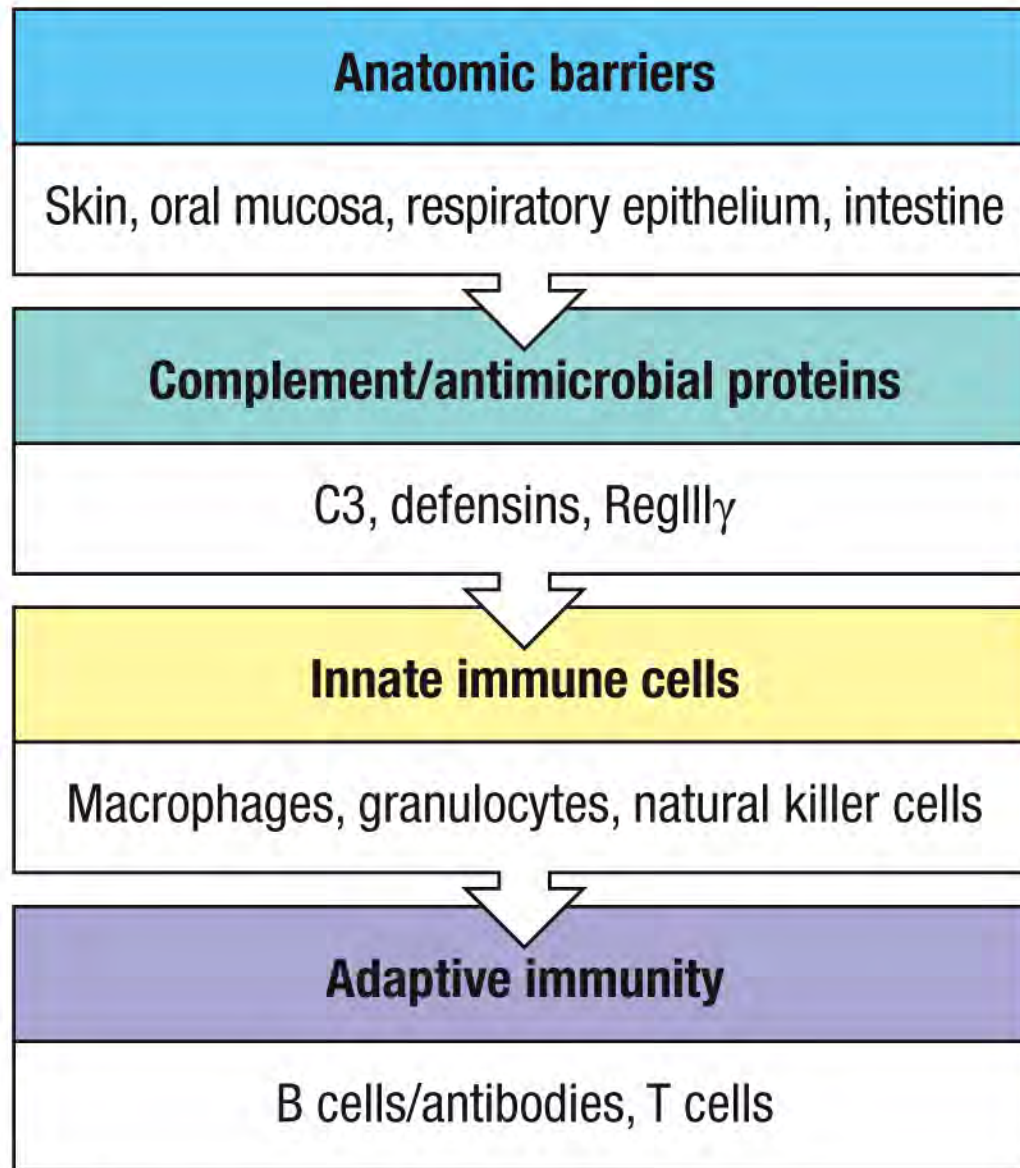
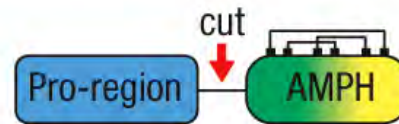


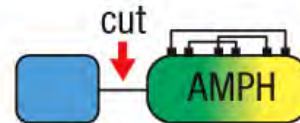
Figure 1.5 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

**Defensins, cathelicidins, and histatins are activated by proteolysis to release an amphipathic antimicrobial peptide**

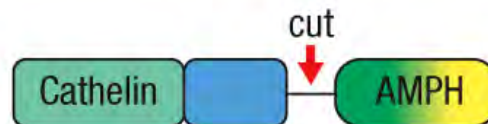
**$\alpha$ -defensins**



**$\beta$ -defensins**



**Cathelicidins**



**RegIII 'lecticidins'**

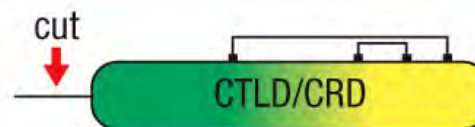


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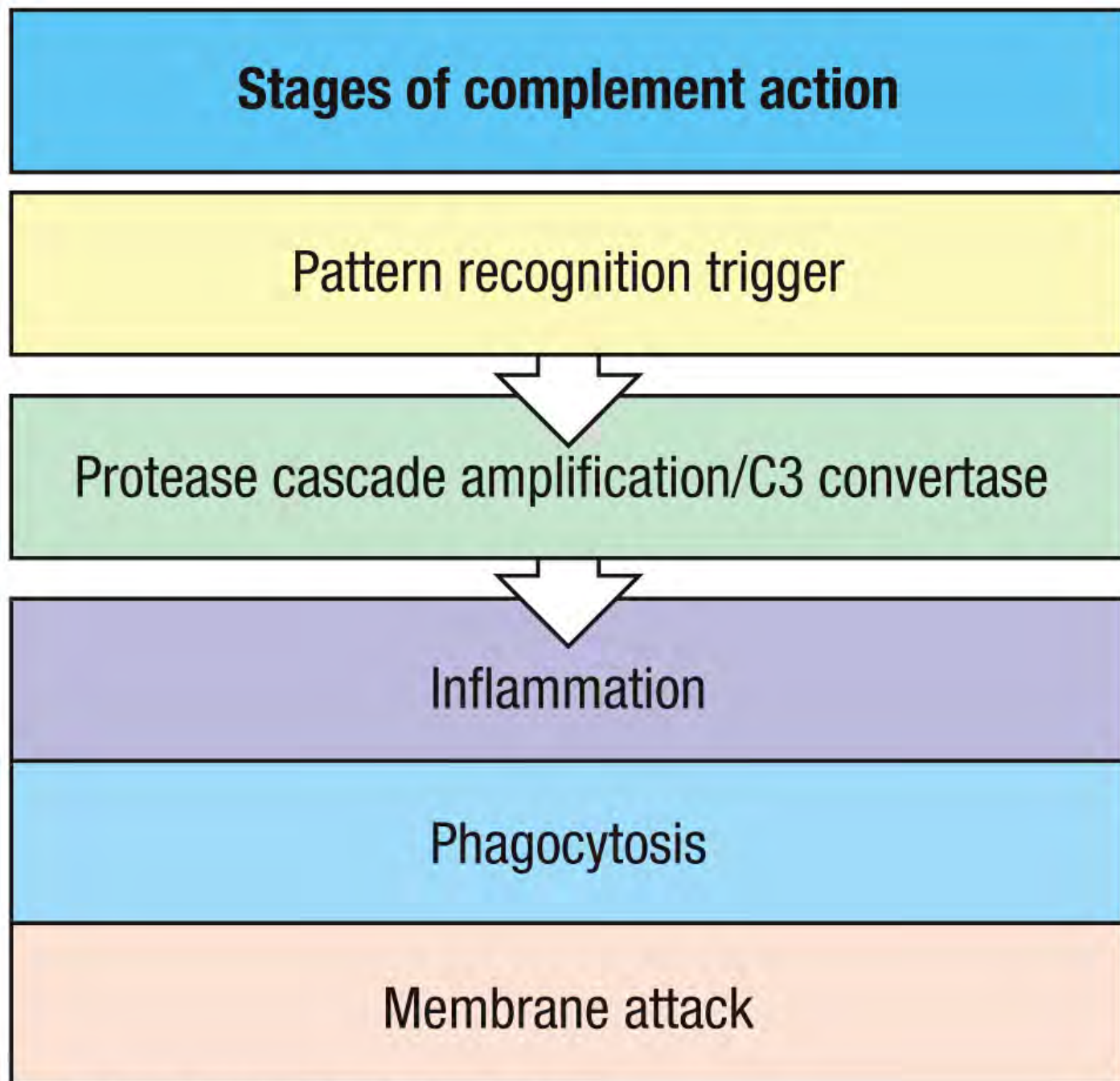
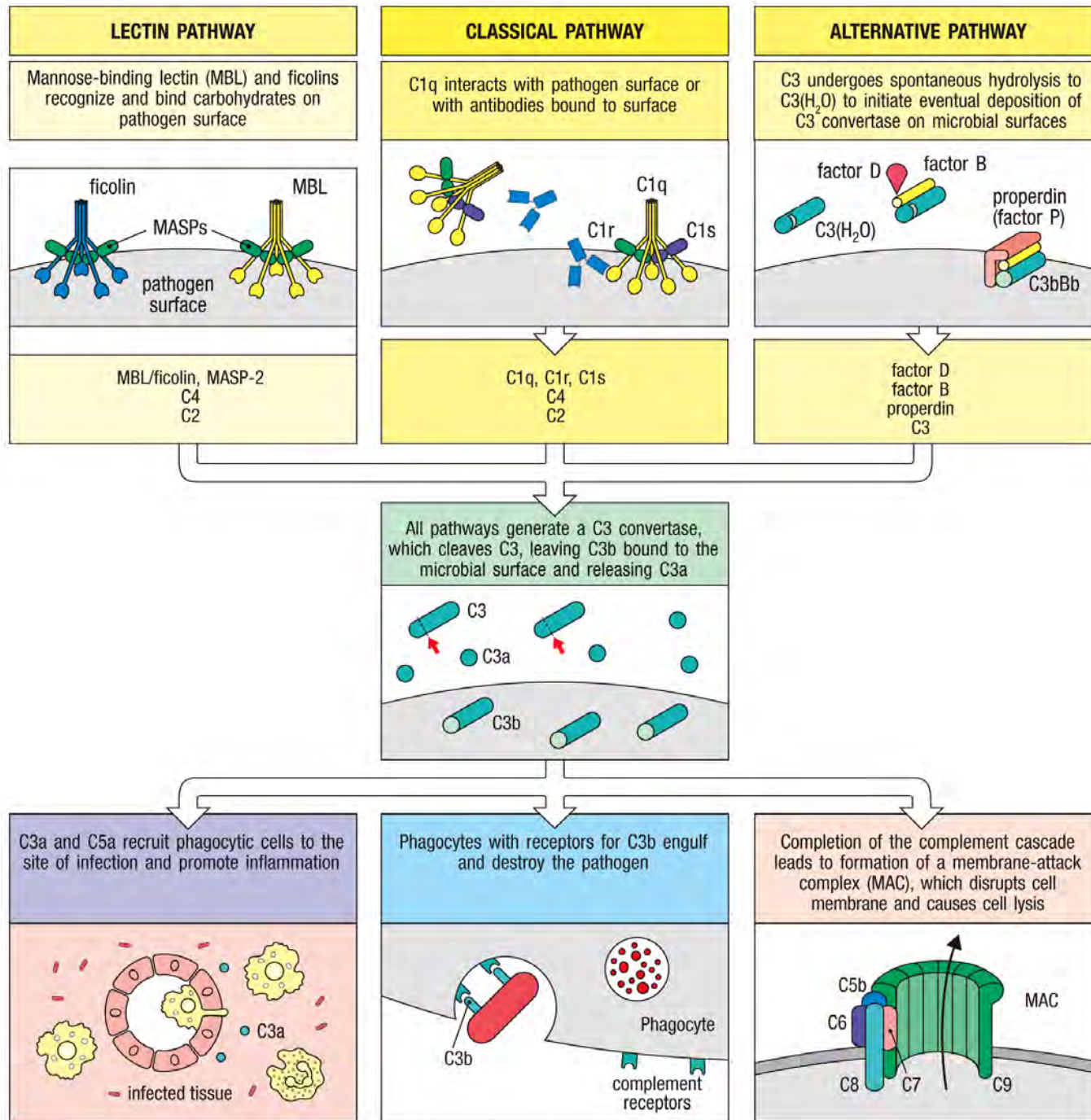


Figure 2.13 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| Functional protein classes in the complement system                                |                                                                          |
|------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Binding to antigen:antibody complexes and pathogen surfaces                        | C1q                                                                      |
| Binding to carbohydrate structures such as mannose or GlcNAc on microbial surfaces | MBL<br>Ficolins<br>Properdin (factor P)                                  |
| Activating enzymes*                                                                | C1r<br>C1s<br>C2a<br>Bb<br>D<br>MASP-1<br>MASP-2<br>MASP-3               |
| Surface-binding proteins and opsonins                                              | C4b<br>C3b                                                               |
| Peptide mediators of inflammation                                                  | C5a<br>C3a<br>C4a                                                        |
| Membrane-attack proteins                                                           | C5b<br>C6<br>C7<br>C8<br>C9                                              |
| Complement receptors                                                               | CR1<br>CR2<br>CR3<br>CR4<br>CRlg                                         |
| Complement-regulatory proteins                                                     | C1INH<br>C4BP<br>CR1/CD35<br>MCP/CD46<br>DAF/CD55<br>H<br>I<br>P<br>CD59 |

Figure 2.14 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)



Bind the outside

Opsonize with C3

Effector Phase

Figure 2.15 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| Receptor                               | Specificity        | Functions                                                                                                                       | Cell types                                                                                |
|----------------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| CR1<br>(CD35)                          | C3b,<br>C4bi       | Promotes C3b and C4b decay<br>Stimulates phagocytosis (requires C5a)<br>Erythrocyte transport<br>of immune complexes            | Erythrocytes,<br>macrophages, monocytes,<br>polymorphonuclear leukocytes,<br>B cells, FDC |
| CR2<br>(CD21)                          | C3d, iC3b,<br>C3dg | Part of B-cell co-receptor<br>Enhances B-cell response to antigens<br>bearing C3d, iC3b, or C3dg<br>Epstein–Barr virus receptor | B cells,<br>FDC                                                                           |
| CR3<br>(Mac-1)<br>(CD11b:<br>CD18)     | iC3b               | Stimulates phagocytosis                                                                                                         | Macrophages, monocytes,<br>polymorphonuclear leukocytes,<br>FDC                           |
| CR4<br>(gp150, 95)<br>(CD11c:<br>CD18) | iC3b               | Stimulates phagocytosis                                                                                                         | Macrophages, monocytes,<br>polymorphonuclear leukocytes,<br>dendritic cells               |
| CR1g                                   | C3b,<br>iC3b       | Phagocytosis of circulating<br>pathogens                                                                                        | Tissue-resident macrophages,<br>hepatic sinusoid macrophages                              |
| C5a<br>receptor<br>(CD88)              | C5a                | Binding of C5a<br>activates G protein                                                                                           | Neutrophils,<br>macrophages,<br>endothelial cells,<br>mast cells                          |
| C5L2<br>(GPR77)                        | C5a                | Decoy receptor,<br>regulates C5a receptor                                                                                       | Neutrophils,<br>macrophages                                                               |
| C3a<br>receptor                        | C3a                | Binding of C3a,<br>activates G protein                                                                                          | Macrophages,<br>endothelial cells,<br>mast cells                                          |

Figure 2.30 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

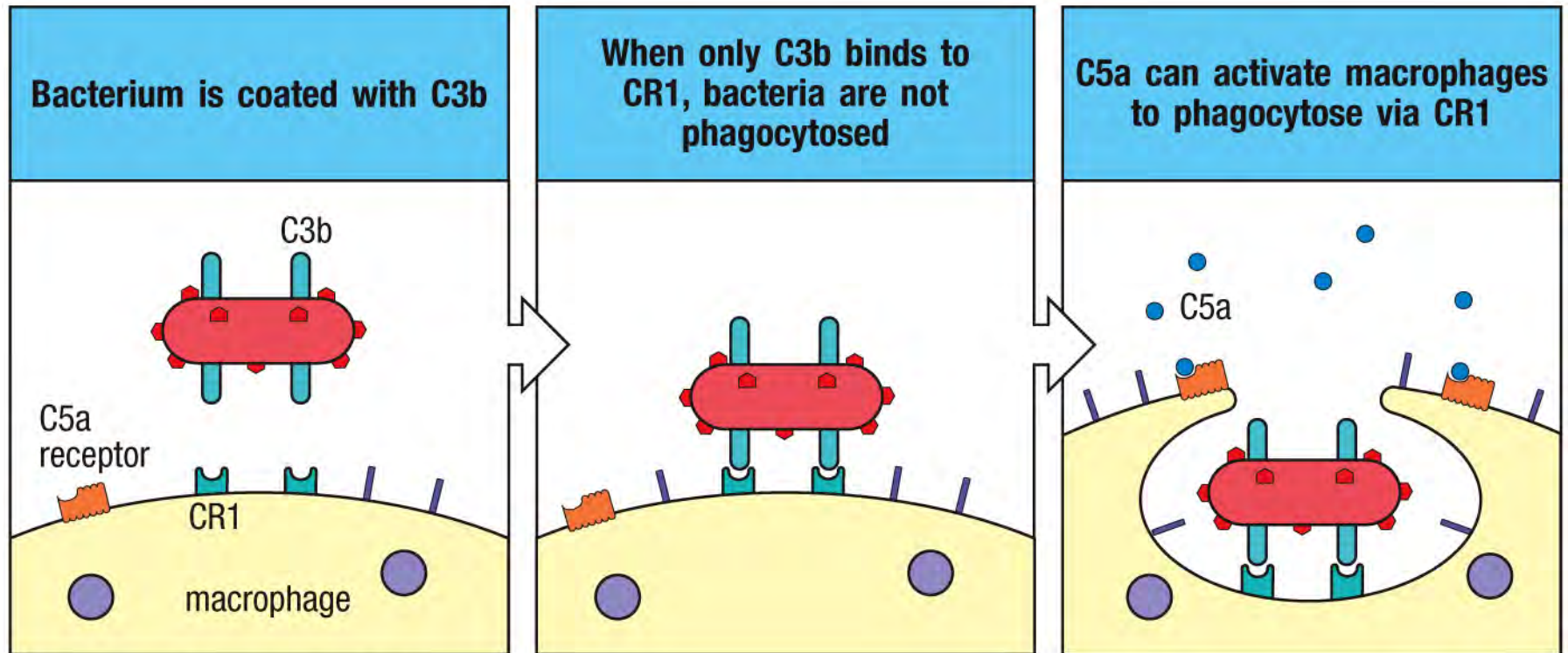


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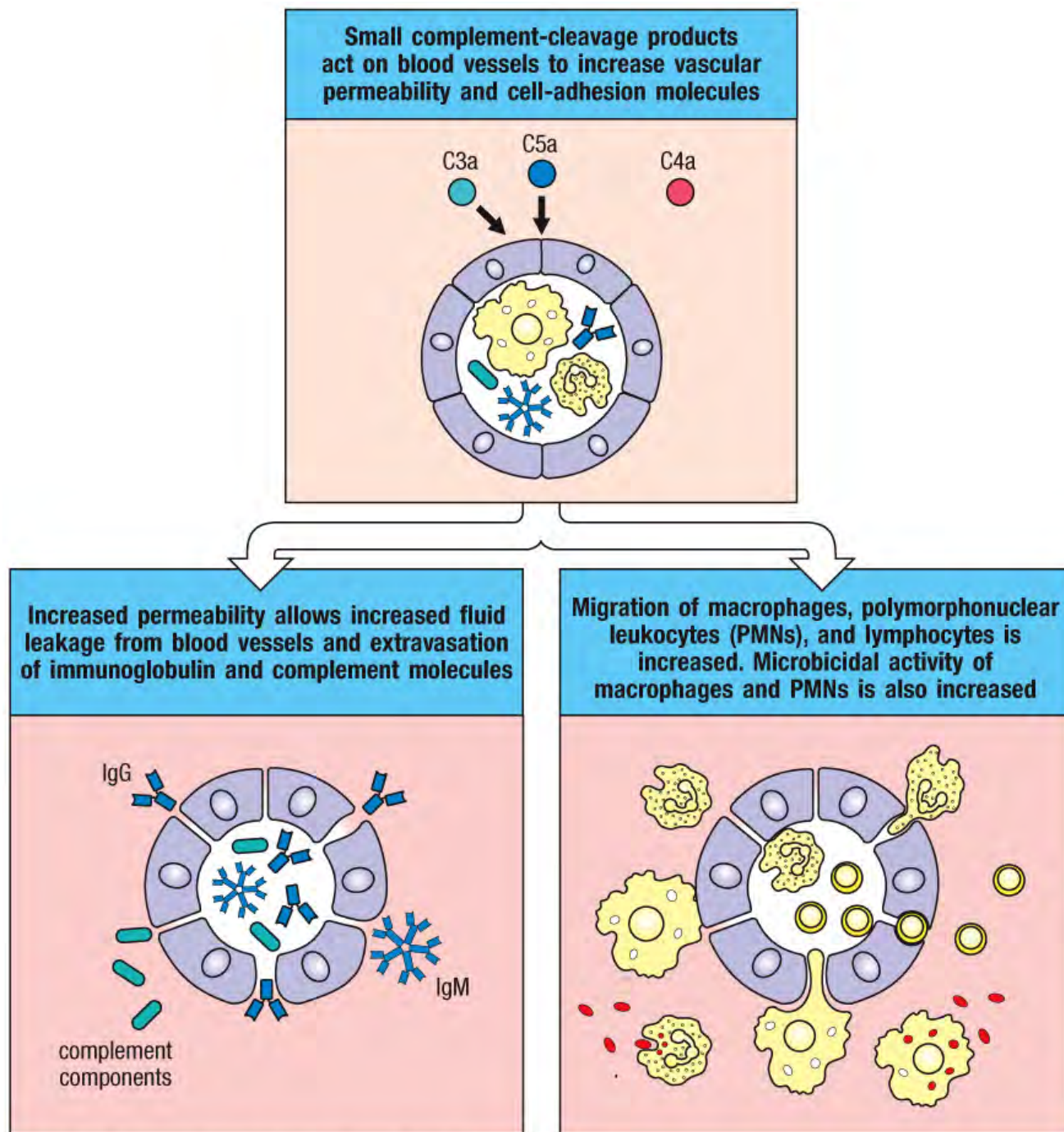


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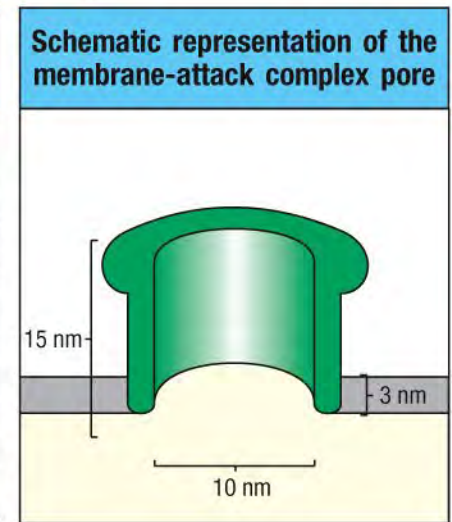
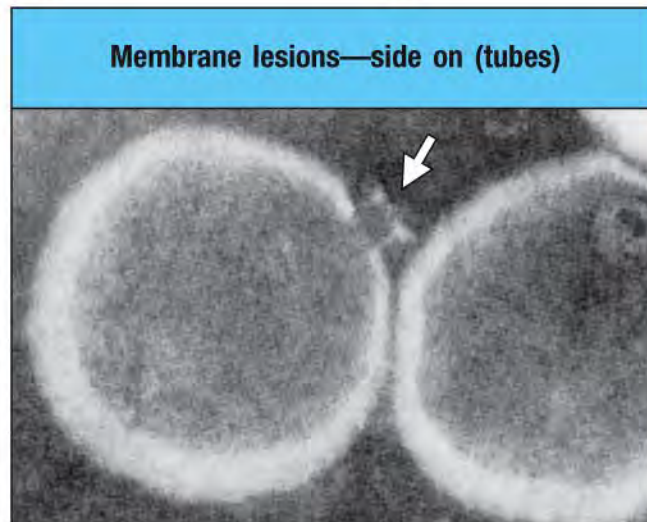
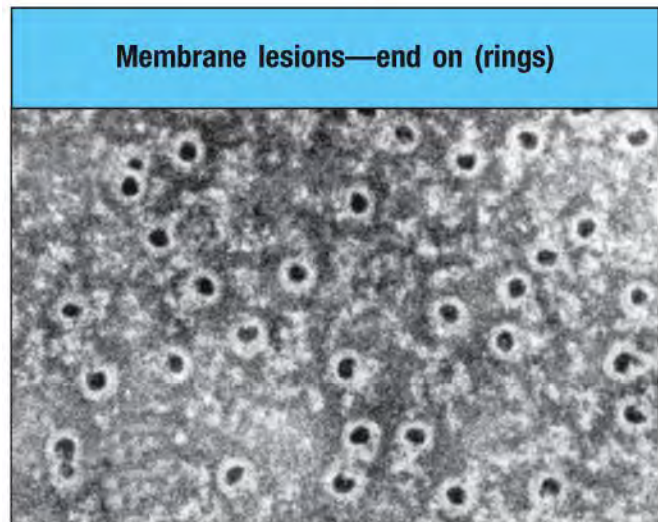
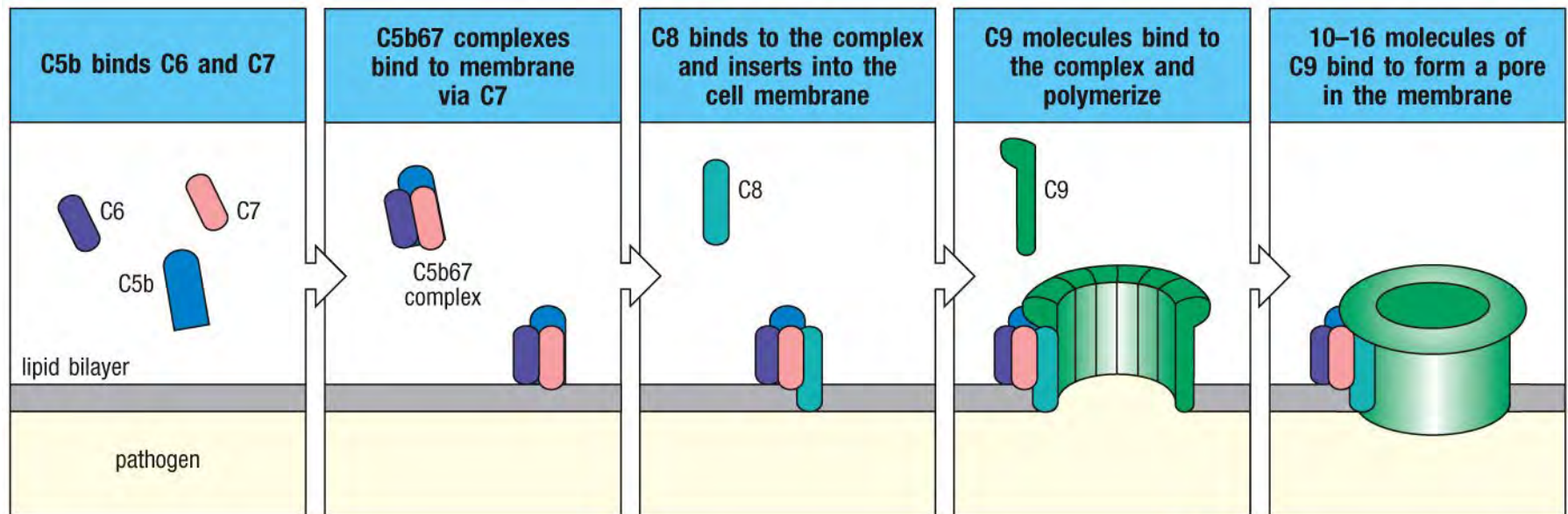


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| Pathogen                        | Evasion molecule                      | Host target                  | Mechanism of action                                   |
|---------------------------------|---------------------------------------|------------------------------|-------------------------------------------------------|
| <b>Membrane proteins</b>        |                                       |                              |                                                       |
| <i>Neisseria meningitidis</i>   | Factor H binding protein (fHbp)       | Factor H                     | Inactivates bound C3b                                 |
| <i>Borrelia burgdorferi</i>     | Outer surface protein E (OspE)        | Factor H                     | Inactivates bound C3b                                 |
| <i>Streptococcus pneumoniae</i> | Pneumococcal surface protein C (PspC) | Factor H                     | Inactivates bound C3b                                 |
| <b>Secreted proteins</b>        |                                       |                              |                                                       |
| <i>Neisseria meningitidis</i>   | PorA                                  | C4BP                         | Inactivates bound C3b                                 |
| <i>Staphylococcus aureus</i>    | Clumping factor A (ClfA)              | Factor I                     | Inactivates bound C3b                                 |
| <i>Staphylococcus aureus</i>    | Staphylococcus protein A (Spa)        | Immunoglobulin               | Binds to Fc regions and interferes with C1 activation |
| <i>Staphylococcus aureus</i>    | Staphylokinase (SAK)                  | Immunoglobulin               | Cleaves immunoglobulins                               |
| <i>Staphylococcus aureus</i>    | Complement inhibitor (SCIN)           | C3 convertase (C3b2a, C3bBb) | Inhibition of convertase activity                     |

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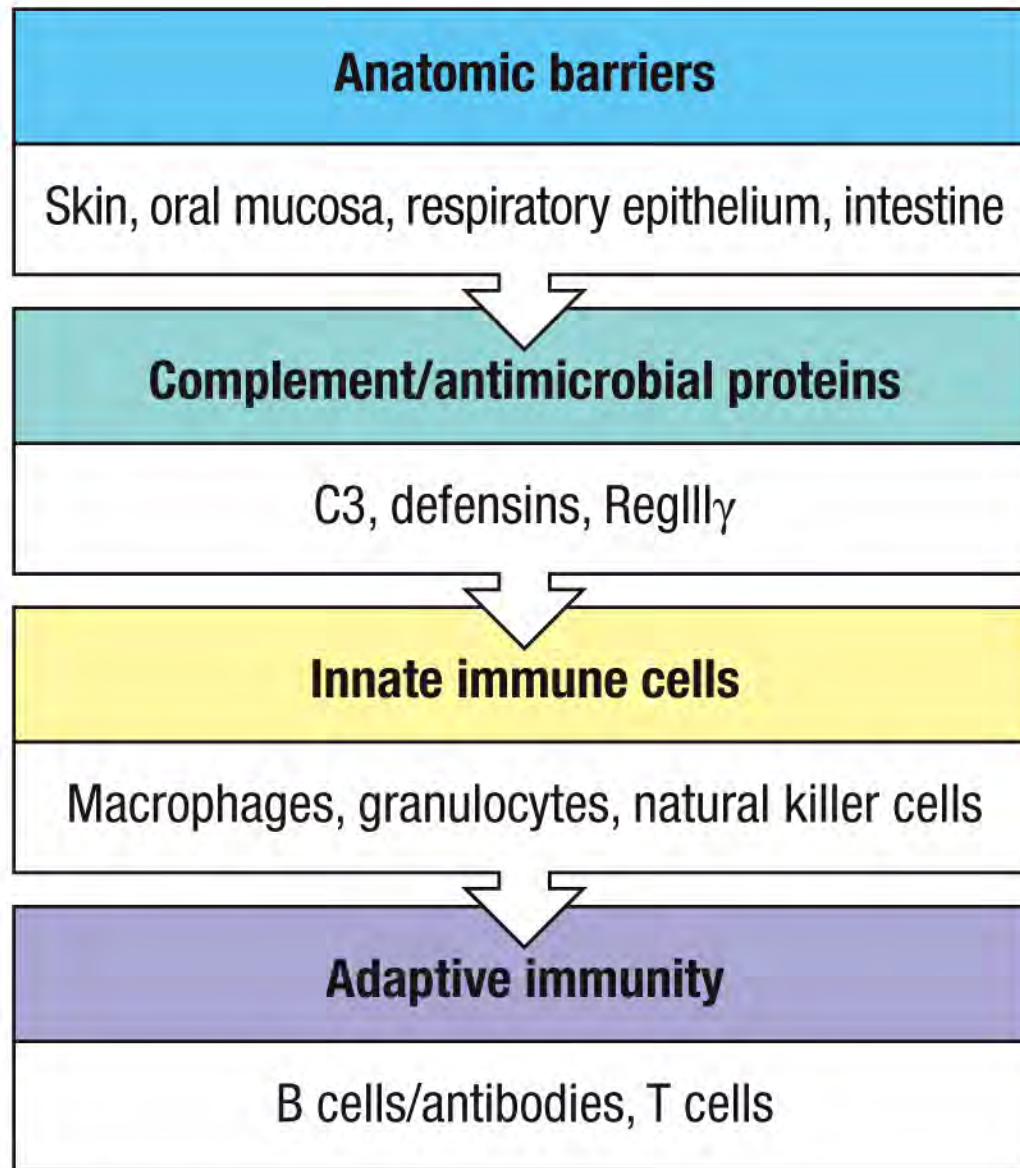


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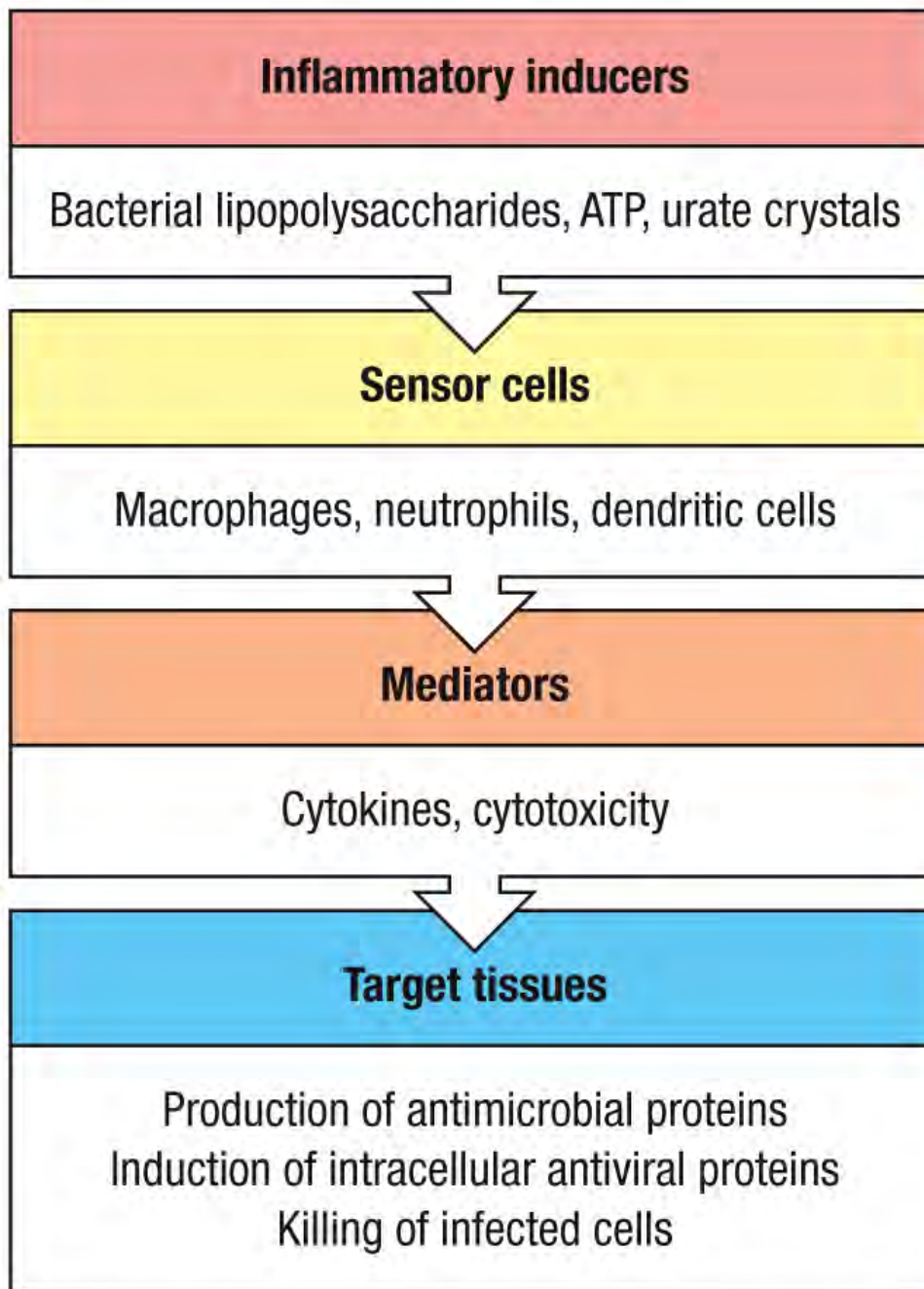


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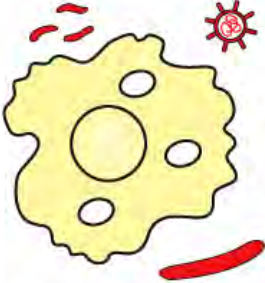
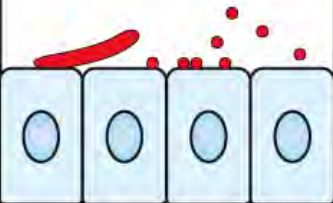
|                     | Extracellular                                                                     |                                                                                                                                                             | Intracellular                                                                       |                                                                                                                                                  |
|---------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
|                     | Interstitial spaces,<br>blood, lymph                                              | Epithelial<br>surfaces                                                                                                                                      | Cytoplasmic                                                                         | Vesicular                                                                                                                                        |
| Site of infection   |  |                                                                           |  |                                                               |
| Organisms           | Viruses<br>Bacteria<br>Protozoa<br>Fungi<br>Worms                                 | <i>Neisseria gonorrhoeae</i><br><i>Streptococcus pneumoniae</i><br><i>Vibrio cholerae</i><br><i>Helicobacter pylori</i><br><i>Candida albicans</i><br>Worms | Viruses<br><i>Chlamydia</i> spp.<br><i>Rickettsia</i> spp.<br>Protozoa              | <i>Mycobacterium</i> spp.<br><i>Yersinia pestis</i><br><i>Legionella pneumophila</i><br><i>Cryptococcus neoformans</i><br><i>Leishmania</i> spp. |
| Protective immunity | Complement<br>Phagocytosis<br>Antibodies                                          | Antimicrobial peptides<br>Antibodies, especially IgA                                                                                                        | NK cells<br>Cytotoxic T cells                                                       | T-cell and NK-cell dependent<br>macrophage activation                                                                                            |

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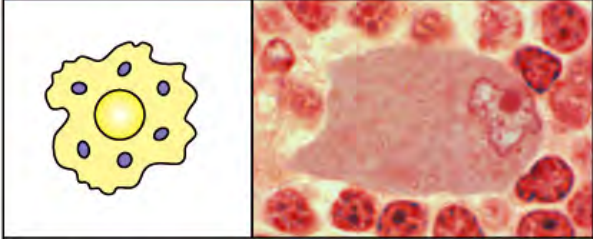
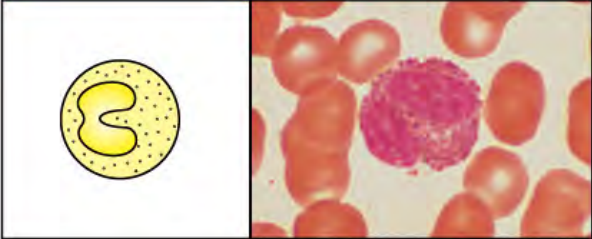
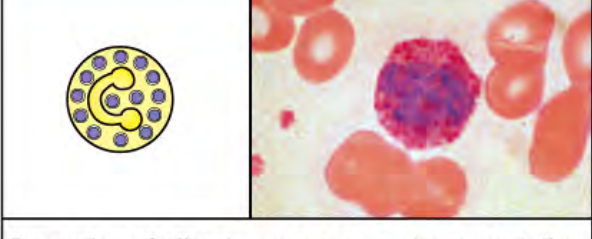
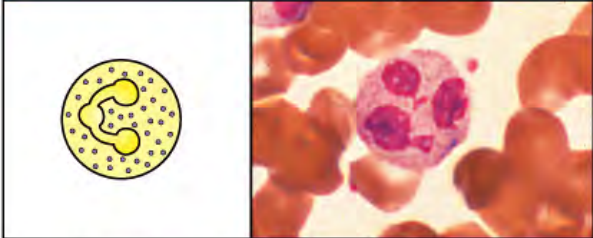
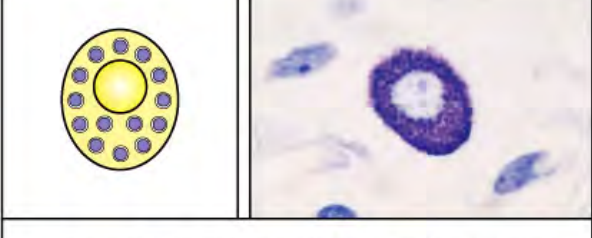
|                                                                                                                                                                                            |                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Macrophage</b>  <p>Phagocytosis and activation of bactericidal mechanisms<br/>Antigen presentation</p> | <b>Eosinophil</b>  <p>Killing of antibody-coated parasites</p>                                      |
| <b>Dendritic cell</b>  <p>Antigen uptake in peripheral sites<br/>Antigen presentation</p>                 | <b>Basophil</b>  <p>Promotion of allergic responses and augmentation of anti-parasitic immunity</p> |
| <b>Neutrophil</b>  <p>Phagocytosis and activation of bactericidal mechanisms</p>                        | <b>Mast cell</b>  <p>Release of granules containing histamine and active agents</p>               |

Figure 1.8 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| Antimicrobial mechanisms of phagocytes |                                                                                                                                                   |                                                                                                                                              |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Class of mechanism                     | Macrophage products                                                                                                                               | Neutrophil products                                                                                                                          |
| Acidification                          | pH≈3.5–4.0, bacteriostatic or bactericidal                                                                                                        |                                                                                                                                              |
| Toxic oxygen-derived products          | Superoxide $O_2^-$ , hydrogen peroxide $H_2O_2$ , singlet oxygen $^1O_2^\bullet$ , hydroxyl radical $^\bullet OH$ , hypohalite $OCl^-$            |                                                                                                                                              |
| Toxic nitrogen oxides                  | Nitric oxide NO                                                                                                                                   |                                                                                                                                              |
| Antimicrobial peptides                 | Cathelicidin, macrophage elastase-derived peptide                                                                                                 | $\alpha$ -Defensins (HNP1–4), $\beta$ -defensin HBD4, cathelicidin, azurocidin, bacterial permeability inducing protein (BPI), lactoferricin |
| Enzymes                                | Lysozyme: digests cell walls of some Gram-positive bacteria<br>Acid hydrolases (e.g., elastase and other proteases): break down ingested microbes |                                                                                                                                              |
| Competitors                            |                                                                                                                                                   | Lactoferrin (sequesters $Fe^{2+}$ ), vitamin $B_{12}$ -binding protein                                                                       |

Figure 3.4 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

A diagram of a macrophage, an irregularly shaped cell. A red and blue rod-shaped microbe is being engulfed by the cell membrane. Inside the cell, there are several small, colored spheres representing granules: yellow, orange, and blue. A larger, multi-colored structure is also visible. Labels with leader lines point to the following components:

- microbe
- primary granule
- secondary granule
- lysosome

Phagosomes fuse with primary and secondary granules. Rac2 induces assembly of a functional NADPH oxidase in the phagolysosome membrane, leading to generation of  $O_2^-$ . Acidification as a result of ion influx releases granule proteases from granule matrix

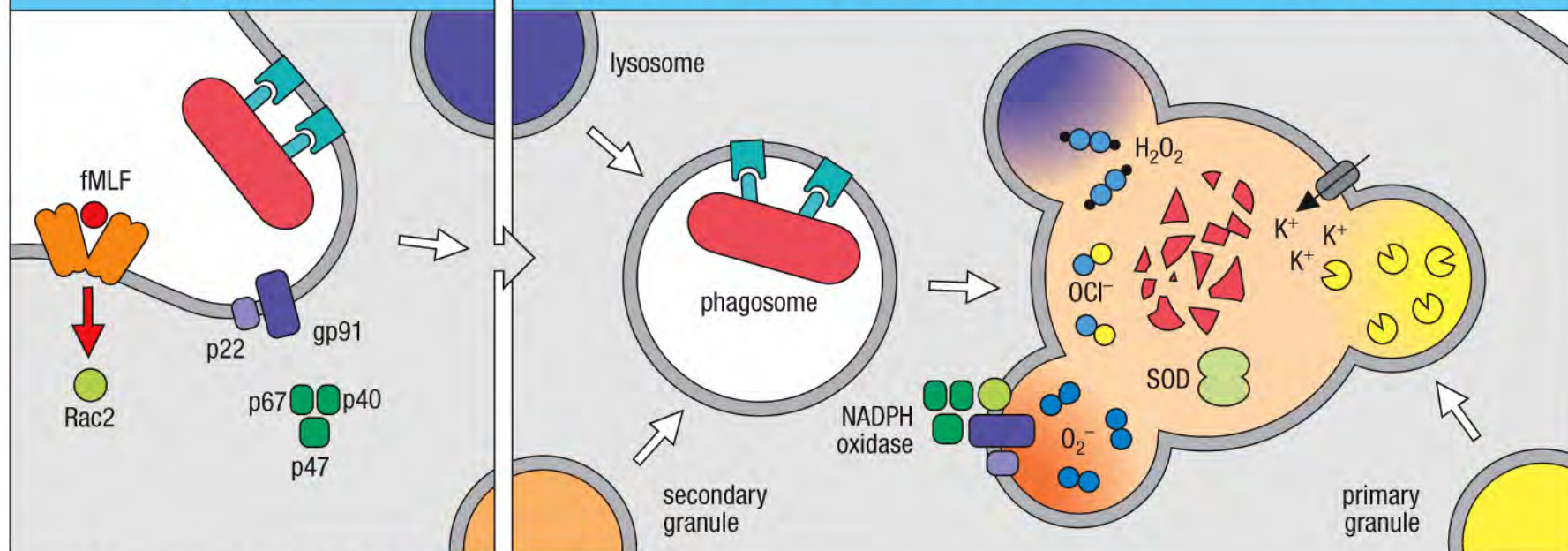


Figure 3.5 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

## Macrophages express receptors for many microbial constituents

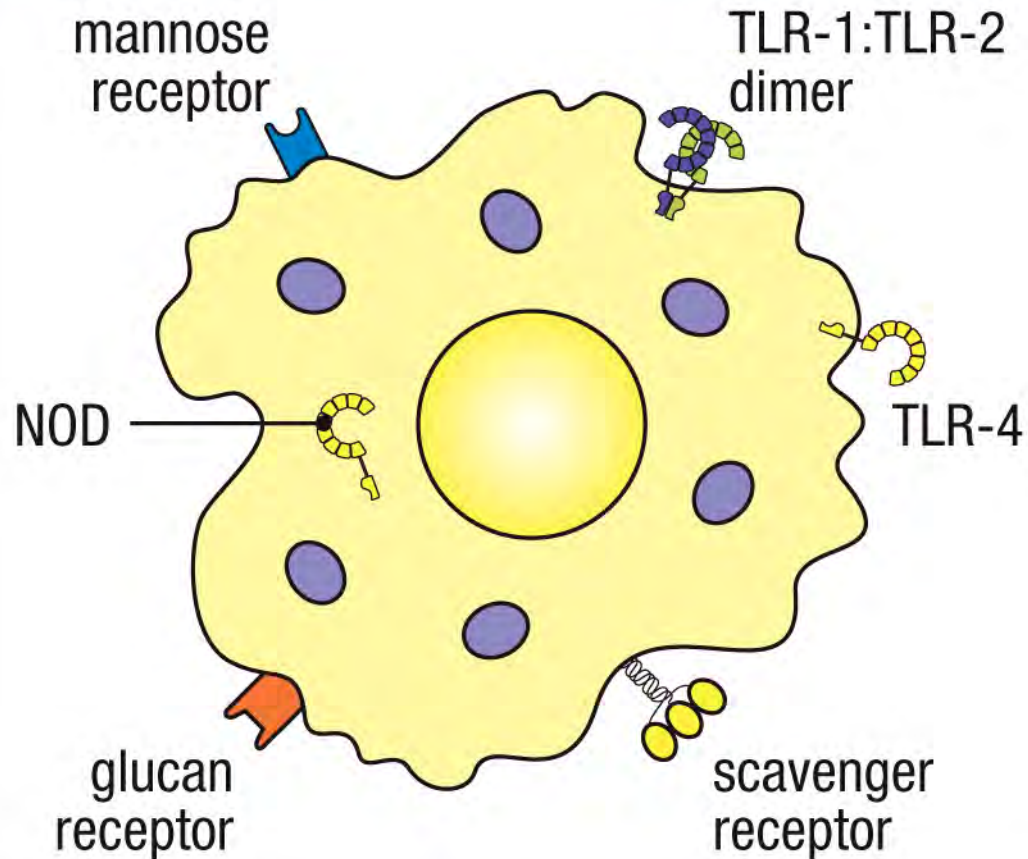
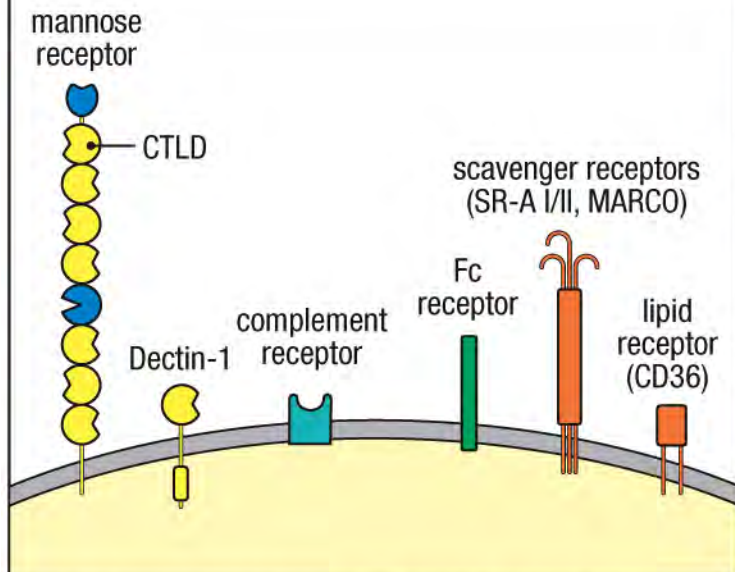
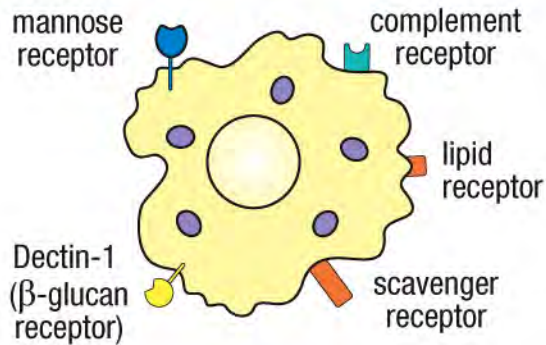


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| Receptor characteristic                                                | Innate immunity | Adaptive immunity |
|------------------------------------------------------------------------|-----------------|-------------------|
| Specificity inherited in the genome                                    | Yes             | No                |
| Expressed by all cells of a particular type (e.g., macrophages)        | Variable        | No                |
| Triggers immediate response                                            | Yes             | No                |
| Recognizes broad classes of pathogens                                  | Yes             | No                |
| Interacts with a range of molecular structures of a given type         | Yes             | No                |
| Encoded in multiple gene segments                                      | No              | Yes               |
| Requires gene rearrangement                                            | No              | Yes               |
| Clonal distribution                                                    | No              | Yes               |
| Able to discriminate between even closely related molecular structures | Yes             | Yes               |

Figure 3.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

**Macrophages have phagocytic receptors that bind microbes and their components**



**Bound material is internalized in phagosomes and broken down in phagolysosomes**

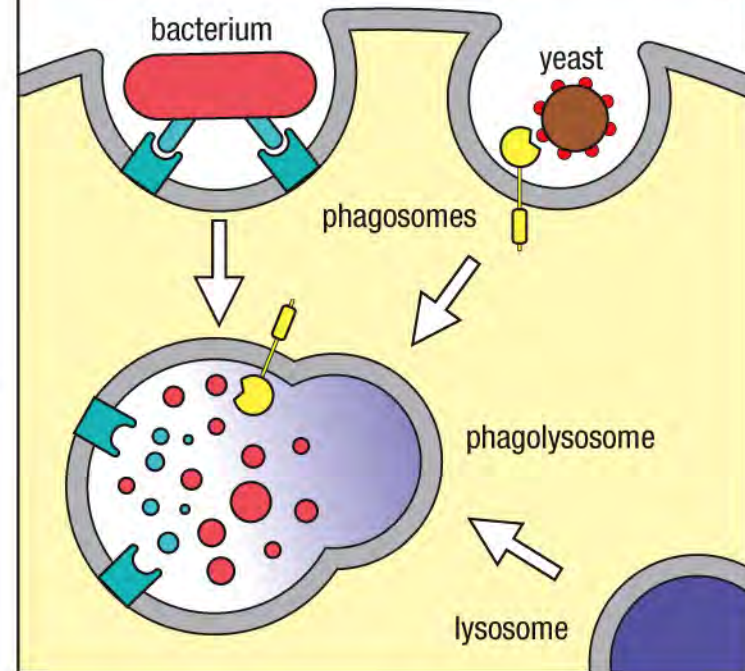


Figure 3.2 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| Innate immune recognition by mammalian Toll-like receptors |                                                                                                                                                                                                             |                                                                 |
|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Toll-like receptor                                         | Ligand                                                                                                                                                                                                      | Hematopoietic cellular distribution                             |
| TLR-1:TLR-2 heterodimer                                    | Lipomannans (mycobacteria)<br>Lipoproteins (diacyl lipopeptides; triacyl lipopeptides)<br>Lipoteichoic acids (Gram-positive bacteria)<br>Cell-wall $\beta$ -glucans (bacteria and fungi)<br>Zymosan (fungi) | Monocytes, dendritic cells, mast cells, eosinophils, basophils  |
| TLR-2:TLR-6 heterodimer                                    |                                                                                                                                                                                                             |                                                                 |
| TLR-3                                                      | Double-stranded RNA (viruses), poly I:C                                                                                                                                                                     | Macrophages, dendritic cells, intestinal epithelium             |
| TLR-4 (plus MD-2 and CD14)                                 | LPS (Gram-negative bacteria)<br>Lipoteichoic acids (Gram-positive bacteria)                                                                                                                                 | Macrophages, dendritic cells, mast cells, eosinophils           |
| TLR-5                                                      | Flagellin (bacteria)                                                                                                                                                                                        | Intestinal epithelium, macrophages, dendritic cells             |
| TLR-7                                                      | Single-stranded RNA (viruses)                                                                                                                                                                               | Plasmacytoid dendritic cells, macrophages, eosinophils, B cells |
| TLR-8                                                      | Single-stranded RNA (viruses)                                                                                                                                                                               | Macrophages, neutrophils                                        |
| TLR-9                                                      | DNA with unmethylated CpG (bacteria and herpesviruses)                                                                                                                                                      | Plasmacytoid dendritic cells, eosinophils, B cells, basophils   |
| TLR-10 (human only)                                        | Unknown                                                                                                                                                                                                     | Plasmacytoid dendritic cells, eosinophils, B cells, basophils   |
| TLR-11 (mouse only)                                        | Profilin and profilin-like proteins ( <i>Toxoplasma gondii</i> , uropathogenic bacteria)                                                                                                                    | Macrophages, dendritic cells (also liver, kidney, and bladder)  |
| TLR-12 (mouse only)                                        | Profilin ( <i>Toxoplasma gondii</i> )                                                                                                                                                                       | Macrophages, dendritic cells (also liver, kidney, bladder)      |
| TLR-13 (mouse only)                                        | Single-stranded RNA (bacterial ribosomal RNA)                                                                                                                                                               | Macrophages, dendritic cells                                    |

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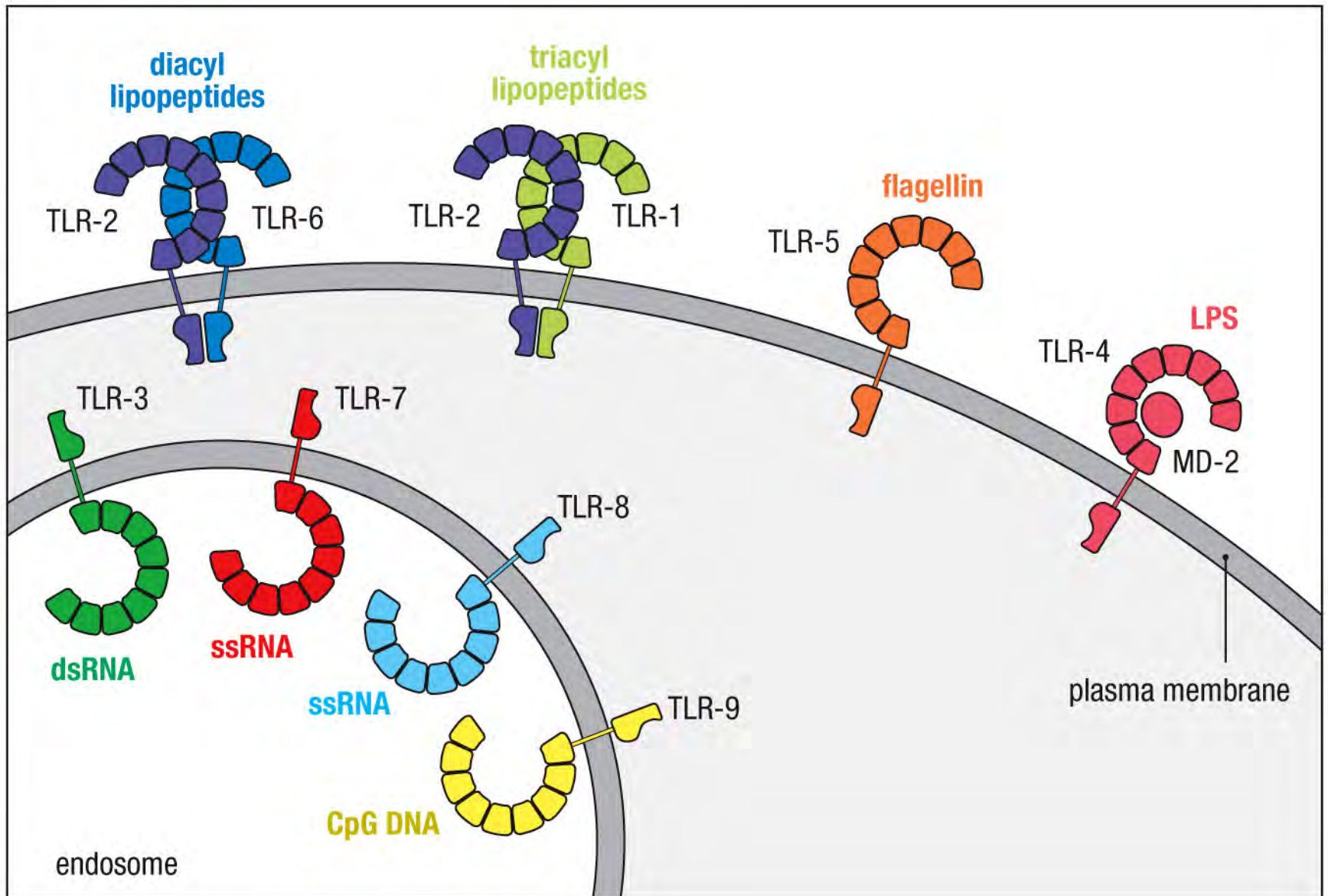
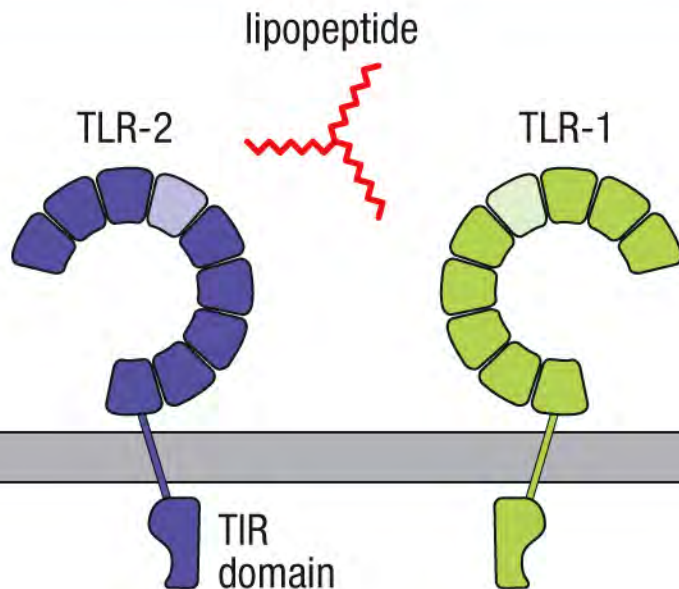


Figure 3.11 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

**The convex surfaces of TLR-1 and TLR-2 have binding sites for lipid side chains of triacyl lipopeptides**



**Binding of each TLR to the same lipopeptide induces dimerization, bringing their cytoplasmic TIR domains into close proximity**

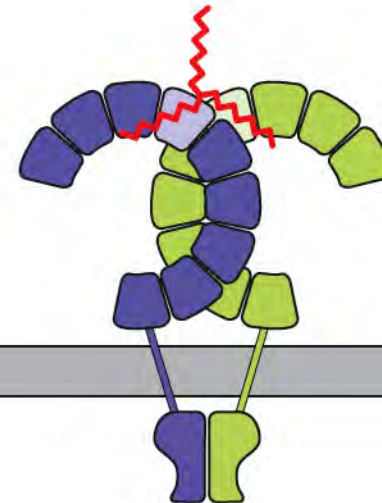


Figure 3.12 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

**LPS has multiple fatty acyl chains linked to a glycan head. Five acyl chains can bind to a pocket within MD-2, but one acyl chain is free**

**The free acyl chain of an LPS molecule then binds to the outer convex surface of another TLR-4 molecule, inducing a dimer. An LPS molecule bound to the second TLR-4/MD-2 molecule stabilizes the dimer (not shown)**

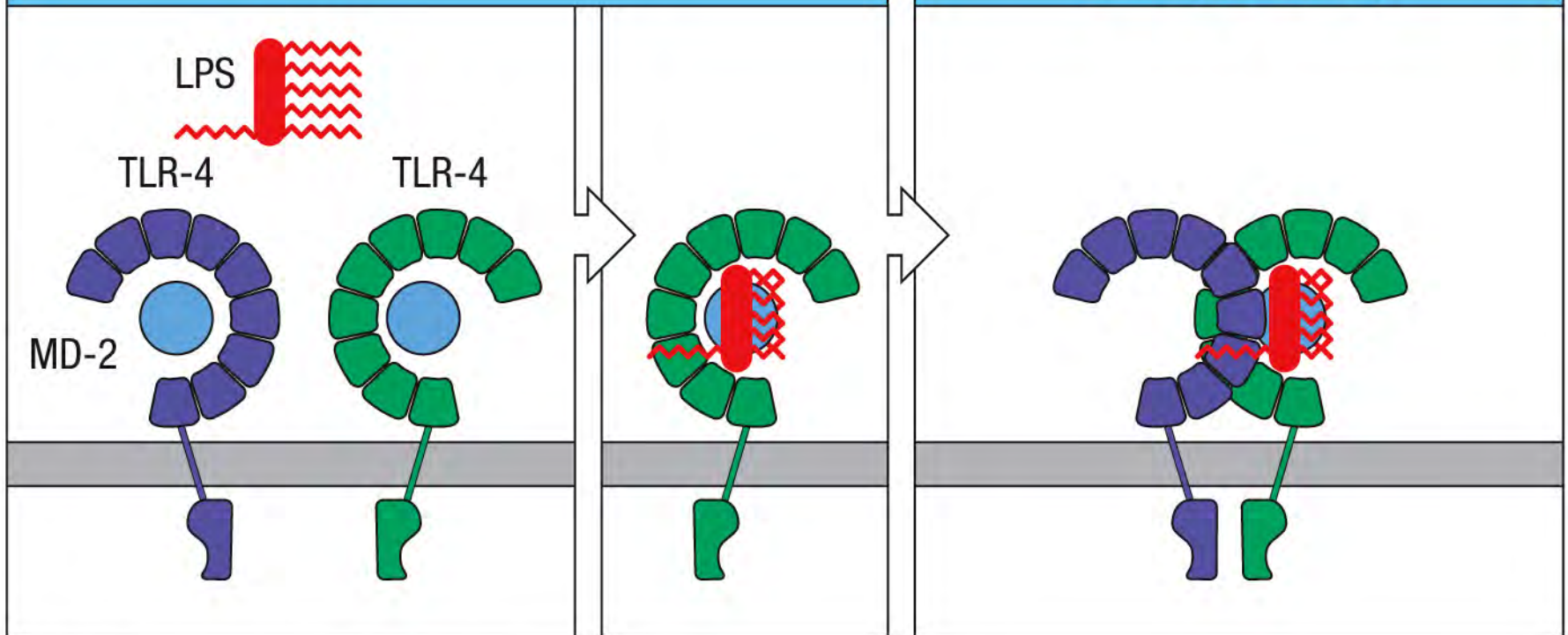


Figure 3.13c Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| TLR      | Adaptor             |
|----------|---------------------|
| TLR-2/1  | MyD88/MAL           |
| TLR-3    | TRIF                |
| TLR-4    | MyD88/MAL TRIF/TRAM |
| TLR-5    | MyD88               |
| TLR-2/6  | MyD88/MAL           |
| TLR-7    | MyD88               |
| TLR-8    | MyD88               |
| TLR-9    | MyD88               |
| TLR11/12 | MyD88               |
| TLR-13   | MyD88               |

Figure 3.14 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

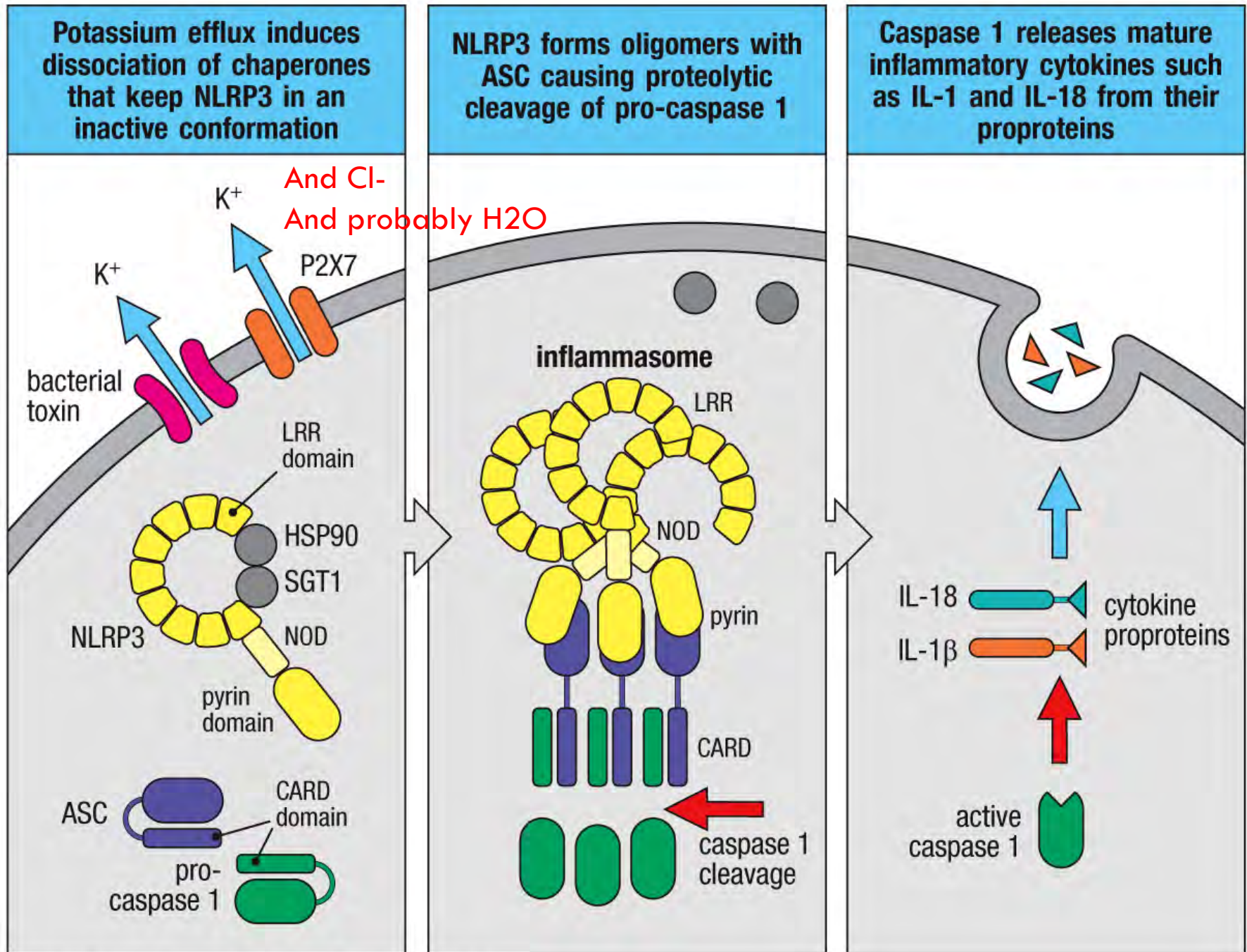
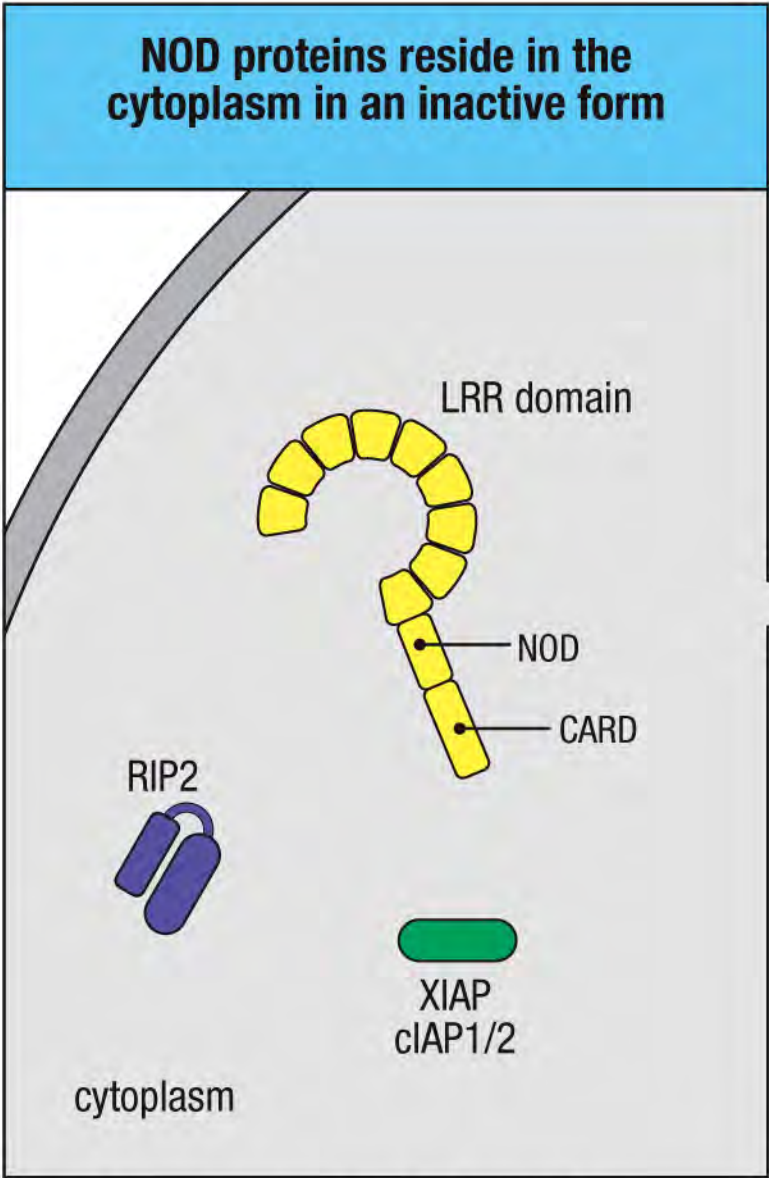


Figure 3.19 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

**NOD proteins reside in the cytoplasm in an inactive form**



**Binding of bacterial ligands to NOD proteins induces recruitment of RIP2, which activates TAK1, leading to NFκB activation**

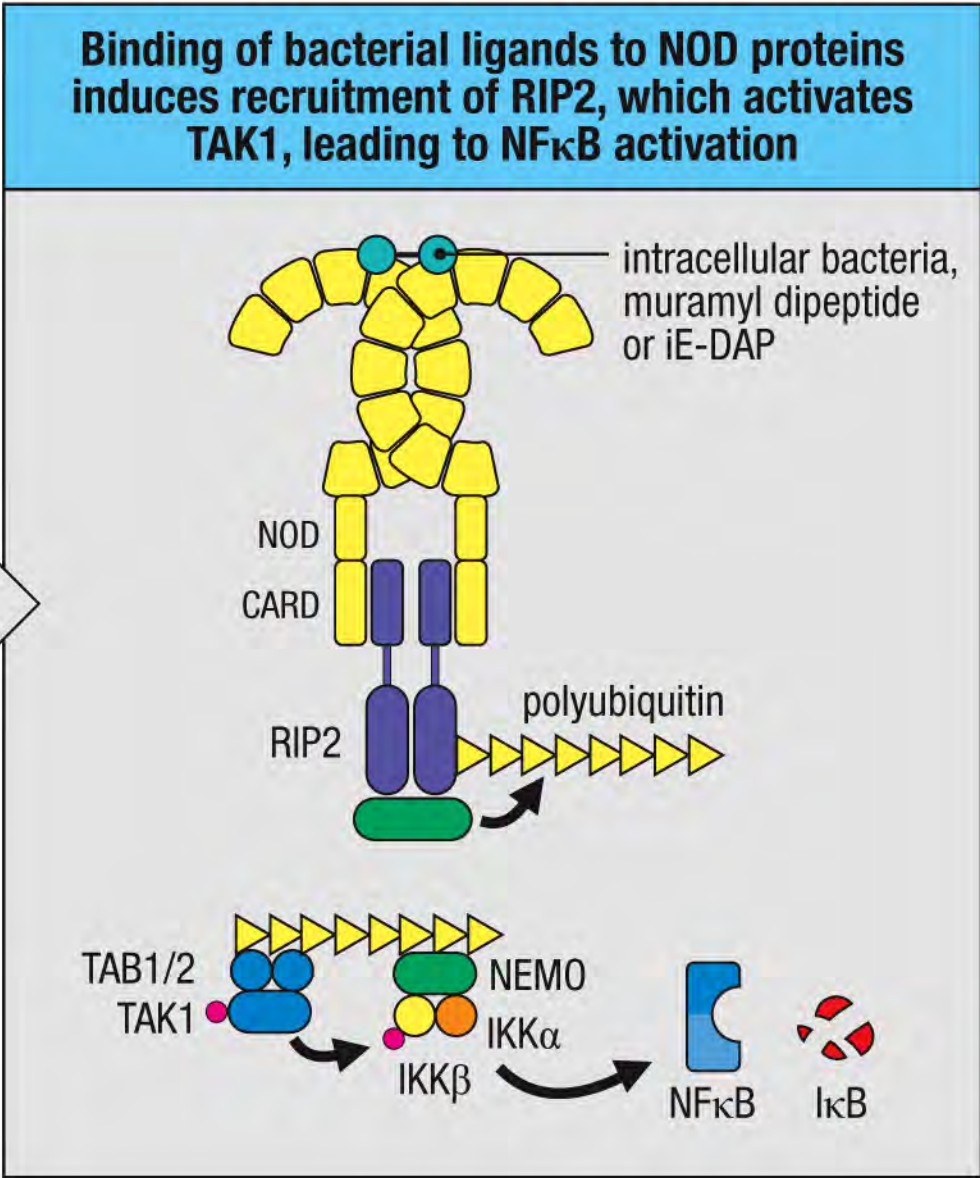
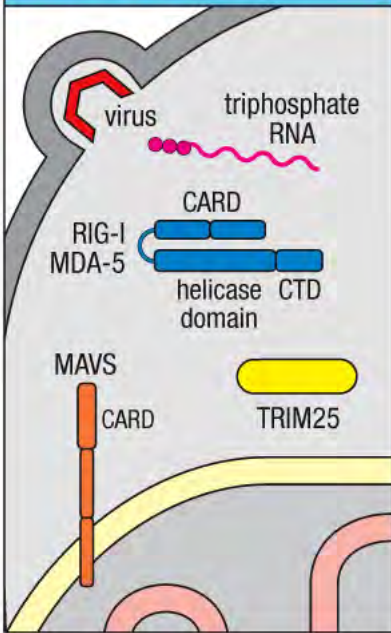
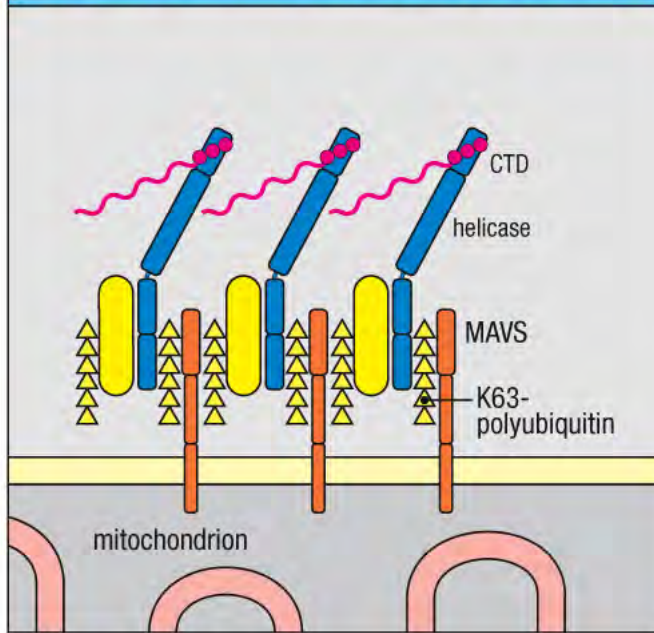


Figure 3.17 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

**Cytoplasmic replication of virus produces uncapped RNA with a 5'-triphosphate**



**Viral RNA alters conformation of RIG-I, and induces binding and aggregation with MAVS in a manner requiring K63-linked polyubiquitin and TRIM25**



**Aggregated MAVS recruits TRAFs and induces the generation of free K63-linked polyubiquitin chains that activate the IRFs and NF $\kappa$ B pathways**

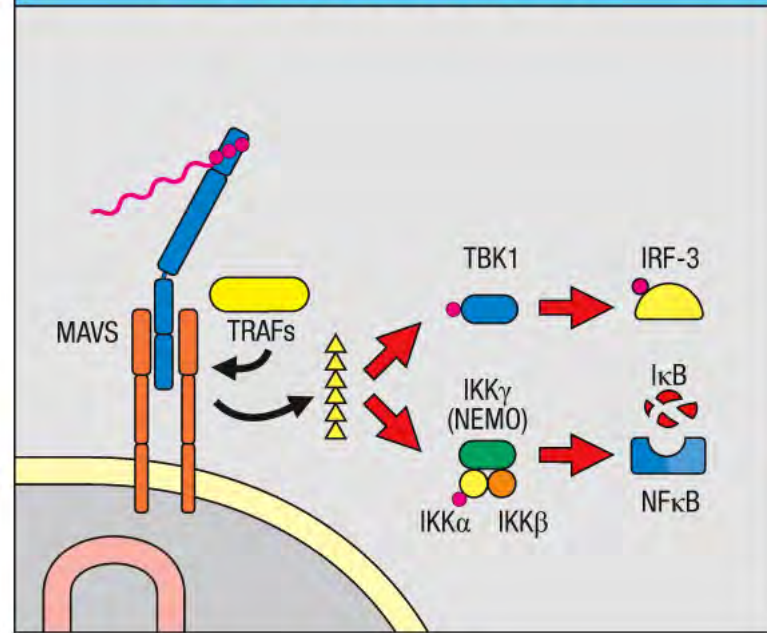


Figure 3.21 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

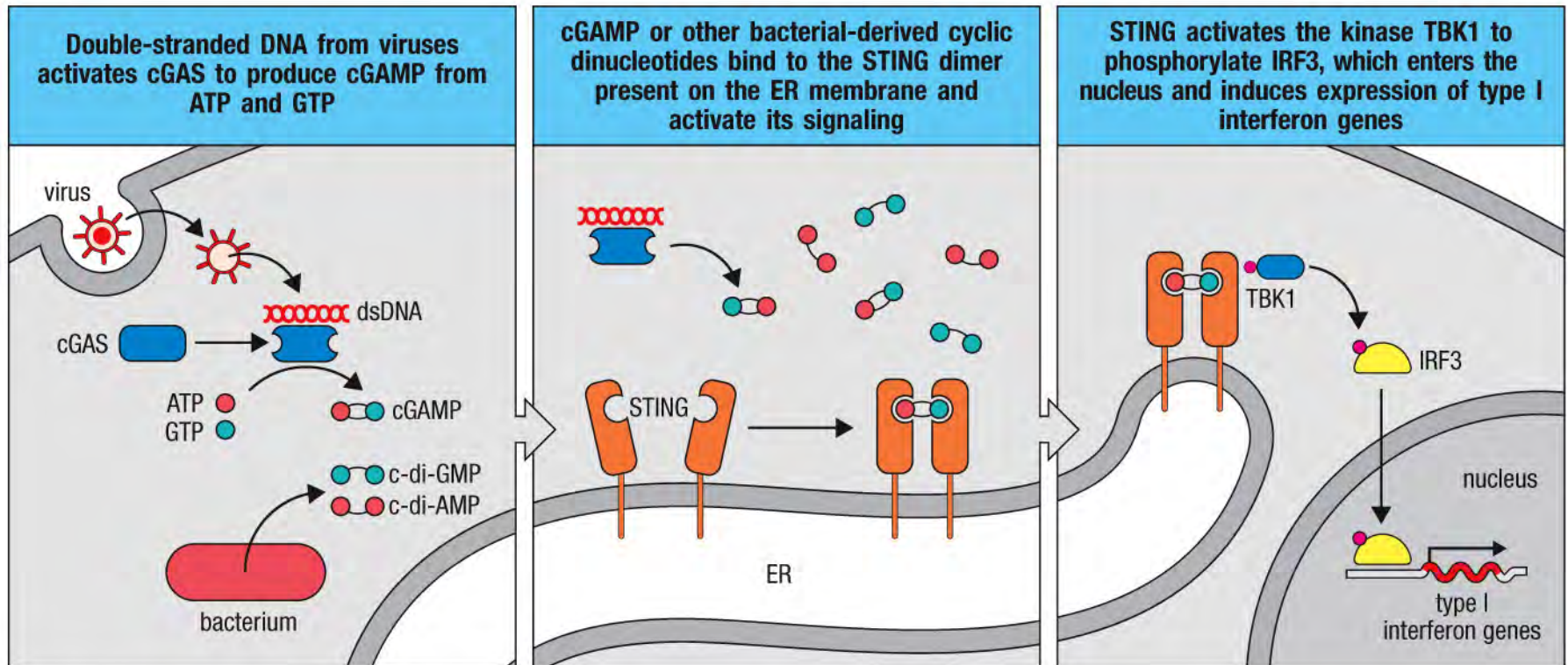


Figure 3.22 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

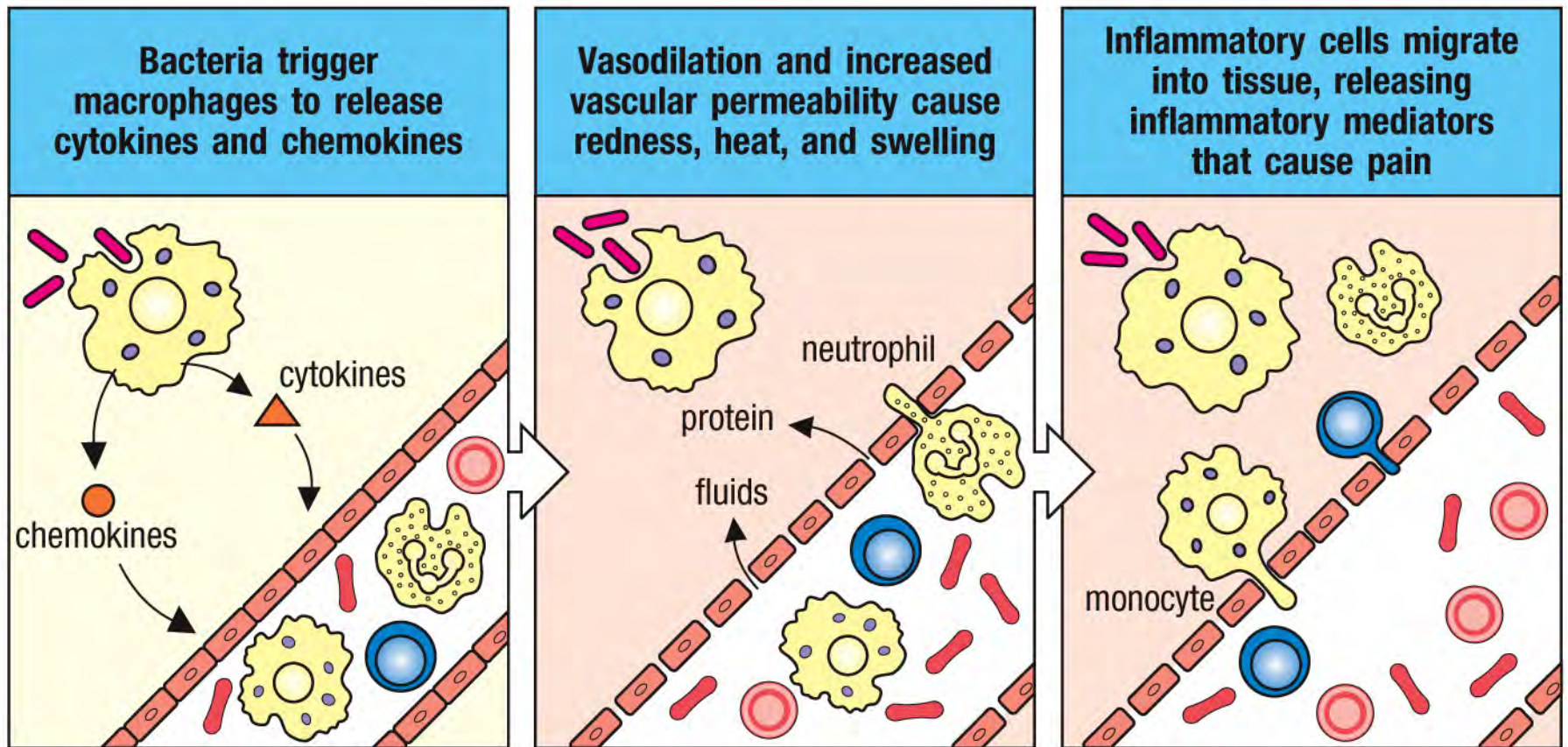


Figure 1.10 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

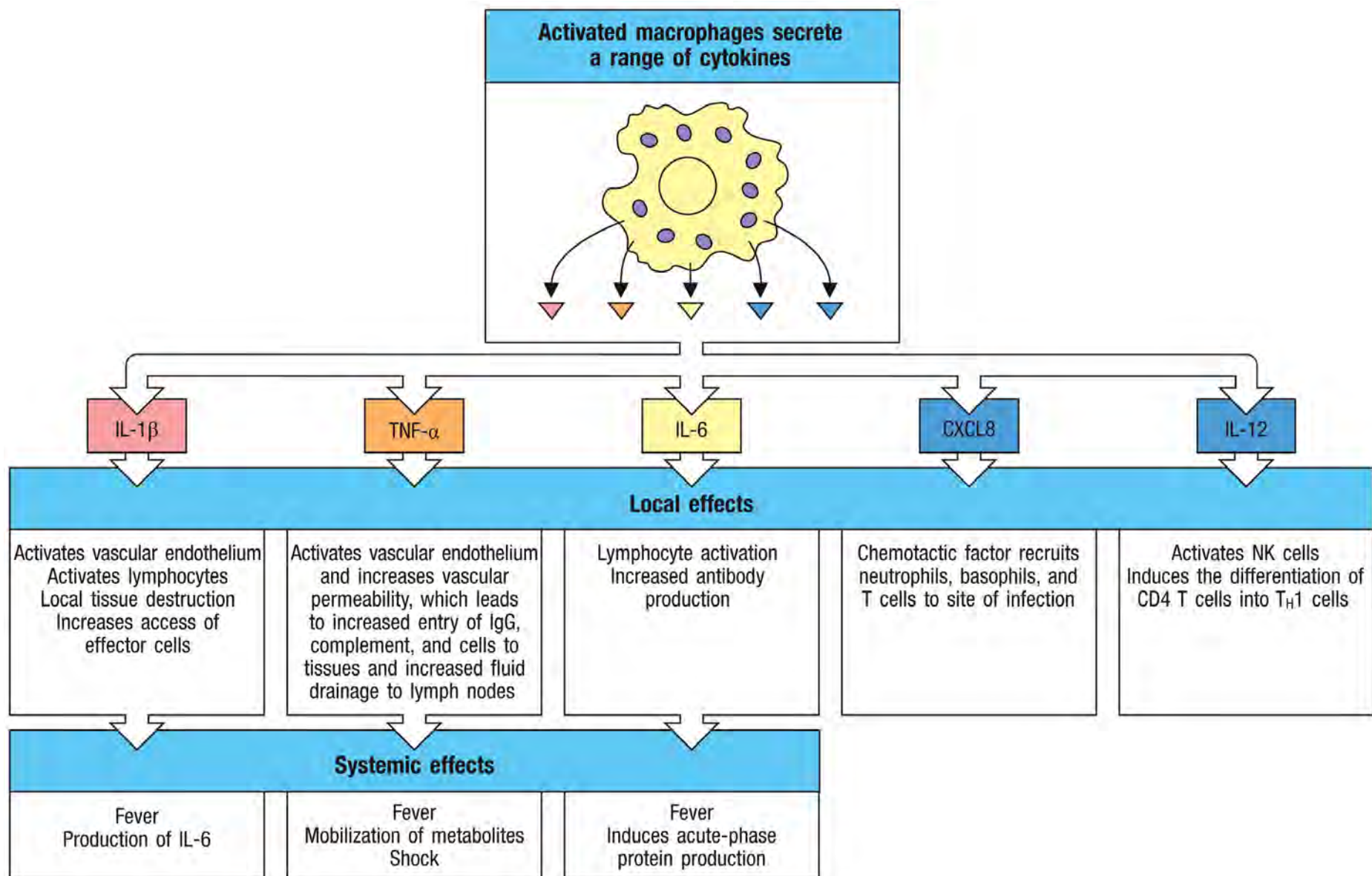


Figure 3.27 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

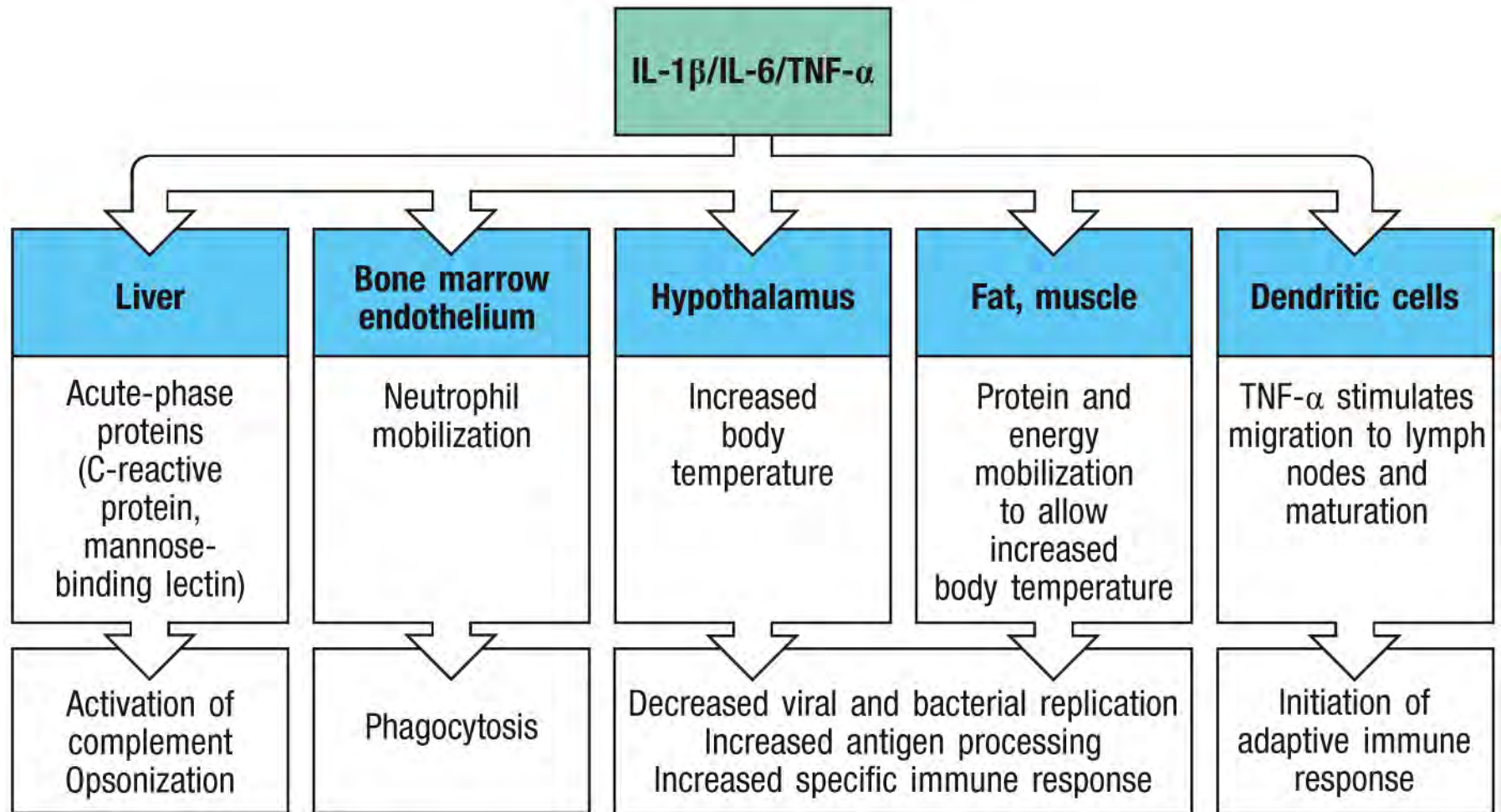
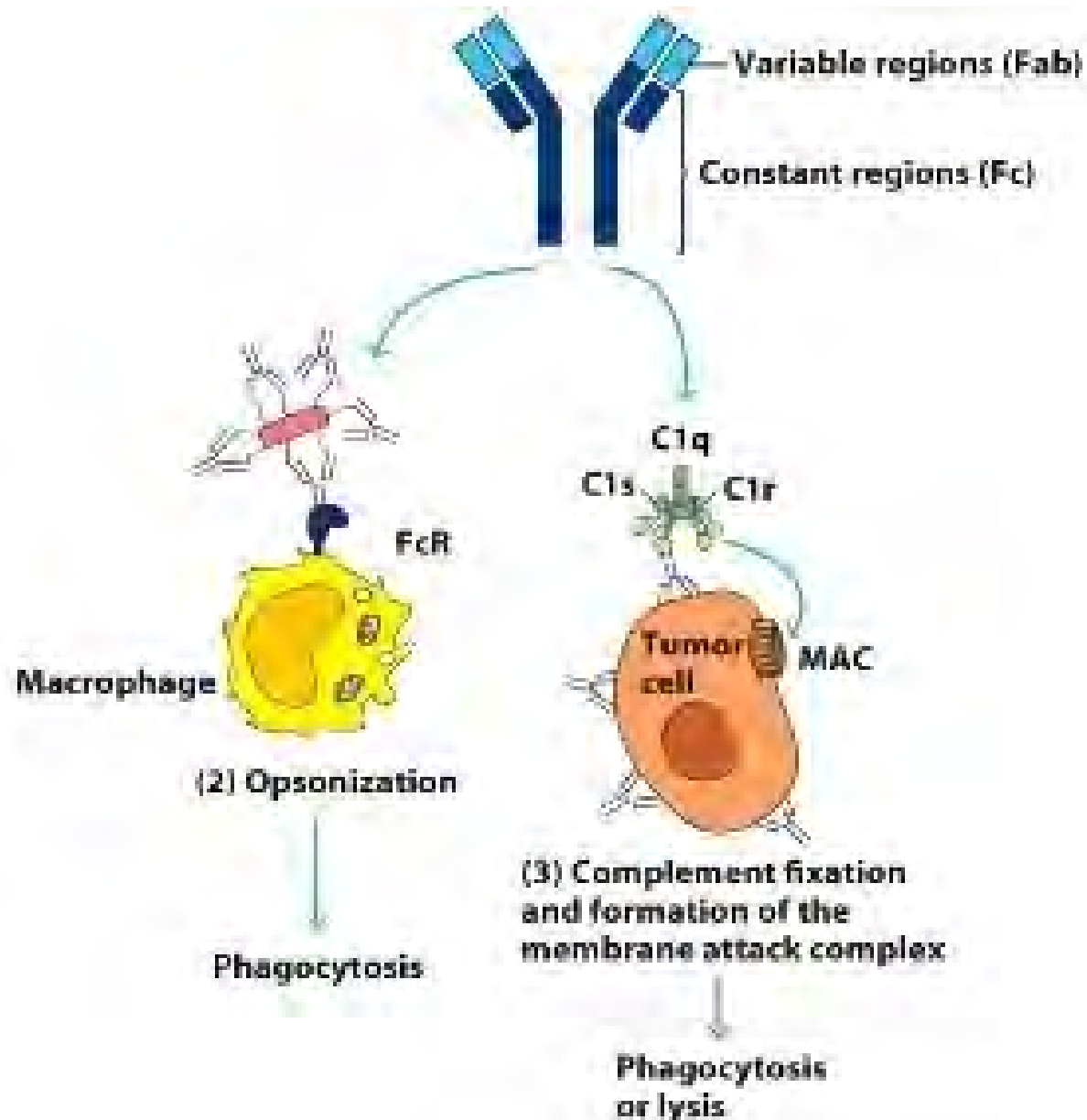


Figure 3.33 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

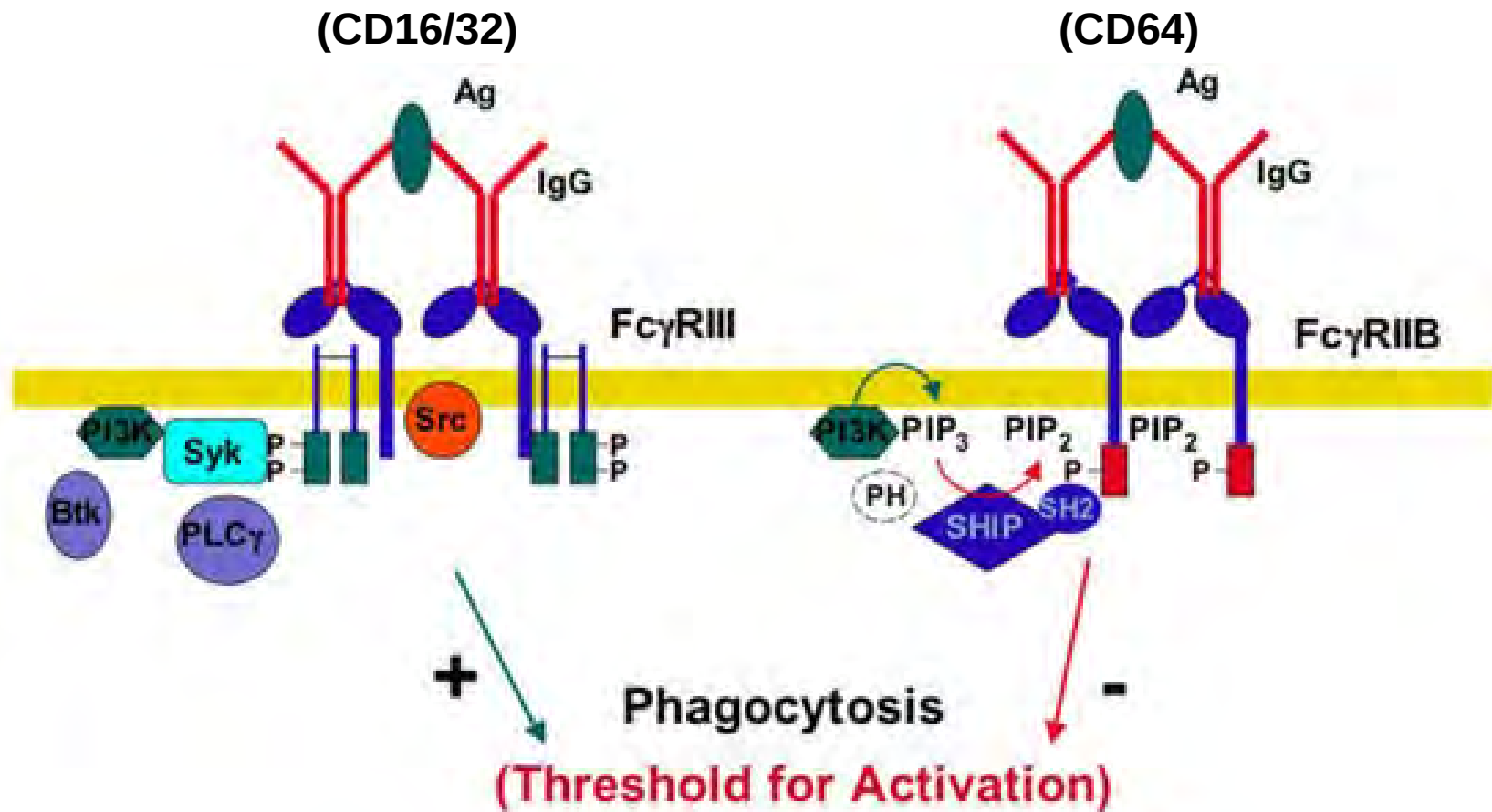
# Phagocytosis

- Fc Receptor (Antibody-mediated)
- Complement Receptor
- Apoptotic Cell (Efferocytosis)

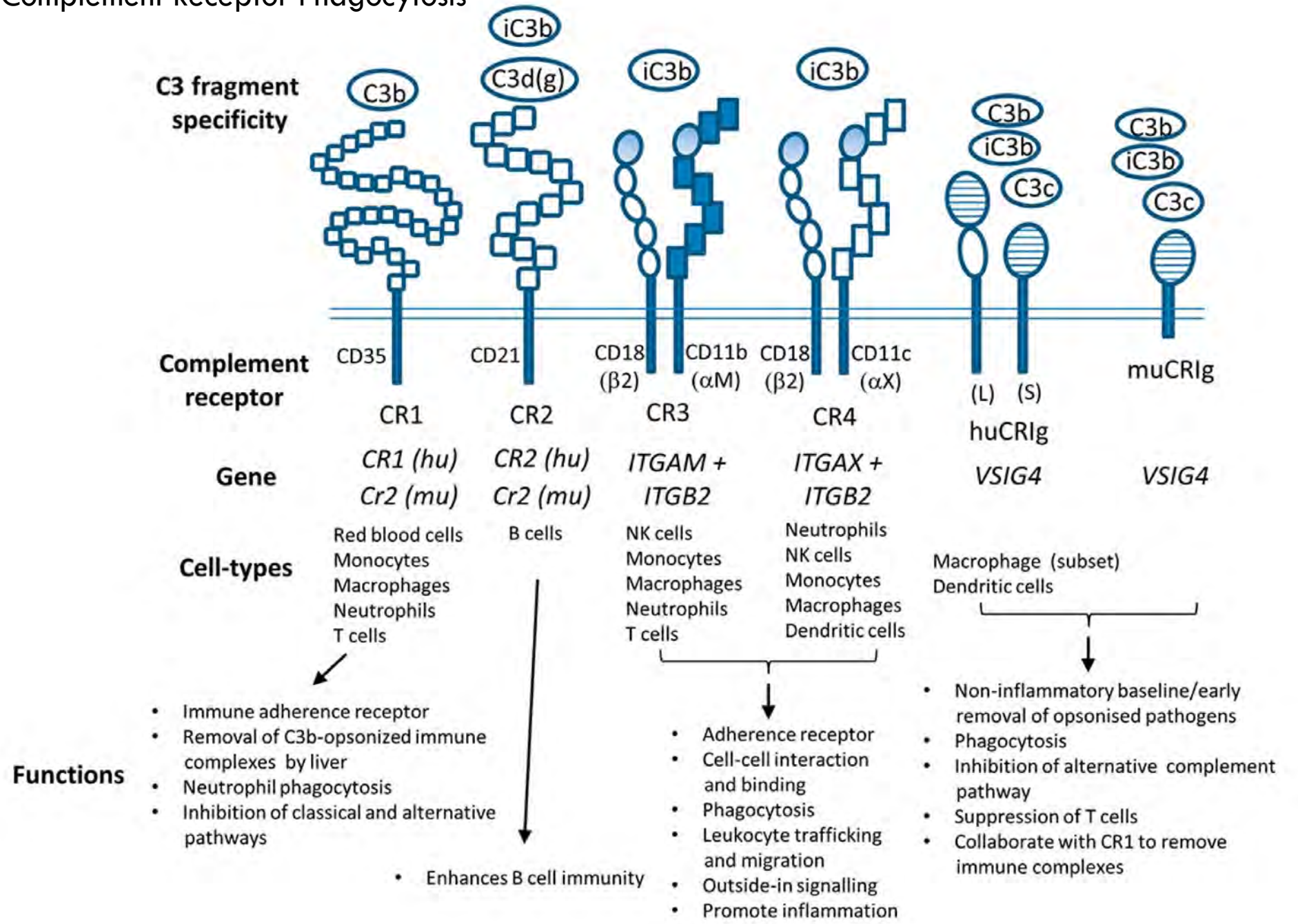
# Fc Receptor (Antibody) Phagocytosis



## Fc Receptor (Antibody) Phagocytosis



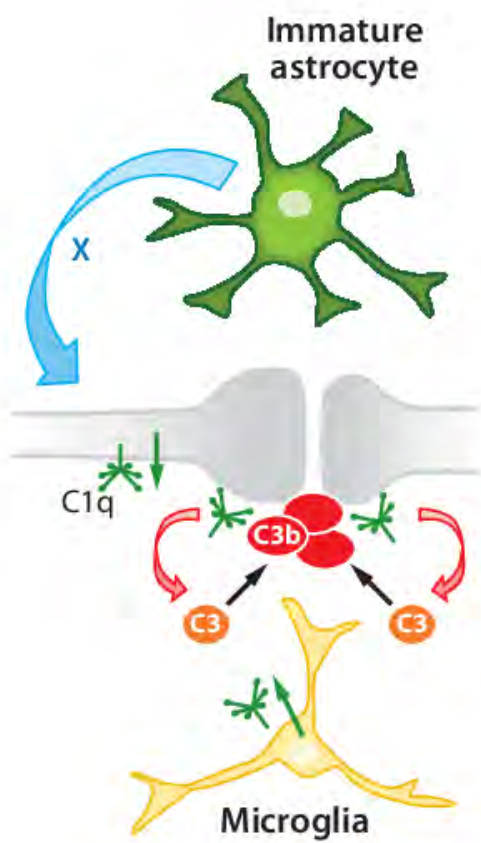
# Complement Receptor Phagocytosis



# Complement Receptor Phagocytosis – Synaptic Pruning???

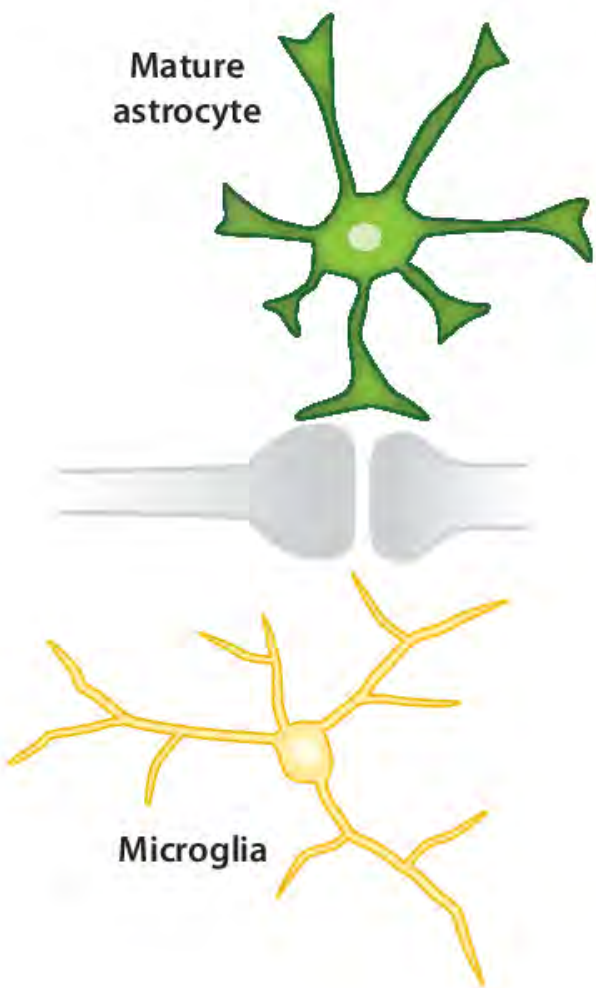
**a**

**Developing brain**  
Synapse elimination



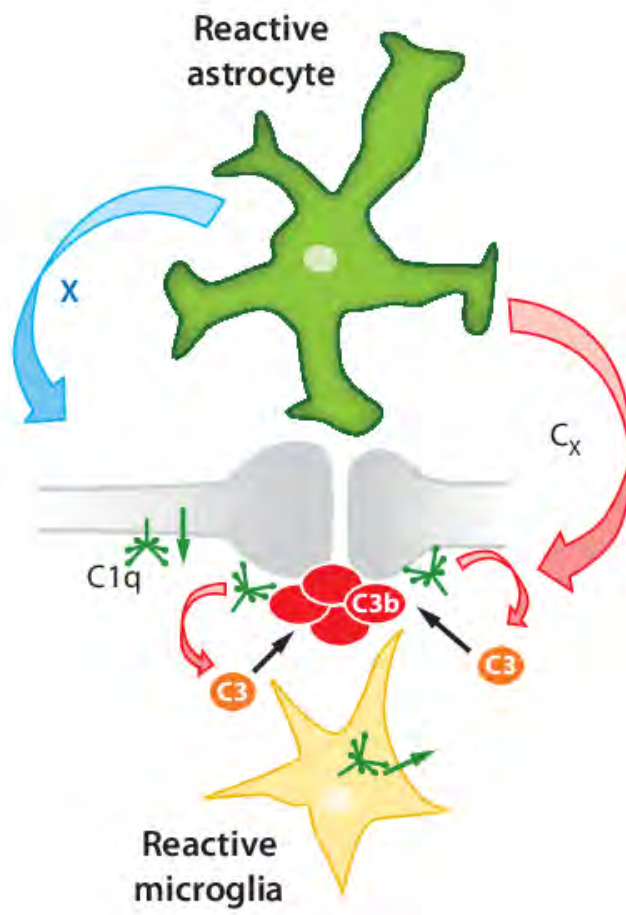
**b**

**Mature brain**  
Stable connections



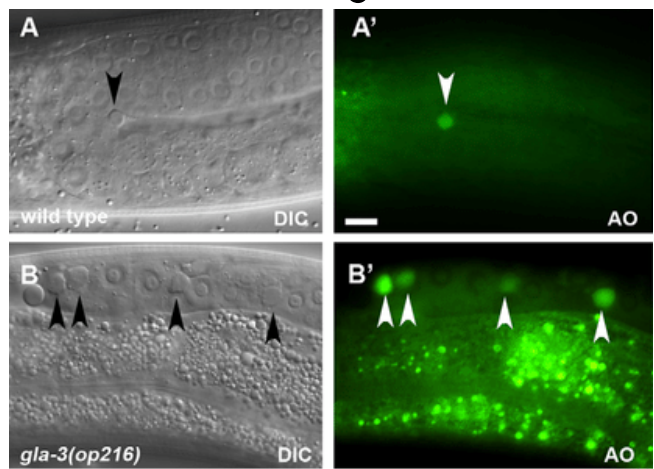
**c**

**Neurodegenerative diseases**  
Excessive synapse elimination

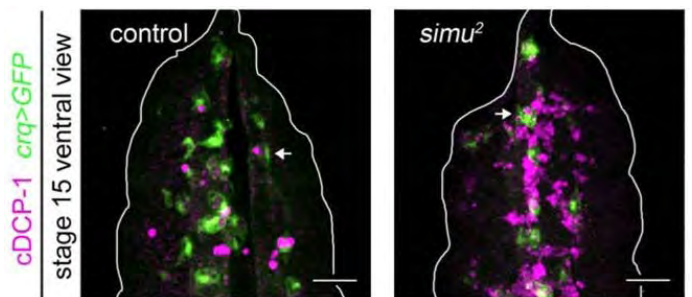


# Apoptotic Cell Clearance (aka Efferocytosis)

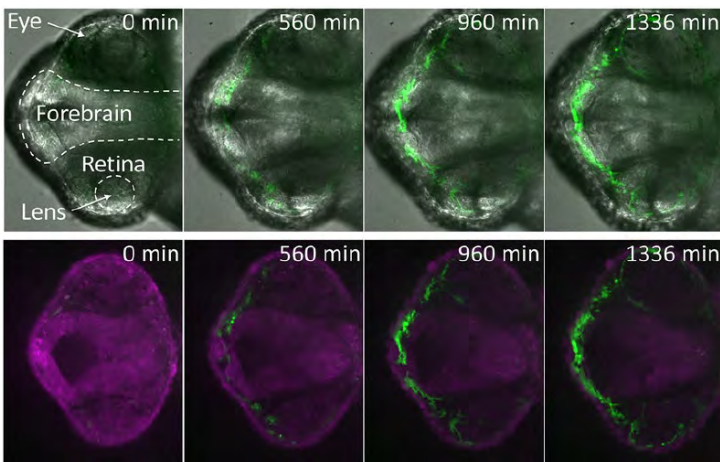
## C. elegans



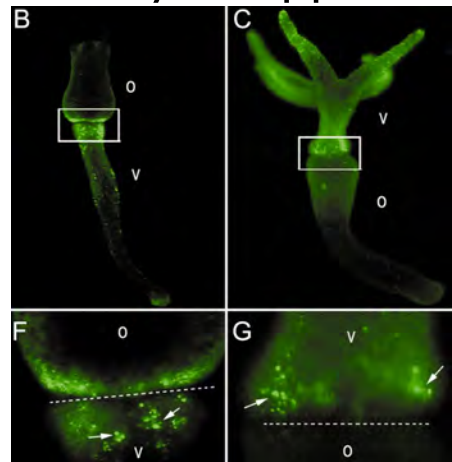
## D. melanogaster



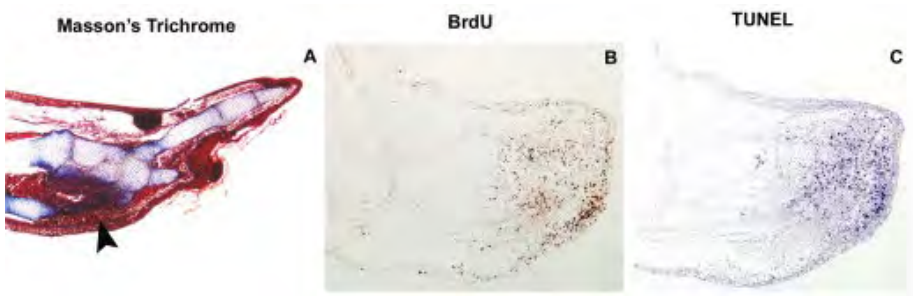
## Zebrafish



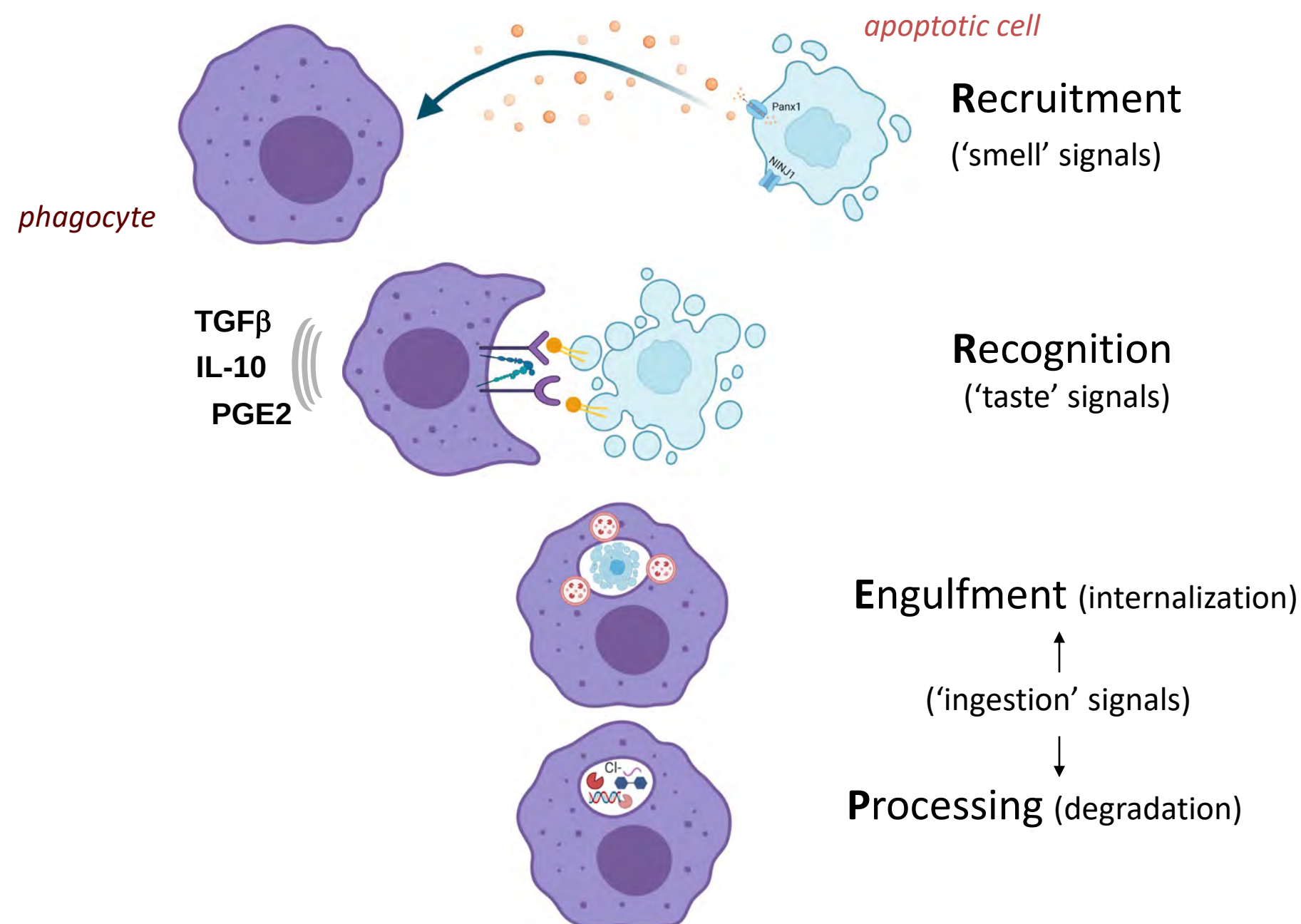
## Hydra spp.



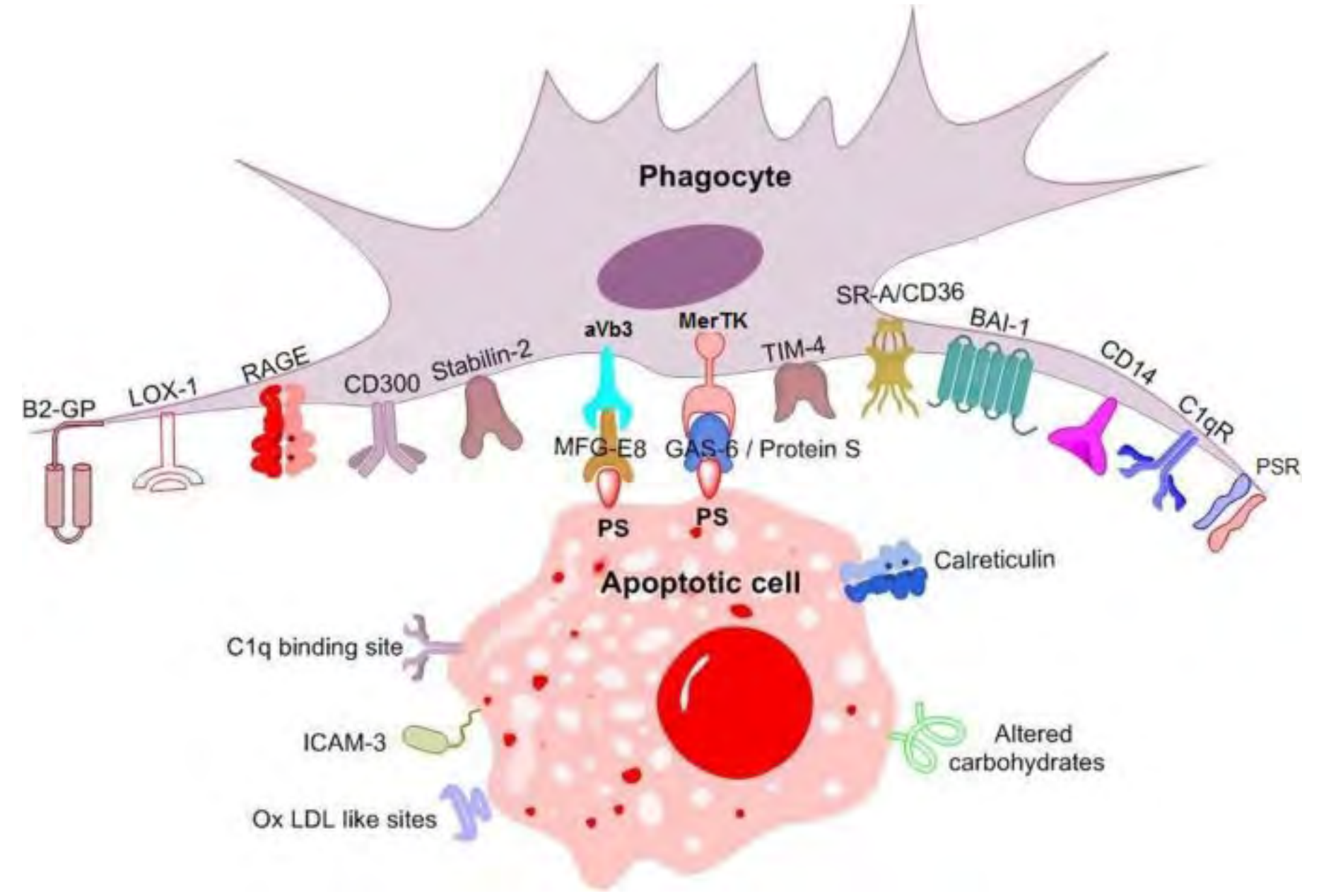
## Axolotl (A. mexicanum)



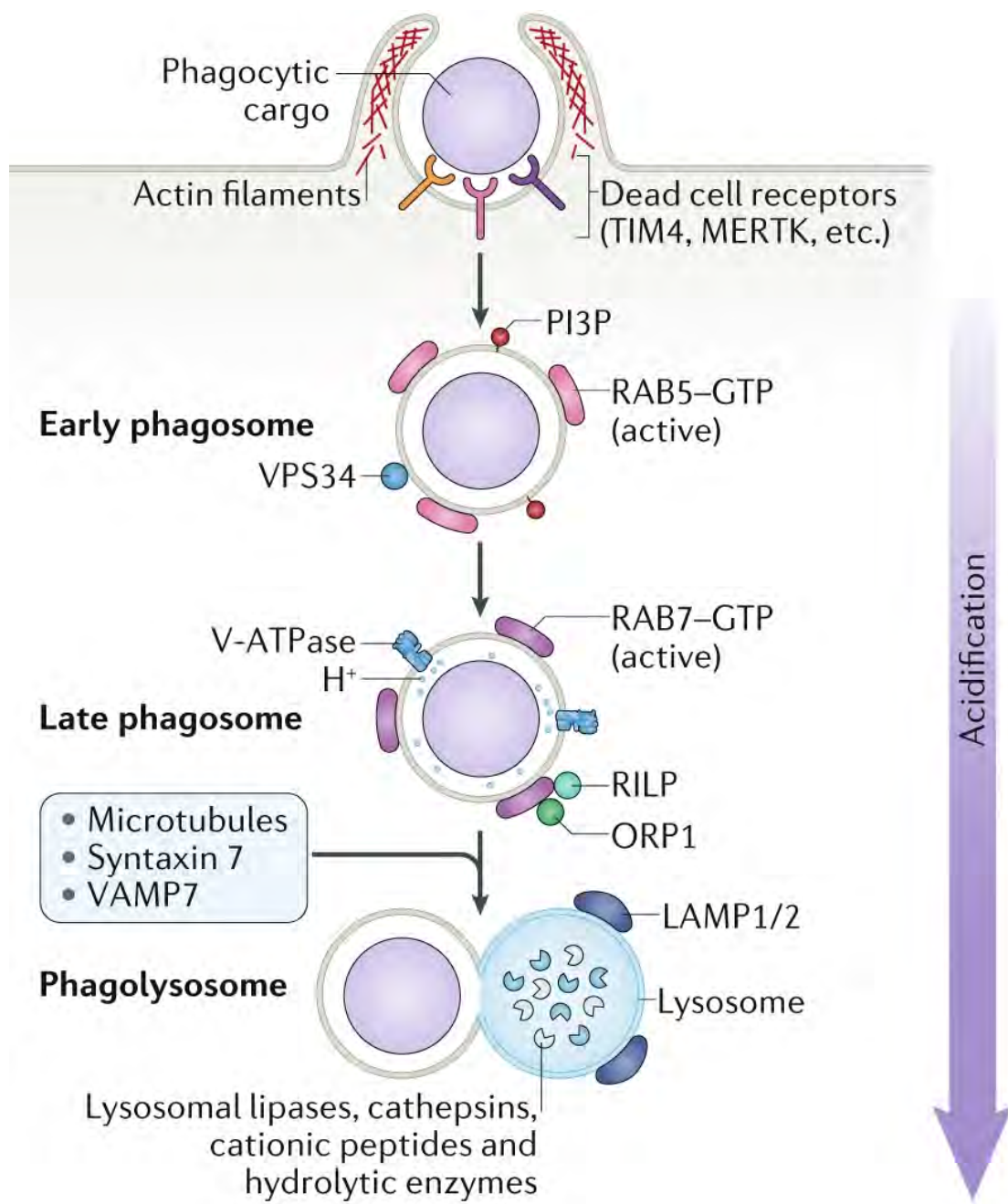
# Apoptotic Cell Clearance (aka Efferocytosis)



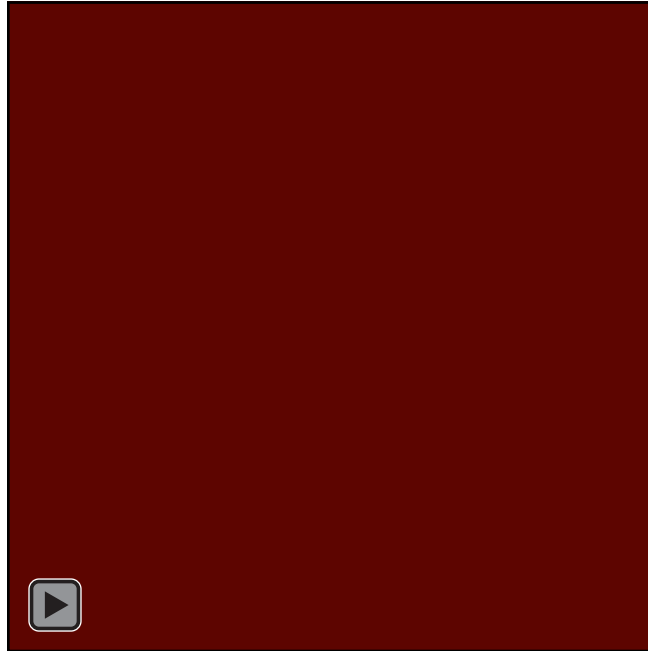
Apoptotic Cell Clearance (aka Efferocytosis)



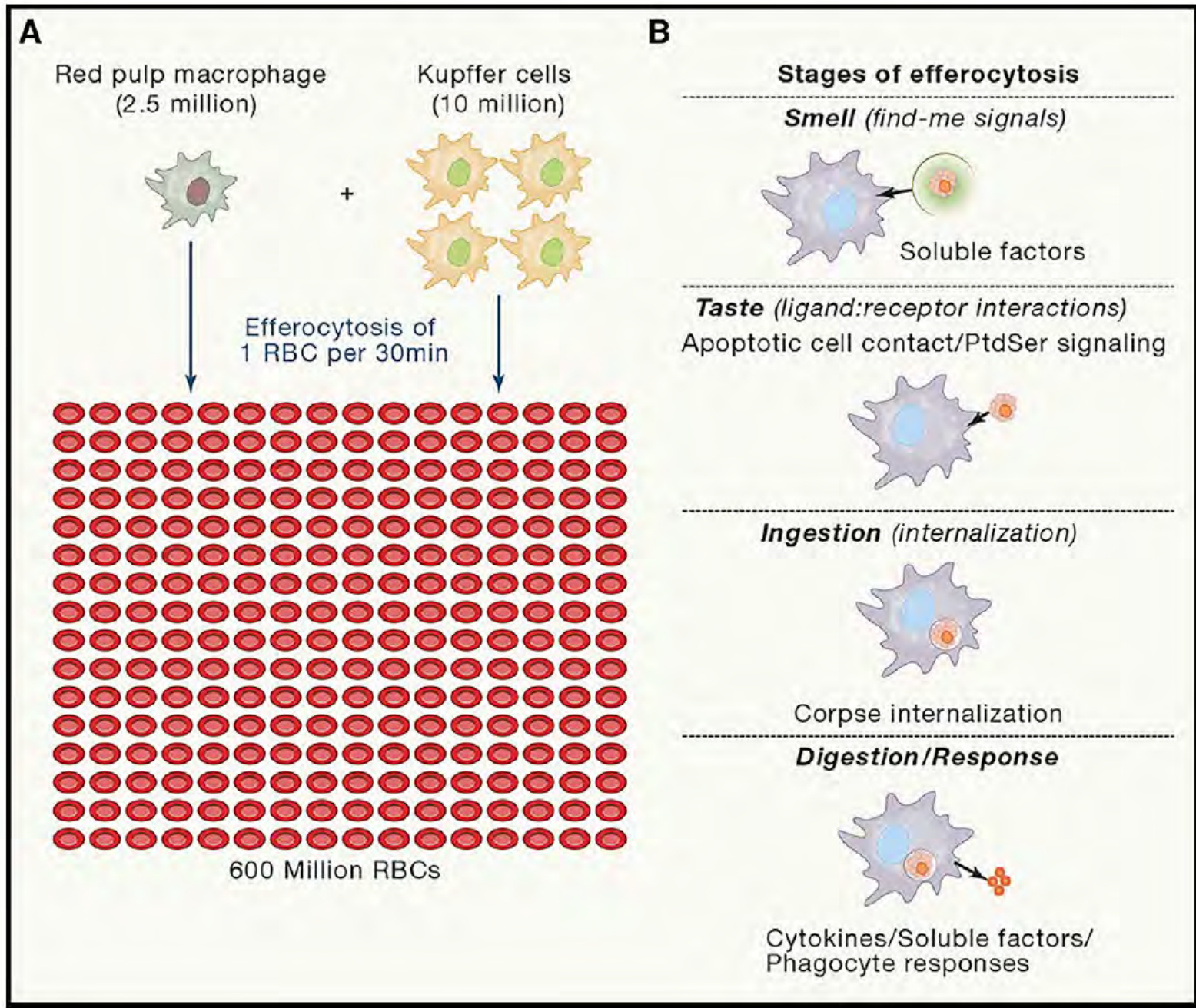
# Apoptotic Cell Clearance (aka Efferocytosis)



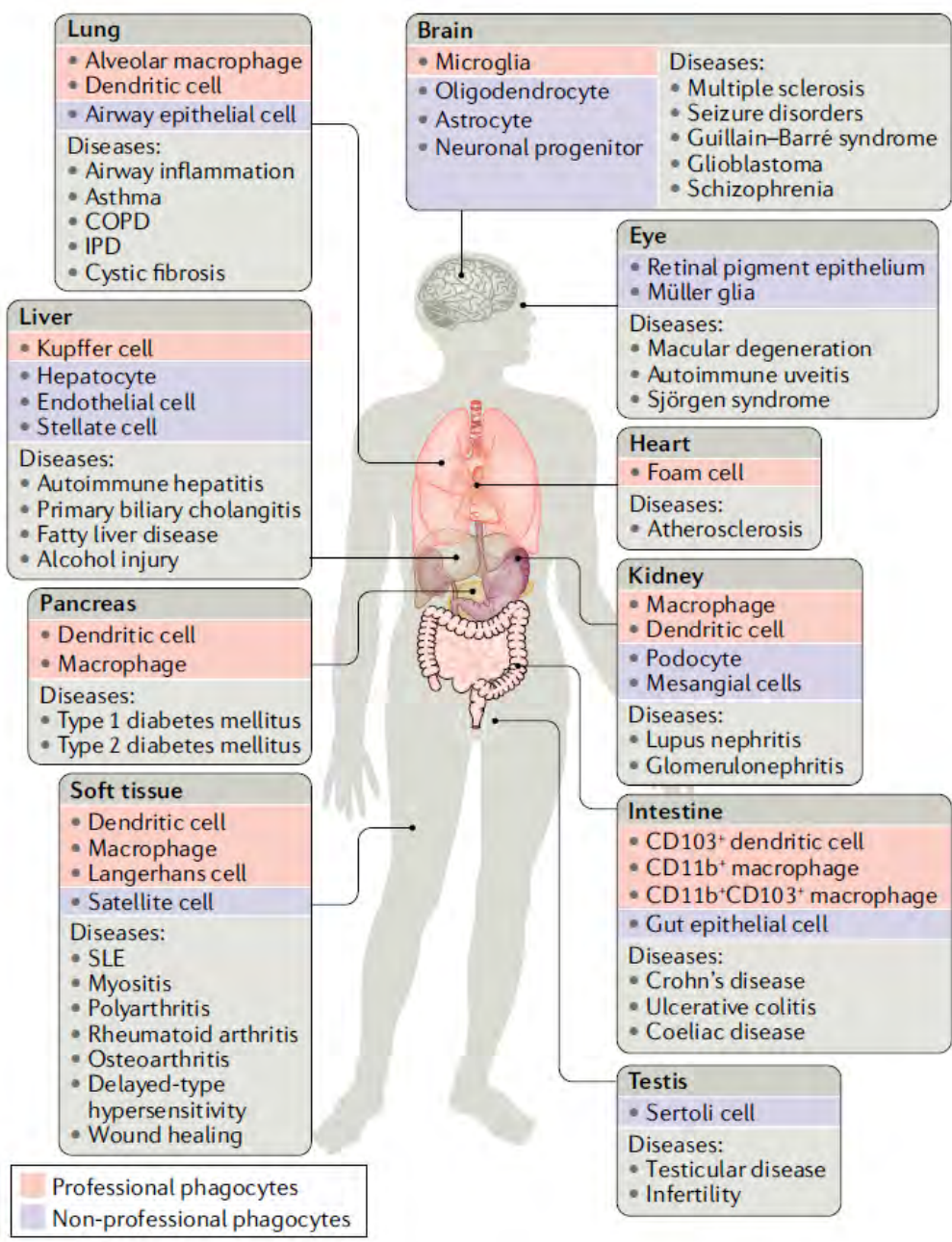
# Apoptotic Cell Clearance (aka Efferocytosis)



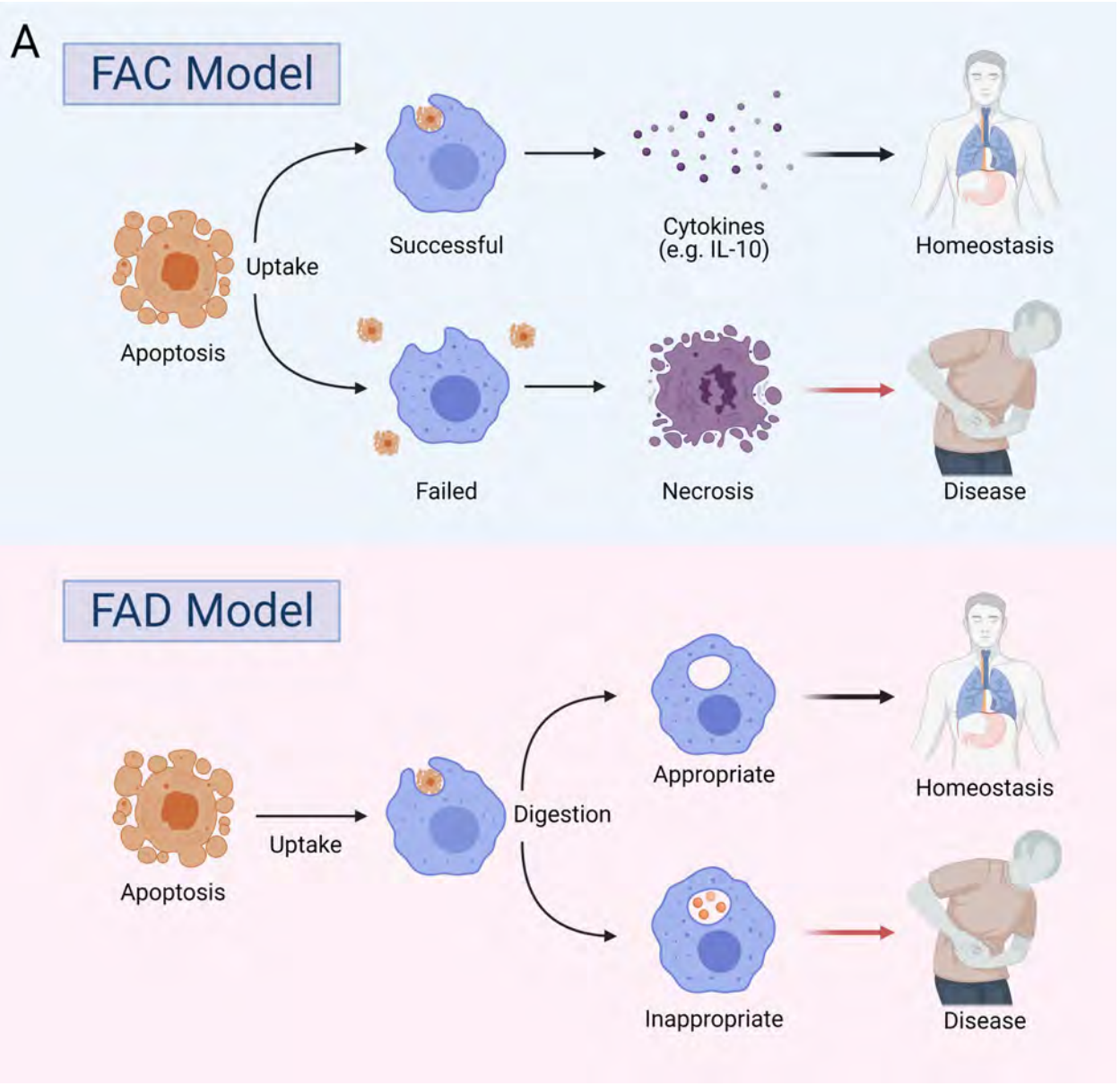
# Apoptotic Cell Clearance (aka Efferocytosis)



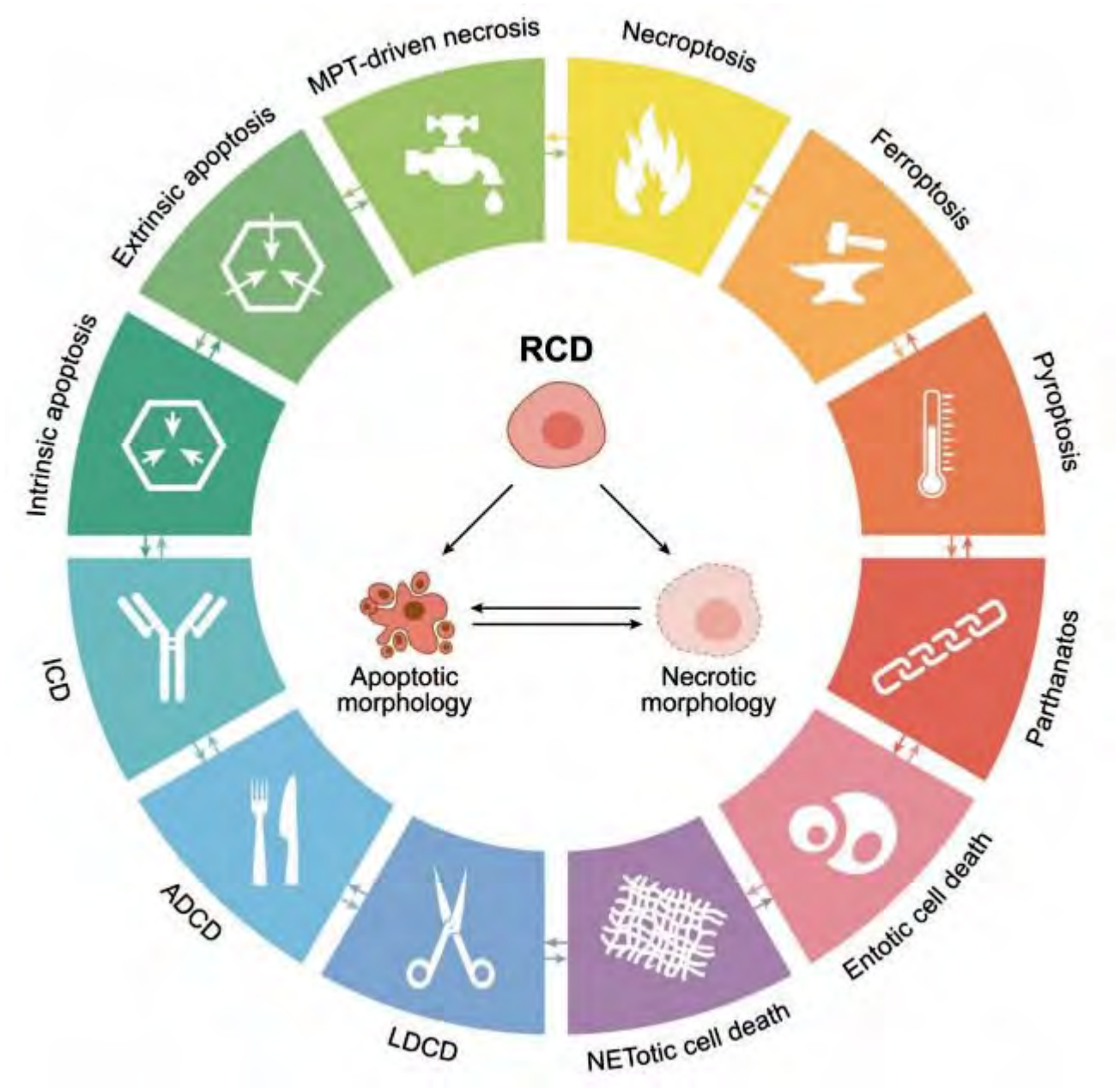
# Apoptotic Cell Clearance (aka Efferocytosis)



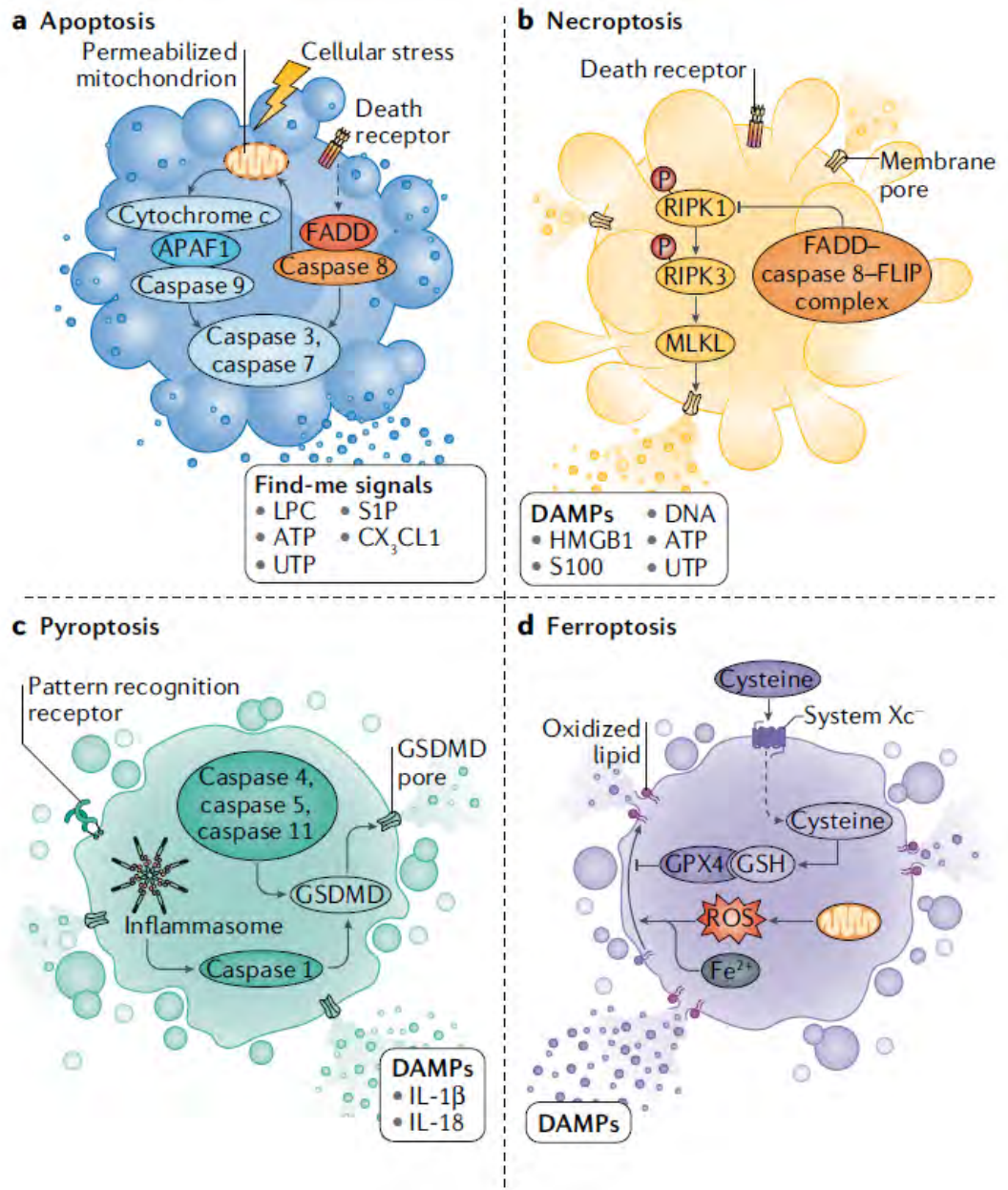
A proposed model for the development of autoimmunity & chronic inflammatory disease



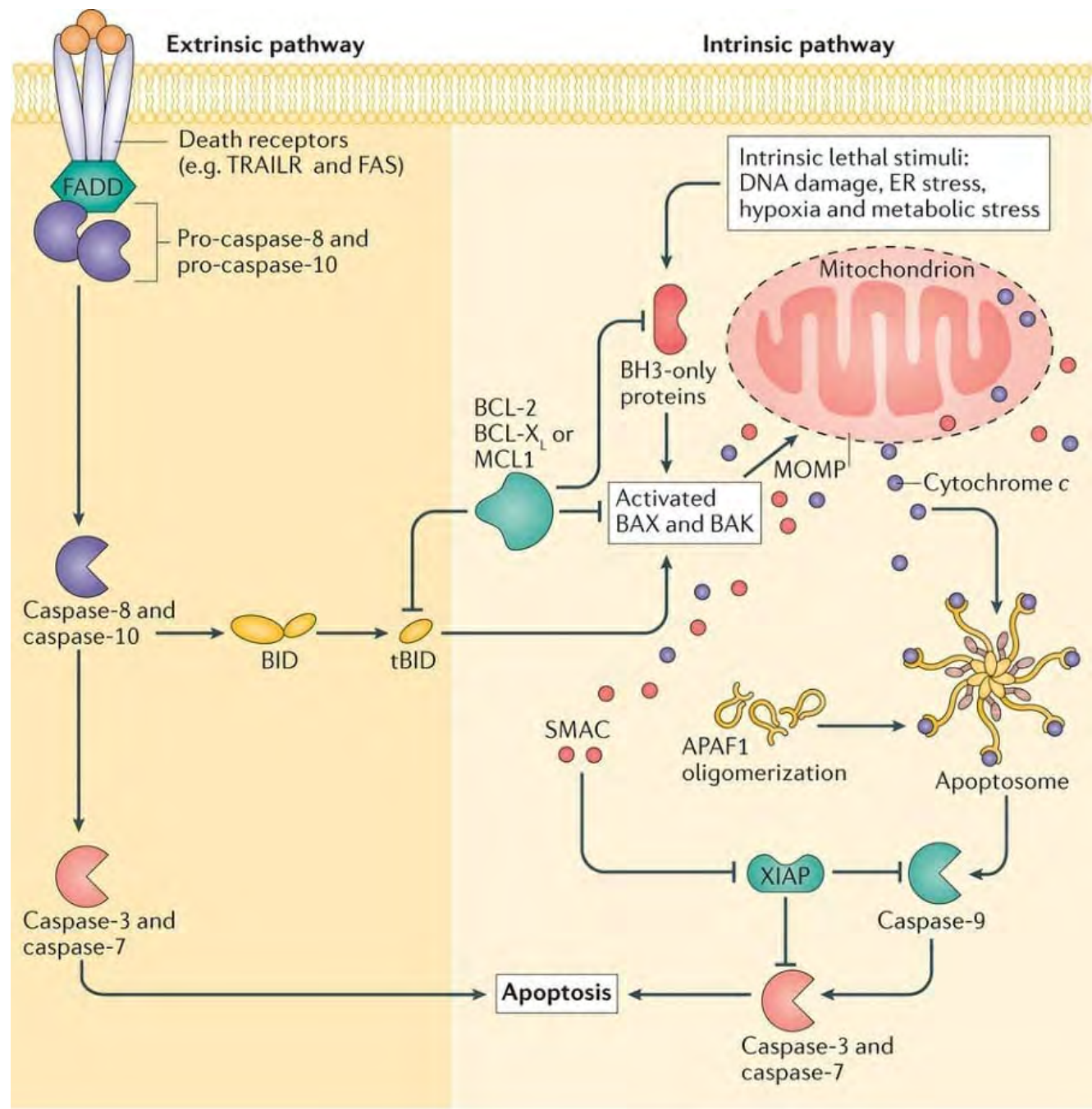
A note on cell death



A note on cell death



# Apoptosis: Pathways



# Innate Immunity

GSK Immunology

Additional Useful Information

| Routes of infection for pathogens   |                                                                       |                                                                                                                                                                               |                                                                                                                         |                                                                                                                                                |
|-------------------------------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| Route of entry                      | Mode of transmission                                                  | Pathogen                                                                                                                                                                      | Disease                                                                                                                 | Type of pathogen                                                                                                                               |
| Mucosal surfaces                    |                                                                       |                                                                                                                                                                               |                                                                                                                         |                                                                                                                                                |
| Mouth and respiratory tract         | Inhalation or ingestion of infective material (e.g., saliva droplets) | Measles virus<br>Influenza virus<br>Varicella-zoster<br>Epstein-Barr virus<br><i>Streptococcus pyogenes</i><br><i>Haemophilus influenzae</i><br><i>Neisseria meningitidis</i> | Measles<br>Influenza<br>Chickenpox<br>Mononucleosis<br>Tonsillitis<br>Pneumonia, meningitis<br>Meningococcal meningitis | Paramyxovirus<br>Orthomyxovirus<br>Herpesvirus<br>Herpesvirus<br>Gram-positive bacterium<br>Gram-negative bacterium<br>Gram-negative bacterium |
|                                     | Spores                                                                | <i>Bacillus anthracis</i>                                                                                                                                                     | Inhalation anthrax                                                                                                      | Gram-positive bacterium                                                                                                                        |
| Gastrointestinal tract              | Contaminated water or food                                            | Rotavirus<br>Hepatitis A<br><i>Salmonella enteritidis</i> ,<br><i>S. typhimurium</i><br><i>Vibrio cholerae</i><br><i>Salmonella typhi</i><br><i>Trichuris trichiura</i>       | Diarrhea<br>Jaundice<br>Food poisoning<br>Cholera<br>Typhoid fever<br>Trichuriasis                                      | Rotavirus<br>Picornavirus<br>Gram-negative bacterium<br>Gram-negative bacterium<br>Gram-negative bacterium<br>Helminth                         |
|                                     |                                                                       |                                                                                                                                                                               |                                                                                                                         |                                                                                                                                                |
| Reproductive tract and other routes | Sexual transmission/<br>infected blood                                | Hepatitis B virus<br>Human immunodeficiency virus (HIV)                                                                                                                       | Hepatitis B<br>Acquired immunodeficiency syndrome (AIDS)                                                                | Hepadnavirus<br>Retrovirus                                                                                                                     |
|                                     | Sexual transmission                                                   | <i>Neisseria gonorrhoeae</i><br><i>Treponema pallidum</i>                                                                                                                     | Gonorrhea<br>Syphilis                                                                                                   | Gram-negative bacterium<br>Bacterium (spirochete)                                                                                              |
| Opportunistic infections            | Resident microbiota                                                   | <i>Candida albicans</i>                                                                                                                                                       | Candidiasis, thrush                                                                                                     | Fungus                                                                                                                                         |
|                                     | Resident lung microbiota                                              | <i>Pneumocystis jirovecii</i>                                                                                                                                                 | Pneumonia                                                                                                               | Fungus                                                                                                                                         |

Figure 2.2 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

## Routes of infection for pathogens

| Route of entry            | Mode of transmission                       | Pathogen                      | Disease           | Type of pathogen        |
|---------------------------|--------------------------------------------|-------------------------------|-------------------|-------------------------|
| <b>External epithelia</b> |                                            |                               |                   |                         |
| External surface          | Physical contact                           | <i>Trichophyton</i>           | Athlete's foot    | Fungus                  |
| Wounds and abrasions      | Minor skin abrasions                       | <i>Bacillus anthracis</i>     | Cutaneous anthrax | Gram-positive bacterium |
|                           | Puncture wounds                            | <i>Clostridium tetani</i>     | Tetanus           | Gram-positive bacterium |
|                           | Handling infected animals                  | <i>Francisella tularensis</i> | Tularemia         | Gram-negative bacterium |
| Insect bites              | Mosquito bites<br>( <i>Aedes aegypti</i> ) | Flavivirus                    | Yellow fever      | Virus                   |
|                           | Deer tick bites                            | <i>Borrelia burgdorferi</i>   | Lyme disease      | Bacterium (spirochete)  |
|                           | Mosquito bites<br>( <i>Anopheles</i> )     | <i>Plasmodium</i> spp.        | Malaria           | Protozoan               |

Figure 2.2 (part 2 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

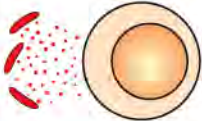
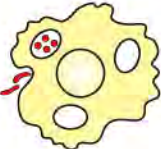
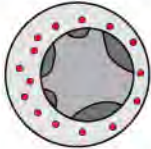
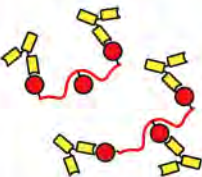
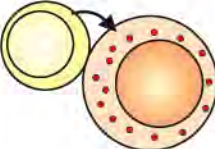
| Pathogenic mechanism | Direct mechanisms of tissue damage by pathogens                                                                                                            |                                                                                                                                                                   |                                                                                                                                                               | Indirect mechanisms of tissue damage by pathogens                                                                            |                                                                                     |                                                                                                                                                                                             |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | Exotoxin production                                                                                                                                        | Endotoxin                                                                                                                                                         | Direct cytopathic effect                                                                                                                                      | Immune complexes                                                                                                             | Anti-host antibody                                                                  | Cell-mediated immunity                                                                                                                                                                      |
|                      |                                                                           |                                                                                  |                                                                              |                                           |  |                                                                                                          |
| Infectious agent     | <i>Streptococcus pyogenes</i><br><i>Staphylococcus aureus</i><br><i>Corynebacterium diphtheriae</i><br><i>Clostridium tetani</i><br><i>Vibrio cholerae</i> | <i>Escherichia coli</i><br><i>Haemophilus influenzae</i><br><i>Salmonella typhi</i><br><i>Shigella</i><br><i>Pseudomonas aeruginosa</i><br><i>Yersinia pestis</i> | Varicella-zoster virus<br>Hepatitis B virus<br>Polio virus<br>Measles virus<br>Influenza virus<br>Herpes simplex virus<br>Human herpes virus 8 (HHV8)         | Hepatitis B virus<br>Malaria<br><i>Streptococcus pyogenes</i><br><i>Treponema pallidum</i><br>Most acute infections          | <i>Streptococcus pyogenes</i><br><i>Mycoplasma pneumoniae</i>                       | Lymphocytic choriomeningitis virus<br>Herpes simplex virus<br><i>Mycobacterium tuberculosis</i><br><i>Mycobacterium leprae</i><br><i>Borrelia burgdorferi</i><br><i>Schistosoma mansoni</i> |
| Disease              | Tonsillitis, scarlet fever<br>Boils, toxic shock syndrome, food poisoning<br>Diphtheria<br>Tetanus<br>Cholera                                              | Gram-negative sepsis<br>Meningitis, pneumonia<br>Typhoid fever<br>Bacillary dysentery<br>Wound infection<br>Plague                                                | Smallpox<br>Chickenpox, shingles<br>Hepatitis<br>Poliomyelitis<br>Measles, subacute sclerosing panencephalitis<br>Influenza<br>Cold sores<br>Kaposi's sarcoma | Kidney disease<br>Vascular deposits<br>Glomerulonephritis<br>Kidney damage in secondary syphilis<br>Transient renal deposits | Rheumatic fever<br>Hemolytic anemia                                                 | Aseptic meningitis<br>Herpes stromal keratitis<br>Tuberculosis<br>Tuberculoid leprosy<br>Lyme arthritis<br>Schistosomiasis                                                                  |

Figure 2.4 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

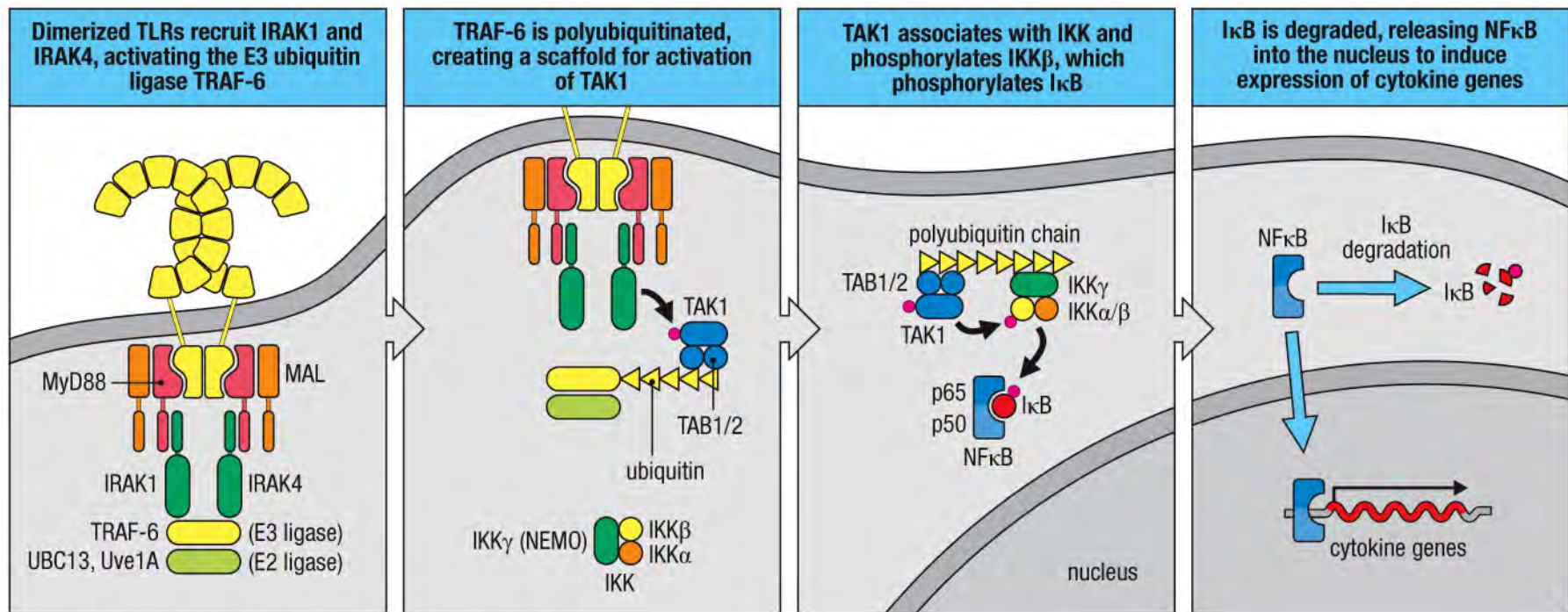


Figure 3.15 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

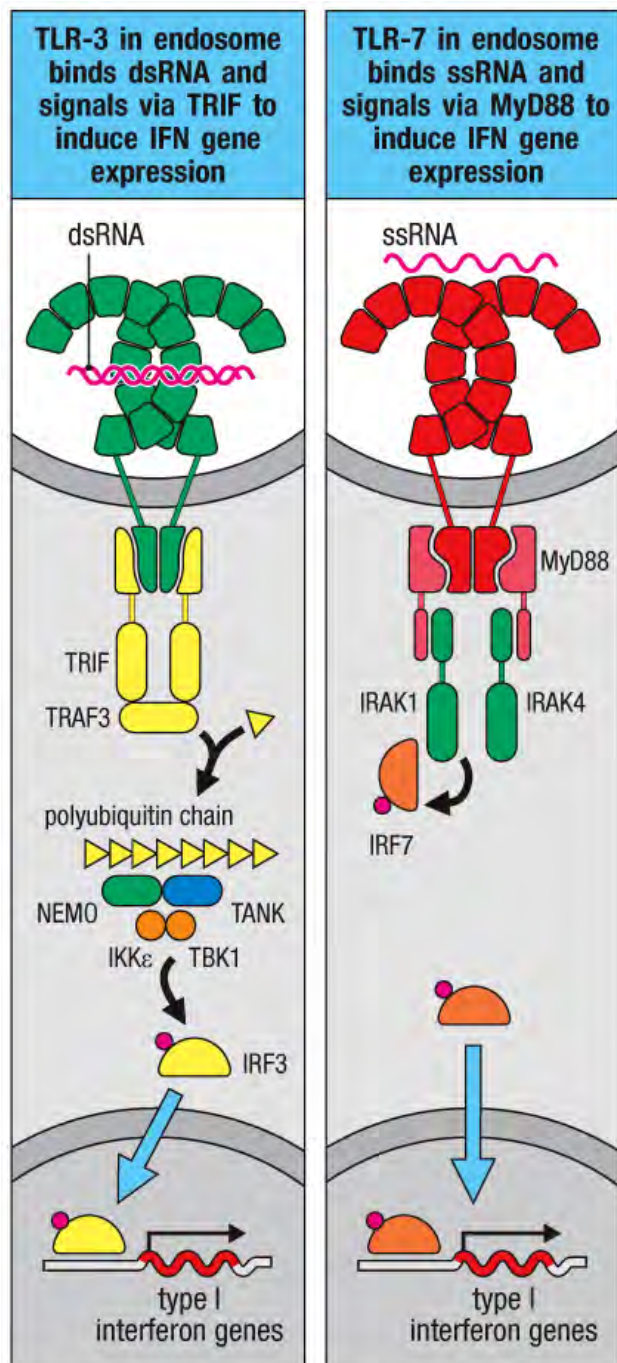


Figure 3.16 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

| Domain                      | Proteins                                                     |
|-----------------------------|--------------------------------------------------------------|
| TIR                         | MyD88, MAL, TRIF, TRAM, all TLRs                             |
| CARD                        | Caspase 1, RIP2, RIG-I, MDA-5, MAVS, NODs, NLRC4, ASC, NLRP1 |
| Pyrin                       | AIM2, IFI16, ASC, NLRP1-14                                   |
| DD (death domain)           | MyD88, IRAK1, IRAK4, DR4, DR5, FADD, FAS,                    |
| DED (death effector domain) | Caspase 8, caspase 10, FADD                                  |

Figure 3.18 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)