Cellular and Molecular Immunology MIC 3004

Introduction to Immune Response

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Distinguishing features of immune response

RECOGNITION

- Self/ Non Self discrimination
- Nonreactive to self
- Specificity: Adaptive more specific than innate
- Diversity: ability to respond to wide range of antigens/foreign material

USE OF CELL SURFACE/

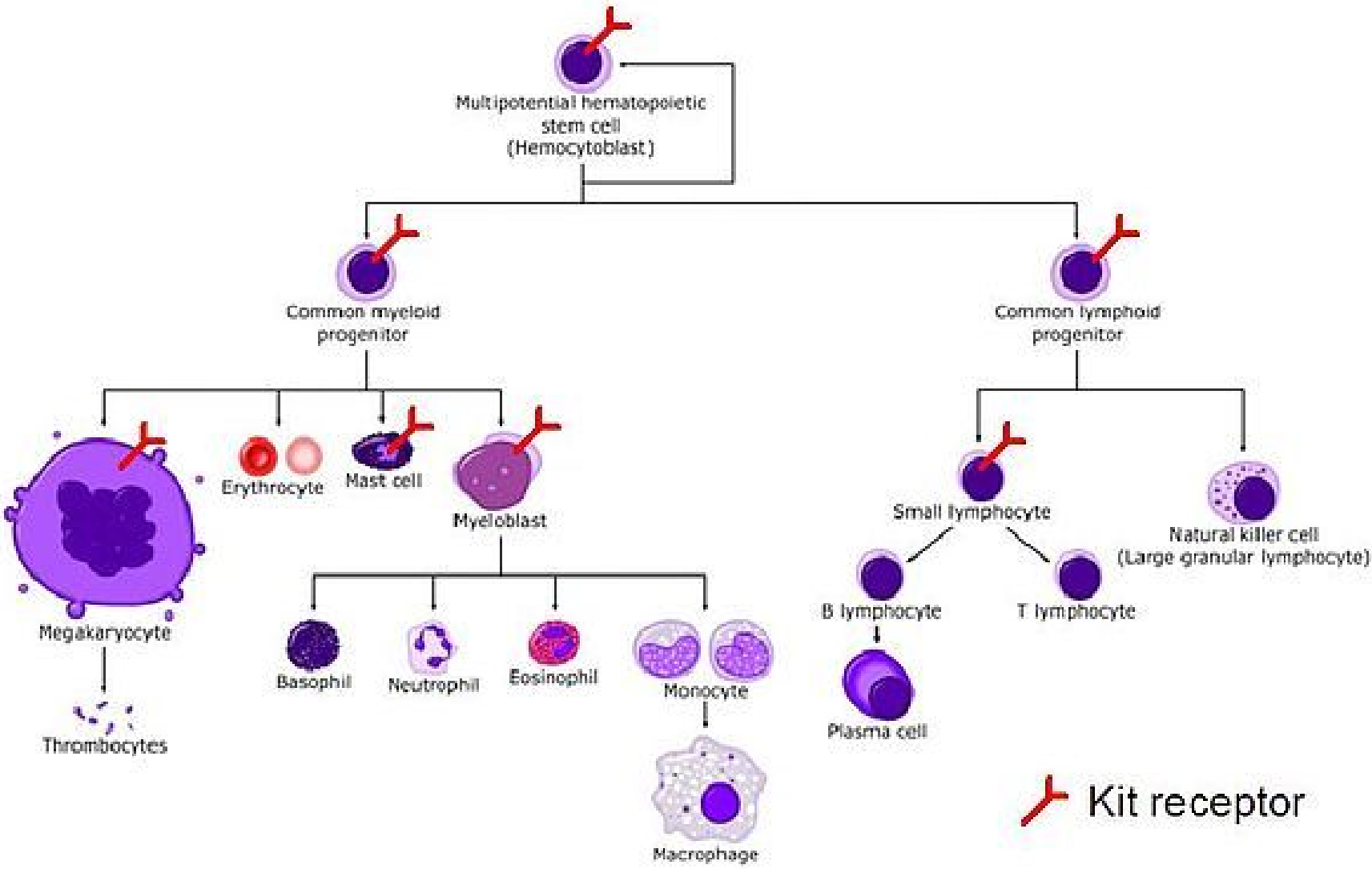
INTRACELLULAR RECEPTOR

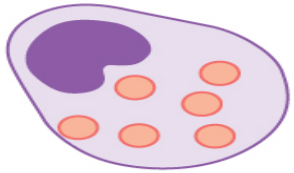
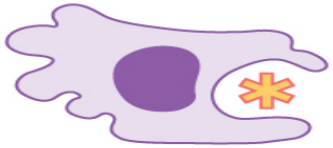
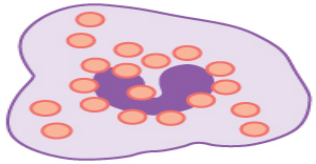
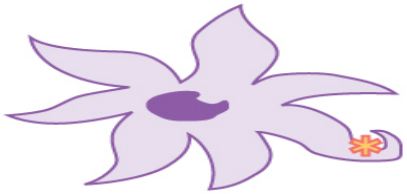
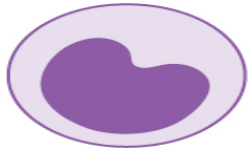
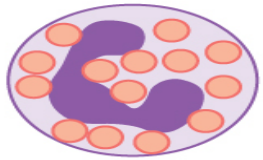
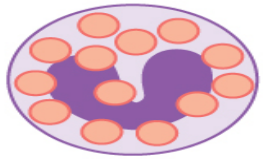
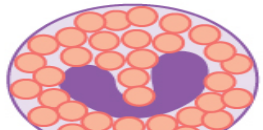
Distinguishing features of adaptive immune response

ACTION

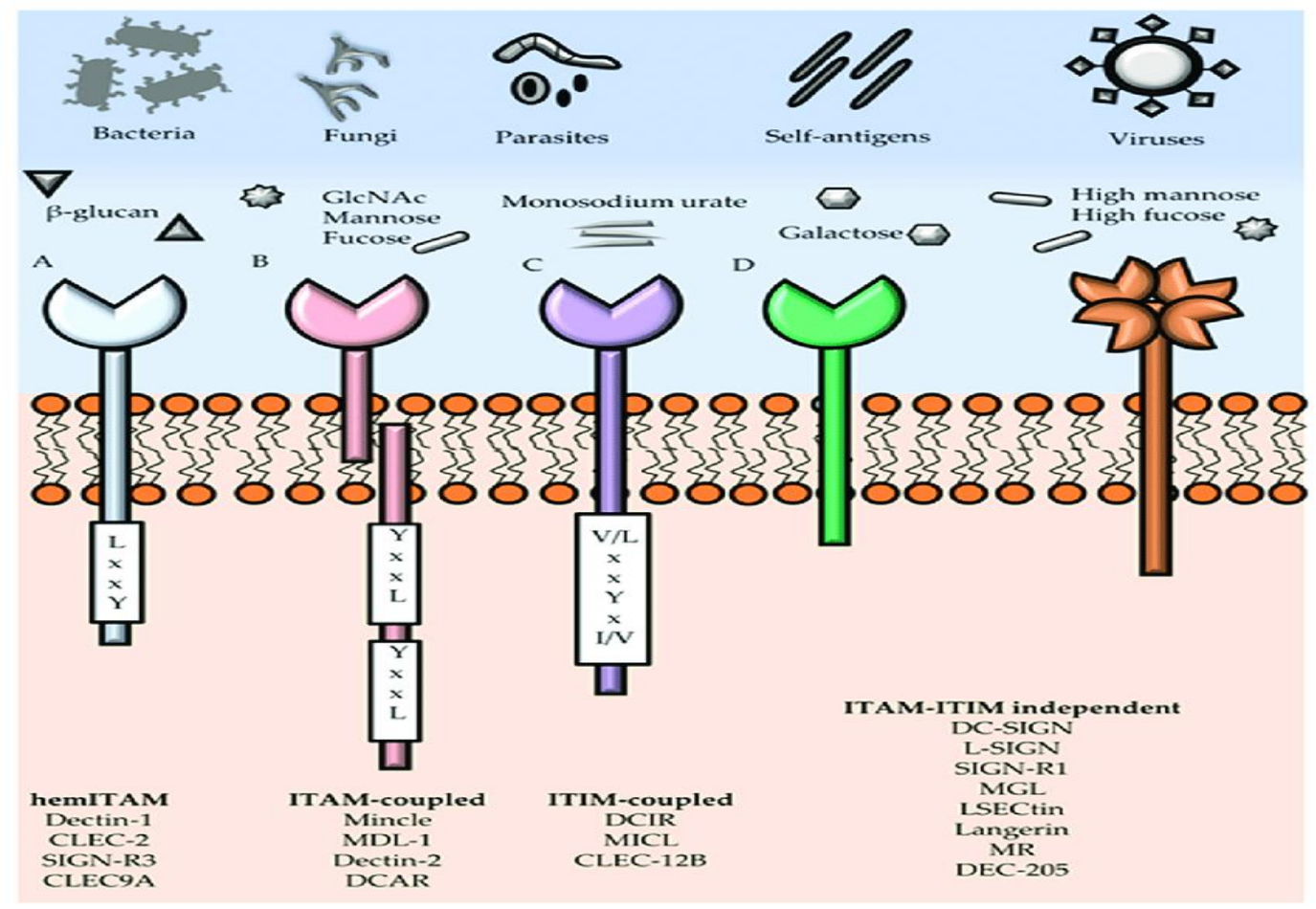
- Specialization: optimal defense against specific type of antigens
- Memory: enhanced response on repeated exposure
- Clonal Expansion: Increase in number of clones specific for particular antigen
- Self limiting/Homeostasis and Contraction: Regulate response and generate balance via feedback regulation

Kit Expression in Hematopoietic Cells

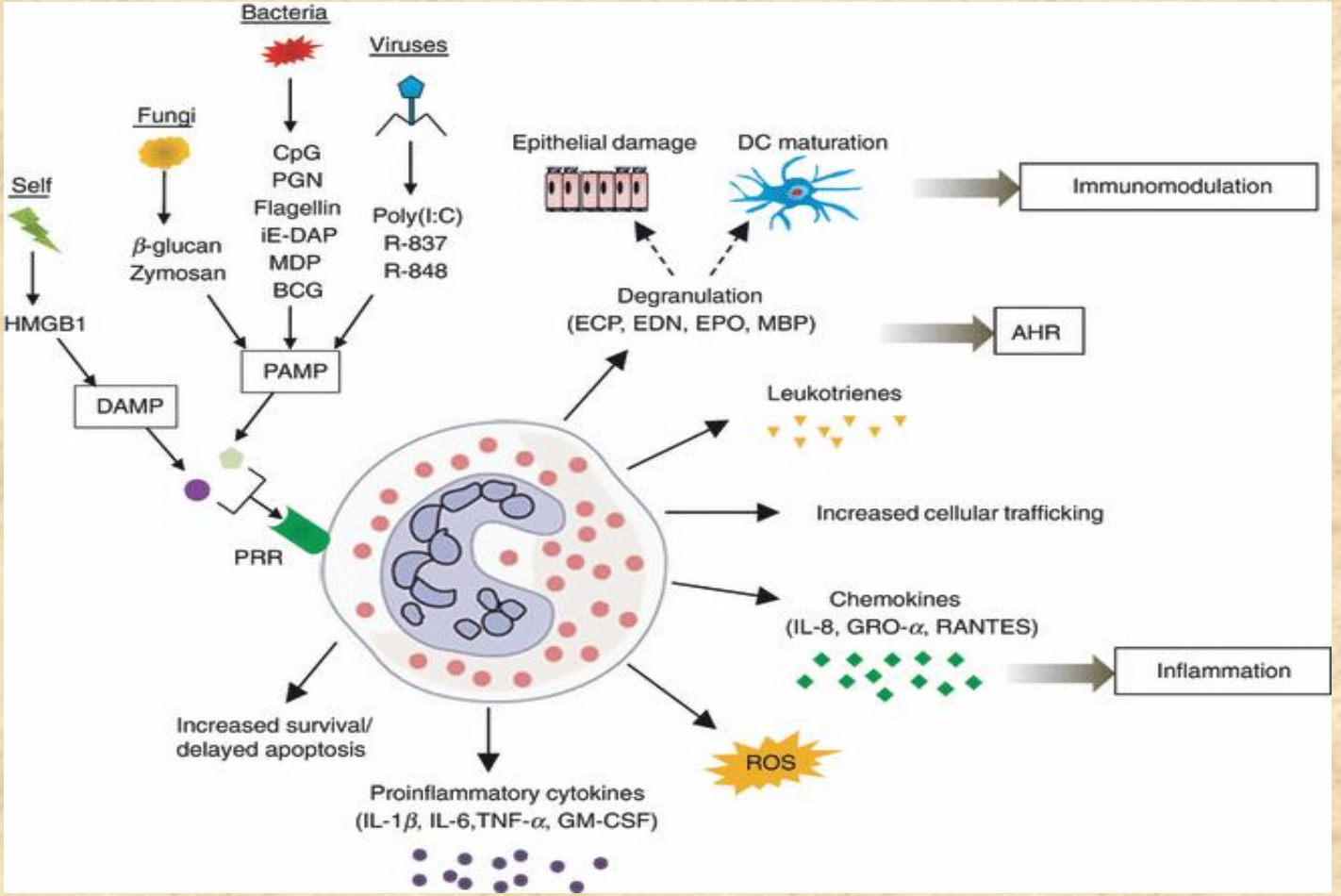


Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign pathogens and cancer cells. Stimulates response of other immune cells.	Migrates from blood vessels into tissues.	
Natural killer cell	Kills tumor cells and virus-infected cells.	Circulates in blood and migrates into tissues.	
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

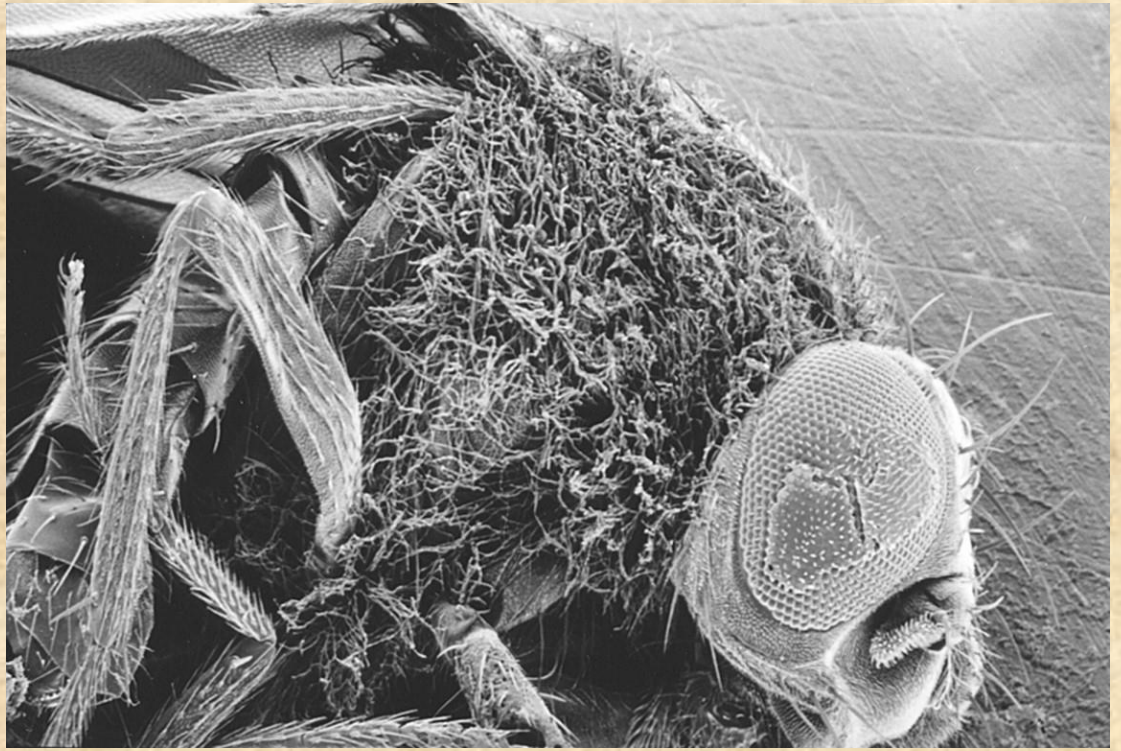
How do innate immunity distinguish self from non self ?



Post recognition of non self (Pathogen Associated Molecular Patterns) using Pathogen Recognition Receptor



Toll-mutant drosophila are susceptible to fungal infections



Discovery of the mammalian Toll-like receptors (TLR):

1997: Janeway and Medzhitov discovered a human protein with structural similarity to drosophila Toll that could activate immune response genes in human cells (TLR4).

1998: Beutler discovered that a mouse strain with an altered response to bacterial lipopolysaccharide (called LPS or endotoxin) was due to a mutation in the TLR4 gene.

There are 11 TLR family members in human and 12 in mice. Each responds to a distinct set of microbial products.

Different mammalian Toll-like receptors (TLRs) are specific for different classes of microbial products

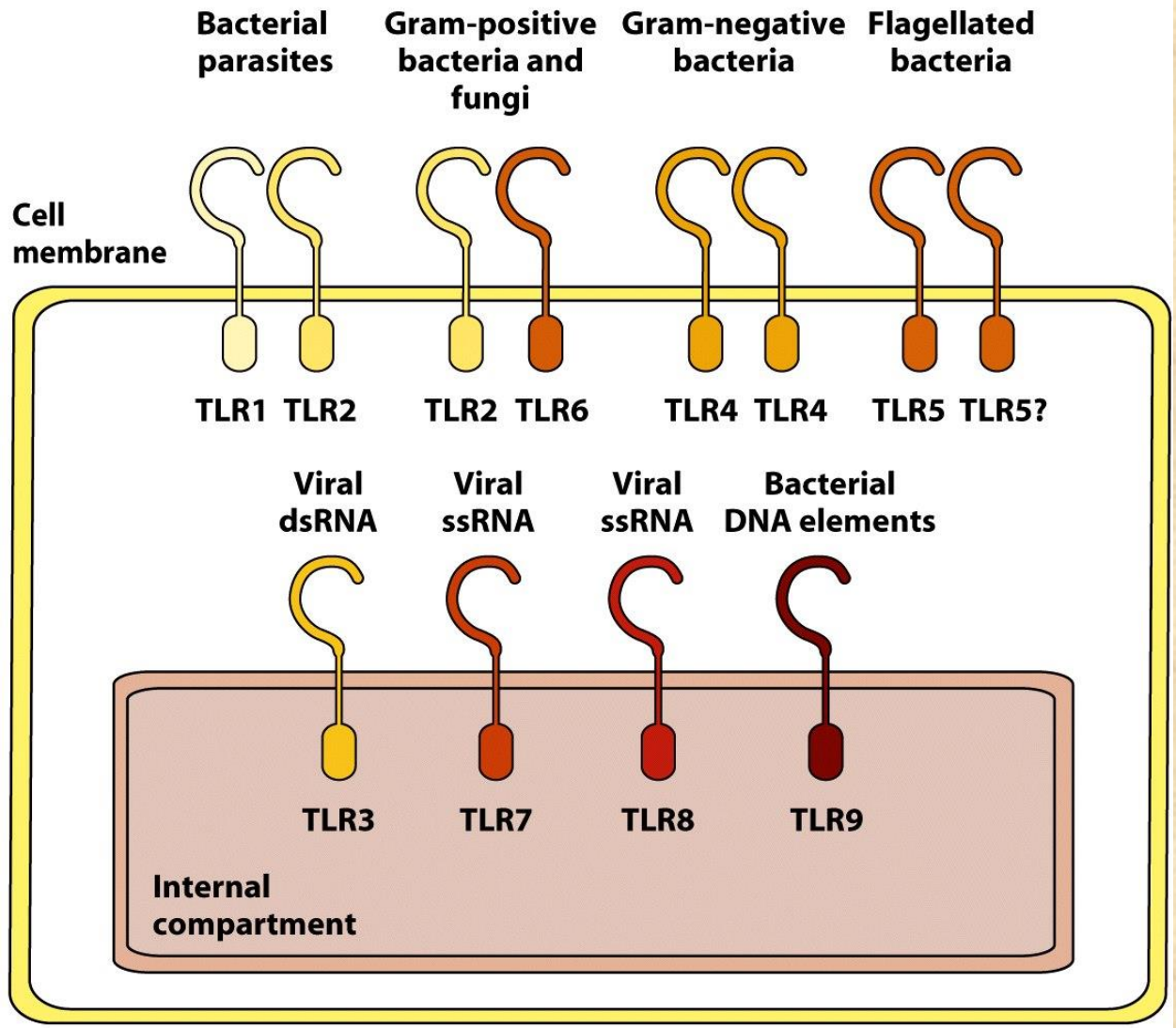
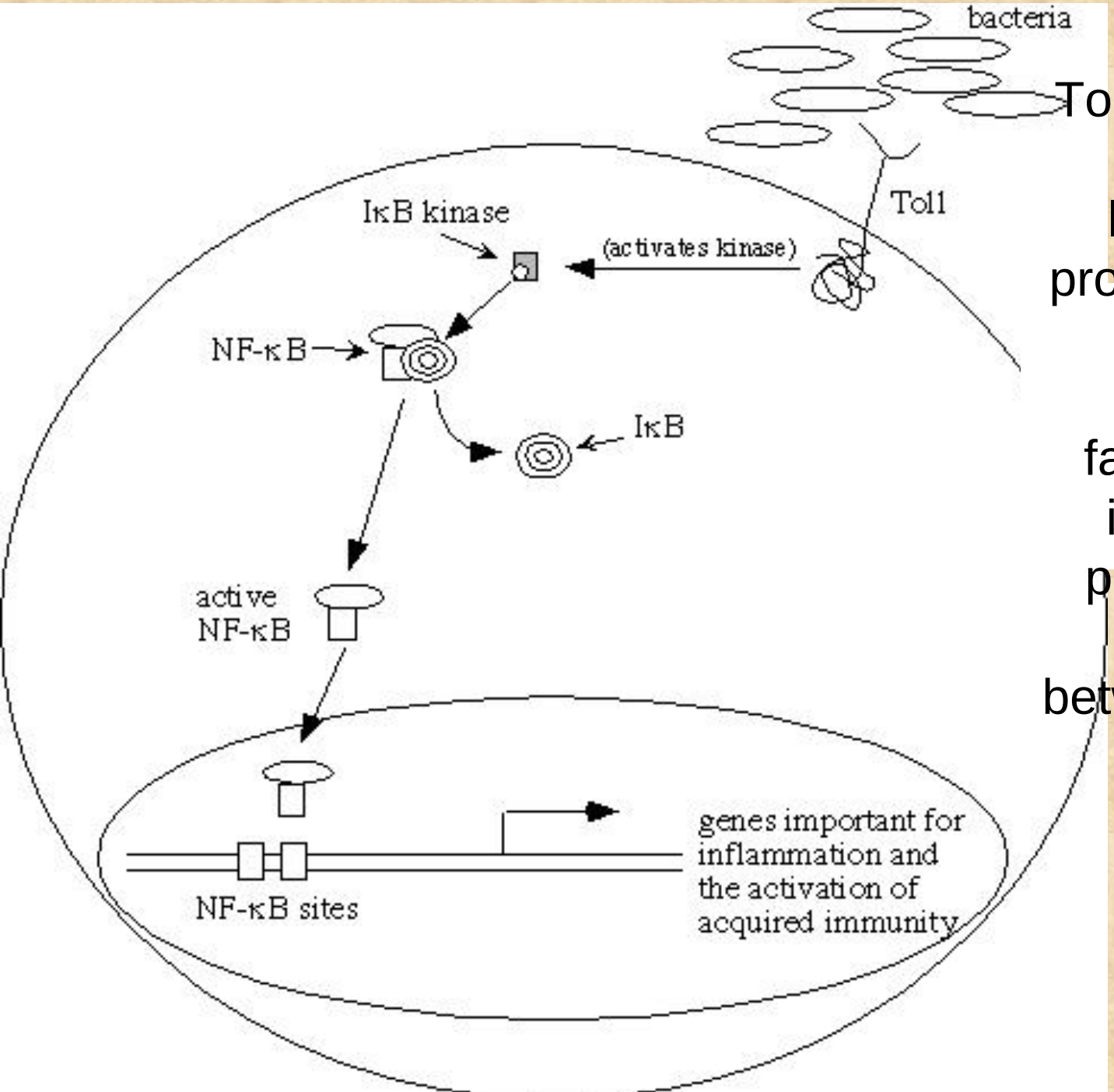


Figure 3-11 part 1
Kuby IMMUNOLOGY, Sixth Edition

Different mammalian Toll-like receptors (TLRs) are specific for different classes of microbial products

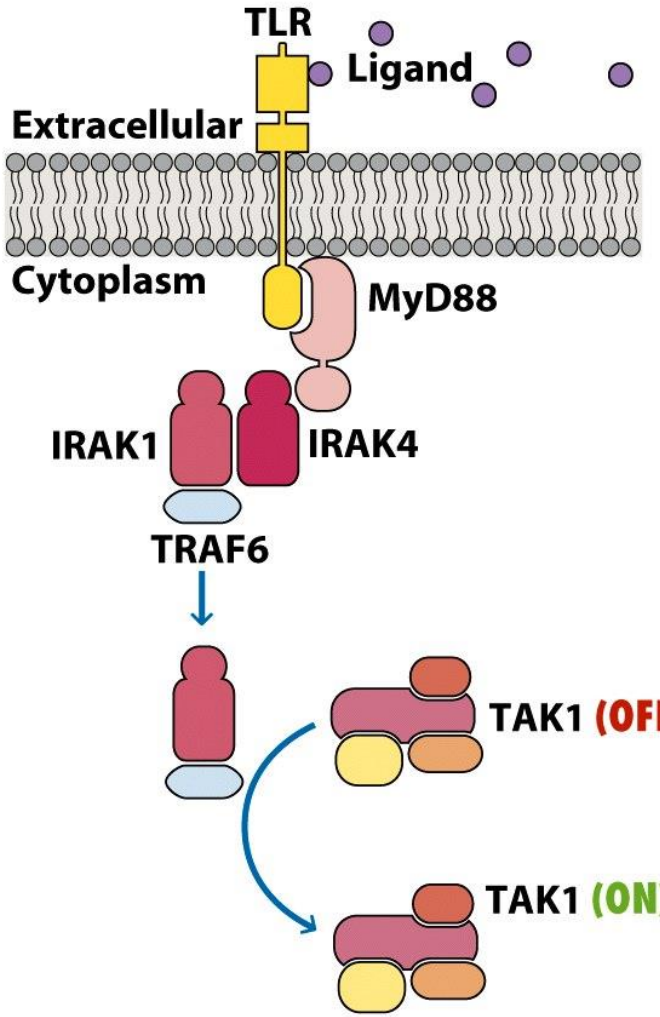
TLRs	Ligands	Target microbes
TLR1	Triacyl lipopeptides	Mycobacteria
TLR2	Peptidoglycans	Gram-positive bacteria
	GPI-linked proteins	Trypanosomes
	Lipoproteins	Mycobacteria
	Zymosan	Yeasts and other fungi
TLR3	Double-stranded RNA (dsRNA)	Viruses
TLR4	LPS	Gram-negative bacteria
	F-protein	Respiratory syncytial virus (RSV)
TLR5	Flagellin	Bacteria
TLR6	Diacyl lipopeptides	Mycobacteria
	Zymosan	Yeasts and fungi
TLR7	Single-stranded RNA (ssRNA)	Viruses
TLR8	Single-stranded RNA (ssRNA)	Viruses
TLR9	CpG unmethylated dinucleotides	Bacterial DNA
	Dinucleotides	
	Herpesvirus infection	Some herpesviruses
TLR10,11	Unknown	Unknown

Figure 3-11 part 2
Kuby IMMUNOLOGY, Sixth Edition



Toll-like receptors (TLRs) link microbial products (PAMPs) to transcription factor activation in a signaling pathway that is conserved between mammals and insects

A more detailed look at the signaling pathway down-stream of Toll-like Receptors (TLRs)



1. Ligand binding to TLR triggers association of MyD88 with TIR domain and assembly of IRAK1/IRAK4 complex

2. IRAK4 phosphorylates IRAK1, creating a binding site for TRAF6

3. The IRAK1-TRAF6 complex dissociates and activates the protein kinase TAK1 complex

Figure 3-14 part 1
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A more detailed look at the signaling pathway down-stream of Toll-like Receptors (TLRs)

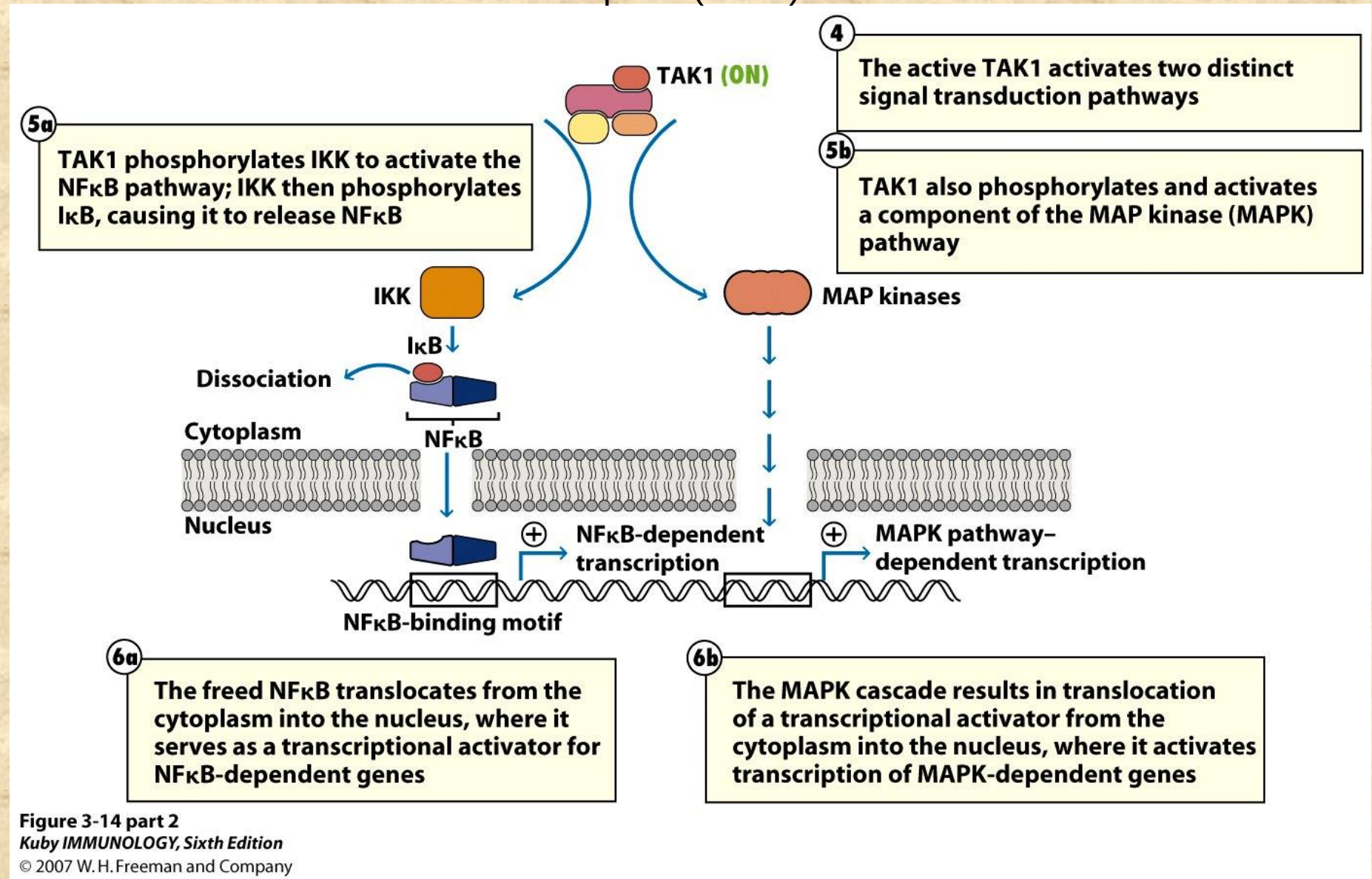

Figure 3-14 part 2
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TABLE 3-3 Receptors of the innate immune system

Receptor (location)	Target (source)	Effect of recognition
Complement (bloodstream, tissue fluids)	Microbial cell wall components	Complement activation, opsonization, lysis
Mannose-binding lectin (MBL) (bloodstream, tissue fluids)	Mannose-containing microbial carbohydrates (cell walls)	Complement activation, opsonization
C-reactive protein (CRP) (bloodstream, tissue fluids)	Phosphatidylcholine, pneumococcal polysaccharide (microbial membranes)	Complement activation, opsonization
Lipopolysaccharide (LPS) receptor;* LPS-binding protein (LBP) (bloodstream, tissue fluids)	Bacterial lipopolysaccharide (gram-negative bacterial cell walls)	Delivery to cell membrane
Toll-like receptors (cell surface or internal compartments)	Microbial components not found in hosts	Induces innate responses
NOD† family receptors (intracellular)	Bacterial cell wall components	Induces innate responses
Scavenger receptors (SRs) (cell membrane)	Many targets; gram-positive and gram-negative bacteria, apoptotic host cells	Induces phagocytosis or endocytosis

* LPS is bound at the cell membrane by a complex of proteins that includes CD14, MD-2, and a TLR (usually TLR4).

† *N*ucleotide-binding *o*ligomerization *d*omain.

Table 3-3
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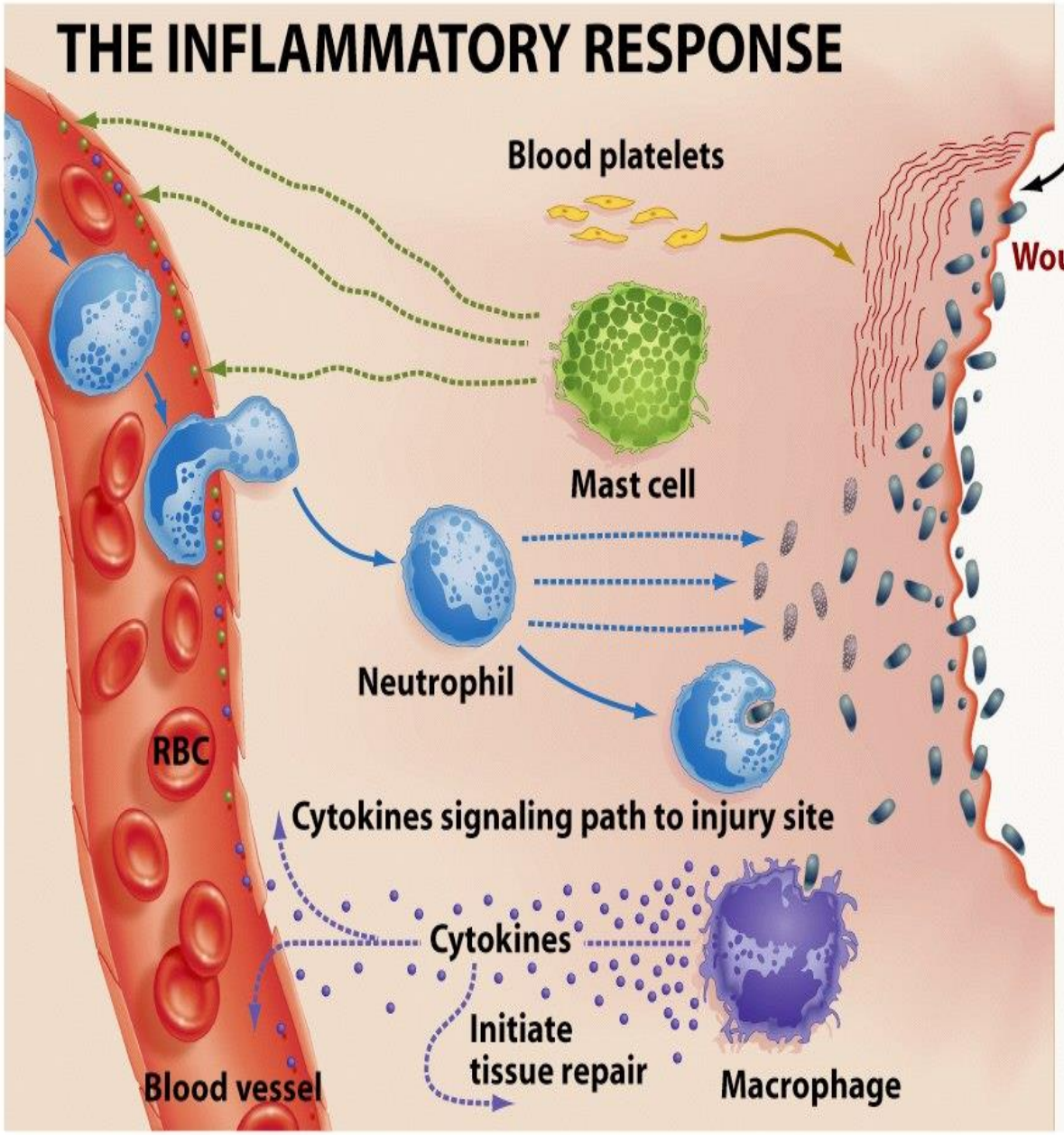
Triggering of PRRs on macrophage or dendritic cells can induce a LARGE variety of events including:

- **Increased phagocytosis**
- **Production of cytokines and inflammatory mediators:**
  - **Interferons to induce anti-viral state**
  - **Chemokines to attract migrating cells**
- **Increased cell migration**
- **Changes in expression of molecules involved in T cell antigen presenting cell function.**



1. Bacteria and other pathogens enter wound.
2. Platelets from blood release blood-clotting proteins at wound site.
3. Mast cells secrete factors that mediate dilation and constriction of blood vessels. Delivery of blood, plasma, and cells to injured area increases.
4. Neutrophils secrete factors that kill and degrade pathogens.
5. Neutrophils and macrophages remove pathogens by phagocytosis.
6. Macrophages secrete cytokines, which attract immune system cells to the site and activate cells involved in tissue repair.
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired.

Figure 49-3 Biological Science, 2/e

Cardinal signs of Inflammation

- Rubor: Redness due to neovascularization
- Tumor: Swelling due to exudation of fluids
- Calor: Heat causing increased blood flow and secretion of cytokines
- Dolor: Pain (pain receptor activation by inflammatory mediators
- Function laeva: Loss of Function due to disruption of tissue structure

References

- Wikipedia
- Owen, Judith A., et al. Kuby Immunology. 7th ed. New York: W.H. Freeman, 2013.
- Biological Sciences, Princeton Publications