

# Innate immunity

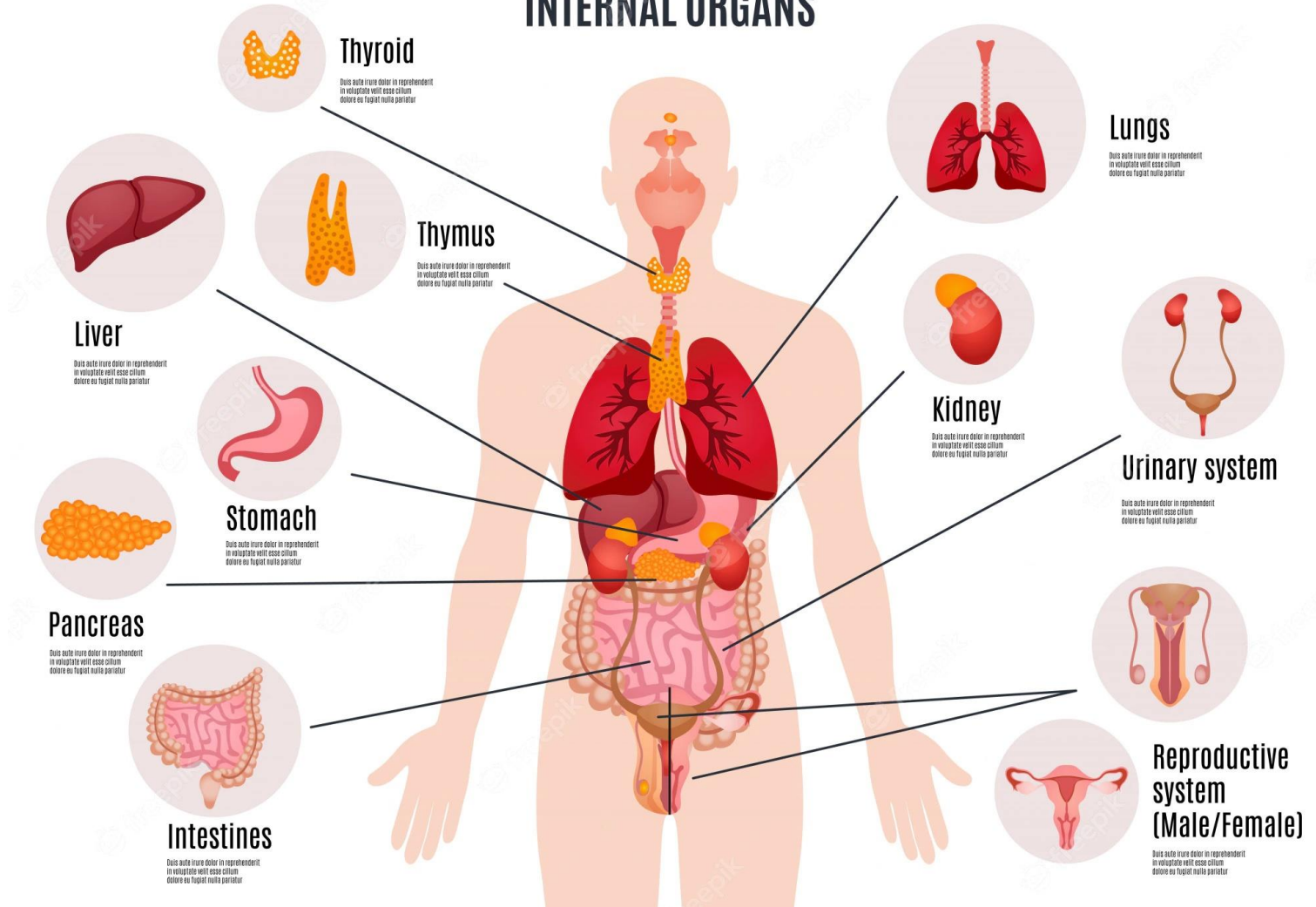
prof. dr Aleksandar Arsenijević

# Innate Immunity (non-specific)

- Early defence, that can provide enough time for adaptive (specific) immunity to develop
- Many types of cells and molecules in tissues and blood make a innate immunity.

# THE HUMAN BODY

## INTERNAL ORGANS

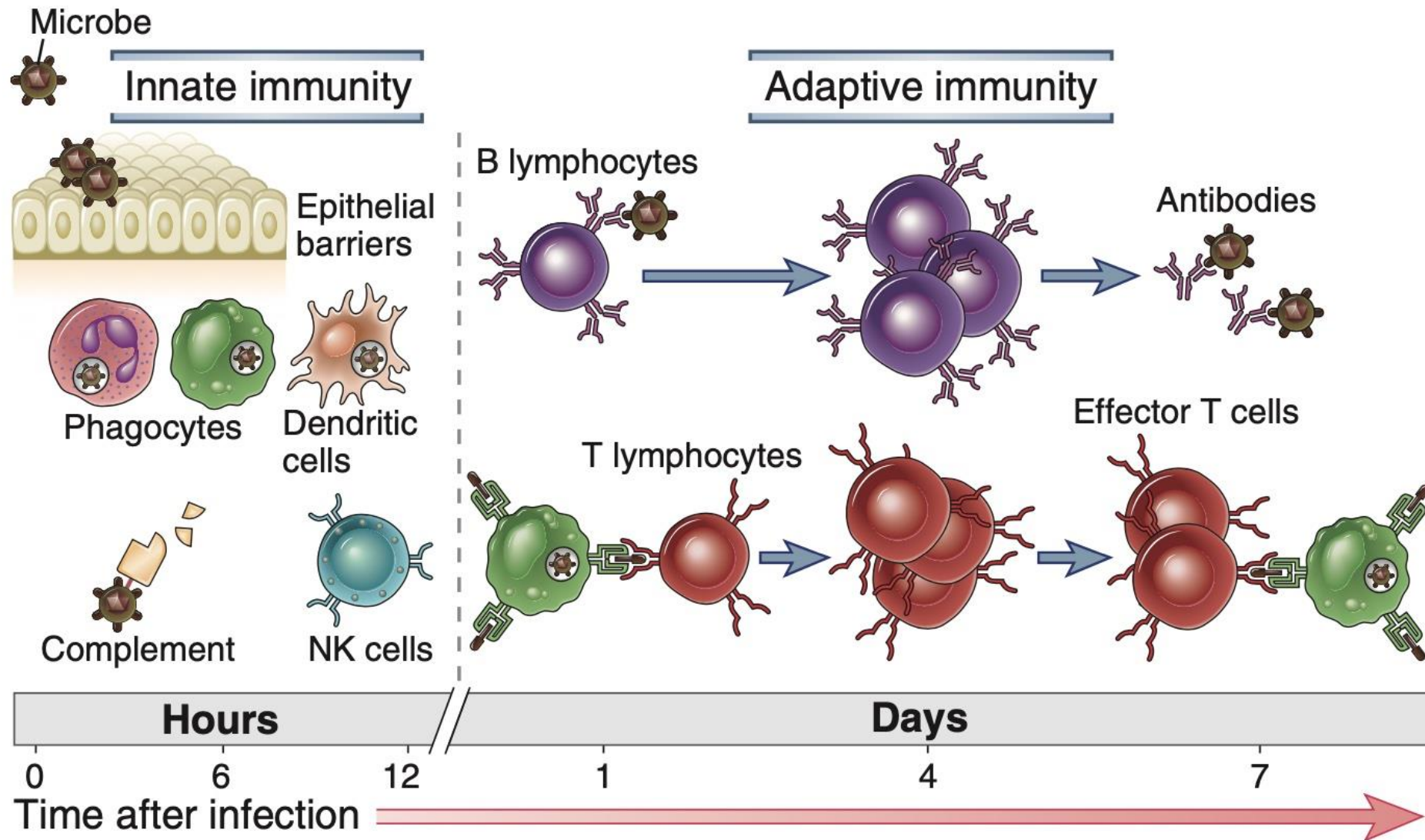


# First (human) Division of Immunity

**Innate and Adaptive immunity**  
(non-specific and specific)

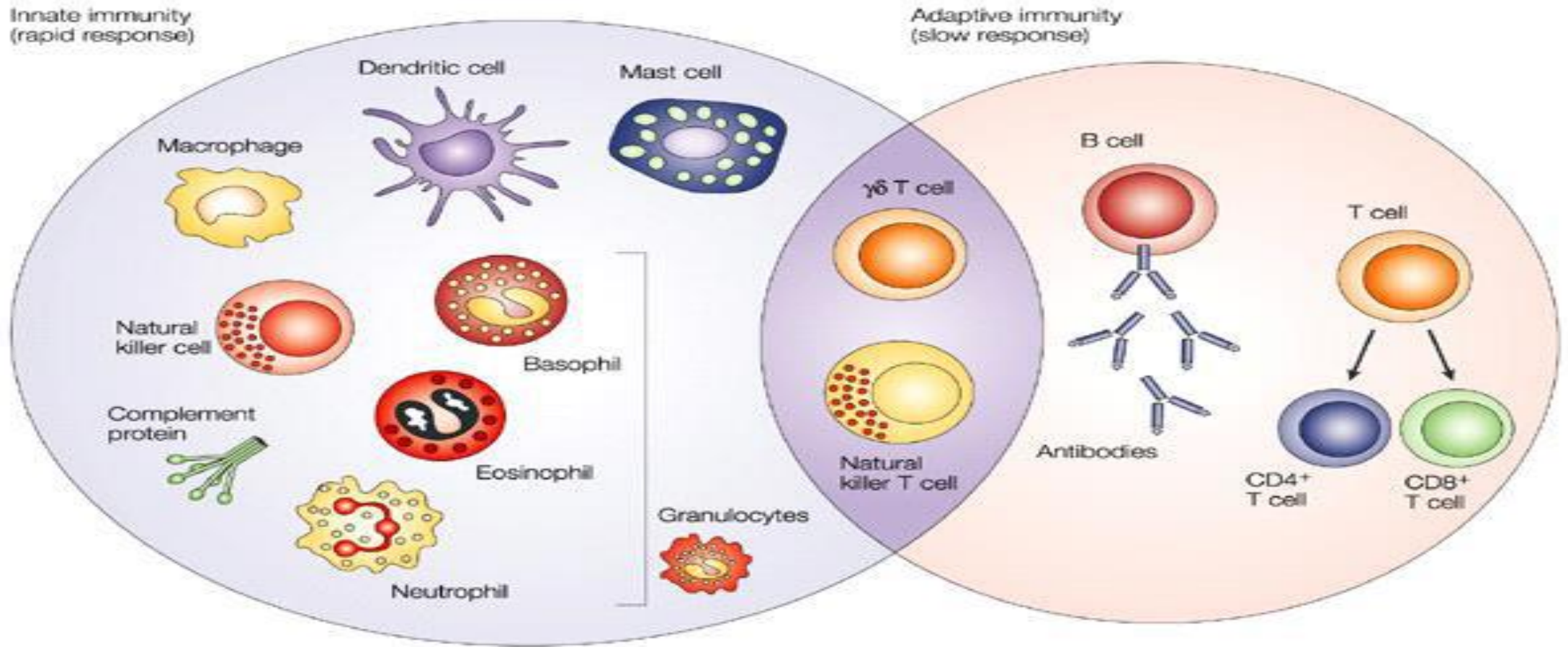
# Innate and Adaptive Immunity

- **Innate** (non-specific, congenital) immunity – provides early protection against infection
- **Adaptive** (specific, acquired) immunity – develops more slowly and provides a later but more effective defence against infection



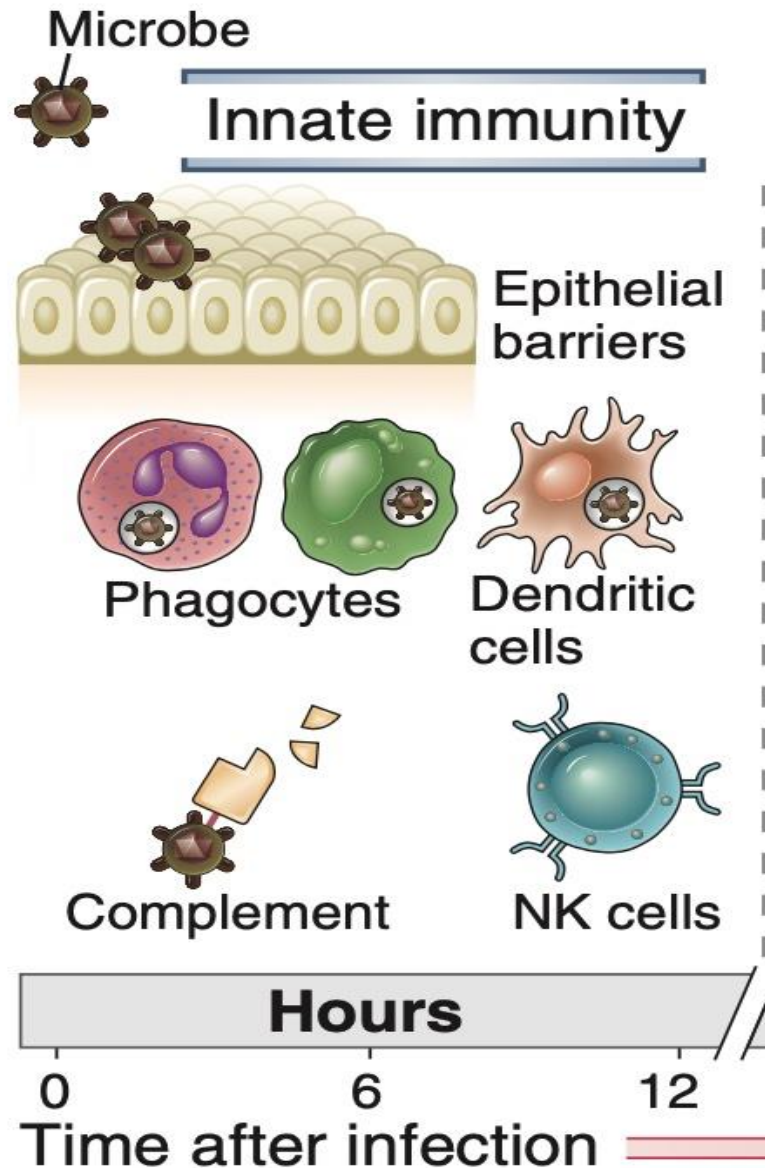
**FIGURE 1–1 Innate and adaptive immunity.** The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

# Innate and adaptive immunity





# Innate Immunity



## Epithelial cells – Barrier

- Preserved integrity
- Specialized cells
- Natural antibiotics

## Tissue resident sentinel cells

- Macrophages
- Dendritic cells (DCs)
- Mast cells

## Neutrophils

## NK Cells

## Complement

In addition to providing early defenses an innate immune response: directs, concentrates and reinforces the adaptive immune response



# Major Protective Reactions of Innate Immunity

- Inflammation

Process in which circulating leukocytes and plasma proteins are brought into sites of infection

- Antiviral Defense

Preventing virus replication and promote killing of the infected cells

# General Features of Innate Immune Responses

- Blocking entry with physical and chemical defenses on epithelial barriers
- Innate immune responses initial reactions that serve to control or eliminate infection
- Innate immunity eliminates damaged cells and initiates the process of tissue repair
- Innate immune responses stimulate adaptive immune responses and can influence on adaptive responses.

# Comparative Features of Innate and Adaptive Immunity

- Innate immune responses develop rapidly, do not require prior exposure to the pathogen
- There is no change in the quality or magnitude of the response upon repeated exposure. There is little or no memory.
- Both immune responses innate and adaptive differ greatly in specificity of the receptors by which they can recognize pathogens.

# What does innate immunity see?

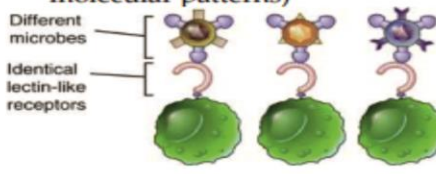
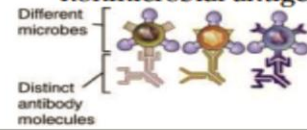
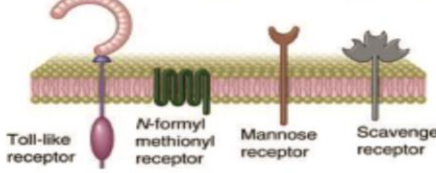
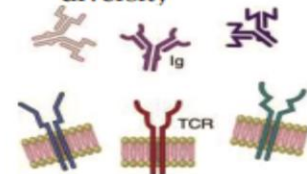
- The components of innate immunity recognize structures – molecular patterns of pathogens (LPS, mannose, double-stranded RNA...) that are common to certain classes of microorganisms and are absent from host cells.
- Molecular patterns are often those structures of microorganisms that are necessary for their survival and infectivity, so by mutating these products the microorganism has no chance of surviving or losing infectivity.
- Pattern recognition receptors are not formed by somatic recombination but are inherited as functional genes. So they're not clone-distributed.

# Recognition of Pathogens and Damaged Tissues by the Innate Immune System

The innate immune system recognizes molecular structures that can be found or produced by microbial pathogens; **PAMPs**

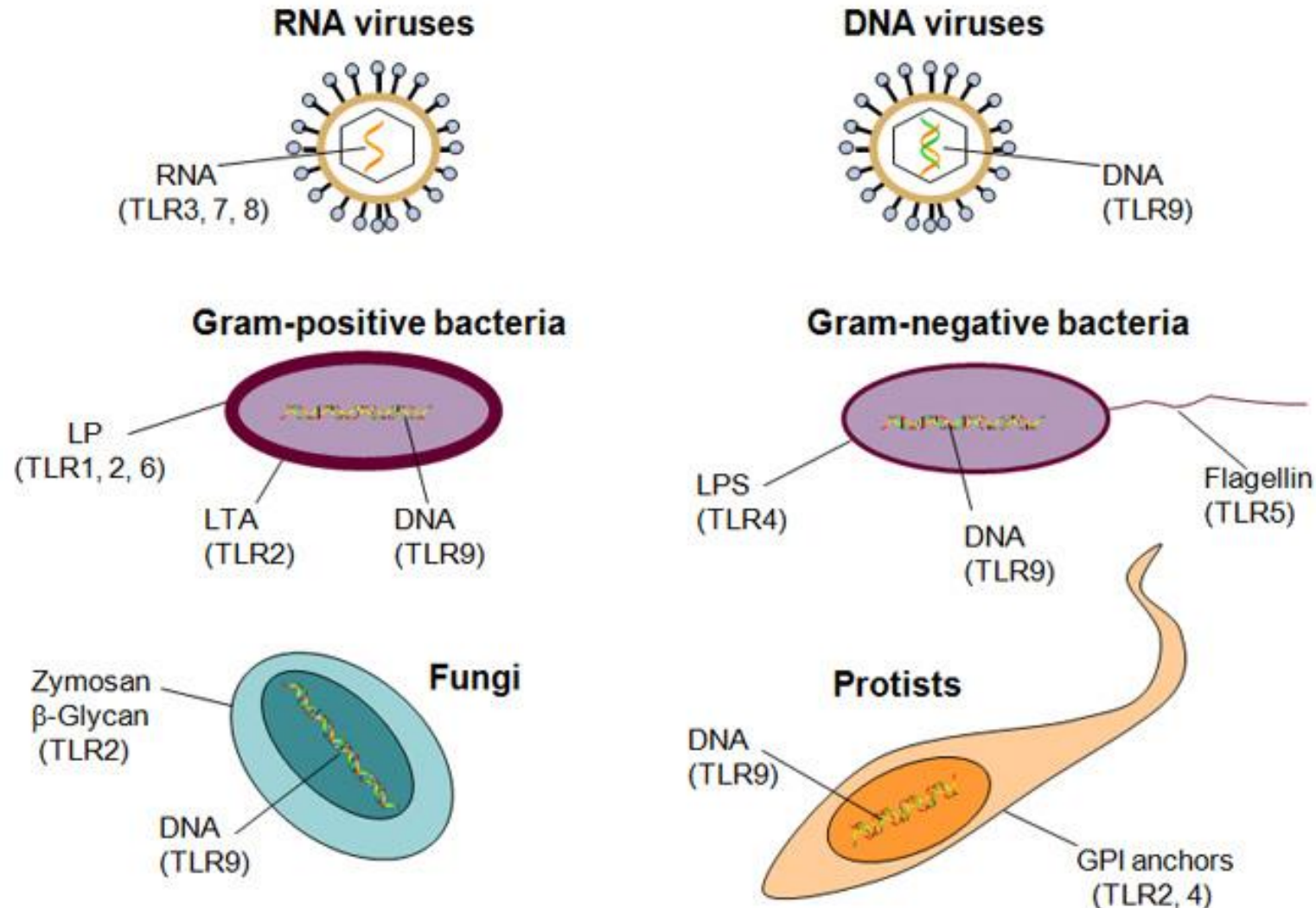
Can detect presence of infection, but not the specific pathogens

## Specificity of Innate and Adaptive Immunity

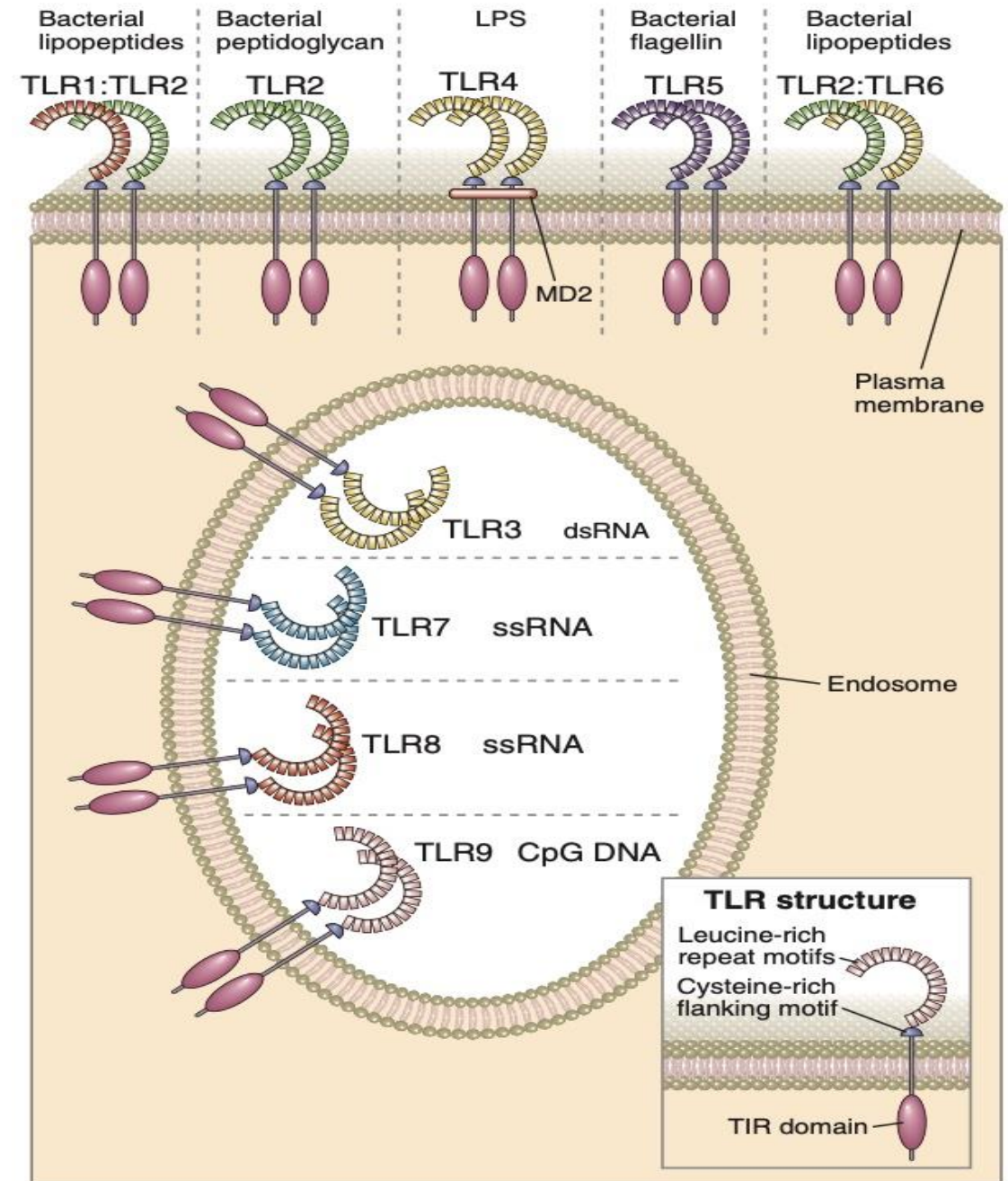
	Innate Immunity	Adaptive Immunity
<b>Specificity</b>	<p>For structures shared by classes of microbes (pathogen-associated molecular patterns)</p> 	<p>For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens</p> 
<b>Number of microbial molecules recognized</b>	About 1000 molecular patterns (estimated)	$>10^7$ antigens
<b>Receptors</b>	<p>Encoded in germline; limited diversity (pattern recognition receptors)</p> 	<p>Encoded by genes produced by somatic recombination of gene segments; greater diversity</p> 
<b>Number and types of receptors</b>	$<100$ different types of invariant receptors	Only two types of receptors (Ig and TCR), with millions of variations of each
<b>Distribution of receptors</b>	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
<b>Genes encoding receptors</b>	Germline encoded, in all cells	Formed by somatic recombination of gene segments only in B and T cells
<b>Discrimination of self and nonself</b>	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self reactive lymphocytes; may be imperfect (giving rise to autoimmunity)



# Pathogen-Associated Molecular Patterns, PAMPs



# Toll-like receptors



# Damage Associated Molecular Patterns, DAMPs

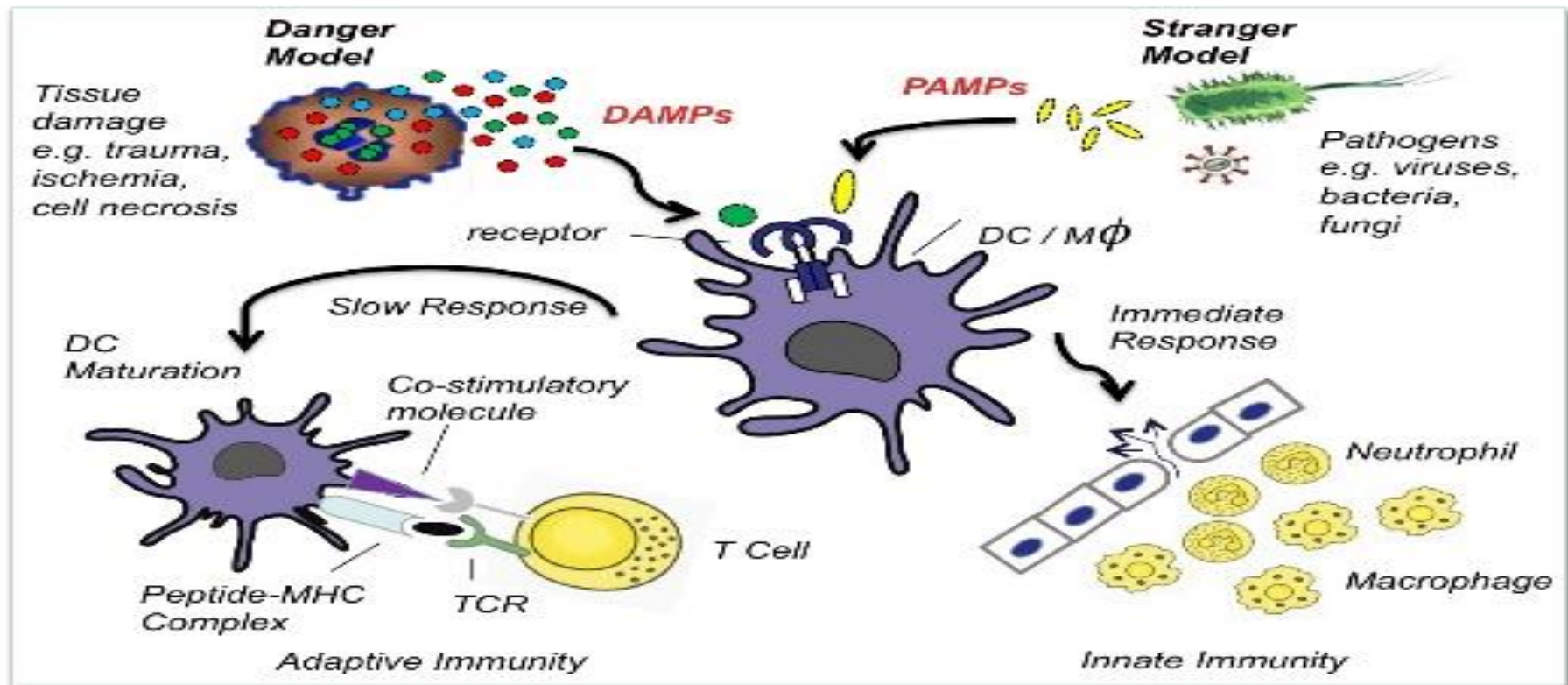
Innate immunity can recognize endogenous molecules that damaged and dying cells produce or release.

Damage-associated molecular patterns (DAMPs)

# Damage Associated Molecular Patterns, DAMPs

## Necrotic cells release Damage Associated Molecular Patterns

Damaged cells are also evidence of danger, and they signal through Damage-Associated Molecular Patterns (DAMPs). HMGB1 is a DAMP.





## Examples of Pathogen-Associated Molecular Patterns and Damage-Associated Molecular Patterns

Pathogen-Associated Molecular Patterns	
Nucleic acids	ssRNA: viruses
	dsRNA: viruses
	Unmethylated CpG: viruses, bacteria
Proteins	Pilin: bacteria
	Flagellin: bacteria
Cell wall lipids	LPS: gram-negative bacteria
	Lipoteichoic acid: gram-positive bacteria
Carbohydrates	Mannan: fungi, bacteria
	Glucans: fungi
Damage-Associated Molecular Patterns	
Stress-induced proteins	HSPs
Crystals	Monosodium urate
Proteolytically cleaved extracellular matrix	Damage Associated Molecular ...
Mitochondrial components found outside mitochondria	Extracellular formylated peptides and ATP
Nuclear proteins or nucleic acids found outside nucleus	Extracellular HMGB1, histones, cytoplasmic dsDNA

ATP, Adenosine triphosphate; CpG, cytosine-guanine-rich oligonucleotide; dsRNA, double-stranded RNA; HMGB1, high-mobility group box 1; HSP, heat shock protein; LPS, lipopolysaccharide; ssRNA, single-stranded RNA.

# NOD-like Receptors, NLRs

- A large family of receptors that detect DAMP and PAMP in the cytoplasm.
- They contain the central domain of oligomerization of nucleotides (Nucleotide Oligomerization Domain-NOD)

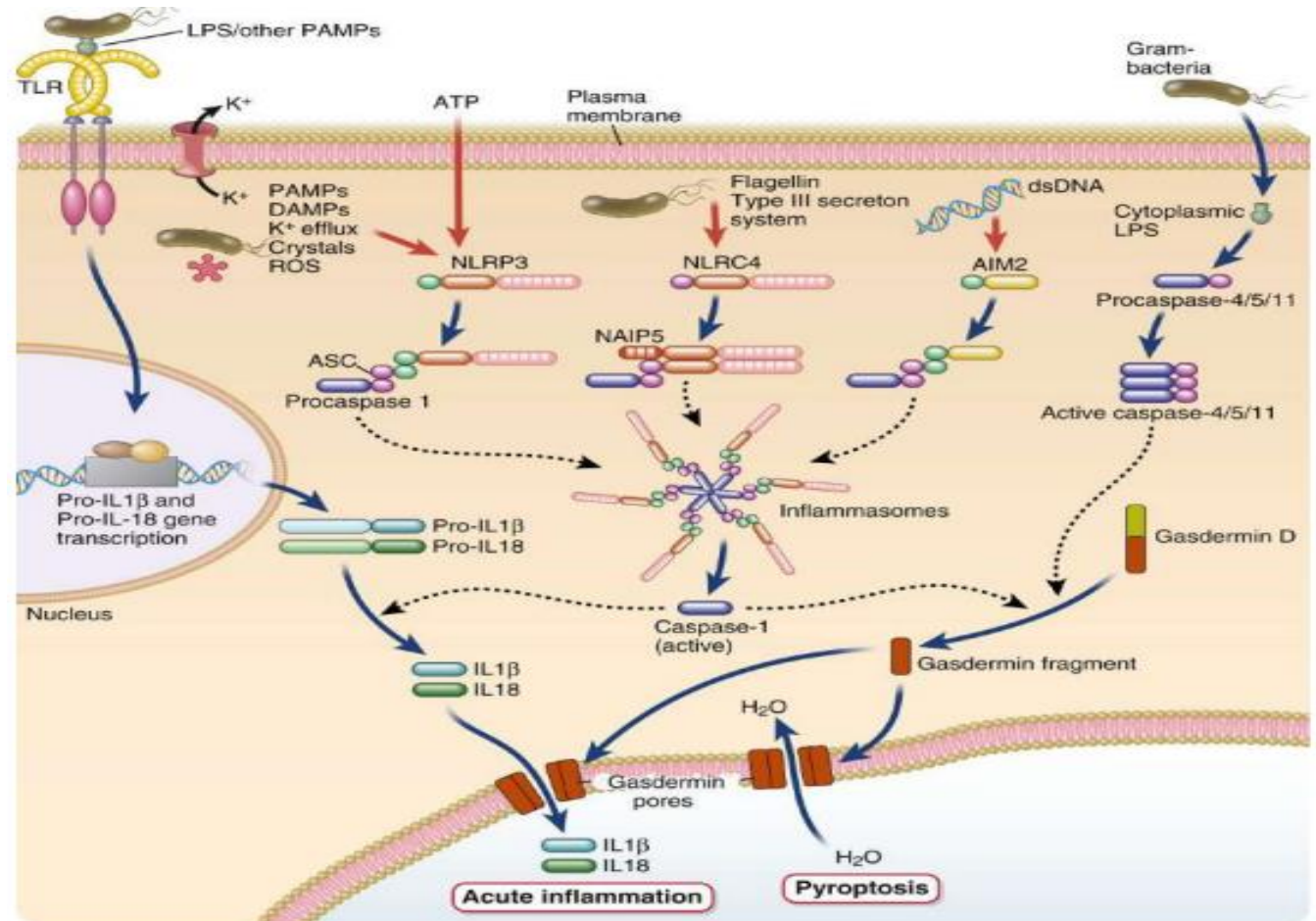


# Other Innate Immune Receptors

- Rig-like receptor family (RLR): recognize viral RNA and induce the production of IFN type I;
- Cytosolic DNA sensors (CDS): recognize viral DNA and induce the production of IFN type I;
- Lectin receptors: recognize fungal glucans and terminal mannose residues
- Receptors expressed on phagocytes that recognize peptides starting with N-formyl methionine, specific to bacterial proteins

# Inflammasomes

Inflammasomes – multiprotein enzymatic complexes that form in the cytosol in response to infections or cell injury, can produce proteolytically active caspase-1 and they generate biologically active forms of the inflammatory cytokines IL-1 $\beta$  and IL-18



# Receptors on Cells of Innate Immunity

**There is no rearranging!**

# Cellular Components of the Innate Immune System

- Barriers
- Sentinels
- Effector cells

# Epithelial Barriers

Physical barriers between external environment and the host:

- Skin, gastrointestinal, respiratory and genitourinary tracts.

Epithelial cells can produce peptides that have antimicrobial properties:

- Defensins
- Cathelicidins

# Phagocytes

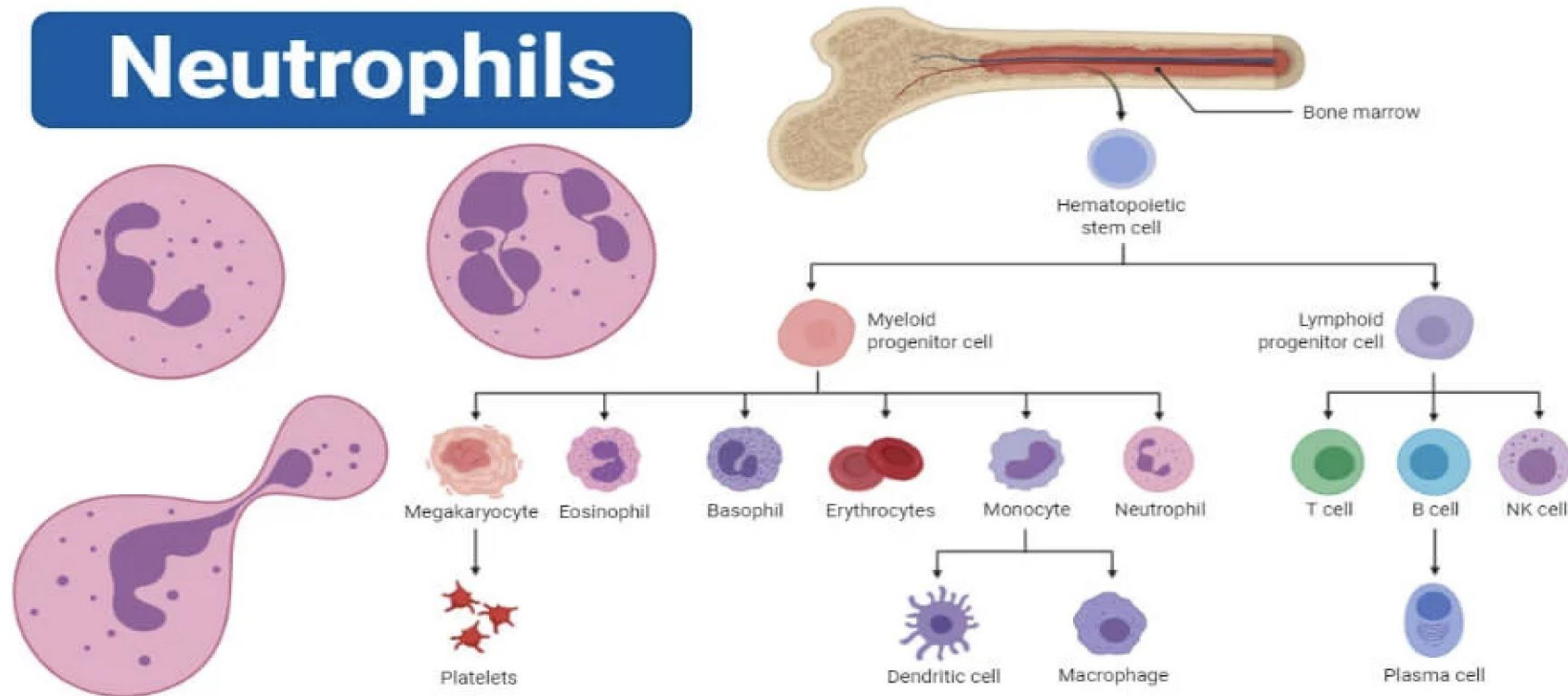
Phagocytes, including neutrophils and macrophages, are cells whose primary function is to identify, ingest, and destroy microbes that breach epithelial barriers.



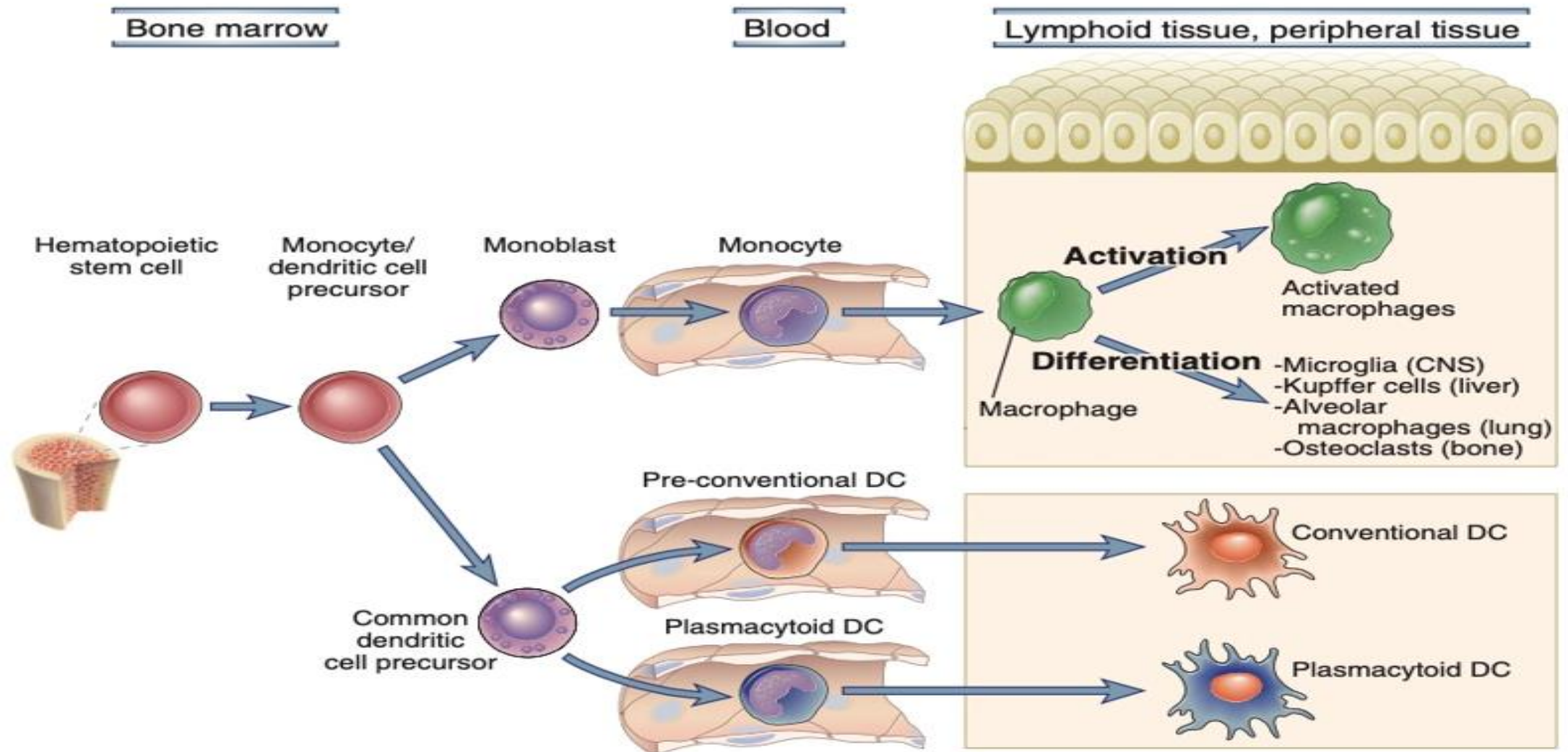


# Neutrophils

Neutrophils, also called polymorphonuclear leukocytes, are the most abundant population of circulating white blood cells and mediate the earliest phases of inflammatory reactions.



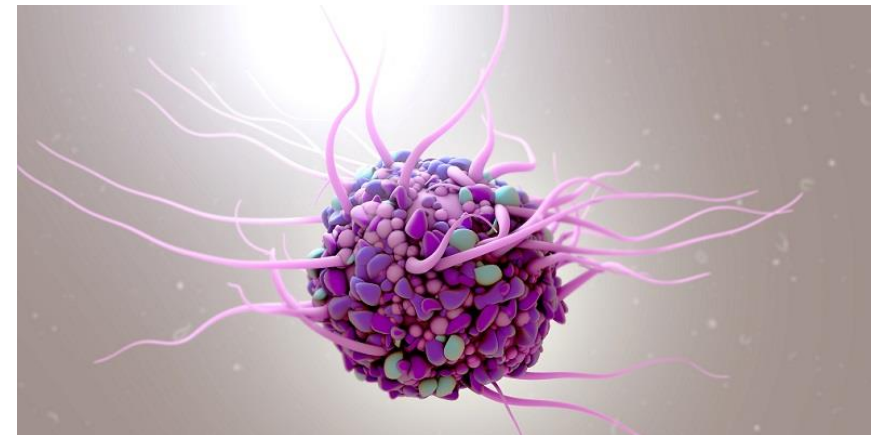
# Macrophages



# Dendritic cells, DCs

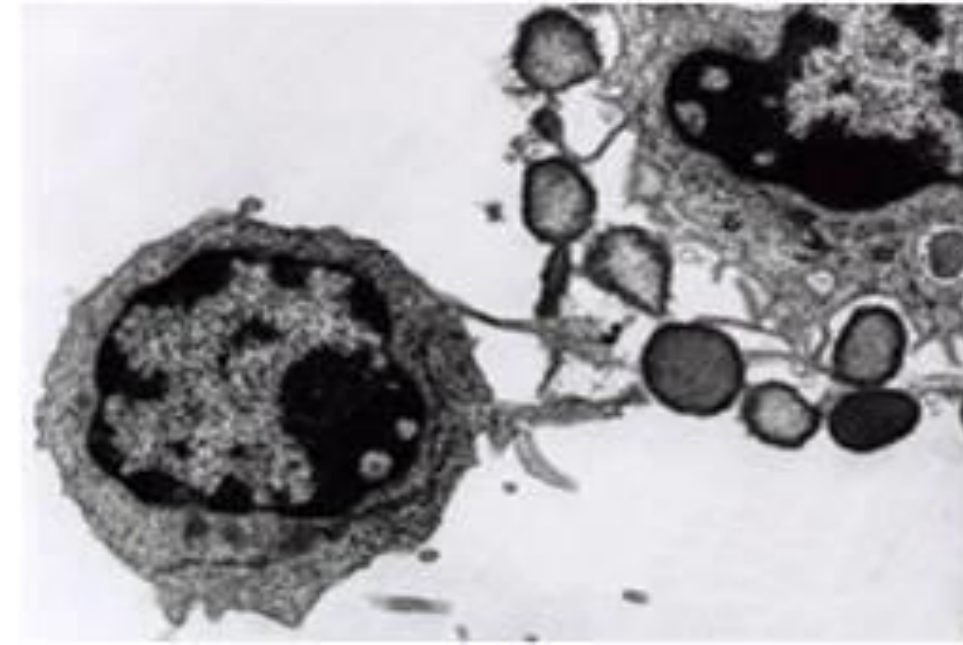
Their location in tissues and their expression of numerous receptors for PAMPs and DAMPs makes them most potent for detection of invading pathogens.

Most important connection between innate and adaptive immunity

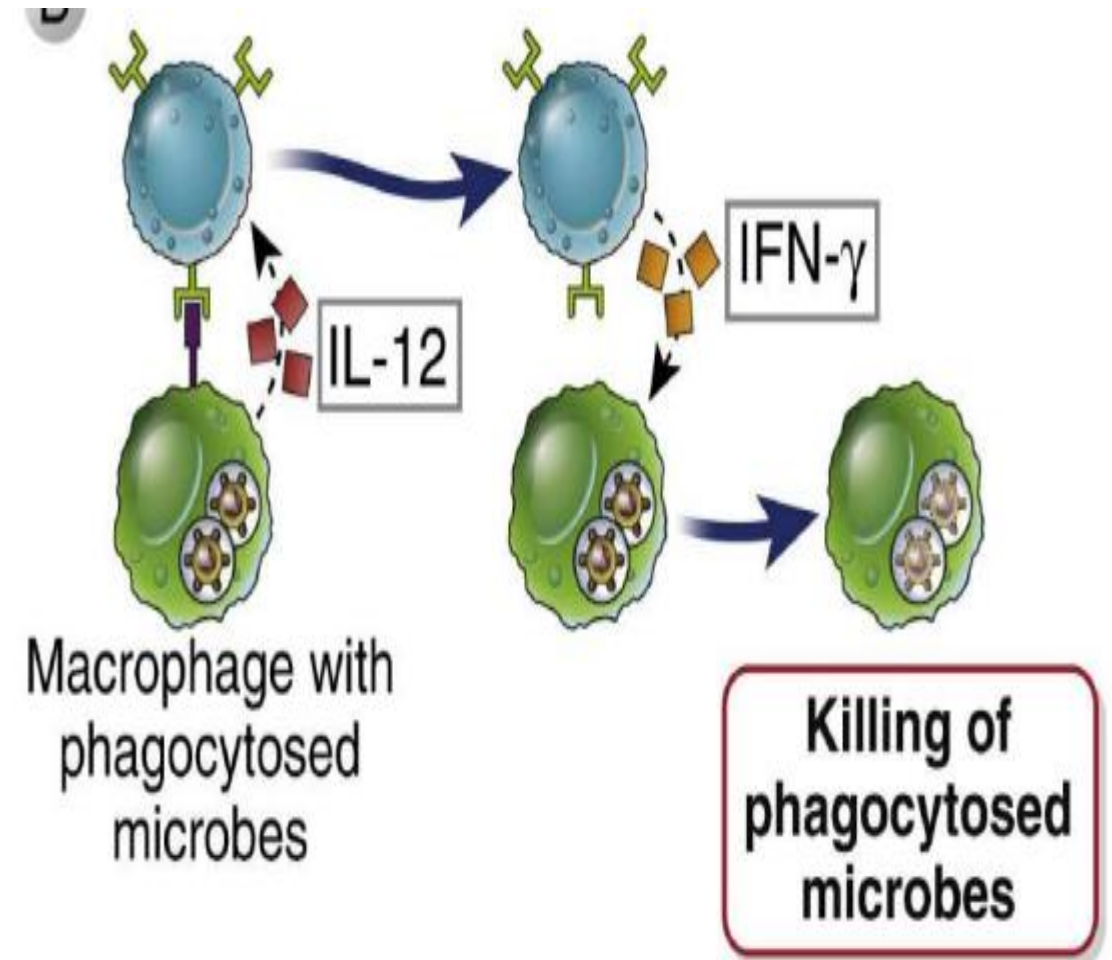
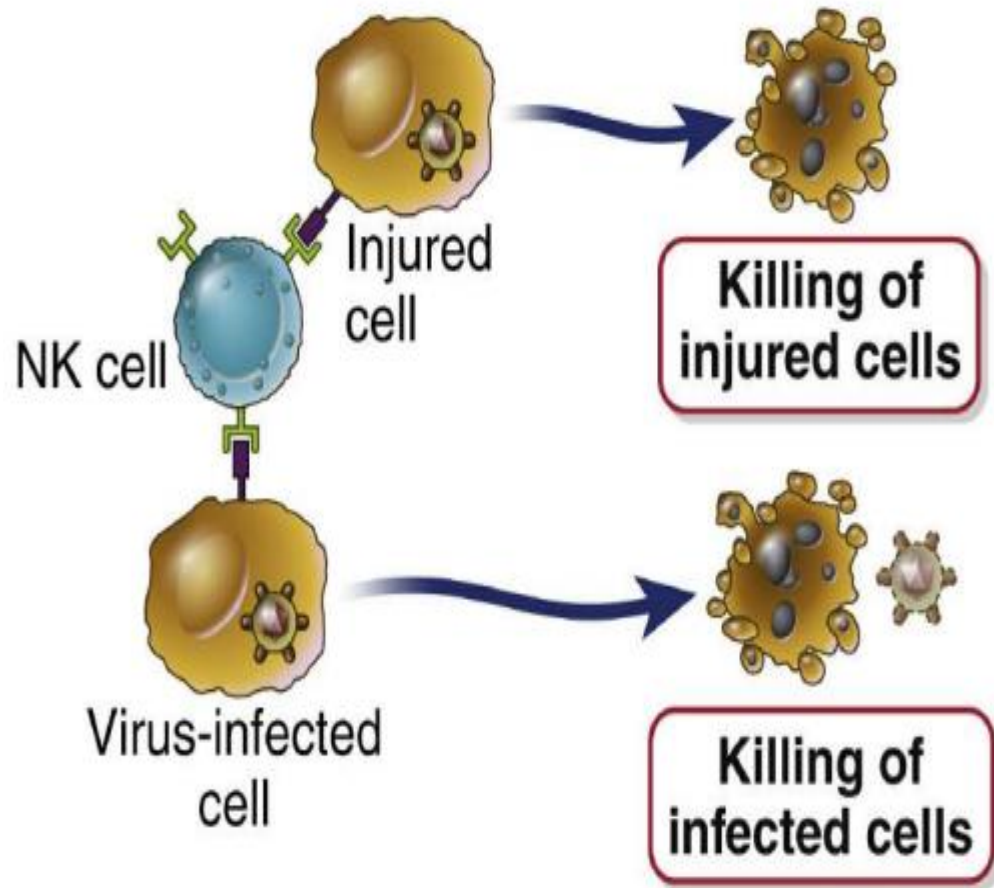


# NK Cells

- NK cells (Natural Killer cells) – congenital killers, innate killer cells. They are lymphocytes, although they do not have specific clone-distributed receptors they belong to the innate immunity.
- Cytotoxic cells, functionally competent to kill other cells



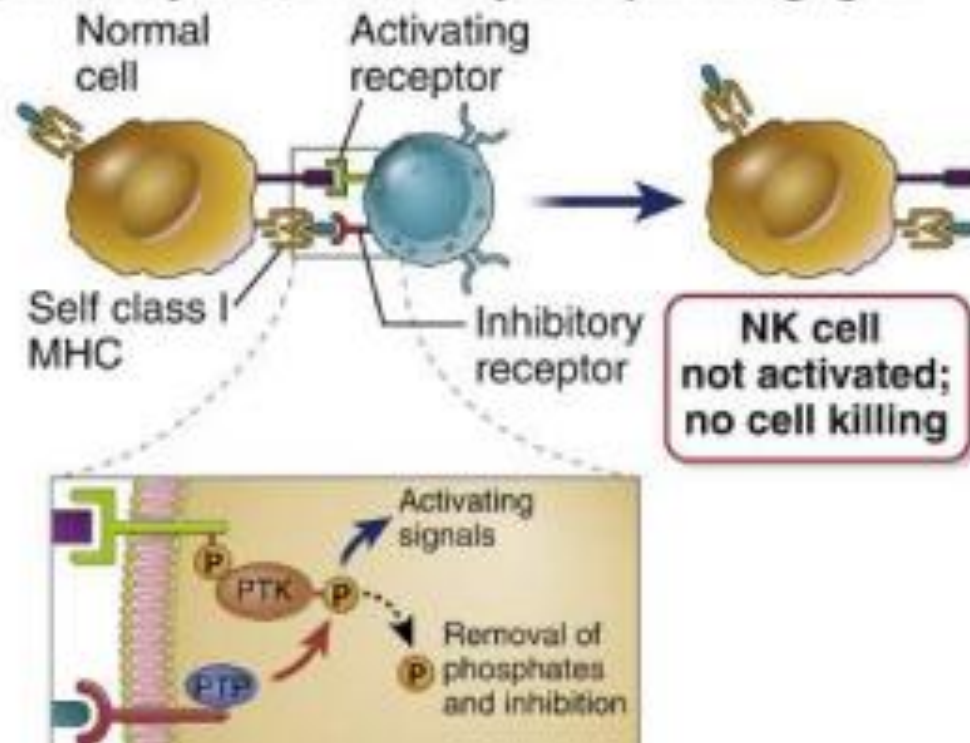
# NK Cells



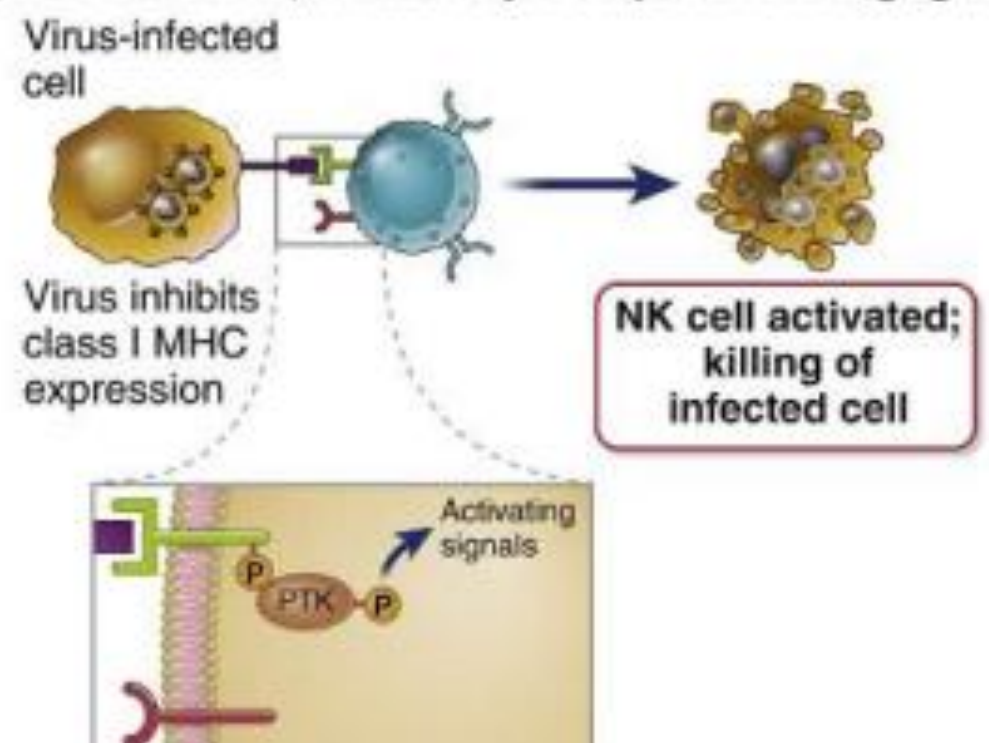


# NK Cells

## A Healthy cell; inhibitory receptor engaged



## B Infected cell; inhibitory receptor not engaged

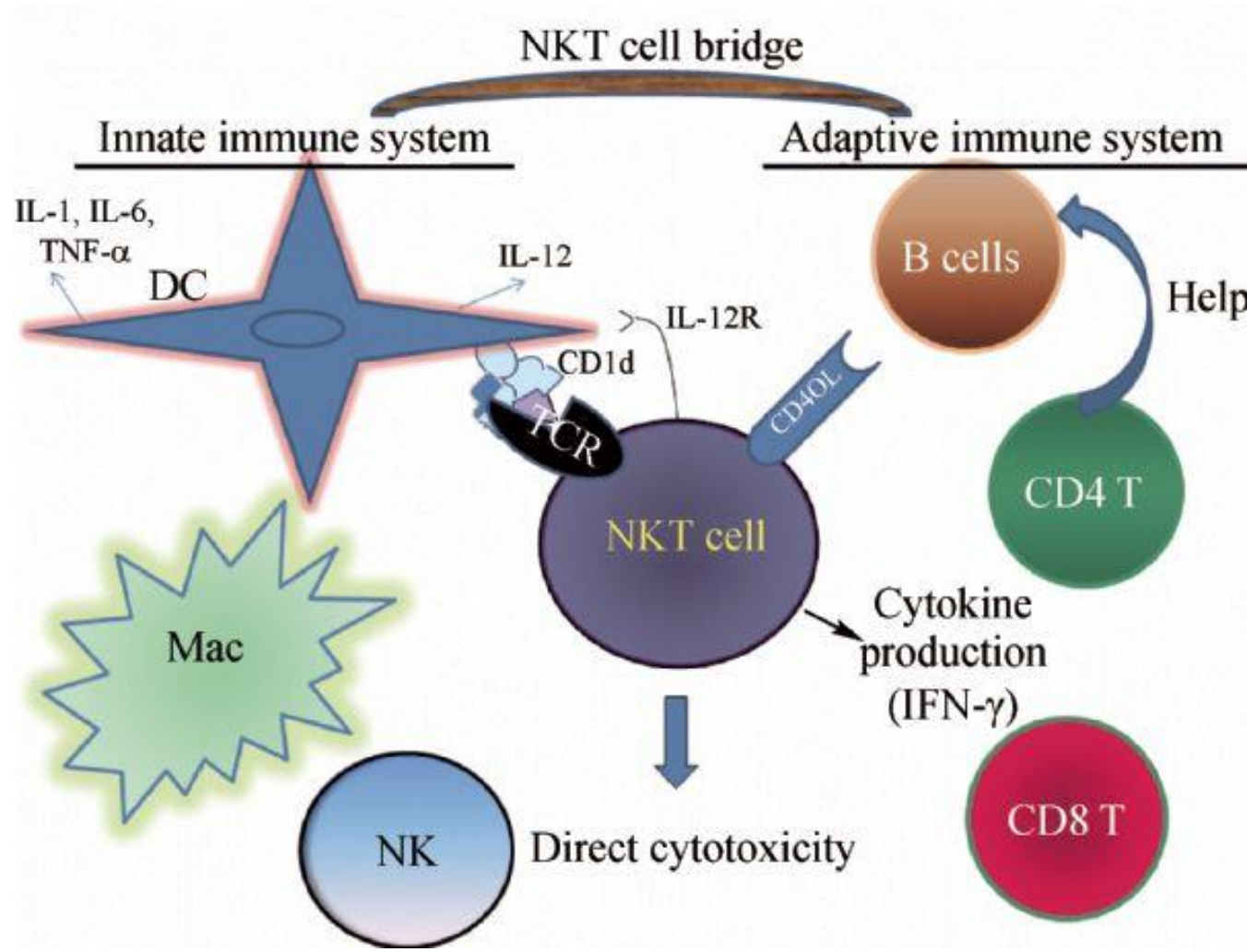
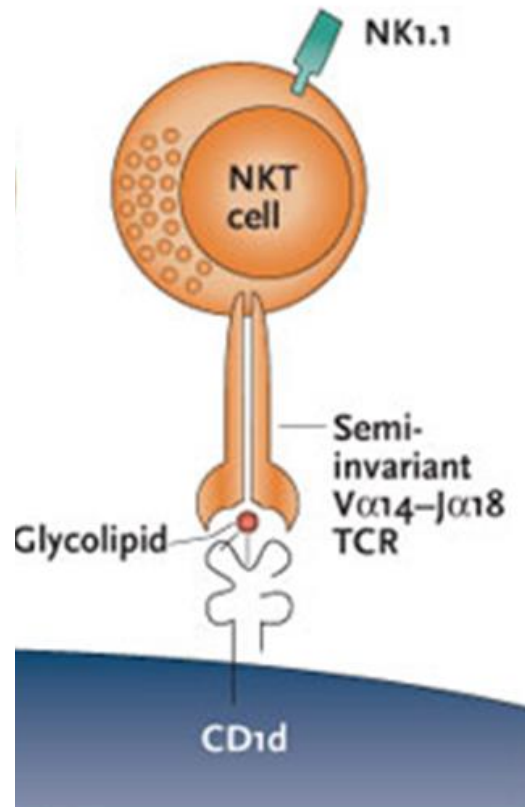




# T and B lymphocytes of Innate Immunity

- NKT cells,  $\gamma\delta$  T cells, mucosa-associated invariant T (MAIT) cells
- B-1 cells, marginal-zone B cells

# NKT cells



# $\gamma\delta$ T cells

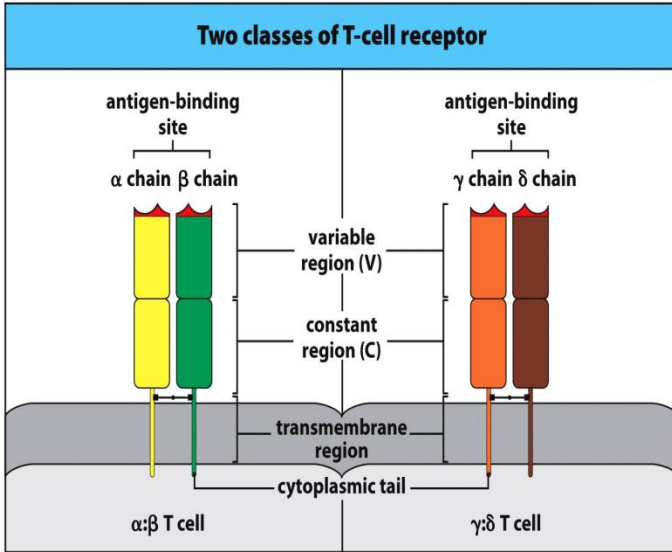
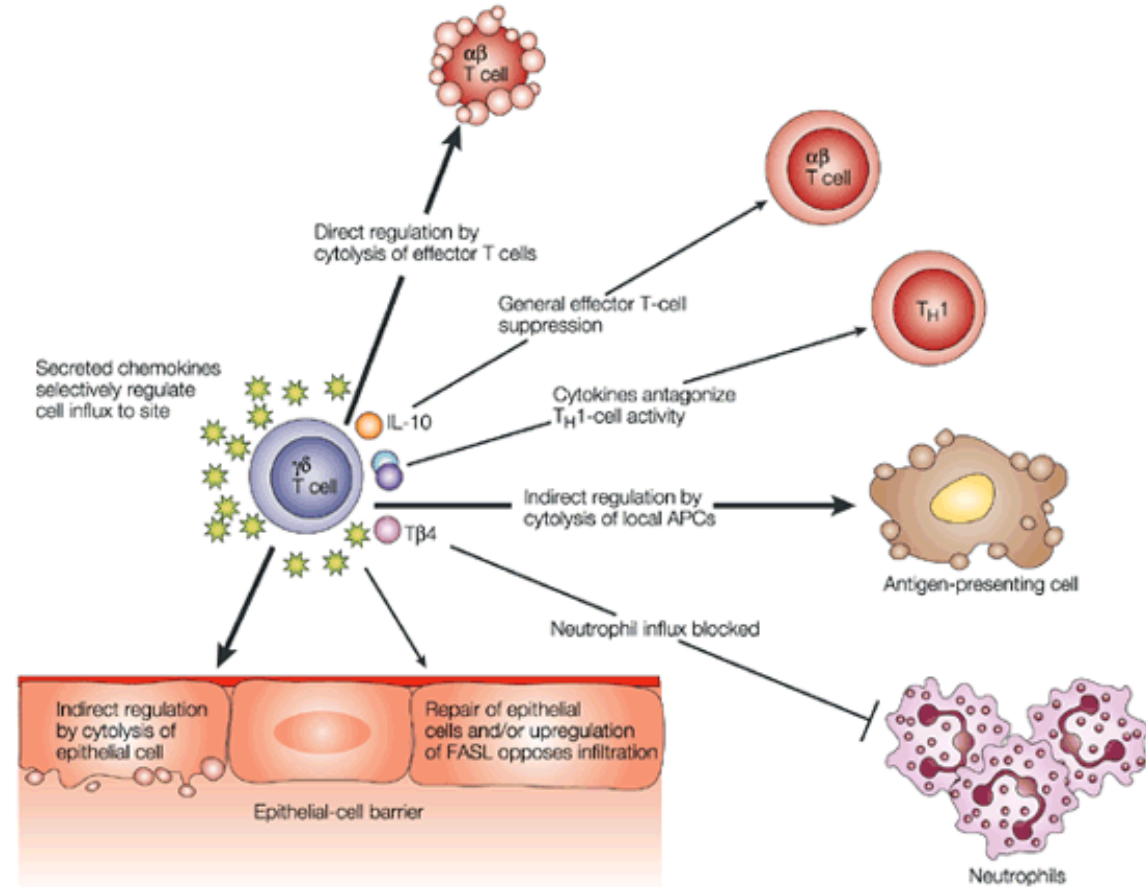
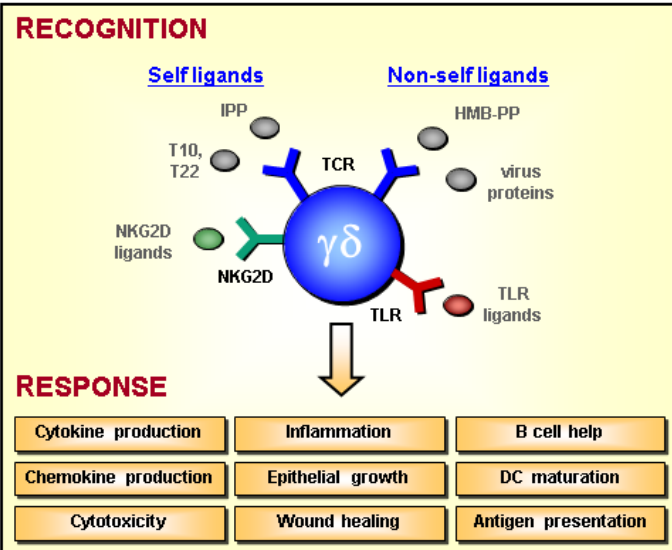


Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)



The diagram illustrates the differentiation of B cells into plasma cells based on their location and the type of antigen they encounter. It is organized into three horizontal tracks representing different anatomical sites: Spleen/other lymphoid organs, Marginal zone, and Mucosal tissues/peritoneal cavity.

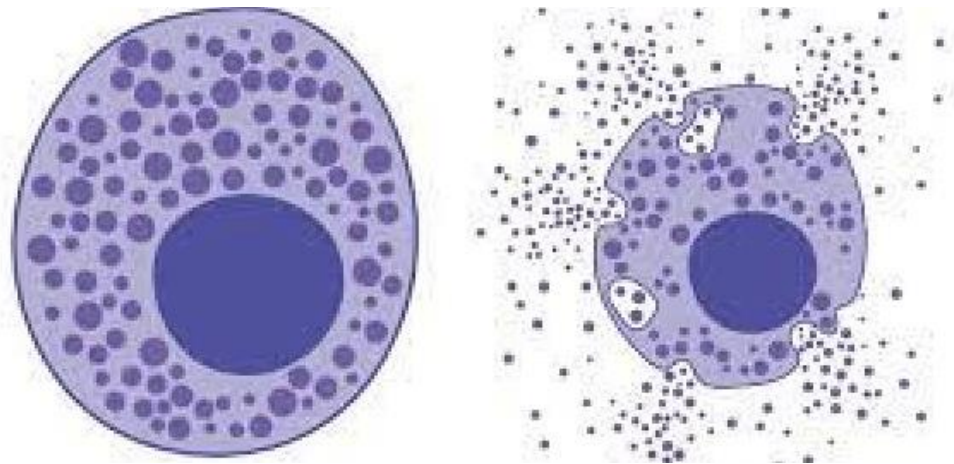
- Spleen, other lymphoid organs:** Follicular B cells (expressing IgD and IgM) encounter a protein antigen with a helper T cell. This leads to isotype-switched, high-affinity antibodies (IgG, IgA, IgE) and long-lived plasma cells.
- Marginal zone:** Marginal zone B cells (expressing IgM) encounter lipids, polysaccharides, etc. This leads to mainly IgM and short-lived plasma cells.
- Mucosal tissues, peritoneal cavity:** B-1 cells (expressing IgM and CD5) encounter lipids, polysaccharides, etc. This leads to mainly IgM and short-lived plasma cells.

Chemical structures for a long-chain fatty acid and a branched polysaccharide are shown as examples of the antigens encountered in the marginal zone and mucosal tissues.

FIGURE 7-2

# Mast Cells

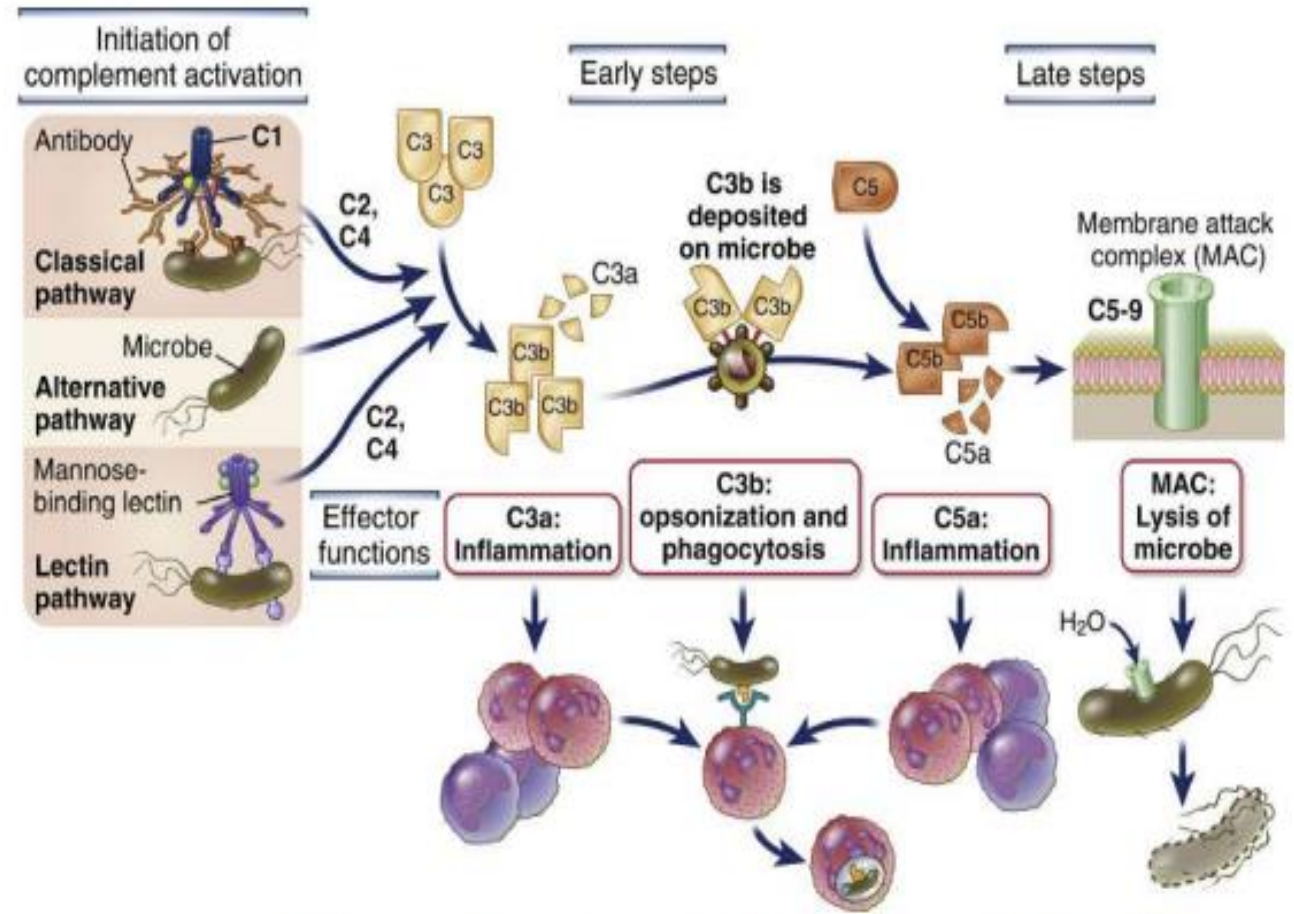
Mast cells are sentinel cells, that are present in the skin, mucosal epithelium and connective tissues that rapidly secrete proinflammatory cytokines and lipid mediators in response to infections and other stimuli.





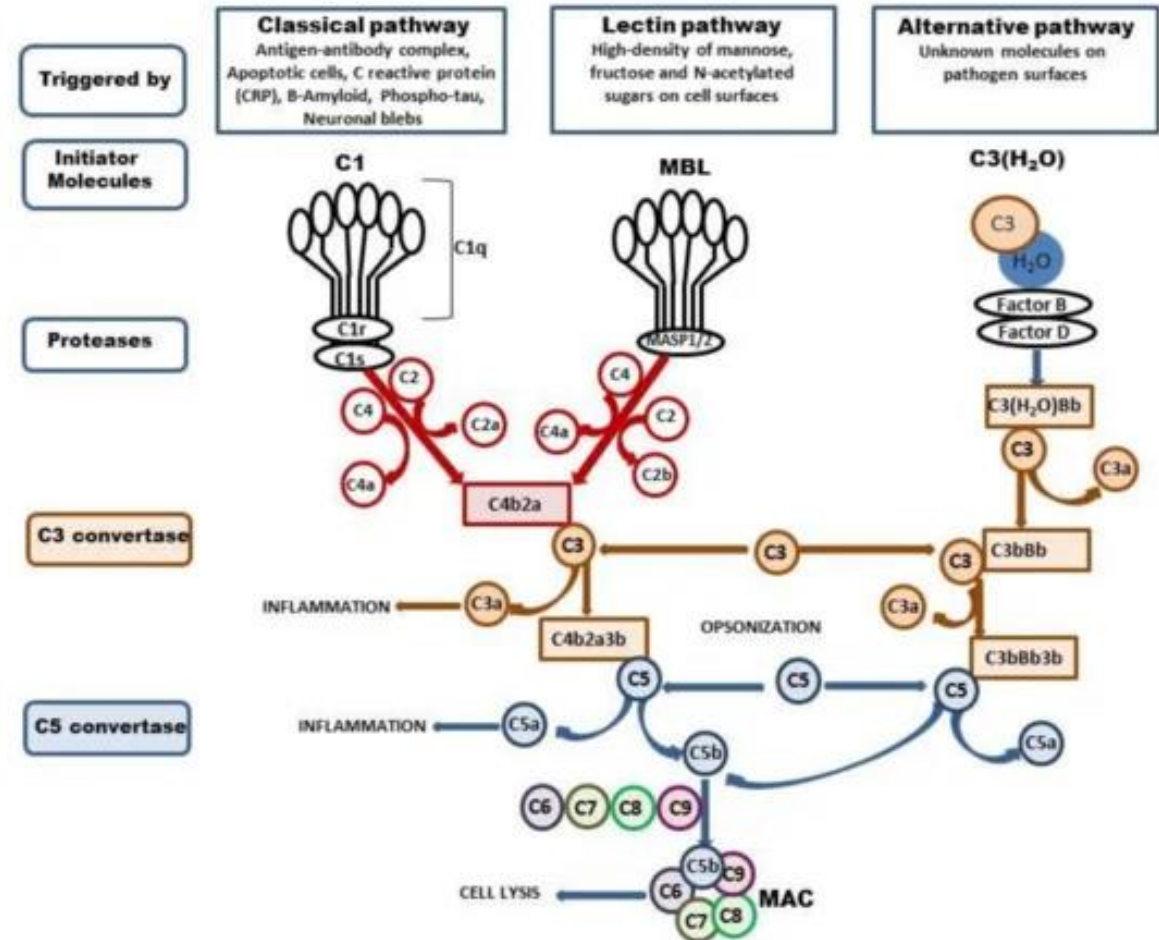
# The Complement System

- Several plasma proteins
- Can opsonize microbes
- Recruit phagocytes to the infection
- Directly kill the microbe



# Pathways of Complement Activation

- Classical pathway
- Alternative pathway
- Lectin pathway



# Cytokines - Soluble Mediators of the Immune System

Cytokines, a large and heterogeneous group of secreted proteins produced by many different cell types, mediate and regulate all aspects of innate and adaptive immunity.



# The Major Proinflammatory Cytokines of Innate Immunity

- TNF (tumor necrosis factor)
- IL-1
- IL-6
- IL-12
- IL-18
- IL-15

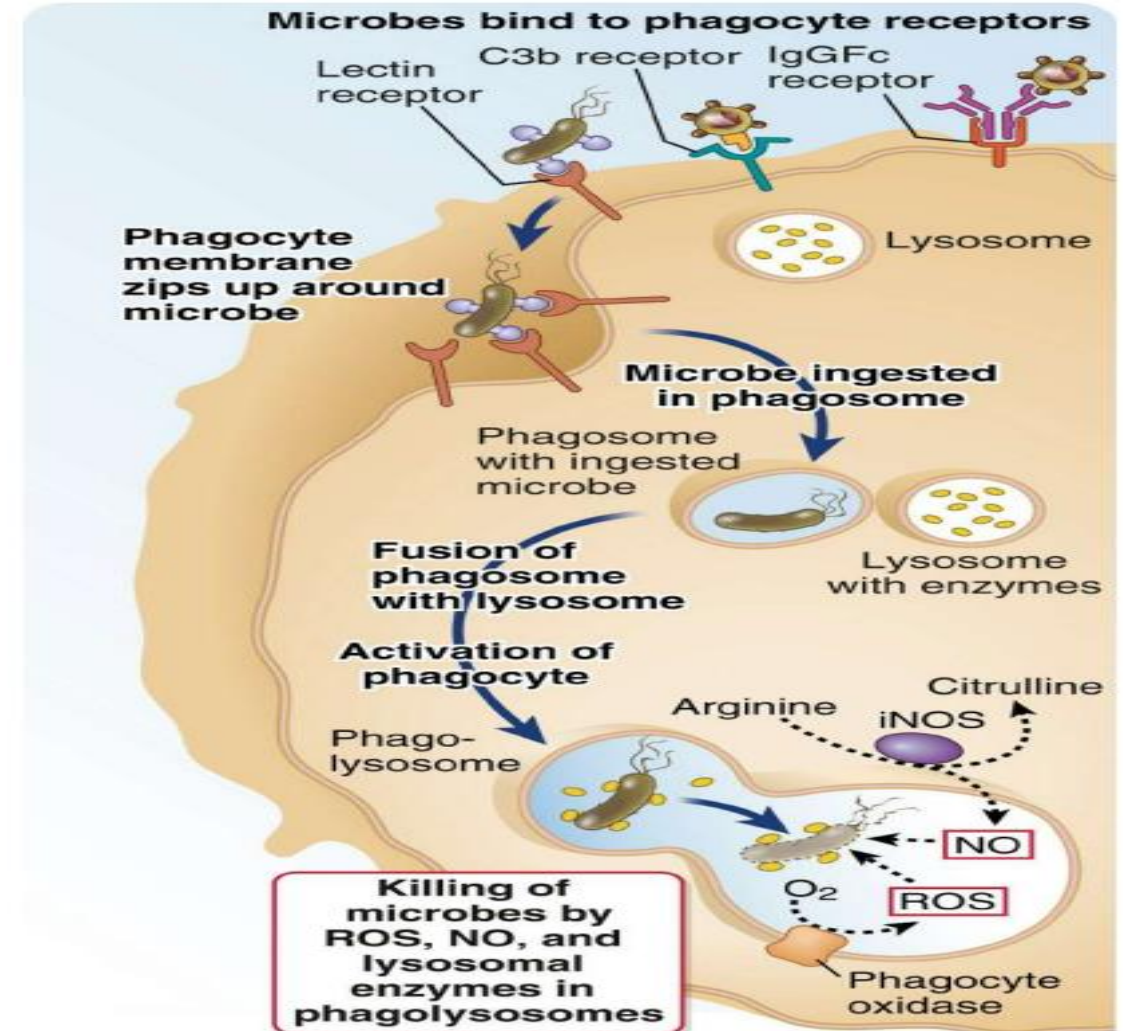
Cytokines of Innate Immunity

Cytokine	Size	Principal Cell Source	Principal Cellular Targets and Biologic Effects
TNF	17 kD; 51 kD homotrimer	Macrophages, T cells	<i>Endothelial cells:</i> activation (inflammation, coagulation) <i>Neutrophils:</i> activation <i>Liver:</i> synthesis of acute-phase proteins <i>Hypothalamus:</i> fever <i>Muscle, fat:</i> catabolism (cachexia) <i>Many cell types:</i> apoptosis
IL-1	17 kD mature form; 33 kD precursors	Macrophages, endothelial cells, some epithelial cells	<i>Endothelial cells:</i> activation (inflammation, coagulation) <i>Hypothalamus:</i> fever <i>Liver:</i> synthesis of acute-phase proteins <i>T cells:</i> Th17 differentiation
Chemokines	8–10 kD	Macrophages, endothelial cells, T cells, fibroblasts, platelets	<i>Leukocytes:</i> chemotaxis, activation; migration into tissues
IL-12	Heterodimer of 35- kD and 40- kD subunits	Macrophages, DCs	<i>T cells:</i> Th1 differentiation <i>NK cells and T cells:</i> IFN- $\gamma$ synthesis, increased cytotoxic activity

Type I interferons (IFN- $\alpha$ , IFN- $\beta$ )	IFN- $\alpha$ : 15–21 kD IFN- $\beta$ : 20–25 kD	IFN- $\alpha$ : macrophages, plasmacytoid DCs IFN- $\beta$ : fibroblasts	<i>All cells:</i> antiviral state, increased class I MHC expression <i>NK cells:</i> activation
IL-10	Homodimer of 34–40 kD and 18-kD subunits	Macrophages, T cells (mainly regulatory T cells)	<i>Macrophages, DCs:</i> inhibition of expression of IL-12, costimulators and class II MHC molecules
IL-6	19–26 kD	Macrophages, endothelial cells, T cells	<i>Liver:</i> synthesis of acute-phase proteins <i>B cells:</i> proliferation of antibody-producing cells <i>T cells:</i> Th17 differentiation
IL-15	13 kD	Macrophages, others	<i>NK cells:</i> proliferation <i>T cells:</i> proliferation (memory CD8 <sup>+</sup> cells)
IL-18	17 kD	Macrophages	<i>NK cells and T cells:</i> IFN- $\gamma$ synthesis
IL-23	Heterodimer of unique 19-kD subunit and 40-kD subunit of IL-12	Macrophages and DCs	<i>T cells:</i> development and maintenance of IL-17-producing T cells
IL-27	Heterodimer of 28-kD and 13-kD subunits	Macrophages and DCs	<i>T cells:</i> Th1 differentiation; inhibition of Th17 cells <i>NK cells:</i> IFN- $\gamma$ synthesis

# How activated phagocytes ingest and kill microbes?

- Neutrophils and macrophages can ingest microbes into vesicles by the process of phagocytosis and destroy these microbes
- Activated neutrophils and macrophages kill microbes with microbicidal molecules in phagolysosomes



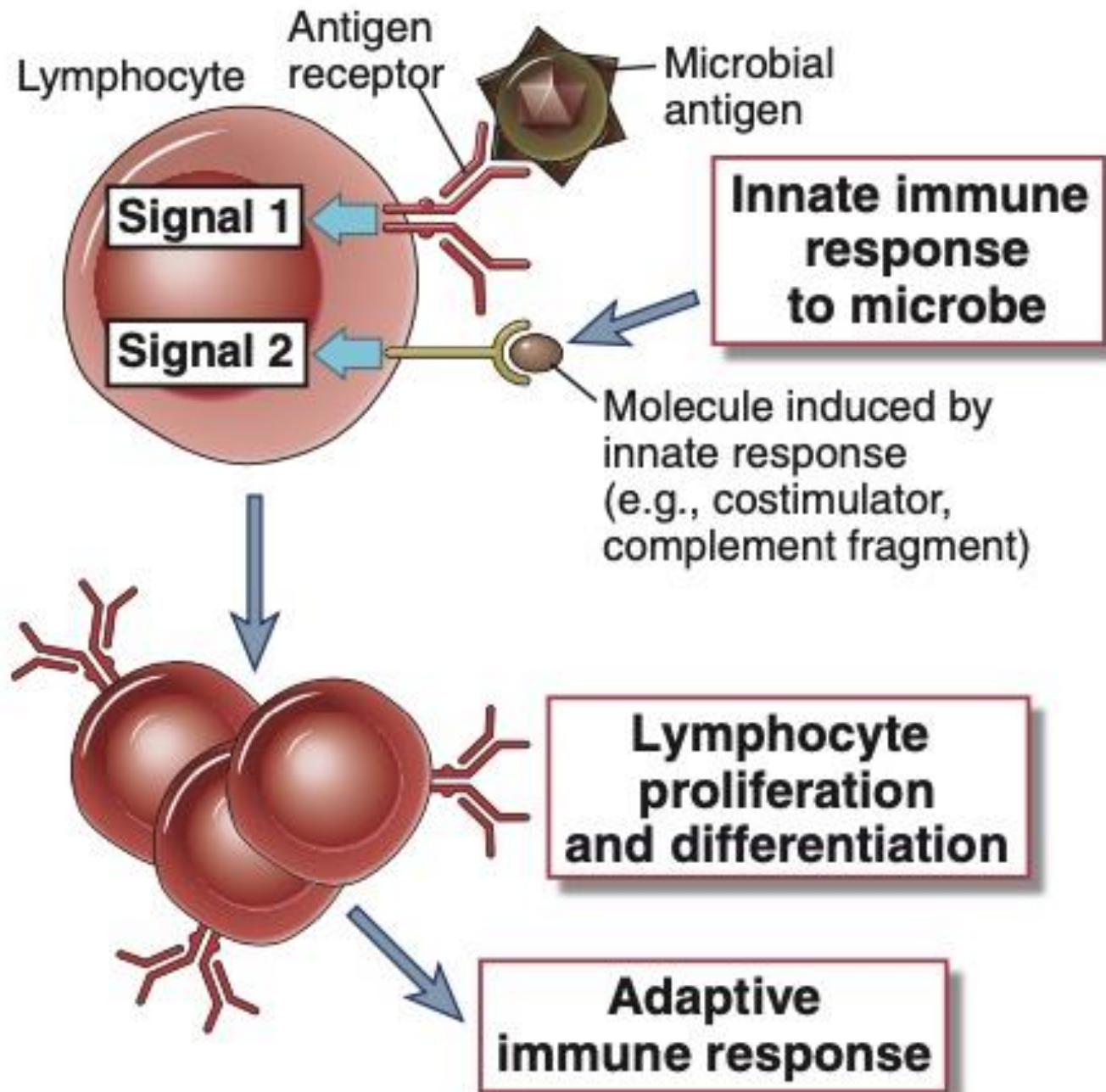
# Most Important Three Classes of Microbicidal Molecules

- Reactive oxygen species (ROS)
- Nitric oxide (NO)
- Proteolytic enzymes

# Stimulation of adaptive immunity

- The innate immune response provides signals that are necessary along with the antigen to activate proliferation and differentiation of cells specific for that antigen, **T and B lymphocytes**.
- **Activation of lymphocytes requires two signals; Two-signal hypothesis**





# Adjuvants

- Substances that are administered together with purified protein antigens to be sure that T cell- dependent immune response will be elicited.
- Useful in experimental immunology and in clinical vaccines.