

Innate immunity

Early defense against infections

Principles of innate immunity

Innate immunity is the initial response to microbes that prevents, controls, or eliminates infection of the host by many microbes

Innate immunity...

... enables early defense against infection

... determines the strength and directs the acquired immune response...

... the acquired immune response often uses the mechanisms of innate immunity to eliminate the infection

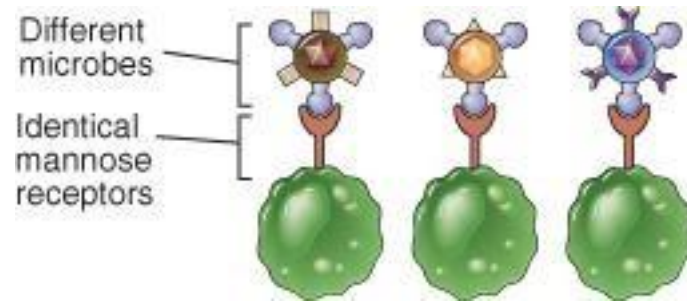
Therefore, in a complete immune response the elements of innate and acquired immunity closely cooperate (in both directions).

The two major types of protective reactions of the innate immune system are

Inflammation

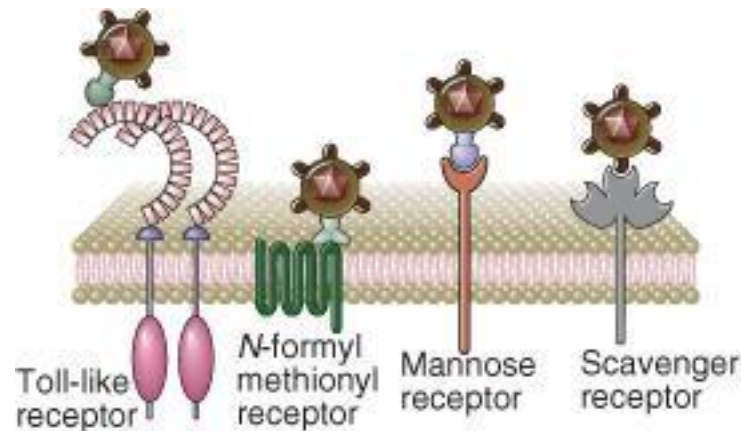
Antiviral defense

Principles of innate immunity



The innate IS
recognizes pathogen-
associated molecular
patterns PAMPs

with

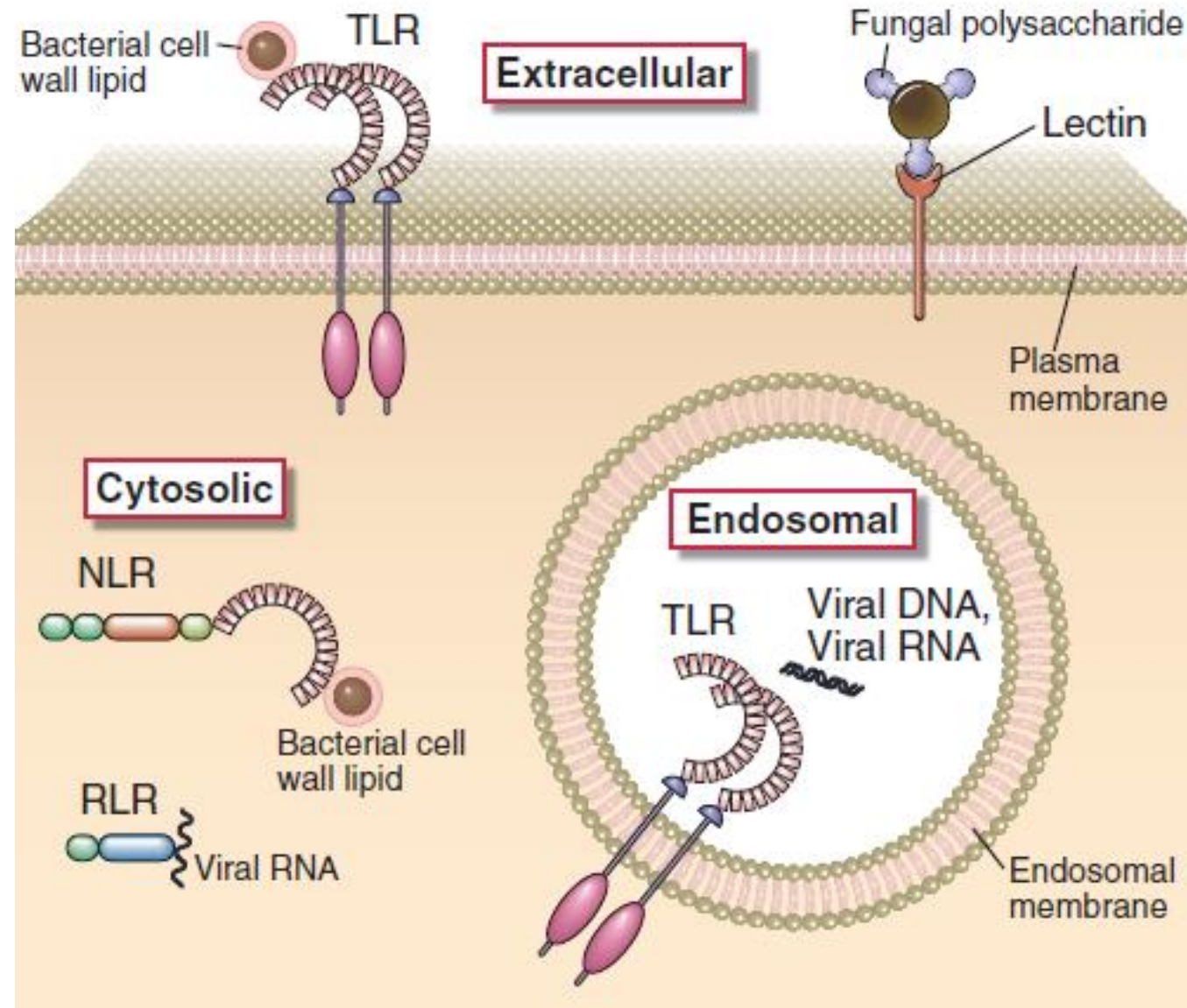


pattern
recognition
receptors
PRRs

Receptors are non-clonal – identical receptors on all cells of the same lineage

Self /non-self discrimination – healthy host cells are not recognized or protected

Cellular locations of pattern recognition receptors of the innate immune system



Examples of PAMPs

Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Dectin glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	
Crystals	Monosodium urate	
Nuclear proteins	HMGB1	

In short

The microbial substances that stimulate innate immunity are often shared by classes of microbes and are called pathogen-associated molecular patterns (PAMPs). Different types of microbes (e.g., viruses, gram-negative bacteria, gram-positive bacteria, fungi) express different PAMPs. Host cells do not express PAMPs.

The innate immune system detects the presence of infection but not the specific pathogens.

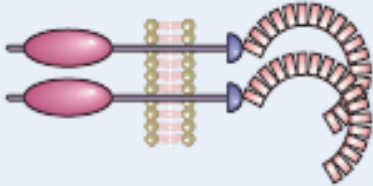
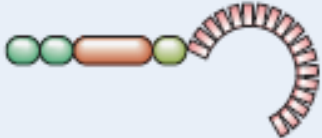




The innate immune system recognizes microbial products that are often essential for survival of the microbes.

The receptors of the innate immune system are encoded by inherited (germline) genes, it is estimated that innate immune recognition is mediated by about 100 (1000) different receptors.


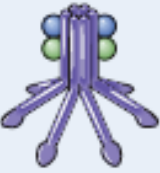


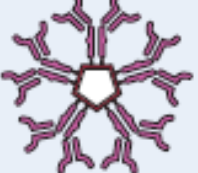
The innate immune system does not react against normal, healthy cells and tissues..

Innate immunity lacks memory.

Cell-Associated PAMPs Receptors

Cell-Associated Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Toll-like receptors (TLRs) 	Plasma membrane and endosomal membranes of dendritic cells, phagocytes, B cells endothelial cells, and many other cell types	TLRs 1-9	Various microbial molecules including bacterial LPS and peptidoglycans, viral nucleic acids
NOD-like receptors (NLRs) 	Cytoplasm of phagocytes epithelial cells, and other cells	NOD1/2 NALP family (inflammasomes)	Bacterial cell wall peptidoglycans Flagellin, muramyl dipeptide, LPS; urate crystals; products of damaged cells
RIG-like receptors (RLRs) 	Cytoplasm of phagocytes and other cells	RIG-1, MDA-5	Viral RNA
C-type lectin-like receptors 	Plasma membranes of phagocytes	Mannose receptor Dectin	Microbial surface carbohydrates with terminal mannose and fructose Glucans present in fungal cell walls
Scavenger receptors 	Plasma membranes of phagocytes	CD36	Microbial diacylglycerides
N-Formyl met-leu-phe receptors 	Plasma membranes of phagocytes	FPR and FPRL1	Peptides containing N-formylmethionyl residues

Soluble Receptors

Soluble Recognition Molecules	Location	Specific Examples	PAMP Ligands
Pentraxins 	Plasma	C-reactive protein	Microbial phosphorylcholine and phosphatidylethanolamine
Collectins 	Plasma Alveoli	Mannose-binding lectin Surfactant proteins SP-A and SP-D	Carbohydrates with terminal mannose and fructose Various microbial structures
Ficolins 	Plasma	Ficolin	<i>N</i> -Acetylglucosamine and lipoteichoic acid components of the cell walls of gram-positive bacteria
Complement 	Plasma	C3	Microbial surfaces
Natural antibodies 	Plasma	IgM	Phosphorylcholine on bacterial membranes and apoptotic cell membranes

Toll-like receptors, TLRs

TLR1-TLR9

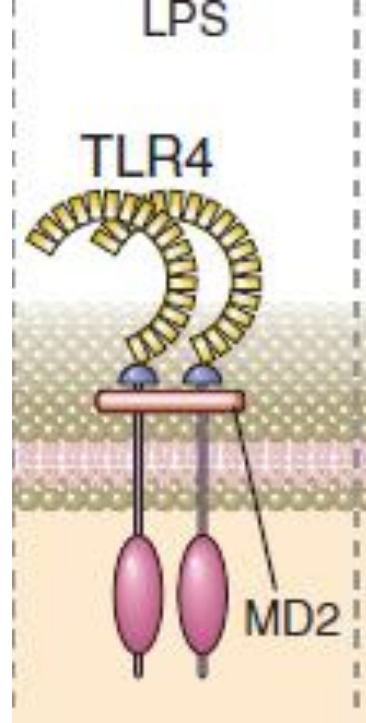
The TLRs are integral membrane glycoproteins that contain leucine-rich repeats flanked by characteristic cysteine-rich motifs in their extracellular regions, which are involved in ligand binding, and a Toll/IL-1 receptor (TIR) domain in their cytoplasmic tails, which is essential for signaling.

TLRs are involved in responses to a wide variety of molecules that are expressed by microbes but not by healthy mammalian cells.

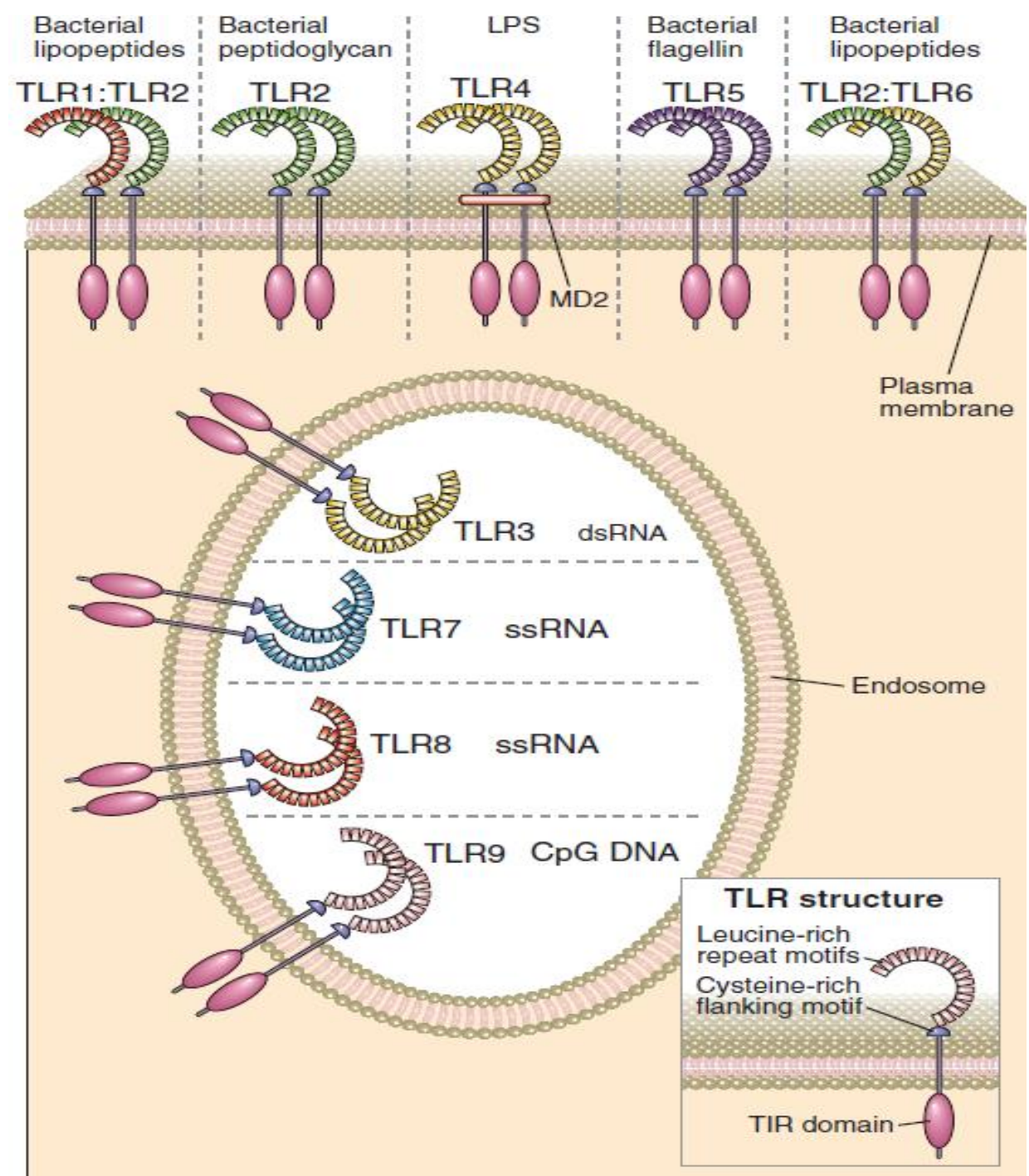
Ligands for TLRs

- **Bacterial cell wall constituents:** LPS of gram-negative bacteria, which binds TLR4; and peptidoglycan and lipoteichoic acid of gram-positive bacteria, which bind TLR2.
- **Bacterial surface proteins:** flagellin, a protein subunit component of the flagella of motile bacteria, which binds to TLR5
- **Viral nucleic acids:** double-stranded RNAs that make up the genomes of some viruses, are generated during the life cycle of most viruses, and bind TLR3; single-stranded RNAs, which are distinguished from cellular cytoplasmic single-stranded RNA transcripts by their location within endosomes and by their high guanosine and uridine content, bind TLR7 and TLR8; and unmethylated CpG nucleotides, which are common in prokaryotic DNA but rare in vertebrate genomes, bind TLR9. –

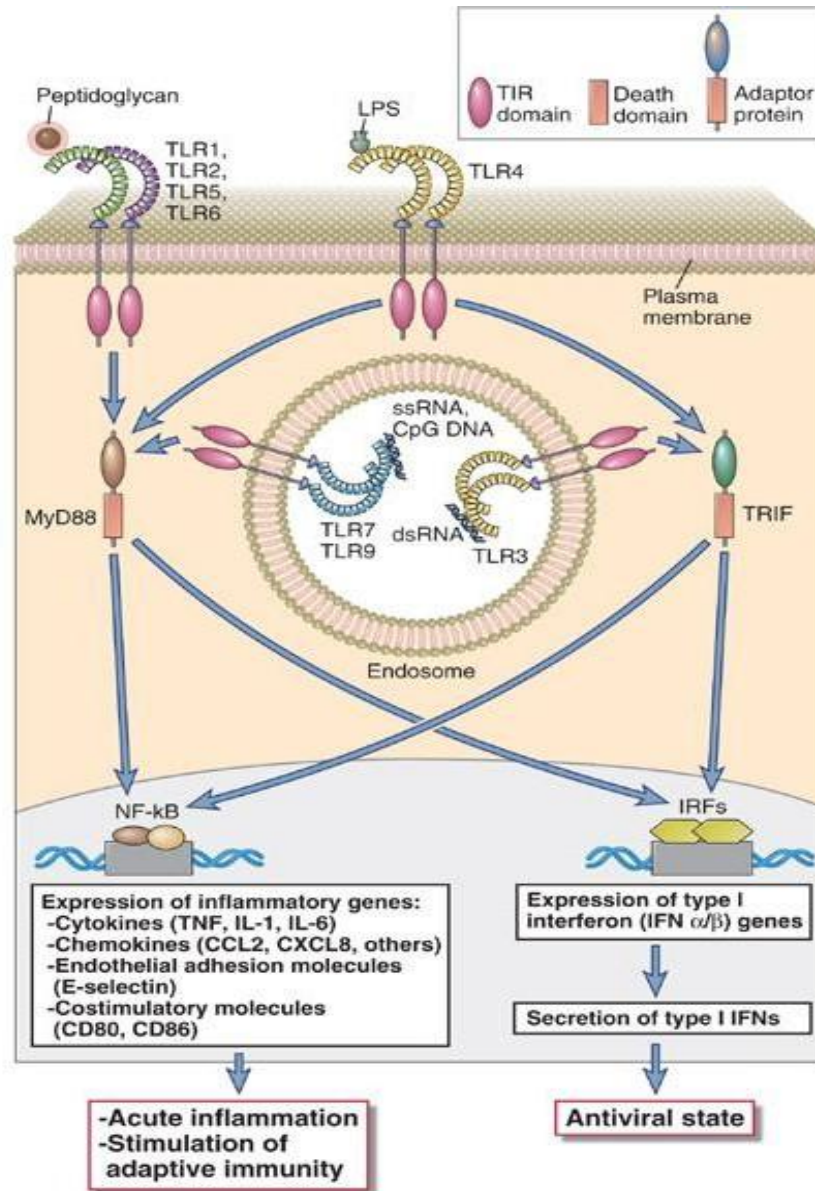
HSPs and HMGB1, endogenous molecules (normally present inside the cells but can be released by damaged and dying cells), in extracellular space activate TLR2 and TLR4 receptors on dendritic cells, macrophages



TLR receptors, structure, location and ligands



TLR signaling



Adaptors:
TRIF=TIR-domain-containing
adapter-inducing interferon- β
MyD88=Myeloid differentiation
primary response gene

Transcription factors:
IRF=interferon regulatory
factor
NF-kappaB=nuclear factor kB

NOD-like receptors, NLRs

a family of more than 20 different cytosolic proteins, some of which recognize PAMPs and DAMPs and recruit other proteins to form signaling complexes that promote inflammation

Typical NLRs include

1. C-terminal leucine-rich repeat domain that senses the presence of ligand;
2. central NOD (nucleotide oligomerization domain, also called NACHT) domain required for NLR proteins to bind to one another and form oligomers; and
3. N-terminal effector domain, which recruits other proteins to form signaling complexes

There are three NLR subfamilies that serve as innate immune receptors, each using a different effector domain to initiate signaling.

NLRB, which uses the BIR (baculovirus inhibition of apoptosis protein repeat) effector domain;

NLRC, which uses CARDs (caspase recruitment and activation domains); and

NLRP, which uses pyrin domains (so called because they are found in proteins involved in causing fever)

We will discuss two NLR sensors of bacterial PAMPs, named NOD1 and NOD2, and other NLRs important for inflammasomes.

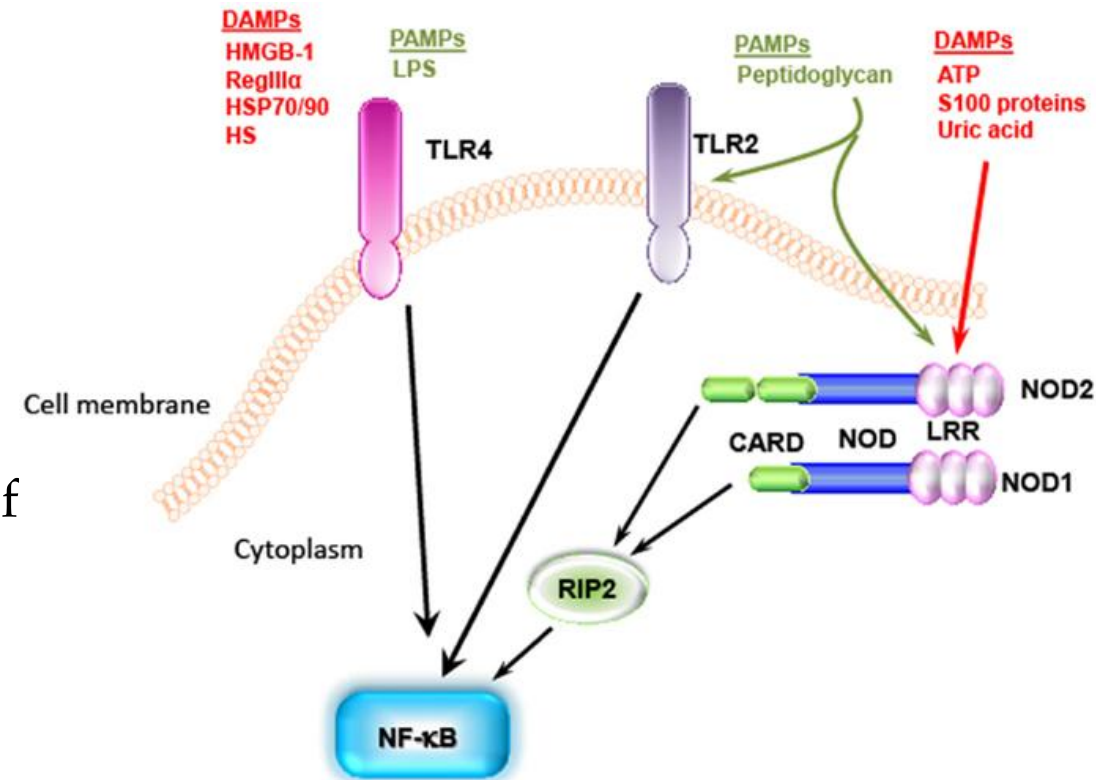
NOD1 and NOD2 are expressed in the cytosol of several cell types, including mucosal epithelial cells and phagocytes, and they respond to bacterial cell wall peptidoglycans.

NOD1 recognizes -parts of cell wall of G(-)bacteria

NOD2 recognizes muramyl dipeptide from G(-) and G(+)bacteria

When oligomers of NODs recognize their ligands, a conformational change occurs that allows the CARD effector domains of the NOD proteins to recruit multiple copies of the kinase RIP2, forming a signaling complex, called the NOD signalosome. The RIP2 kinases in these complexes activate NF- κ B, which stimulates production of cytokines and other molecules involved in inflammation, similar to TLRs that signal through MyD88.

- **NOD1 and NOD2** are important for the innate immune responses to bacterial pathogens in the gastrointestinal tract, such as *Helicobacter pylori* and *Listeria monocytogenes*.
- **NOD2 polymorphism** increases risk for the Crohn's disease.

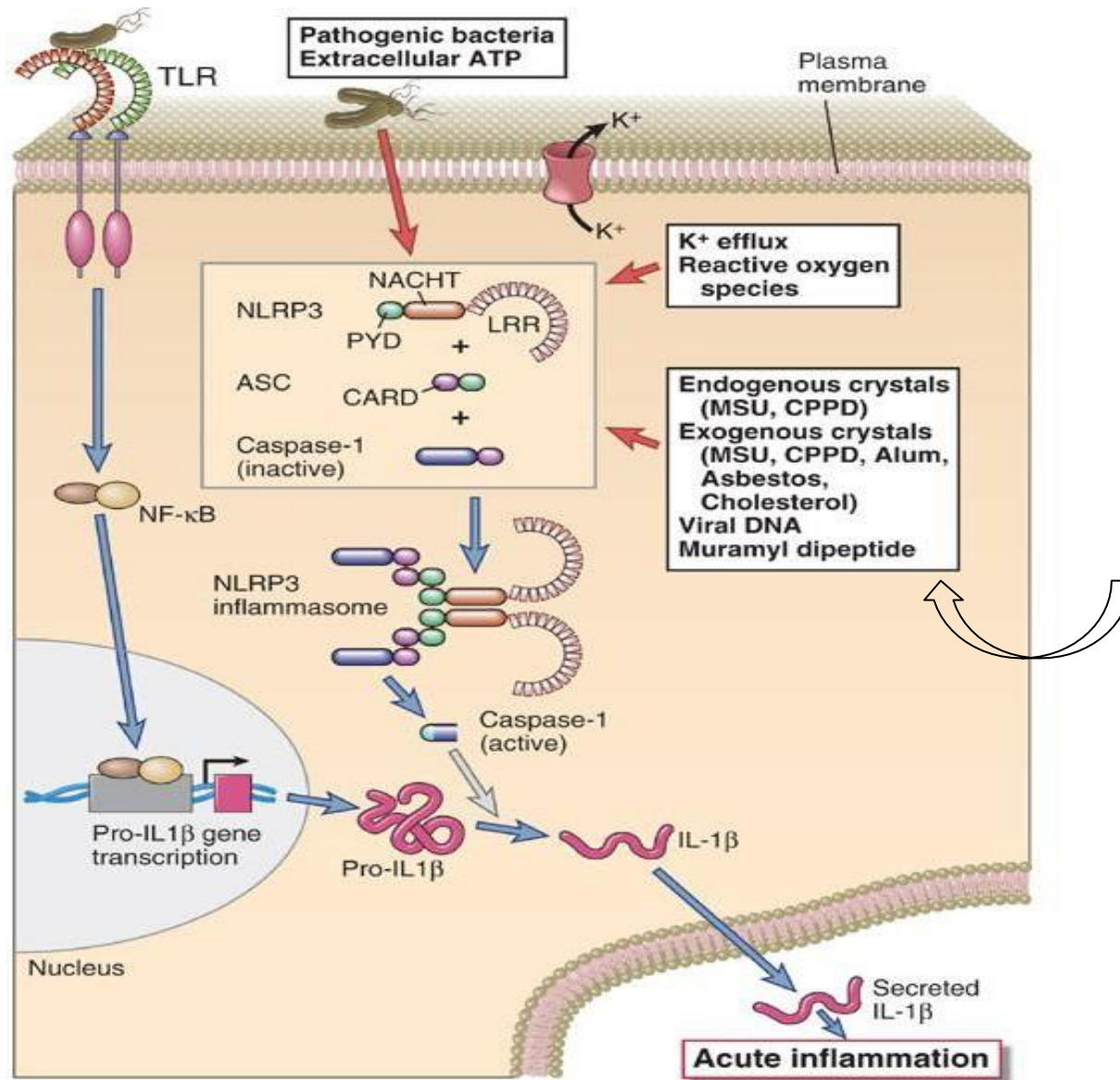


NLRP subfamily of NLRs receptors

Recognizes cytoplasmic PAMPs and DAMPs and induces formation of **inflammasome** and subsequently induce production of active form of inflammatory cytokine IL-1.

Inflammasome activation is induced by a wide variety of cytoplasmic stimuli that are often associated with infections and cell stress, including microbial products, environmentally or endogenously derived crystals, and reduction in cytosolic potassium ion (K^+) concentrations

The inflammasome



Dysregulated activation of inflammasomes, most often due to autosomal gain-of-function mutations in one or another of their component proteins, leads to inappropriately triggered and excess IL-1 production, resulting in recurrent attacks of fever and localized inflammation, most commonly in the skin, joints, and abdominal cavity. These disorders are called inflammasomopathies.

- Familial Mediterranean fever, caused by mutation of the *MEFV* gene, which encodes pyrin.
- Autoinflammatory diseases caused by mutations in NLRP3 (cryopyrin) are called cryopyrin-associated periodic syndromes (CAPS).

Inflammasomes may be activated by excessive amounts of endogenous substances deposited in tissues in the setting of various diseases (cholesterol crystals within macrophages in atherosclerosis, free fatty acids and lipids in adipose tissue in obesity-associated metabolic syndrome and type 2 diabetes, and β -amyloid in Alzheimer's disease).

Other Cell-Associated Pattern Recognition Receptors

C-Type Lectin-Like Receptors

	Mannose Receptor (CD206)	Dectin-1 (CD369)	Dectin-2 and Mincle	DC-Sign (CD209)
Ligand	Terminal mannose and fucose on microbial cell surfaces	β -Glucan on fungal cell surfaces	High mannose on fungal hyphae and bacteria	Terminal mannose fucose or microbial cell surface
Signaling	Uncertain	ITAM/SYK/CARD9 pathway of NF- κ B activation	ITAM/SYK/CARD9 pathway of NF- κ B activation	Uncertain
Cellular expression	Macrophages	Dendritic cells	Dendritic cells	Dendritic cells, macrophages and sinusoidal endothelial cells
Function	Phagocytosis; antifungal immunity	Inflammation and antigen presentation; Th17 differentiation; antifungal immunity	Inflammation and antigen presentation; Th17 differentiation; antifungal and mycobacterial immunity	Adhesion; hepatitis virus and HIV-1 infection

Other Cell-Associated Pattern Recognition Receptors

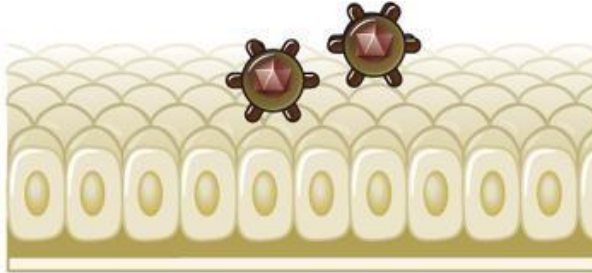
Scavenger receptors comprise a structurally and functionally diverse collection of cell surface proteins that were originally grouped on the basis of the common characteristic of mediating the uptake of oxidized lipoproteins into cells (scavenger receptor A (SR-A) and CD36)

The **formyl peptide receptor-1** (FPR1), expressed on leukocytes, recognizes bacterial peptides containing *N*-formylmethionyl residues and stimulates directed movement of the cells. Because all bacterial proteins and few mammalian proteins (only those synthesized within mitochondria) are initiated by *N*-formylmethionine, FPR1 enables phagocytes to detect and respond preferentially to bacterial proteins.

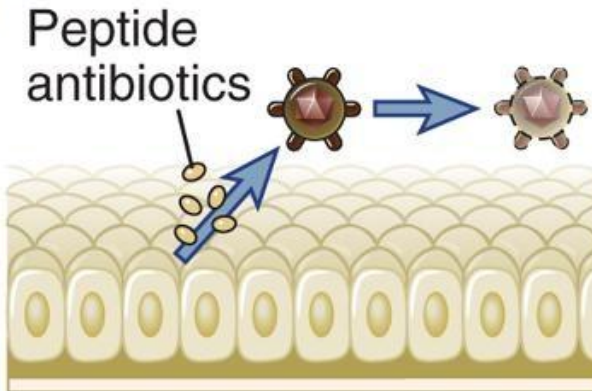
Cytosol sensors of viral RNA which in answer to viral nucleic acids induce production of IFN type 1 (**RIG-inducible gene 1 for retinoic acid** and **MDA5 gene associated with by differentiation melanoma 5**)

Epithelial barriers

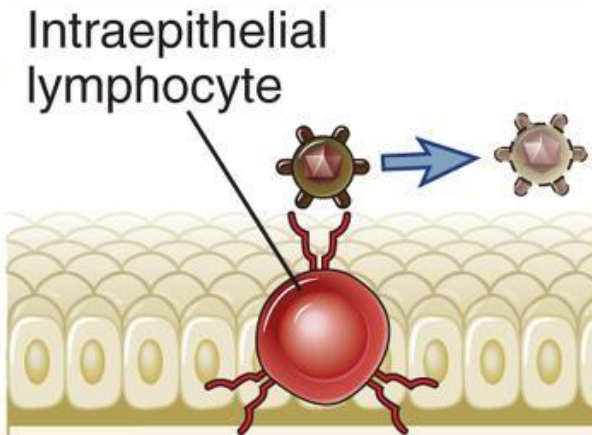
Physical barrier
to infection



Killing of microbes
by locally produced
antibiotics,
defensins,
cathelicidins



Killing of microbes
and infected cells
by intraepithelial
lymphocytes



Defensins:

29-34 aa-long peptides

Cathelicidins:

polypeptide from a 18kD precursor

**made by epithelial cells,
neutrophils, NKs, CTLs,
paneth cells ...**

**can permeabilize bacterial
membranes**

IE lymphocytes:

alpha/beta and gamma/delta

TCR positive cells

low diversity

specific for bacterial proteins

activate phagocytes

kill infected cells

Phagocytes

Cells that have specialized phagocytic functions, primarily macrophages and neutrophils, eliminate microbes that breach epithelial barriers.

Neutrophils and monocytes are circulating phagocytes that are recruited into tissues in response to signals generated by innate sentinel cells. The monocytes rapidly differentiate into macrophages after leaving the blood. Tissue-resident macrophages are always present in most tissues under normal conditions and also serve as sentinel cells.

Phagocytes:

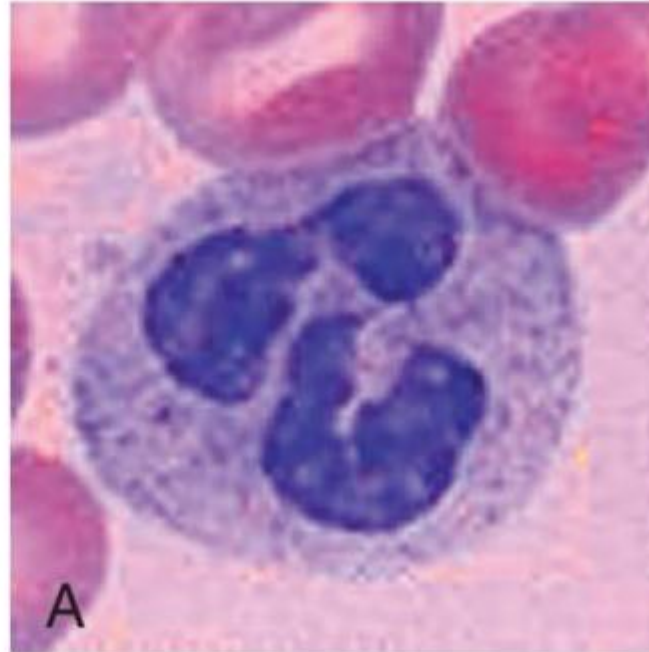
- internalize and kill microbes
- produce different cytokines in response to microbes recognition and stimulate inflammatory response
- have the role in reparation of damaged tissues

The essential role that phagocytes play in innate immune defense against microbes is demonstrated by the high rate of bacterial and fungal infections in patients with low blood neutrophil counts caused by bone marrow cancers or chemotherapy and irradiation for cancer and in patients with inherited deficiencies in the functions of neutrophils and macrophages.

Neutrophils

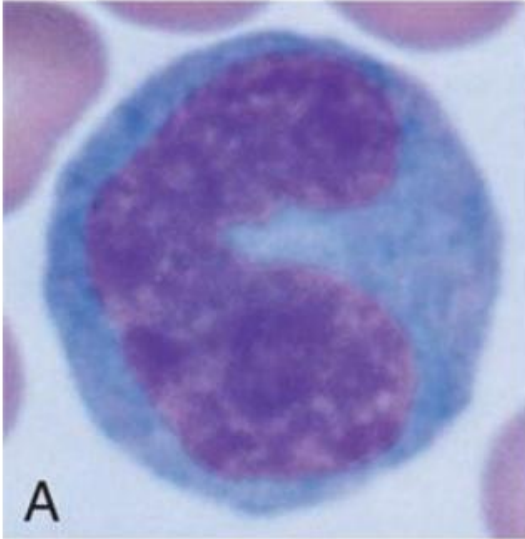
polymorphonuclear
leukocytes

lysozyme
collagenase
elastase
defensins

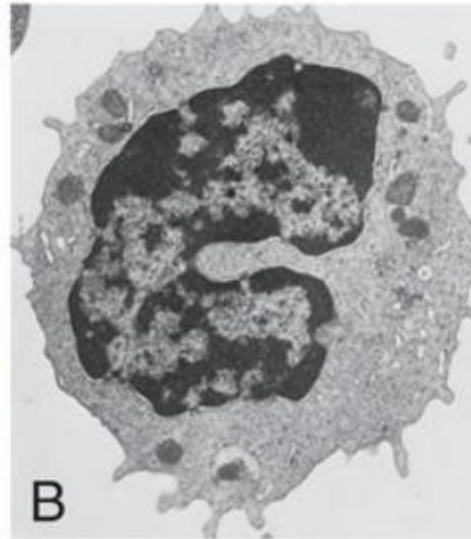


Monocytes/macrophages

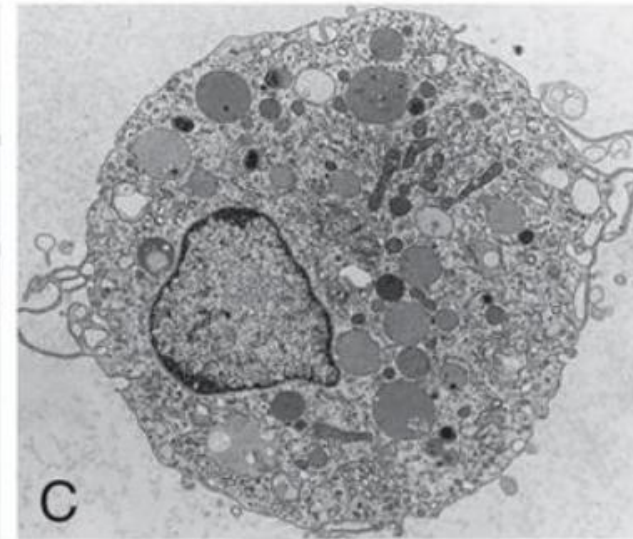
Monocyte (LM)
in peripheral blood smear



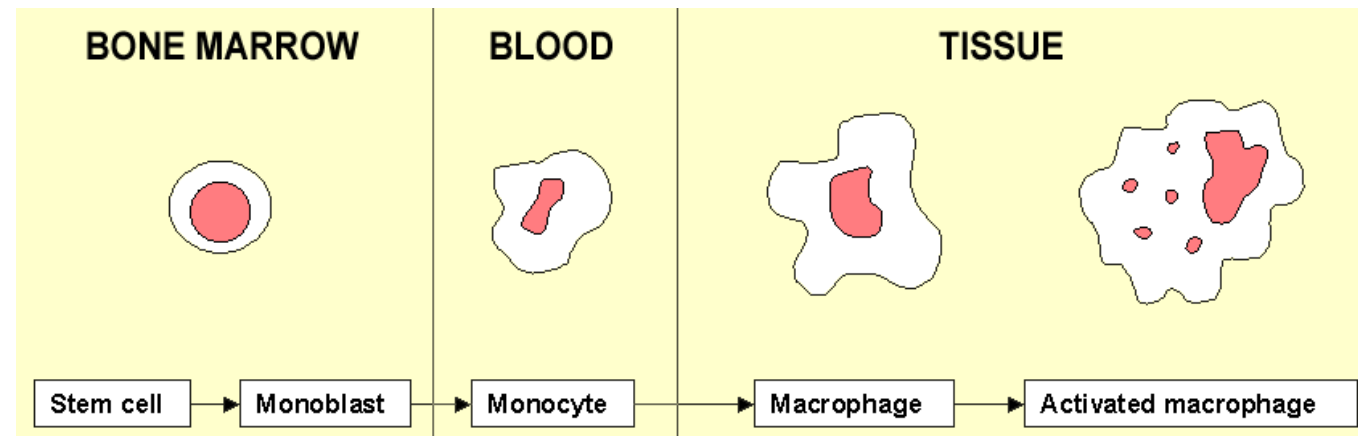
Monocyte (ELMI)
in peripheral blood



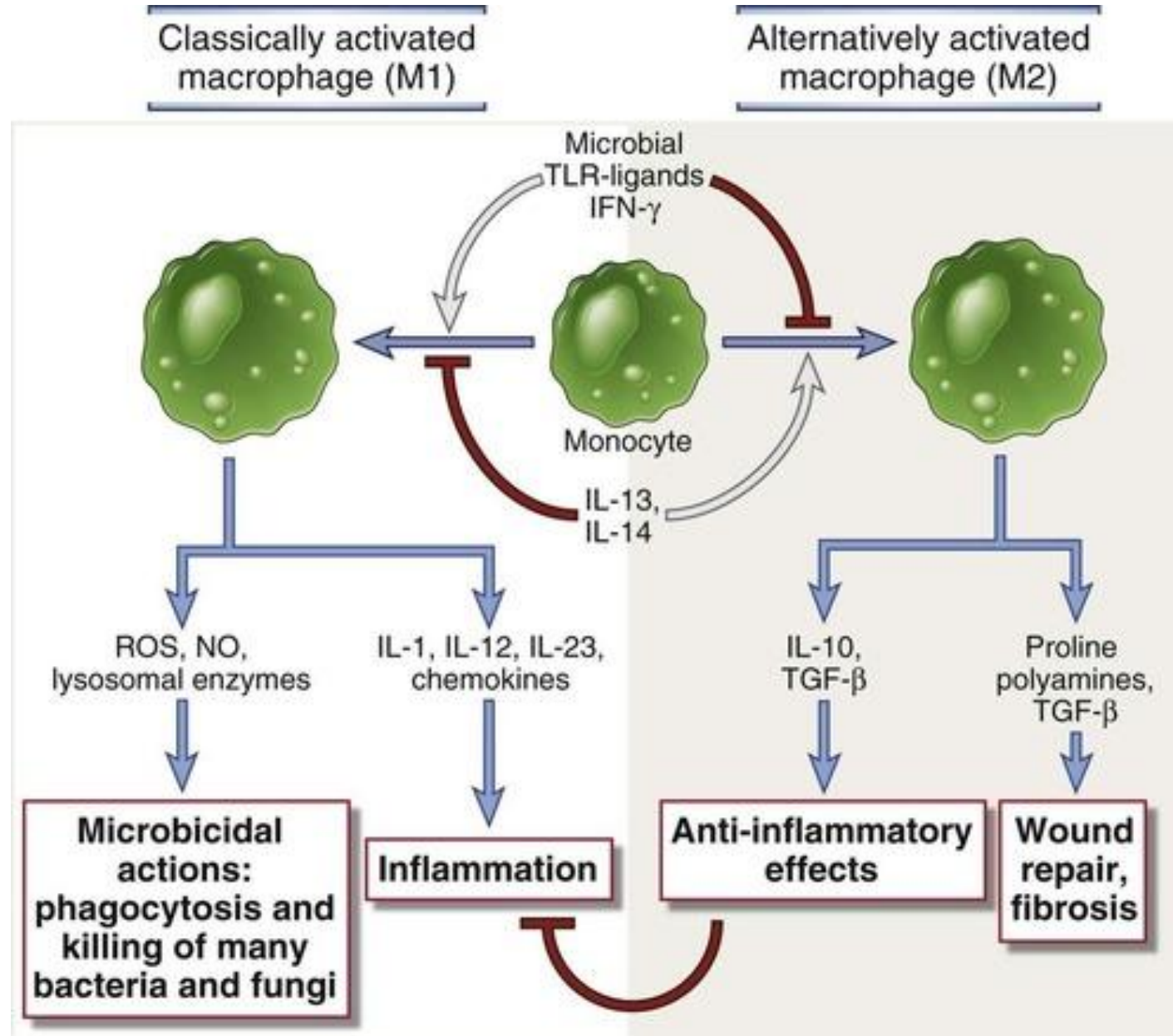
Activated macrophage
in tissue – numerous vacuoles/organelles



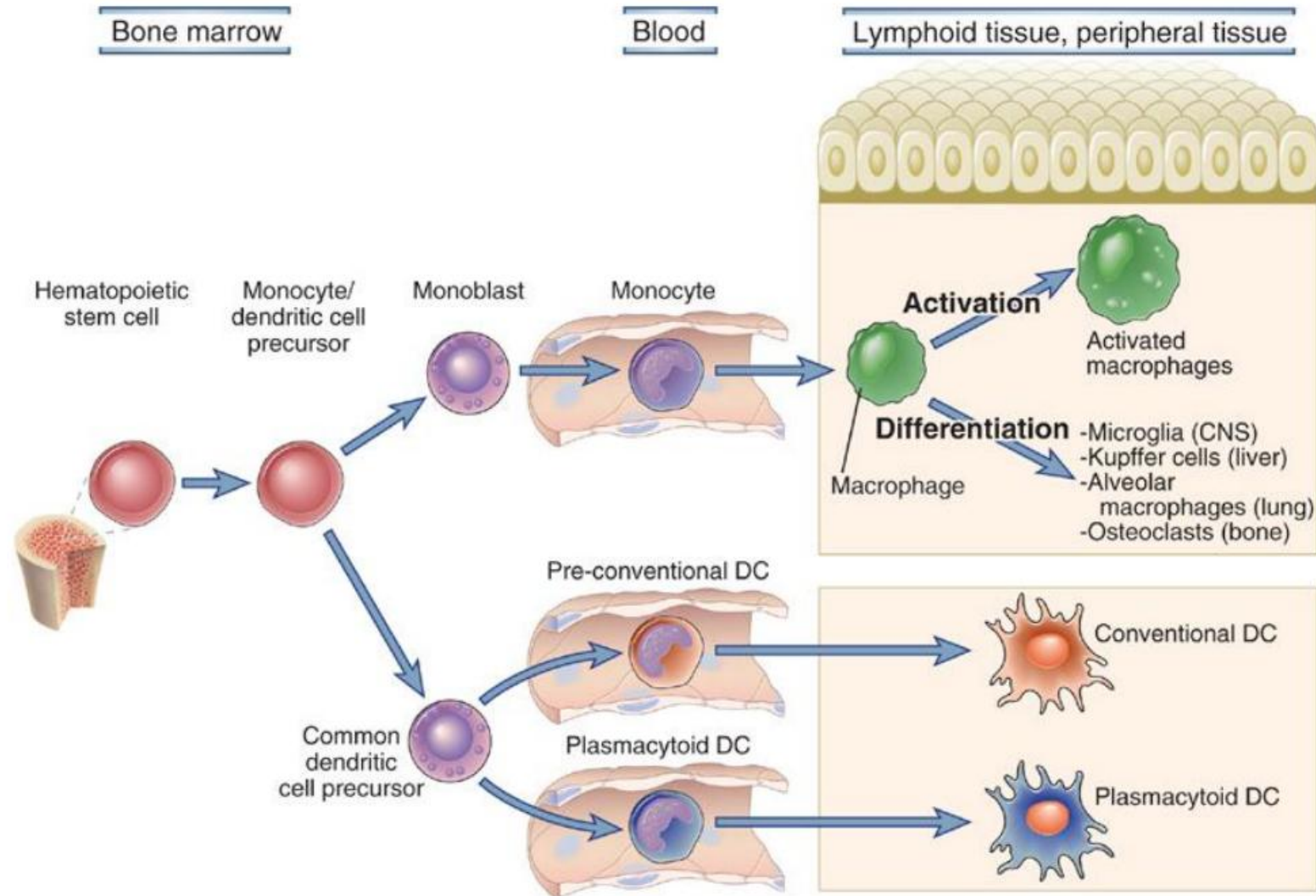
<https://www.youtube.com/watch?v=IZWOH3NEsag&t=15s>



Classical and Alternative Activation of Macrophages



Maturation of Phagocytes



Dendritic cells

Dendritic cells rapidly and efficiently detect invading microbes because of their location in tissues and their expression of numerous pattern recognition receptors for PAMPs and DAMPs.

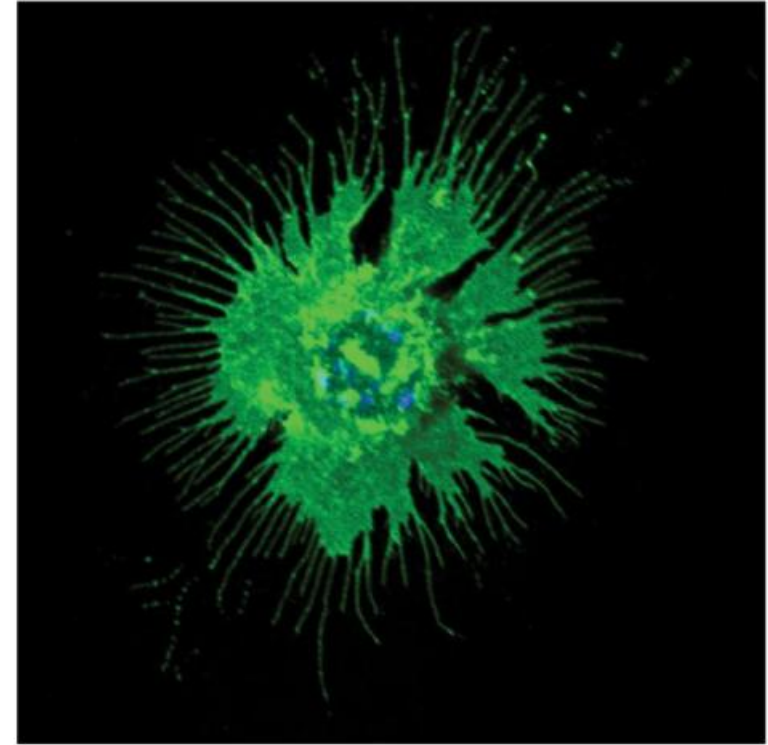
In response to invading microbes, they secrete inflammatory cytokines that promote recruitment of additional leukocytes from the blood.

The plasmacytoid subset of DCs is a major source of the antiviral cytokines type I IFNs, produced in response to viral infections.

The ability of DCs to promote T lymphocyte responses after innate immune activation also makes them an important bridge between innate and adaptive immunity.

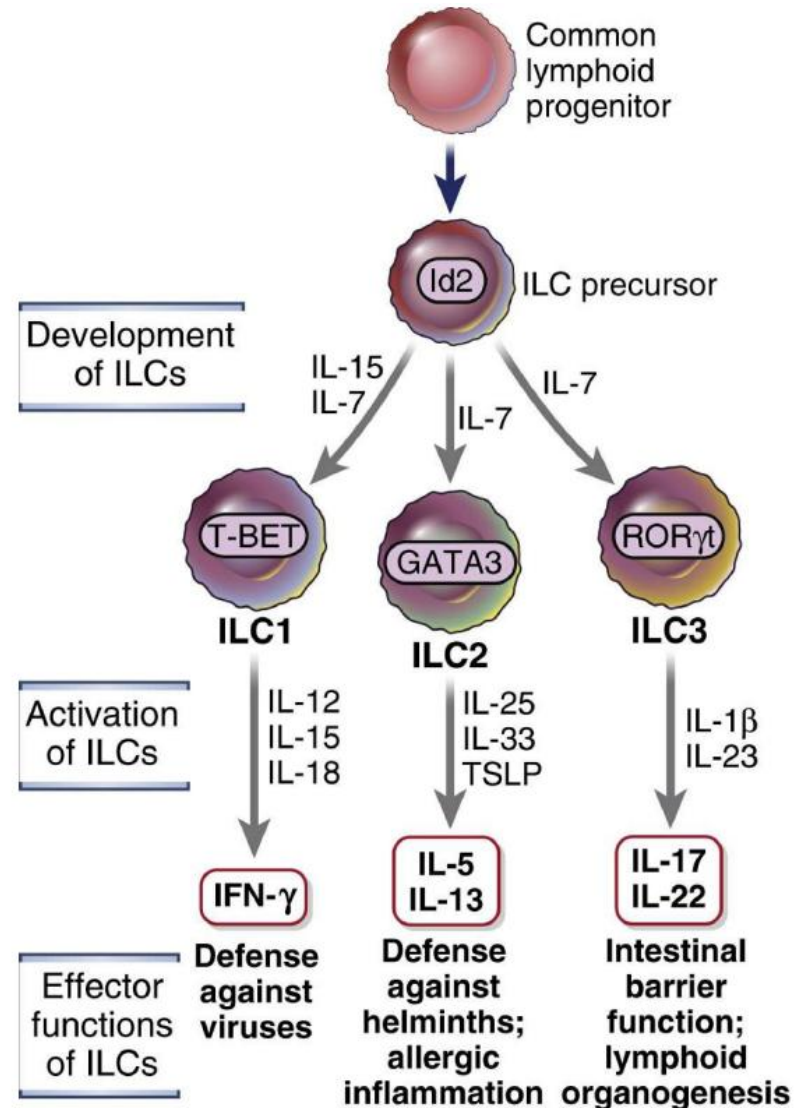
depending on the nature of the microbe that induces the innate response, a DC will direct naive T cell differentiation into distinct types of effector cells, such as IFN- γ -producing Th1 cells or IL-17-producing Th17 cells.

Dendritic cell (fluorescence micrograph)
bone marrow-derived, MHCII=green, nucleus=blue



Innate lymphoid cells (ILCs)

bone marrow– derived cells with lymphocyte morphology that were discovered as cells that produced cytokines similar to those made by helper T cells but lacked TCRs



NK cells

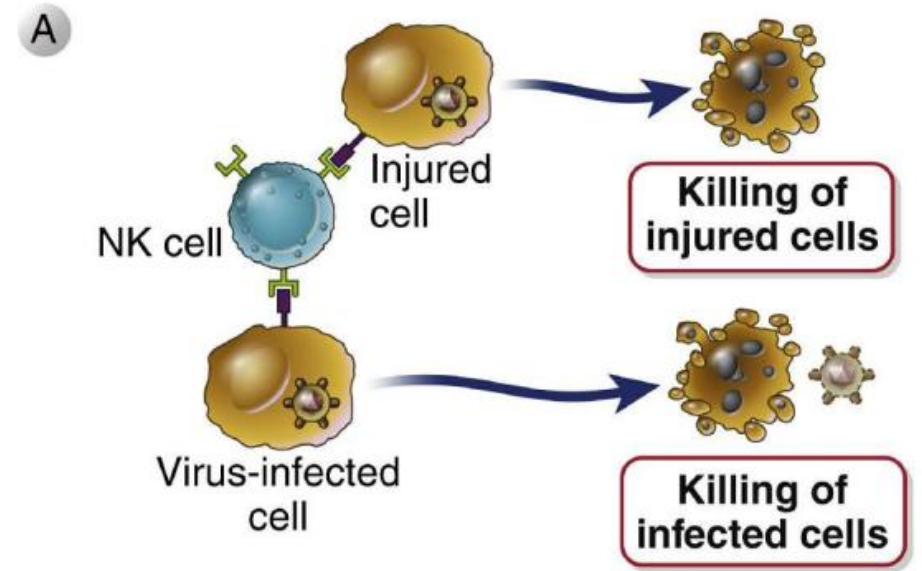
NK cells are cytotoxic cells that play important roles in innate immune responses, mainly against viruses and intracellular bacteria

The major function of NK cells is killing infected cells, similar to the adaptive immune system's killer cells, the CTLs, but unlike naive CD8 + T cells, NK cells are functionally competent to kill other cells when they are present in the blood or tissues without further differentiation (hence natural)

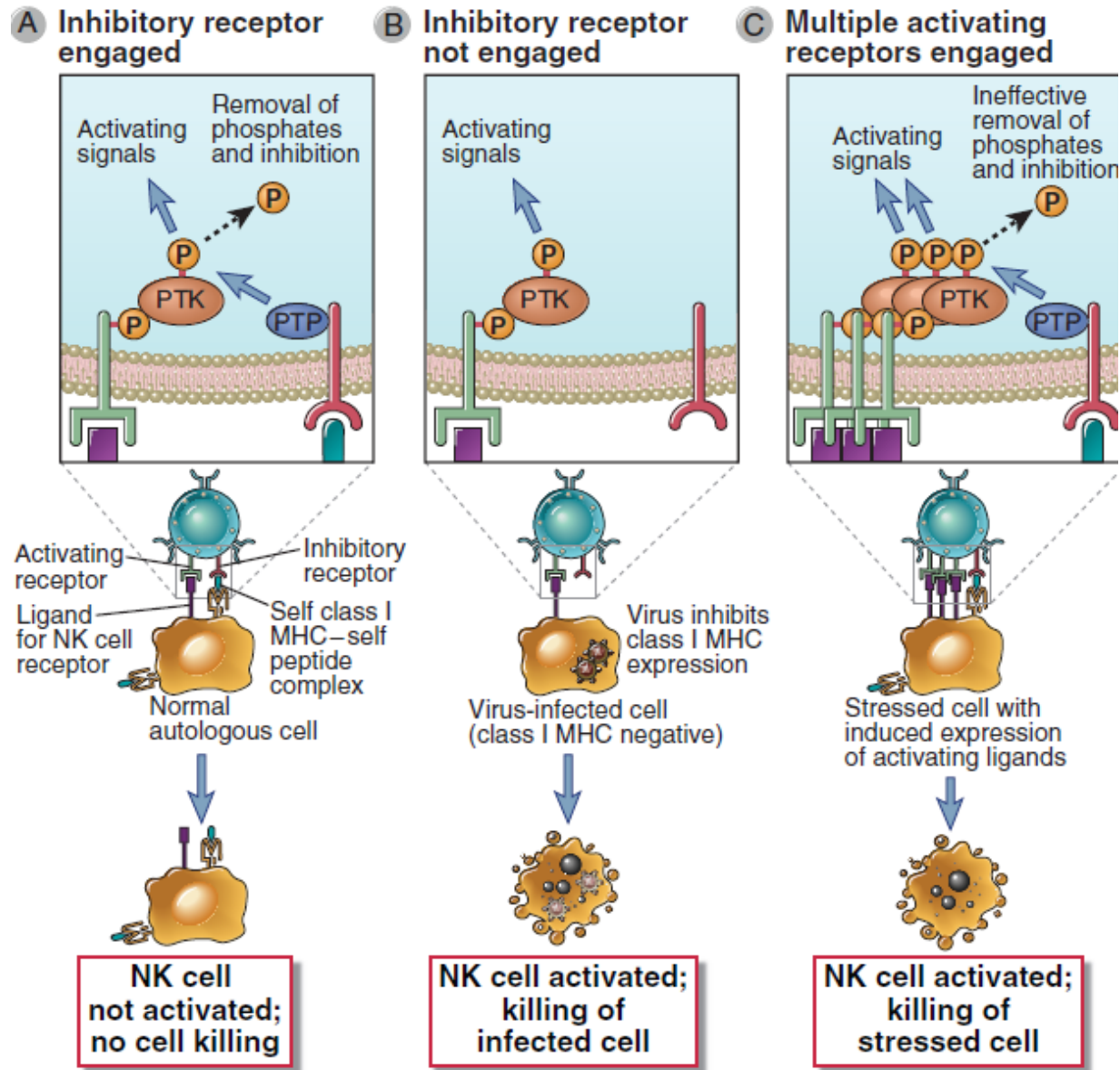
NK cells constitute 5% to 20% of lymphocytes in the blood and spleen.

They are rare in other lymphoid organs and in most nonlymphoid tissues but are numerous in the liver and placenta. NK cells in the blood appear as large lymphocytes with numerous cytoplasmic granules

Identification of NK cells in blood (CD56+ CD3-)



Activating and Inhibitory Receptors of Natural Killer Cells

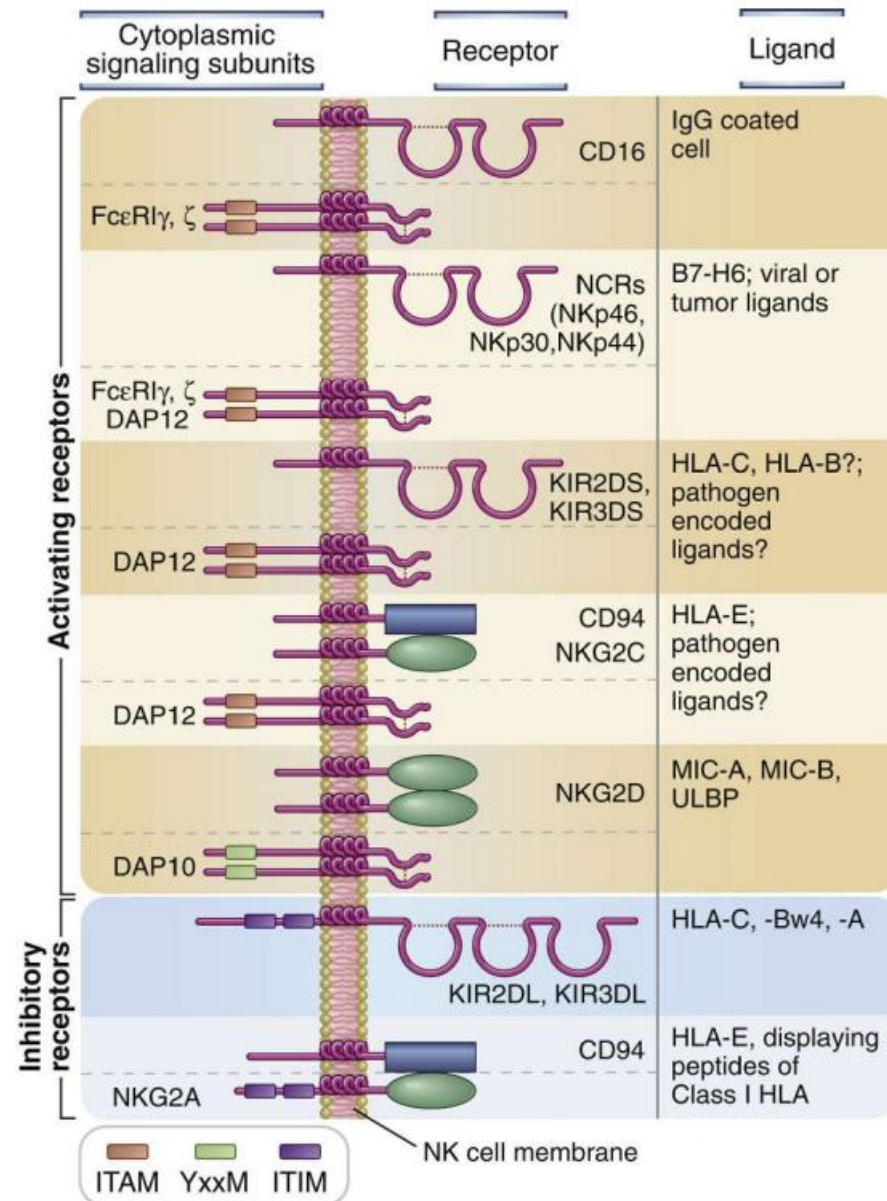


NK cells distinguish infected and stressed cells from healthy cells, and NK cell function is regulated by a balance between signals that are generated by activating and inhibitory receptors.

In general, the activating receptors recognize ligands on infected and injured cells, and the inhibitory receptors recognize ligands on healthy normal cells.

When an NK cell interacts with another cell, the outcome is determined by the integration of signals generated from the array of inhibitory and activating receptors that are expressed by the NK cell and that interact with ligands on the other cell.

Structure and ligands of activating and inhibitory receptors of natural killer cells



NK Cell Functions

Kill infected cells and activate macrophages to destroy phagocytized microbes

NK cells contain granules with proteins ... **perforin**, facilitates entry others proteins called **granzymes** to the target cells

NK cells produce **IFN- γ** which stimulates macrophages to destroy phagocytized microbes (for example *Listeria monocytogenes*).

NK cells kill virus infected cells before Ag specific cytotoxic lymphocytes become completely active

IL-12 and IL-15 stimulate the antiviral function of NK cells

Significance NK: depletion of NK cells is associated with increased sensitivity to viral infections and infections with intracellular bacteria

T and B lymphocytes with limited antigen receptor specificity

Certain subgroups of T and B lymphocytes that have very small diversity

These T and B subsets recognize PAMPs.

T subgroups- invariant NKT cells (iNKT)
 $\gamma\delta$ T lymphocytes

Subsets of B cells B-1 B cells
B cells of marginal zones

$\gamma\delta$ T cells

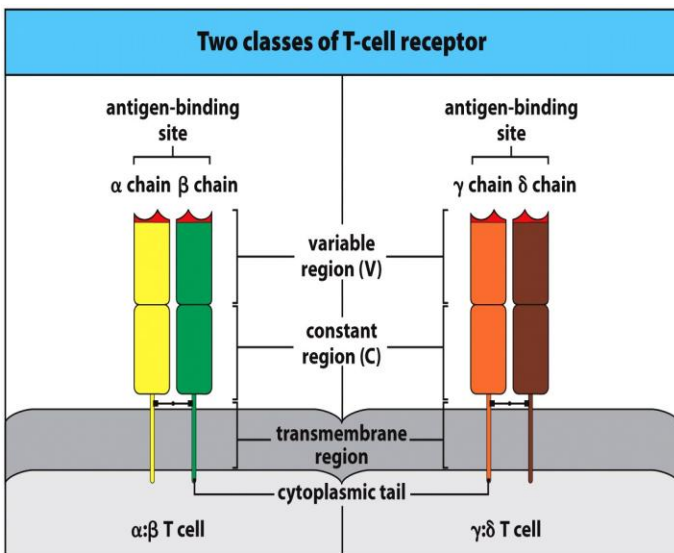
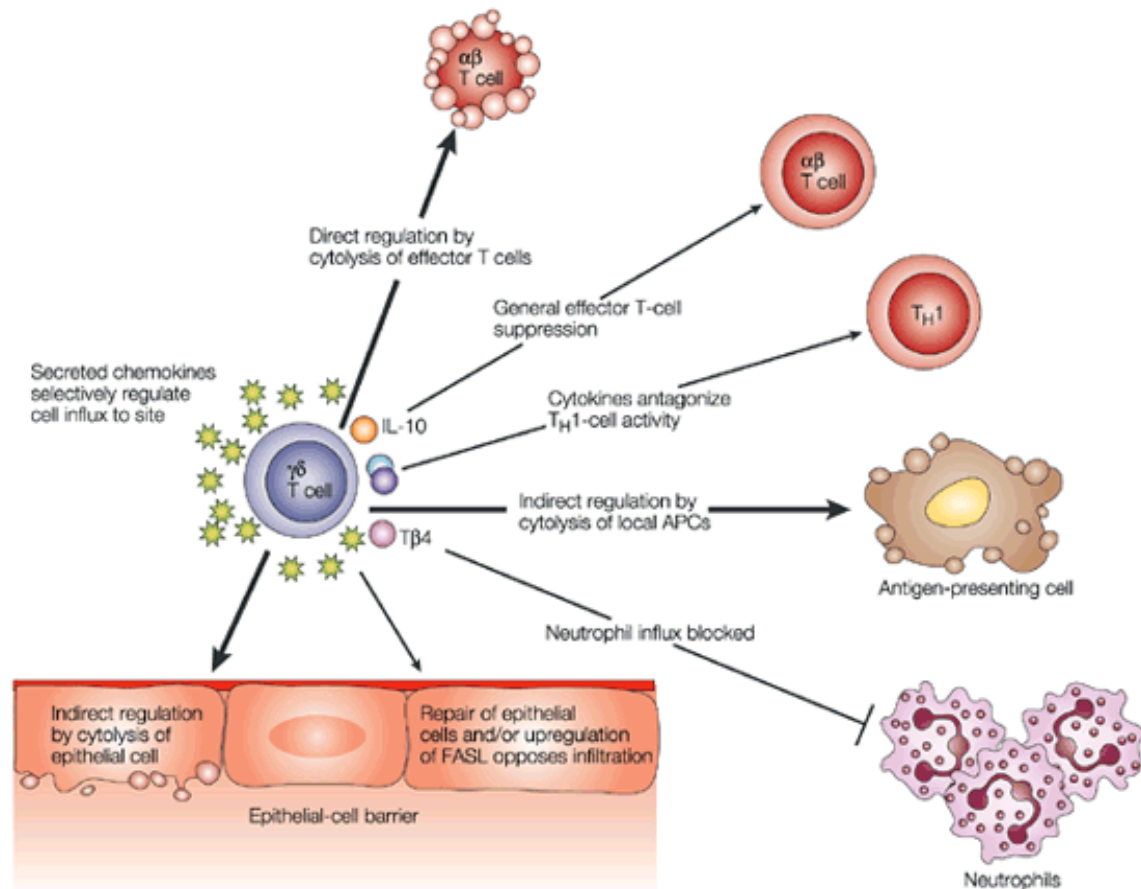
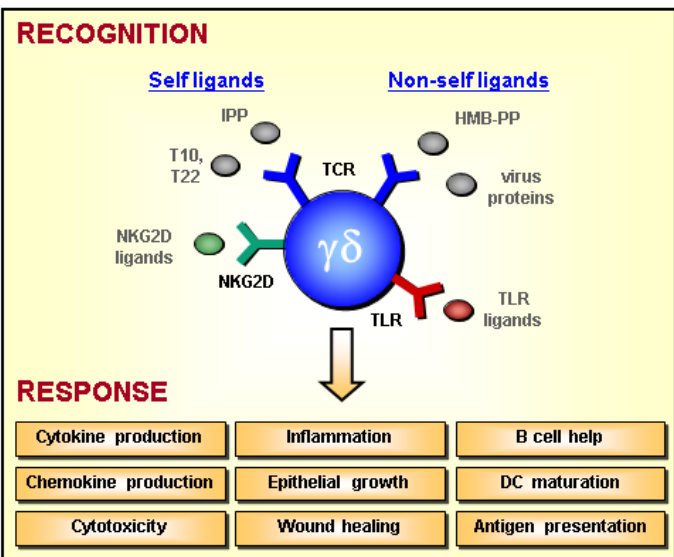
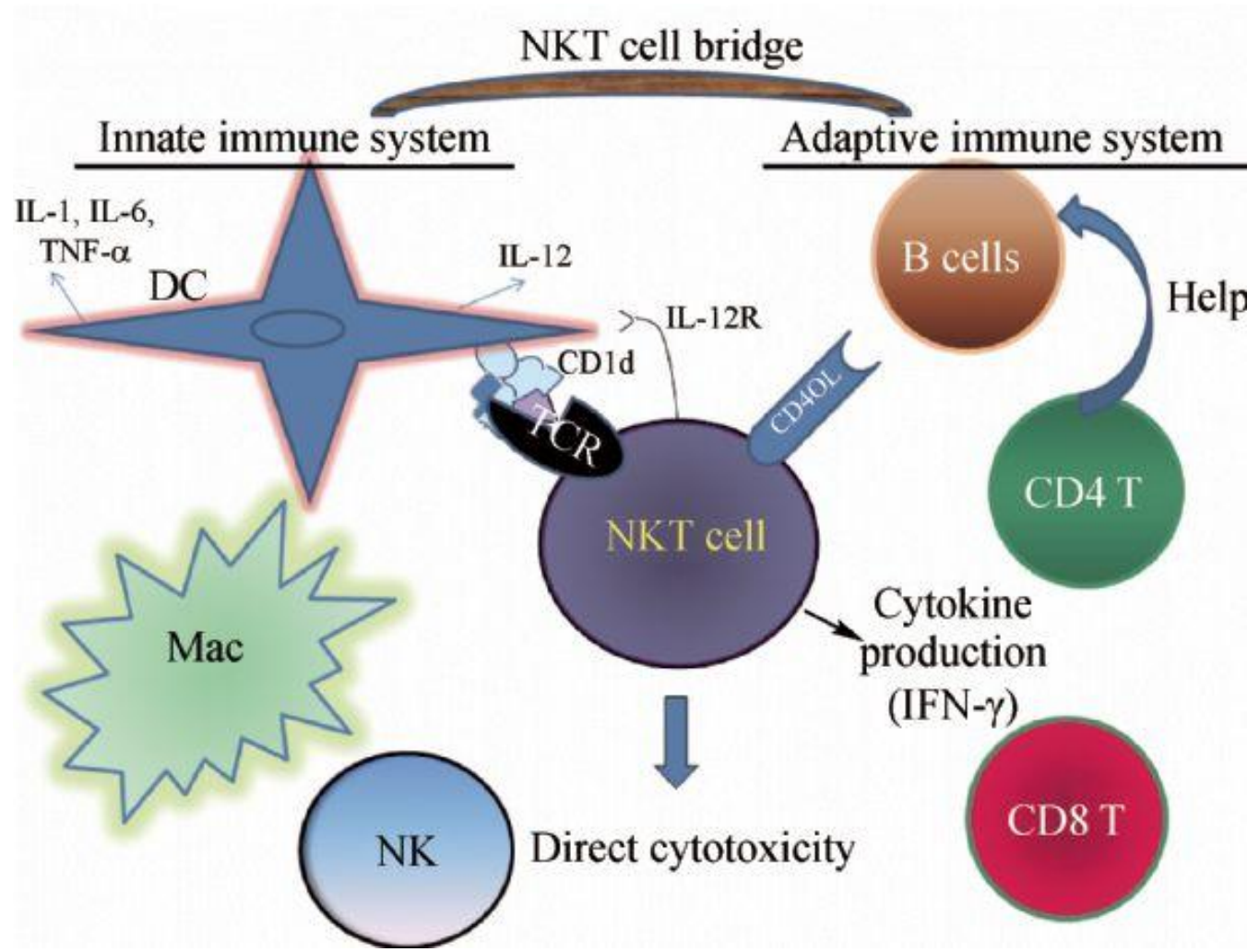
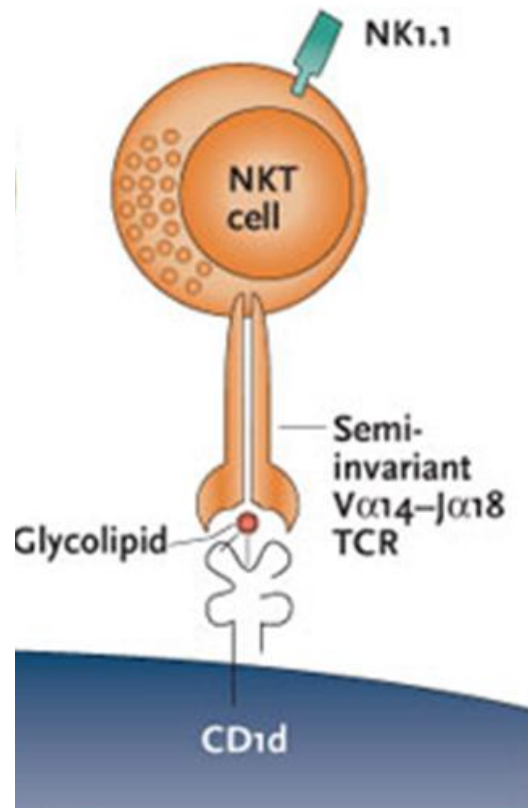


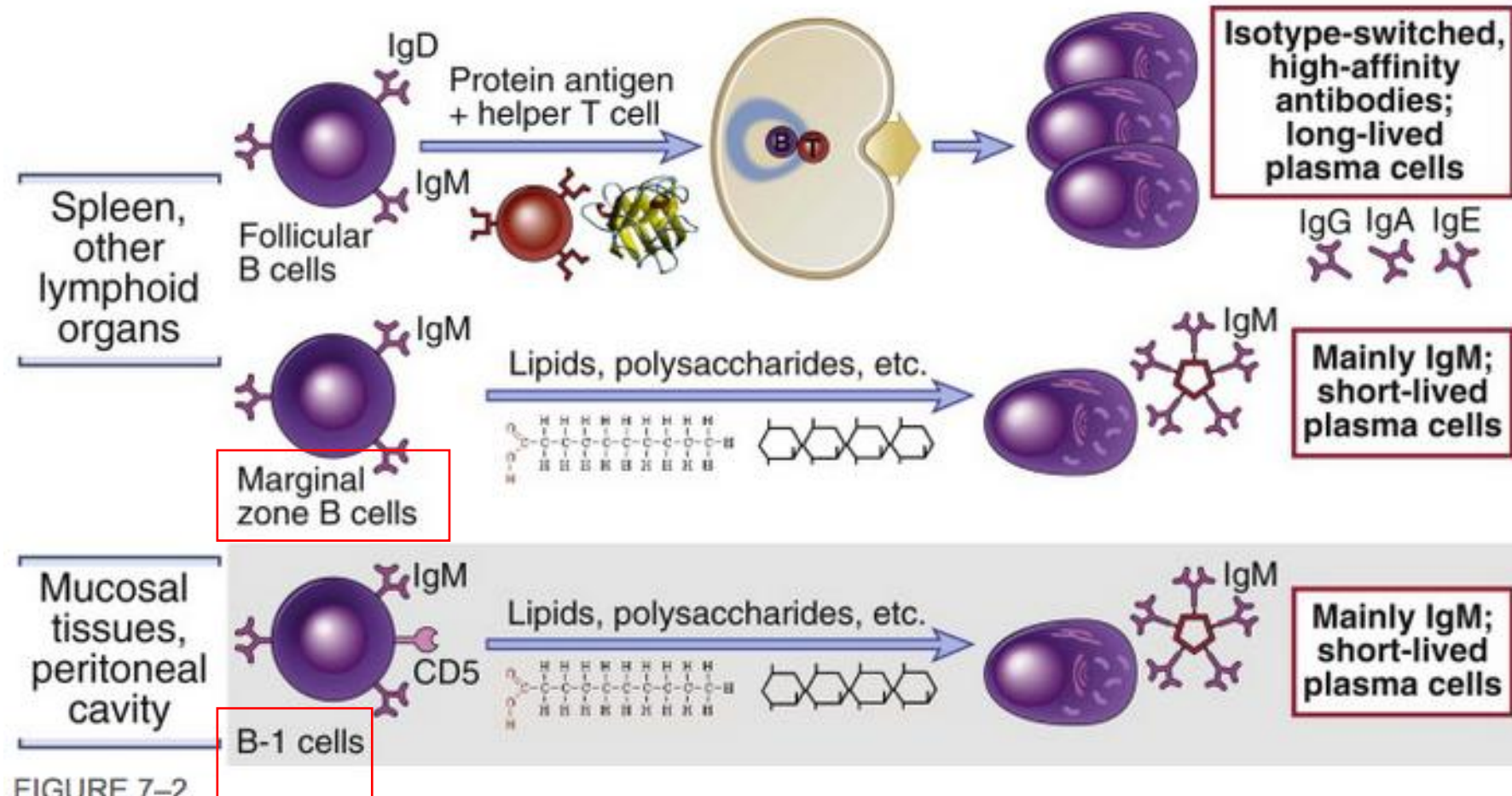
Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)



NKT cells

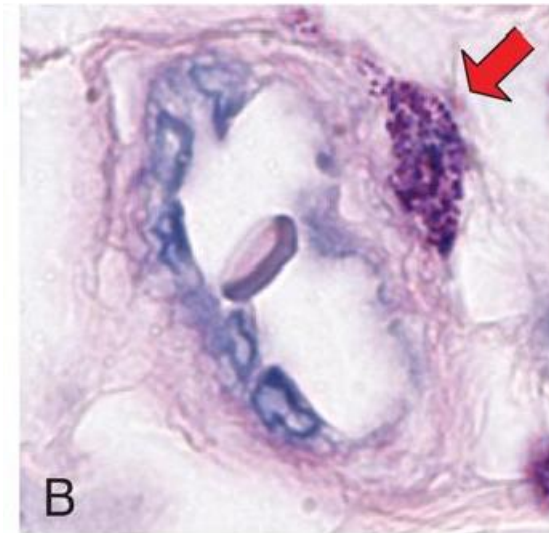


B-1cells and B cells of marginal zones



Mast cells

- sentinel cells present in the skin, mucosal epithelium, and connective tissues that rapidly secrete proinflammatory cytokines and lipid mediators in response to infections and other stimuli.
- contain abundant cytoplasmic granules filled with various inflammatory mediators that are released when the cells are activated, either by microbial products or by a special antibody-dependent mechanism.
- The granule contents include **vasoactive amines** (such as histamine) that cause vasodilation and increased capillary permeability, and **proteolytic enzymes** that can kill bacteria or inactivate microbial toxins, and also secrete **lipid mediators** (such as leukotrienes and prostaglandins) and cytokines (such as TNF).
- Because mast cells are usually located adjacent to blood vessels, their released granule contents rapidly induce changes in the blood vessels that promote acute inflammation.
- Mast cells express TLRs, and TLR ligands can induce mast cell degranulation.



Mast cells

IgE-receptor+

histamine
leukotriens
cytokines

Soluble Effector Molecules of Innate Immunity

- different kinds of molecules that recognize microbes and promote innate responses and exist in soluble form in the blood and extracellular fluids.
- provide early defense against pathogens
- function in two major ways: 1) by binding to microbes, they act as opsonins and enhance the ability of macrophages and neutrophils to phagocytose the microbes, 2) after binding to microbes, promote inflammatory responses that bring more phagocytes to sites of infections and they may also directly kill microbes.

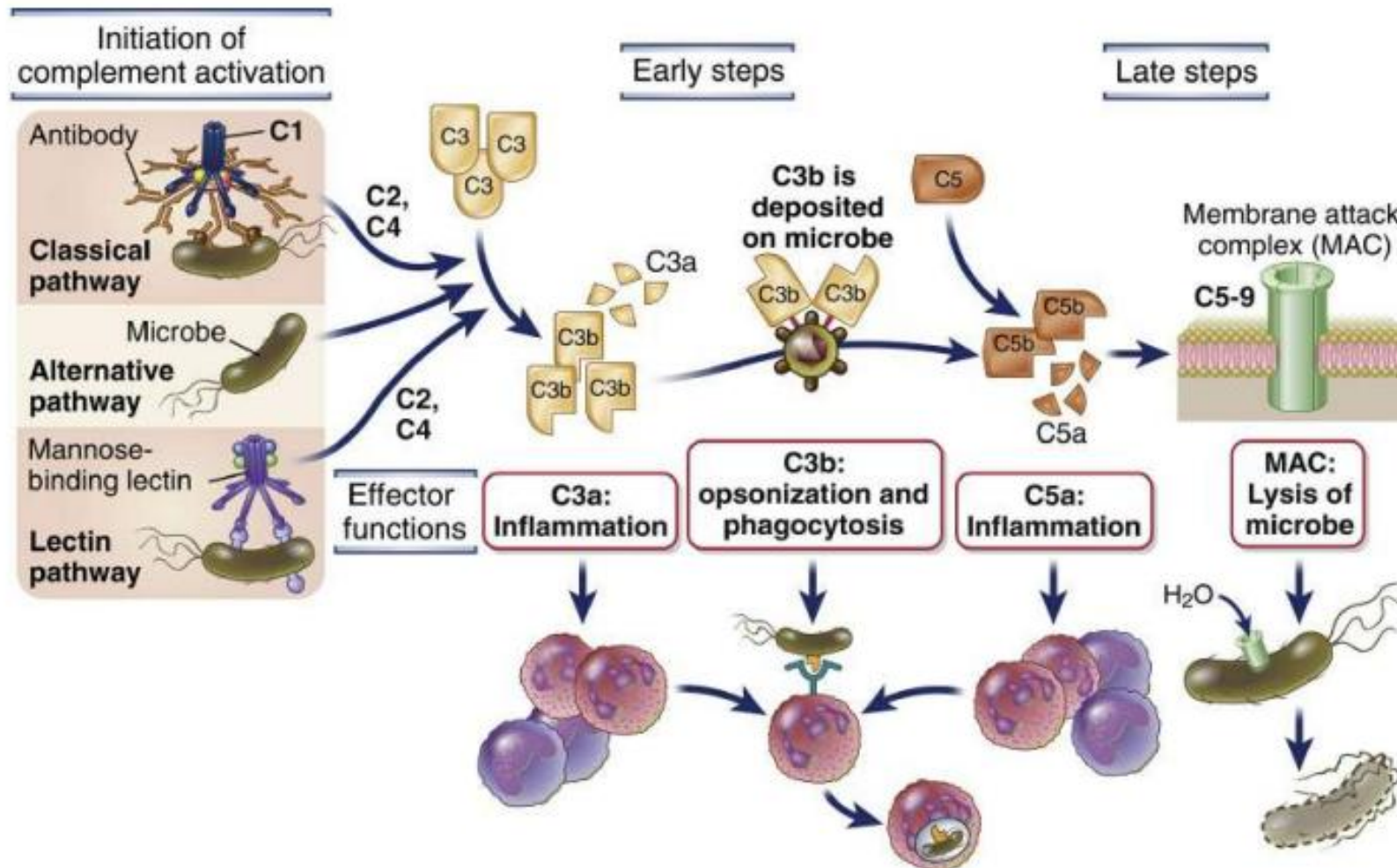
The major components of the humoral innate immune system are:

- complement system,
- collectins,
- pentraxins, and
- ficolins

The Complement System

- The complement system consists of several plasma proteins that work together to
- opsonize microbes, to promote the recruitment of phagocytes to the site of infection, and in some cases to directly kill the microbes
- Complement activation involves proteolytic cascades in which an inactive protein, called a zymogen, is altered to become an active protease that cleaves and thereby induces the proteolytic activity of the next complement protein in the cascade.
- Enzymatic cascades result in tremendous amplification of the amount of proteolytic products that are generated at each step.
- These products perform the effector functions of the complement system.

Pathways of complement activation

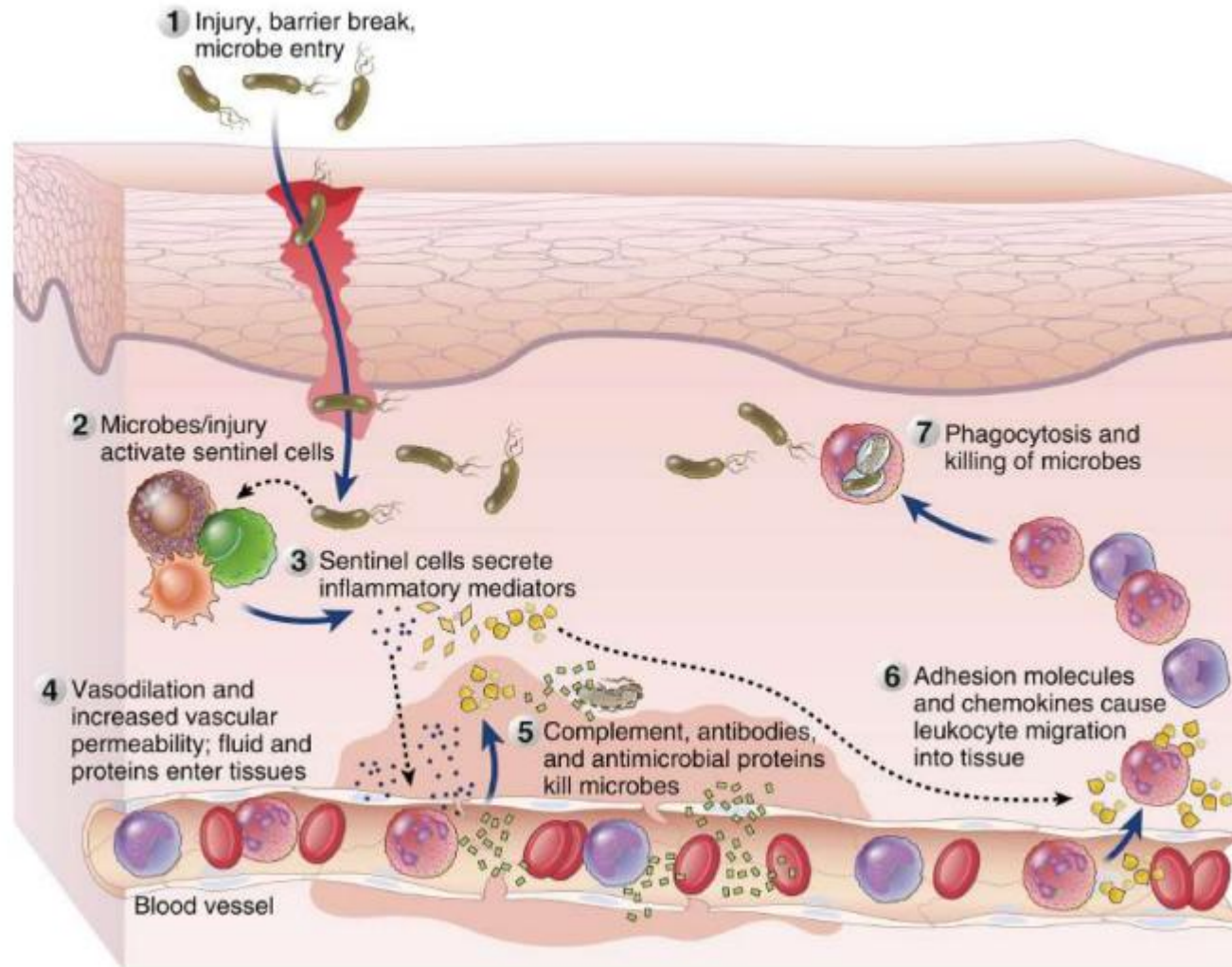


The Complement System, Importance

- The complement system, activated by the alternative and lectin pathways, is an essential component of innate immunity, and patients with deficiencies in C3 are highly susceptible to recurrent, often lethal, bacterial infections.
- Genetic deficiencies in MAC formation (the terminal product of the classical pathway) cause increased susceptibility to only a limited number of microbes, notably *Neisseria* bacteria, which have thin cell walls that make them especially susceptible to the lytic action of the MAC.
- The complement system also contributes to cell and tissue injury in many inflammatory and autoimmune diseases.

The Inflammatory Response

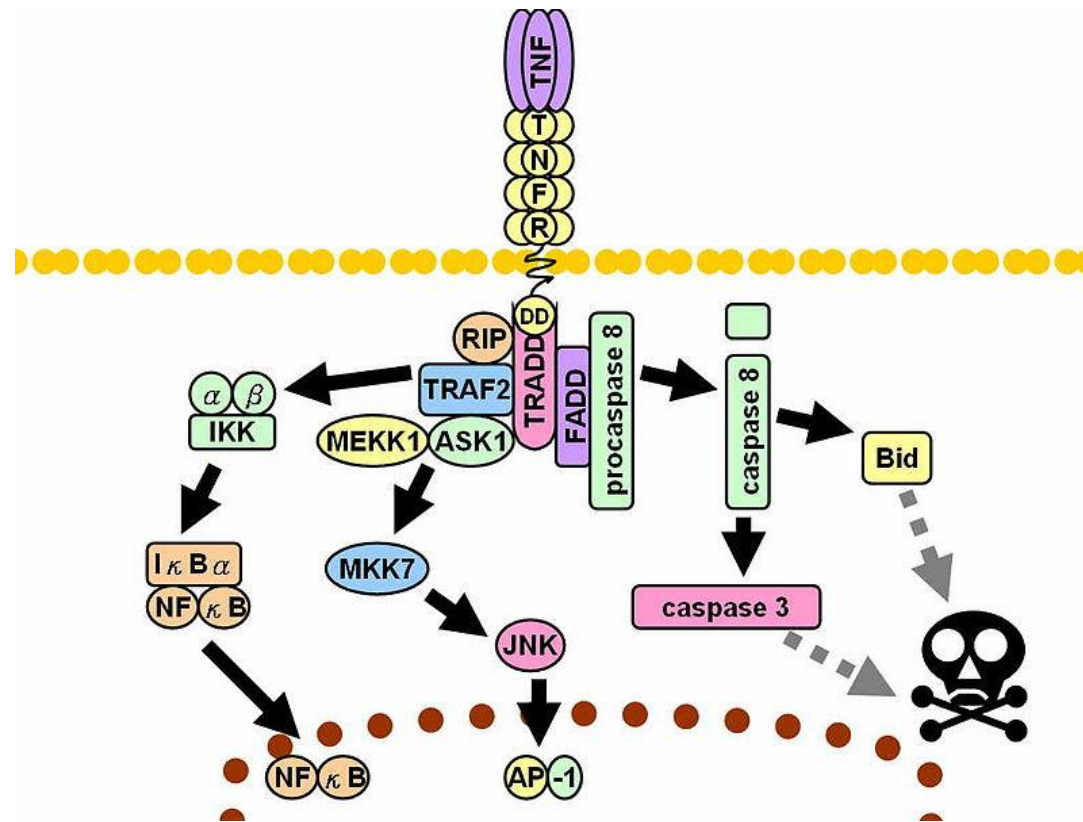
The principal way by which the innate immune system deals with infections and tissue injury is to stimulate acute inflammation, which is the accumulation of leukocytes, plasma proteins, and fluid derived from the blood at an extravascular tissue site of infection or injury



The Major Proinflammatory Cytokines of Innate Immunity

- Are produced mainly by tissue macrophages and DCs, although other cell types, including mast cells, endothelial cells, and some epithelial cells, can also produce them.
- Most of them act on cells close to their cell of origin (paracrine action). In some severe infections, enough of the cytokines may be produced so that significant amounts enter the circulation and act at a distance (endocrine action).
- Different cytokines have similar or overlapping actions or are functionally unique. One cytokine may stimulate the production of others, thus setting up cascades that amplify the reaction or induce new reactions.
- The cytokines of innate immunity serve several roles: inducing inflammation, inhibiting viral replication, promoting T cell responses, and limiting innate immune responses.
- Many cytokines that are produced by innate immune cells, such as TNF, IL-17, IL-5, and IFN- γ , are also produced by T lymphocytes in adaptive immune responses.
- Three of the most important proinflammatory cytokines of the innate immunity are TNF, IL-1, and IL6.

TNF – the major pro-inflammatory cytokine



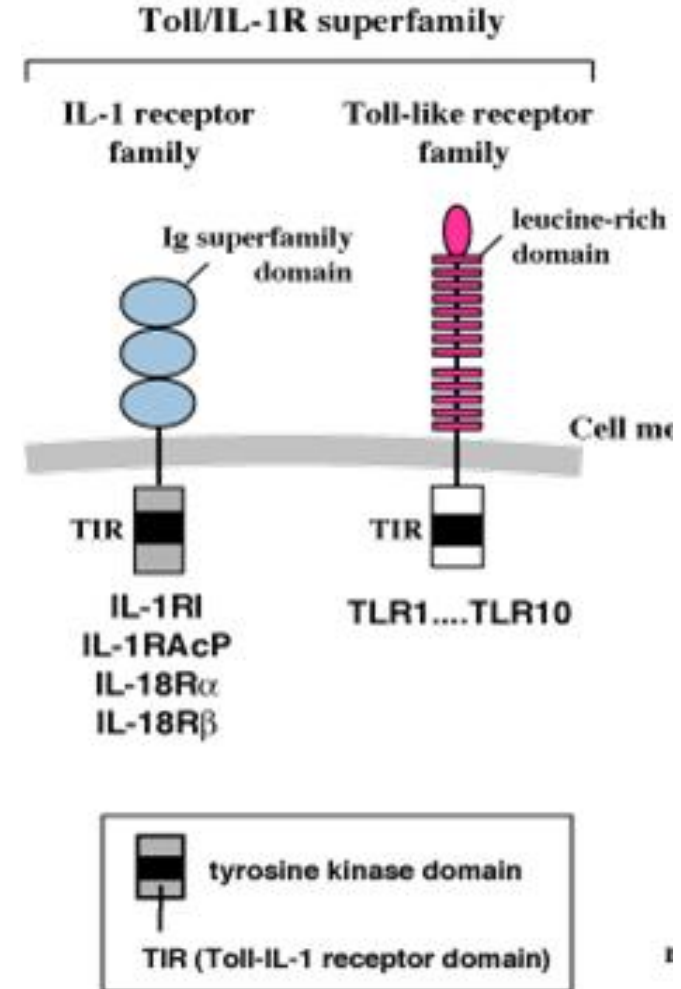
TNF alpha is mainly produced by macrophages and activates pro-inflammatory transcription factors (e.g. NF kappa B and AP-1)

Interleukin 1

IL-1 is produced by activated macrophages, neutrophils, epithelial cells and endothelial cells

Exists in two forms IL-1 α and IL-1 β

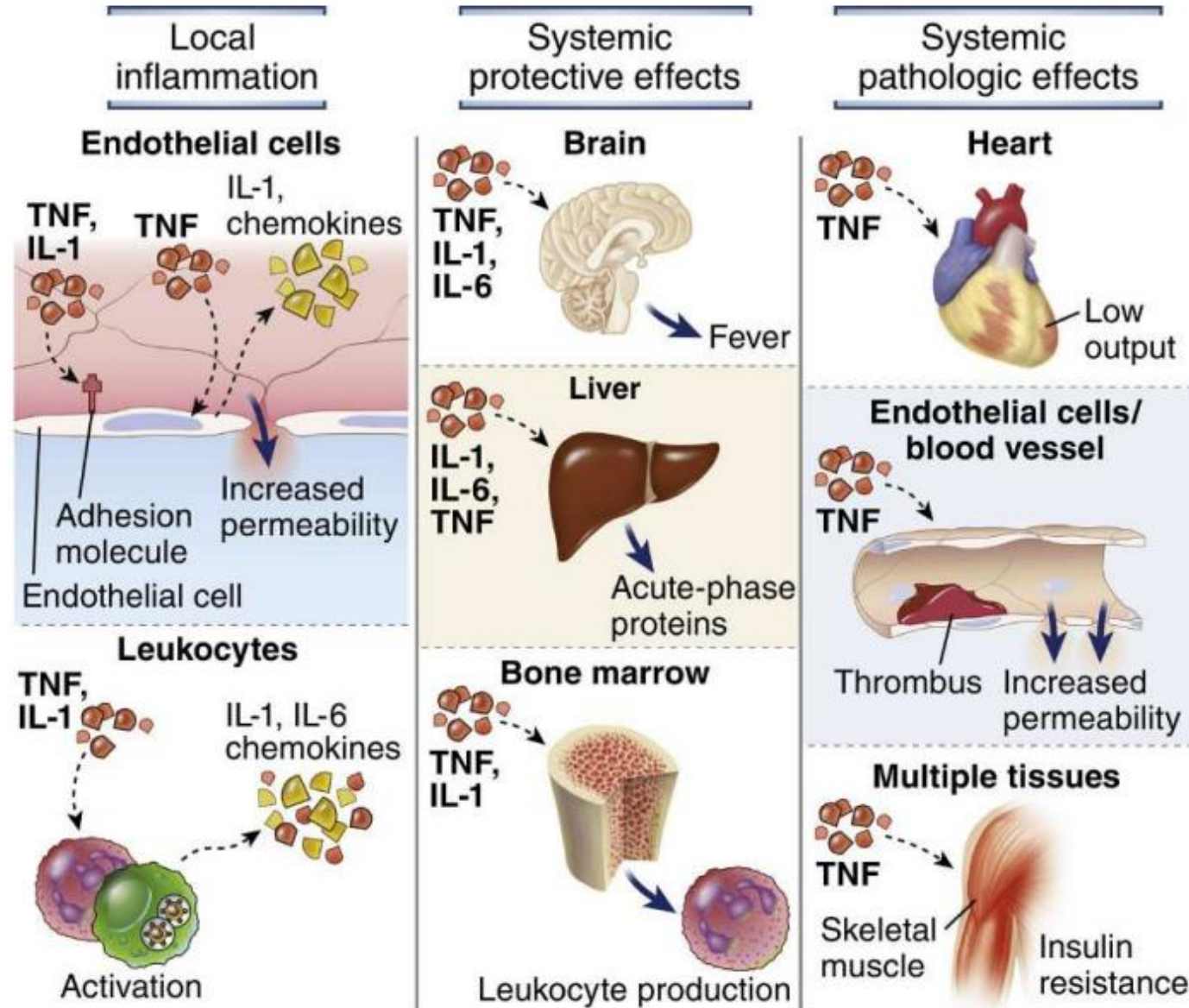
The NLRP3 inflammasome activates pro-IL-1 β , IL-1 is released when cells are killed by pathogens



Interleukin 6, another pro-inflammatory cytokine

IL-6 is made by various cells in response to PAMPs IL-6 has both, local and systemic effects (inflammatory mediators from the liver, stimulation of neutrophils in the bone marrow, differentiation of Th17 cells)

Local and systemic actions of cytokines in inflammation

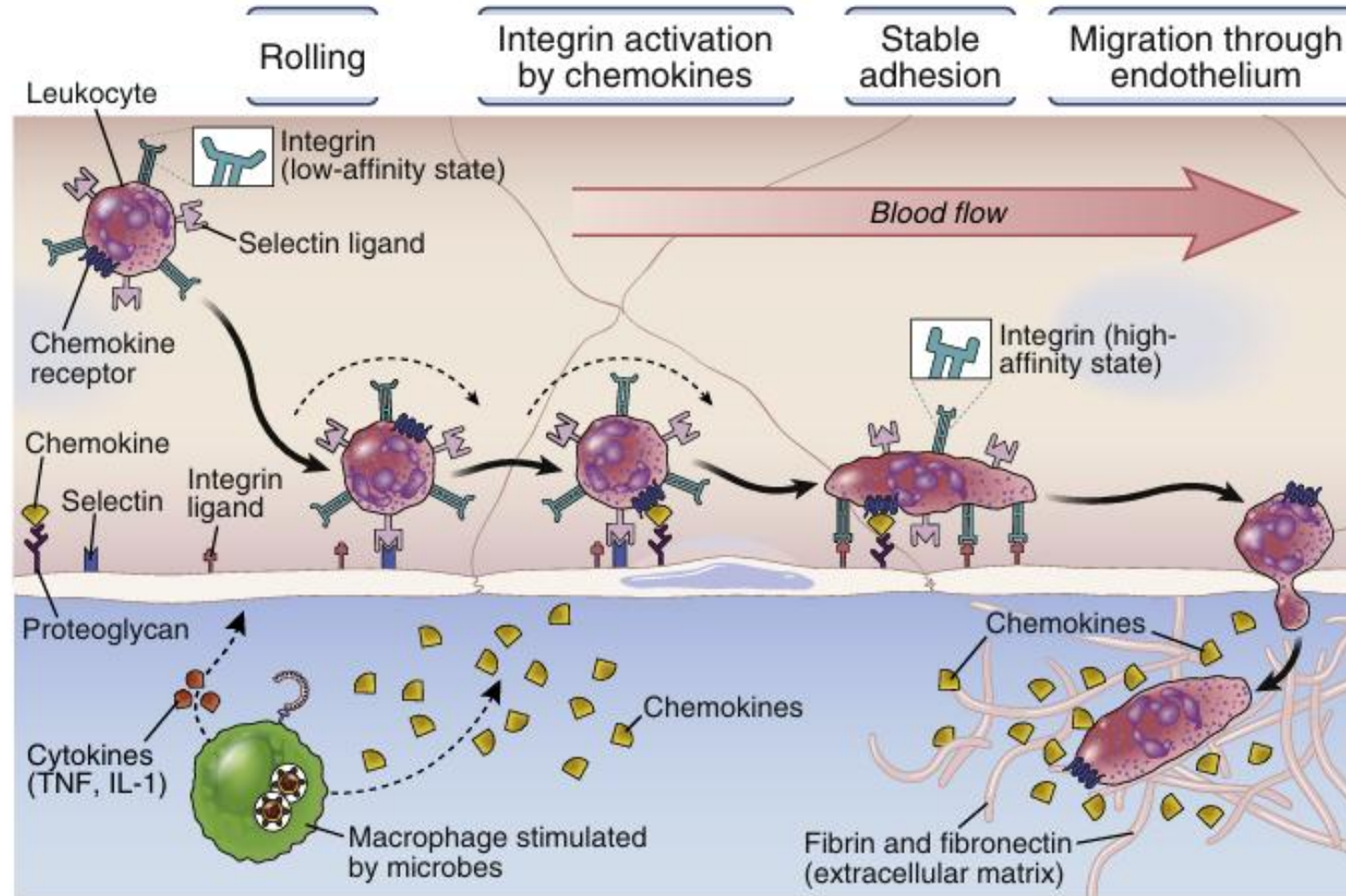


Recruitment of Leukocytes to Sites of Infection

Both **TNF** and **IL-1** induce postcapillary venule endothelial cells to express E-selectin and to increase their expression of ICAM-1 and VCAM-1, the ligands for leukocyte integrins

TNF and **IL-1** also stimulate various cells to secrete chemokines, such as CXCL1 and CCL2, that bind to receptors on neutrophils and monocytes, and stimulate directional movement of leukocytes

Recruitment of Leukocytes to Sites of Infection



Other Cytokines Produced During Innate Immune Responses

IL-12 is secreted by dendritic cells and macrophages and stimulates **IFN- γ** production by NK cells and T cells, and promotes differentiation of Th1 cells

IL-18 enhances the functions of NK cells, similar to **IL-12**

IL-15 is a cytokine that serves important growthstimulating and survival functions for both NK cells and T cells, similar to **IL-2**

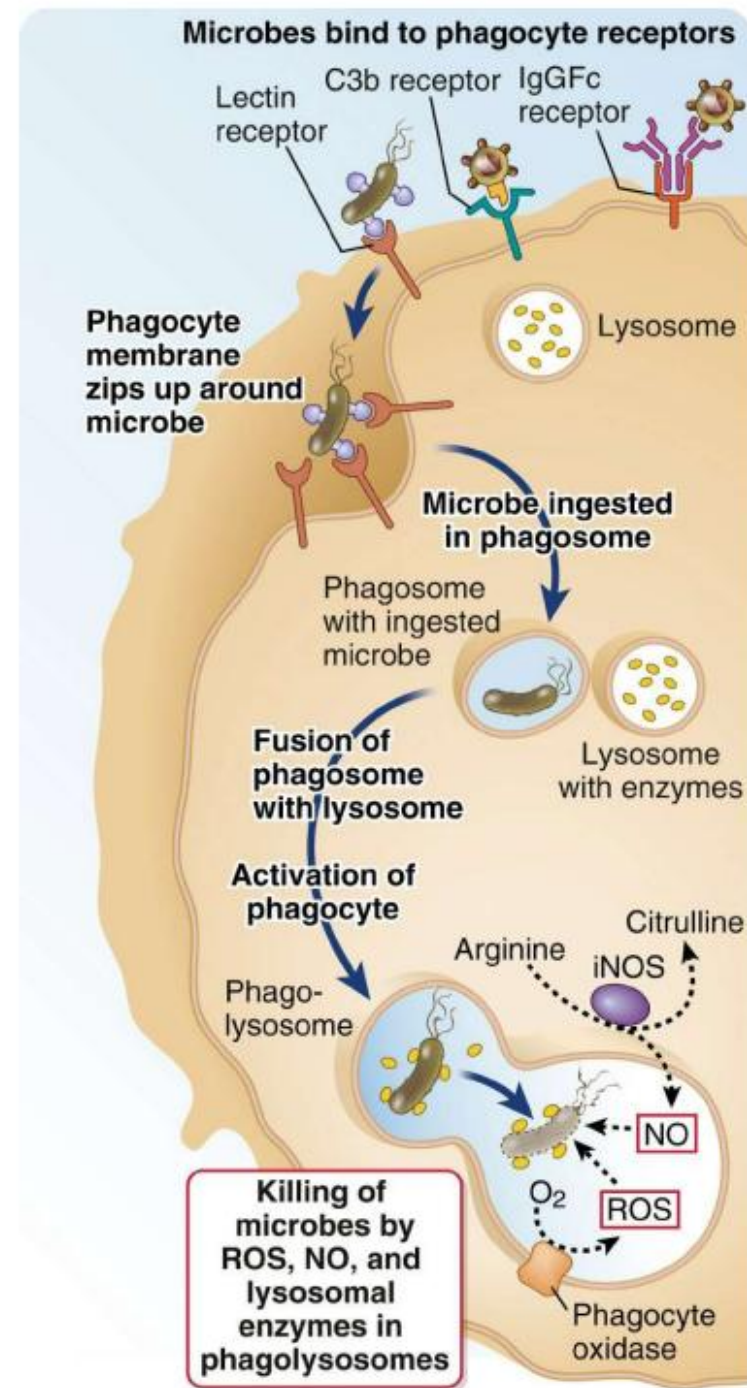
Systemic and Pathologic Consequences of the Acute Inflammatory Responses

- **TNF**, **IL-1**, and **IL-6** all act on the hypothalamus to induce an increase in body temperature (fever), and these cytokines are therefore called **endogenous pyrogens** (LPS=exogenous pyrogen)
- **IL-1**, **TNF**, and **IL-6** induce hepatocytes to express **acute-phase reactants**, including **CRP**, **SAP** (serum amyloid P), and **fibrinogen**, which are secreted into the blood
- In severe infections, **TNF** may be produced in large amounts and causes systemic clinical and pathologic abnormalities
 - TNF inhibits myocardial contractility and vascular smooth muscle tone, resulting in a marked fall in blood pressure, or shock
 - TNF causes intravascular thrombosis, mainly as a result of loss of the
 - normal anticoagulant properties of the endothelium
 - Prolonged production of TNF causes wasting of muscle and fat cells, called cachexia

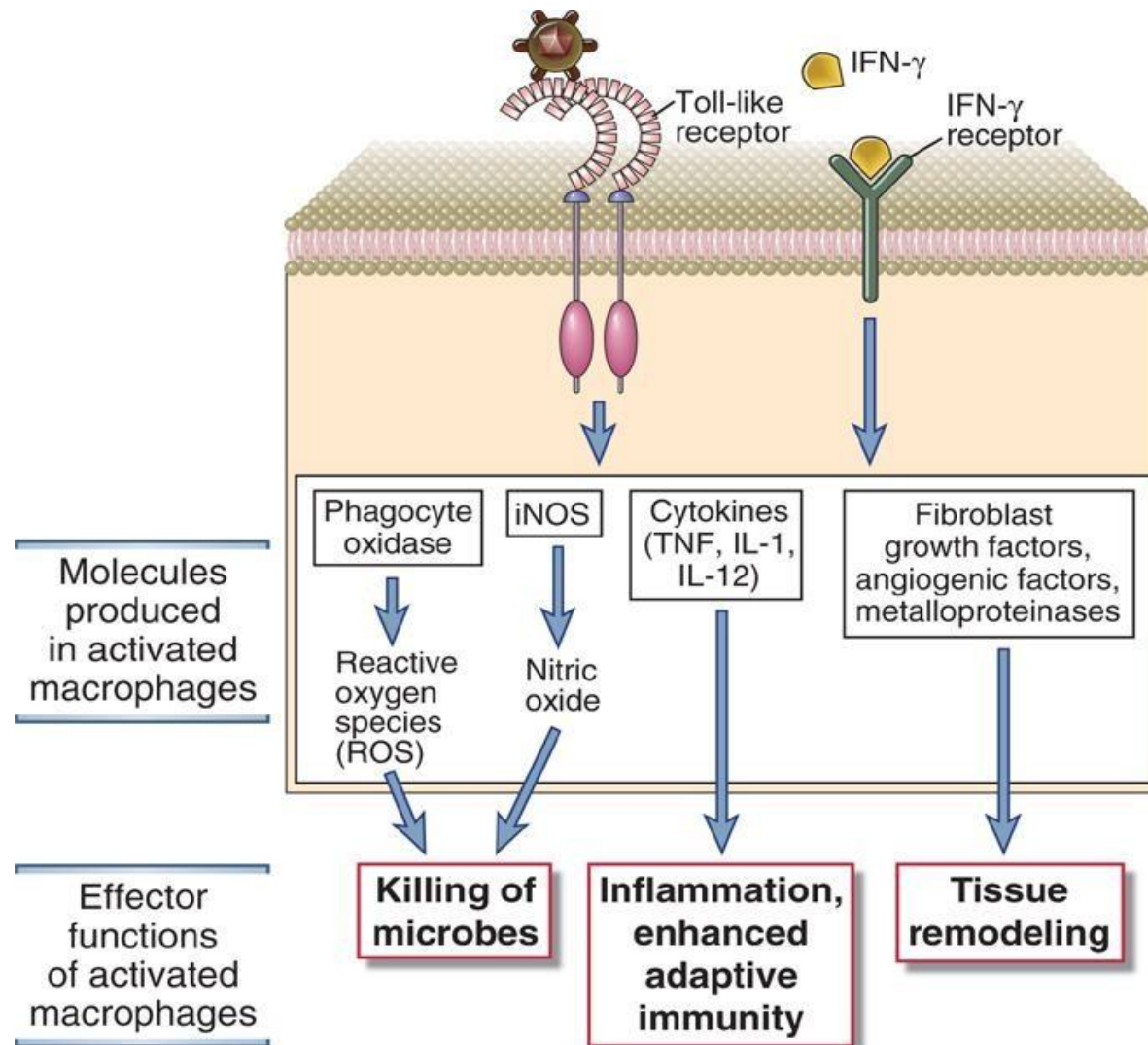
Septic Shock

A complication of severe bacterial sepsis is a syndrome called **septic shock**, which may be caused by LPS released from gram-negative bacteria (in which case it is called endotoxin shock) or lipoteichoic acid from grampositive bacteria. Septic shock is characterized by vascular collapse, disseminated intravascular coagulation, and metabolic disturbances. This syndrome is due to LPS- or lipoteichoic acid-induced TLR signaling leading to the production of TNF and other cytokines, including IL-12, IFN- γ , and IL-1

Phagocytosis and destruction of microbes



Effector functions of macrophages



Antiviral Responses

Type I interferons are a large family of structurally related cytokines that mediate the early response to viral infections

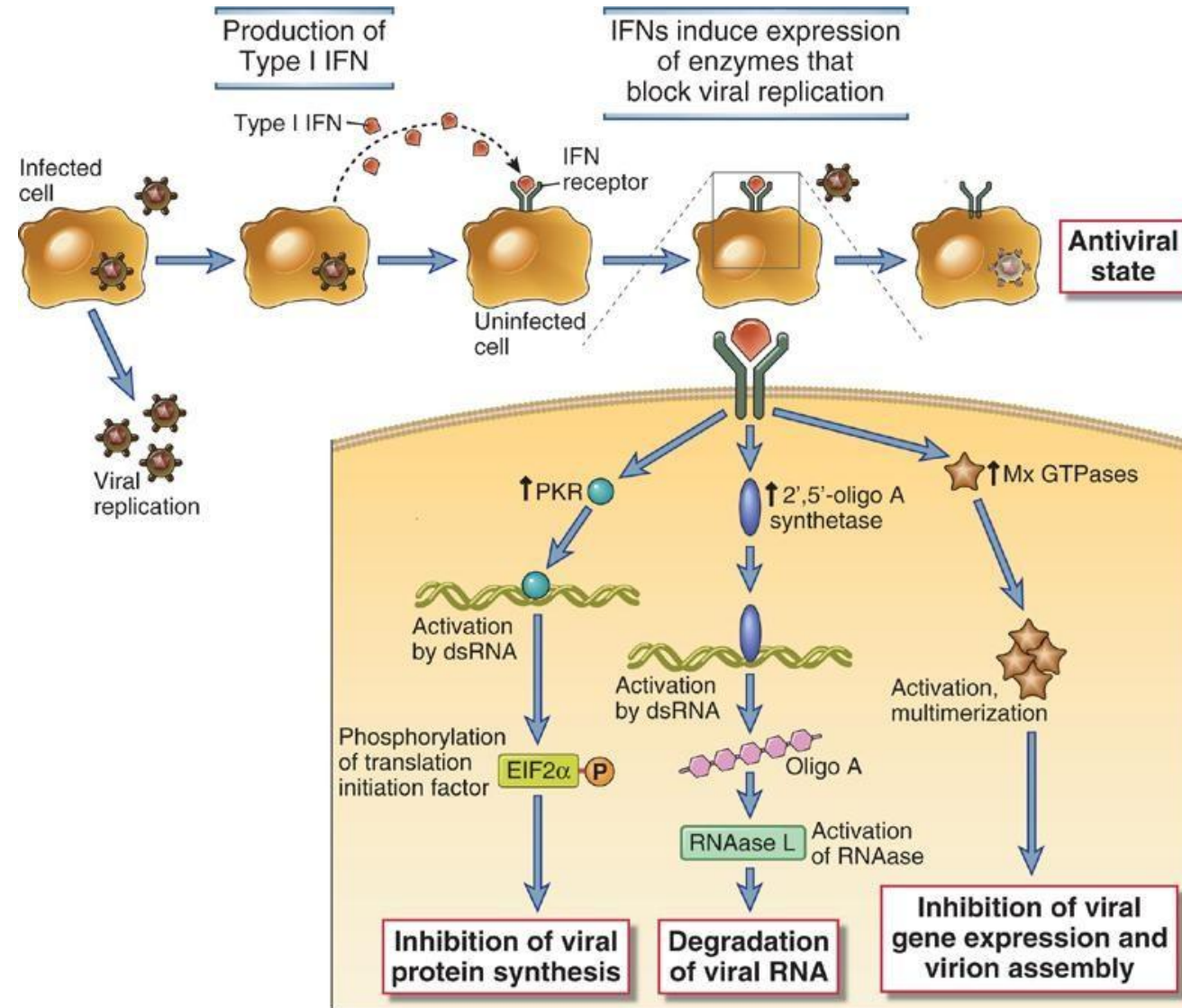
Type I interferons, signaling through the type I interferon receptor, activate transcription of several genes that confer a resistance to viral infection, called an antiviral state

Type I interferons cause sequestration of lymphocytes in lymph nodes, thus maximizing the opportunity for encounter with microbial antigens

Type I interferons increase the cytotoxicity of NK cells and CD8⁺ CTLs and promote the differentiation of naive T cells to the TH1 subset of helper T cells

Type I interferons upregulate expression of class I MHC molecules and thereby increase the probability that virally infected cells will be recognized and killed by CD8⁺ CTLs

Biological actions of type I interferons



Feedback Mechanisms that Regulate Innate Immunity

The magnitude and duration of innate immune responses are regulated by a variety of feedback inhibition mechanisms that limit potential damage to tissues

IL-10 is a cytokine that inhibits macrophages and dendritic cells (typical feedback mechanisms)

Competitive **IL-1 receptor antagonist** (biologically inactive IL-1 homolog) represents another feedback loop

Autophagy regulates secretion of inflammatory cytokines (degradation of self-organelles and proteins in lysosomes)

Negative regulatory signaling pathways block activation, such as suppressors of cytokine signaling (**SOCS**) proteins, which inhibit JAK- STAT signaling.

Table 1 | **Innate immune effectors used by host cells to control intracellular pathogens**

Effector	Action	Protective bacterial proteins	Protective bacterial mechanisms
ROS (superoxide, hydrogen peroxide and hydroxyl radical)	Generation of oxidative stress into the bacterial phagosome	Catalase, superoxide dismutase, heat shock proteases and mycobacterial glycolipids	NADH and NADPH redox pathways, DNA repair systems and inhibition of the recruitment of oxidase components to the phagosome
Peroxynitrite	Potent oxidant	Superoxide dismutase and peroxiredoxins	NA
RNI (nitric oxide, NONOates, S-nitrosothiols, nitrite and nitrous acid)	Diffusion into bacterial phagosome and generation of oxidative stress	Flavo-haemoglobin, heat shock proteases and mycobacterial glycolipids	DNA repair systems, avoidance of NOS2 induction and blockage of active NOS2 accumulation at the phagosome
Antimicrobial peptides (defensins, cathelicidin, ubiquitin, ubiquicidin, histones and HMGN2)	Disruption of bacterial membranes; can be found in phagosomes and the cytosol or can be secreted	NA	Escape from the phagosome, intracellular motility, interaction with endocytic pathway and control of vesicular trafficking
Lysosome (vacuolar ATPase, cathepsin G and lysozyme)	Acidification of lysosomal lumen and disruption of bacterial membranes	NA	Inhibition of fusion with lysosome and escape from the phagosome
NRAMP and ferroportin	Depletion of key nutrients and divalent metals from phagosomes	Iron chelators and siderophores	Interaction with endocytic pathway and control of vesicular trafficking

The role of Innate Immunity in Stimulation of the Adaptive Immune Response

Innate immune response together with antigen, stimulates proliferation and differentiation of antigen specific T and B lymphocytes.

Hypothesis of two signal- first originates from antigen and the others from molecules which are produced during innate immune response to microbes or damaged cells .

Signal 1 ensures the specificity of the immune response, while signal 2 activates the immune response only in case of dangerous infection.

The molecules involved in providing of signal 2 are:

- costimulators** (for T lymphocytes),
- cytokines** (for T and B lymphocytes),
- products of complement** (for B lymphocytes).