Innate and Adaptive immunity

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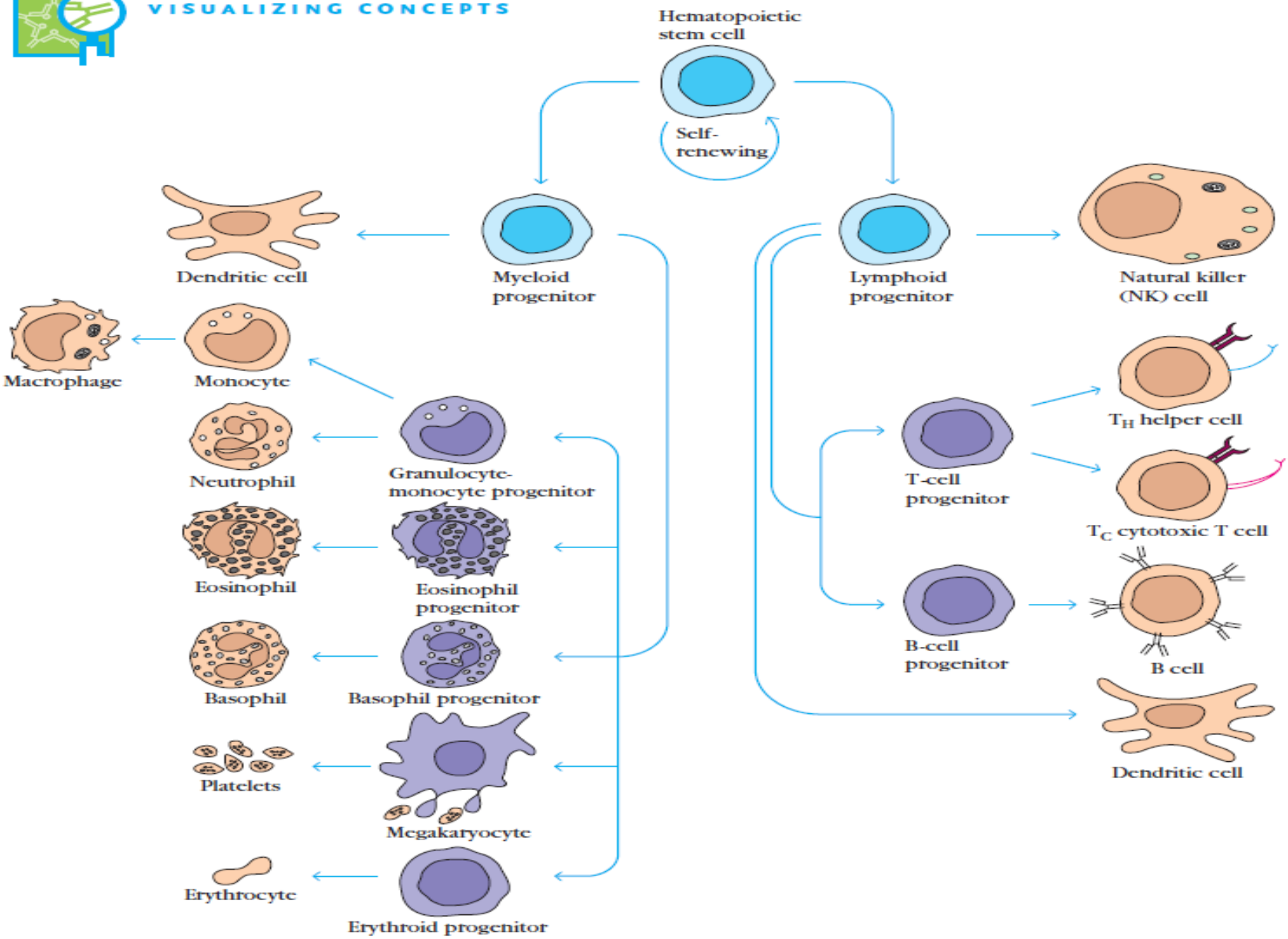
VISUALIZING CONCEPTS



Organs of the immune system

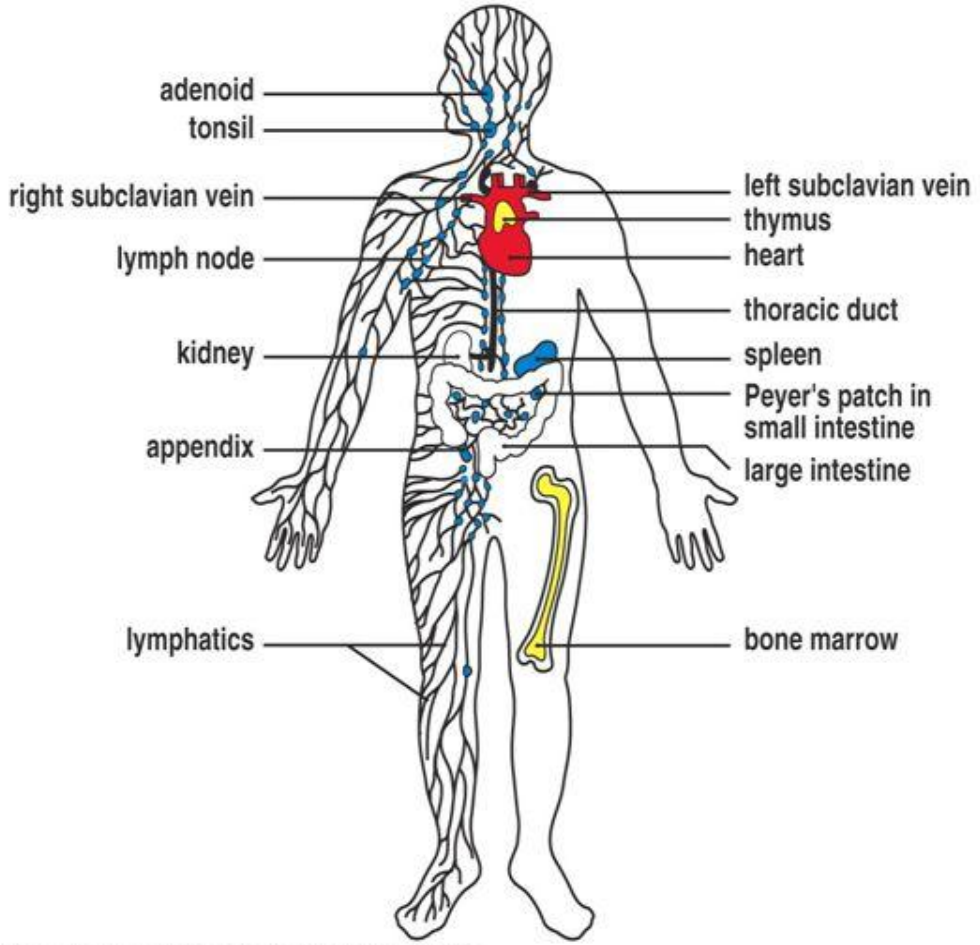


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

Primary:

- Thymus
- Bone Marrow

Secondary:

- Spleen
- Lymph nodes
- Mucosal Associated Lymphoid Tissue

Blood
Lymphatics

- The immune system is complex and is divided in two categories:
- i) the innate or nonspecific immunity, which consists of the activation and participation of preexistent mechanisms including the natural barriers (skin and mucosa) and secretions;
- ii) the adaptive or specific immunity, which is targeted against a previously recognized specific microorganism or antigen.
- Thus, when a given pathogen is new to the host, it is initially recognized by the innate immune system and then the adaptive immune response is activated .

- Innate immunity is the host's first line of defense and is intended to prevent infection and attack the invading pathogens.
- This nonspecific mechanism is fast (minutes to hours) while the adaptive response takes longer (days to weeks)
- The innate immune response is the first mechanism for host defense found in all multicellular organisms.
- The innate immune system is more ancient than the acquired or adaptive immune response, and it has developed and evolved to protect the host from the surrounding environment in which a variety of toxins and infectious agents including bacteria, fungi, viruses and parasites are found

- Innate immunity is comprised of different components including:
- physical barriers enzymes (i.e., lysozyme,pH of stomach)
- anatomical barriers; (tight junctions in the skin, epithelial and mucous membrane surfaces, mucus itself); epithelial and phagocytic cell,
- phagocytosis (i.e., neutrophils, monocytes, macrophages),
- inflammation-related serum proteins (e.g., complement, C-reactive protein, lectins such as mannose-binding lectin, and ficolins); surface and phagocyte granule antimicrobial peptides (e.g., defensins, cathelicidin, etc.);

Components of the innate immune system

FUNCTION	COMPONENT
Barriers	
Prevents microbial entrance	Skin
Prevents microbial entrance, secretes proteins and enzymes, absorbs metabolic substrates	Mucosa
Effector cells	
Phagocytosis, cytokine production, protein and enzyme secretion, destruction of pathogens	Granulocytes

Phagocytosis, cytokine production, protein and enzyme secretion, destruction of pathogens	Monocytes/macrophages
Phagocytosis, cytokine production, protein and enzyme secretion, destruction of pathogens	Dendritic cells
Lysis of infected and tumoral cells, activation of macrophages through cytokine production	Natural killer (NK) cells
Mediate immune response and regulate tissue homeostasis and inflammation	Innate lymphoid cells
Microbial recognition, cytokine production	Endothelial/epithelial cells
Antimicrobial peptides	
Destruction of invading pathogens	

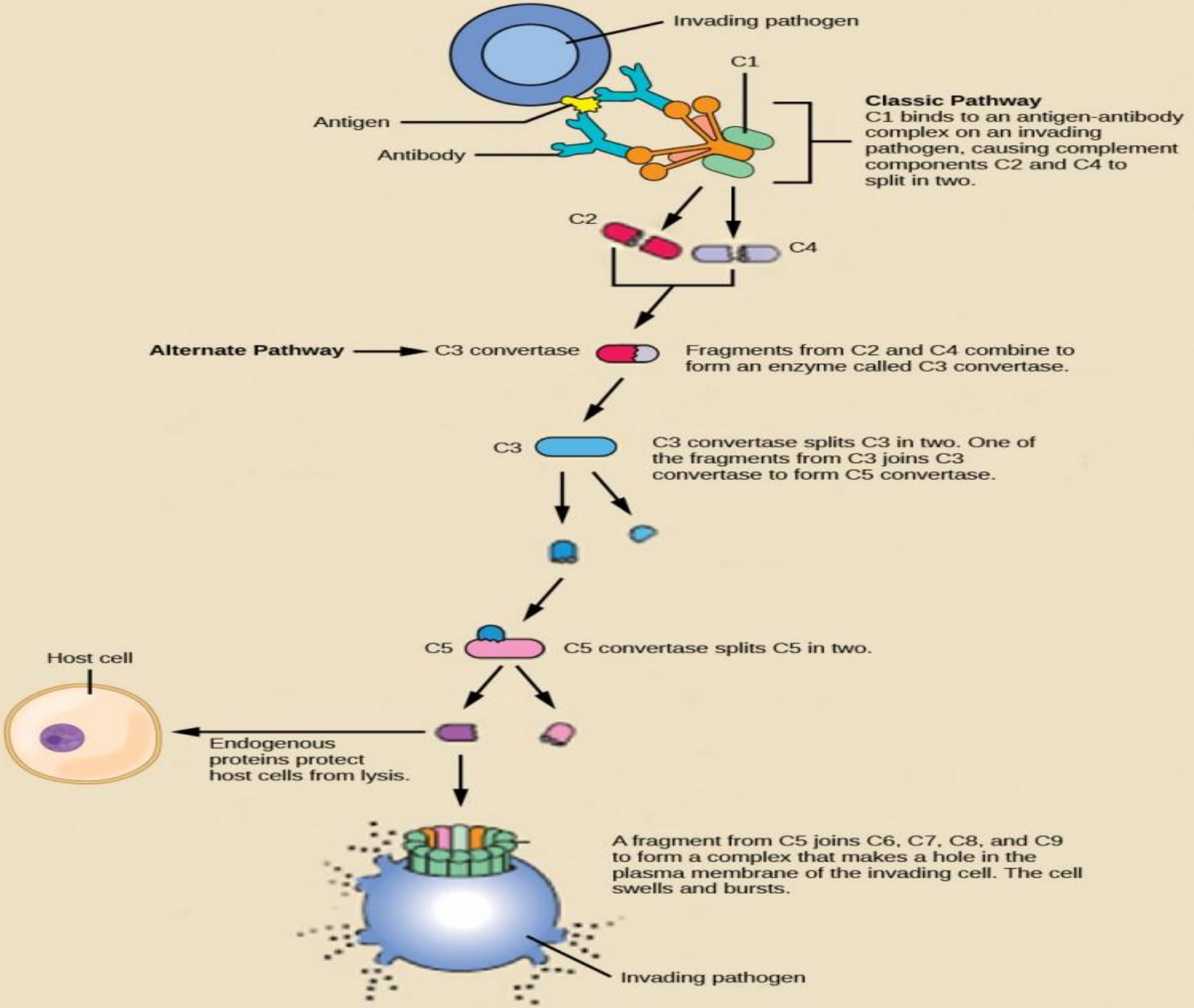
Soluble mediators	
Cytokines	
Mediate immune response and inflammation	TNF-α, IL-1, chemokines
Involved in resistance to viral infection	IFN-α
Involved in resistance to intracellular pathogen infection and activation of macrophages	IFN-γ
Stimulates IFN-γ production by NK cells and T lymphocytes	IL-12
Stimulates NK cell proliferation	IL-15
Regulates and controls the inflammation process	IL-10
Regulates and controls the inflammation process	TGF-β

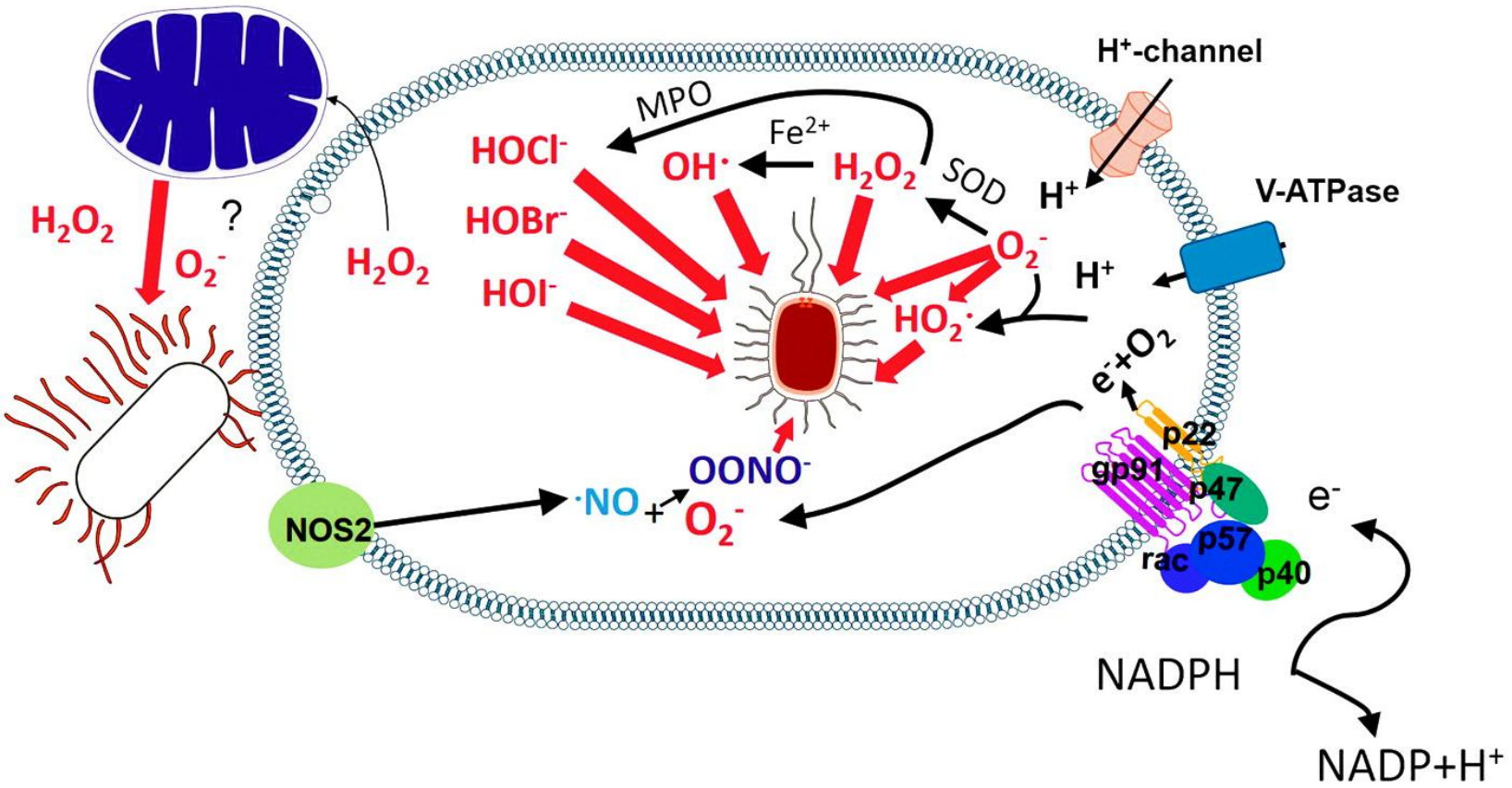
Serum proteins	
Opsonization, destruction of pathogens, and T lymphocyte activation	Complement system
Opsonization of pathogens and complement activation	Collectins
Opsonization of pathogens and complement activation	C reactive protein
Localization of damage or infected tissue	Coagulation system
Cellular receptors	
Recognize a variety of microbial components	TLRs
Sense bacterial components present in the cytoplasm	NLRs
Recognize sugar moieties of bacteria and fungi	CLRs
Sense viral RNA	RLRs

Effectors molecules and microbicidal mechanisms of innate immunity

- **There are several chemical and enzymatic compounds capable of inhibiting and destroying microbial pathogens.**
- **-lysozyme, which is present in the saliva, tears, and nasal secretions**
- **hydrochloric acid and digestive proteins**
- **C- transferrin, lactoferrin and fibronectin that can control the growth of the host's normal microbiota**
- **Plasma proteins include the secreted PRRs: MBL and CRP. These molecules recognize carbohydrates which are acting as opsonins. In addition, these PRRs may bind and activate complement factors such as C1q thus enhancing the inflammatory response**
- **The coagulation system, in addition to its role in controlling bleeding and clotting formation during a tissue injury, is also involved in the innate immune response by preventing microbial dissemination. Fibrinogen**,

- Complement is considered one of the most important enzymatic systems involved in the innate immune response
- Reactive oxygen species (ROS) and reactive oxygen intermediates (ROI) are produced by mammalian cells, particularly phagocytes, as a reaction against several microbial pathogens . These molecules are generated by activation of the enzymatic complex nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX2) and include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (·OH), peroxynitrite (ONOO-),hypochlorous acid (-OCl), . Both ROS and ROI are known to play diverse roles in inflammation, host defense, and homeostasis.


Invading pathogen
C1
Antigen
Antibody
Classic Pathway
C1 binds to an antigen-antibody complex on an invading pathogen, causing complement components C2 and C4 to split in two.
C2
C4
Alternate Pathway
C3 convertase
Fragments from C2 and C4 combine to form an enzyme called C3 convertase.
C3
C3 convertase splits C3 in two. One of the fragments from C3 joins C3 convertase to form C5 convertase.
C5
C5 convertase splits C5 in two.
Host cell
Endogenous proteins protect host cells from lysis.
A fragment from C5 joins C6, C7, C8, and C9 to form a complex that makes a hole in the plasma membrane of the invading cell. The cell swells and bursts.
Invading pathogen

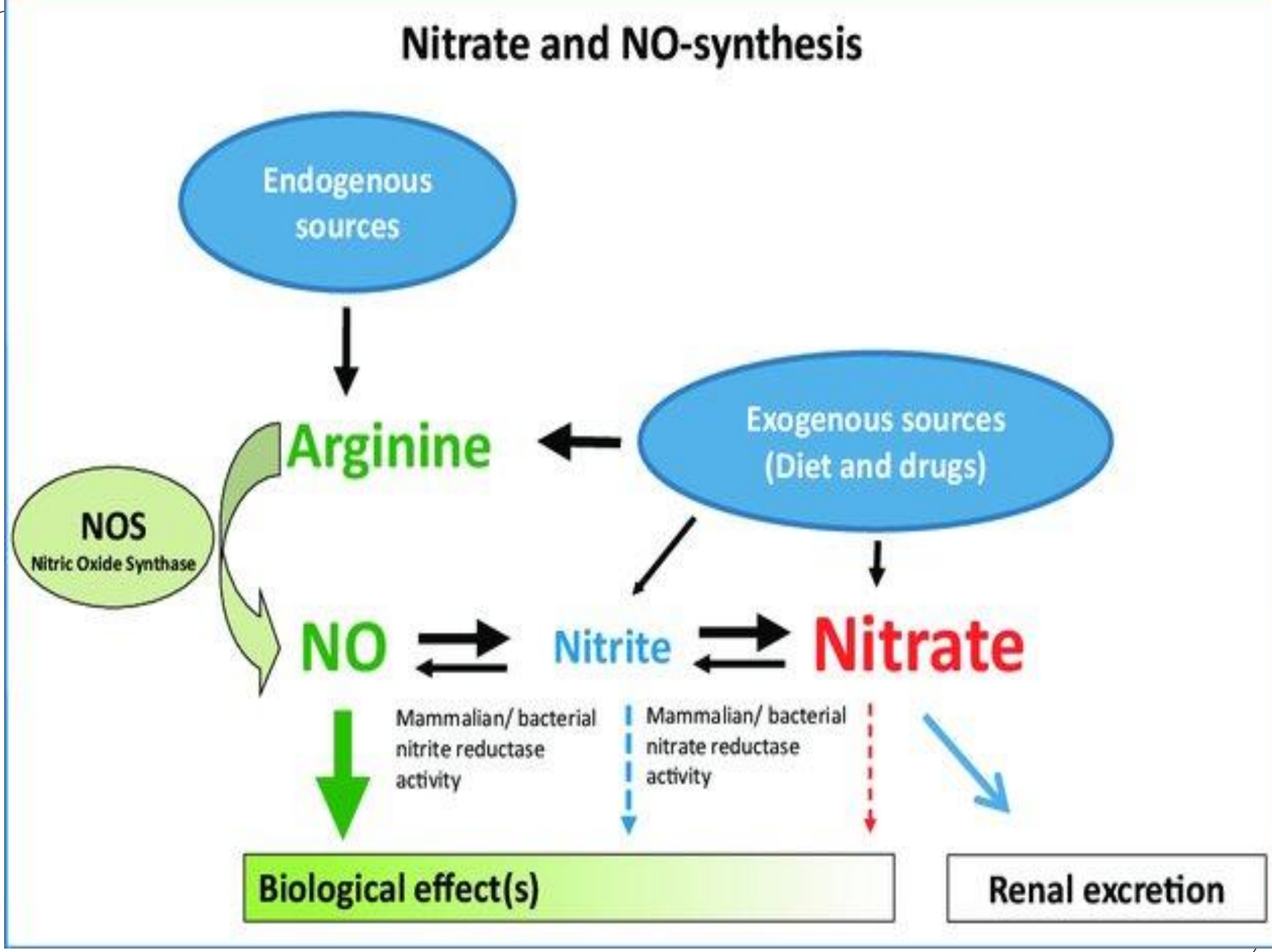

H+-channel
MPO
Fe2+
HOCl-
OH·
H2O2
SOD
H+
V-ATPase
HOBr-
O2-
H+
HOI-
HO2·
e-+O2
p22
gp91
p47
OONO-
·NO +
O2-
NOS2
e-
p57
rac
p40
NADPH
NADP+H+
H2O2
?
O2-
H2O2

- **Oxygen-independent mechanisms**

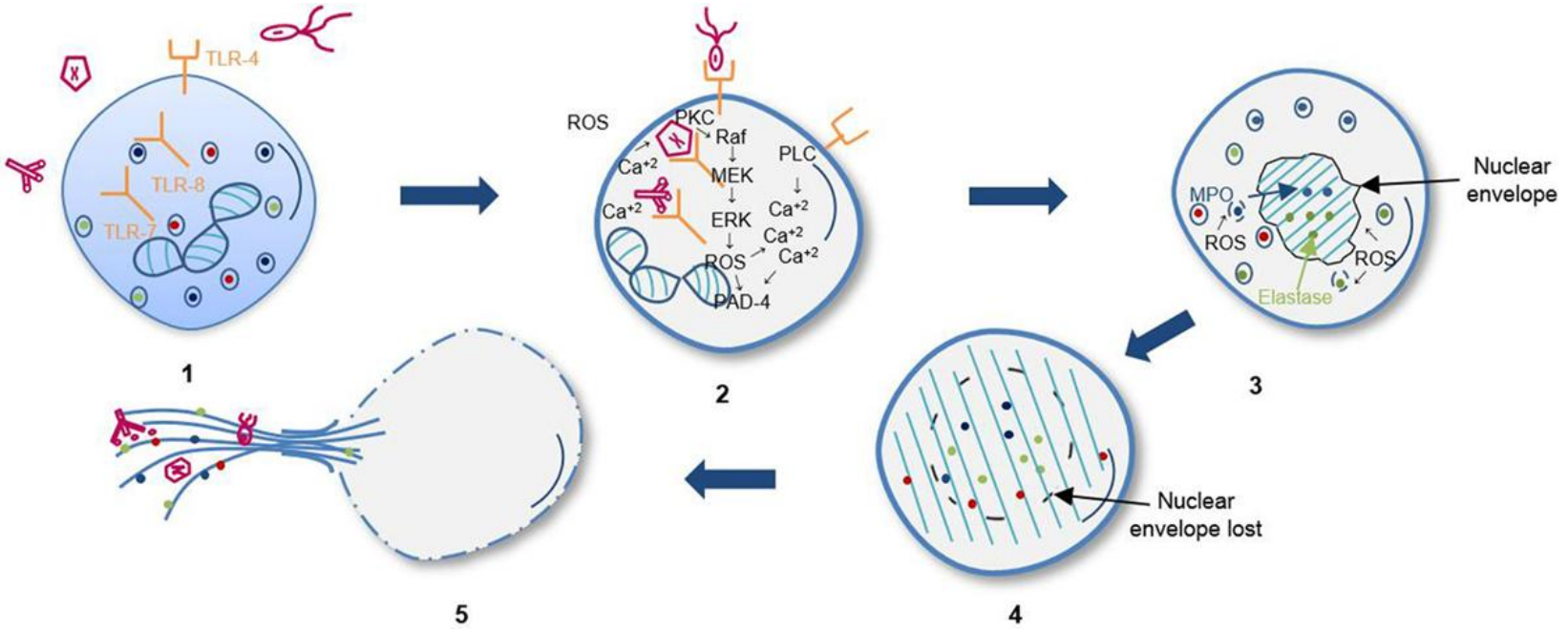
Innate cells, mainly phagocytes, are equipped with an enzymatic arsenal capable of destroying several microorganisms. These enzymes include proteases, cationic proteins, lysozyme, elastases, capthesin G, defensins, etc., all of which exhibit microbicidal activities

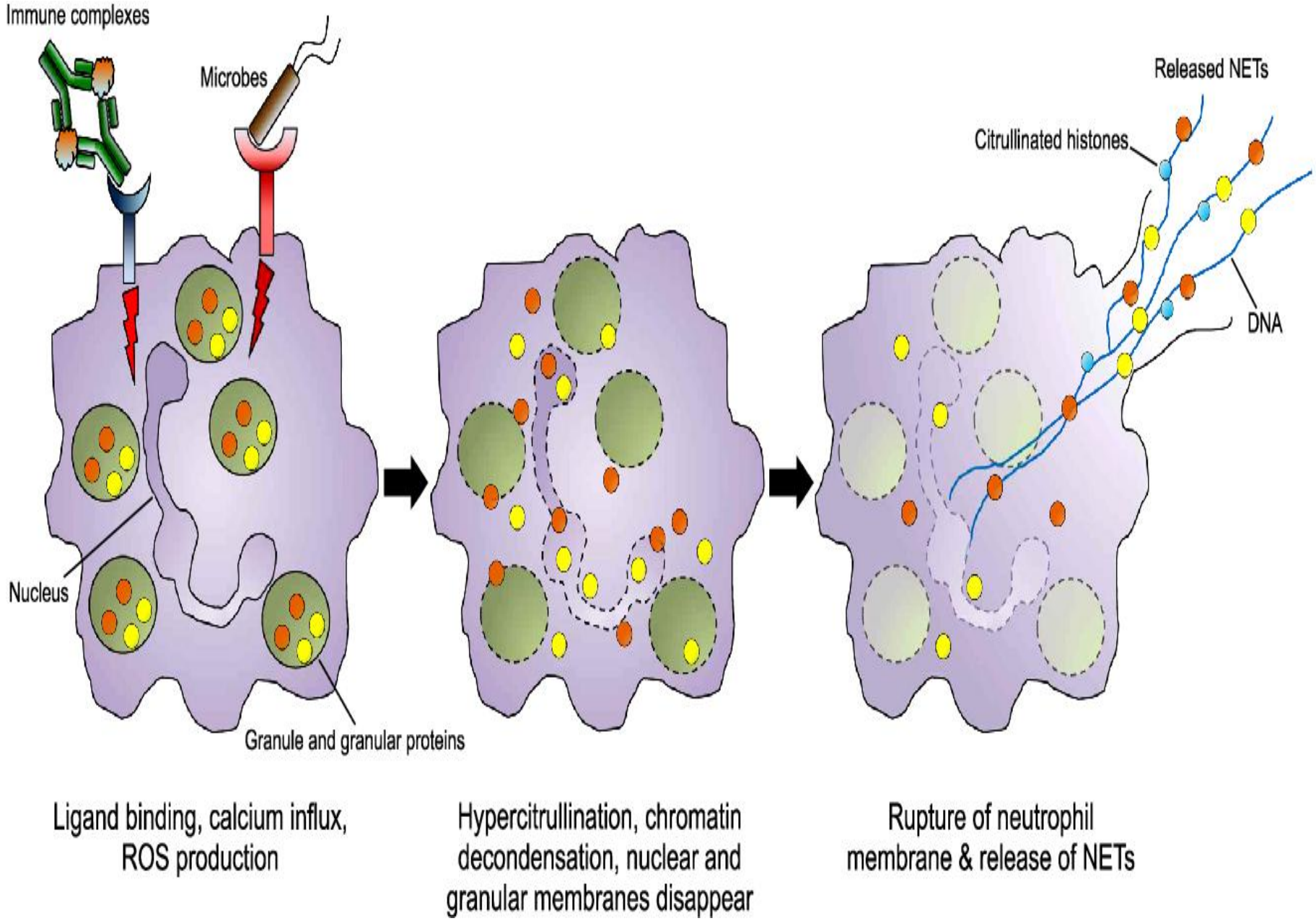
- **Antimicrobial peptides (AMPs)**
- AMPs are host defense peptides secreted mainly by innate and epithelial cells including keratinocytes. Their antimicrobial activity is broadly based especially against fungi, bacteria, and viruses . About 1700 AMPs have been described so far. They are found constitutively or can be induced after activation of the host cells through several PRRs during an infection or injury.
- Additionally, these AMPs are involved in other cell processes including cell migration, proliferation, differentiation, cytokine production, angiogenesis, and wound healing, along with other functions

- **Nitric oxide (NO)**
- produced by an oxidative mechanism involving the catabolism of L-arginine . NO production by the enzymatic action of inducible nitric oxide synthase (iNOS) represents one of the major microbicidal mechanisms that phagocytic cells use against several pathogens .
- In turn, iNOS can be induced by several stimuli, including IFN-γ, TNF-α, and LPS, and is expressed by immune cells such as macrophages, neutrophils, dendritic cells, and NK cells .
- Like ROS, NO may be involved in inflammation and its regulation process.


Nitrate and NO-synthesis
Endogenous sources
Arginine
Exogenous sources (Diet and drugs)
NOS
Nitric Oxide Synthase
NO
Nitrite
Nitrate
Mammalian/ bacterial nitrite reductase activity
Mammalian/ bacterial nitrate reductase activity
Biological effect(s)
Renal excretion

- **Extracellular traps**
- Extracellular DNA traps are part of innate immunity and are associated with infectious processes and allergic and autoimmune diseases.
- These structures are generated by different leukocytes including neutrophils, eosinophils, monocytes, and mast cells. They are called NETs, EETs, METs, and MCETs respectively.
- Extracellular traps are composed of DNA, histones, and the content of the intracellular granules such as elastase, myeloperoxidase (MPO), cathelicidins, tryptase, cationic proteins, and major basic protein, etc.
- These traps are induced by the action of the granulocyte/macrophage-colony stimulating factor (GM-CSF), interferons, IL-8, C5a, and LPS. Once formed, extracellular traps are capable of binding to and killing microbial pathogens. As was mentioned, these DNA traps may be involved in the development of autoimmune and chronic inflammatory diseases


TLR-4
TLR-8
TLR-7
1
ROS
PKC
Raf
MEK
ERK
ROS
PAD-4
PLC
Ca+2
Ca+2
Ca+2
Ca+2
Ca+2
2
MPO
ROS
ROS
Elastase
Nuclear envelope
3
Nuclear envelope lost
4
5


Immune complexes
Microbes
Nucleus
Granule and granular proteins
Released NETs
Citrullinated histones
DNA
Ligand binding, calcium influx, ROS production
Hypercitrullination, chromatin decondensation, nuclear and granular membranes disappear
Rupture of neutrophil membrane & release of NETs

Characteristics of the innate immune system and its recognition mechanisms

- 1-Innate immune response is characterized by its ability to distinguish structural components from microbial pathogens, which are present only in these microorganisms and are absent in the normal host cells. This recognition process is mediated by a variety of proteins present in the host cells such as the PRRs,
- innate immunity may identify clusters of microorganisms while adaptive immunity may distinguish between different antigens from one microorganism

- 2- Another characteristic is that the innate immune response does not generate immunological memory after the recognition of the pathogen while adaptive immunity does

Pattern Recognition Receptors PRPs

- PRRs are evolutionarily conserved receptors that detect relatively invariant molecular patterns found in most microbial agents, the PAMPs. PRRs not only recognize PAMPs from invading pathogens but also have the ability to sense inflammatory components, also called damage-associated molecular patterns (DAMPs), released from damaged cells.

❑ PRRs include

- TLRs,
- NOD-like receptors (NLRs),
- C-type lectin receptors (CLRs),
- and RIG-I-like receptors (RLRs)

CYTOKINE	CELLULAR SOURCE	FUNCTION
TNF-α	Macrophages and T cells	Activates endothelial cells and neutrophils Induces fever and synthesis of acute phase protein
Type I Interferons (IFN-α, IFN-β)	Macrophages and fibroblasts	Activate NK cells Induce expression of MHC-I
IL-1	Macrophages and endothelial cells	Activates endothelial cells and neutrophils Induces fever and synthesis of acute phase proteins
IL-6	Macrophages, endothelial and T cells	Induces synthesis of acute phase proteins Induces proliferation of B cells and antibody production
IL-10	Macrophages and Th2 cells	Induce proliferation of B cells Inhibits proinflammatory cytokine production and MHC-II expression
IL-12	Macrophages and dendritic cells	Activates NK and T cells Induces synthesis of IFN-γ Increases cytolytic activity Induces differentiation of T cells toward Th1 cells
IL-15	Macrophages	Induces NK and T cell proliferation
IL-18	Macrophages	Activates NK and T cells Induces IFN-g synthesis
Chemokines	Macrophages, endothelial and T cells	Induce chemotaxis and cell activation

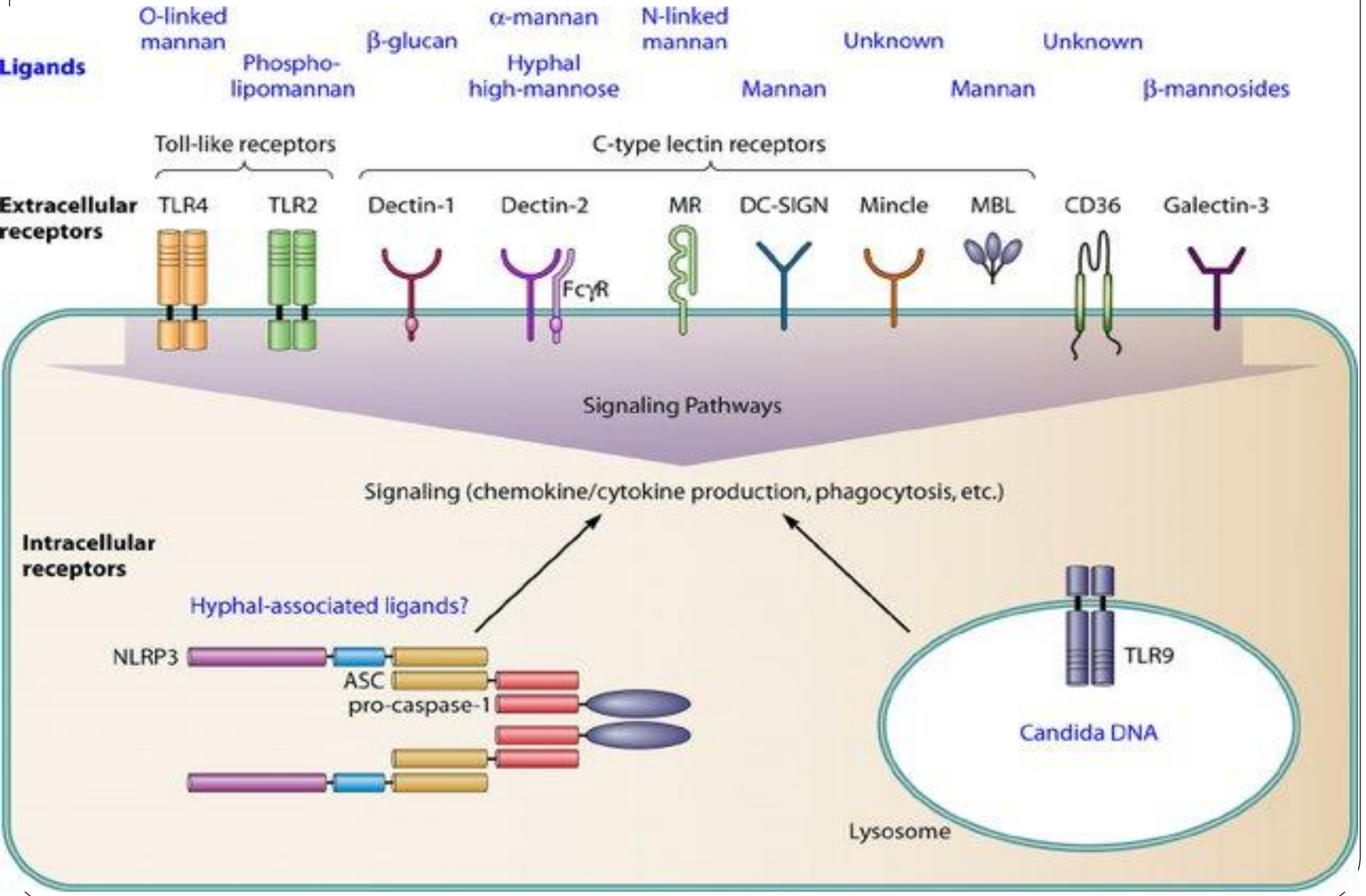
TLR

- To date, 10 TLRs have been identified in humans (TLR1-10) and 12 in mice. TLRs 1, 2, 4, 5, and 6 are expressed on the cell surface, while TLRs 3, 7, 8, 9, and 10 are found at the cytoplasm level.
- The main interactions of TLRs and their ligands are the following:
- TLR1/TLR2 recognize triacylated lipopetides,
- TLR3 binds double-strand (dsRNA),
- TLR4 recognizes LPS,
- TLR5 binds flagellin,
- TLR2/TLR6 bind diacylated lipopetides and lipoteichoic acid (LTA),
- TLR4/TLR6 recognize oxidized lipids (OxLDL) and β-amyloid,
- TLR7 and TLR8 sense single-strand (ssRNA),
- and TLR9 recognizes unmethylated CpG DNA and hemozoin

- **C-type lectin receptors (CLRs)**
- CLRs are considered the other major PRR family. These PRRs recognize not only sugar moieties from bacteria and fungi but also molecules associated with dead or dying cells .
- This family consists of two groups, those present on the cell membrane and the soluble forms, which are secreted mainly by immune cells. Membrane CLRs include :
- Dectin-1, which recognizes β-glucans present in the fungal cells;
- Dectin-2, which recognizes both high-mannose structures and α-mannan; mannose receptors (MR) that recognize N-linked mannan

- **NOD-like receptors (NLRs)**
- The nucleotide-binding oligomerization domain (NOD) receptors (NLRs) are intracellular PRRs that sense bacterial components including peptidoglycans, which are directly introduced into the cytoplasm .
- NLRs include several family members such as NODs (NOD 1–4), NLRPs (NLRP 1–14), and IPAF. These molecules are regulators of immunity in response to a variety of pathogens .
- NOD expression is regulated by IFN-γ and TNF-α, and polymorphisms in NOD2 gene influence the risk of acquiring Crohn’s disease

- **RIG-like receptors (RLRs)**
- Retinoic acid inducible gen-I (RIG)-like receptor (RLRs) is an intracellular protein able to sense viral dsRNA during viral replication.
- RIG-I consists of two N-terminal caspase recruitment domains (CARD) and a RNA helicase domain. After interaction with its ligand, this receptor induces the production of antiviral cytokines such as IFNs and thus modulates the anti-viral immune response


Ligands
O-linked mannan
Phospho-lipomannan
β-glucan
α-mannan
Hyphal high-mannose
N-linked mannan
Mannan
Unknown
Mannan
Unknown
β-mannosides
Toll-like receptors
C-type lectin receptors
Extracellular receptors
TLR4
TLR2
Dectin-1
Dectin-2
FcγR
MR
DC-SIGN
Mincle
MBL
CD36
Galectin-3
Signaling Pathways
Signaling (chemokine/cytokine production, phagocytosis, etc.)
Intracellular receptors
Hyphal-associated ligands?
NLRP3
ASC
pro-caspase-1
TLR9
Candida DNA
Lysosome

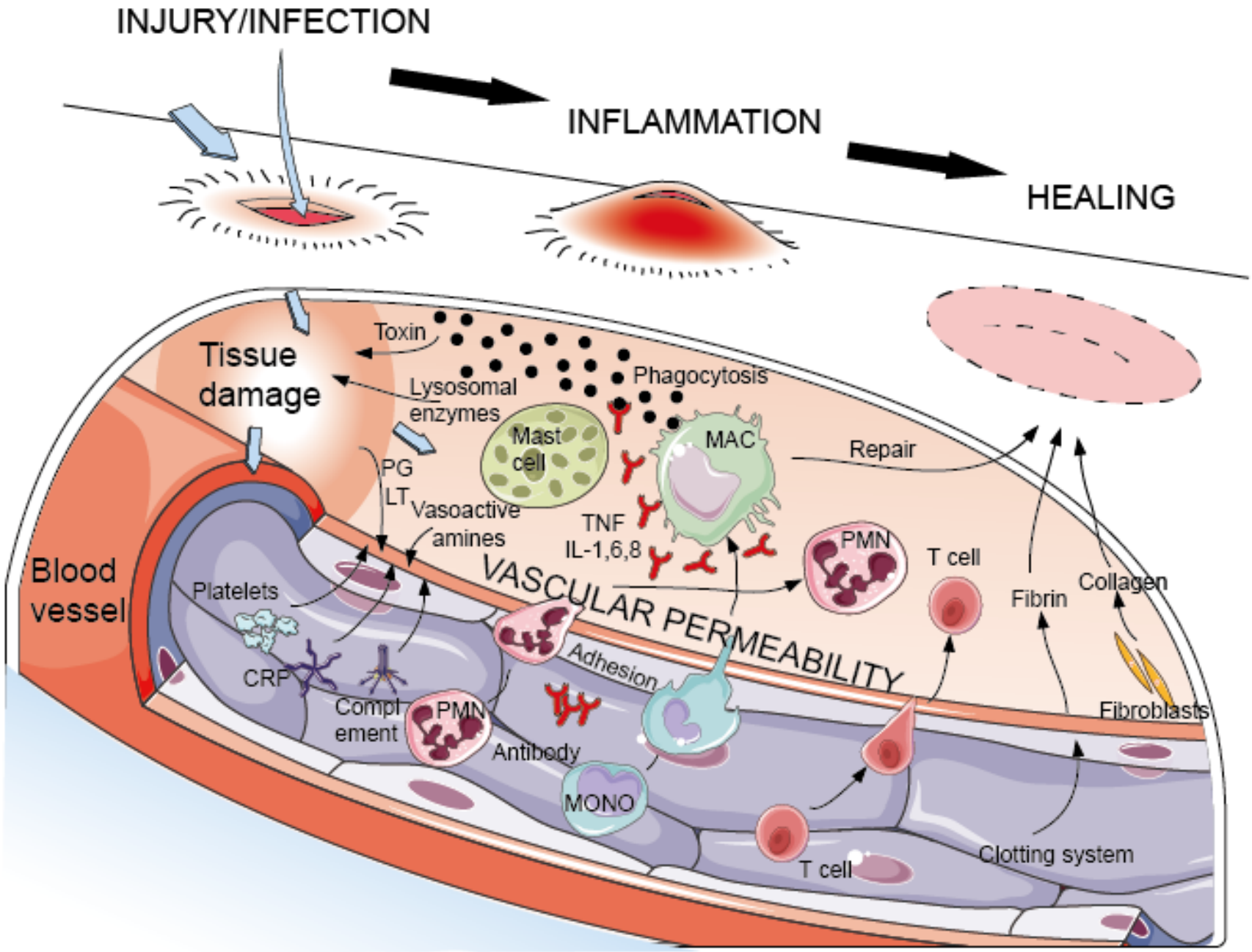
Pathogen–associated molecular patterns (PAMPs)

- PAMPs are polysaccharides and polynucleotides in nature and they are shared by several groups of pathogens. These molecules are conserved at the molecular level within a class of pathogens.
- PAMPs include a variety of molecules recognized mainly by PRRs. The most characteristic PAMP molecules are: LPS, an endotoxin found in the Gram negative bacterial membranes, lipoteichoic acid from Gram positive bacteria, bacterial flagellin, peptidoglycan, ssRNA and dsRNA from viruses, unmethylated DNA (CpG motifs), mannose present on yeast surfaces, and β-glucans present on the fungal cell wall

- **Damage-associated molecular patterns (DAMPs)**
- Besides recognition of microbial PAMPs, the immune system has the ability to sense other signals associated with infection or tissue damage, including host components released from infected, damaged, or necrotic cells, which, in turn, are able to activate and amplify the immune response.
- These components are called damage-associated molecular patterns (DAMPS) or alarmins. These inflammatory components liberated from damaged cells include **nucleic acids, intracellular proteins, extracellular matrix components, oxidized lipids, crystals such as uric acids, silica, β-amyloid, and cholesterol .**
- One of the differences between PMAPs and DAMPs is that the previous stimulate the synthesis of pro-IL-1β, but not its secretion while the latter stimulates the assembly of inflammasome with subsequent activation of caspase-1. This, in turn, cleaves pro-IL-1β into IL-1β thus allowing its secretion . Sensing these endogenous ligands by the corresponding PRRs induce persistent inflammation, a phenomenon associated with the development of chronic inflammatory and autoimmune diseases

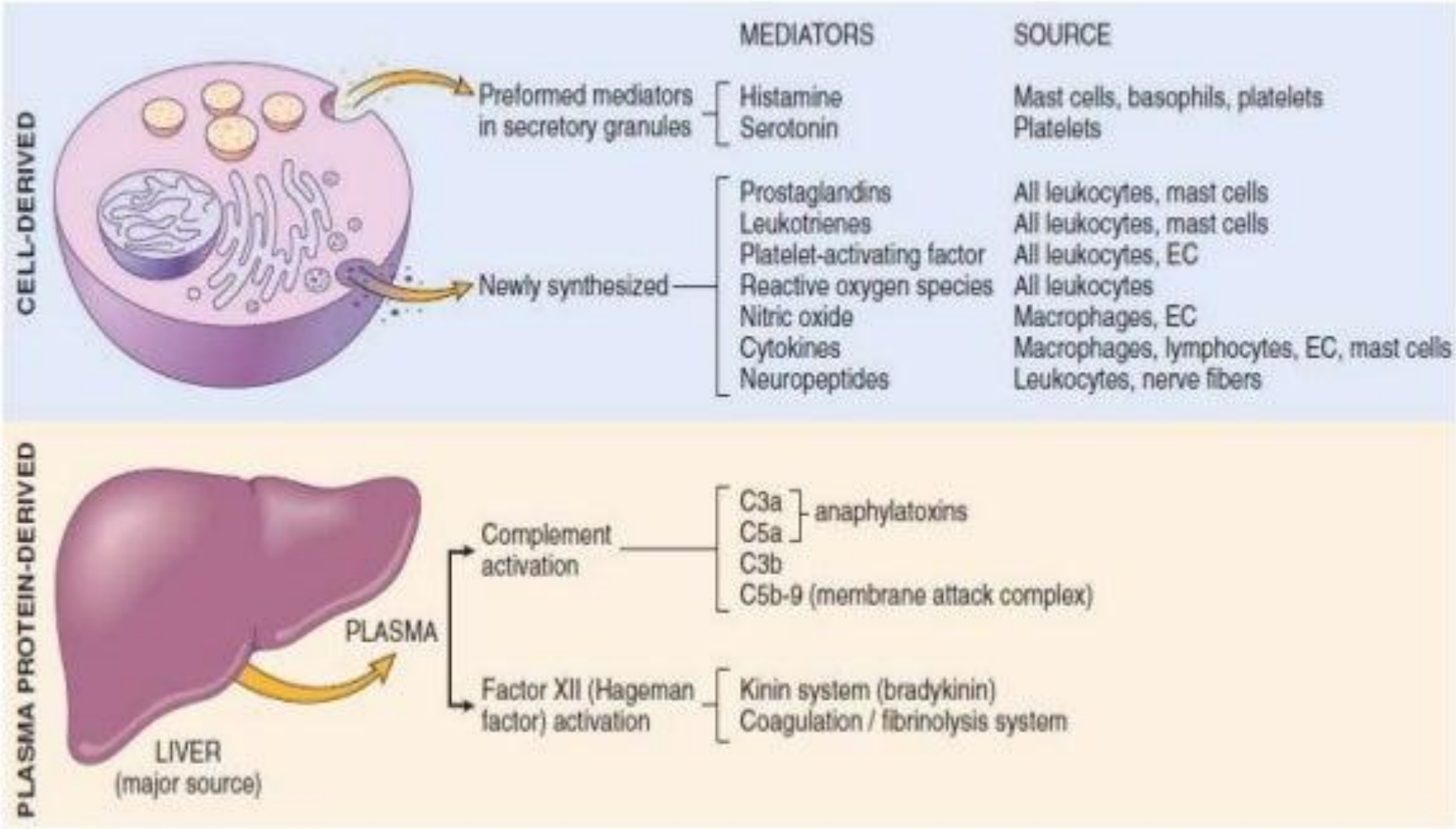
- **Inflammation**
- Inflammation is a nonspecific mechanism generated by the host in response to an infectious, physical, or chemical injury with recruitment of peripheral blood leukocytes and plasma proteins to the site of injury or tissue damage.
- In this process, there is an increase in both blood flow and vascular permeability, mainly in the vascular endothelial at the local level. Vascular permeability is a consequence of the endothelial cell retraction to allow the transmigration of leukocytes and the ingress of plasmatic proteins such as complement, coagulation factors, and antibodies,

- After an injury, there is tissue damage with the release of components by epithelial or endothelial cells as well as by cells present in that tissue such as mast cells or ILCs.
- These substances include histamine, leukotrienes, extracellular matrix components, and pro-inflammatory cytokines and chemokines, all of which have the ability to induce chemotaxis and cell adhesion molecule (CAM) expression in both endothelium and leucocytes.
- These CAMs include selectins, integrins, immunoglobuline-like superfamily molecules and cadherins. Expression of these CAMs allows interaction between leukocytes and endothelium and the subsequent leukocyte transmigration at the site of the injury. In the latter process, cells are guided by chemoattractant stimuli


INJURY/INFECTION
INFLAMMATION
HEALING
Tissue damage
Toxin
Lysosomal enzymes
Phagocytosis
Mast cell
MAC
Repair
PG
LT
Vasoactive amines
TNF
IL-1,6,8
PMN
T cell
Blood vessel
Platelets
VASCULAR PERMEABILITY
Fibrin
Collagen
CRP
Adhesion
Compl ement
PMN
Antibody
Fibroblasts
MONO
T cell
Clotting system

- The cell migration process is complex and depends on cell type as well as on the differentiation and activation state of the cells .
- As was mentioned, the first cells recruited at the site of the injury are neutrophils. They are also the most abundant during the first hours or days of the inflammation process followed by mononuclear cells. If the inflammatory reaction cannot be resolved, this process may become chronic with other implications for the host.

Mediators of inflammation



Adaptive immunity

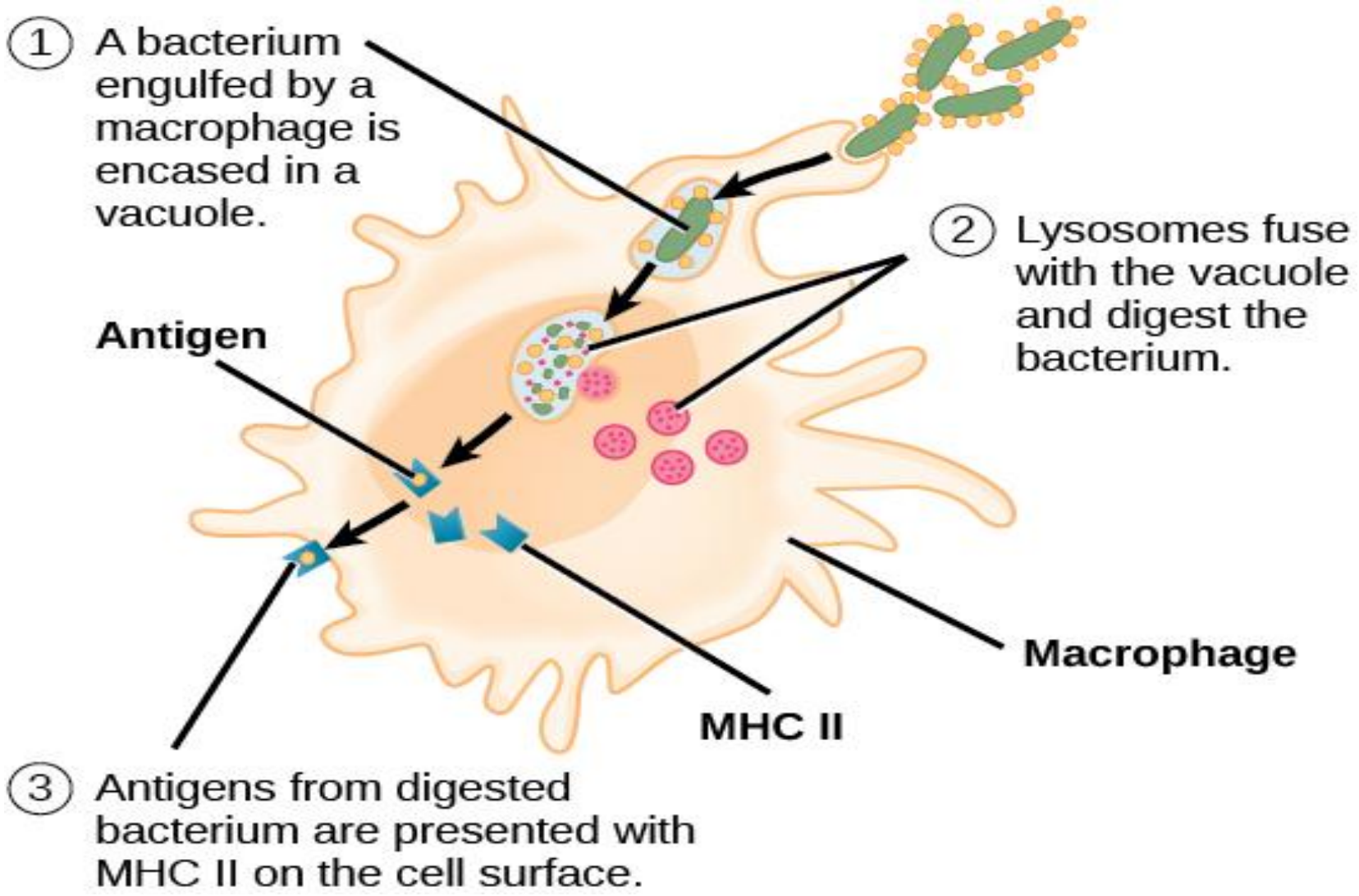
- The adaptive, or acquired, immune response takes days or even weeks to become established—much longer than the innate response;
- adaptive immunity is more specific to pathogens
- involves a memory to provide the host with long-term protection from reinfection with the same type of pathogen; on re-exposure, this memory will facilitate an efficient and quick response.
- **Adaptive immunity** is an immunity that occurs after exposure to an antigen either from a pathogen or a vaccination. This part of the immune system is activated when the innate immune response is insufficient to control an infection.

- There are two types of adaptive responses: the **cell-mediated immune response**, which is carried out by T cells, and the **humoral immune response**, which is controlled by activated B cells and antibodies. Activated T cells and B cells that are specific to molecular structures on the pathogen proliferate and attack the invading pathogen.

- The innate immune system contains cells that detect potentially harmful antigens, and then inform the adaptive immune response about the presence of these antigens.
- An **antigen-presenting cell (APC)** is an immune cell that detects, engulfs, and informs the adaptive immune response about an infection. When a pathogen is detected, these APCs will phagocytose the pathogen and digest it to form many different fragments of the antigen. Antigen fragments will then be transported to the surface of the APC, where they will serve as an indicator to other immune cells.

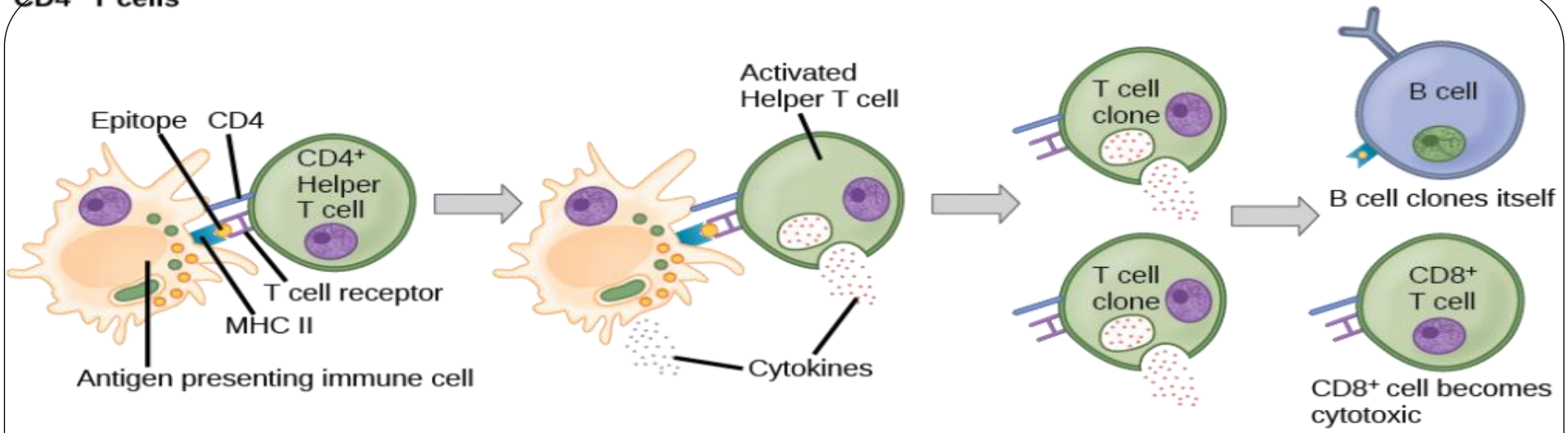
- **Dendritic cells** are immune cells that process antigen material; they are present in the skin (Langerhans cells) and the lining of the nose, lungs, stomach, and intestines. Sometimes a dendritic cell presents on the surface of other cells to induce an immune response, thus functioning as an antigen-presenting cell.
- **Macrophages** also function as APCs.
- Before activation and differentiation, **B cells** can also function as APCs.

- After phagocytosis by APCs, the phagocytic vesicle fuses with an intracellular lysosome forming phagolysosome. Within the phagolysosome, the components are broken down into fragments; the fragments are then loaded onto MHC class I or MHC class II molecules and are transported to the cell surface for antigen presentation,
- T lymphocytes cannot properly respond to the antigen unless it is processed and embedded in an MHC II molecule. APCs express MHC on their surfaces, and when combined with a foreign antigen, these complexes signal a “non-self” invader. Once the fragment of antigen is embedded in the MHC II molecule, the immune cell can respond. Helper T- cells are one of the main lymphocytes that respond to antigen-presenting cells. Recall that all other nucleated cells of the body expressed MHC I molecules, which signal “healthy” or “normal.”


1 A bacterium engulfed by a macrophage is encased in a vacuole.
2 Lysosomes fuse with the vacuole and digest the bacterium.
Antigen
Macrophage
MHC II
3 Antigens from digested bacterium are presented with MHC II on the cell surface.

- **T and B Lymphocytes**
- Lymphocytes in human circulating blood are approximately 80 to 90 percent T cells and 10 to 20 percent B cells.
- the T cells are involved in the cell-mediated immune response, whereas B cells are part of the humoral immune response.
- T cells encompass a heterogeneous population of cells with extremely diverse functions.
- Some T cells respond to APCs of the innate immune system, and indirectly induce immune responses by releasing cytokines.
- Other T cells stimulate B cells to prepare their own response.
- Another population of T cells detects APC signals and directly kills the infected cells.
- Other T cells are involved in suppressing inappropriate immune reactions to harmless or “self” antigens.

CD4⁺ T cells



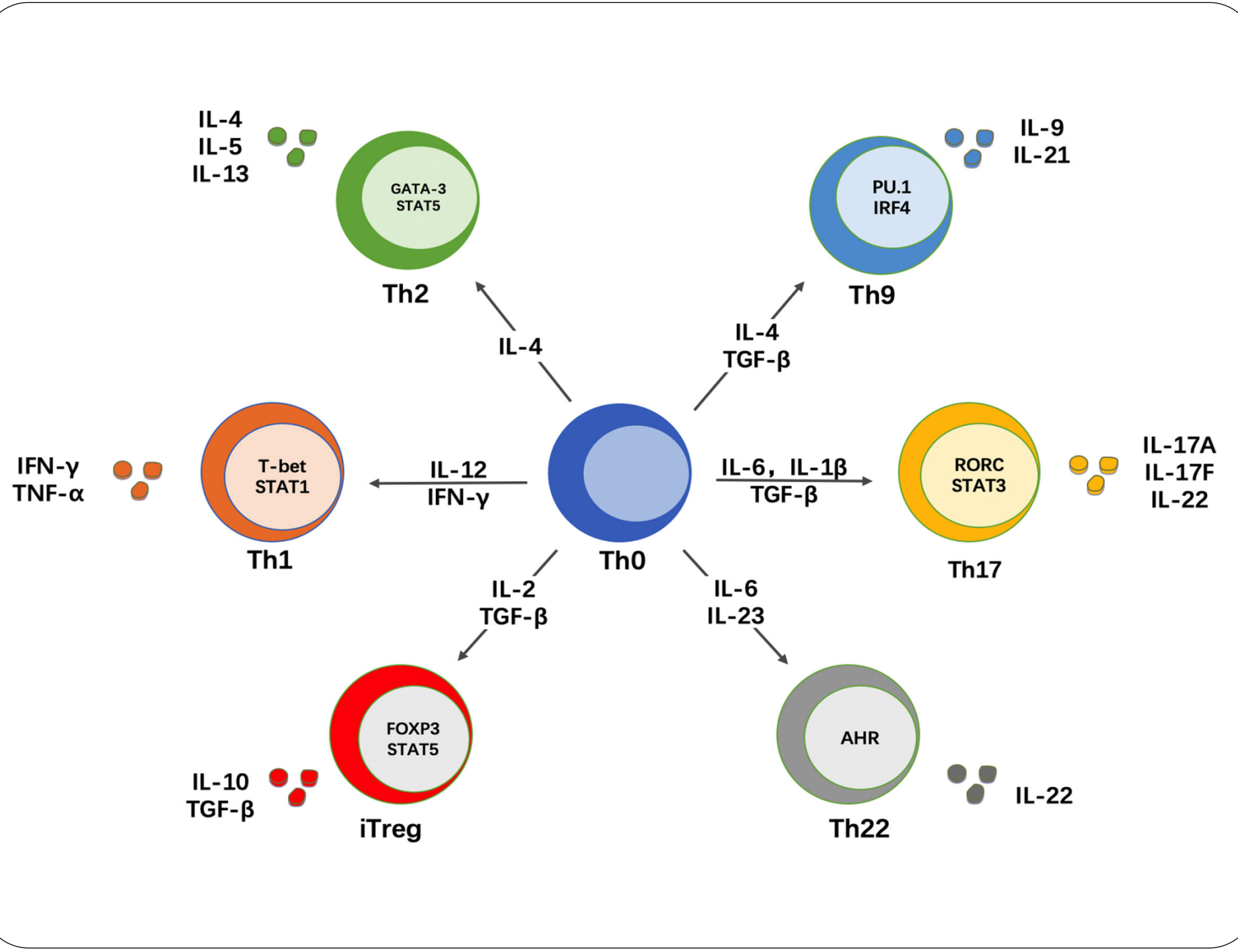
1. When a CD4⁺ helper T cell binds MCH II-antigen complex on an antigen-presenting cell, both the antigen-presenting cell and the T cell release cytokines.
2. In response to cytokines the T cells clones itself.
3. The cloned T cells produce different cytokines that activate B cells and CD8⁺ cells.

CD8⁺ T cells

1. When a cytotoxic T cell interacts with the MHC I-epitope complex on an infected cell it produces granzymes and perforins.
2. The perforins form pores in the plasma membrane. Granzymes enter the cell and break down proteins, lysing the cell.

Helper T Lymphocytes

- The T_H lymphocytes function indirectly to identify potential pathogens for other cells of the immune system. These cells are important for extracellular infections, such as those caused by certain bacteria, helminths, and protozoa. T_H lymphocytes recognize specific antigens displayed in the MHC II complexes of APCs.
- There are two major populations of T_H cells: T_H1 and T_H2. T_H1 cells secrete cytokines to enhance the activities of macrophages and other T cells. T_H1 cells activate the action of cytotoxic T cells, as well as macrophages. T_H2 cells stimulate naïve B cells to destroy foreign invaders via antibody secretion.
- Whether a T_H1 or a T_H2 immune response develops depends on the specific types of cytokines secreted by cells of the innate immune system, which in turn depends on the nature of the invading pathogen.


IL-4
IL-5
IL-13
GATA-3
STAT5
Th2
IL-9
IL-21
PU.1
IRF4
Th9
IL-4
IL-4
TGF-β
IFN-γ
TNF-α
T-bet
STAT1
Th1
IL-12
IFN-γ
Th0
IL-6，IL-1β
TGF-β
RORC
STAT3
Th17
IL-17A
IL-17F
IL-22
IL-2
TGF-β
IL-6
IL-23
IL-10
TGF-β
FOXP3
STAT5
iTreg
AHR
Th22
IL-22

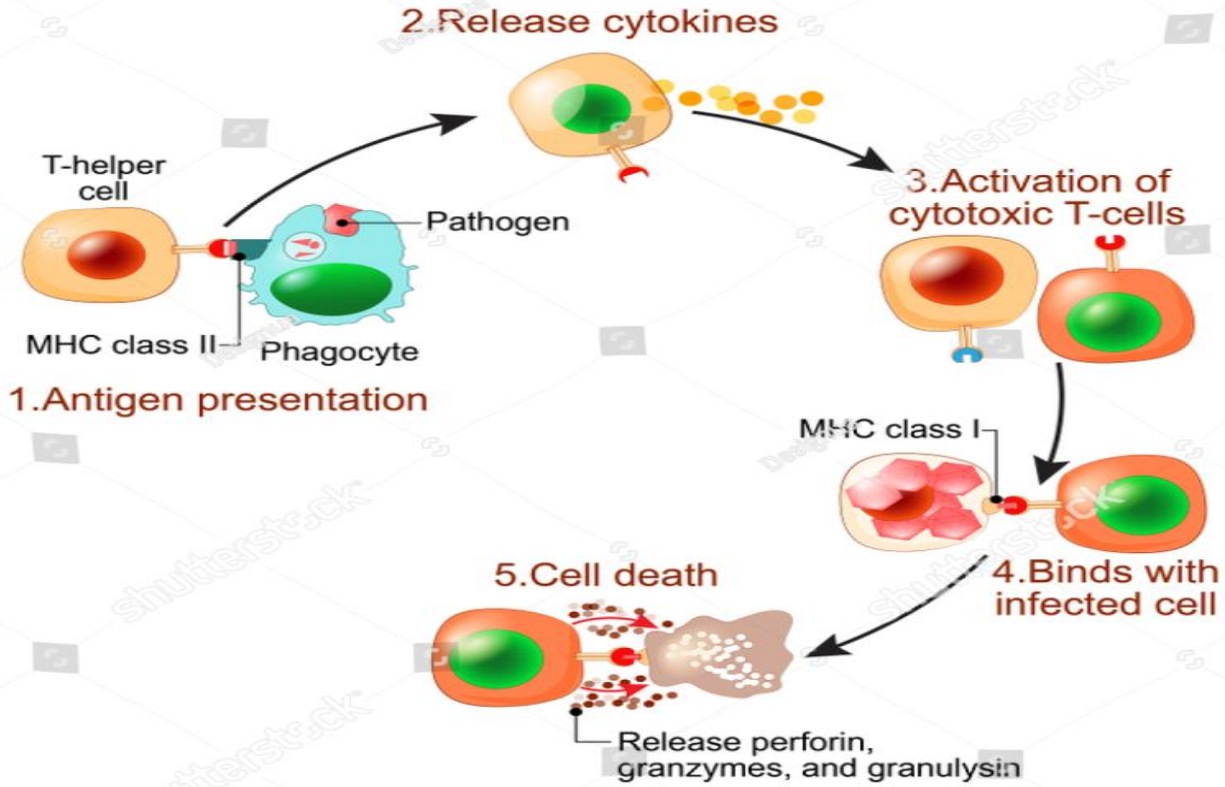
- The T_H1-mediated response involves macrophages and is associated with inflammation
- Some intracellular bacteria, such as *Mycobacterium tuberculosis*, have evolved to multiply in macrophages after they have been engulfed. These pathogens evade attempts by macrophages to destroy and digest the pathogen.
- When *M. tuberculosis* infection occurs, macrophages can stimulate naïve T cells to become T_H1 cells. These stimulated T cells secrete specific cytokines that send feedback to the macrophage to stimulate its digestive capabilities and allow it to destroy the colonizing *M. tuberculosis*. In the same manner, T_H1-activated macrophages also become better suited to ingest and kill tumor cells. In summary; T_H1 responses are directed toward intracellular invaders while T_H2 responses are aimed at those that are extracellular.

Cytotoxic T Lymphocytes

- CTLs, a subclass of T cells, function to clear infections directly. The cell-mediated part of the adaptive immune system consists of CTLs that attack and destroy infected cells. CTLs are particularly important in protecting against viral infections; this is because viruses replicate within cells where they are shielded from extracellular contact with circulating antibodies. When APCs phagocytize pathogens and present MHC I-embedded antigens to naïve $CD8^+$ T cells that express complementary TCRs, the $CD8^+$ T cells become activated to proliferate according to clonal selection. These resulting CTLs then identify non-APCs displaying the same MHC I-embedded antigens (for example, viral proteins)—for example, the CTLs identify infected host cells

- Intracellularly, infected cells typically die after the infecting pathogen replicates to a sufficient concentration and lyses the cell, as many viruses do. CTLs attempt to identify and destroy infected cells before the pathogen can replicate and escape, thereby halting the progression of intracellular infections. CTLs also support NK lymphocytes to destroy early cancers. Cytokines secreted by the T_H1 response that stimulates macrophages also stimulate CTLs and enhance their ability to identify and destroy infected cells and tumors

Cytotoxic T-cell



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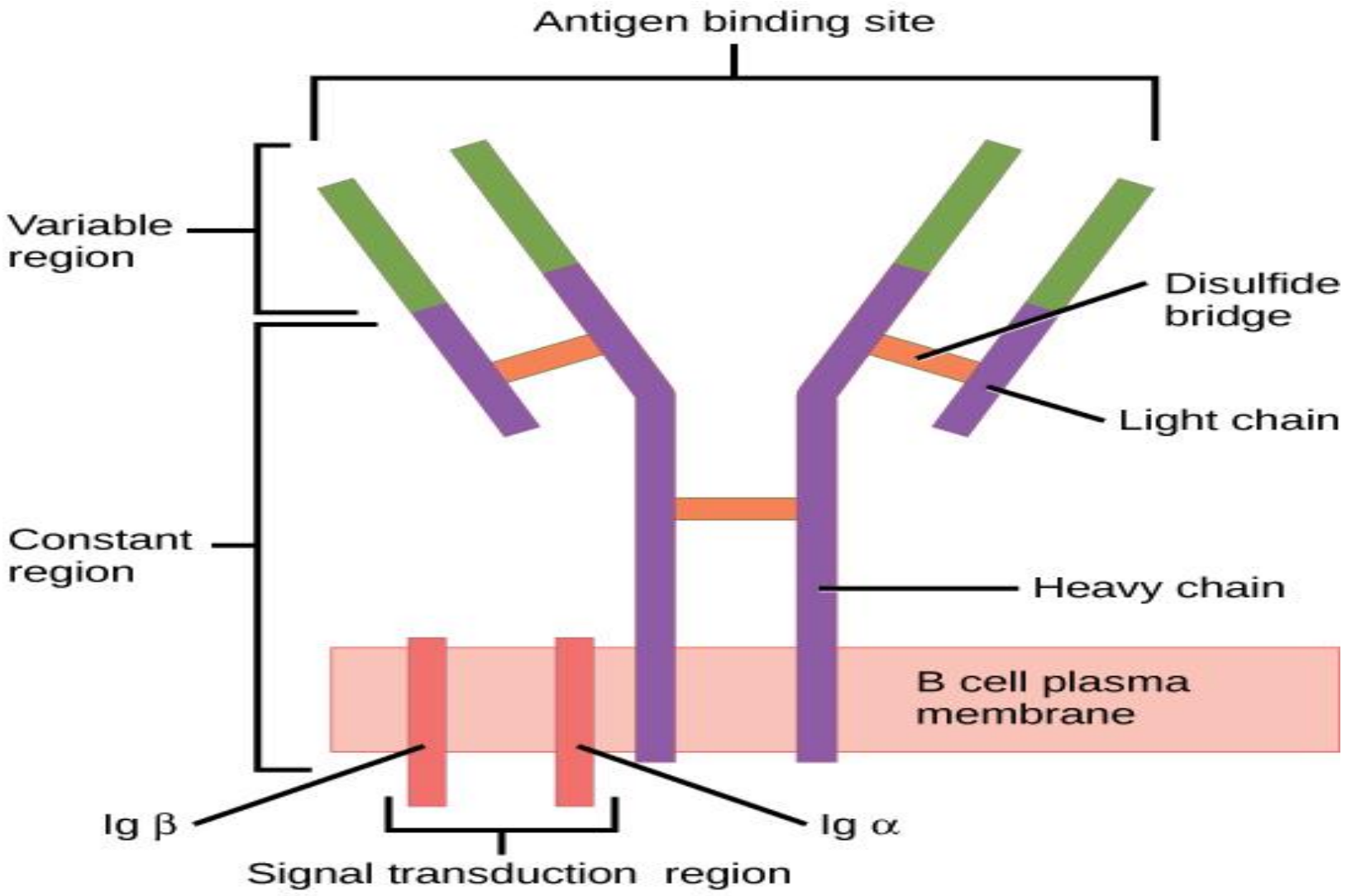
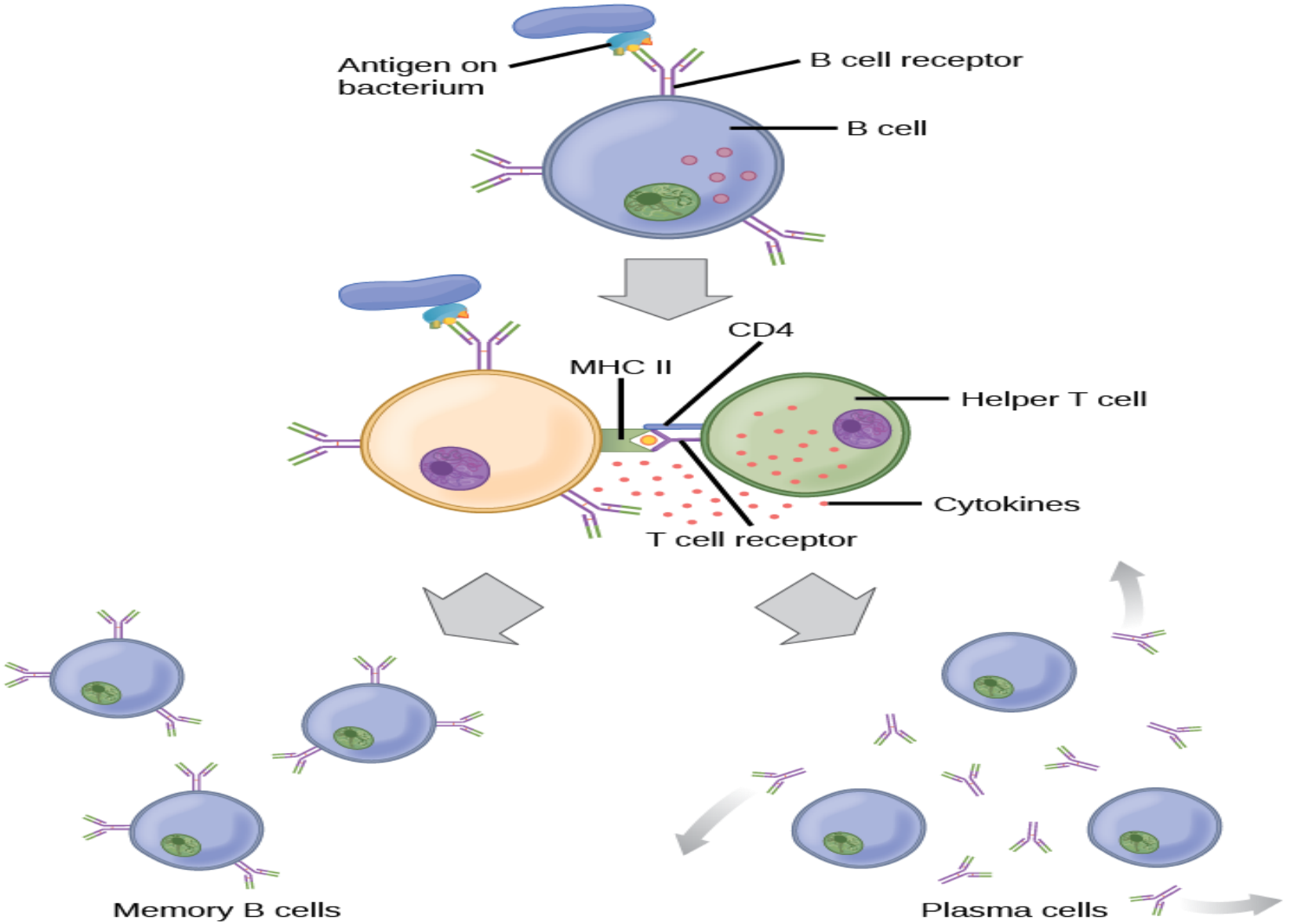
- *B Lymphocytes*
- When stimulated by the T_H2 pathway, naïve B cells differentiate into antibody-secreting plasma cells. A **plasma cell** is an immune cell that secrets antibodies; these cells arise from B cells that were stimulated by antigens. Similar to T cells, naïve B cells initially are coated in thousands of B cell receptors (BCRs), which are membrane-bound forms of Ig (immunoglobulin, or an antibody). The B cell receptor has two heavy chains and two light chains connected by disulfide linkages. Each chain has a constant and a variable region; the latter is involved in antigen binding. Two other membrane proteins, Ig alpha and Ig beta, are involved in signaling

- The receptors of any particular B cellare all the same, but the hundreds of millions of different B cells in an individual have distinct recognition domains that contribute to extensive diversity in the types of molecular structures to which they can bind.
- In this state, B cells function as APCs. They bind and engulf foreign antigens via their BCRs and then display processed antigens in the context of MHC II molecules to T_H2 cells. When a T_H2 cell detects that a B cell is bound to a relevant antigen, it secretes specific cytokines that induce the B cell to proliferate rapidly, which makes thousands of identical (clonal) copies of it, and then it synthesizes and secretes antibodies with the same antigen recognition pattern as the BCRs. The activation of B cells corresponding to one specific BCR variant and the dramatic proliferation of that variant is known as **clonal selection**.

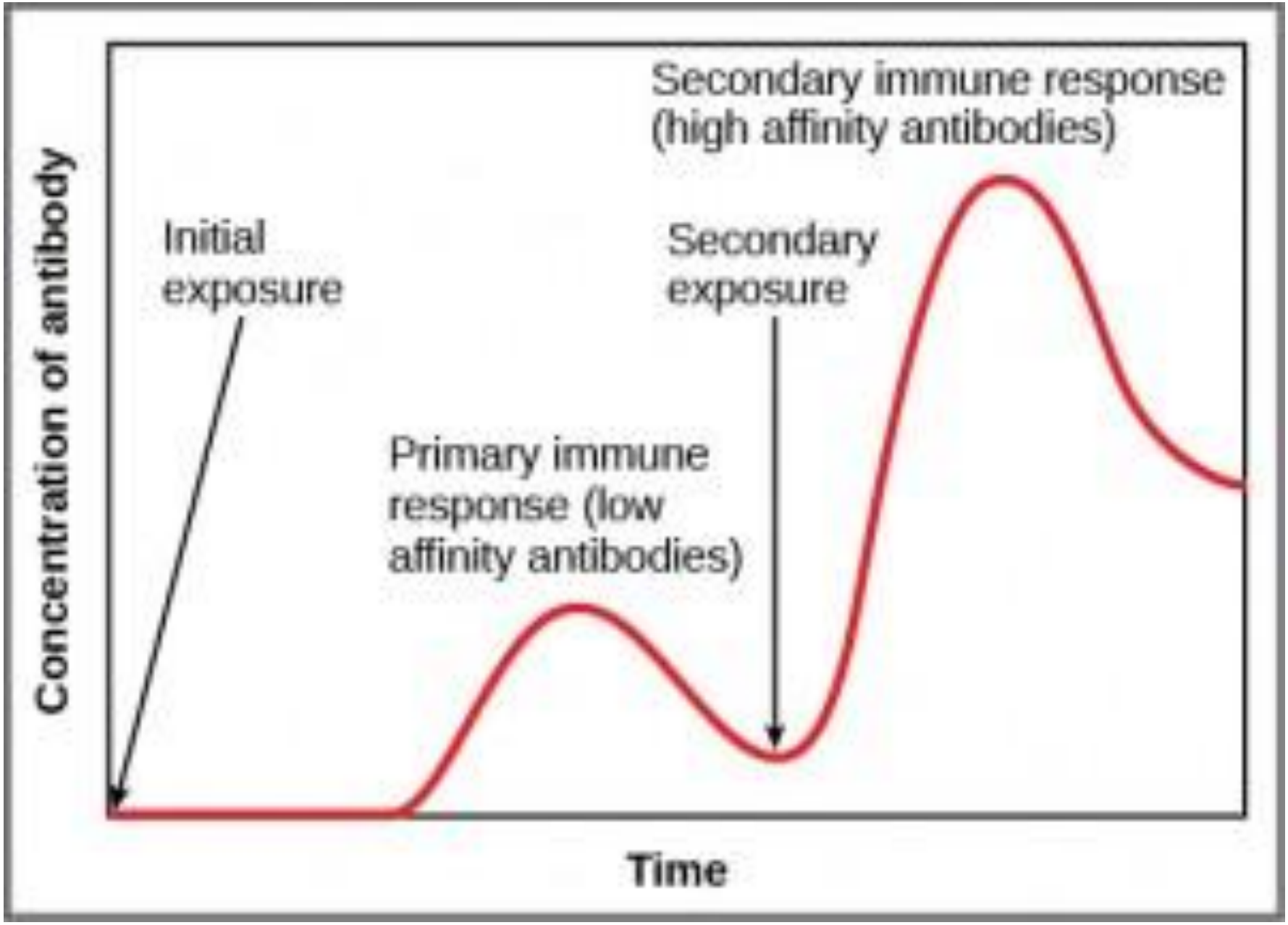

Antigen binding site
Variable region
Disulfide bridge
Light chain
Constant region
Heavy chain
B cell plasma membrane
Ig β
Ig α
Signal transduction region

A memory cell

- is an antigen-specific B or T lymphocyte that does not differentiate into effector cells during the primary immune response, but that can immediately become effector cells upon re-exposure to the same pathogen. During the primary immune response, memory cells do not respond to antigens and do not contribute to host defenses. As the infection is cleared and pathogenic stimuli subside, the effectors are no longer needed, and they undergo apoptosis. In contrast, the memory cells persist in the circulation


Antigen on bacterium
B cell receptor
B cell
CD4
MHC II
Helper T cell
Cytokines
T cell receptor
Memory B cells
Plasma cells

- If the pathogen is never encountered again during the individual's lifetime, B and T memory cells will circulate for a few years or even several decades and will gradually die off, having never functioned as effector cells. However, if the host is re-exposed to the same pathogen type, circulating memory cells will immediately differentiate into plasma cells and CTLs without input from APCs or T_H cells. One reason the adaptive immune response is delayed is because it takes time for naïve B and T cells with the appropriate antigen specificities to be identified and activated. Upon reinfection, this step is skipped, and the result is a more rapid production of immune defenses. Memory B cells that differentiate into plasma cells output tens to hundreds-fold greater antibody amounts than were secreted during the primary response,


Secondary immune response
(high affinity antibodies)
Initial
exposure
Secondary
exposure
Primary immune
response (low
affinity antibodies)
Concentration of antibody
Time

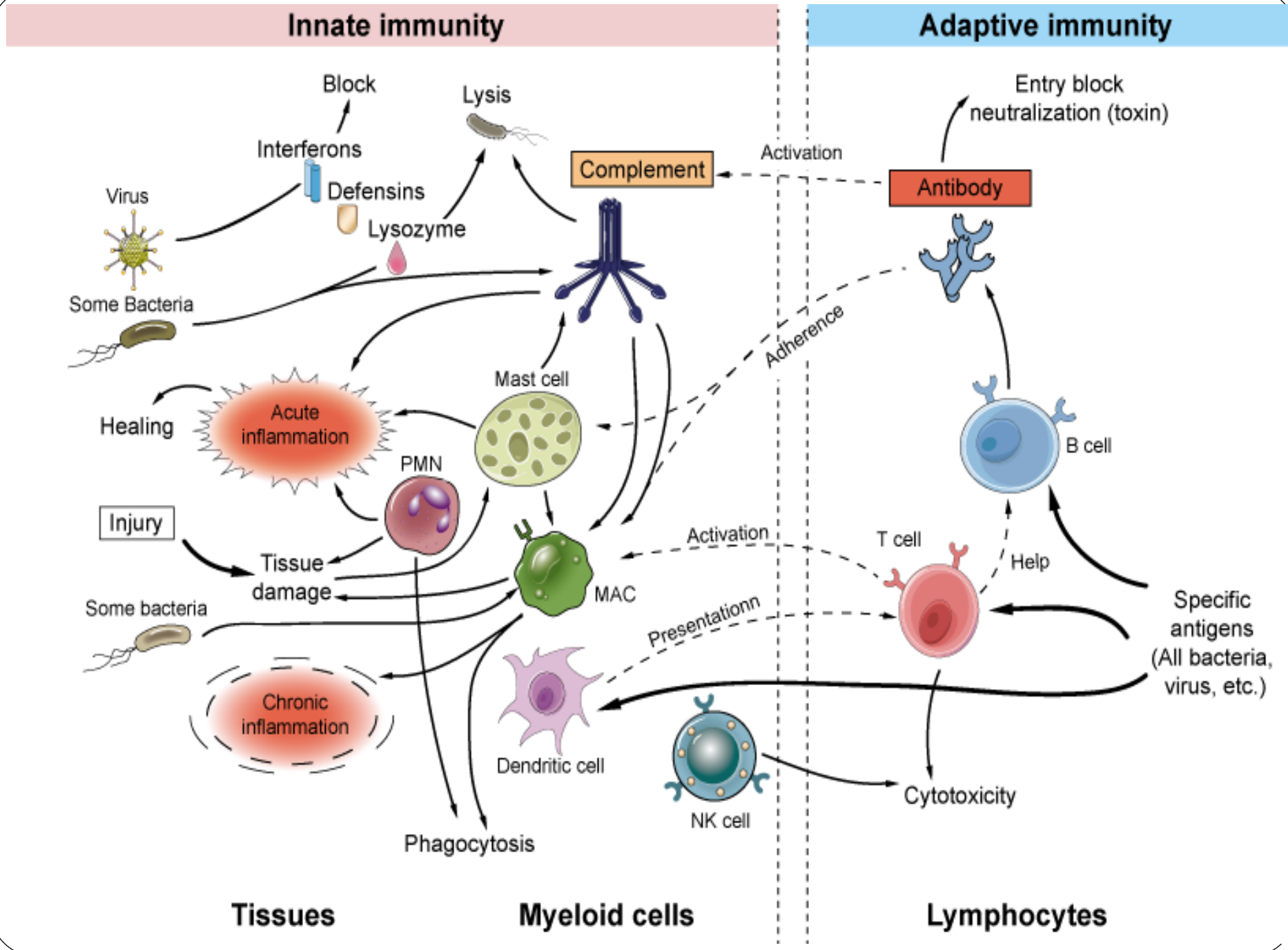
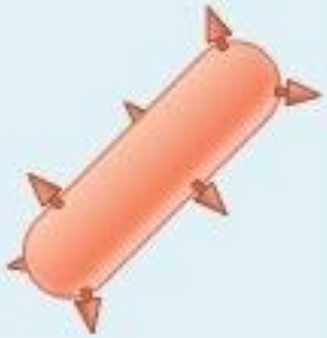
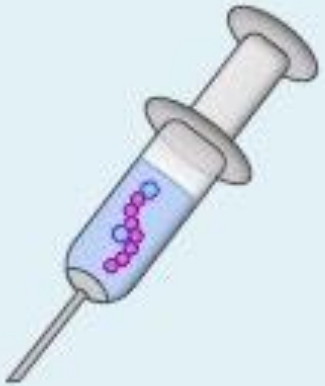
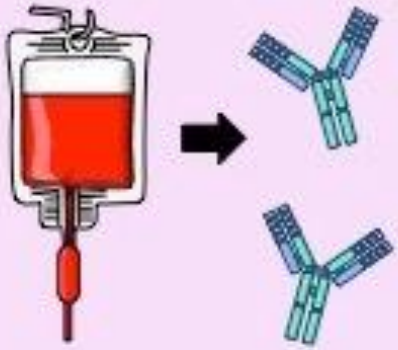

Innate immunity
Adaptive immunity
Block
Lysis
Interferons
Defensins
Lysozyme
Virus
Some Bacteria
Complement
Activation
Entry block
neutralization (toxin)
Antibody
Adherence
Mast cell
Healing
Acute
inflammation
PMN
B cell
Injury
Tissue
damage
Activation
T cell
Help
MAC
Some bacteria
Presentationn
Specific
antigens
(All bacteria,
virus, etc.)
Chronic
inflammation
Dendritic cell
NK cell
Cytotoxicity
Phagocytosis
Tissues
Myeloid cells
Lymphocytes

Table 1: Differences between Innate and Adaptive Immunity

Feature	Innate Immunity	Adaptive Immunity
Cells involved	Dendritic leukocyte, Natural killer cells, Mast cell, Granulocytes/ Macrophages, Basophils, etc.	Killer CD8+ T-cells, Helper CD4+ T-cells, B-cells, Antigen presenting cells, etc.
Molecules involved	Cytokines, Complement cells, Interferon, Acute phase reactants/ proteins	Antibodies, Cytokines
Receptors	Germline encoded	Encoded in gene segments
	No somatic rearrangement	Somatic rearrangement necessary
	Non-clonal distribution	Clonal distribution
Action time	Immediate effector activation	Delayed effector activation
Response	Rapidly occurs (0-6 h ours)	Occurs over days to weeks
Order of defence	It is the first line of defense of immune system	Action against pathogens that are able to evade or overcome innate immune defense
Immunological memory	None	Confer Immunological memory
Types of Immune response	Inflammation, Complement mediated killing, Phagocytosis	Antibodies generation, microbial destruction by Helper T cells and Cytotoxic T cells
Subsequent exposure	Immune response does not get alter on repeated exposure	Immune response get improves with subsequent exposure
Reason behind immune evasion	Caused by pathogenic virulence	Caused by mutation of the recognized antigen
Allery or	None	Immediate and delay

hypersensitivity reaction		hypersentivity
Potency	Lower	Higher
Physio-anatomicalcal barriers	Skin, Mucous membranes, Temp, pH, chemicals, etc	Lymph nodes, spleen, mucosal associated lymphoid tissue
Functions	(a) Recruiting immune cells to site of infection; (b) Activation of complement cascade to identify antigens; (c) Identification & removal of foreign substances present in organs, tissues, blood and lymph; (d) Activation of adaptive immune system through antigen presentation; (e) Acting as physical & chemical barrier to infectious agents.	(a) Recognition of specific "non-self" antigens during the process of antigen presentation; (b) Generation of responses that are tailored to maximally eliminate specific pathogens or infected cells; (c) Development of immunological memory, through memory B cells and memory T cells.

	Innate	Adaptive
Features	Primitive and broad	Highly specific (T and B cell reports)
Speed of onset	Immediate	Approx. 3-day lag
Regulation	+/-	++++
Potency	Lower	Higher
Kinetics	Fast (hours-days)	Slow (days-wks.)
Amplification	No (insignificant)	Yes
Duration	Short (days)	Long (months/yrs.)
Memory	No	Yes
Activity	Always present	Normally silent
Specificity	Unspecific	Highly specific

ACTIVE IMMUNITY		PASSIVE IMMUNITY	
Natural	**Artificial**	**Natural**	**Artificial**
			
Infection	Vaccination	Maternal antibodies	Monoclonal antibodies

- Innate lymphoid cells
- Netosis
- AMP