

**Immunology Course
Faculty of Medicine**

**Lecture 2
2025-2026
Innate Immunity**

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Objectives

- To understand the meaning of the innate immune response
- The definition of adaptive immunity
- To study the different lines of the innate immune response
- To understand the interaction between the different lines of the innate immune response

Types of Immune Response

Adaptive immunity

1. Respond to specific foreign substances.
2. It is characterized by its specificity, attacking only the particular invader.
3. Has memory, allowing for a faster and stronger response to future encounters with the same pathogen.
4. Involves B cells and T cells.

Innate Immunity

Definition

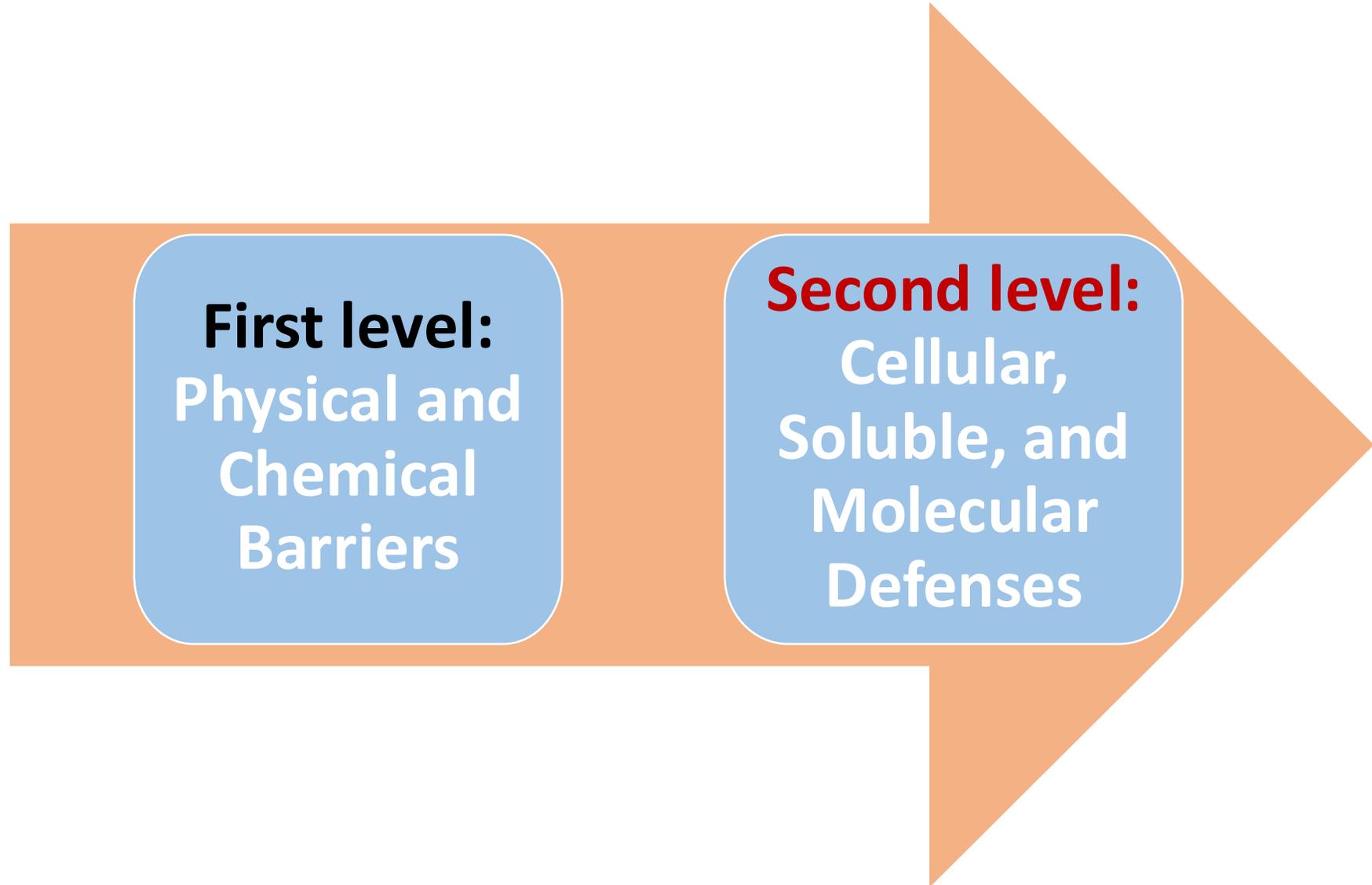
Innate immunity responses are the first defense during the first critical hours and days against invading pathogens and start immediately after an infection begins.

Characteristics

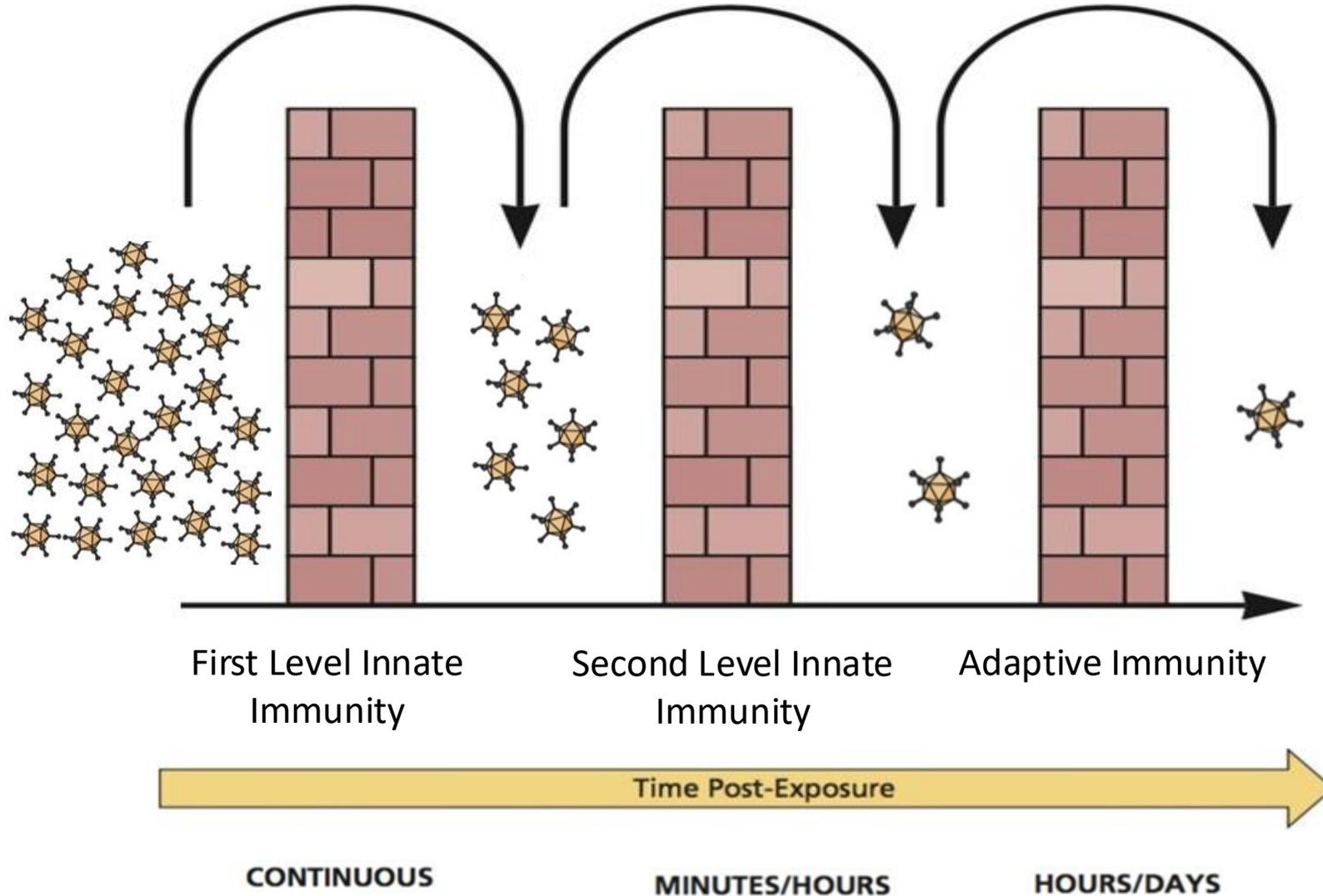
- General and non-specific,
- Immediate response
- No immunological memory
- Inherent
- Not specific to a particular pathogen.
- Ability to recognize conserved features of pathogens

levels of Innate Immunity

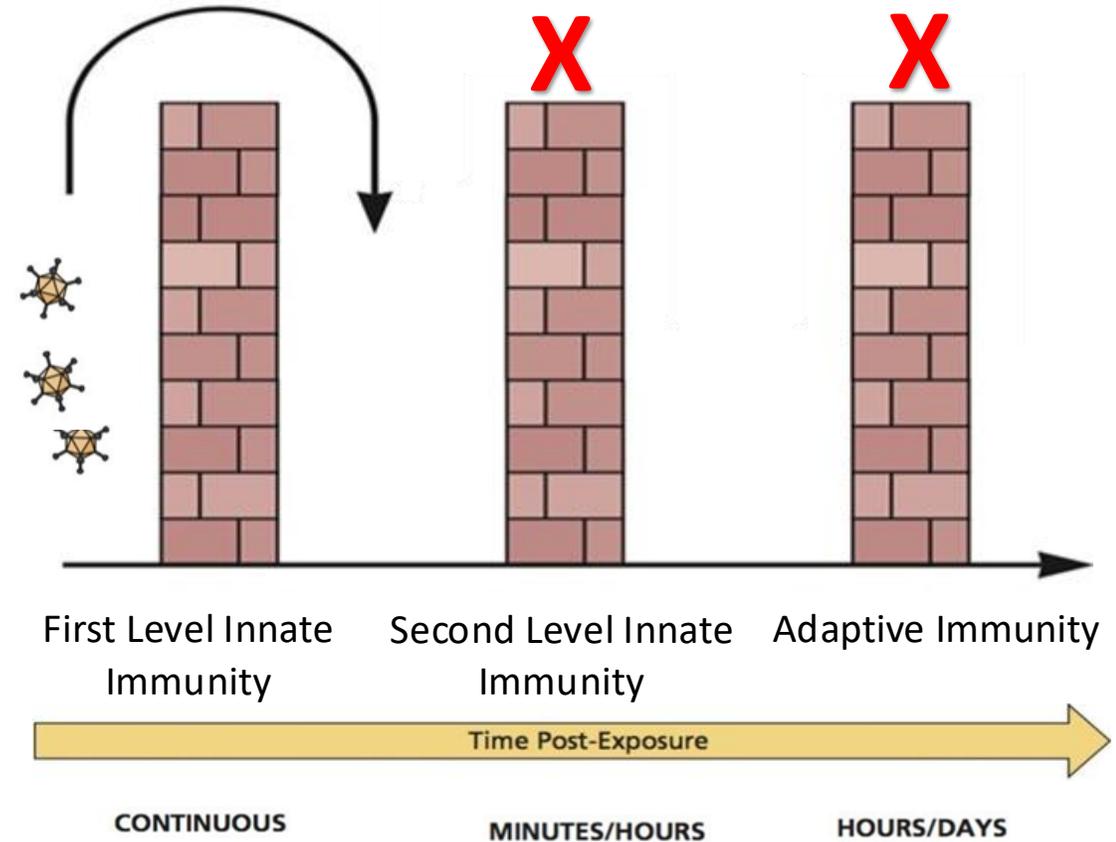
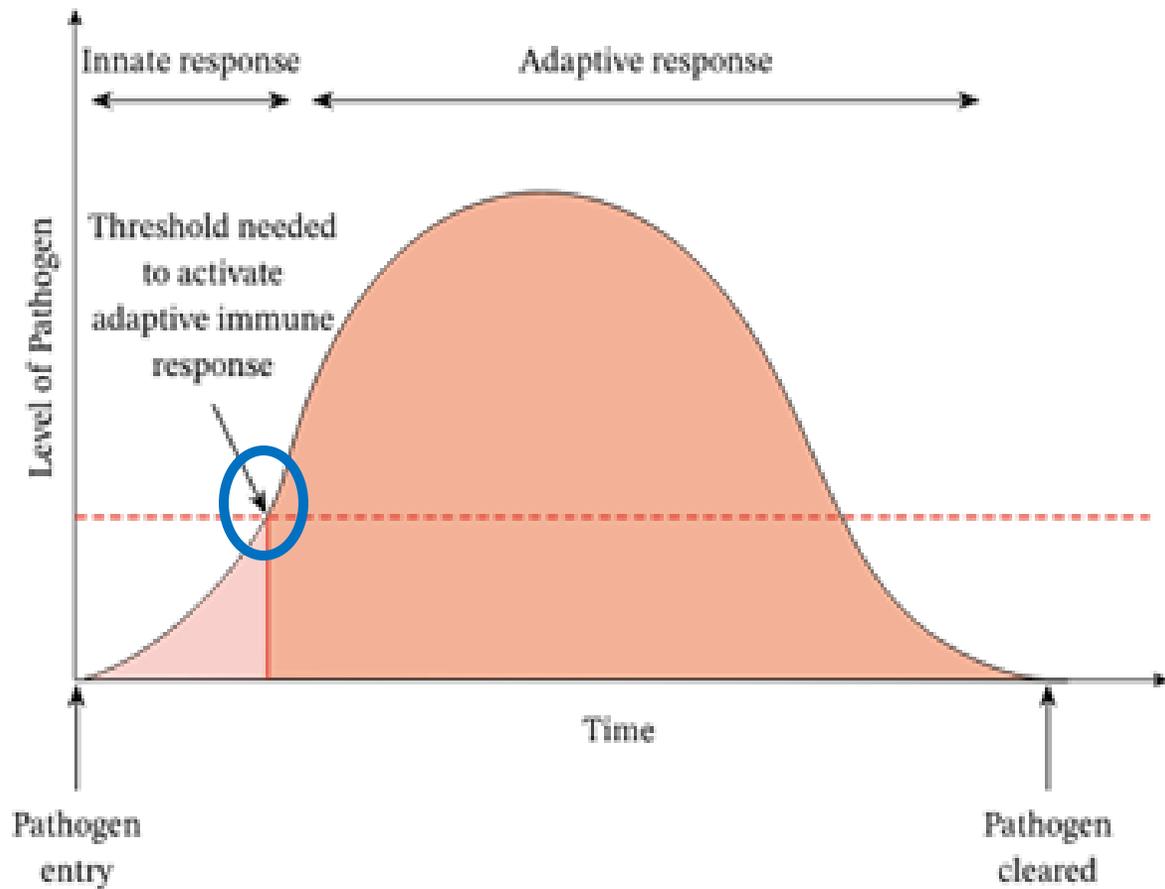
Innate immunity has **two levels of defense**



levels of Immunity



levels of Immunity



levels of Innate Immunity

Innate immunity has **Two** levels of defense

First line:
Physical and
Chemical
Barriers

First Level:

Physical Barriers: aim to **prevent pathogens from entering the body.**

- **Skin** –dry, acidic surface hostile to microbes
- **Mucous membranes** – Trap and expel pathogens (e.g., in respiratory tract)
- **Cilia** – Sweep mucus and trapped microbes out of airways
- **Tears, saliva, sweat** – Contain **lysozyme**, which breaks down bacterial cell walls
- **Normal flora (microbiota)** – Compete with harmful microbes.
- **Urine**: inhibits the bacterial growth in the urinary tract by the flushing action. Therefore, the indwelling catheters increase the probability of UTI because the urine will be in direct contact with the catheter wall not with tract itself

levels of Innate Immunity

Innate immunity has **Two** levels of defense

First line:
Physical and
Chemical
Barriers

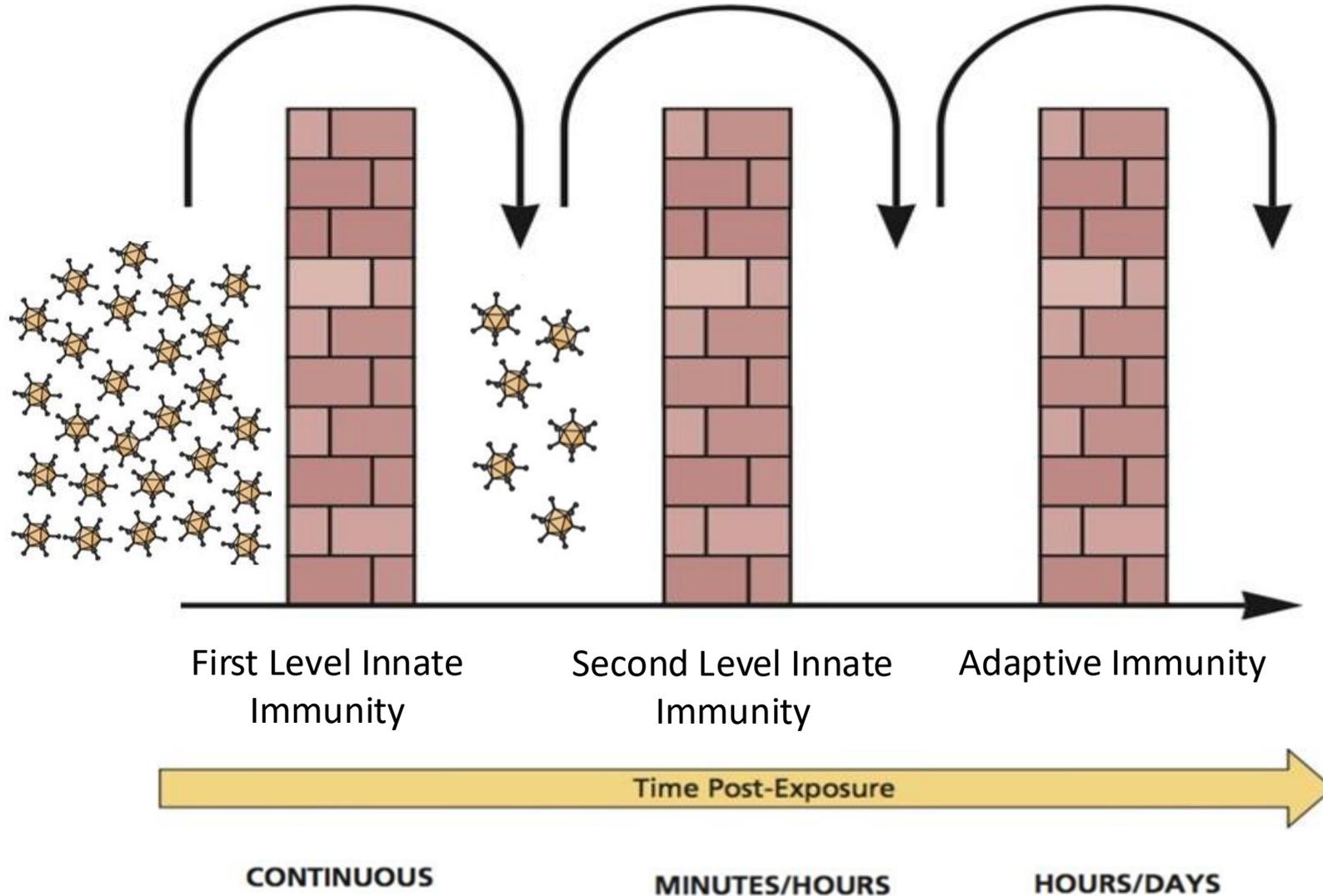
First Level:

Chemical Barriers

The pH of different organs also adds in the prevention of pathogenic bacterial colonization and growth for example:

- Skin: about 5,5 due to the fatty acids produced by the sebaceous glands
- Stomach: the pH 1-3 (HCL).
- Vagina: the pH 4.4-4.6 (acid producing bacteria called Lactobacillus).
- Urinary tract: pH (4.5 to 5.0). Microbicidal barriers:
- Different destructive enzymes such as lysozymes and pore producing proteins called defensins that are produced by the skin, respiratory, GIT, and tears are important in defending against pathogens

levels of Immunity



levels of Innate Immunity

Innate immunity has **Two** levels of defense

Second line:
Cellular,
Soluble, and
Molecular
Defenses

Second line

Cellular Defenses

- These act when pathogens **bypass the barriers** and enter the body.
- **Phagocytes:**
 - **Neutrophils** – First responders that engulf pathogens
 - **Macrophages** – Long-lasting phagocytes that also alert other immune cells
 - **Dendritic cells** – Engulf microbes and activate adaptive immunity
- **Natural Killer (NK) Cells** – Destroy virus-infected and abnormal (e.g., cancer) cells
- **Inflammation** – Local response that includes redness, swelling, heat, and pain
- **Fever** – Increases body temperature to delay microbial growth

levels of Innate Immunity

Innate immunity has **Two** levels of defense

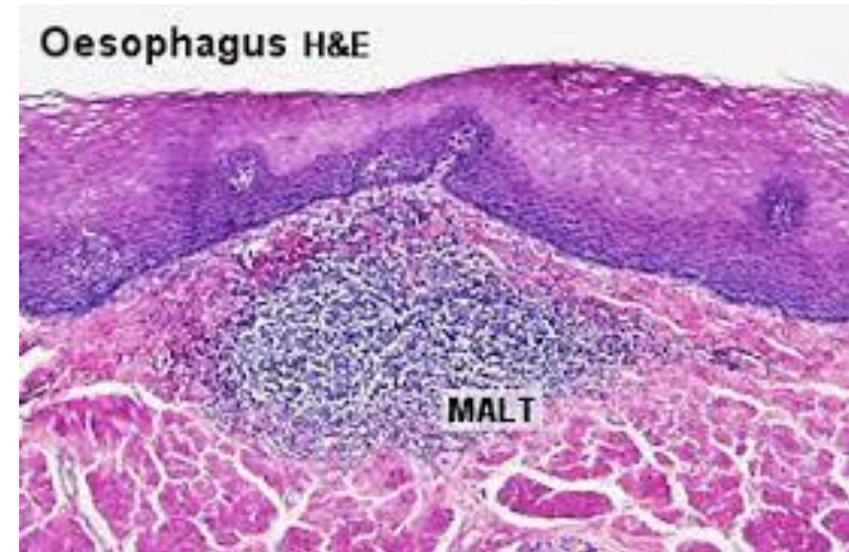
Second line:
Cellular,
Soluble, and
Molecular
Defenses

Second line

Cellular Defenses

MALT (mucosa-associated lymphoid tissue)

- MALT: can be further classified based on location:
 - GALT (gut-associated lymphoid tissue)
 - BALT (bronchus-associated lymphoid tissue)
 - NALT (nasopharynx-associated lymphoid tissue)



Mucosa-associated lymphoid tissue (MALT) is not exclusively part of the innate immune system; it also includes components of the adaptive immune system. While MALT does contain innate immune cells like natural killer cells and , it also houses lymphocytes involved in adaptive immunity, such as T and B cells.

levels of Innate Immunity

Innate immunity has **Two** levels of defense

Second line:
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Second line

Soluble Defenses

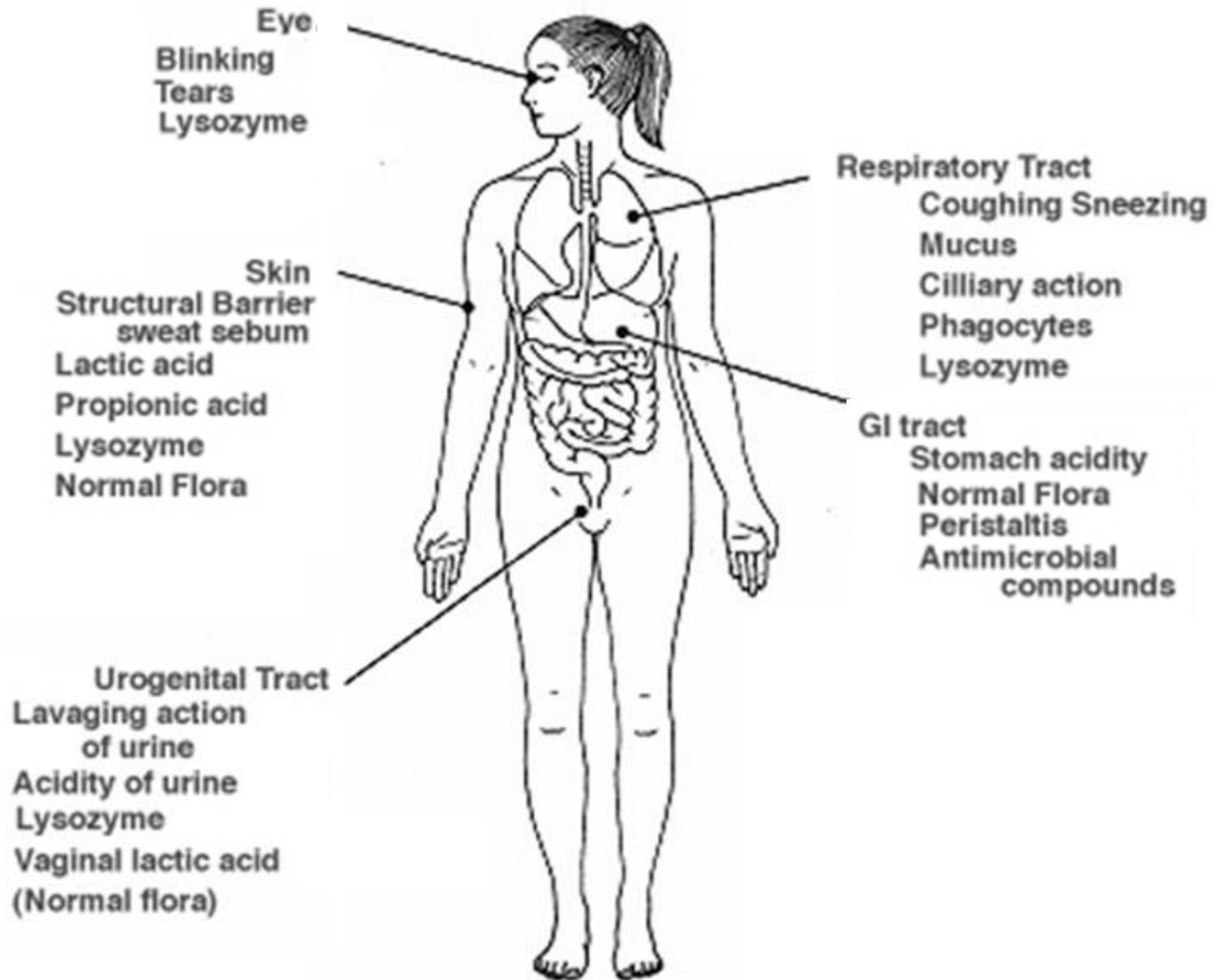
- These are **chemical and protein-based systems** that enhance immune responses.
- **Complement system** – A group of proteins that:
 - Kill microbes directly
 - Facilitate phagocytosis
 - Promote inflammation
- **Cytokines** – Chemical messengers that activate and direct immune cells
- **Interferons** – Help protect neighboring cells from viral infection
- **Acute-phase proteins** – Produced by the liver to fight infections

levels of Innate Immunity

Acute-phase proteins – Produced by the liver to fight infections

Acute Phase Protein	Primary Function
C-Reactive Protein (CRP)	complement activation and promotes phagocytosis
Serum Amyloid A (SAA)	Recruits immune cells and modulates inflammation
Fibrinogen	Promotes blood clotting, forms fibrin mesh, limits pathogen spread
Alpha-1 Antitrypsin	Inhibits proteases (e.g., neutrophil elastase), protects tissues from damage.
Alpha-2 Macroglobulin	Broad protease inhibitor.
Ceruloplasmin	Copper transport, antioxidant role, oxidizes iron (Fe^{2+} to Fe^{3+}).
Ferritin	Stores and sequesters iron to reduce availability to pathogens

Innate immunity

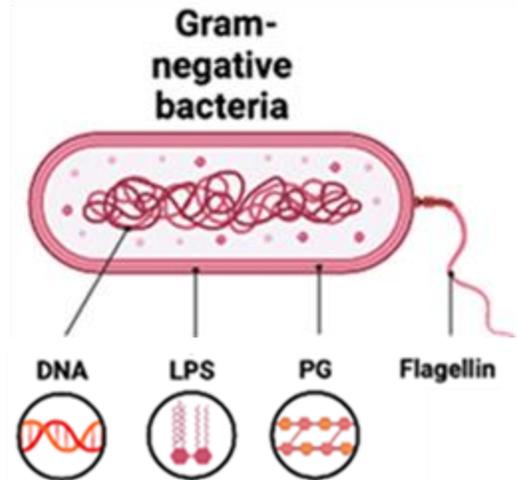
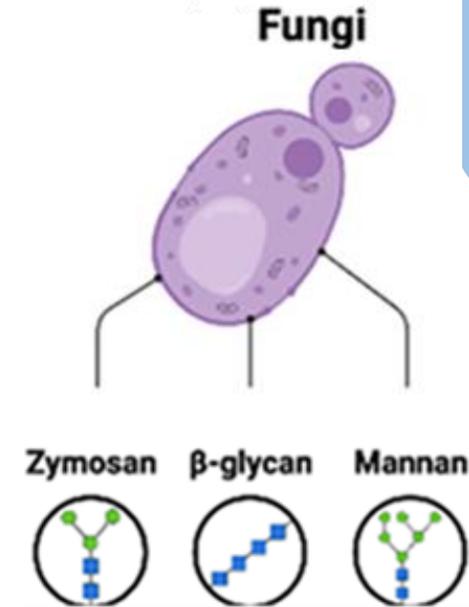
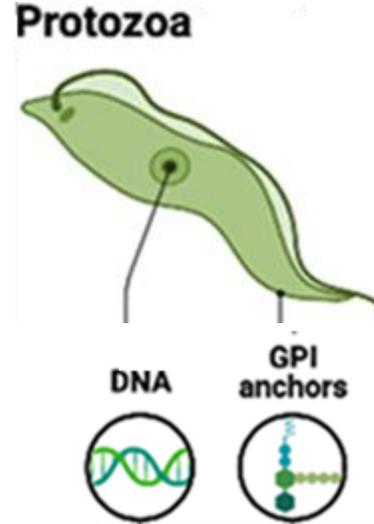
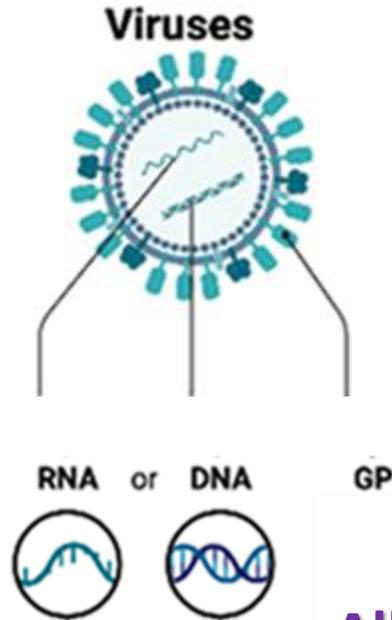
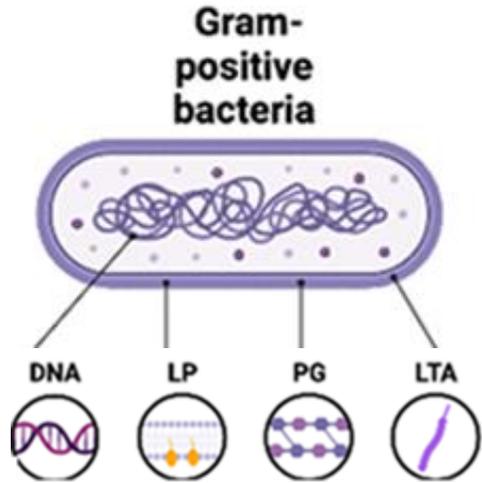


levels of Innate Immunity

Innate immunity has Two levels of defense

Pathogens surface antigens

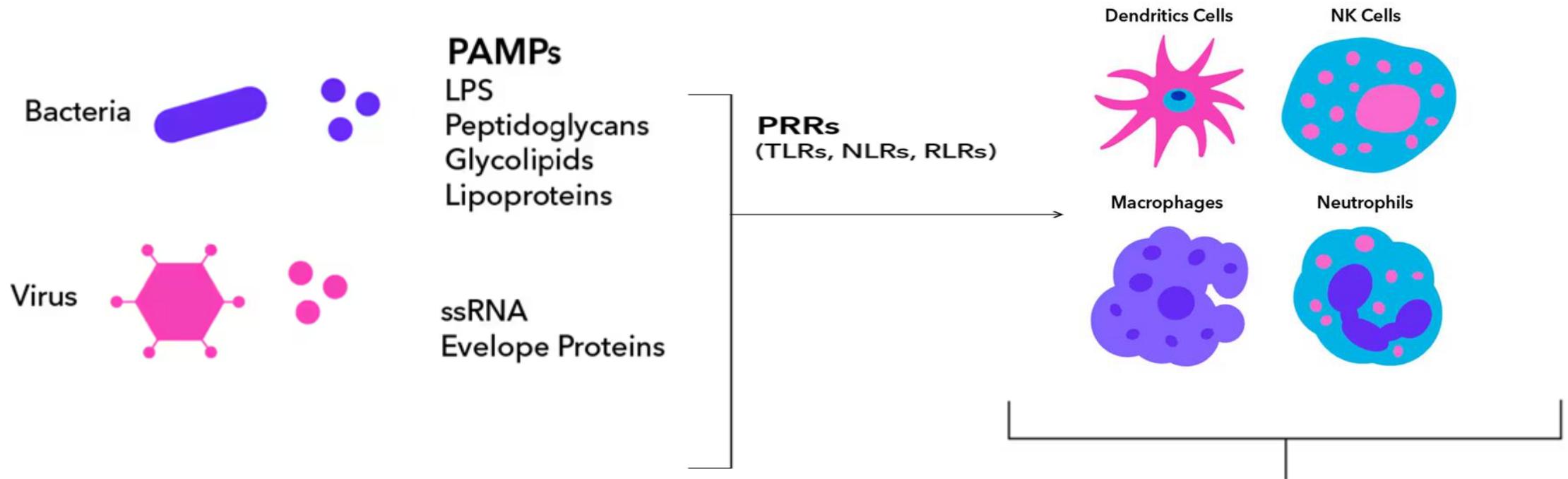
Second line:
Cellular, Soluble, and Molecular Defenses



All are called **Pathogen Associated Molecular Pattern PAMPs**

↓
Recognized by **Pattern Recognition Receptor PRR**

Different Components of pathogens



The innate immune system relies on the recognition of particular types of molecules or parts of them that are **common to many pathogens** but are absent in the host. Overall these molecules are called **pathogen-associated molecular pattern (PAMP)**.

The various classes of pathogen-associated immunostimulants often occur on the pathogen surface in repeating **patterns**

- Inflammatory response, release of cytokines and chemokines
- Adaptive immune cell activation
- Activation of repair mechanisms

levels of Innate Immunity

Innate immunity has **Two** levels of defense

Second line:
Cellular,
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Molecular Defenses

Recognition Mechanisms

- **Pattern Recognition Receptors (PRRs)** play a key role in **detecting** invaders.
- Recognize **Pathogen-Associated Molecular Patterns (PAMPs)**
- Examples:
 - **Toll-Like Receptors (TLRs)**
 - **NOD-like receptors (NLRs):** **N**ucleotide-binding and **O**ligomerization **D**omain
 - RLR (**RIG-I-like** receptor family): **R**etinoic Acid-**I**nducible **G**ene **I**.

**pathogen-associated molecular pattern
(PAMPs)**

Pathogen-associated molecular pattern

PAMPs are of various types:

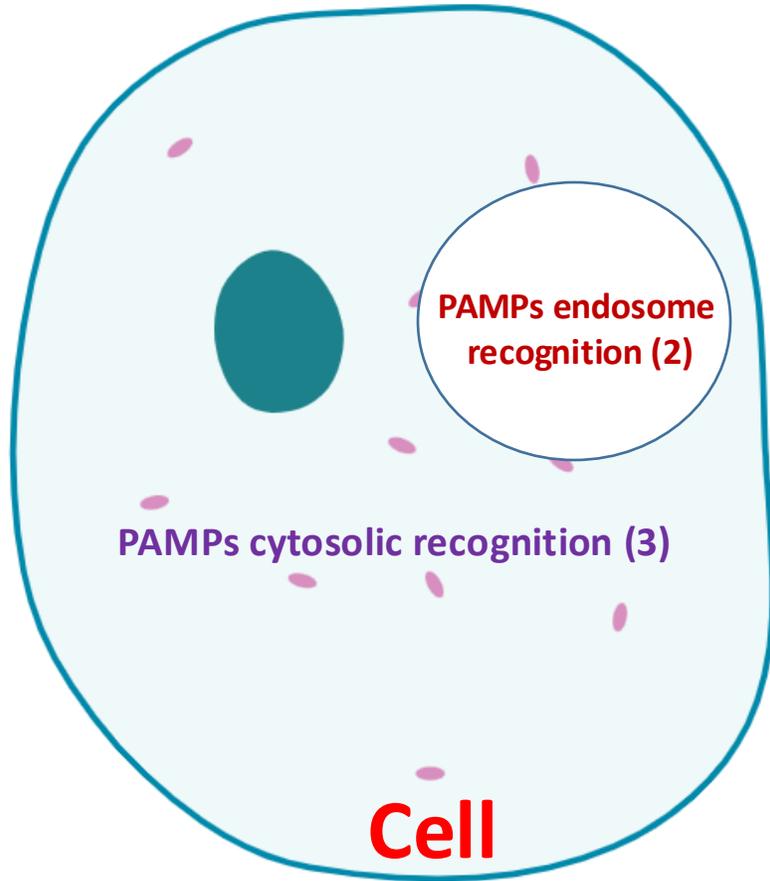
- **Formylmethionine-containing peptides:** Procaryotic translation initiation differs from eucaryotic translation initiation in that formylated methionine. Any peptide containing formylmethionine at the N-terminus must be of bacterial origin.
- **The peptidoglycan cell wall as well as lipopolysaccharide (LPS) on Gram-negative bacteria and teichoic acids on Gram-positive bacteria.**
- **Flagellin**
- **Chitin and other β -glucans (zymosan) which constitute cell walls of fungi**
- **Short DNA sequences in bacterial cells**
- **Ss and Ds RNA of viral origin.**

PRRs: Pattern Recognition Receptors

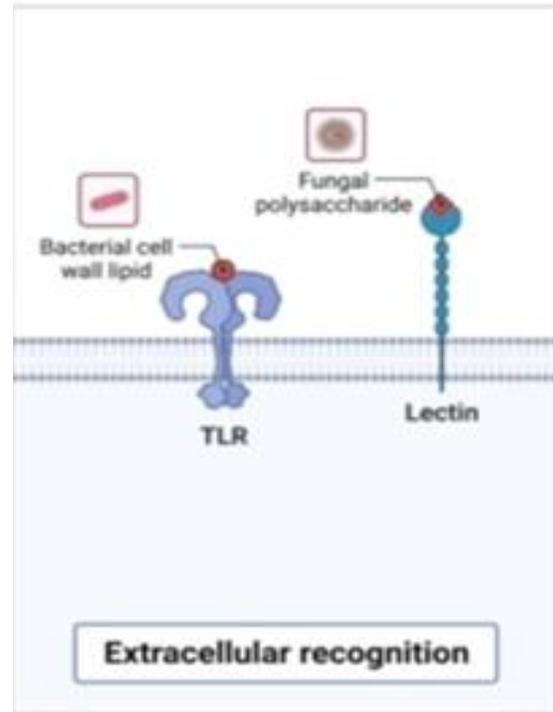
- They are germline encoded, independent of immunologic memory.
- PRRs are expressed constitutively in the host. They are mainly expressed immune cells (dendritic cells, macrophages, neutrophils, and monocytes) and non-immune cells.

Levels of PAMPs Recognition

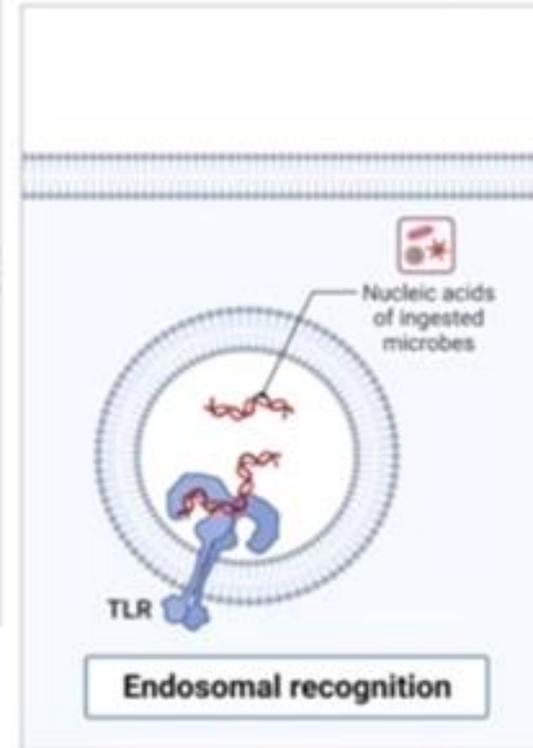
PAMPs Extracellular recognition (1)



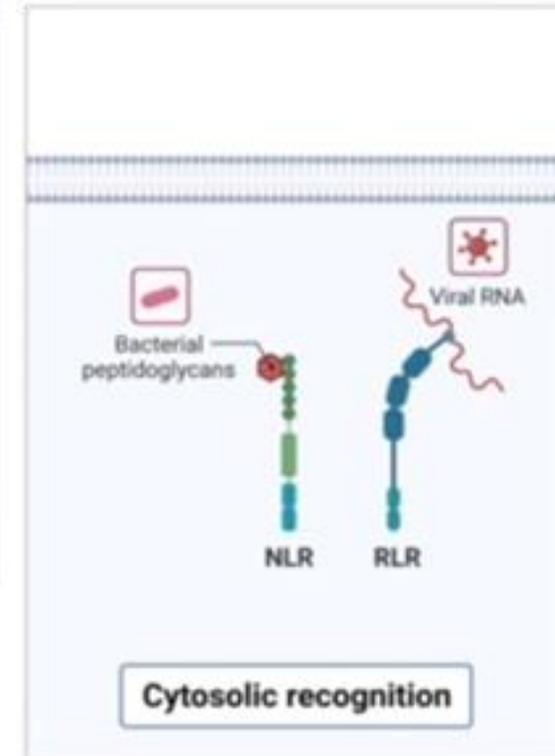
Extracellular (1)



Endosome (2)

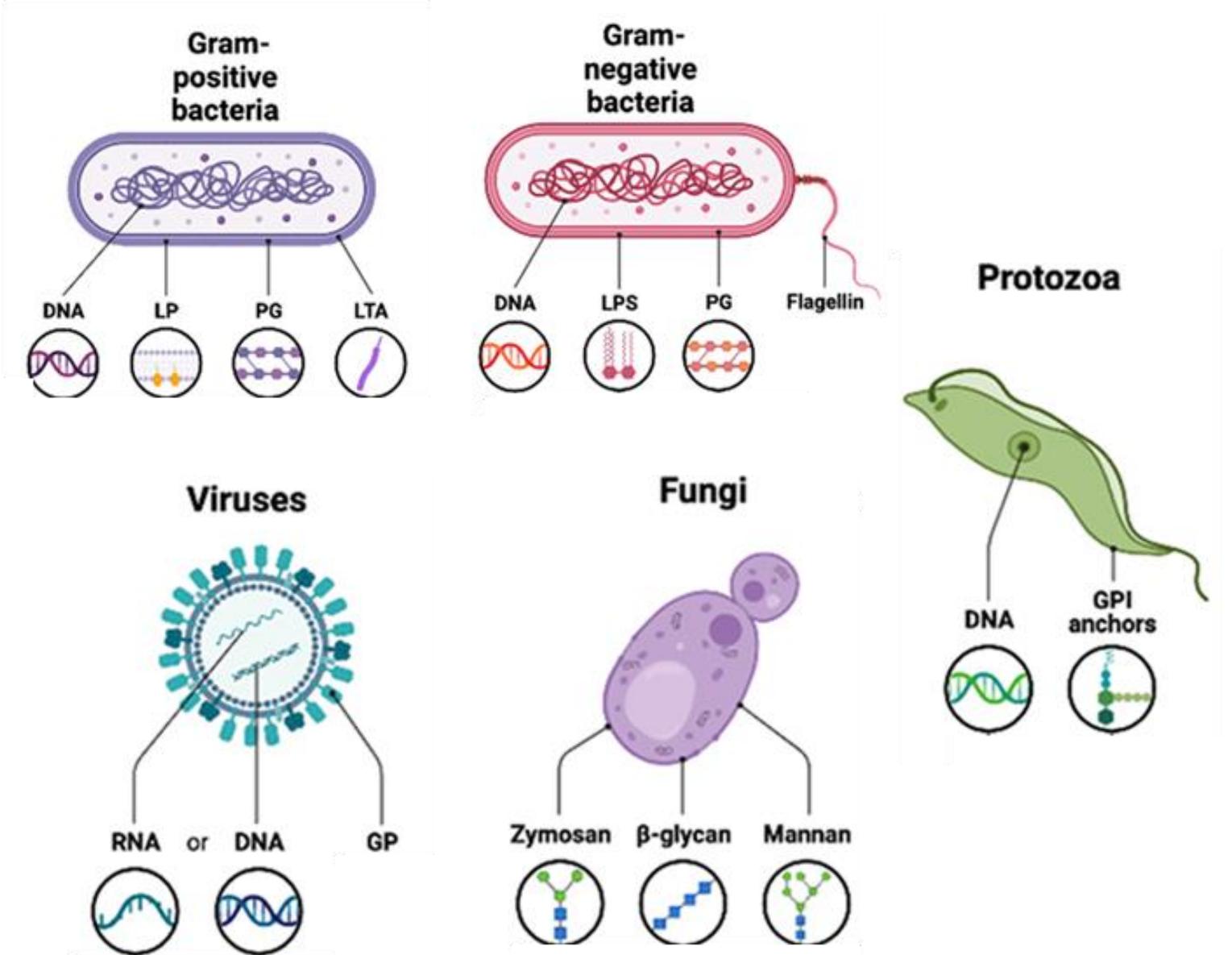
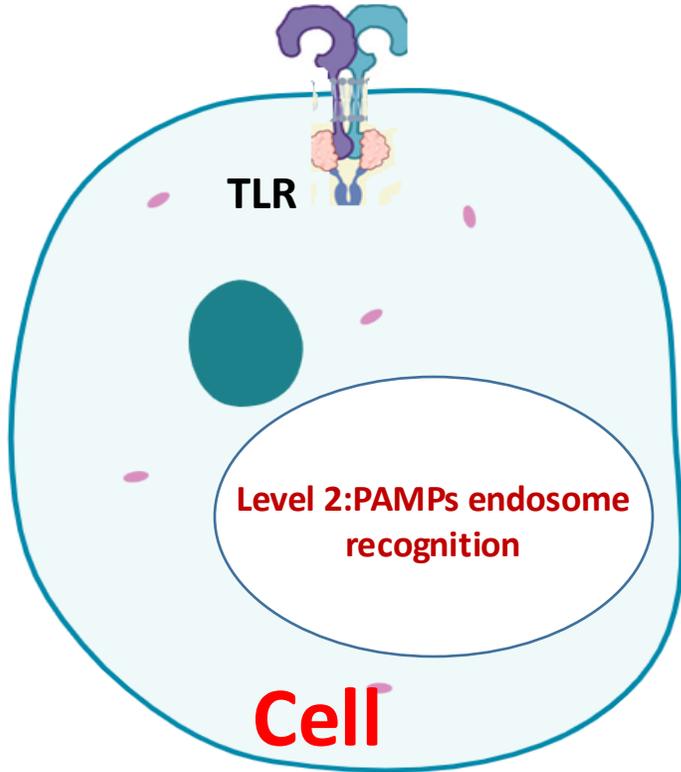


Cytosolic(3)

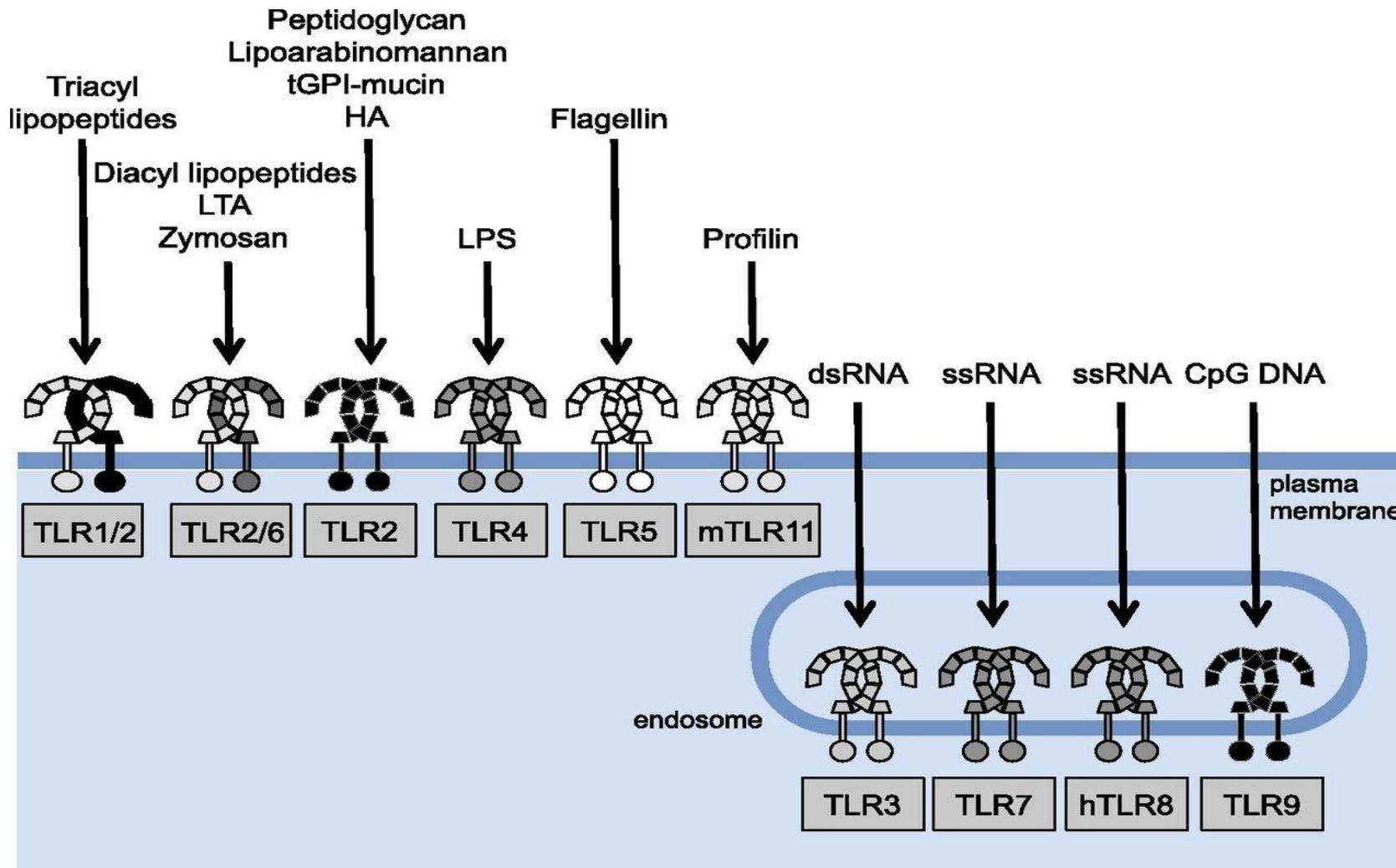


Levels of PAMPs Recognition

Level 1: PAMPs Extracellular recognition



Multiple TLRs are expressed in Humans



How to remember TLRs

- TLR **2** → “**T**wo” → **T**B and other mycobacteria (**T**riacyl lipopeptides)
- TLR **4** → Recognizes **LPS** (lipopolysaccharide)
- TLR **5** → “**F**ive” → **F**lagellin
- TLR **7** → “**S**even” → **s**sRNA
- TLR **9** → “**N**ine” → **N**on-methylated CpG DNA motif (“Nonmethylated”)

You can make a short phrase:

“**Lipo's 1,2,4,6**, **Flag's 5**, **RNA's 3,7,8**, **DNA's 9**”

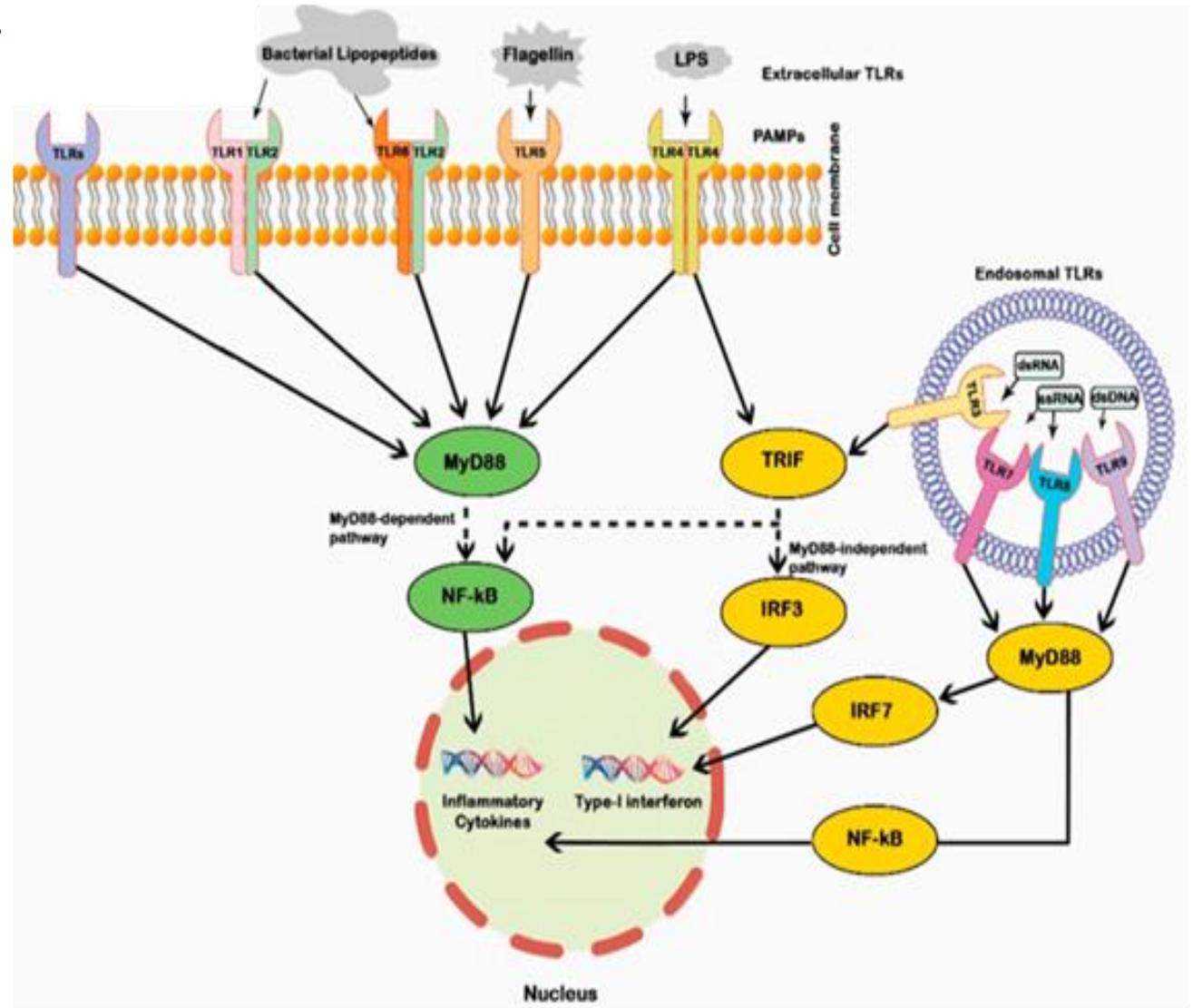
Signaling transduction pathway of TLRs

Recognition of PAMPs by TLRs leads to transcriptional upregulation of distinct genes, depending on the TLRs and cell types involved.

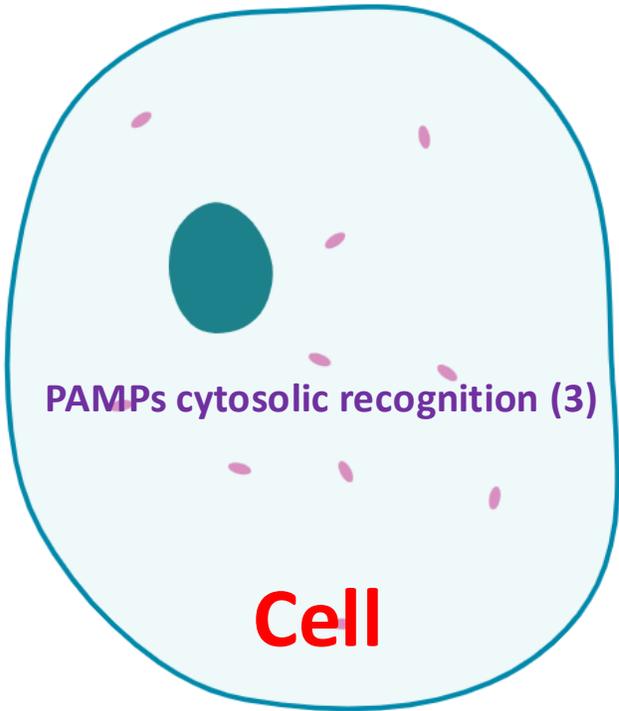
TLR signaling is roughly divided into two distinct pathways depending adaptor molecules.

Adaptor molecules **MyD88** and **TRIF** are responsible for the activation of distinct signaling pathways, culminating in the activation of transcription factors such as:

- A. nuclear factor- κ B (NF κ B): regulate the production of pro-inflammatory cytokines
- B. interferon- regulatory factors (IRFs): regulate the production of type 1 interferon (IFNs).



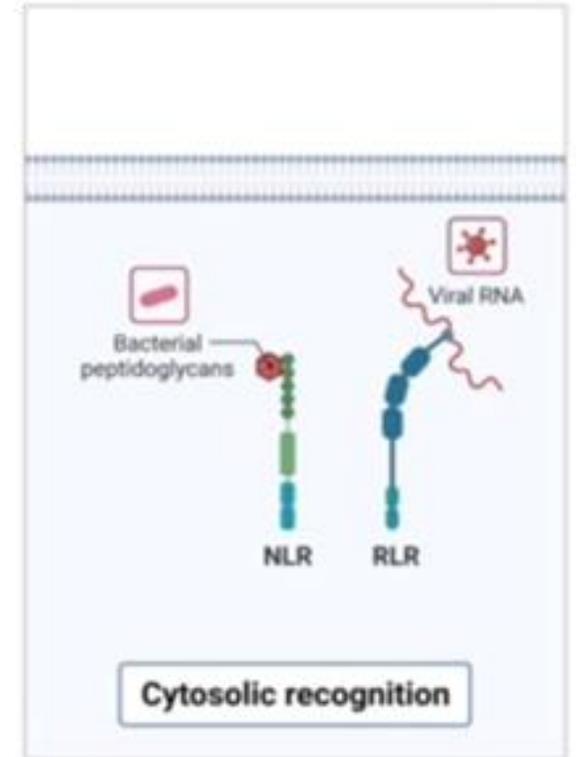
Levels of PAMPs Recognition



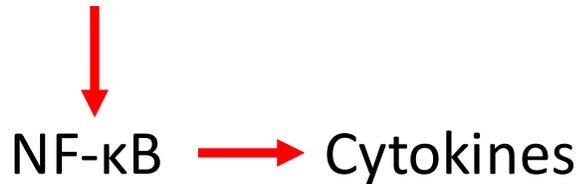
Pathogens that have invaded the cytosol are detected by sensors for cytoplasmic pathogens including:

1. **NOD-like receptors (NLRs).**
2. RLR (**RIG-I-like** receptor family)

Cytosolic(3)



NLR (**NOD-like receptors**) + peptidoglycan



NFκB (Nuclear factor kappa B)

Function:

NF-κB is a central regulator of both innate and adaptive immunity, driving the production of pro-inflammatory mediators like TNF-α, IL-1, IL-6, and IL-8, as well as chemokines and adhesion molecules that attract immune cells to sites of inflammation

Inflammatory Disorders:

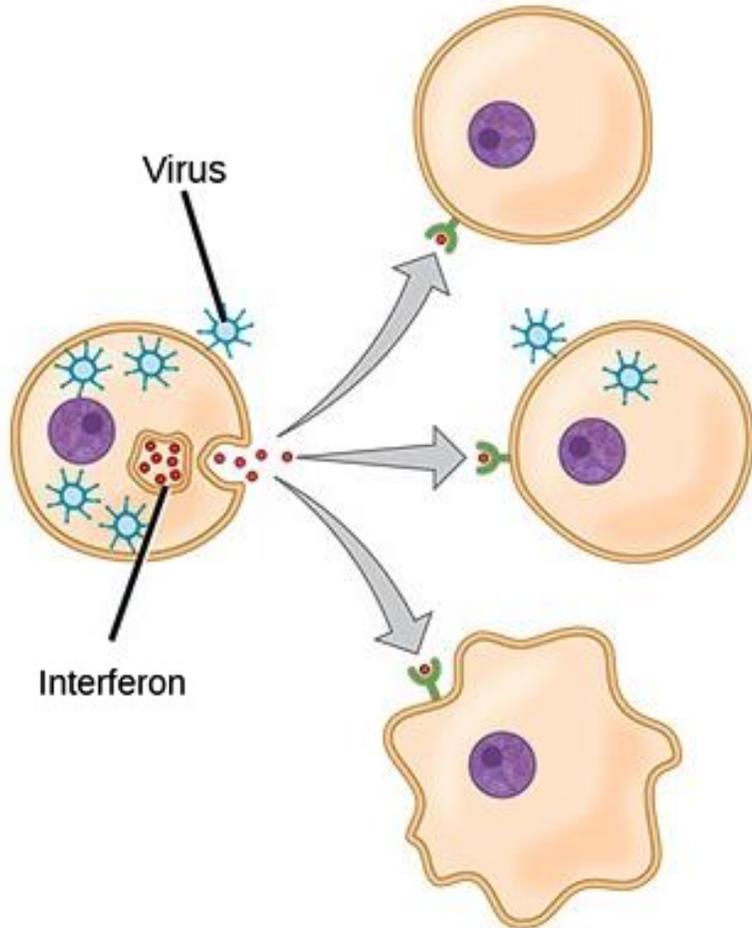
- It is involved in many inflammatory diseases, including asthma, ulcerative colitis, rheumatoid arthritis, and atherosclerosis.

Therapeutic Potential

- Because of its central role in disease, the NF-κB pathway is a significant therapeutic target.
- Inhibitors of NF-κB are being explored for their potential to reduce inflammation and treat various diseases.

IRFs functions

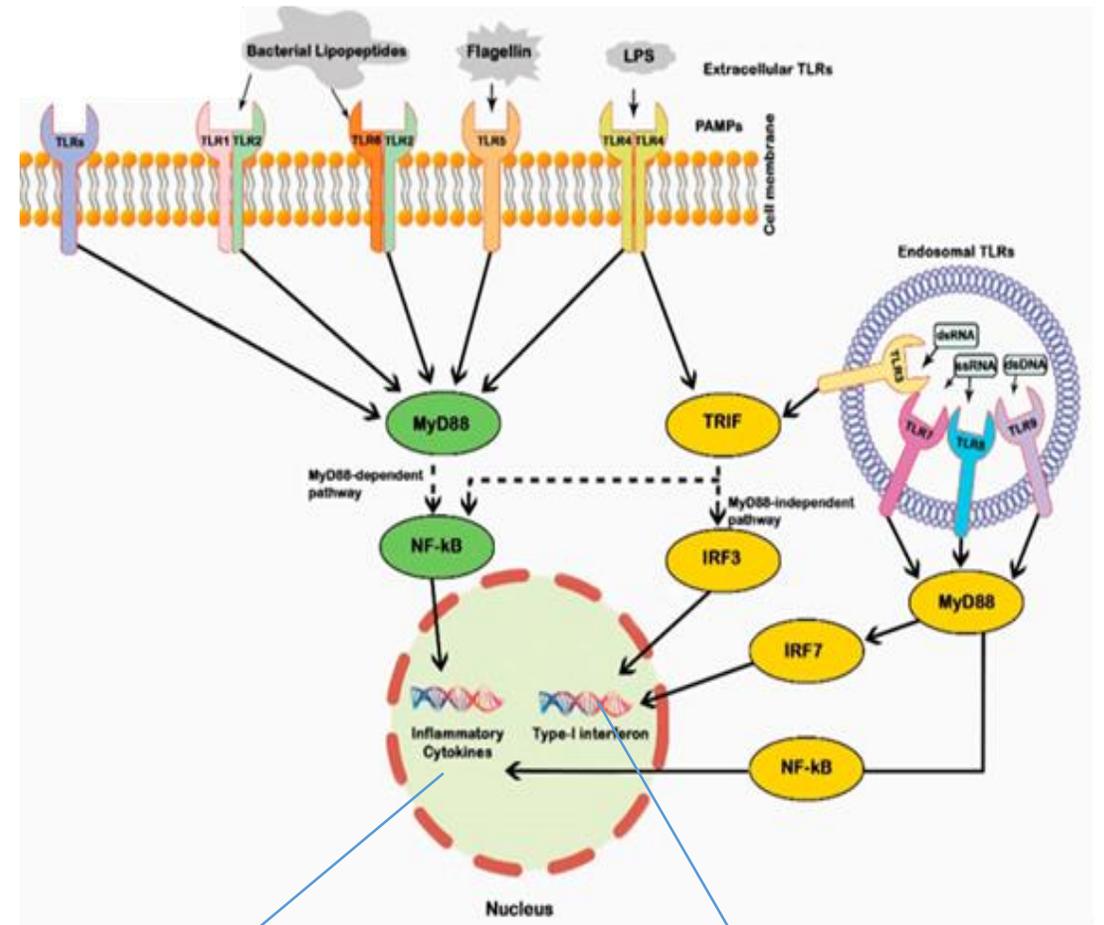
Interferon regulatory factor (IRF) is a transcription factor that is activated in response to PAMPs that leads to the transcription of interferons.



Signals neighboring uninfected cells to destroy RNA and reduce protein synthesis.

Signals neighboring infected cells to undergo apoptosis.

Activates immune cells.



TNF- α
IL-1
IL-6
IL-8

Interferon

Function of cytokines

Functions of each cytokine:

TNF- α :

- A pro-inflammatory cytokine that triggers local and systemic inflammation and plays a role in both local and systemic inflammation.

IL-1 (specifically IL-1 β):

- A pro-inflammatory cytokine.

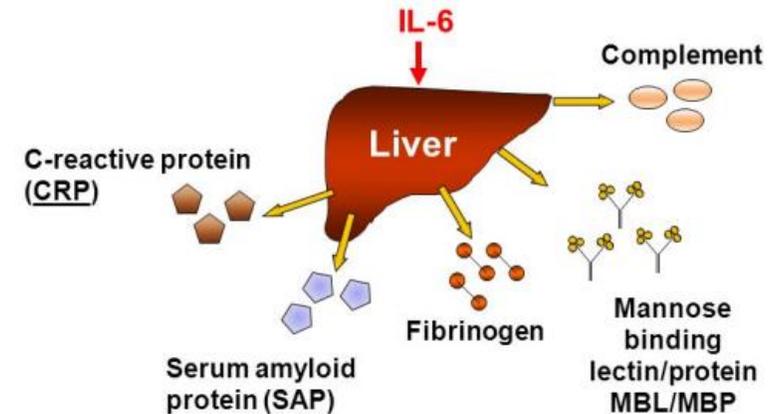
IL-6:

- A pro-inflammatory cytokine with a wide range of functions, often linked to disease severity and prognosis.

IL-8:

- A potent promoter of angiogenesis (new blood vessel formation) and a key chemoattractant for neutrophils, drawing them to sites of infection or injury.

ACUTE PHASE REACTION



Innate (Nonspecific) immunity

First line of defense

A) Physical/Mechanical	B) Chemical	C) Biological
<ul style="list-style-type: none">• Skin• Epithelial layers• Mucous membranes• Lacrimal apparatus• Saliva• Earwax• Hair• Coughing & sneezing• Vomiting & diarrhea• Urination• Vaginal secretions	<ul style="list-style-type: none">• Sebum• Lysozyme• Gastric Juice• Vaginal Fluid• Transferrins• Mother's milk	<ul style="list-style-type: none">• Microbiota

Innate (Nonspecific) immunity

Second line of defense

A) Defensive cells	B) Inflammation	C) Fever	D) Antimicrobial substances
<ul style="list-style-type: none">• Phagocytes• Natural killers• Neutrophils• Recognition receptors	<ul style="list-style-type: none">• Acute/Chronic response• Released chemicals	<ul style="list-style-type: none">• Temperature• Metabolism	<ul style="list-style-type: none">• Complement system• Interferons• Iron-binding proteins• Antimicrobial peptides