Pattern-Recognition Receptors (PRRs)

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What are PRRs?

- Are receptors capable of binding specifically to conserved portions of Pathogen associated molecular pattern molecules.

❑ cellular receptors, present in different locations in cells, and soluble molecules in the blood and mucosal secretions to recognize PAMPs and DAMPs

- Cells that typically have pattern recognition receptors include macrophages, dendritic cells, endothelial cells, mucosal epithelial cells, and lymphocytes

- Many pattern-recognition receptors are located **on the surface** of these cells where they can interact with PAMPs on the surface of microbes.

- Others **PRRs** are found with in the phagolysosomes of phagocytes where they can interact with PAMPs located within microbes that have been phagocytosed.

Some PRRs are found **in the cytosol** of the cell.

Cellular locations of pattern recognition molecules of the innate immune system

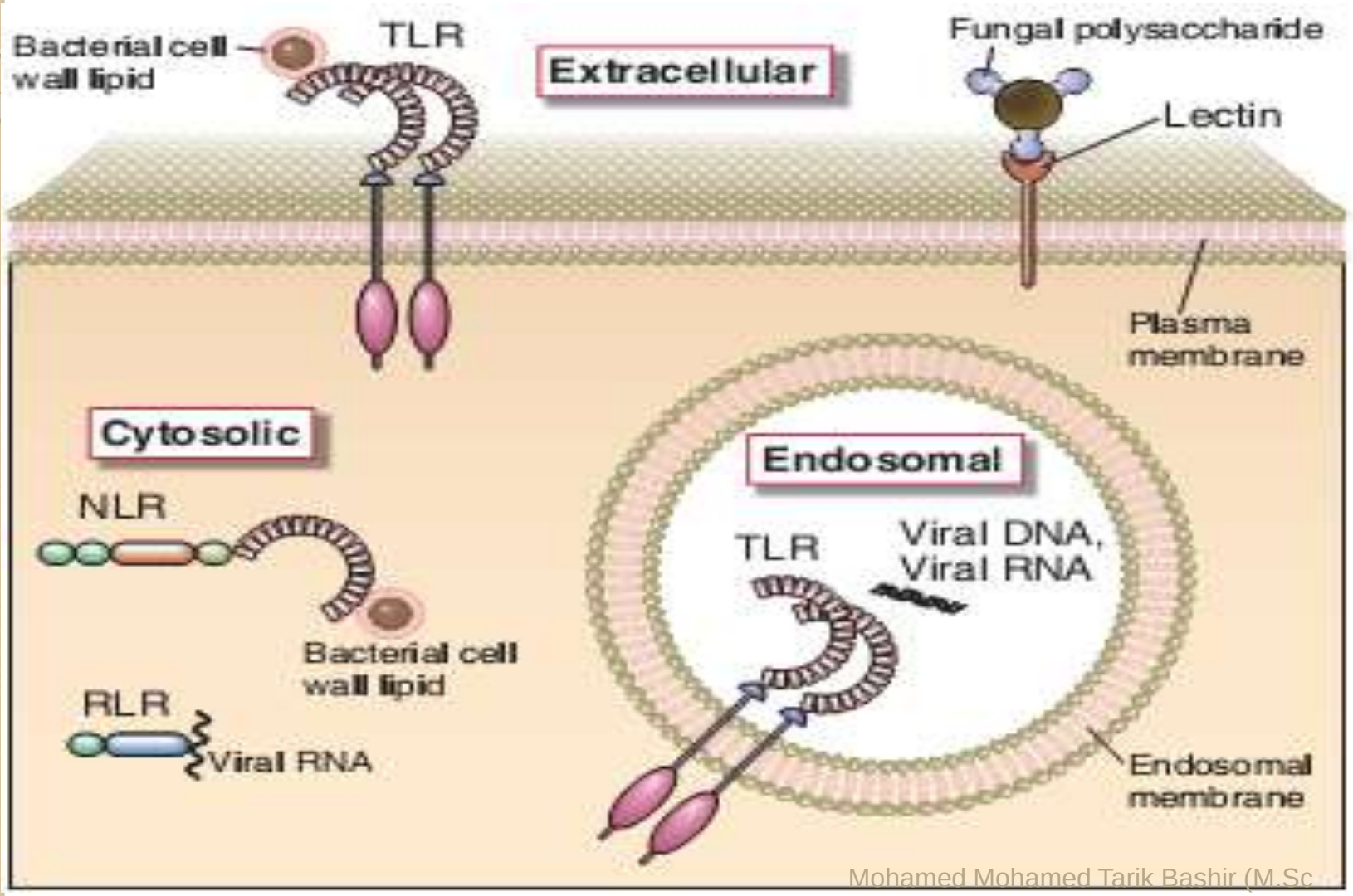
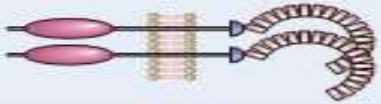
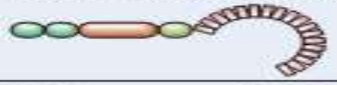


TABLE 4–3 Pattern Recognition Molecules of the Innate Immune System

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 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	*N*-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

Pathogen Associated Molecular Pattern (PAMP)

- Are molecular structures that are characteristic of microbial pathogens but mammalian cells.

- damage-associated molecular patterns (DAMPs) are endogenous molecules that are produced by or released from damaged and dying cells.

- DAMPs are generally not released from cells dying by apoptosis.

TABLE 4–2 Examples of PAMPs and DAMPs

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	

CpG, cytidine-guanine dinucleotide; dsRNA, double-stranded RNA; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; LPS, lipopolysaccharide; ssRNA, single-stranded RNA.

There are two functionally different major classes of pattern-recognition receptors

- **Endocytic pattern-recognition:** receptors found on the surface of phagocytes and promote the attachment of microorganisms to phagocytes leading to their subsequent engulfment and destruction.
- **Signaling Pattern-Recognition receptors**: Binding of microbial PAMPs to their PRRs promotes the synthesis and secretion of intracellular regulatory molecules such as cytokines that are crucial to initiating innate immunity and adaptive immunity.

Endocytic Pattern-Recognition Receptors

1. **mannose receptors:**

- bind mannose-rich glycans, short carbohydrate chains with the sugar mannose or fructose as the terminal sugar, commonly found in microbial glycoproteins and glycolipids.

- Human glycoproteins and glycolipids typically have terminal N-acetylglucosamine and sialic acid groups. C-type lectins found on the surface of phagocytes are mannose receptors.

2. Scavenger receptors

- Found on the surface of phagocytic cells bind to bacterial cell wall components such as LPS,peptidoglyan and teichoic acids.
- There are also scavenger receptors for certain components of other types of microorganisms, as well as for stressed, infected, or injured cells . Scavenger receptors include CD-36, CD-68, and SRB-1.

3. opsonin receptors

- Are soluble molecules produced as a part of the body's immune defenses that bind microbes to phagocytes. One portion of the opsonin binds to a PAMP on the microbial surface and another portion binds to a specific receptor on the phagocytic cell.
- Acute phase proteins circulating in the plasma, Complement pathway proteins, Surfactant proteins in the alveoli of the lungs, such as SP-A and SP-D and During adaptive immunity, the antibody molecule IgG can function as an opsonin.

4. *N*-formyl Met receptors

- *N*-formyl methionine is the first amino acid produced in bacterial proteins since the f-met-tRNA in bacteria has an anticodon complementary to the AUG start codon .
- This form of the amino acid is not typically seen in mammalian proteins. FPR and FPRL1 are *N*-formyl receptors on neutrophils and macrophages.
- Binding of *N*-formyl Met to its receptor promotes the motility and the chemotaxis of these phagocytes. It also promotes phagocytosis

2. Signaling Pattern-Recognition Receptors

- bind a number of microbial molecules: LPS, peptidoglycan, teichoic acids, flagellin, pilin, unmethylated cytosine-guanine dinucleotide or CpG sequences from bacterial and viral genomes; lipoteichoic acid, glycolipids, and zymosan from fungi; double-stranded viral RNA, and certain single-stranded viral RNAs.
- Binding of microbial PAMPs to their PRRs stimulate the transcription and translation of inflammatory cytokines.

1. signaling PRRs found on cell surfaces

- A series of signaling pattern-recognition receptors known as toll-like receptors (TLRs) are found on the surface of a variety of defense cells and other cells. Such as

a. TLR-2 - recognizes peptidoglycan, bacterial lipoproteins, lipoteichoic acid (LTA), and porins.

b. TLR-4 - recognizes lipopolysaccharide (LPS) from gram-negative cell wall, fungal mannans, viral envelope proteins, parasitic phospholipids, heat-shock proteins.

c. TLR-5 - recognizes bacterial flagellin

d. TLR-1/TLR-2 pairs - bind uniquely bacterial lipopeptides and glycosylphosphatidylinositol (GPI)-anchored proteins in parasites.

e. TLR-2/TL6 pairs - bind lipoteichoic acid (LTA) from gram-positive cell walls, bacterial lipopeptides, and peptidoglycan.

- **CD14** is found on monocytes, macrophages, and neutrophils and promotes the ability of TLR-4 to respond to LPS. (TiAg)

2. Signaling PRRs found in the membranes of the endosomes phagolysosomes used to degrade pathogens

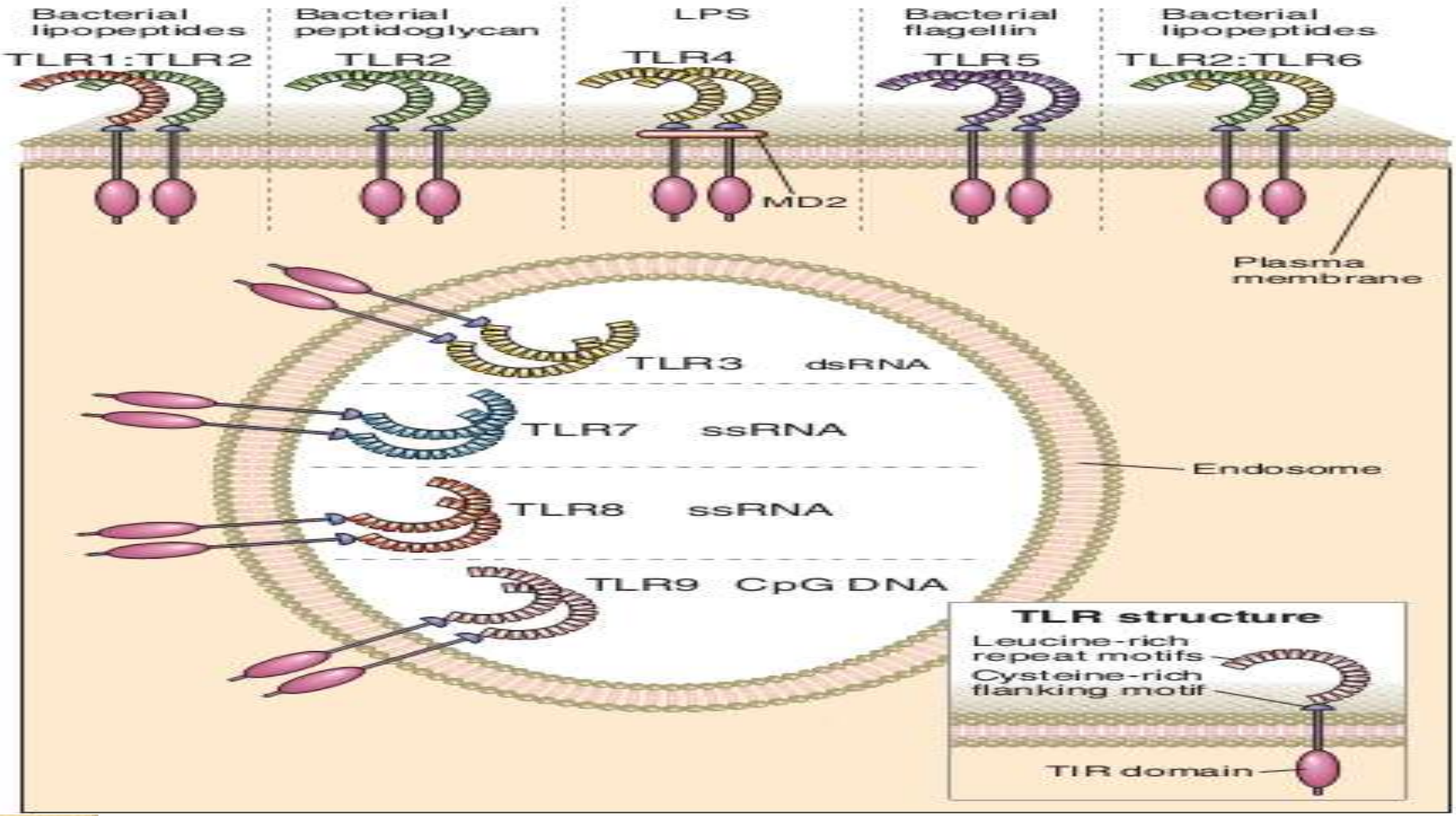
a. TLR-3 - binds double-stranded viral RNA.

b. TLR-7 - binds single-stranded viral RNA, such as in HIV, rich in guanine/uracil nucleotide pairs.

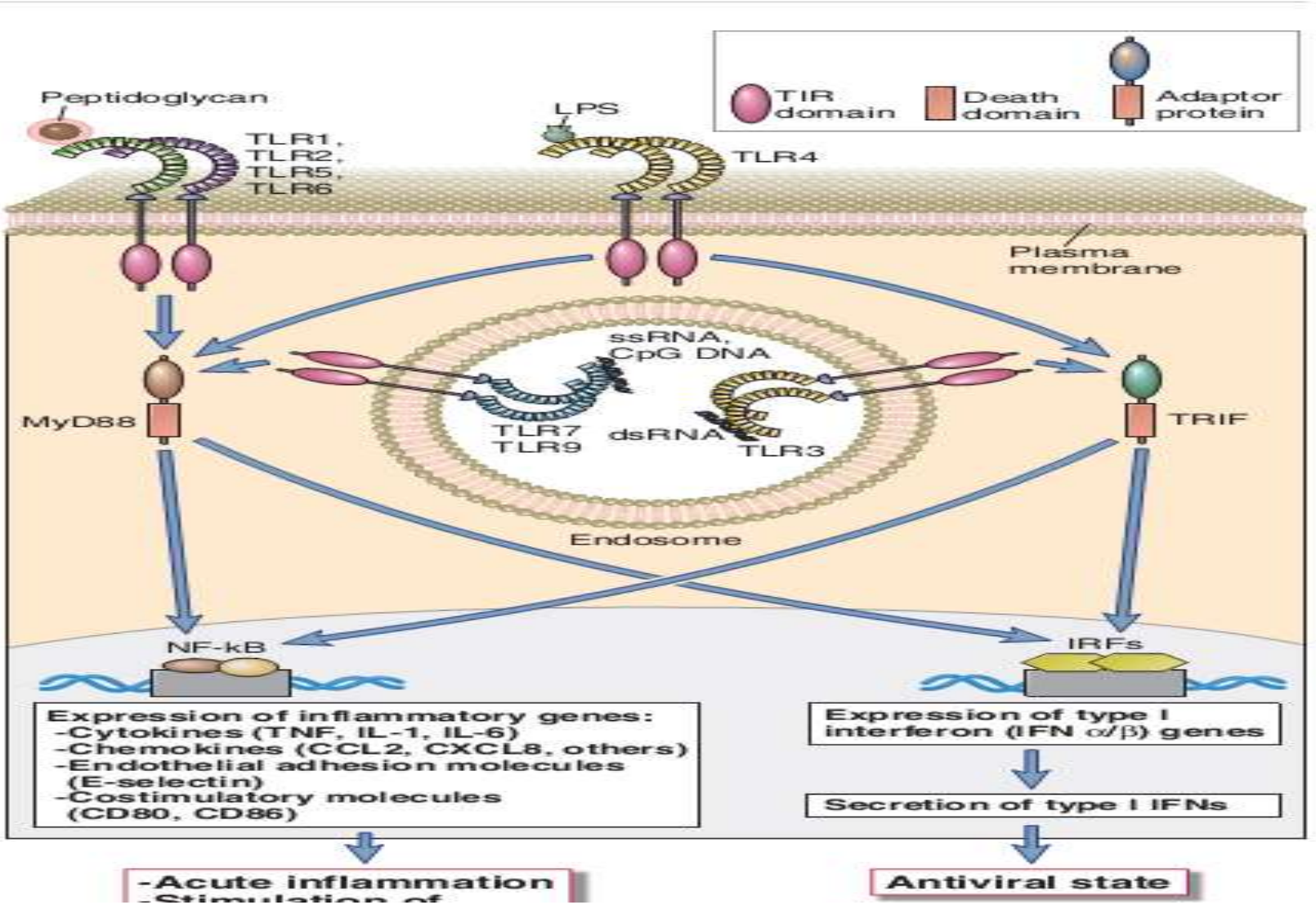
c. TLR-8 - binds single-stranded viral RNA.

d. TLR-9 - binds unmethylated cytosine-guanine dinucleotide sequences (CpG DNA) found in bacterial and viral genomes but uncommom or masked in human DNA and RNA.

Structure , location and specificities of TLRs



Signaling function of TLRs



3. Signaling PRRs found in the cytoplasm

a. **NODs** (nucleotide-binding oligomerization domain):

1. **NOD-1** recognizes peptidoglycan containing the **muramyl dipeptide** NAG-NAM-gamma-D-glutamyl-meso diaminopimelic acid, part of the peptidoglycan monomer in common gram-negative bacteria and just a few gram-positive bacteria.
2. **NOD-2** recognizes peptidoglycan containing the **muramyl dipeptide** NAG-NAM-L-alanyl-isoglutamine found in practically all bacteria.

b. CARD-containing proteins

- **CARD** (caspase activating and recruitment domain)-containing proteins, such as **RIG-1** (retinoic acid-inducible gene-1) and **MDA-5** (melanoma differentiation-associated gene-5), are cytoplasmic sensors that **both viral double-stranded and single-stranded RNA molecules** produced in viral-infected cells and trigger the synthesis of interferon cytokines

4. Secreted signaling PRRs found in plasma and tissue fluid:

- These PRRs bind to microbial cell walls and enable them to activate the complement pathways, as well as by phagocytes such as mannan-binding lectin.

- Can bind to the carbohydrates on bacteria, yeast, some viruses, and some parasites This, in turn, activates the lectin complement pathway