Toll-Like Receptors (TLR)

Toll-Like Receptor Signaling

- Toll receptor initially discovered in *Drosophila* as important receptor in dorso-ventral embryonic pattern
  - Toll in German means ‘great’, apparently this was one of the words describing the scientists’ enthusiasm after observing the mutant flies
- Hoffman and colleagues showed that Toll-mutant flies susceptible to fungal infections
- Mammalian homologues discovered and designated as Toll-Like Receptors (TLR)
- TLRs recognize specific patterns in pathogens which are not observed in mammals

INTRODUCTION

- Toll receptors in insects, mammals and plants are key players that sense the invasion of pathogens. Toll-like receptors (TLRs) in mammals have been established to detect specific components of bacterial and fungal pathogens.

- TLR is a part of innate immune system and it facilitates recognition of pathogens by the help of pathogen recognition regions (PRR). It is present on sentinel cells like macrophages and dendritic cells and on few non immune cells like Human Choroidal Melanocytes.

- TLR recognizes certain Pathogen-Associated Molecular Patterns (PAMP) present on the microorganisms and when the ligands bind to the receptors to activate certain cytokines.

STRUCTURE AND FUNCTION OF TLR

- The TLR family now consists of 10 members (TLR1-TLR10). The cytoplasmic portion of Toll-like receptors shows high similarity to that of the IL-1 receptor family, and is now called the Toll/IL-1 receptor (TIR) domain.

Toll-Like Receptors

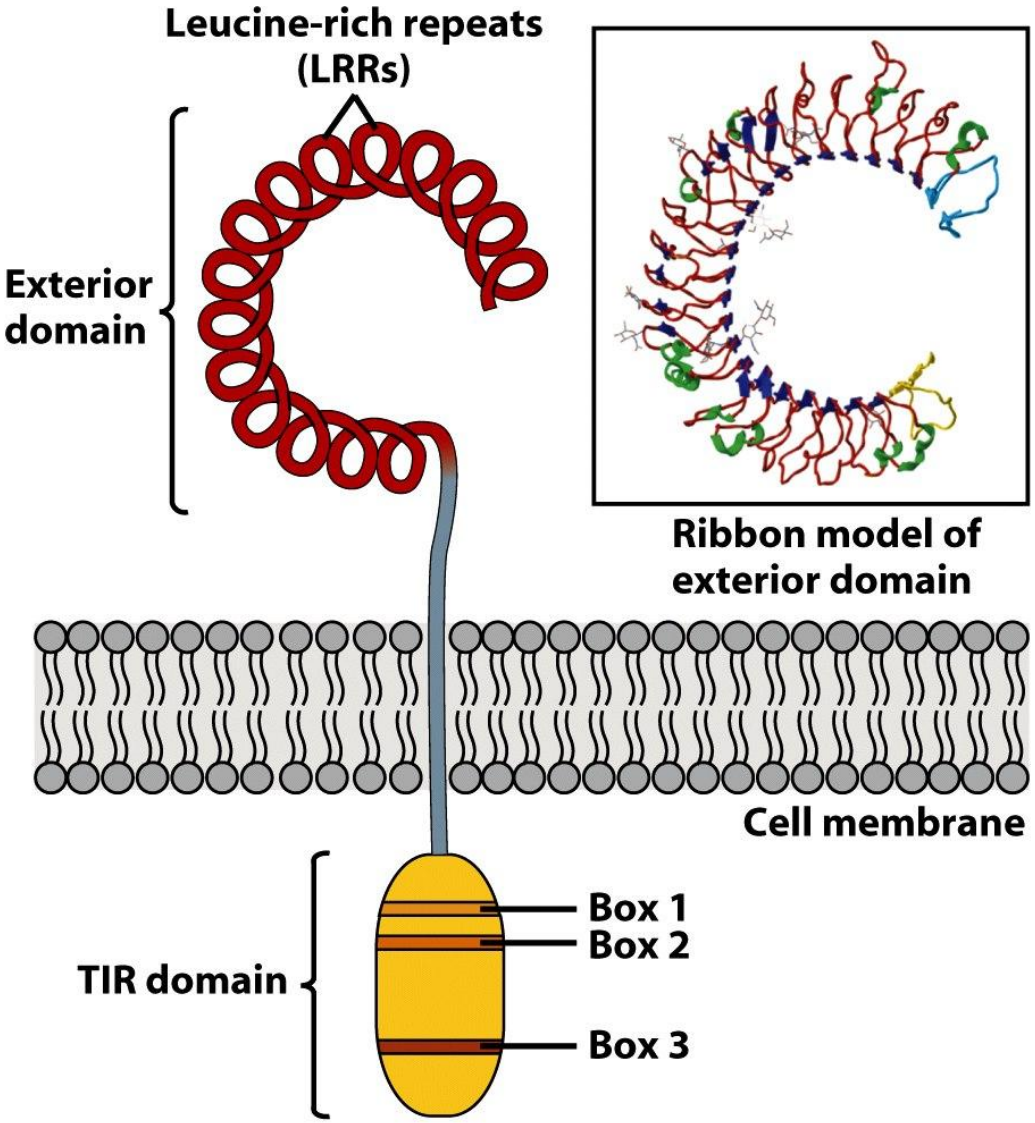

Figure 3-10
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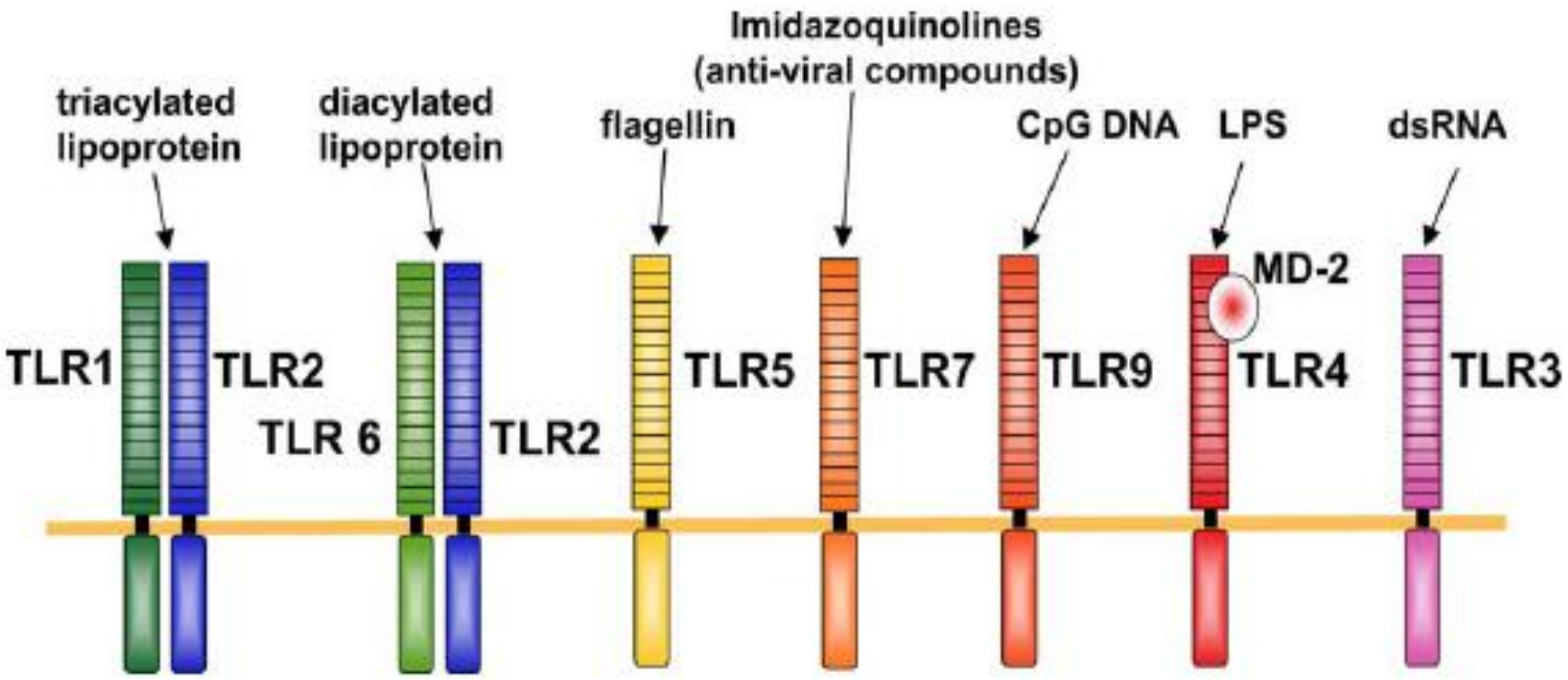
Toll-Like Receptors



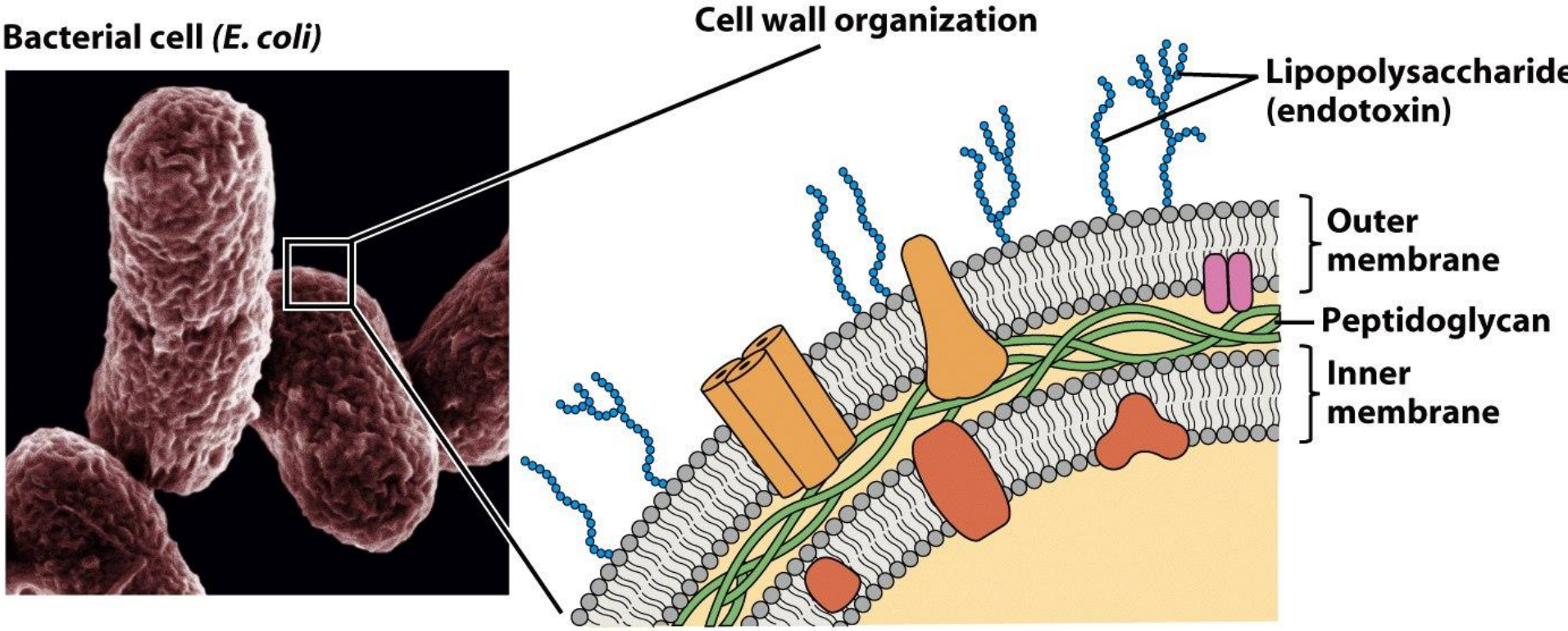


Figure 3-9
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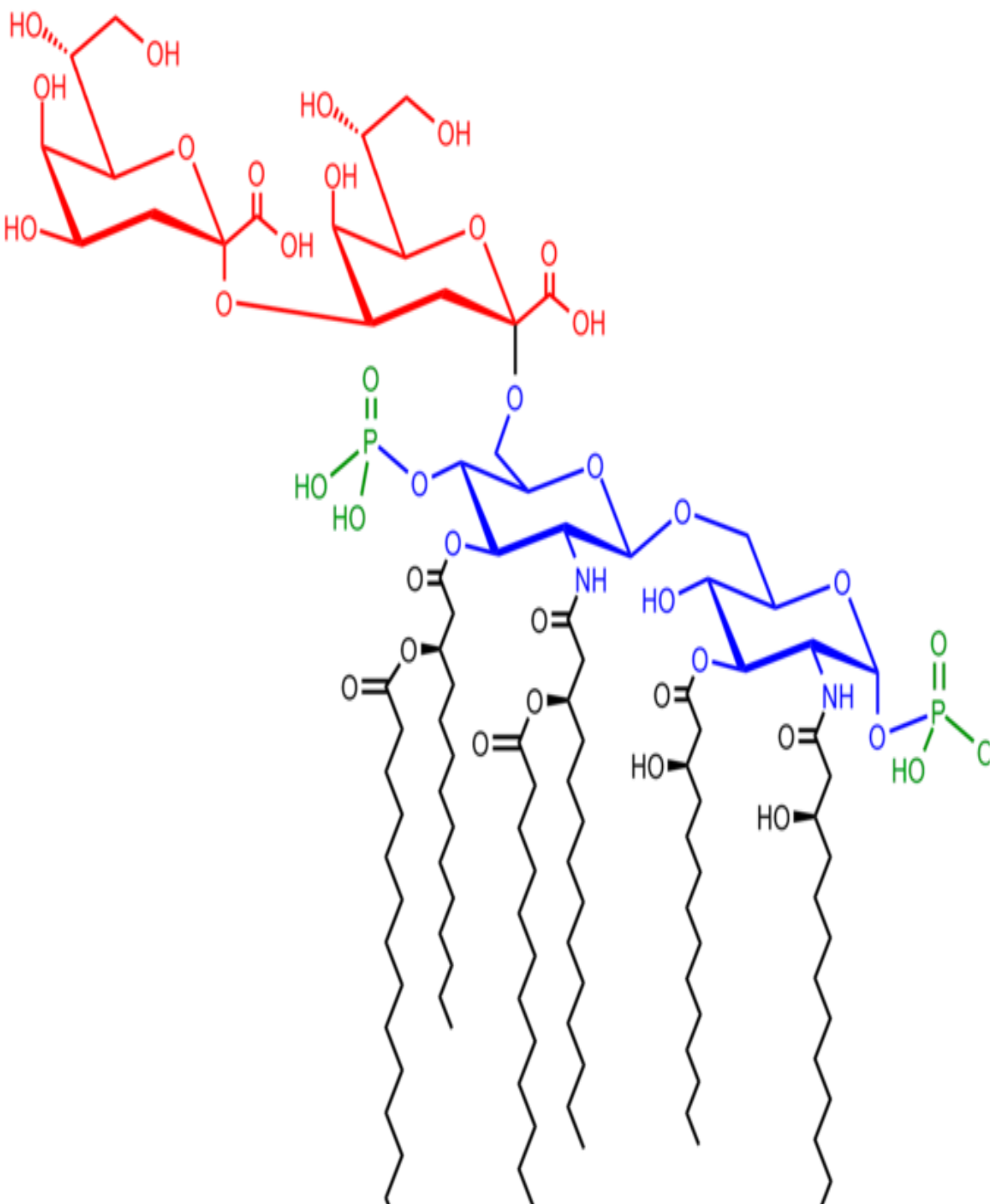

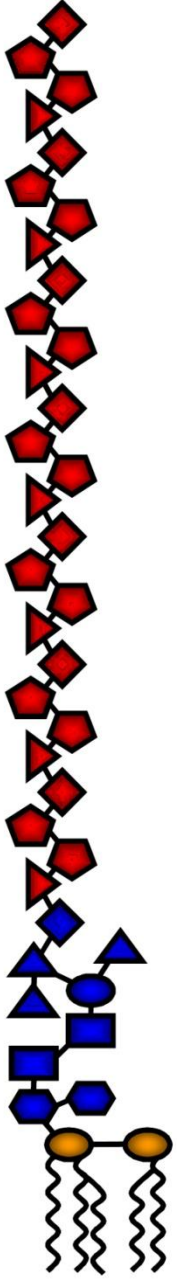

O antigen

Core

Lipid A

TLR LIGANDS

- Various ligands can bind to TLR and activate the signaling pathway. These ligands are parts of pathogenic microbes.
- They are a part of superfamily with 10 types of TLR to which different ligands bind to.
- The ligands that bind can be LPS, peptidoglycan, LTA, flagellin, dsRNA, CpG DNA.

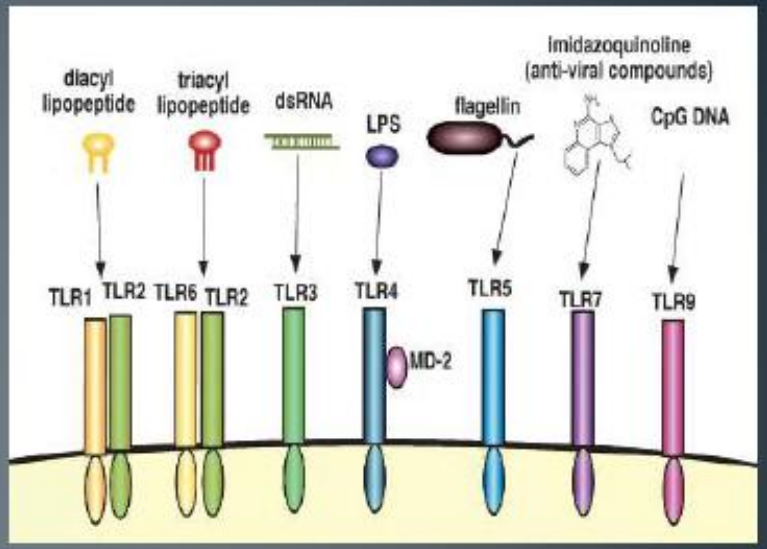

FIGURE 3: LIGAND BINDING TO TLR
Takeda, Kiyoshi & Akira, Shizuo. (2003). Toll receptors and pathogen resistance. Cellular microbiology. 5. 143-53. 10.1046/j.1462-5822.2003.00264.x.

LipoPolySaccharides (LPS)

- Large molecules found in outer membrane of Gram-negative bacteria
- Comprised of a lipid and saccharide component
- Highly immunogenic
- Recognized by TLR4
- Can cause septic shock and lead to death
- Often referred to as Endotoxin since it is not secreted but is a byproduct of bacterial lysis
- Great variability among different bacterial strains

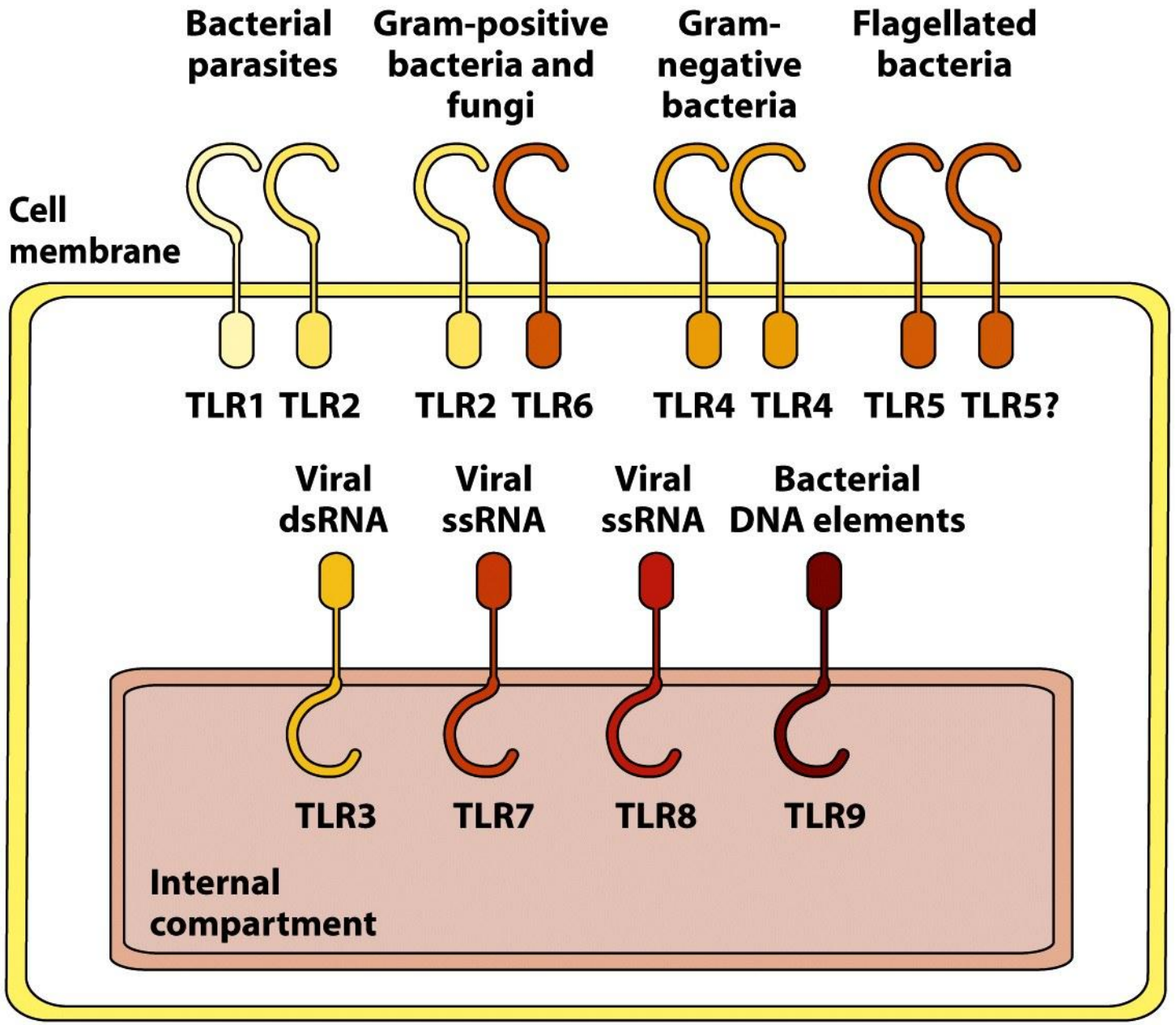

Figure 3-11 part 1
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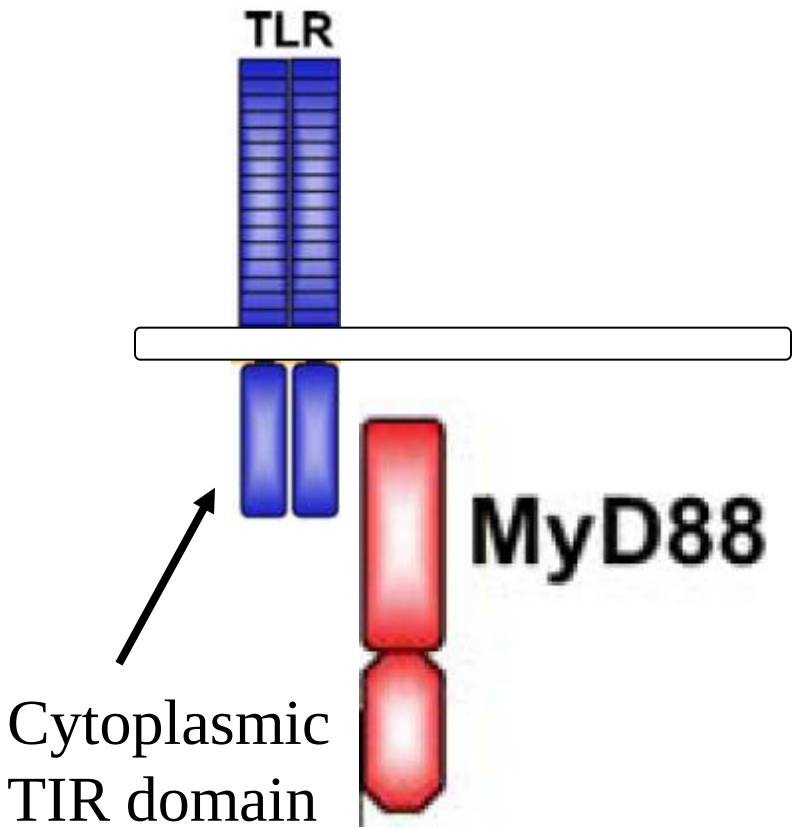
Viral Nucleic Acids

- TLR3, TLR7 and TLR8 detect viral nucleic acids
- Found in intracellular membranes since viral nucleic acids are endogenously generated
- Note the TIR domains of these TLRs face the cytosol of the cell
- Poly I:C is an agonist for TLR3 that mimics binding of dsRNA to TLR3

TLRs and TIR Domain

- Cytoplasmic tails of TLRs show similarities to IL-1 receptor (TIR)
- Common adaptor to TLRs is MyD88
- Crucial proline residue in all TLR TIR domains, except TLR3
- All TLRs likely have a MyD88 pathway (TLR3 is an exception)



TLR TYPES

- TLR 1,2,6 recognizes lipoteichoic acid from Gram positive organisms and lipoarabinomannan from Mycobacterium .
- TLR 2 in specific recognizes Lipopolysaccharides and it cooperates with TLR 1 and 6.

- Macrophages from TLR 6 deficient mice did not produce CD36 on its surface. Similarly they reacted with Triacyl lipopeptide
- TLR 1 deficient mice reacted with diacyl but not triacyl lipopeptide. Thus TLR 1 and 6 associate with TLR 2 to discriminate diacyl and triacyl lipopeptide.

TLR 3:

- It recognizes dsDNA produced during viral replication. Type 1 interferon is produced.

TLR 4:

- It is the LPS receptor and transduces its signals.
- LPS-LBP complex is formed and this is associated with CD14 on macrophages.
- MD2, a secreted protein reacts with extracellular region of TLR 4.

TLR 5:

- Flagellin in flagellated bacteria acts as a ligand to activate TLR 5.

TLR 7:

- It is used in the treatment of infectious diseases as its used as an antiviral Imidazoquinolones that is against HPV.

TLR 9:

- It helps in the recognition of CpG DNA . CpG DNA recognizes endosomes after non-specific uptake into cells.

- It is **NOT A CELL-SURFACE RECEPTOR** unlike others which indicates a different mechanism.

TLR 10:

- It has an anti-inflammatory reactions unlike other TLR. It is very helpful in suppressing cytokines.
- TLR 10 mechanism was found to suppress NF-κB and MAP kinase signalling.
- It is found in spleen, lymph nodes, B cell surface but not on T cell surface.

TLR 11:

- It is present on monocytes, macrophages and dendritic cells.
- When an infection of *Toxoplasma gondii* occurs profilin from it acts as a ligand for TLR 11 to activate Dendritic cells to induce T cell production.

TLR ACTIVITIES

TLR protects against variety of diseases like

- TLR3- herpes simplex encephalitis
- TLR2- leprosy, Lyme disease, Tuberculosis, Colorectal cancer
- TLR5- Legionnaire's disease, resistance to SLE
- TLR7- Antitumor and antiviral properties

FUTURE TLR PROSPECTS

- TLR agonists as Vaccine adjuvants
- TLR used in antiviral therapy
- Used to treat neurotoxic infection.
- Used to treat atherosclerosis,
- To treat Parkinson's and alzheimer's disease
- To treat multiple sclerosis and many more neurodegenrative diseases

Thank you