


TOLL LIKE RECEPTORS



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- INTRODUCTION:

- Innate immunity is an evolutionarily ancient system that provides multicellular organisms with immediately available defense mechanisms against a wide variety of pathogens without requiring prior exposure.
- Hallmarks of innate immune responses include the ability to (i) **recognize** structures that are present in large groups of microorganisms and are distinct from self, (ii) **activate** effector mechanisms that will destroy **within hours** most microorganisms encountered in life, and (iii) activate and orientate **an adaptive immune response** that, through clonal expansion of lymphocytes, will be aimed specifically at persistent microorganisms .

DEFINITION

- Toll-like receptors (TLRs) are a class of proteins that play a key role in the innate immune system.
- They are single, membrane-spanning, non-catalytic receptors usually expressed in sentinel cells such as macrophages and dendritic cells, that recognize structurally conserved molecules derived from microbes.

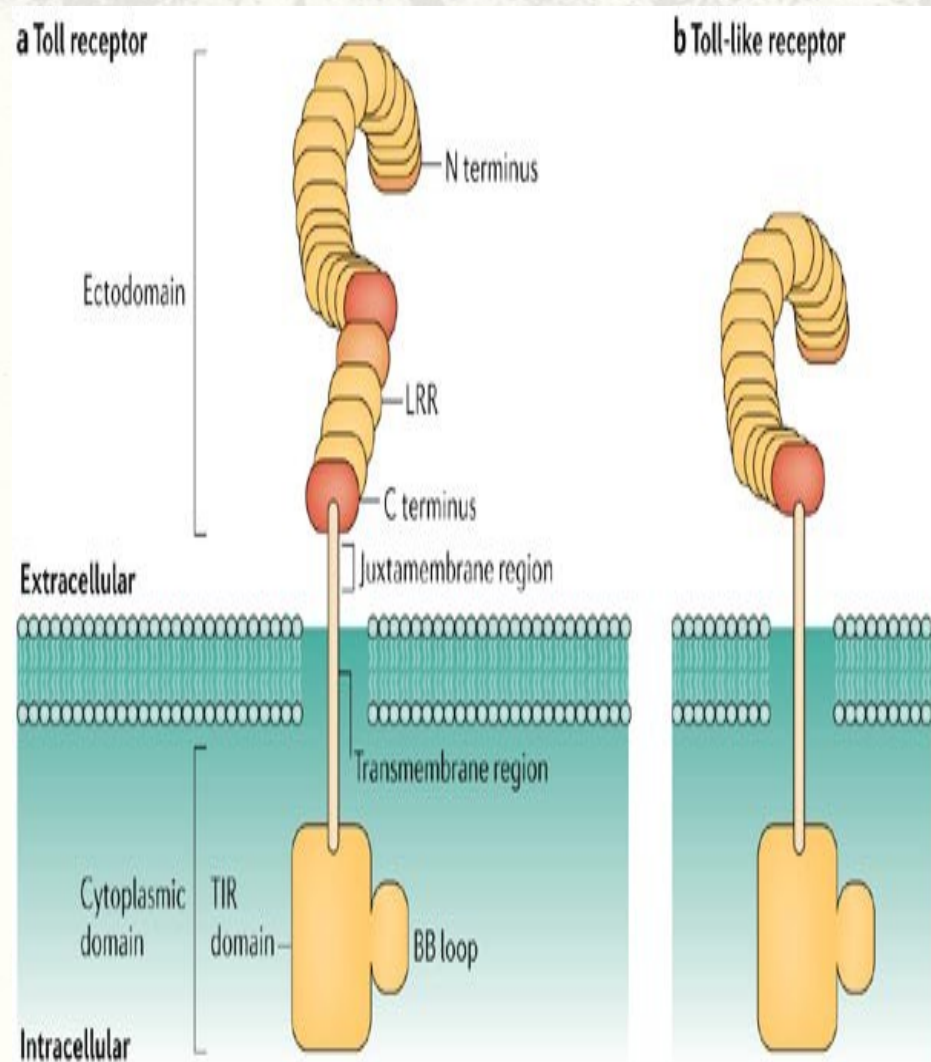
- TLRs are predominantly expressed in tissues involved in immune function, such as **spleen** and **peripheral blood leukocytes**, as well as those exposed to the external environment such as lung and the gastrointestinal tract.
- In recent years TLRs were identified also in the **mammalian nervous system**. Members of the TLR family were detected on glia, neurons and on neural progenitor cells .
- Once these microbes have breached physical barriers such as the **skin or intestinal tract mucosa**, they are recognized by TLRs, which activate immune cell responses.

- The Toll family of receptors, a family that is conserved throughout **evolution from flies to humans**, plays a central role in the initiation of cellular innate immune responses.
- The Toll family of receptors **provides** us with the long sought **transmembrane molecules** linking the extracellular compartment, where contact with and recognition of microbial pathogens occurs, and the intracellular compartment, where signaling cascades leading to cellular responses are initiated.

DISCOVERY

- Toll-like receptors are now counted among the key molecules that alert the immune system to the presence of microbial infections.
- They are named for their similarity to toll, a receptor first identified in the **fruit fly** *Drosophila melanogaster*, and originally known for its developmental function in that organism.
- In 1996, toll was found by *Jules A Hoffmann* and his colleagues to have an essential role in the fly's immunity to fungal infection, which it achieved by activating the synthesis of antimicrobial peptides.
- The first reported **human toll-like receptor** was described by Nomura and his colleagues .

- Toll and its mammalian homologs are type I transmembrane proteins, with an ectodomain consisting of leucine-rich repeats (LRRs) and one or two cysteine-rich regions.
- The intracellular domain of Toll-related receptors contains a Toll/IL-1 receptor (TIR) domain, based on homology of the region with a similar intracellular domain of the IL-1 receptor (IL-1R).
- The TIR domain in mammalian Toll-related receptors provides the initial internal scaffold for the interaction of the members of a well-defined signaling cascade.



- TLRs are a type of *pattern recognition receptor (PRR)* and recognize molecules that are broadly shared by pathogens but distinguishable from host molecules, collectively referred to as **pathogen-associated molecular patterns (PAMPs)**.
- Other **pattern recognition receptor –PRR** are:
 - Mannose receptor
 - Scavenger receptors
- Also recognition of bacteria also occur in absence of cells via:
 - Complement
 - C-reactive protein
 - Surfactant protein A in lungs

LIGANDS

- Because of the specificity of toll-like receptors (and other innate immune receptors) they cannot easily be changed in the course of evolution, these receptors recognize molecules that are constantly associated with threats (i.e., pathogen or cell stress) and are highly specific to these threats.

- Receptor recognise the following conserved features in pathogens:
- bacterial **cell-surface** lipopolysaccharides (LPS), lipoproteins, lipopeptides, lipoarabinomannan
- proteins such as **flagellin** from bacterial flagella
- double-stranded RNA of viruses
- RNA and DNA molecules.
- For most of the TLRs, ligand recognition specificity has now been established by gene targeting (also known as "gene knockout"): a technique by which individual genes may be selectively deleted in mice.

Endogenous ligands

- The stereotypic inflammatory response provoked by toll Like-Receptor activation has prompted speculation that **endogenous activators of toll-like receptors might participate in autoimmune diseases.**
- TLRs have been suspected of **binding to host molecules** including
 - fibrinogen (involved in blood clotting),
 - heat shock proteins (HSPs),
 - extracellular matrix components and
 - self DNA (it is normally degraded by nucleases, but under inflammatory and autoimmune conditions it can form a complex with endogenous proteins, become resistant to these nucleases and gain access to endosomal TLRs as TLR7 or TLR9).
- These endogenous ligands are usually produced as a result of non-physiological cell death.

TLR FAMILY

- Thirteen TLRs (named simply **TLR1 to TLR13**) have been identified in humans and mice together, and equivalent forms of many of these have been found in other mammalian species.
- However, equivalents of certain TLR found in humans are not present in all mammals. For example, a gene coding for a protein analogous to **TLR10 in humans is present in mice, but appears to have been damaged at some point in the past by a retrovirus.**
- On the other hand, mice express **TLRs 11, 12, and 13**, none of which is represented in humans. Other mammals may express TLRs that are not found in humans.
- This may complicate the process of using experimental

Different microbes are recognised by different TLR

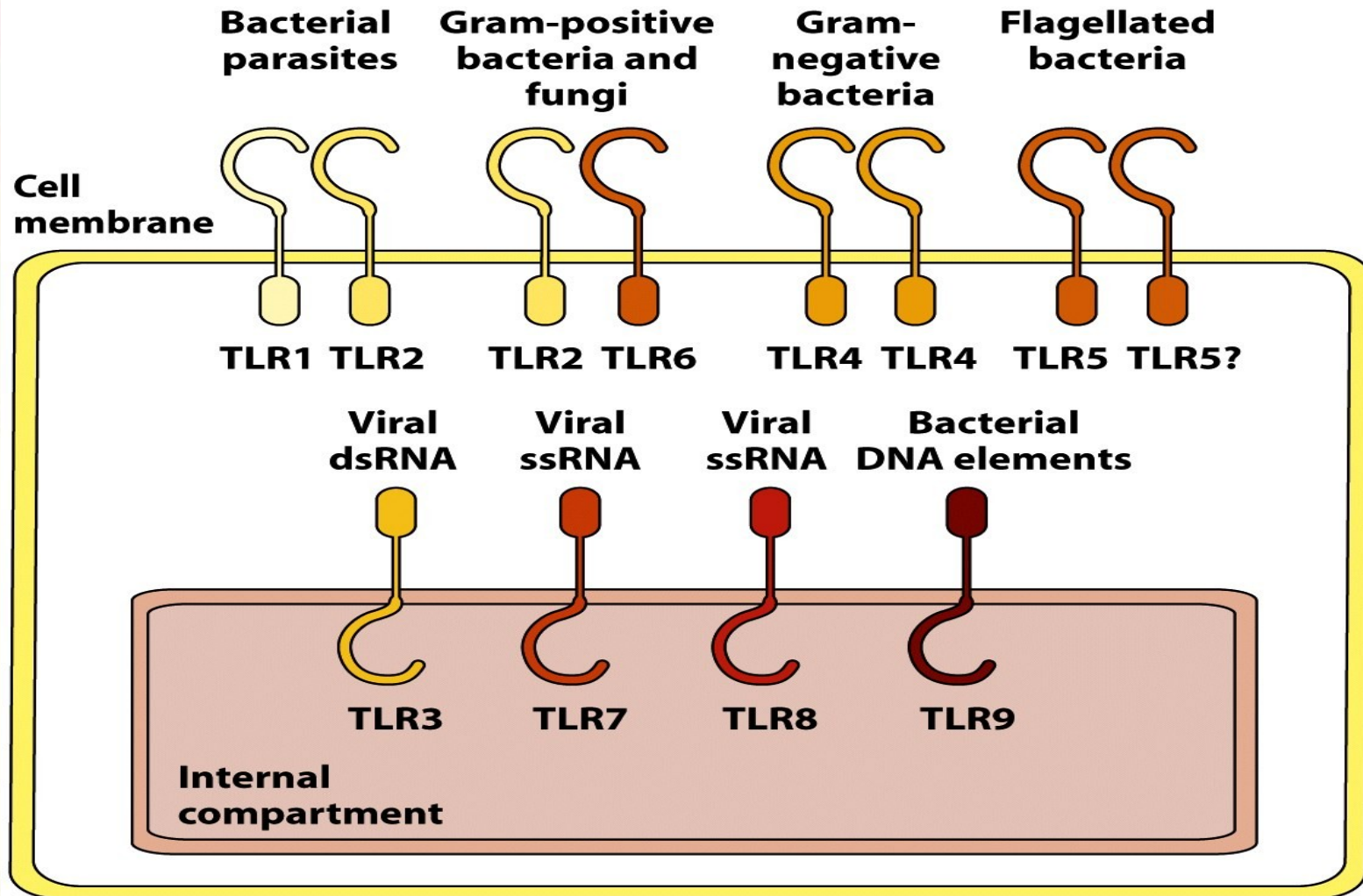
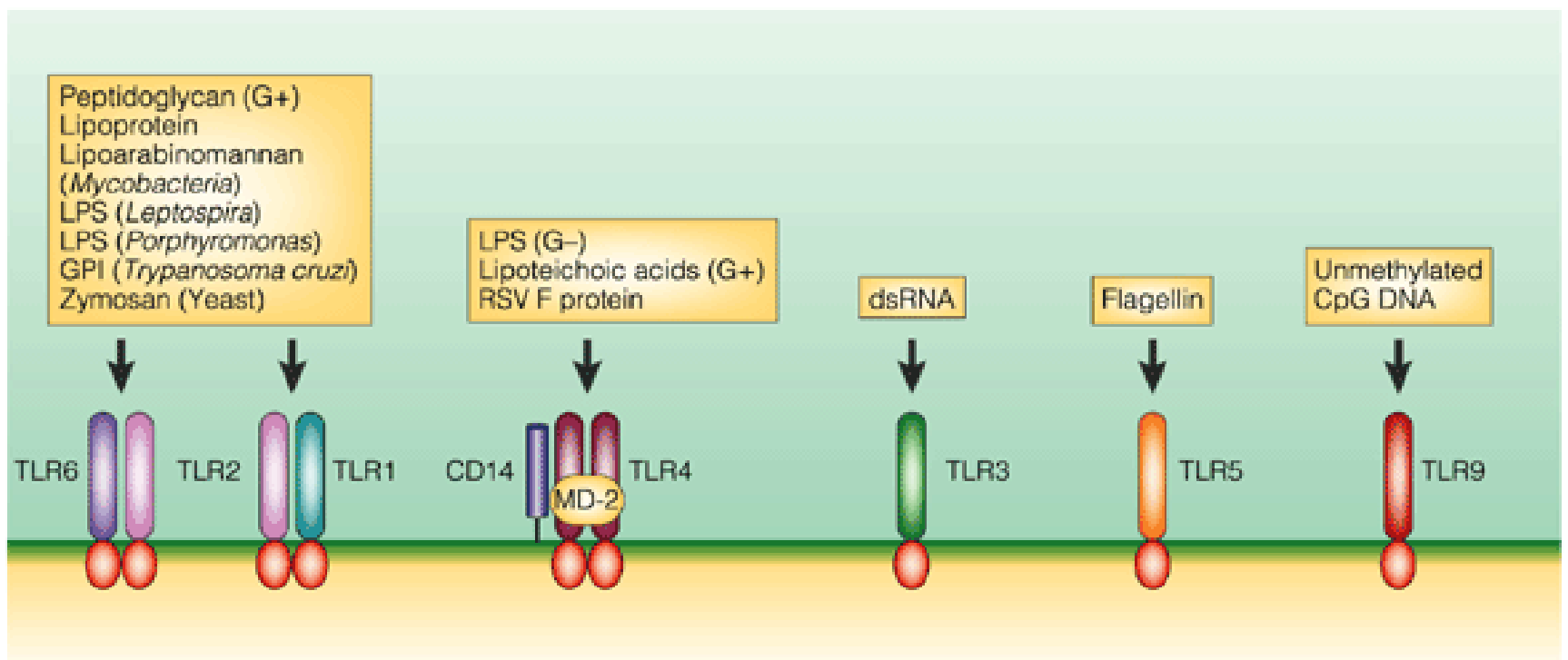


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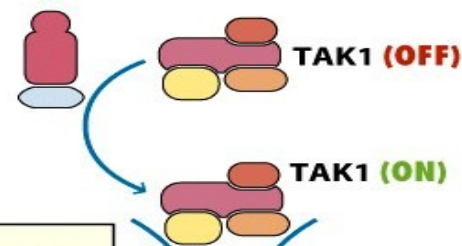
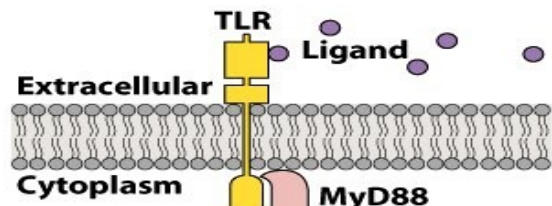
- TLR3, TLR7 and TLR8 detect viral nucleic acids found in intracellular membranes since viral nucleic acids are endogenously generated

TLR SIGNALING

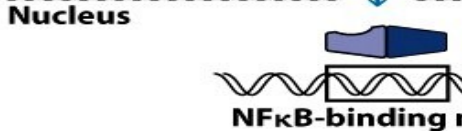
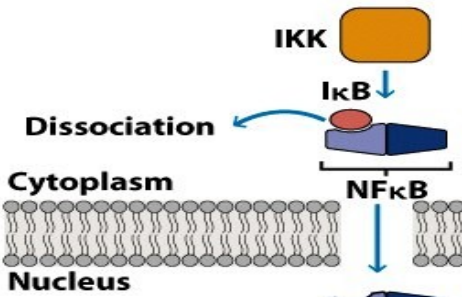
- TLR signaling is divided into two distinct signaling pathways:
- the MyD88-dependent and
- TRIF-dependent pathway.

MyD88-dependent pathway

- The MyD88-dependent response occurs on dimerization of the TLR receptor, and is utilized by every TLR except TLR3.
- Its primary effect is activation of NF κ B and Mitogen-activated protein kinase(MAPK).
- Ligand binding and conformational change that occurs in the receptor recruits the adaptor protein MyD88, a member of the TIR family.
- MyD88 then recruits IRAK 4, IRAK1 and IRAK2. IRAK kinases then phosphorylate and activate the protein TRAF6, which in turn polyubiquinates the protein TAK1, as well as itself in order to facilitate binding to IKK- β . On binding, TAK1 phosphorylates IKK- β , which then phosphorylates I κ B causing its degradation and allowing NF κ B to diffuse into the cell nucleus and activate transcription and consequent induction of inflammatory cytokines.



5a TAK1 phosphorylates IKK to activate the NFκB pathway; IKK then phosphorylates IκB, causing it to release NFκB



6a The freed NFκB translocates from the cytoplasm into the nucleus, where it serves as a transcriptional activator for NFκB-dependent genes

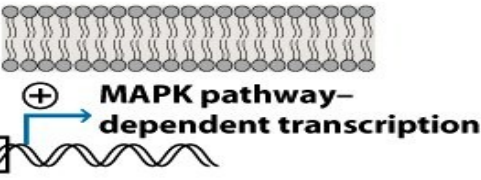
1 Ligand binding to TLR triggers association of MyD88 with TIR domain and assembly of IRAK1/IRAK4 complex

2 IRAK4 phosphorylates IRAK1, creating a binding site for TRAF6

3 The IRAK1-TRAF6 complex dissociates and activates the protein kinase TAK1 complex

4 The active TAK1 activates two distinct signal transduction pathways

5b TAK1 also phosphorylates and activates a component of the MAP kinase (MAPK) pathway



6b The MAPK cascade results in translocation of a transcriptional activator from the cytoplasm into the nucleus, where it activates transcription of MAPK-dependent genes

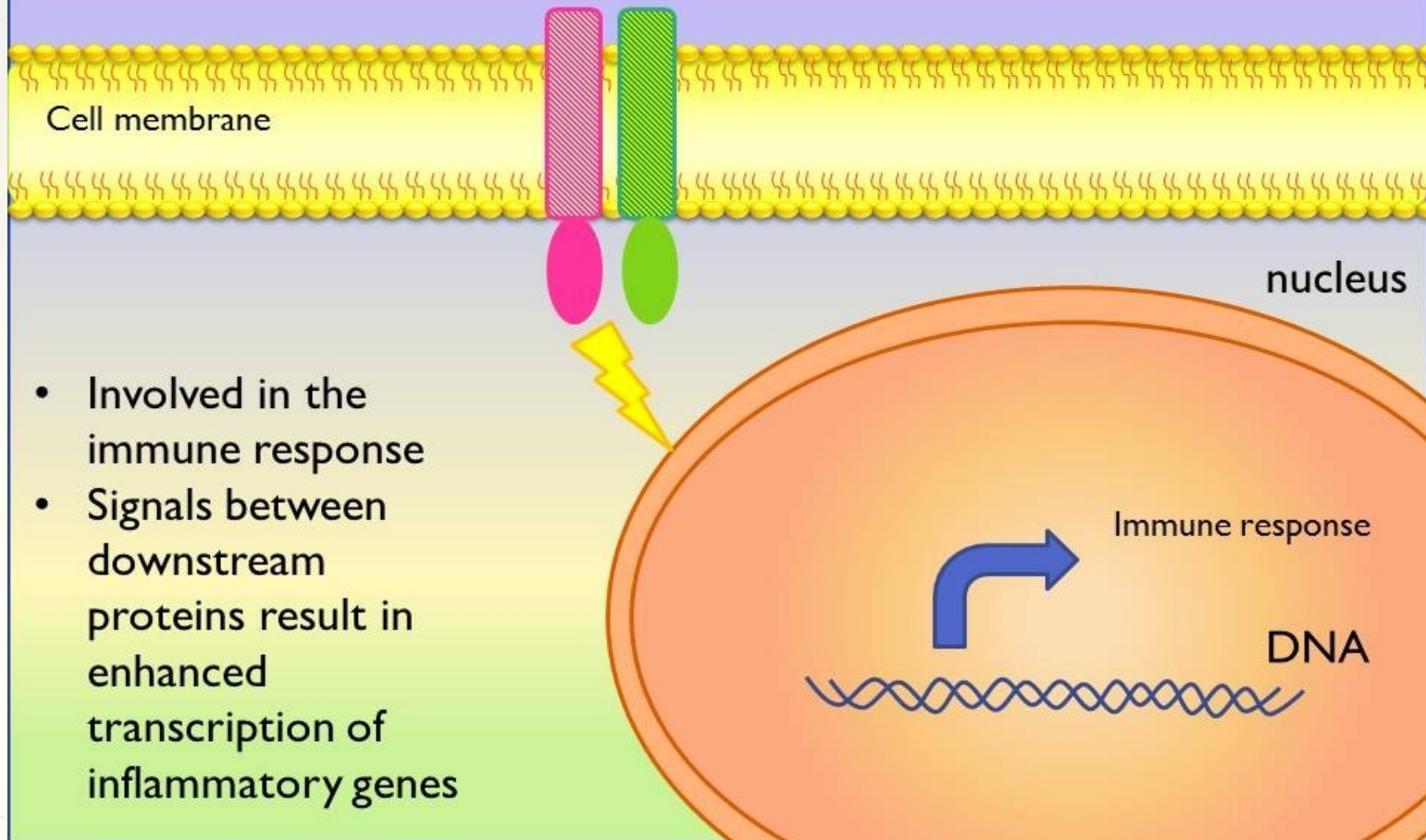
Figure 3-14
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- Individual TLRs induce different signaling responses by usage of the different adaptor molecules.
- TLR3 triggers the production of IFN- β in response to double-stranded RNA, in **a MyD88-independent manner**, through the adaptor TRIF/TICAM-1.
- TRAM/TICAM-2 is another adaptor molecule involved in the MyD88-independent pathway.

TRIF-dependent pathway/ MyD88-independent pathway

- Both TLR3 and TLR4 utilize the TRIF-dependent pathway, which is triggered by dsRNA and LPS, respectively. For TLR3, dsRNA leads to activation of the receptor, recruiting the adaptor TRIF.
- TLR signaling ultimately leads to the induction or suppression of genes that augments the inflammatory response. In all, thousands of genes are activated by TLR signaling, and collectively, the TLRs constitute one of the most pleiotropic yet tightly regulated gateways for gene modulation.

Toll-like receptors



TLR-Targeted Therapeutics

- Significant progress has been made over the past years in the understanding of TLR function .
- TLRs are essential receptors in host defense against pathogens by activating the innate immune system, a prerequisite to the induction of adaptive immune responses.
- Although TLR-mediated signaling is paramount in eradicating microbial infections and promoting tissue repair, the regulation must be tight. TLRs are implicated in a **number of inflammatory and immune disorders** and play a role in cancer .
- Many single nucleotide polymorphisms have been identified in various TLR genes and are associated with particular diseases. **Several therapeutic agents targeting the TLRs** are now under pre-clinical and clinical evaluation .

- However, the complexity lies in that TLRs act as **double-edged swords** either promoting or inhibiting disease progression. Furthermore, therapeutic agents targeting the TLRs must be able to antagonize the harmful effects resulting without affecting host defense functions.

EFFECTS OF TOLL LIKE RECEPTORS

- Following activation by ligands of microbial origin, several reactions are possible.
- Immune cells can produce signalling factors called **cytokines**, which trigger inflammation.
- In the case of a **bacterial factor**, the pathogen might be **phagocytosed and digested**, and its antigens presented to **CD4+ T cells**.
- In the case of a **viral factor**, the infected cell may shut off its protein synthesis and may undergo **programmed cell death (apoptosis)**.
- Immune cells that have detected a virus may also release anti-viral factors such as **interferons**.

- Toll-like receptors have also been shown to be an important link between innate and adaptive immunity through their presence in dendritic cells.
- The TLRs 3 and 4 are present on the surface of monocyte derived dendritic cells and use the Myd88-dependent pathway to produce interleukins 12 and 18 which signal naive T-cells to mature into type 1 helper T cells.
- TLRs 7 and 9 are present on the endosome of plasmacytoid dendritic cells. These proteins solely make use of the Myd88 dependent pathway to produce interleukins for the maturation of naive T-cells to type 1 helper T-cells.

REFERENCES

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- Toll-Like Receptors Review, 2012
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The background features a light, textured surface with diagonal rainbow-colored stripes in the corners. The stripes are composed of multiple parallel lines in the colors of the rainbow: red, orange, yellow, green, blue, and purple.

• **THANK YOU**