

Innate Immune Sensors and Invading Pathogens



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The defense of the host to the invading pathogens is evoked by the immune system that is made up of two components i.e., innate immune response and acquired immune response. Innate immunity contains sensors termed as pattern recognition receptors (PRRs), which are expressed on the immune and non-immune cells. These PRRs recognize conserved pathogen-associated molecular patterns (PAMPs) in different booths of host cells. The sensing of the PAMPs by PRRs activates effector responses against microbial agents through the expression of proinflammatory cytokines and Type-I interferons (IFNs). The PRRs have been categorized as Toll-like receptors (TLRs); NOD-like receptors (NLRs); RIG-I-like receptors (RLRs); and DNA sensors and their respective PAMPs have been well studied in innate immunity and host defense.

The range of PRRs is very broad, and similarly, the groups of invading microbes recognized by PRRs are very miscellaneous. A central attribute of innate pathogen sensing is that microbes of rather different biochemical composition and with completely dissimilar life cycles are identified by quite similar mechanisms by host PRRs. Furthermore, an essential characteristic of this coordination is that no single class of microbe is sensed by only one type of PRR. Rather, a number of different PRRs are occupied by a given pathogen by means of various PAMPs, hence securing a quick and strong

inflammatory response and also permitting for some specificity of the response.

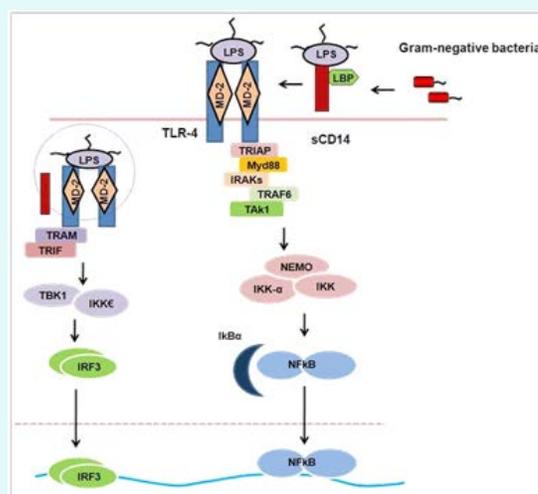


Figure 1: Toll like receptor-4 (TLR-4) sense the Gram-negative bacteria. Lipopolysaccharides (LPS) activate the TLR-4 signalling via LPS binding protein and CD14 that pass on LPS to the TLR-4 and myeloid differentiation factor 2 (MD-2) complex. Finally, TLR-4 oligomerization elicits the intracellular signaling cascade, which drives myeloid differentiation primary response gene 88 (MyD88) and TIR domain-containing adaptor inducing IFN- β (TRIF) dependent gene expression.

In the last of 20th century, Toll was identified in *Drosophila* and proven to be an essential receptor for the host defense against fungal infection that only has innate immune system. After one year, a mammalian homolog of the Toll receptor was publicized to elicit the expression of genes responsible for inflammatory pathways, now termed as TLR-4. Later researchers proved that a point mutation in a gene encoding TLR-4 was found unable to sense lipopolysaccharides (LPS) in a mouse model. TLR-4 is a critical receptor for the recognition of LPS. Lipopolysaccharides are the foremost structural constituents of the outer membrane of Gram-negative bacteria. LPS are made up of three major components, i.e., a serotype-specific O-antigen polysaccharide, a centrally located core oligosaccharide, and a lipidated disaccharide (lipid A) that anchors the LPS molecule in the bacterial membrane. LPS is a prototypical PAMP, which stimulates the immune system of the metazoan hosts. Extracellular LPS induces the pattern recognition receptor TLR-4 to signal from the plasma membrane and endosomes that was long held accountable for inducing lethality in metazoan hosts. TLR4 signaling is started when lipid A is captured by the available LPS binding protein (LBP) that transfers it to either soluble or membrane-bound CD14. LPS is then relayed to myeloid differentiation factor 2 (MD2) molecules that are associated with TLR4. Eventually, binding of LPS to TLR4/MD2 results in dimerization of the receptor complex and initiation of an intracellular signaling cascade that drives broad myeloid differentiation primary response gene 88 (MyD88), and TIR domain-containing adaptor inducing IFN- β (TRIF)-dependent gene transcription (Figure 1).

These research findings draw the researcher's attention and have made innate immunity an attractive research area. In the current scenario, there has been a vast and speedy advancement in the understanding of scientific community that how innate immunity is crucial to sense the invasion of microbial pathogens by TLRs. Additionally, the activation of innate immune response is an essential step for the development of antigen-derived acquired immunity.

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