Toll Like Receptor 4 (TLR4) Cascade

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 71

This document contains 4 pathways and 6 reactions (see Table of Contents)
Toll-like Receptor 4 (TLR4) Cascade

Stable identifier: R-HSA-166016

Toll-like Receptor 4 (TLR4) is a microbe-associated molecular pattern receptor well known for its sensitivity to bacterial lipopolysaccharides (LPS). LPS is assembled within diverse Gram-negative bacteria, many of which are human or plant pathogens. It is a component of the outer membrane of Gram-negative bacteria and consists of lipid A, a core polysaccharide and an O-polysaccharide of variable length (often more than 50 monosaccharide units). LPS is a potent activator of the innate immune response in humans, causing reactions including fever, headache, nausea, diarrhoea, changes in leukocyte and platelet counts, disseminated intravascular coagulation, multiorgan failure, shock and death. All these reactions are induced by cytokines and other endogenous mediators which are produced after interaction of LPS with the humoral and cellular targets of the host. In macrophages and dendritic cells, LPS-mediated activation of TLR4 triggers the biosynthesis of diverse mediators of inflammation, such as TNF-alpha and IL6, and activates the production of co-stimulatory molecules required for the adaptive immune response. In mononuclear and endothelial cells, LPS also stimulates tissue factor production. These events are desirable for clearing local infections, but when these various mediators and clotting factors are overproduced, they can damage small blood vessels and precipitate shock accompanied by disseminated intravascular coagulation and multiple organ failure.

TLR4 is unique among the TLR family in its ability to recruit four adapters to activate two distinct signaling pathways. One pathway is activated by the pair of the adapters Mal or TIRAP (Toll/interleukin-1-receptor (TIR)-domain-containing adapter protein) and MyD88, which leads to the NFkB activation and the induction of pro-inflammatory cytokines. The second pathway is activated by the adapters TRIF (TIR-domain-containing adapter protein inducing interferon-beta) and TRAM (TRIF-related adapter molecule). The combined use of TRIF and TRAM adapters is specific for TLR4 signaling pathway and leads to the induction of type I interferons and delayed activation of NFkB.

The previous model of TLR4 signaling pathway described the simultaneous activation of these two signaling pathways at the plasma membrane, however the later studies suggested that upon activation TLR4 first induces TIRAP-MyD88 signaling at the plasma membrane and is then endocytosed and activates TRAM-TRIF signaling from the early endosome [Kagan JC et al 2008; Tanimura N et al 2008; Zanoni I et al 2011].
Literature references


Editions

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Association of LBP with LPS

Location: Toll Like Receptor 4 (TLR4) Cascade

Stable identifier: R-HSA-166015

Type: binding

Compartments: extracellular region