Gene name: TLR4

External Ids for TLR4 Gene: HGNC: 11850 NCBI Gene: 7099 Ensembl: ENSG00000136869 OMIM®: 603030 UniProtKB/Swiss-Prot: O00206

NCBI Gene Summary: The protein encoded by this gene is a member of the Toll-like receptor (TLR) family which plays a fundamental role in pathogen recognition and activation of innate immunity. TLRs are highly conserved from Drosophila to humans and share structural and functional similarities. They recognize pathogen-associated molecular patterns that are expressed on infectious agents, and mediate the production of cytokines necessary for the development of effective immunity. The various TLRs exhibit different patterns of expression. In silico studies have found a particularly strong binding of surface TLR4 with the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus disease-2019 (COVID-19). This receptor has also been implicated in signal transduction events induced by lipopolysaccharide (LPS) found in most gram-negative bacteria. Mutations in this gene have been associated with differences in LPS responsiveness, and with susceptibility to age-related macular degeneration. Multiple transcript variants encoding different isoforms have been found for this gene.

GeneCards Summary: TLR4 (Toll Like Receptor 4) is a Protein Coding gene. Diseases associated with TLR4 include Macular Degeneration, Age-Related, 10 and Pertussis. Among its related pathways are Toll Like Receptor 7/8 (TLR7/8) Cascade and Diseases of Immune System. Gene Ontology (GO) annotations related to this gene include *signaling receptor activity* and *lipopolysaccharide binding*. An important paralog of this gene is TLR8.

UniProtKB/Swiss-Prot Summary: Transmembrane receptor that **functions as a pattern recognition receptor recognizing pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) to induce innate immune responses** via downstream signaling pathways (PubMed:10835634, 15809303, 16622205, 17292937, 17478729, 20037584, 20711192, 23880187, 27022195, 29038465). At the plasma membrane, cooperates with LY96 to mediate the innate immune response to bacterial lipopolysaccharide (LPS) (PubMed:27022195). Also involved in LPS-independent inflammatory responses triggered by free fatty acids, such as palmitate, and Ni(2+) (PubMed:20711192). Mechanistically, acts via MYD88, TIRAP and TRAF6, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response (PubMed:10835634, 21393102, 27022195, 36945827, 9237759). Alternatively, CD14-mediated TLR4 internalization via endocytosis is associated with the initiation of a MYD88-independent signaling via the TICAM1-TBK1-IRF3 axis leading to type I interferon production (PubMed:14517278). In addition to the secretion of proinflammatory cytokines, initiates the activation of NLRP3 inflammasome and formation of a positive feedback loop between autophagy and NF-kappa-B signaling cascade (PubMed:32894580). In complex with TLR6, promotes inflammation in monocytes/macrophages by associating with TLR6 and the receptor CD86 (PubMed:23880187). Upon ligand binding, such as oxLDL or amyloid-beta 42, the TLR4:TLR6 complex is internalized and triggers inflammatory response, leading to NF-kappa-B-dependent production of CXCL1, CXCL2 and CCL9 cytokines, via MYD88 signaling pathway, and CCL5 cytokine, via TICAM1 signaling pathway (PubMed:23880187). In myeloid dendritic cells, vesicular stomatitis virus glycoprotein G but not LPS promotes the activation of IRF7, leading to type I IFN production in a CD14-dependent manner (PubMed:15265881, 23880187). Required for the migration-promoting effects of ZG16B/PAUF on pancreatic cancer cells. (TLR4_HUMAN,O00206)

Cellular localization: mainly in the endosome and plasma membrane.

Full name: TLR4 stands for *Toll-like Receptor 4*, a crucial pattern recognition receptor (PRR) in the innate immune system.Best known as the primary receptor for lipopolysaccharide (LPS), the major component of Gram-negative bacterial outer membranes.

🔬 Biological Function

- Recognizes pathogen-associated molecular patterns (PAMPs), particularly:
    - LPS from Gram-negative bacteria
    - Certain fungal and viral components
    - Endogenous danger signals (such as, HMGB1, HSPs)
- Forms a complex with MD-2 and sometimes CD14 to detect LPS.
- Upon activation, initiates intracellular signaling cascades, including:
    - MyD88-dependent pathway → rapid activation of NF-κB and production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β).
      TRIF-dependent pathway → delayed activation leading to type I interferon (IFN-β) production.

🦠 Role of TLR4 in Sepsis

- Central player in the pathogenesis of sepsis, especially Gram-negative sepsis.
- TLR4 activation triggers:
    - Massive cytokine production (cytokine storm)
    - Endothelial activation → increased vascular permeability, hypotension
    - Coagulation cascade activation → contributing to DIC (disseminated intravascular coagulation)
    - Multi-organ dysfunction
- Excessive TLR4 signaling is a major cause of systemic inflammatory response syndrome (SIRS) in septic patients.
- Animal models show that TLR4-deficient mice are resistant to LPS-induced septic shock.

🧪 Expression and Regulation

- TLR4 is highly expressed on:
    - Monocytes/macrophages
    - Neutrophils
    - Dendritic cells
    - Endothelial and epithelial cells
- Upregulated by:
    - Infection
    - Inflammatory cytokines (like IFN-γ, TNF-α)
- Downregulated or modulated by:
  Anti-inflammatory cytokines (like IL-10)
    - Soluble decoy receptors (such as, soluble MD-2)

⚕️ Diagnostic Role of TLR4 in Sepsis

- TLR4 activation is a hallmark of early bacterial infection, especially from Gram-negative bacteria.
- Increased TLR4 expression on monocytes and neutrophils has been observed very early in sepsis.
  Higher TLR4 mRNA or protein levels in blood can help differentiate sepsis from non-infectious systemic inflammatory responses (like trauma or surgery).

Clinical studies have found that measuring TLR4 expression or activation can aid in early sepsis diagnosis, particularly for Gram-negative bacteremia. Example: TLR4 expression on peripheral blood mononuclear cells was significantly higher in septic patients compared to healthy controls.

📈 Prognostic Role of TLR4 in Sepsis

- Persistent elevation of TLR4 is associated with:
  - More severe inflammatory responses
  - Increased risk of septic shock
  - Worse organ dysfunction (like, lungs, kidneys)
  - Higher mortality rates
- High TLR4 activity early in sepsis often correlates with poor outcomes, particularly if negative regulatory mechanisms (like IL-10) fail to dampen the response.

Clinical studies show that patients with high TLR4 expression or hyperresponsiveness to LPS have higher SOFA scores and higher ICU mortality.

In some cohorts, low or suppressed TLR4 responses in late-phase sepsis (immune paralysis) also predict poor outcomes — timing matters!

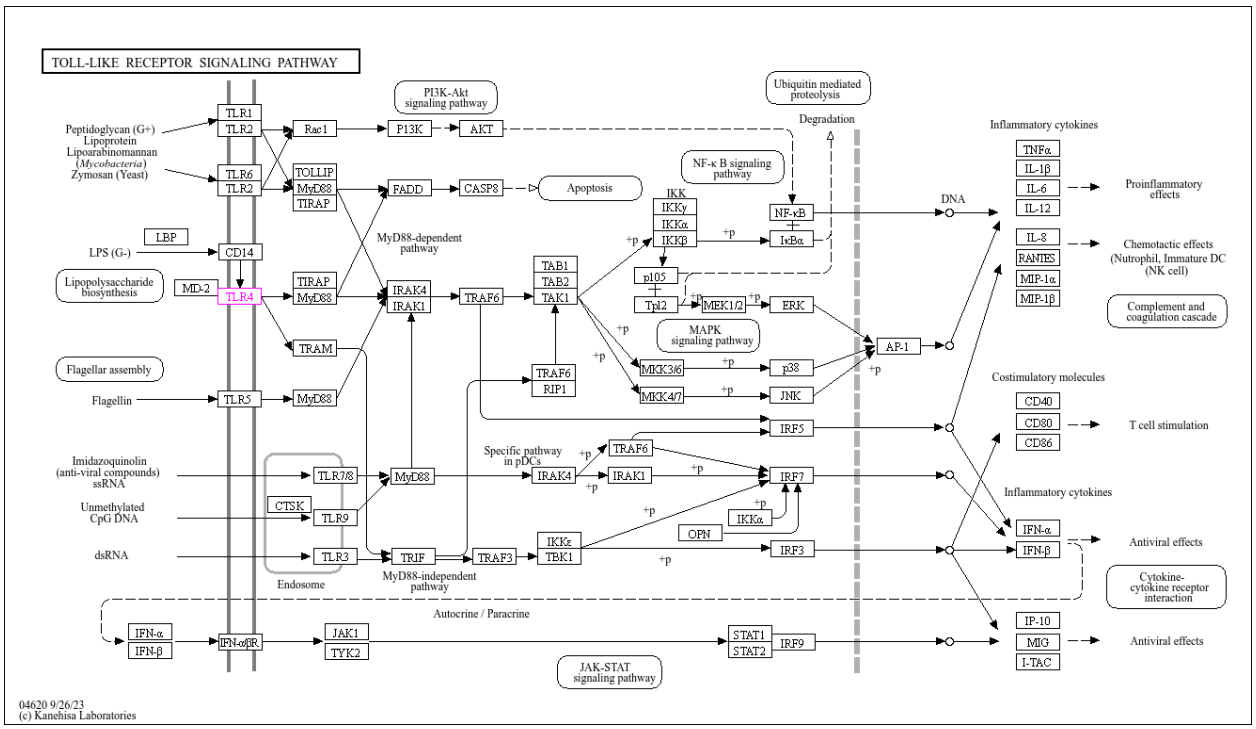
🧬 Pathways Involving TLR4

- Toll-like receptor signaling pathway (KEGG hsa04620) → primary innate immunity activation
- NF-κB signaling pathway → production of pro-inflammatory mediators
- TRIF-mediated signaling → production of interferons and anti-viral response
- Cytokine-cytokine receptor interaction pathway → communication between immune cells
- NOD-like receptor signaling (indirect connection) → inflammasome activation

🧪 Supporting Literature

Doi:10.1016/j.injury.2010.05.021
Doi: 10.1097/01.shk.0000217815.57727.29
Doi: 10.1097/01.shk.0000142256.23382.5d
Doi:10.1111/j.1365-2249.2004.02433.x

KEGG:



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