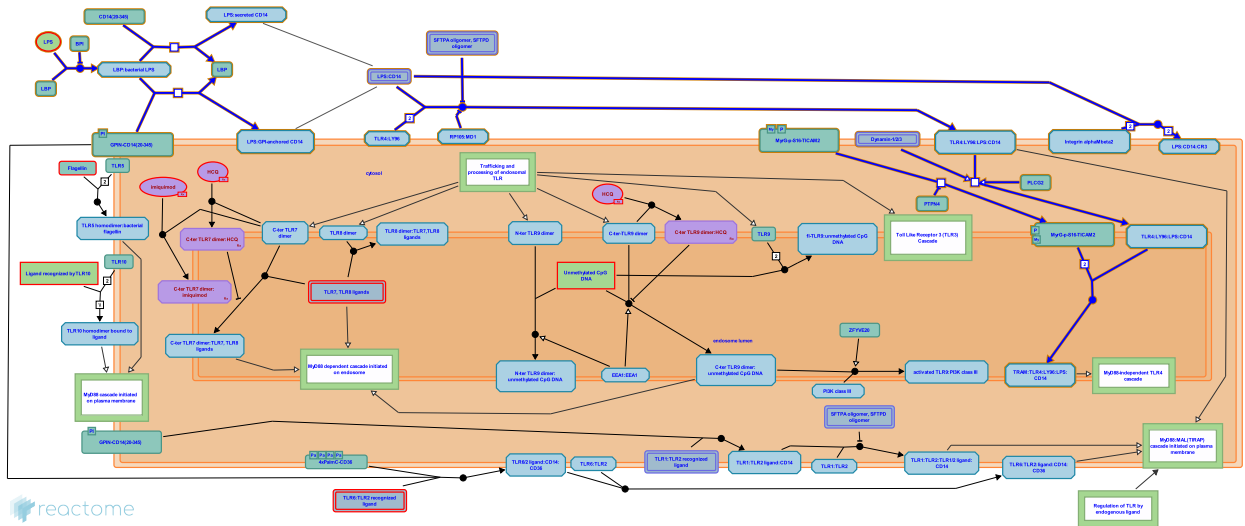


# Toll Like Receptor 4 (TLR4) Cascade



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

27/04/2024

## 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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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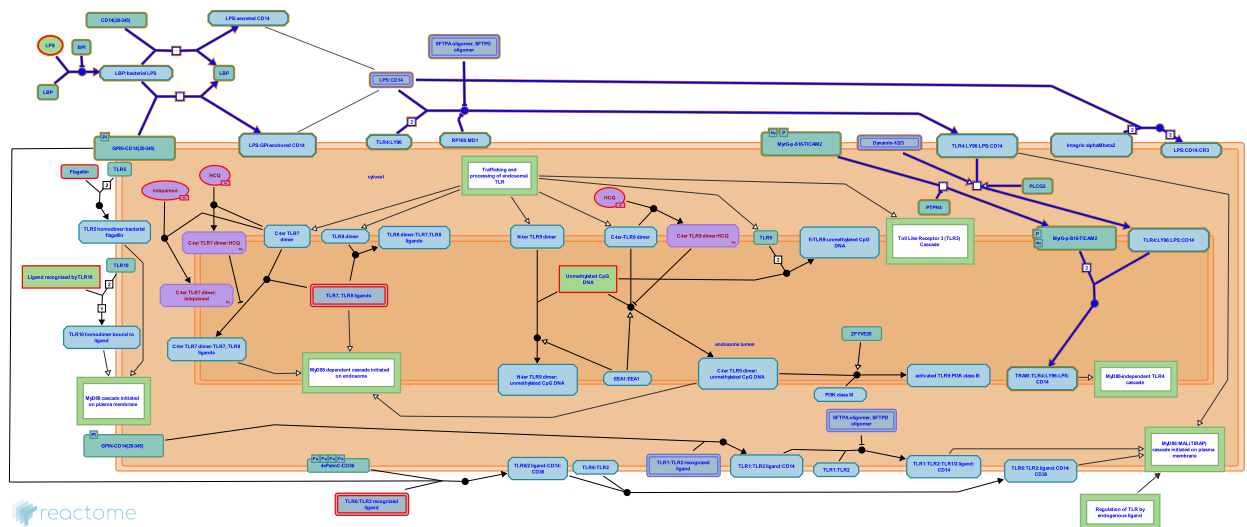
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Reactome database release: 88

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 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 NFκB 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 NFκB.

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

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## Editions

2005-08-16	Authored	de Bono, B.
2006-04-24	Reviewed	Gay, NJ.
2010-11-15	Edited	Shamovsky, V.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-02	Revised	Shamovsky, V.

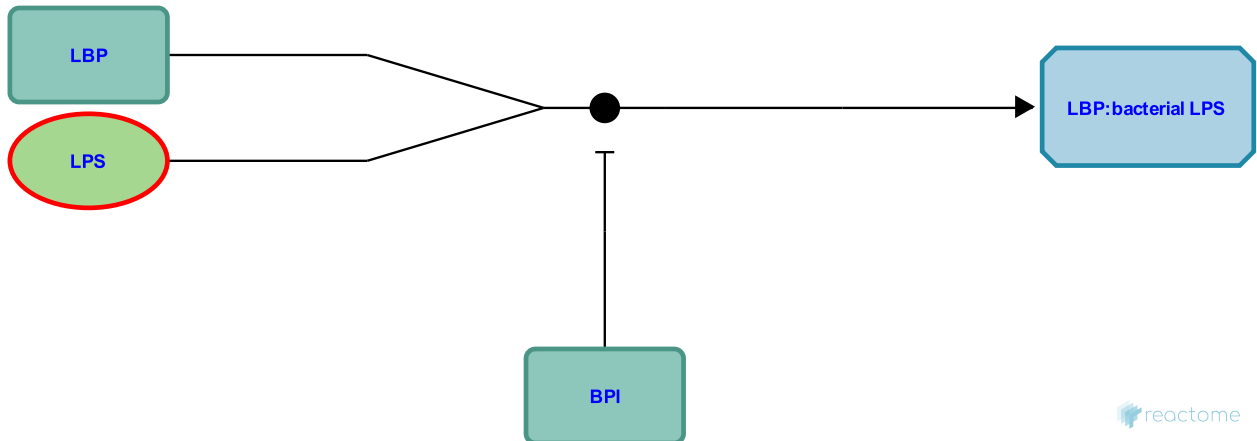
## Association of LBP with LPS ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-166015

**Type:** binding

**Compartments:** extracellular region



Lipopolysaccharide-binding protein (LBP) is a ~60-kDa serum glycoprotein which transfers LPS to both membrane-bound and soluble CD14. The LPS binding site of LBP consists of basic residues that bind the phosphorylated head of the bacterial lipid A.

LBP is an acute-phase opsonin that binds gram-negative bacteria and bacterial fragments and promote the interaction of coated bacteria with phagocytes.

### Literature references

Ramos, RA., Ulevitch, RJ., Wright, SD., Tobias, PS. (1989). Lipopolysaccharide (LPS) binding protein opsonizes LPS-bearing particles. *J Exp Med*, 170, 1231-41. ↗

### Editions

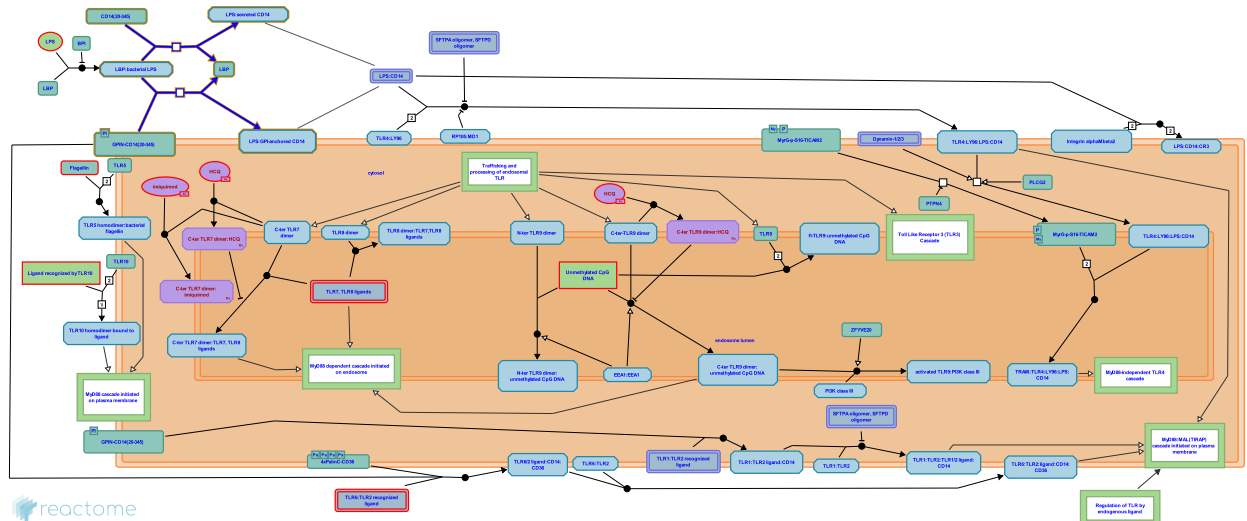
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# Transfer of LPS from LBP carrier to CD14 ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-166020

**Compartments:** plasma membrane, extracellular region



LBP delivers LPS from bacteria (or bacterial membrane fragments) to CD14 on the surfaces of phagocytes, where it is recognised by the MD2:TLR4 complex. Thus, LBP is an opsonin and CD14 is an opsonic receptor for complexes of LPS (or LPS-containing particles such as bacteria) and LBP. CD14 exists as two isoforms. CD14 can be either secreted into the extracellular compartment, or it can be anchored to the plasma membrane via its GPI module.

## Literature references

Fenton, MJ., Golenbock, DT. (1998). LPS-binding proteins and receptors. *J Leukoc Biol*, 64, 25-32. ↗

## Editions

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2012-11-13	Reviewed	Zanoni, I., Granucci, F.

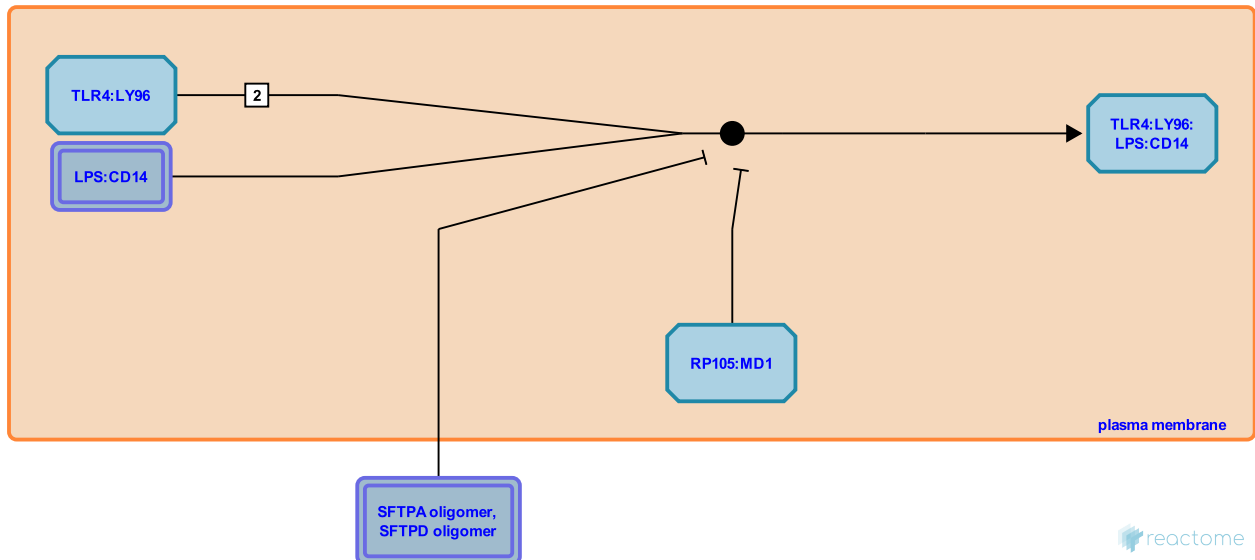
## Transfer of LPS onto TLR4 ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-166041

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The Toll-like receptor 4 (TLR4) is a membrane-spanning protein distantly related to the IL1 receptor. Both CD14 and members of the Toll family contain multiple leucine-rich repeats. In addition, the latter possess a Toll-homology domain in the cytoplasmic tail, which is important in the generation of a transmembrane signal linked to LPS-induced cell activation. Of all Toll family members, TLR4 is probably the exclusive receptor for LPS from most Gram negative organisms.

Toll-like receptor 4 and lymphocyte antigen 96 (LY96, also known as myeloid differentiation factor 2 (MD2)) form a heterodimer that specifically recognizes structurally diverse LPS molecules. A structural study of TLR4:LY96 complex revealed that LY96 (MD2) interaction with TLR4 relies on hydrogen and electrostatic bonds (Kim HM et al, 2007). LPS binds to the hydrophobic pocket of LY96 and directly mediates the dimerization of the two TLR4:LY96 complexes in a symmetrical manner. Both hydrophobic and hydrophilic interactions contribute to the main dimerization interaction between LY96, LPS and TLR4 multimer components. The phosphate groups of LPS also contribute to the receptor multimerization by forming ionic interactions with positively charged residues of TLR4 and LY96. (Park BS et al, 2009).

The activated TLR4 receptor is composed of two copies of the TLR4:LY96:LPS complex and initiates signal transduction by recruiting intracellular adaptor molecules.

**Followed by:** Endocytosis of TLR4:LY96:LPS:CD14

### Literature references

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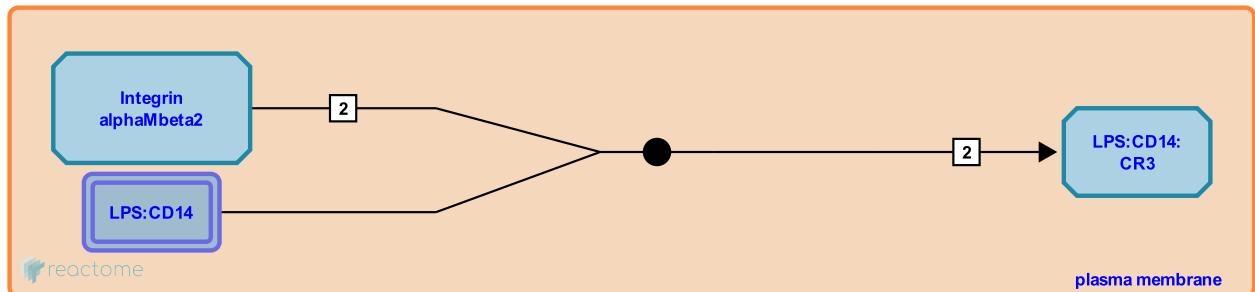
## CD14:LPS binds CR3 ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-2559439

**Type:** binding

**Compartments:** plasma membrane, extracellular region



Upon LPS stimulation, CD14, in addition to promote endotoxin transfer to TLR4, also triggers complement receptor 3 (CR3) activation [Troelstra A et al 1999; Kagan JC and Medzithov R 2007]. LPS-mediated CR3 upregulation results in induction of PIP5K-dependent de novo synthesis of PIP2 in the lipid rafts through the phosphorylation of PI(4)P. Mal(TIRAP) is then recruited at the site of the newly generated PIP2 where it binds TLR4 via the TIR domain. Finally, MyD88 is recruited to the activated TLR4-CD14 complex via the TIRAP molecule and initiates a signaling cascade leading to a first wave of NF- $\kappa$ B activation from the plasma membrane [Kagan JC and Medzithov R 2007].

CR3 (CD11b/CD18) is a member of CD18 receptor family of cell surface glycoproteins, which are expressed in human phagocytes. Each of the three receptors (CR3, lymphocyte function-associated antigen LFA-1, and p150-95) is a heterodimer composed of a beta-chain (CD18) that is identical in all three receptors and a noncovalently associated alpha chain (CD11) that is unique to each molecule [ . CR3 is known as a receptor for the surface-bound complement protein C3bi, but it has been also reported to recognize several other ligands, including bacterial patterns such as LPS and lipid A. Two distinct binding sites on CR3 have been described: 1) a protein-binding-site that binds C3bi, fibrinogen, and Leishmania glycoprotein 63, and 2) a lipid- binding-site involved in the binding of LPS, lipid A [Wright SD et al 1989; Van Strijp J.A.G et al 1993].

CR3, LFA-1 and p150-95 have been reported to mediate not only LPS interaction but also promote the binding of Escherichia coli to human macrophages [Wright SD and Jong MTC 1986].

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- Jong, MT., Wright, SD. (1986). Adhesion-promoting receptors on human macrophages recognize Escherichia coli by binding to lipopolysaccharide. *J. Exp. Med.*, 164, 1876-88. ↗
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## Editions

2012-05-15	Authored	Shamovsky, V.
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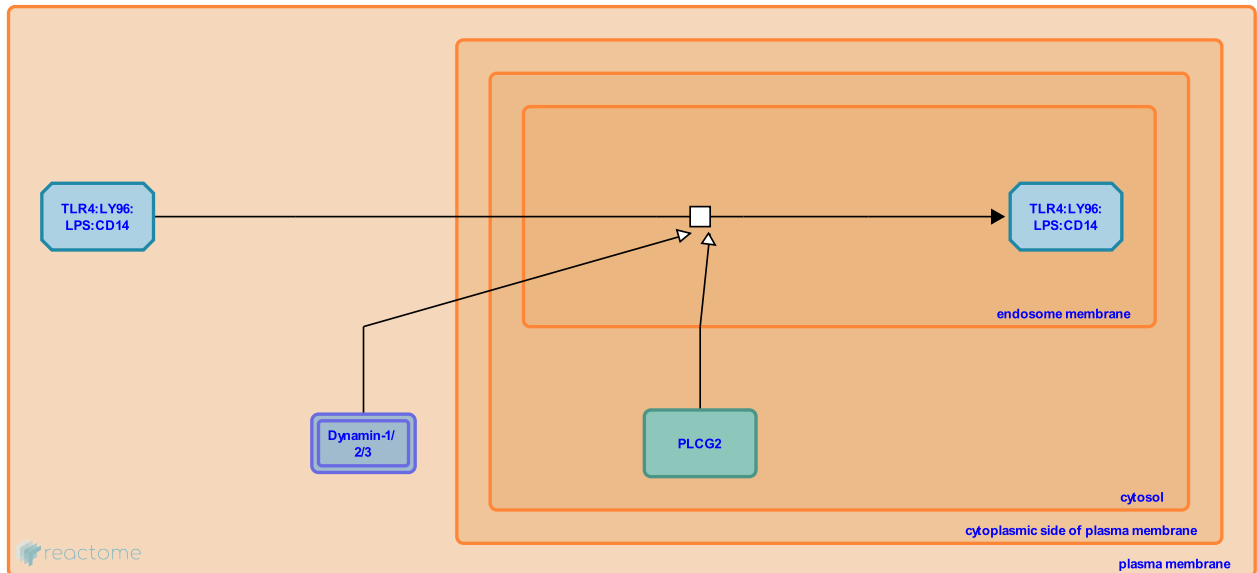
## Endocytosis of TLR4:LY96:LPS:CD14 ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-2201293

**Type:** transition

**Compartments:** endosome membrane, plasma membrane



Upon LPS stimulation TLR4 is internalized into endosomes where the signaling pathway is triggered through the adaptors TRAM and TRIF leading to the activation of IRF3 and induction of IFN-beta [Tanimuro N et al 2008; Kagan JC et al 2008]. While TLR4 translocation to endosomes is governed by known regulators of general endocytic processes such as dynamins and clathrin, other proteins that specifically regulate LPS-stimulated TLR4 endocytosis have been also identified [Husebye et al 2006; Kagan JC et al 2008; Zanoni I et al 2011]. Thus, CD14 has been implicated both in transporting LPS to TLR4 and in delivering TLR4 to an endosomal compartment. TLR4 translocation activated by CD14 appears to be Syk-mediated, and requires its downstream effector phospholipase C gamma 2 (PLCgamma2), which in turn induces a drop in the concentration of PIP2 required for endosomal sealing [Zanoni I et al 2011]. It has also been shown that PLCgamma2 induces inositol 1,4,5-trisphosphate (IP(3)) production and subsequent calcium (Ca<sup>2+</sup>) release. Released intracellular Ca<sup>2+</sup> was reported to mediate TLR4 trafficking and subsequent activation of IRF3. [Aki D et al 2008; Chiang CY et al 2012].

**Preceded by:** [Transfer of LPS onto TLR4](#)

**Followed by:** [TLR4:LY96:LPS:CD14 recruits TRAM \(TICAM2\)](#)

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2012-05-25	Edited	Shamovsky, V.
2012-11-13	Reviewed	Zanoni, I., Granucci, F.

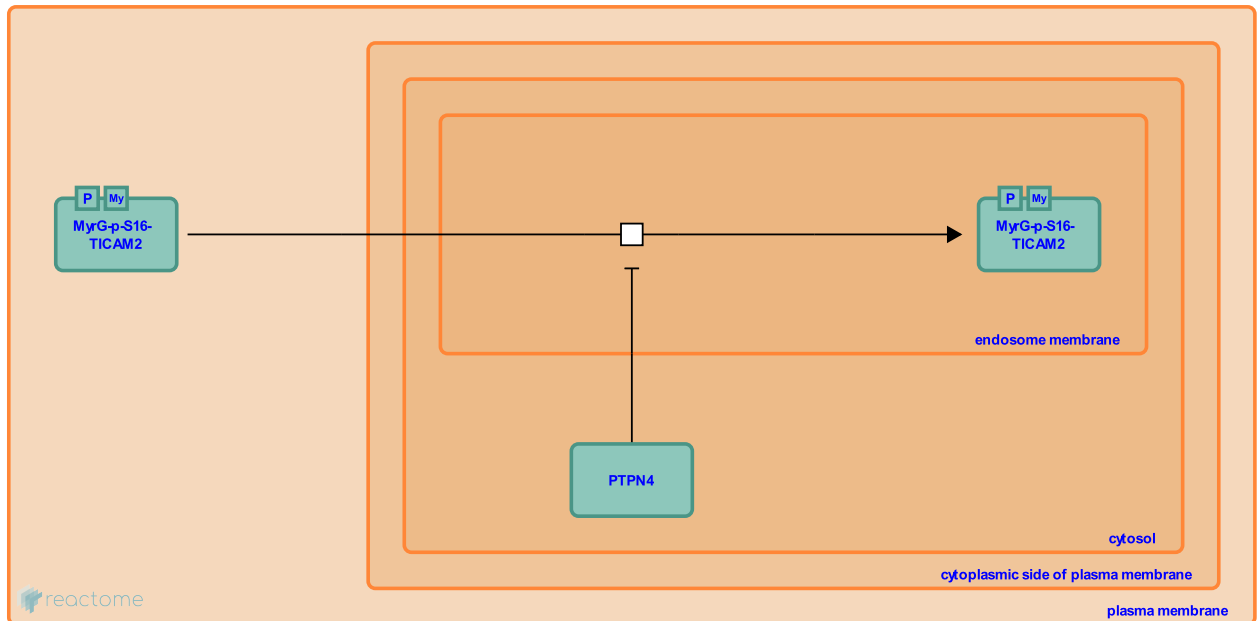
## Endocytosis of TRAM (TICAM2) ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-2201341

**Type:** transition

**Compartments:** endosome membrane, plasma membrane



TRIF-related adapter molecule (TRAM or also known as TICAM2) is a sorting adapter which recruits TRIF to activated TLR4. Like TLR4, TRAM (TICAM2) was detected both at the plasma membrane and in the endosomal compartment. TICAM2 was reported to recruit TRIF to the plasma membrane (Tanimuro N et al. 2008). However, TICAM2 did not induce TRIF-mediated signaling from the cell surface, instead, TICAM2 endocytosis was required for activation of IRF3 and induction of IFN-beta (Tanimuro N et al. 2008; Kagan JC et al. 2008). Although, endocytosis of both TLR4 and TICAM2 and their association are required to trigger TRIF-mediated signaling, TICAM2 can target endosomes independently on its interaction with TLR4. TICAM2 cellular localization is controlled by myristoylation and phosphorylation of its N-terminal bipartite sorting signal motif (Kagan JC et al 2008).

TICAM2 has been shown to undergo phosphorylation on Ser-16 by protein kinase C (PKC) epsilon in LPS-treated human THP1 and murine embryonic fibroblasts (MEF) cells (McGettrick AF et al. 2006). The phosphorylation at Ser-16 by PKC epsilon was required for TICAM2 to be depleted from the membrane (McGettrick AF et al. 2006).

It has recently been demonstrated that phosphorylation of TICAM2 at tyrosine residue Y167 by an unknown protein tyrosine kinase is needed for TICAM2 translocation from the plasma membrane to the endosomal membrane, where it can associate with the activated TLR4 complex (Huai et al. 2015). PTPN4, a protein tyrosine phosphatase, dephosphorylates Y167 of TICAM2, thus inhibiting TICAM2 endocytosis (Huai et al. 2015).

### Literature references

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2012-11-13	Reviewed	Zanoni, I., Granucci, F.

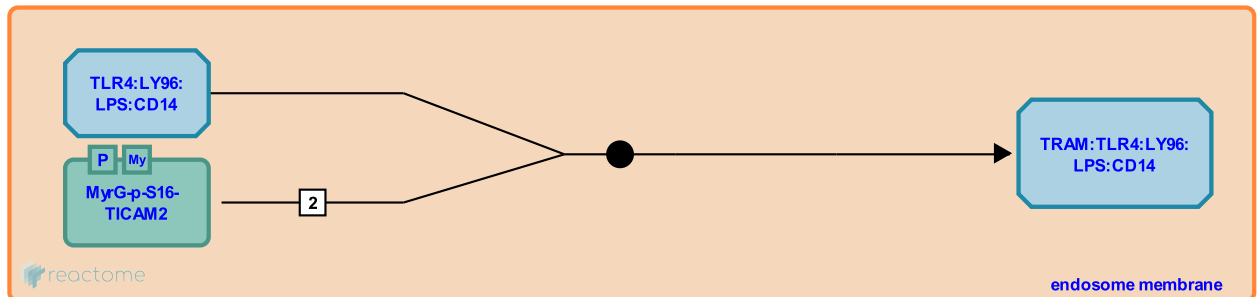
## TLR4:LY96:LPS:CD14 recruits TRAM (TICAM2) ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-166168

**Type:** binding

**Compartments:** endosome membrane



TRIF-related adapter molecule (TRAM, also called TIRP or TICAM2) is 235 amino acids in length, and its TIR domain is most closely related to TRIF (and hence its name). Notably, both human and mouse TRAM contain a cysteine (C117 in humans) at the position where other adapters and TLRs have a conserved proline, although an adjacent proline (P116) is present. TRAM associates with TLR4 and TRIF, as well as the non-canonical NFκB kinases, IKK epsilon, and TBK1, which phosphorylate IRF3. TRAM provides specificity for the MyD88-independent component of TLR4 signaling.

**Preceded by:** Endocytosis of TLR4:LY96:LPS:CD14

### Literature references

- Fitzgerald, KA., Rowe, DC., Golenbock, DT. (2004). Endotoxin recognition and signal transduction by the TLR4/MD2-complex. *Microbes Infect*, 6, 1361-7. ↗
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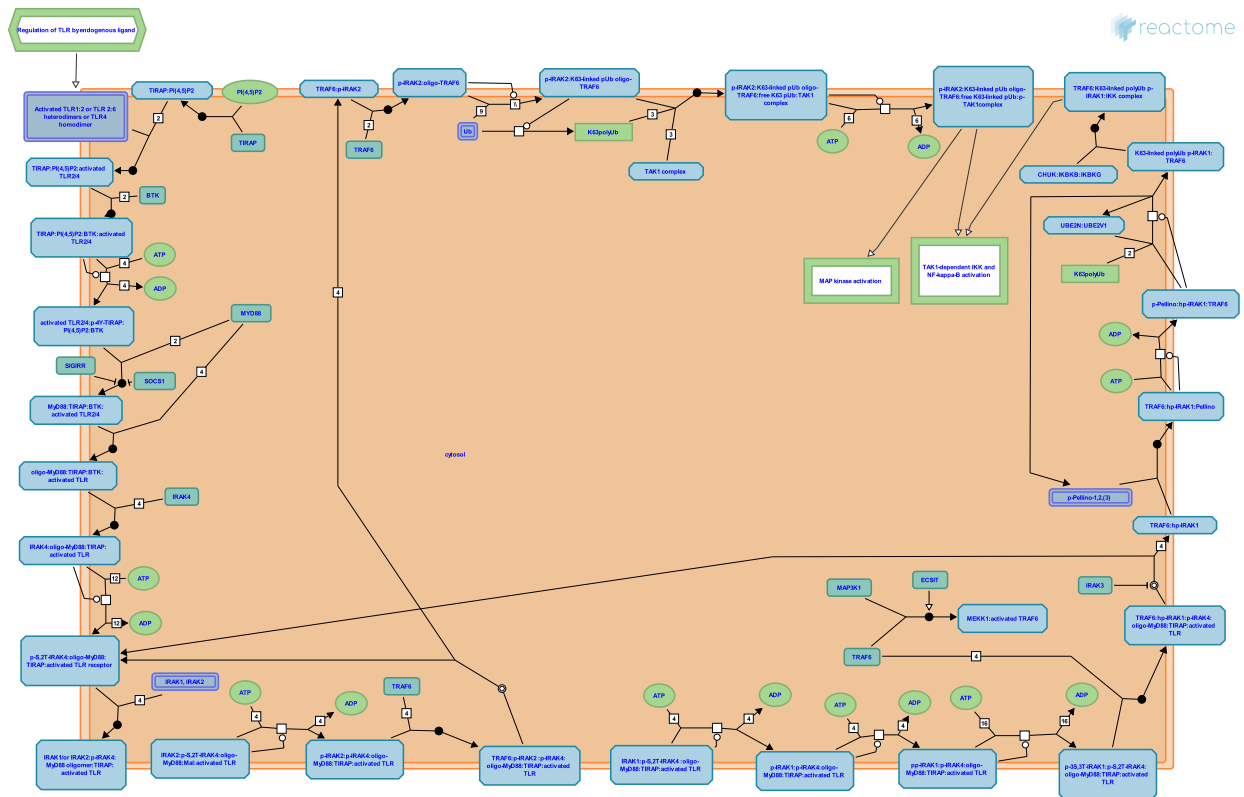
### Editions

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2012-11-13	Reviewed	Zanoni, I., Granucci, F.

# MyD88:MAL(TIRAP) cascade initiated on plasma membrane ↗

Location: Toll Like Receptor 4 (TLR4) Cascade

Stable identifier: R-HSA-166058



The first known downstream component of TLR4 and TLR2 signaling is the adaptor MyD88-adaptor-like (Mal; also known as TIR-domain-containing adaptor protein or TIRAP) has also been described for TLR4 and TLR2 signaling. MyD88 comprises an N-terminal Death Domain (DD) and a C-terminal TIR, whereas Mal lacks the DD. The TIR homotypic interactions bring adaptors into contact with the activated TLRs, whereas the DD modules recruit serine/threonine kinases such as interleukin-1-receptor-associated kinase (IRAK). Recruitment of these protein kinases is accompanied by phosphorylation, which in turn results in the interaction of IRAKs with TNF-receptor-associated factor 6 (TRAF6). The oligomerization of TRAF6 activates TAK1, a member of the MAP3-kinase family, and this leads to the activation of the IκB kinases. These kinases, in turn, phosphorylate IκB, leading to its proteolytic degradation and the translocation of NF-κB to the nucleus. Concomitantly, members of the activator protein-1 (AP-1) transcription factor family, Jun and Fos, are activated, and both AP-1 transcription factors and NF-κB are required for cytokine production, which in turn produces downstream inflammatory effects.

## Literature references

Gay, NJ., Gangloff, M. (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. *Trends Biochem Sci*, 29, 294-300. ↗

## Editions

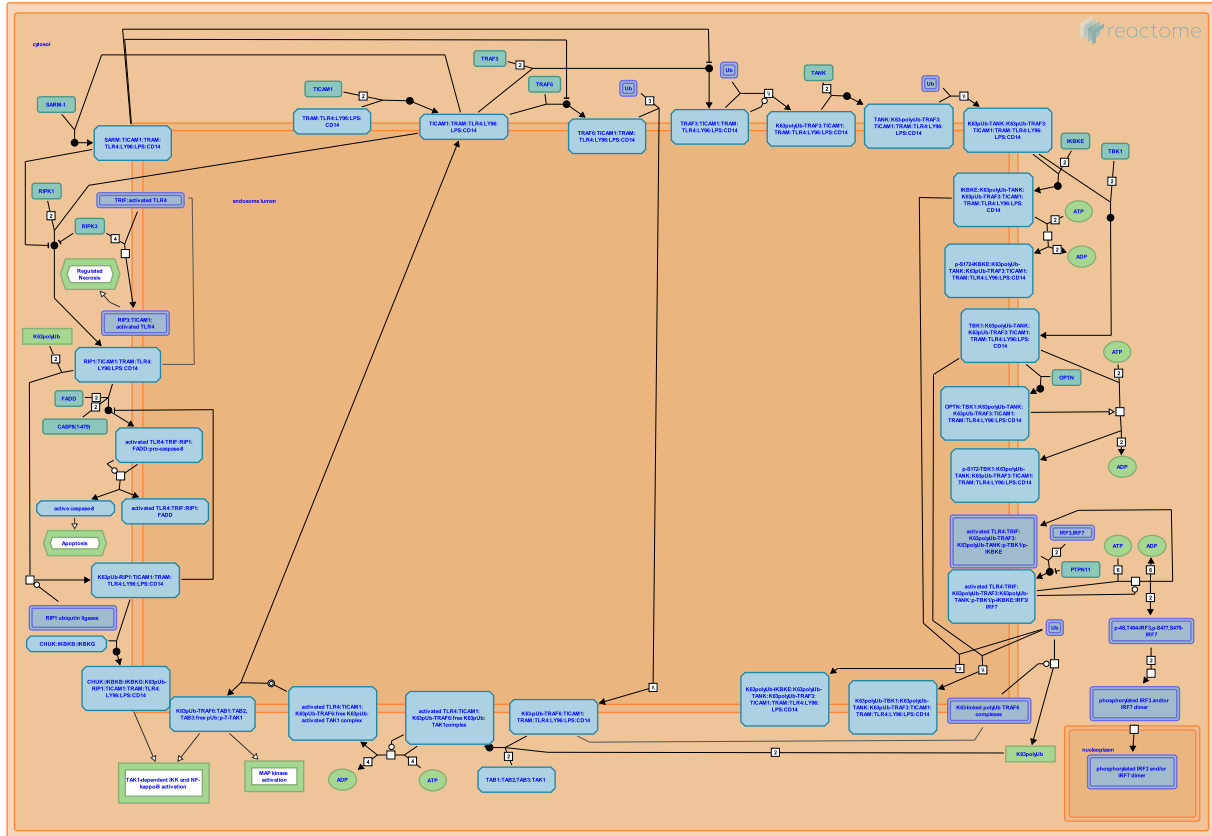
2005-08-16	Authored	de Bono, B.
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# MyD88-independent TLR4 cascade ↗

**Location:** Toll Like Receptor 4 (TLR4) Cascade

**Stable identifier:** R-HSA-166166

**Compartments:** cytosol



The MyD88-independent signaling pathway is shared by TLR3 and TLR4 cascades. TIR-domain-containing adapter-inducing interferon-beta (TRIF or TICAM1) is a key adapter molecule in transducing signals from TLR3 and TLR4 in a MyD88-independent manner (Yamamoto M et al. 2003a). TRIF is recruited to the ligand-stimulated TLR3 or 4 complex via its TIR domain. TLR3 directly binds TRIF (Oshiumi H et al 2003). In contrast, the TLR4-mediated signaling pathway requires two adapter molecules, TRAM (TRIF-related adapter molecule or TICAM2) and TRIF. TRAM(TICAM2) is thought to bridge the activated TLR4 complex and TRIF (Yamamoto M et al. 2003b, Tanimura N et al. 2008, Kagan LC et al. 2008).

TRIF recruitment to the TLR complex stimulates distinct pathways leading to the production of type I interferons (IFNs) and pro-inflammatory cytokines and to the induction of programmed cell death.

## Literature references

Gay, NJ., Gangloff, M. (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. *Trends Biochem Sci*, 29, 294-300. ↗

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