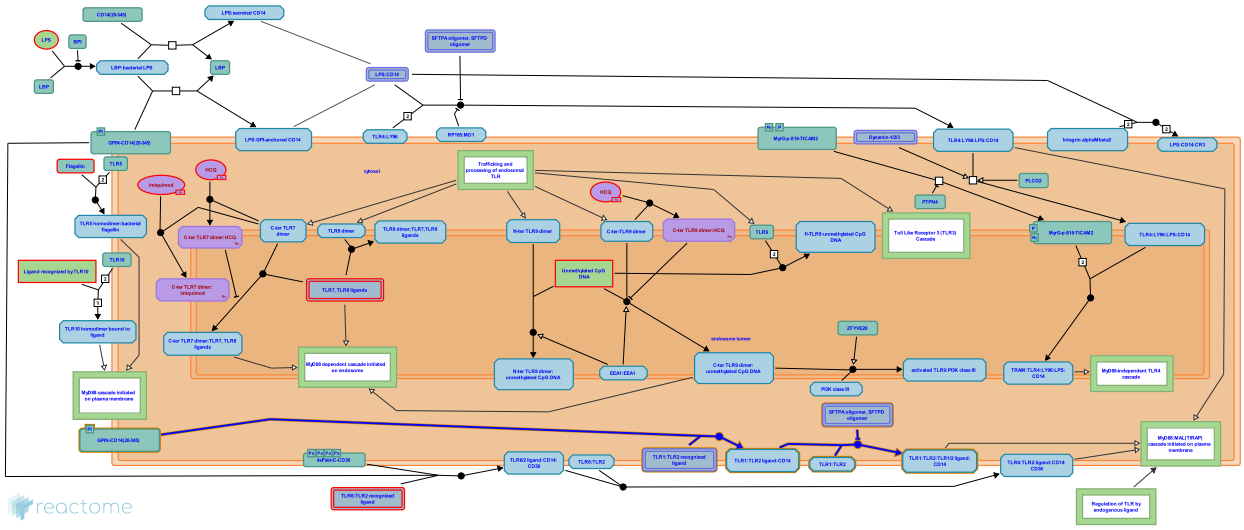
Toll Like Receptor TLR1:TLR2 Cascade



D'Eustachio, P., Gale M, Jr., Gay, NJ., Gillespie, ME., Granucci, F., Napetschnig, J., Shamovsky, V., Zanoni, I., Zwaginga, JJ., de Bono, B.

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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.
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).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

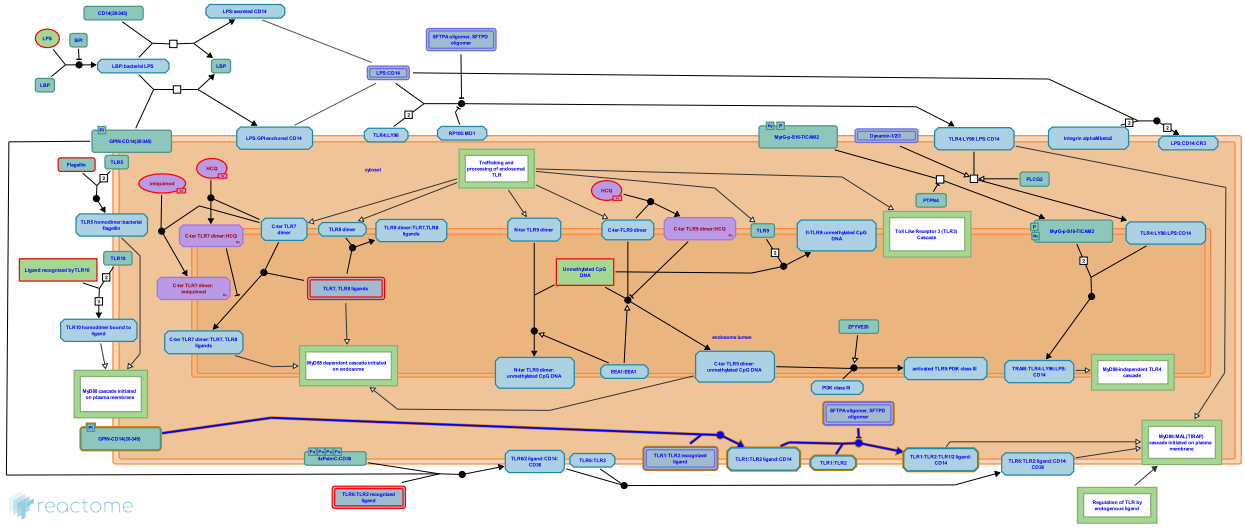
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Toll Like Receptor TLR1:TLR2 Cascade ↗

Stable identifier: R-HSA-168179



TLR1 is expressed by monocytes. TLR1 and TLR2 cotranslationally form heterodimeric complexes on the cell surface and in the cytosol. The TLR2:TLR1 complex recognizes Neisserial PorB and Mycobacterial triacylated lipoproteins and peptides, amongst others, triggering up-regulation of nuclear factor-kappaB production and apoptotic cascades. Such cooperation between TLR1 and TLR2 on the cell surface of normal human peripheral blood mononuclear cells, for instance, leads to the activation of pro-inflammatory cytokine secretion (Sandor et al. 2003).

Literature references

Latz, E., Mandell, L., Re, F., Repik, G., Finberg, RW., Golenbock, DT. et al. (2003). Importance of extra- and intracellular domains of TLR1 and TLR2 in NFkappa B signaling. *J Cell Biol, 162*, 1099-110. ↗

Editions

2006-04-19	Authored	D'Eustachio, P., Gay, NJ., Gale M, Jr., Zwaginga, JJ.
2006-07-04	Reviewed	D'Eustachio, P.
2012-11-02	Revised	Shamovsky, V.
2012-11-06	Edited	Shamovsky, V.

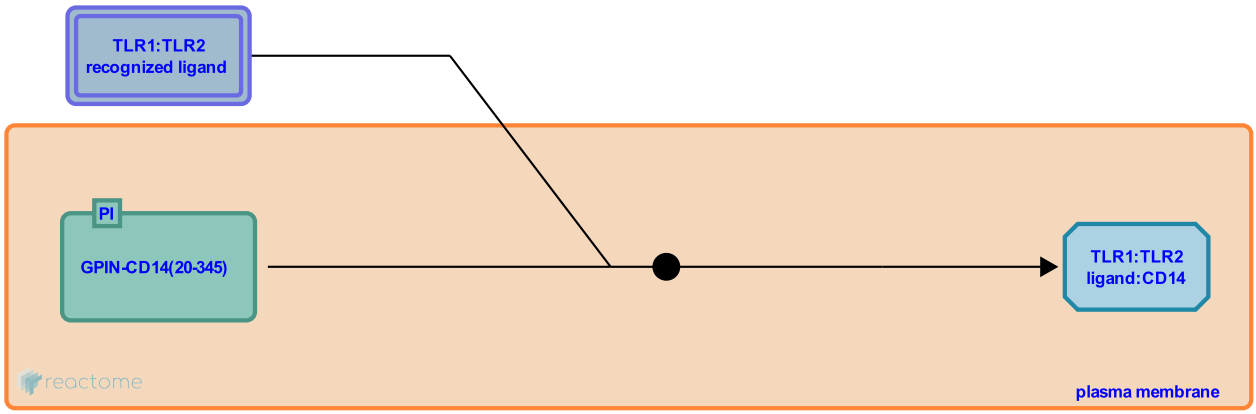
TLR1/2 ligand binds to CD14 ↗

Location: Toll Like Receptor TLR1:TLR2 Cascade

Stable identifier: R-HSA-2559468

Type: binding

Compartments: plasma membrane, extracellular region



CD14, a GPI-anchored molecule found on the cell surface of human phagocytes, has been identified as a co-receptor that interacts with LPS. CD14 has been also implicated in TLR-2 signalling [Hajishengallis G et al 2006; Zivkovic A et al 2011]. Studies have demonstrated that CD14 can bind to triacylated lipoproteins and mediate the activation of the innate immune system trough TLR2:TLR1 complex [Nakata T et al 2006; Manukyan M et al 2005; Triantafilou M et al 2006]

Followed by: TLR1:TLR2 is recruited to ligand:CD14

Literature references

Triantafilou, M., Manukyan, M., Nilsen, N., Triantafilou, K., Ulmer, AJ., Heine, H. et al. (2005). Binding of lipopeptide to CD14 induces physical proximity of CD14, TLR2 and TLR1. *Eur. J. Immunol., 35*, 911-21. ↗

Gamper, FG., Mouratis, MA., Triantafilou, M., Triantafilou, K., Morath, S., Haston, RM. et al. (2006). Membrane sorting of toll-like receptor (TLR)-2/6 and TLR2/1 heterodimers at the cell surface determines heterotypic associations with CD36 and intracellular targeting. *J. Biol. Chem., 281*, 31002-11. ↗

Editions

2012-05-15	Authored	Shamovsky, V.
2012-11-13	Reviewed	Zanoni, I., Granucci, F.
2012-11-19	Edited	Shamovsky, V.

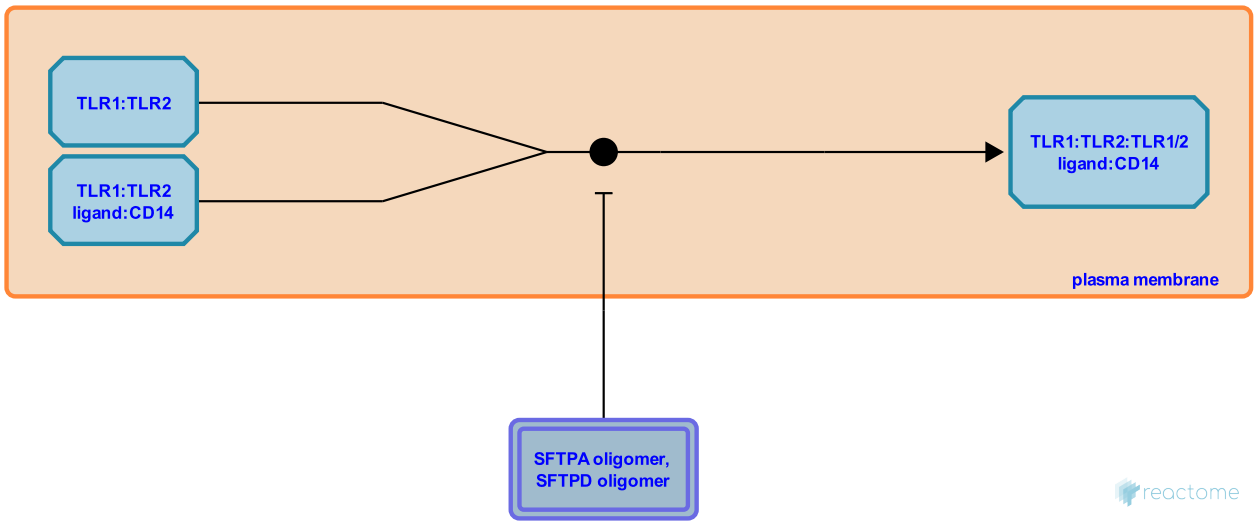
TLR1:TLR2 is recruited to ligand:CD14 ↗

Location: Toll Like Receptor TLR1:TLR2 Cascade

Stable identifier: R-HSA-168951

Type: binding

Compartments: plasma membrane



The TLR2:TLR1 complex recognizes Neisserial PorB and Mycobacterial triacylated lipoproteins and peptides, amongst others.

Preceded by: TLR1/2 ligand binds to CD14

Literature references

Zychlinsky, A., Klimpel, GR., Devaux, B., Yang, RB., Radolf, JD., Mark, MR. et al. (1999). Cell activation and apoptosis by bacterial lipoproteins through toll-like receptor-2. *Science, 285*, 736-9. ↗

Beutler, B. (2004). Inferences, questions and possibilities in Toll-like receptor signalling. *Nature, 430*, 257-63. ↗

Wetzler, LM., King, CA., Gunawardana, J., Golenbock, DT., Halmen, KA., Massari, P. et al. (2006). Meningococcal porin PorB binds to TLR2 and requires TLR1 for signaling. *J Immunol, 176*, 2373-80. ↗

Editions

2006-04-19	Authored	D'Eustachio, P., Gay, NJ., Gale M, Jr., Zwaginga, JJ.
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2010-11-30	Reviewed	Gillespie, ME.
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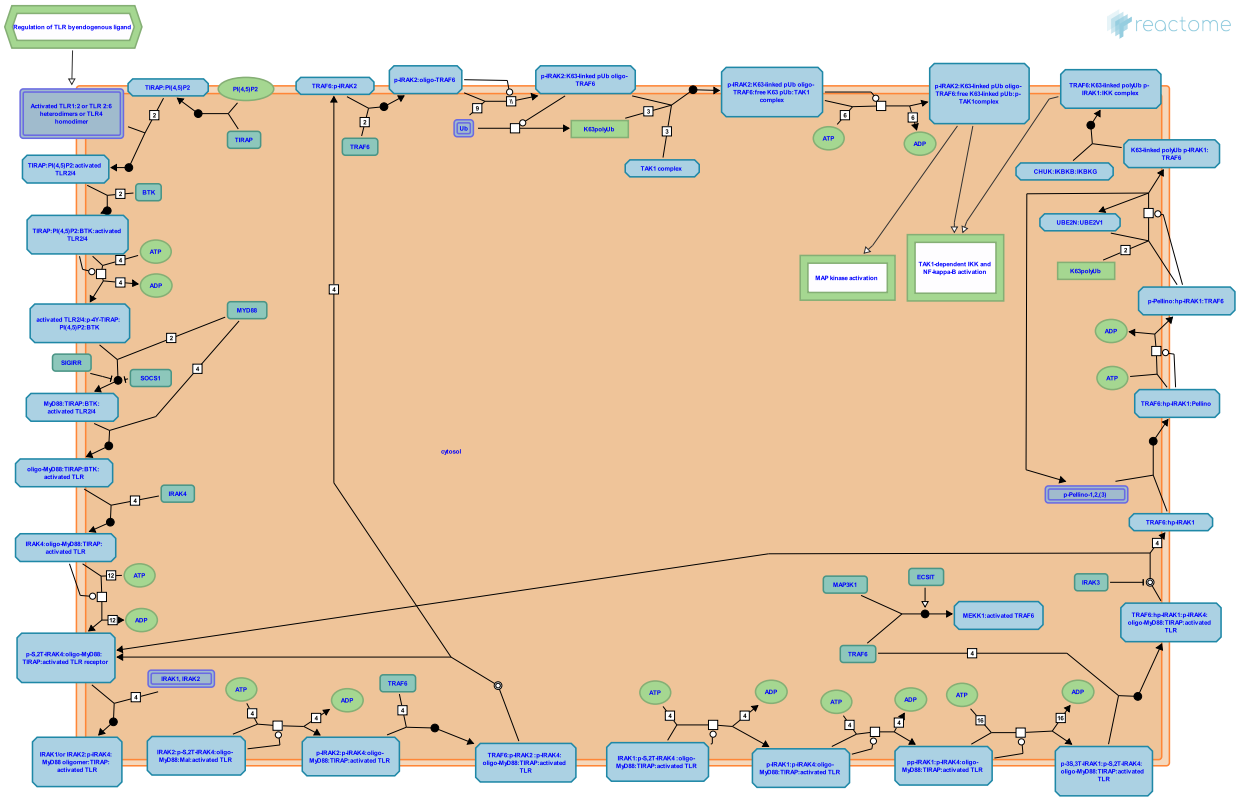
MyD88:MAL(TIRAP) cascade initiated on plasma membrane ↗

Location: Toll Like Receptor TLR1:TLR2 Cascade

Stable identifier: R-HSA-166058



The first known downstream component of TLR4 and TLR2 signaling is the adaptor MyD88. Another adapter 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 adapters 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 IkB kinases. These kinases, in turn, phosphorylate IkB, leading to its proteolytic degradation and the translocation of NF-kB 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-kB 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.
2006-04-24	Reviewed	Gay, NJ.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-02	Revised	Shamovsky, V.
2012-11-06	Edited	Shamovsky, V.
2012-11-16	Reviewed	Napetschnig, J.

Table of Contents