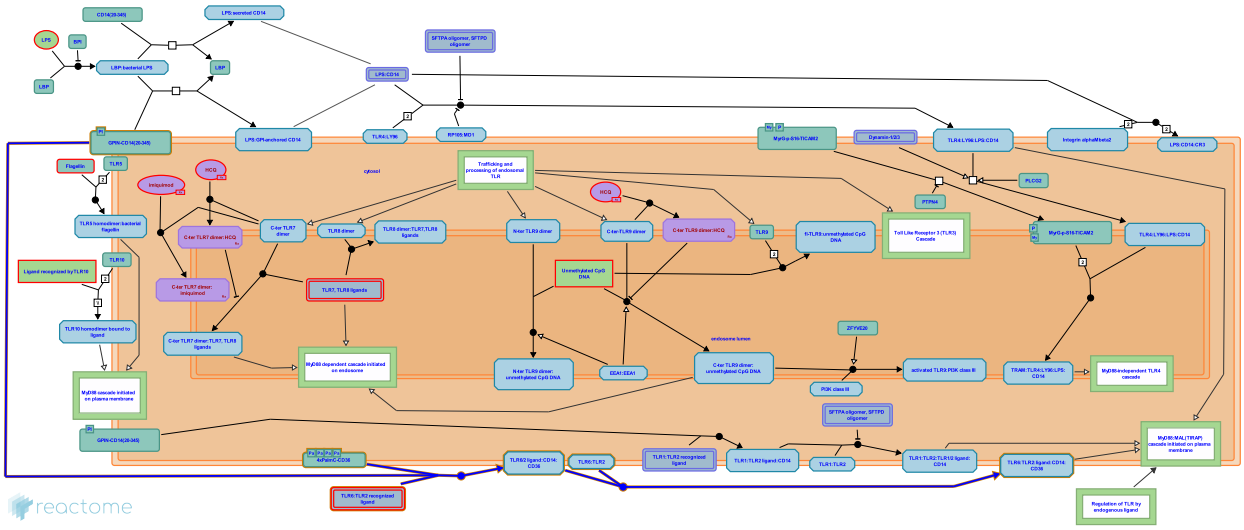
Toll Like Receptor TLR6:TLR2 Cascade



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

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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.

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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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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. ↗

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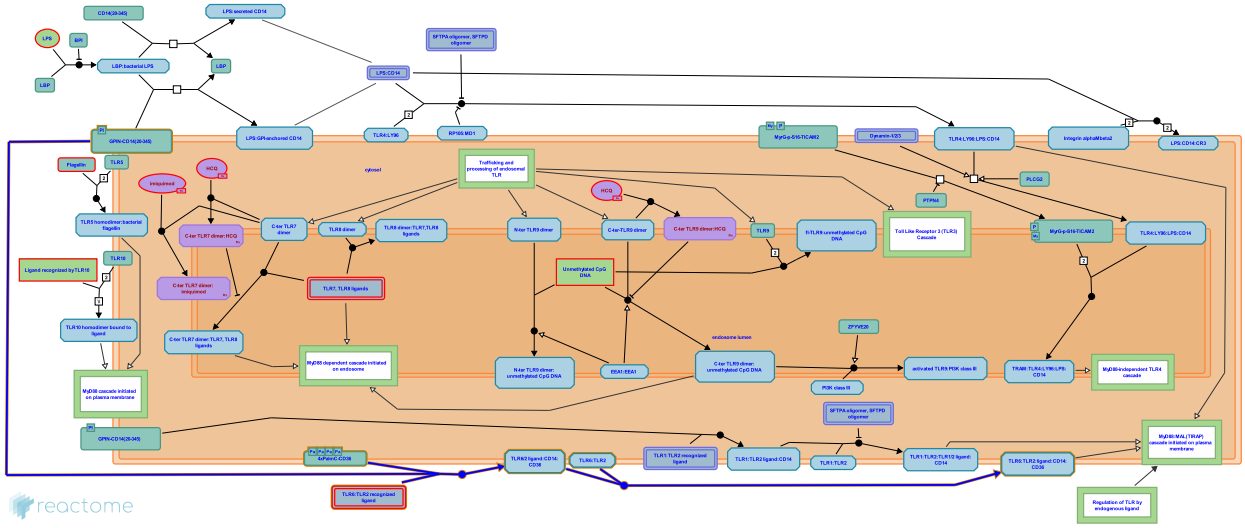
Toll Like Receptor TLR6:TLR2 Cascade ↗

Stable identifier: R-HSA-168188



TLR2 and TLR4 recognize different bacterial cell wall components. While TLR4 is trained onto Gram-negative lipopolysaccharide components, TLR2 - in combination with TLR6 - plays a major role in recognizing peptidoglycan wall products from Gram-positive bacteria, as well as Mycobacterial diacylated lipopeptides. In particular, TLR6 appears to participate in discriminating the subtle differences between dipalmitoyl and tripalmitoyl cysteinyl residues (Okusawa et al. 2004).

Literature references

Hasebe, A., Shibata, K., Into, T., Hara, Y., Nakamura, J., Ogawa, T. et al. (2004). Relationship between structures and biological activities of mycoplasmal diacylated lipopeptides and their recognition by toll-like receptors 2 and 6. *Infect Immun, 72*, 1657-65. ↗

Editions

2006-04-19	Authored	D'Eustachio, P., Gay, NJ., Gale M, Jr., Zwaginga, JJ.
2006-07-04	Reviewed	D'Eustachio, P.
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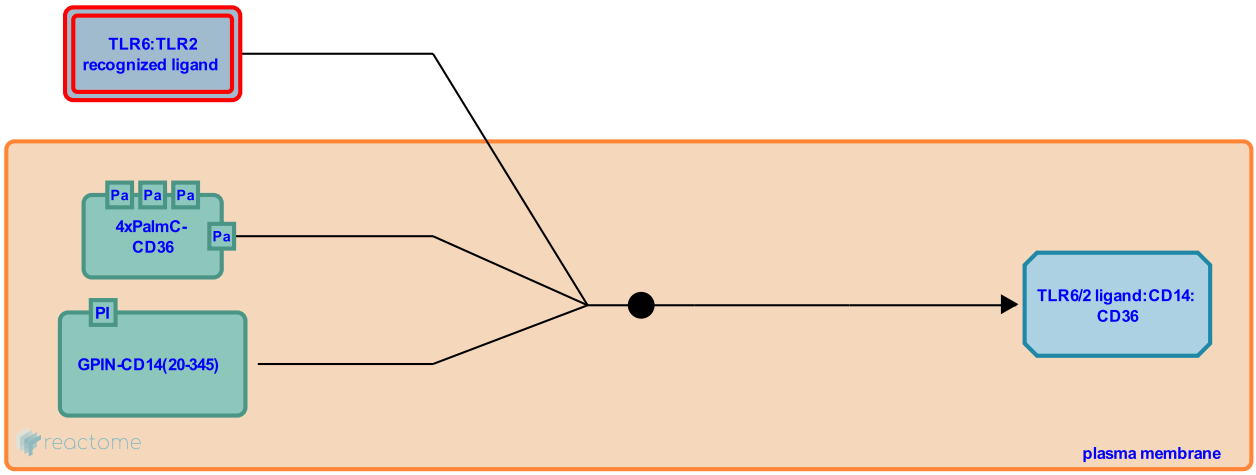
TLR6/2 ligand associates with CD14 and CD36 within lipid rafts ↗

Location: Toll Like Receptor TLR6:TLR2 Cascade

Stable identifier: R-HSA-2559464

Type: binding

Compartments: plasma membrane, extracellular region



Scavenger receptor CD36 has been reported to function as an essential co-receptor involved in recognition of LTA and certain diacylated lipoproteins and presenting them to the TLR2:TLR6 heterodimer at the cell surface. CD14, a GPI-anchored molecule found on the cell surface of human phagocytes, has been also implicated in TLR2:TLR6 signaling [Stuart L et al 2005; Hoebe KP et al 2005; Triantafilou M et al 2006; Nilsen NJ et al 2008]

Followed by: TLR6:TLR2 is recruited to ligand:CD14:CD36

Literature references

Matsumoto, M., Bas, S., Gabay, C., Seya, T., Vuillet, M., Spenato, U. et al. (2008). The proinflammatory cytokine response to Chlamydia trachomatis elementary bodies in human macrophages is partly mediated by a lipoprotein, the macrophage infectivity potentiator, through TLR2/TLR1/TLR6 and CD14. *J. Immunol., 180*, 1158-68. ↗

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

2006-07-04	Reviewed	D'Eustachio, P.
2010-11-30	Reviewed	Gillespie, ME.
2012-05-15	Authored	Shamovsky, V.
2012-11-13	Reviewed	Zanoni, I., Granucci, F.
2012-11-16	Edited	Shamovsky, V.

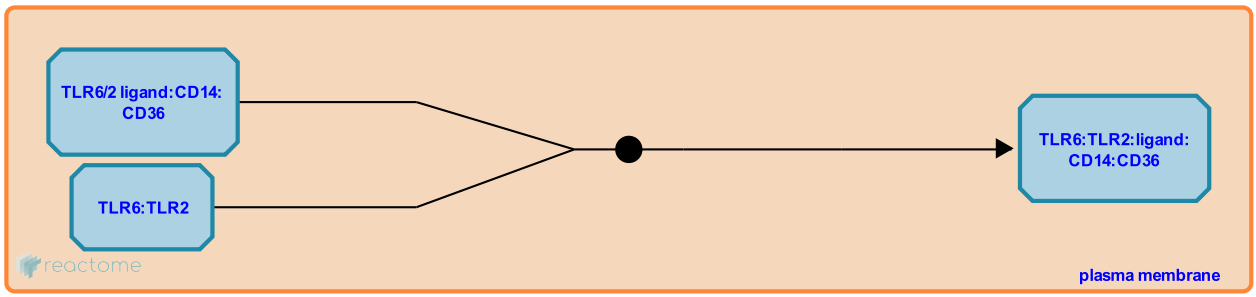
TLR6:TLR2 is recruited to ligand:CD14:CD36 ↗

Location: Toll Like Receptor TLR6:TLR2 Cascade

Stable identifier: R-HSA-168950

Type: binding

Compartments: plasma membrane, extracellular region



TLR2 - in combination with TLR6 - plays a major role in recognizing lipoteichoic acid (LTA) and peptidoglycan wall products from Gram-positive bacteria, as well as Mycobacterial diacylated lipopeptides.

Preceded by: TLR6/2 ligand associates with CD14 and CD36 within lipid rafts

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. ↗

Schwandner, R., Wesche, H., Kirschning, CJ., Rothe, M., Dziarski, R. (1999). Peptidoglycan- and lipoteichoic acid-induced cell activation is mediated by toll-like receptor 2. *J Biol Chem, 274*, 17406-9. ↗

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Hasebe, A., Shibata, K., Into, T., Hara, Y., Nakamura, J., Ogawa, T. et al. (2004). Relationship between structures and biological activities of mycoplasmal diacylated lipopeptides and their recognition by toll-like receptors 2 and 6. *Infect Immun, 72*, 1657-65. ↗

Takeuchi, O., Sanjo, H., Hoshino, K., Takeda, K., Akira, S., Ogawa, T. et al. (1999). Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. *Immunity, 11*, 443-51. ↗

Editions

2006-04-19	Authored	D'Eustachio, P., Gay, NJ., Gale M, Jr., Zwaginga, JJ.
2006-07-04	Reviewed	D'Eustachio, P.
2010-11-30	Reviewed	Gillespie, ME.
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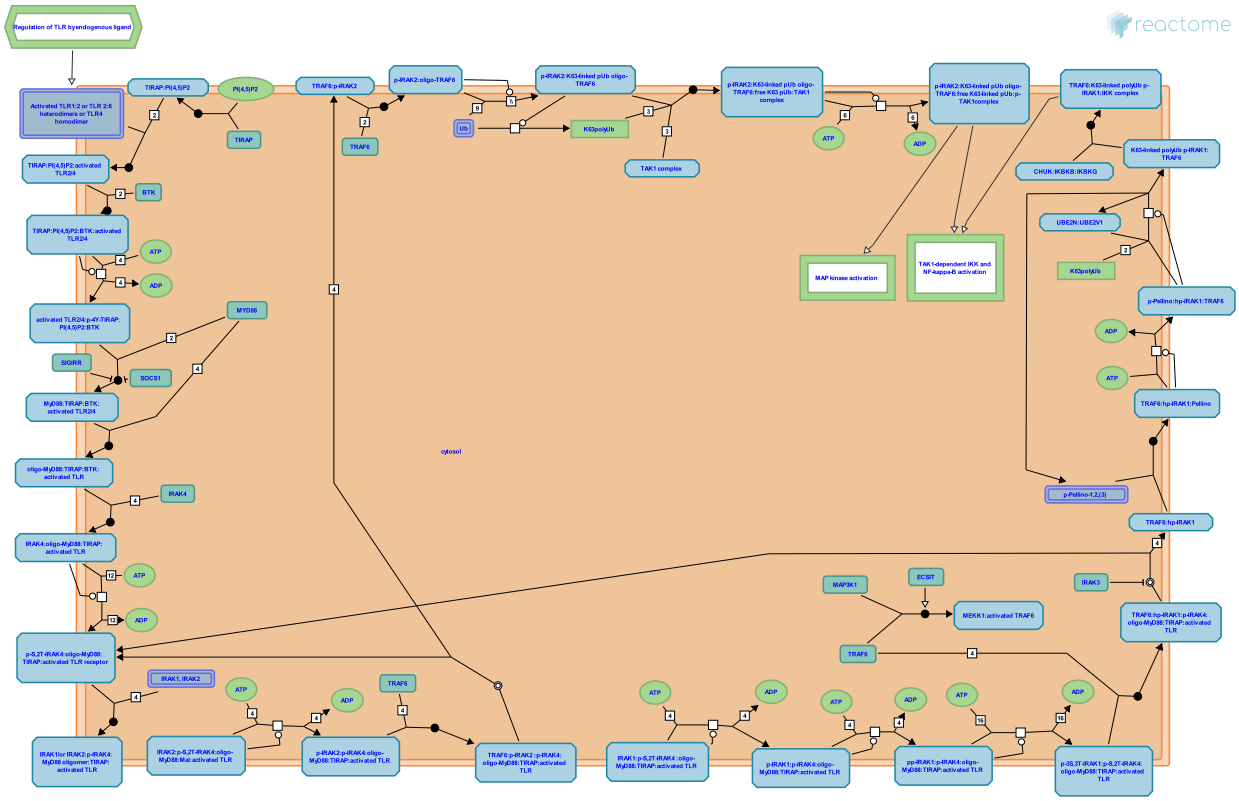
MyD88:MAL(TIRAP) cascade initiated on plasma membrane ↗

Location: Toll Like Receptor TLR6: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.
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