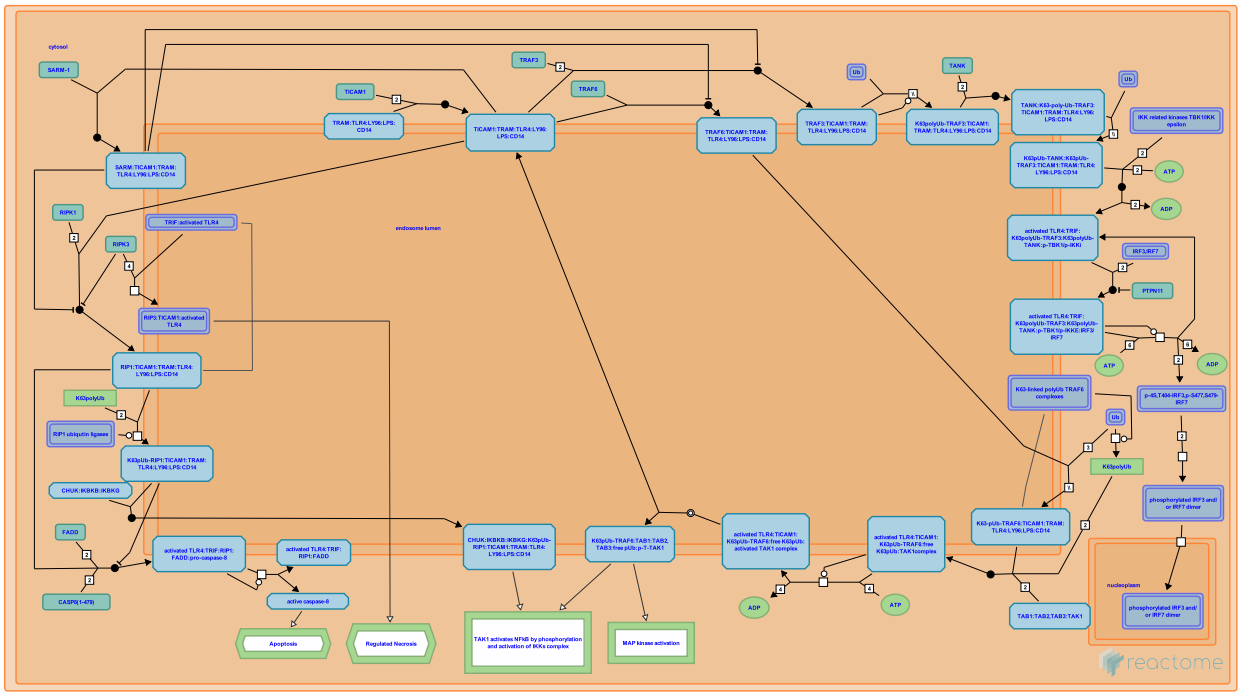
MyD88-independent TLR4 cascade



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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

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. ↗

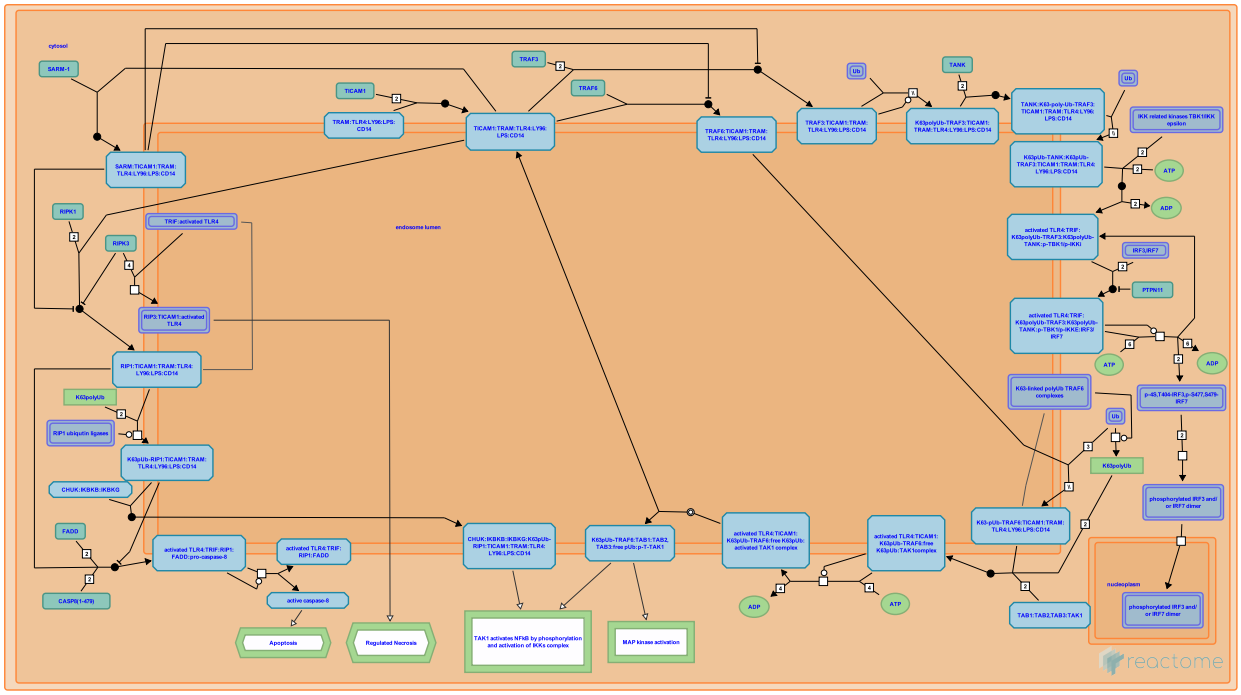
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

MyD88-independent TLR4 cascade

Stable identifier: R-HSA-166166

Compartments: cytosol



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 ligand-stimulated TLR3 or 4 complex via its TIR domain. TLR3 directly binds TRIF (Oshiumi H et al 2003). In contrast, TLR4-mediated signaling pathway requires two adapter molecules, TRAM (TRIF-related adapter molecule or TICAM2) and TRIF. TRAM(TICAM2) is thought to bridge between the activated TLR4 complex and TRIF (Yamamoto M et al. 2003b, Tanimura N et al. 2008, Kagan LC et al. 2008).

TRIF recruitment to TLR complex stimulates distinct pathways leading to production of type 1 interferons (IFNs), pro-inflammatory cytokines and induction of programmed cell death.

Literature references

Gangloff, M., Gay, NJ. (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.
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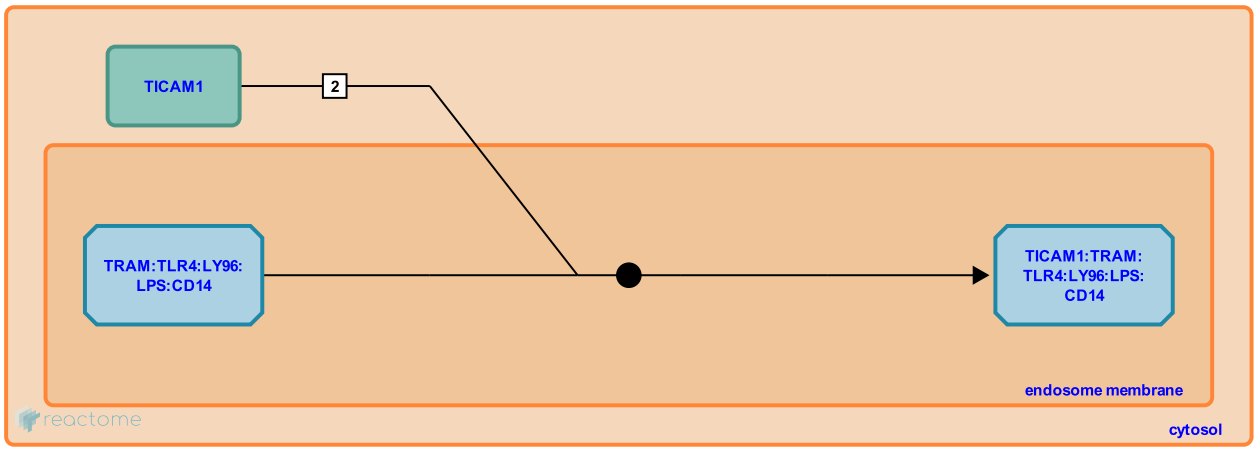
TRAM:TLR4:LY96:LPS:CD14 recruits TRIF (TICAM1) ↗

Location: MyD88-independent TLR4 cascade

Stable identifier: R-HSA-166175

Type: binding

Compartments: endosome membrane, cytosol



TRIF (TICAM1) mediates the MyD88-independent pathway from TLR4.

Followed by: SARM binds TICAM1:TRAM:TLR4:LY96:LPS:CD14

Literature references

Yamamoto, M., Sato, S., Hemmi, H., Hoshino, K., Kaisho, T., Sanjo, H. et al. (2003). Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science, 301*, 640-3. ↗

Yamamoto, M., Sato, S., Hemmi, H., Uematsu, S., Hoshino, K., Kaisho, T. et al. (2003). TRAM is specifically involved in the Toll-like receptor 4-mediated. *Nat Immunol, 4*, 1144-50. ↗

Fitzgerald, KA., Rowe, DC., Barnes, BJ., Caffrey, DR., Visintin, A., Latz, E. et al. (2003). LPS-TLR4 signaling to IRF-3/7 and NF-kappaB involves the toll adapters. *J Exp Med, 198*, 1043-55. ↗

Editions

2005-08-16	Authored	de Bono, B.
2006-04-24	Reviewed	Gay, NJ.
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2012-11-13	Reviewed	Fitzgerald, KA.

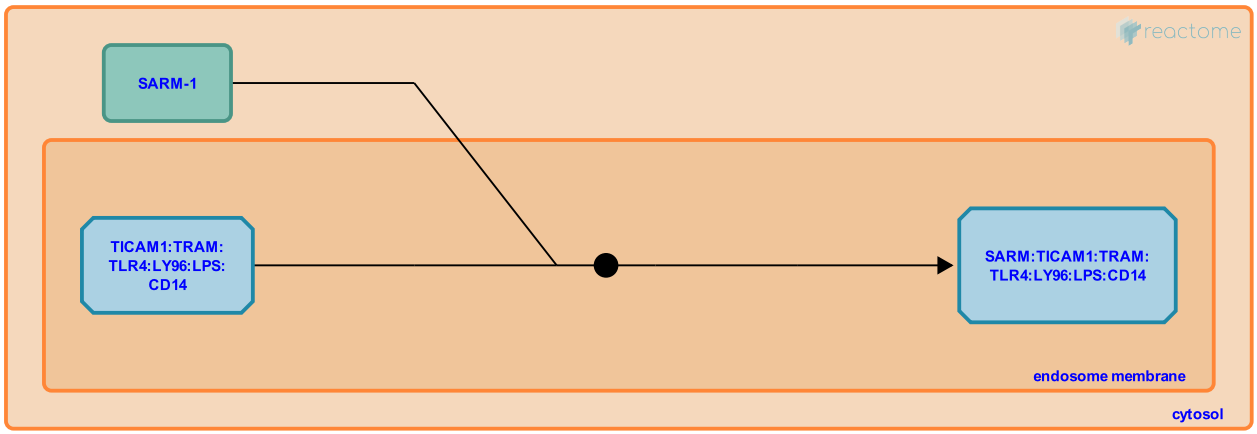
SARM binds TICAM1:TRAM:TLR4:LY96:LPS:CD14

Location: MyD88-independent TLR4 cascade

Stable identifier: R-HSA-2559568

Type: binding

Compartments: endosome membrane, cytosol



SARM (sterile alpha-and armadillo-motif-containing protein) is a TIR-domain-containing adaptor, which functions as a negative regulator of TRIF (TICAM1)-dependent Toll-like receptor signaling in humans. A pairwise yeast two-hybrid assay demonstrated that SARM is capable of binding directly to TICAM1 (Carty M et al. 2006). GST pulldown studies suggest that protein-protein interactions occur between the TIR domains of SARM and TICAM1 (Carlsson E et al. 2016). The complex of TICAM1:SARM is thought to inhibit downstream TRIF signaling by preventing the recruitment of TRIF effector proteins (Carty M et al. 2006).

LPS treatment led to a rapid increase of the SARM expression in peripheral blood mononuclear cells (PBMCs) and as a result an increased association between SARM and TICAM1 (Carty M et al. 2006). Moreover, suppression of endogenous SARM expression by siRNA led to enhanced TLR4-dependent gene induction in both transformed HEK293 and primary PBMC cells, while endotoxin-tolerant human monocytes showed increased expression of SARM and decreased activation of TICAM1-dependent cytokines (Carty M et al. 2006; Piao W et al. 2009). Thus, SARM negatively regulates TICAM1 (TRIF)-dependent TLR4 signaling pathway.

Preceded by: TRAM:TLR4:LY96:LPS:CD14 recruits TRIF (TICAM1)

Literature references

Carty, M., Goodbody, R., Schröder, M., Stack, J., Moynagh, PN., Bowie, AG. (2006). The human adaptor SARM negatively regulates adaptor protein TRIF-dependent Toll-like receptor signaling. *Nat. Immunol., 7*, 1074-81.

Piao, W., Song, C., Chen, H., Diaz, MA., Wahl, LM., Fitzgerald, KA. et al. (2009). Endotoxin tolerance dysregulates MyD88- and Toll/IL-1R domain-containing adapter inducing IFN-beta-dependent pathways and increases expression of negative regulators of TLR signaling. *J. Leukoc. Biol., 86*, 863-75.

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2012-05-15	Authored	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
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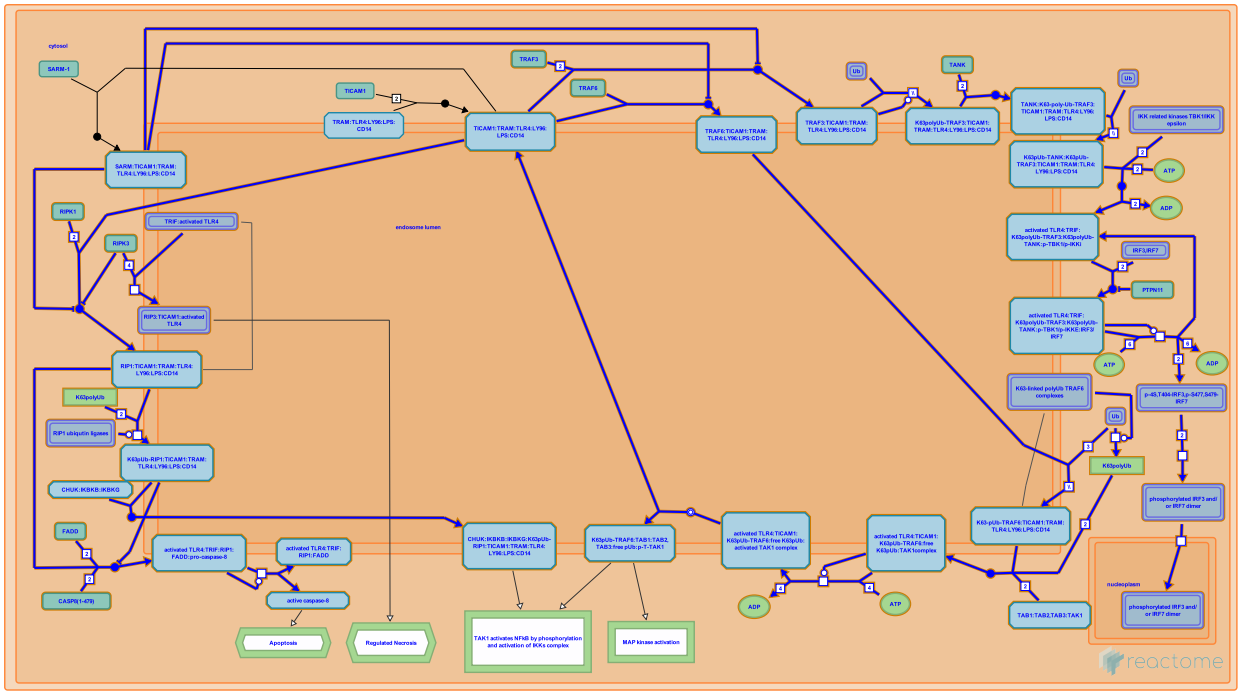
TRIF(TICAM1)-mediated TLR4 signaling ↗

Location: MyD88-independent TLR4 cascade

Stable identifier: R-HSA-937061



TRIF(TICAM1) was shown to induce IRF3/7 and NFkappaB activation and apoptosis through distinct intracellular signaling pathways [Han KJ et al 2004; Kaiser WJ and Offermann MK et al 2005]. TRIF consists of an N-terminal region (1-234), a TIR domain (235-500), and a C-terminal region (501-680).

The N-terminal region of TRIF harbors TRAF (TNF receptor associated factor) family proteins and forms complexes containing IRF-3 and/or NFkB -activating kinases. The C-terminal region of TRIF can recruit receptor-interacting protein-1 (RIP-1), and this event is followed by the activation of IKK complex.

Literature references

Kaiser, WJ., Offermann, MK. (2005). Apoptosis induced by the toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. *J Immunol, 174*, 4942-52. ↗

Han, KJ., Su, X., Xu, LG., Bin, LH., Zhang, J., Shu, HB. (2004). Mechanisms of the TRIF-induced interferon-stimulated response element and NF-kappaB activation and apoptosis pathways. *J. Biol. Chem., 279*, 15652-61. ↗

Yamamoto, M., Sato, S., Hemmi, H., Hoshino, K., Kaisho, T., Sanjo, H. et al. (2003). Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science, 301*, 640-3. ↗

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