TIRAP is phosphorylated by BTK

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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

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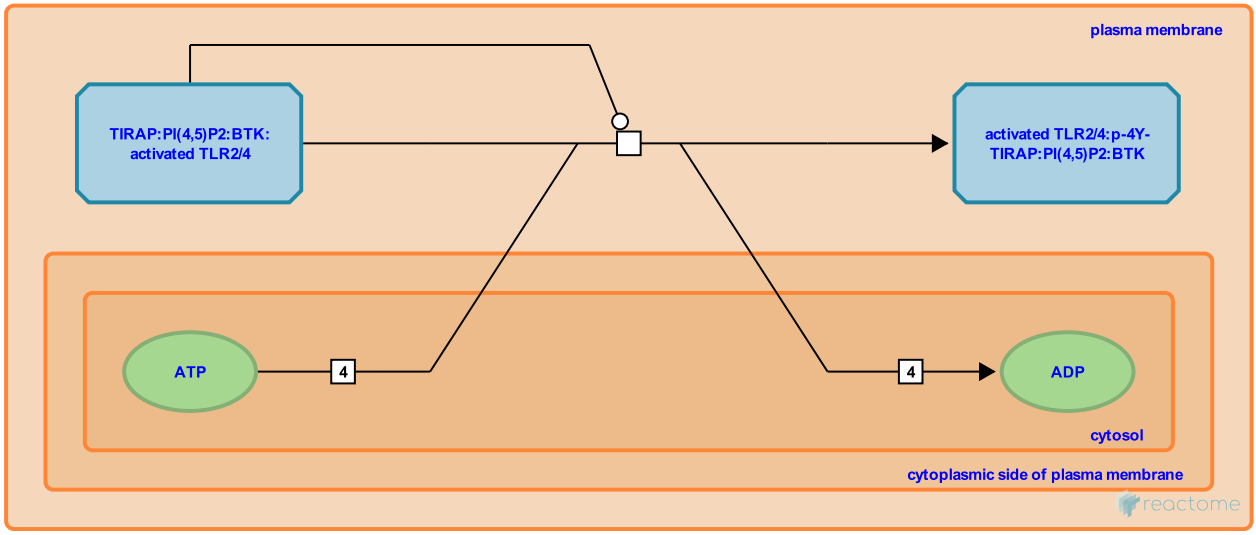
Stable identifier: R-HSA-2201322

Type: transition

Compartments: plasma membrane, cytosol



Upon activation of TLR2/or 4 signaling pathway TIRAP(MAL), a TIR domain–containing adapter protein, undergoes tyrosine phosphorylation (Piao W et al. 2008; Gray P et al. 2006). Bruton's tyrosine kinase (BTK) was shown to mediate the TIRAP phosphorylation (Jefferies CA et al. 2003; Gray P et al. 2006). BTK-specific inhibitor, LFM-A13, blocked the phosphorylation of TIRAP in human monocytic cell line THP-1 stimulated with LPS or macrophage-activating lipopeptide-2 (MALP-2) (Gray P et al. 2006). LFM-A13 also inhibited activation of NFkappaB in LPS-treated THP-1 (Jefferies CA et al. 2003). Besides BTK kinase TIRAP was shown to associate with other kinases such as protein kinase C delta (PKC delta) suggesting their regulatory role in TIRAP activation (Kubo-Murai M et al. 2007).

Tyr-86, Tyr-106 and Tyr-187 were identified as possible phosphorylation sites (Gray P et al. 2006). An additional study has shown that Tyr-86, Tyr-106, and Tyr-159 are important residues, as mutagenesis of these residues impaired TIRAP (MAL) phosphorylation, affected its interaction with BTK and also impaired downstream signaling (Piao W et al. 2008). BTK-mediated phosphorylation of TIRAP leads to recruitment of suppressor of cytokine signaling 1 (SOCS1), which assembles K48-linked polyubiquitin chains resulting in TIRAP's proteosomal degradation, disrupting the TLR complex, and terminating signaling (Mansell A et al. 2006). TIRAP function is also regulated by the cysteine protease caspase-1, which cleaves the protein in a region of the molecule that interacts with MyD88 and TLR4 (Ulrichts P et al. 2010).

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Editions

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