MLKL binds PIPs

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

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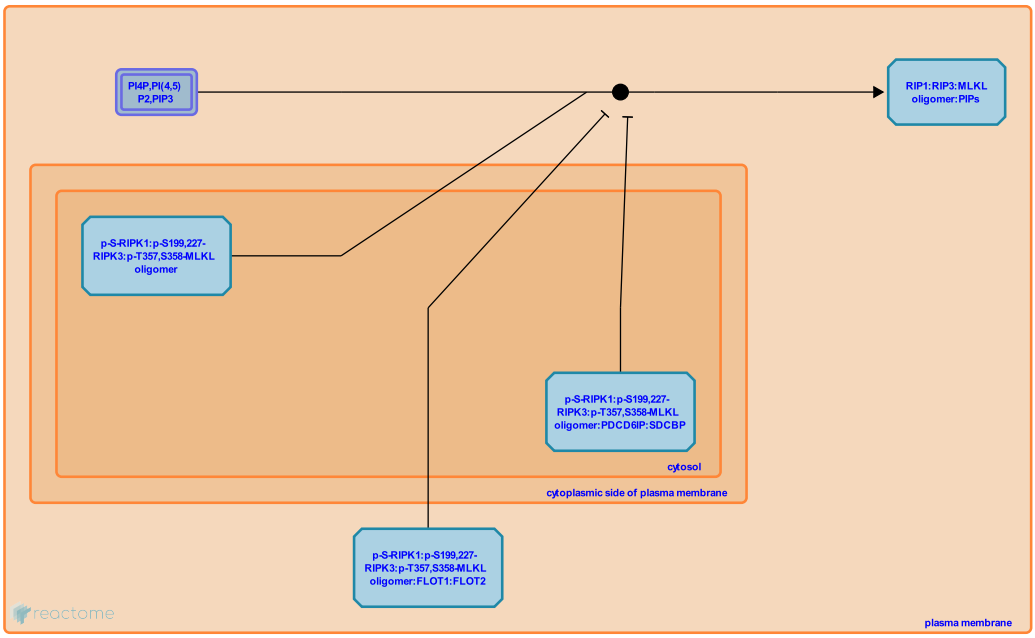
Stable identifier: R-HSA-5620975

Type: binding

Compartments: plasma membrane, cytosol



Activated by phosphorylation, mixed lineage kinase domain-like protein (MLKL) was found to translocate to the plasma membrane, where MLKL interacts with phosphatidylinositol phosphates (PIPs) via a patch of positively charged amino acids at the surface of a four-helical bundle domain (4HBD) located in its N-terminal region (Dondelinger Y et al. 2014; Wang H et al. 2014; Hildebrand JM et al. 2014; Su L et al. 2014; Quarato G et al. 2016). Interfering with the formation of PI(5)P or PI(4,5)P2 using PIP binders such as PIKfyve (P5i) efficiently inhibited TNF-induced necroptosis in both mouse L929 and the human FADD-null Jurkat cells (Dondelinger Y et al. 2014). In vitro liposome experiments revealed that MLKL induces leakage of PIP- or cardiolipin-containing liposomes suggesting that MLKL may have pore-forming capacities to mediate cell death by membrane's permeabilizing (Dondelinger Y et al. 2014; Wang H et al. 2014; Tanzer MC et al. 2016; Petrie EJ et al. 2018). Liposome permeabilization assays demonstrated that the N-terminal 4HB domain of MLKL compromised membrane integrity, and was more effective on liposomes whose composition resembled that of plasma membranes than on those mimicking mitochondrial membranes (Tanzer MC et al. 2016). One study has proposed the 4HB domain might reorganize in membranes to assemble into ion channels (Xia B et al. 2016); however, this remains to be fully explored in cellular contexts and structurally. Other studies implicated MLKL in engaging mitochondrial membranes to provoke mitochondrial fission or promote ion channel activity (Cai Z et al. 2014), although subsequent studies have discounted these possibilities (Murphy JM et al. 2013; Tait SW et al. 2013; Moujalled DM et al. 2014; Wang H et al. 2014; reviewd by Murphy JM 2020). Studies in human cell lines suggest that upon induction of necroptosis MLKL shifts to the plasma membrane and membranous organelles such as mitochondria, lysosome, endosome and ER (Wang H et al. 2014), but MLKL trafficking via a Golgi-microtubule-actin-dependent mechanism facilitates plasma membrane accumulation of MLKL, where membrane disruption causes death (Samson AL et al. 2020). Based on studies showing that the 4HB domain can permeabilize membranes in vitro (Dondelinger Y et al. 2014; Su L et al. 2014; Wang H et al. 2014; Tanzer MC et al. 2016; Petrie EJ et al. 2018), it is thought that MLKL kills cells via direct action on the plasma membrane (Murphy JM 2020).

Various studies showed that the endosomal sorting complexes required for transport (ESCRT) pathway can remove phosphorylated MLKL-containing membrane vesicles from cells undergoing necroptosis, thereby attenuating the cell death process (Gong YN et al. 2017; Yoon S et al. 2017; Zargarian S et al. 2017; Fan W et al. 2019). The ESCRT-associated proteins, programmed cell death 6-interacting protein (PDCD6IP or ALG-2-interacting protein X, ALIX) and syntenin-1 (SDCBP), were found to antagonize MLKL-mediated plasma membrane alteration (Fan W et al. 2019). In addition, flotillin-mediated endocytosis was proposed to suppress necroptosis by removing MLKL from the plasma membrane and redirecting it for lysosomal degradation (Fan W et al. 2019).

Literature references

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Editions

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