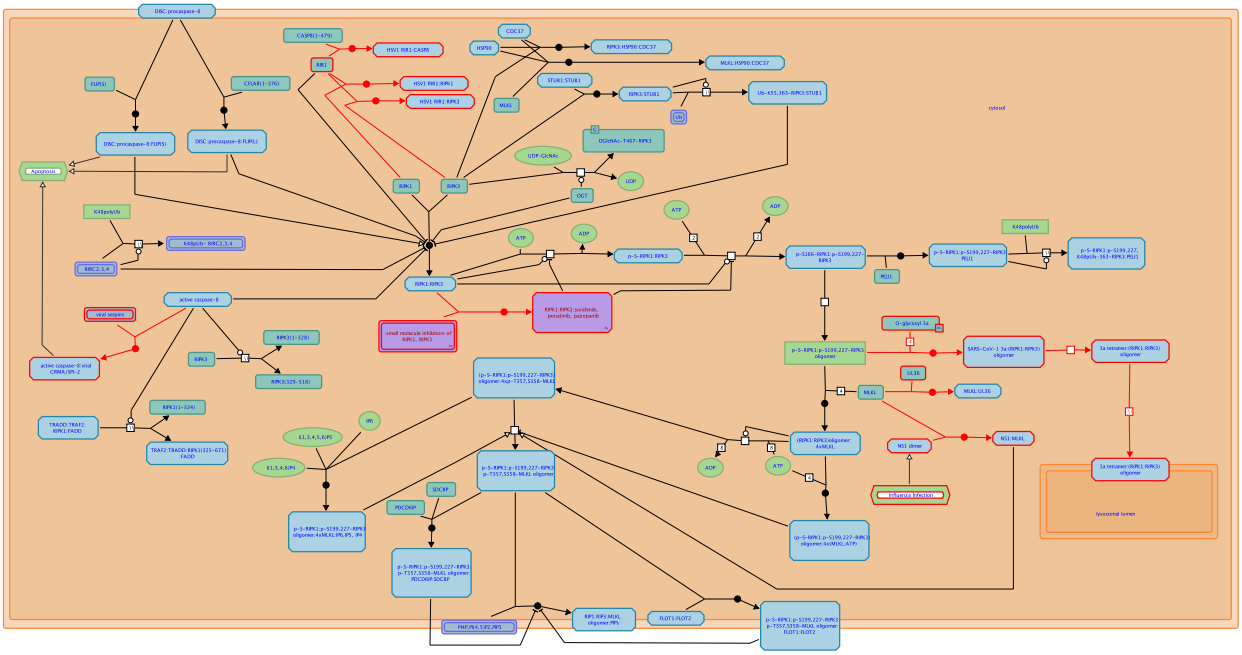
RIPK1-mediated regulated necrosis



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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. ↗

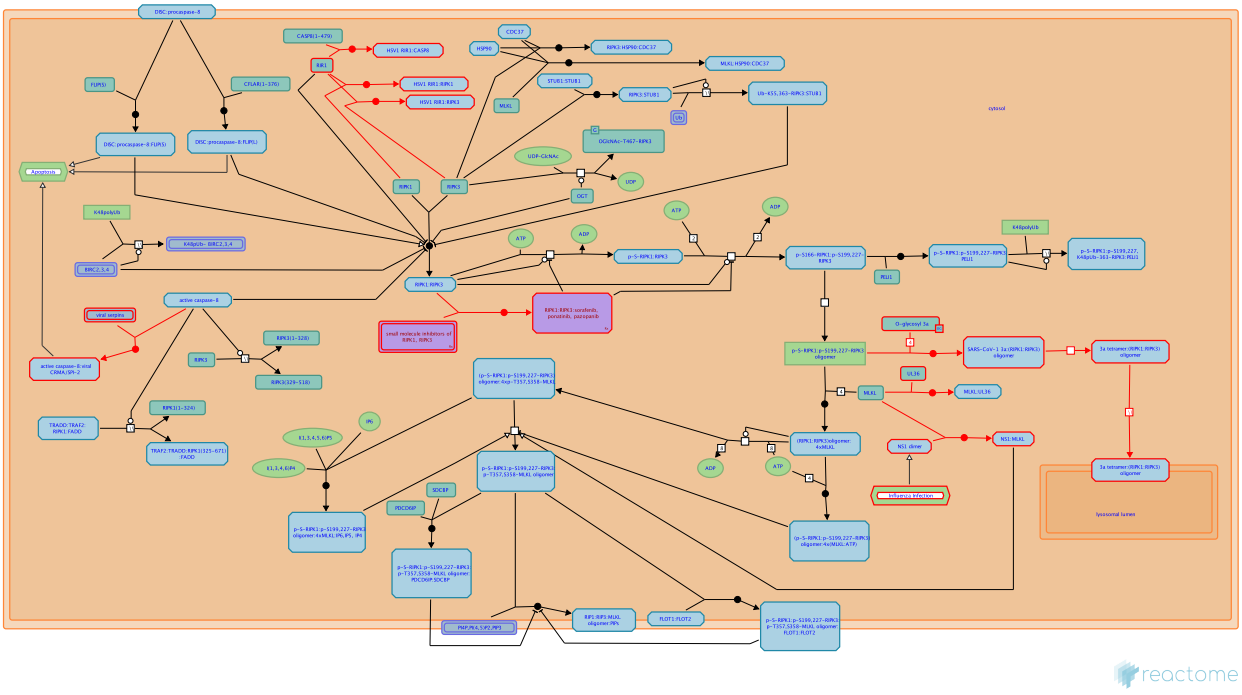
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RIPK1-mediated regulated necrosis ↗

Stable identifier: R-HSA-5213460



Receptor-interacting serine/threonine-kinase protein 1 (RIPK1) and RIPK3-dependent necrosis is called necroptosis or programmed necrosis. The kinase activities of RIPK1 and RIPK3 are essential for the necroptotic cell death in human, mouse cell lines and genetic mice models (Cho YS et al. 2009; He S et al. 2009, 2011; Zhang DW et al. 2009; McQuade T et al. 2013; Newton et al. 2014). The initiation of necroptosis can be stimulated by the same death ligands that activate extrinsic apoptotic signaling pathway, such as tumor necrosis factor (TNF) alpha, Fas ligand (FasL), and TRAIL (TNF-related apoptosis-inducing ligand) or toll like receptors 3 and 4 ligands (Holler N et al. 2000; He S et al. 2009; Feoktistova M et al. 2011; Voigt S et al. 2014). In contrast to apoptosis, necroptosis represents a form of cell death that is optimally induced when caspases are inhibited (Holler N et al. 2000; Hopkins-Donaldson S et al. 2000; Sawai H 2014). Specific inhibitors of caspase-independent necrosis, necrostatins, have recently been identified (Degterev A et al. 2005, 2008). Necrostatins have been shown to inhibit the kinase activity of RIPK1 (Degterev A et al. 2008). Importantly, cell death of apoptotic morphology can be shifted to a necrotic phenotype when caspase 8 activity is compromised, otherwise active caspase 8 blocks necroptosis by the proteolytic cleavage of RIPK1 and RIPK3 (Kalai M et al. 2002; Degterev A et al. 2008; Lin Y et al. 1999; Feng S et al. 2007). When caspase activity is inhibited under certain pathophysiological conditions or by pharmacological agents, deubiquitinated RIPK1 is engaged in physical and functional interactions with the cognate kinase RIPK3 leading to formation of necrosome, a necroptosis-inducing complex consisting of RIPK1 and RIPK3 (Sawai H 2013; Moquin DM et al. 2013; Kalai M et al. 2002; Cho YS et al. 2009, He S et al. 2009, Zhang DW et al. 2009). Within the necrosome RIPK1 and RIPK3 bind to each other through their RIP homotypic interaction motif (RHIM) domains. The RHIMs can facilitate RIPK1:RIPK3 oligomerization, allowing them to form amyloid-like fibrillar structures (Li J et al. 2012; Mompean M et al. 2018). RIPK3 in turn interacts with mixed lineage kinase domain-like protein (MLKL) (Sun L et al. 2012; Zhao J et al. 2012; Murphy JM et al. 2013; Chen W et al. 2013). The precise mechanism of MLKL activation by RIPK3 is incompletely understood and may vary across species (Davies KA et al. 2020). Mouse MLKL activation relies on transient engagement of RIPK3 to facilitate phosphorylation of the pseudokinase domain (Murphy JM et al. 2013; Petrie EJ et al. 2019a), while it appears that stable recruitment of human MLKL by necrosomal RIPK3 is an additional crucial step in human MLKL activation (Davies KA et al.

2018; Petrie EJ et al. 2018, 2019b). RIPK3-mediated phosphorylation is thought to initiate MLKL oligomerization, membrane translocation and membrane disruption (Sun L et al. 2012; Wang H et al. 2014; Petrie EJ et al. 2020; Samson AL et al. 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 it is trafficking via a Golgi-microtubule-actin-dependent mechanism that facilitates plasma membrane translocation, where membrane disruption causes death (Samson AL et al. 2020). The mechanisms of necroptosis regulation and execution downstream of MLKL remain elusive. The precise oligomeric form of MLKL that mediates plasma membrane disruption has been highly debated (Cai Z et al. 2014; Chen X et al. 2014; Dondelinger Y et al. 2014; Wang H et al. 2014; Petrie EJ et al. 2017, 2018; Samson AL et al. 2020). However, microscopy data revealed that MLKL assembles into higher molecular weight species upon cytoplasmic necrosomes within human cells, and upon phosphorylation by RIPK3, MLKL is trafficked to the plasma membrane (Samson AL et al. 2020). At the plasma membrane, phospho-MLKL forms heterogeneous higher order assemblies, which are thought to permeabilize cells, leading to release of DAMPs to invoke inflammatory responses. While RIPK1, RIPK3 and MLKL are the core signaling components in the necroptosis pathway, many additional molecules have been proposed to positively and negatively tune the signaling pathway. Currently, this picture is evolving rapidly as new modulators continue to be discovered.

The Reactome module describes MLKL-mediated necroptotic events on the plasma membrane.

Literature references

Murphy, JM. (2020). The Killer Pseudokinase Mixed Lineage Kinase Domain-Like Protein (MLKL). *Cold Spring Harb Perspect Biol, 12*. ↗

Sawai, H. (2014). Characterization of TNF-induced caspase-independent necroptosis. *Leuk. Res., 38*, 706-13. ↗

Vanden Berghe, T., Linkermann, A., Jouan-Lanhouet, S., Walczak, H., Vandenabeele, P. (2014). Regulated necrosis: the expanding network of non-apoptotic cell death pathways. *Nat. Rev. Mol. Cell Biol., 15*, 135-47. ↗

Editions

2013-12-20	Authored	Shamovsky, V.
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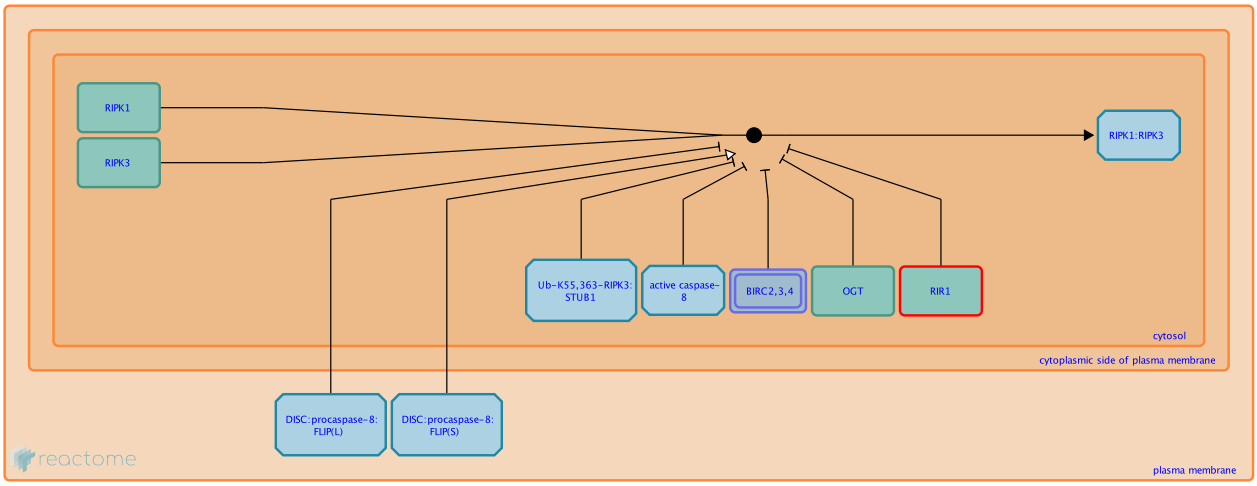
RIPK3 binds RIPK1 ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5213462

Type: binding

Compartments: cytosol



Necroptosis is a regulated form of necrotic cell death that is mediated by receptor-interacting serine-/threonine-protein kinase 1 (RIPK1), RIPK3 and mixed-lineage kinase domain-like protein (MLKL). The initiation of necroptosis can be stimulated by the same death ligands that activate apoptosis, such as tumor necrosis factor (TNF) alpha, Fas ligand (FasL), and TRAIL (TNF-related apoptosis-inducing ligand) or ligands for toll like receptors 3 (TLR3) and TLR4 (Holler N et al. 2000; He S et al. 2009; Feoktistova M et al. 2011; Voigt S et al. 2014). In contrast to apoptosis, however, necroptosis is optimally induced when caspases are inhibited (Holler N et al. 2000; Sawai H 2014). Otherwise active caspase 8 (CASP8) blocks necroptosis by the proteolytic cleavage of RIPK1 and RIPK3 (Kalai M et al. 2002; Degterev A et al. 2008; Feng S et al. 2007). When CASP8 activity is inhibited under certain pathophysiological conditions or by pharmacological agents, RIPK1 is engaged in physical and functional interactions with its homolog RIPK3 leading to formation of the necrosome, a cytosolic necroptosis-inducing complex consisting of RIPK1 and RIPK3 (Sawai H 2013; Moquin DM et al. 2013; Kalai M et al. 2002; He S et al. 2009, Zhang DW et al. 2009). RIPK3 was found to be essential for necroptosis (He S et al. 2009; Cho YC et al. 2009; Zhang DW et al. 2009). Embryonic fibroblasts from RIPK3 knockout mice were resistant to necrosis induced by TNF or during virus infection (He S et al. 2009; Cho YC et al. 2009). RIPK3-/- mice exhibited severely impaired vaccinia virus (VV)-induced tissue necrosis, inflammation, and control of viral replication (Cho YC et al. 2009). RIPK3 knockout animals were devoid of inflammation inflicted tissue damage in an acute pancreatitis model (He S et al. 2009). Further, RIPK3 knockdown in the human colorectal adenocarcinoma (HT-29) cell line, that stably expressed a shRNA targeting RIPK3, led to blockage of TNF-alpha, TRAIL or FAS-induced pronecrotic signaling pathway (He S et al. 2009). Knockdown of RIPK3 in human keratinocyte HaCaT cells blocked TLR3-mediated necroptosis without affecting the apoptotic response. Moreover, overexpression of RIPK3 in human epithelial carcinoma (HeLa) cells led to increased caspase-independent TLR3-induced cell death in the absence of inhibitors of apoptosis (IAPs) (Feoktistova M et al. 2011). Within the necrosome RIPK1 and RIPK3 bind to each other through their RIP homotypic interaction motif (RHIM) domains (Sun X et al. 2002; Li J et al. 2012; Mompean M et al. 2018). The RHIMs can facilitate RIPK1:RIPK3 oligomerization, allowing them to form amyloid-like fibrillar structures (Li J et al. 2012; Mompean M et al. 2018). RIPK1 serves as a scaffold to enable RIPK3 to assemble into homooligomers. Owing to the size and the toxicity arising from overexpressing RIPK1 and RIPK3 in cells, this has been problem-

atic to study in detail. The underlying mechanism is still debated, but RIPK3 transphosphorylation is believed to be crucial for MLKL activation (Orozco S et al. 2014; Cook WD et al. 2014). Necroptosis is a tightly regulated process. The balance between caspase-dependent apoptosis and RIPK-dependent necroptosis was found to depend on the levels of CASP8 and cellular FADD-like interleukin-1 beta converting enzyme (FLICE)-inhibitory protein (cFLIP, encoded by the CFLAR gene) (Feoktistova M et al. 2011). cFLIP exists in two main isoforms: long cFLIP(L) and short cFLIP(S) forms. cFLIP(L) (CFLAR) prevented apoptosis and necroptosis, whereas FLIP(S) inhibited apoptosis but promoted necroptosis (Feoktistova M et al. 2011; Dillon CP et al. 2012). A blockage of CASP8 activity in the presence of viral FLIP-like protein was found to switch signaling to necrotic cell death (Sawai H 2013). Cell level of free active RIPK1 can be controlled by targeting RIPK1 for proteasomal degradation via K48-linked polyubiquitination mediated by baculoviral IAP repeat containing proteins BIRC2 and BIRC3 (also known as cellular inhibitor of apoptosis proteins cIAP1 and cIAP2) (Varfolomeev E et al, 2008; Bertrand MJM et al. 2008; Tenev T et al. 2011). The carboxyl terminus of Hsp70-interacting protein (CHIP or STUB1) was shown to negatively regulate necroptosis by ubiquitylation-mediated degradation of RIPK3 (Seo J et al. 2016). Further, O-linked β-N-acetylglucosamine (O-GlcNAc) transferase (OGT) was found to prevent necroptosis by suppressing RIPK3 activity (Li X et al. 2019; Zhang B et al. 2019). During infection in human cells, herpes simplex virus (HSV)-1 and HSV-2 can modulate cell death pathways using the large subunit (R1) of viral ribonucleotide reductase (RIR1 or UL39). Viral RIR1 blocked necroptosis in infected human cells by interactions with RIPK1, RIPK3 and CASP8 (Guo H et al. 2015; Mocarski ES et al. 2015).

This Reactome event shows RHIM-dependent interaction of RIPK1 and RIPK3.

Followed by: RIPK1 is phosphorylated, RIPK3 is phosphorylated

Literature references

He, S., Wang, L., Miao, L., Wang, T., Du, F., Zhao, L. et al. (2009). Receptor interacting protein kinase-3 determines cellular necrotic response to TNF-alpha. *Cell, 137*, 1100-11. ↗

Li, J., McQuade, T., Siemer, AB., Napetschnig, J., Moriwaki, K., Hsiao, YS. et al. (2012). The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. *Cell, 150*, 339-50. ↗

Mompeán, M., Li, W., Li, J., Laage, S., Siemer, AB., Bozkurt, G. et al. (2018). The Structure of the Necrosome RIPK1-RIPK3 Core, a Human Hetero-Amyloid Signaling Complex. *Cell, 173*, 1244-1253.e10. ↗

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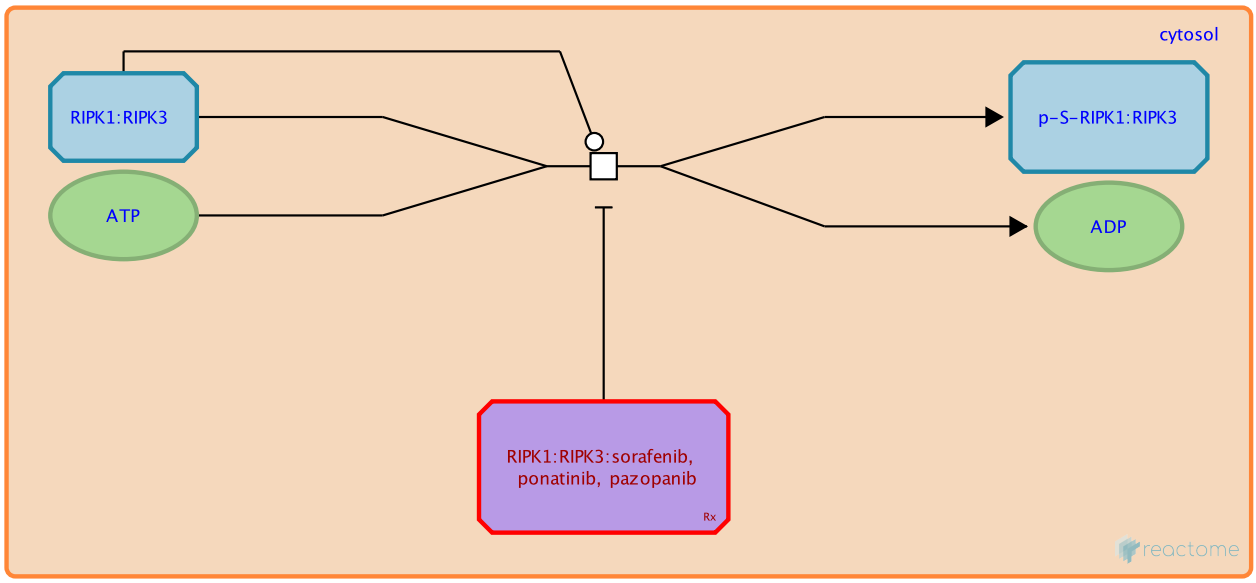
RIPK1 is phosphorylated ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5213464

Type: transition

Compartments: cytosol



RIPK1 interaction with RIPK3 further potentiates their kinase activation through autophosphorylation and/or cross-phosphorylation (Cho YS et al. 2009). The kinase function of RIPK1 and RIPK3 is thought to stabilize RIPK1:RIPK3 association within the pronecrotic complex.

Reconstitution of RIPK1-deficient human Jurkat cells with mutated kinase-inactive RIPK1 or RIPK1 lacking the N-terminal serine/threonine kinase domain did not trigger FASL-induced necrotic cell death (Holler N et al. 2000). Similarly, mutations in the kinase domain and RIP homotypic interaction motif (RHIM) of RIPK1 also abolished the RIPK1-mediated rescue of tumor necrosis factor (TNF)/zVAD-fmk-induced regulated necrosis in RIPK1-deficient Jurkat cells (Cho YS et al. 2009). Furthermore, the results of structural and mutagenesis studies using necrostatins, which inhibit RIPK1 kinase activity by targeting the kinase domain, revealed that the N-terminal kinase domain of RIPK1 is required for propagating the pronecrotic signal (Degterev A et al. 2008; Cho YS et al. 2009; Xie T et al. 2013). Mass spectroscopy showed that human RIPK1 is phosphorylated within the kinase domain at multiple serine residues, such as Ser14/15, Ser20, Ser161 and Ser166, suggesting that the phosphorylation might regulate RIPK1 kinase activity (Degterev A et al. 2008). Using in vitro cellular systems, two independent studies reported that alanine substitution at Ser161 (S161A) leads to a reduction in RIPK1 kinase activity (Degterev A et al. 2008; McQuade T et al. 2013). RIPK1 autophosphorylation at Ser166 was found to modulate RIPK1 kinase activation (Laurien L et al. 2020). Studies with Ripk1 S166A/S166A knock-in mice revealed that abolishing phosphorylation at S166 prevented the development of RIPK1-mediated inflammatory conditions in vivo in four relevant mouse models of inflammation. Further, abolishing phosphorylation at S166 considerably inhibited RIPK1 kinase activity-dependent cell death downstream of tumor necrosis factor receptor 1 (TNFR1), toll-like receptor 3 (TLR3) and TLR4 in mouse cells isolated from Ripk1 S166A/S166A mice (Laurien L et al. 2020). Phosphorylation of S166 RIPK1 has been established as a biomarker of RIPK1 target engagement (Degterev A et al. 2008; Ofengeim D et al. 2015). The biological role of phosphorylation of individual serine residues in the kinase domain of RIPK1 remains to be further characterized (McQuade T et al. 2013).

RIPK1 is subjected to complex phosphorylation including several events possibly mediated by other kinases such as MAPK-activated protein kinase 2 (MK2) (Dondelinger Y et al. 2016; Jaco I et al. 2017; Delanghe T et al. 2020). S320 and S335 on human RIPK1 (S321 and S336 in mouse RIPK1) were identified as MK2 phosphorylation sites (Jaco I et al. 2017; Menon NB et al. 2017; Dondelinger Y et al. 2017). Transforming growth factor β-activated kinase 1 (TAK1) was also shown to phosphorylate RIPK1 along with TANK binding kinase 1 (TBK1) and I-kappa-B kinase epsilon (IKKε) to prevent TNF-induced necroptosis or to dictate the multiple cell death pathways in mammalian cells (Lafont E et al. 2018; Xu D et al. 2018). In addition, IKKα/IKKβ is also able to phosphorylate RIPK1 in order to block RIPK1-dependent cell death in mouse models of infection and inflammation (Dondelinger Y et al. 2015, 2019). RIPK3 might also regulate RIPK1 phosphorylation in mammalian cells. For instance, RIPK3 was shown to directly phosphorylate RIPK1 when kinase-dead RIPK1 and RIPK3 were co-expressed in human embryonic kidney HEK293 cells, immunoprecipitated, and subjected to an in vitro kinase assay (Sun X et al. 2002; Cho et al. 2009). Importantly, mutation within RHIM motif of RIPK3 abrogated RIPK1 phosphorylation by RIPK3, suggesting that RIPK1 phosphorylation by RIPK3 is dependent on the formation of the RIPK1:RIPK3 complex (Sun X et al. 2002).

Several FDA-approved anticancer drugs, including sorafenib, pazopanib and ponatinib showed anti-necroptotic activity (Fauster A et al. 2015; Martens S et al. 2017; Fulda S 2018). RIPK1 has been identified as the main functional target of pazopanib, while sorafenib and ponatinib directly targeted both RIPK1 and RIPK3 (Fauster A et al. 2015; Najjar M et al. 2015; Martens S et al. 2017).

Preceded by: RIPK3 binds RIPK1

Followed by: RIPK1:RIPK3 oligomerizes to form amyloid-like fibrils

Literature references

Cho, YS., Challa, S., Moquin, D., Genga, R., Ray, TD., Guildford, M. et al. (2009). Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. *Cell, 137*, 1112-23. ↗

McQuade, T., Cho, Y., Chan, FK. (2013). Positive and negative phosphorylation regulates RIP1- and RIP3-induced programmed necrosis. *Biochem. J., 456*, 409-15. ↗

Laurien, L., Nagata, M., Schünke, H., Delanghe, T., Wiederstein, JL., Kumari, S. et al. (2020). Autophosphorylation at serine 166 regulates RIP kinase 1-mediated cell death and inflammation. *Nat Commun, 11*, 1747. ↗

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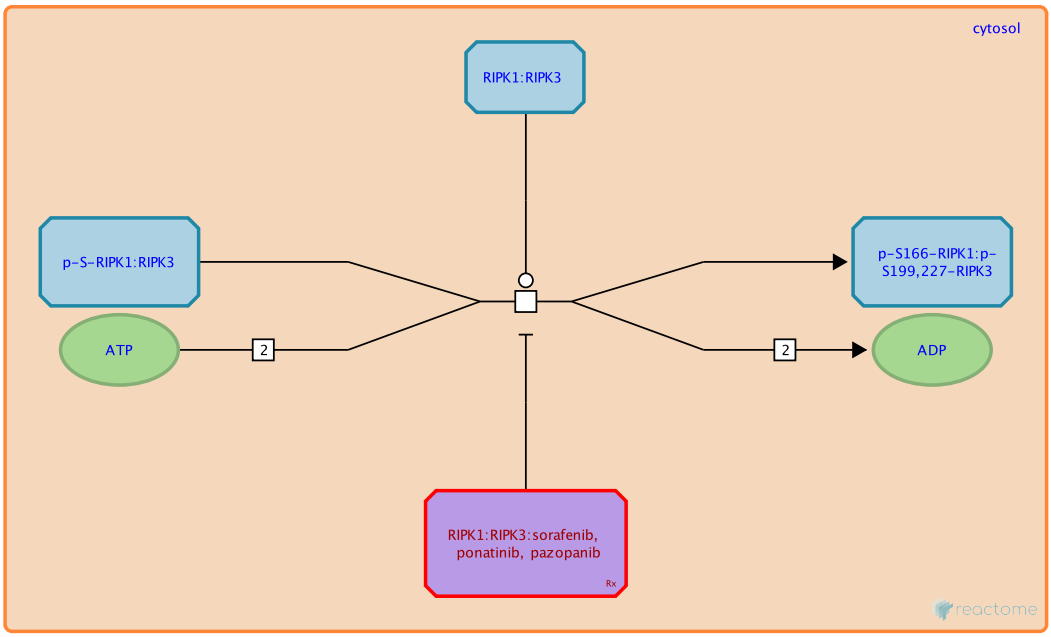
RIPK3 is phosphorylated ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5213466

Type: transition

Compartments: cytosol



Necroptosis is a form of regulated necrotic cell death mediated by interaction of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and RIPK3 via a RIP homotypic interaction motif (RHIM) domain. RIPK1:RIPK3 complex formation further potentiates kinase activation through autophosphorylation and/or transphosphorylation, propagating the pronecrotic signal. RIPK1, RIPK3 and their kinase activities were shown to be essential for necroptosis (Degterev A et al. 2008; Cho YS et al. 2009). A RIPK3 kinase-dead mutant (K50A) was found to function as a dominant negative mutant, which blocked tumor necrosis factor alpha (TNFα)-induced necrotic pathway in human colorectal adenocarcinoma HT-29 cells (He S et al. 2009). Studies in mice expressing catalytically inactive RIPK3 showed that RIPK3 D161N stimulated RIPK1-dependent apoptosis and embryonic lethality in RIPK3 D161N homozygous mice, while K51A knock in mice developed into fertile and immunocompetent adults, suggesting that the kinase activity of RIPK3 determines whether cells die by necroptosis or caspase-8-dependent apoptosis (Mandal P et al. 2014; Newton K et al. 2014; Raju S et al. 2018). Further, differentially tagged constructs of RIPK3 kinase domain (KD) were found to form dimers after their co-expression in human embryonic kidney (HEK) 293T cells, and mutation of residues at the dimer interface impaired dimerization (Raju S et al. 2018). Phosphorylation on the serine residue 227 (S227) of human RIPK3 (S231 and S232 on mouse RIPK3) is thought to mediate recruitment and activation of mixed-lineage kinase domain-like (MLKL), a crucial downstream substrate of RIPK3 in the necrosis pathway (Sun et al. 2012; Chen et al. 2013). The phosphorylation occurs in the αG helix in the C-lobe of the RIPK3 kinase, not the activation loop (Petrie EJ et al. 2019;. Consequently it remains unclear why this would be an activating event and how this would lead to MLKL interaction Although RIPK1 activation is associated with phosphorylation of the RIPK3 activation loop, most studies, however, suggest that RIPK1 does not phosphorylate RIPK3 (Cho YS et al. 2009). Rather, it is thought that active RIPK1 serves as a scaffold to enable RIPK3 to assemble into homooligomers. The precise mechanism of MLKL activation by RIPK3 is incompletely understood and may vary across species (Davies KA et al. 2020). The underlying mechanism is still debated, but the point is that RIPK3 transphosphorylation is crucial for MLKL activation (Cook WD et al. 2014; Orozco S et al. 2014; Mo-

mpean M et al. 2018).

FDA-approved anticancer drugs, including sorafenib and ponatinib, showed anti-necroptotic activity (Fauster A et al. 2015; Martens S et al. 2017; Fulda S 2018). These compounds are tyrosine kinase inhibitors (TKI) that directly targeted RIPK3 and RIPK1 and blocked their kinase activity (Fauster A et al. 2015; Martens S et al. 2017; Fulda S 2018). Pazopanib, another multi-targeting TKI, was shown to suppress necroptosis preferentially by targeting RIPK1 (Fauster A et al. 2015).

Preceded by: RIPK3 binds RIPK1

Followed by: RIPK1:RIPK3 oligomer binds MLKL, RIPK1:RIPK3 oligomerizes to form amyloid-like fibrils

Literature references

Cho, YS., Challa, S., Moquin, D., Genga, R., Ray, TD., Guildford, M. et al. (2009). Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. *Cell, 137*, 1112-23. ↗

McQuade, T., Cho, Y., Chan, FK. (2013). Positive and negative phosphorylation regulates RIP1- and RIP3-induced programmed necrosis. *Biochem. J., 456*, 409-15. ↗

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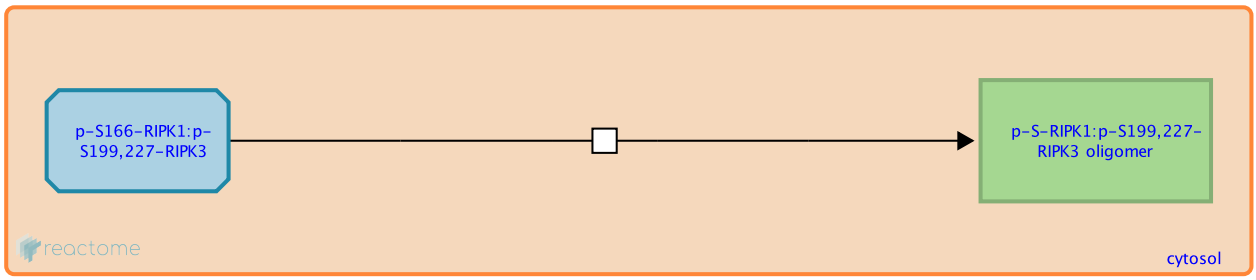
RIPK1:RIPK3 oligomerizes to form amyloid-like fibrils ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5218905

Type: transition

Compartments: cytosol



Structural studies showed that activation of RIPK3 by RIPK1 involves the formation of a functional hetero-oligomeric amyloidal signaling complex that mediated programmed necrosis (Li J et al. 2012; Mompean M et al. 2018). The RIP homotypic interaction motifs (RHIMs) of RIPK1 and RIPK3 were found to mediate the assembly of these heterodimeric filamentous structures (Li J et al. 2012). RIPK1 was reported to control RIPK3 oligomerization in both postive and negative manners (Orozco S et al. 2014). RIPK3 recruitment to other RIPK3 protomers within this assembly may be favored by allosteric interactions between their kinase domains and activation by autophosphorylation of a site in the C-lobe of their kinase domains (Raju S et al. 2018). Presumably this autophosphorylation leads to an electrostatic repulsion or conformational change that disfavors RIPK3 hetero-oligomer formation to allow RIPK3 to preferentially self-associate within the necrosome complex. Owing to the size and the toxicity arising from overexpressing RIPK1 and RIPK3 in cells, this has been problematic to study in detail. The underlying mechanism is still debated, but RIPK3 transphosphorylation is believed to be crucial for MLKL activation (Orozco S et al. 2014; Cook WD et al. 2014).

Preceded by: RIPK1 is phosphorylated, RIPK3 is phosphorylated

Followed by: RIPK1:RIPK3 oligomer binds MLKL

Literature references

Li, J., McQuade, T., Siemer, AB., Napetschnig, J., Moriwaki, K., Hsiao, YS. et al. (2012). The RIP1/RIP3 necrosome forms a functional amyloid signaling complex required for programmed necrosis. *Cell, 150*, 339-50. ↗

Mompeán, M., Li, W., Li, J., Laage, S., Siemer, AB., Bozkurt, G. et al. (2018). The Structure of the Necrosome RIPK1-RIPK3 Core, a Human Hetero-Amyloid Signaling Complex. *Cell, 173*, 1244-1253.e10. ↗

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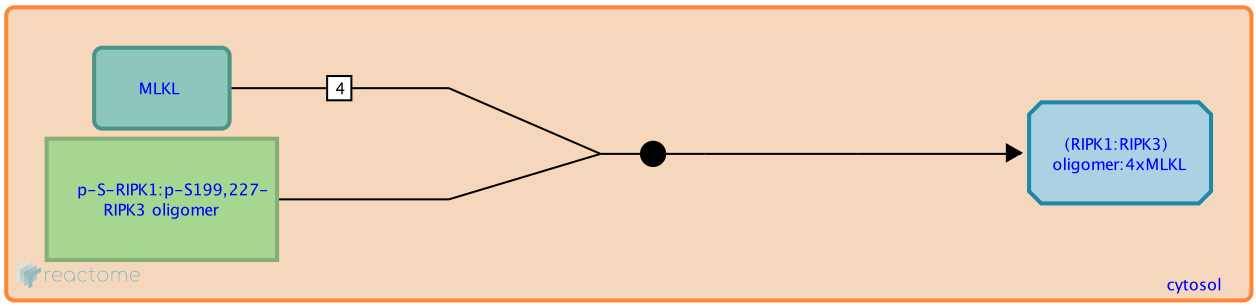
RIPK1:RIPK3 oligomer binds MLKL ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5218891

Type: binding

Compartments: cytosol



Exogenous stimuli provoke assembly of the receptor-interacting serine/threonine protein kinase RIPK1:RIPK3 oligomeric complex termed the necrosome, which acts as a platform for recruiting and activating mixed lineage kinase domain-like protein (MLKL), the terminal effector pseudokinase in the necroptotic signaling pathway (Sun L et al. 2012; Zhao J et al. 2012; reviewed by Murphy JM 2020). Mass spectrometry analysis identified MLKL as a necrosome component associated with RIPK3 in a HeLa cell line in which RIPK3 was expressed and caspase-8 was knocked down to induce necrosis in the presence of necrosulfonamide (NSA) (Sun L et al. 2012). NSA was found to specifically block TNFα-induced necroptosis downstream of RIPK3 activation in human colon cancer HT-29 cells, FADD null human T cell leukemia Jurkat cells and other RIPK3-expressing cells (Sun L et al. 2012). Short hairpin (sh) RNA-mediated genetic screens targeting human kinases, phosphatases, genes involved in protein ubiquination also identified MLKL as a key RIPK3 downstream component of TNFα-induced necroptosis in HT-29 cells (Zhao J et al. 2012). Further, MLKL knockout mice and cells derived from MLKL-deficient mice demonstrated the indispensable role of Mlkl in necroptosis (Wu J et al. 2013; Murphy JM et al. 2013). MLKL knockout in human myeloid leukaemia U937cells was shown to abrogate necroptosis, while induced expression of wild-type human MLKL in MLKL-/- U937 cells restored sensitivity to the necroptotic stimulus (Petrie EJ et al. 2018; Davies KA et al. 2020). Knockdown of MLKL by shRNA in HT-29 or gastric cancer MKN45 cells inhibited tumor necrosis factor alpha (TNFα)-induced necroptosis (Sun L et al. 2012; Zhao J et al. 2012; Wang H et al. 2014). The RIPK3 kinase activity is required for interaction and activation of MLKL in necroptosis as kinase-dead RIPK3 mutants were unable to bind MLKL or mediate TNF-induced necroptosis (Zhao J et al. 2012; Murphy JM et al. 2013; Chen W et al. 2013). The precise mechanism of MLKL activation by RIPK3 is incompletely understood and may vary across species (Davies KA et al. 2020). The pseudokinase domain (psKD) of MLKL is known to engage the kinase domain (KD) of RIPK3, stably in the case of the human system (Sun L et al. 2012; Zhao J et al. 2012; Davies KA et al. 2018; Petrie EJ et al. 2018), but transiently in the mouse system (Murphy JM et al. 2013; Chen W et al. 2013; Petrie EJ et al. 2019a). Structural studies of the mouse MLKL pseudokinase domain in complex with the mouse RIPK3 kinase domain revealed juxtaposition of RIPK3 active site next to the pseudoactive site of mouse MLKL for phosphorylation of the latter's activation loop (Xie T et al. 2013). The KD:psKD complex is governed by extensive lobe-to-lobe interaction interfaces, stabilized by hydrophobic and electrostatic interactions. The C-lobe interface is mediated by mouse RIPK3 autophosphorylated residues. It was observed that F373 of mouse MLKL projects from the αF-αG loop into a cavity adjacent to αG in RIPK3 (Xie T et al. 2013). The structure of the human RIPK3:MLKL complex has not been determined, but its modeling based on the mouse complex suggests that similar interaction may occur, governed by different electrostatic surface potentials (Petrie EJ et al. 2019b). Ala substitution of the equivalent human MLKL residue,

F386, abrogated reconstitution of necroptotic signaling in MLKL-/- U937 cells, suggesting more broadly that this C-lobe:C-lobe interaction underpins RIPK3 engagement by MLKL (Petrie EJ et al. 2019b).

MLKL is composed of an amino-terminal four-helix bundle (4HB) domain, a two-helix “brace” region, and a carboxy-terminal pseudokinase domain (Murphy JM et al. 2013; Petrie EJ et al. 2018). The 4HB domain functions as the executioner domain by virtue of its membrane permeabilization activity (Cai Z et al. 2014; Chen X et al. 2014; Dondelinger Y et al. 2014; Hildebrand JM et al. 2014; Su L et al. 2014; Wang H et al. 2014; Tanzer MC et al. 2016). The 4HB domain enables membrane translocation of MLKL and is responsible for the plasma membrane permeabilization that characterizes necroptotic cell death (Chen X et al. 2014; Cai Z et al. 2014; Dondelinger Y. et al. 2014; Hildebrand JM et al. 2014; Petrie EJ et al. 2020). The 4HB domain executioner function is regulated by the C-terminal pseudokinase domain, which serves as a receiver for upstream signals, such as activation loop phosphorylation by RIPK3 (Hildebrand JM et al. 2014; Sun L et al. 2012; Rodriguez DA et al. 2016; Petrie EJ et al. 2018). Studies using mouse:human MLKL chimeras showed that the first brace helix and the adjacent loop (that connect the 4HB to the pseudokinase domain) of MLKL mediate interdomain communication and oligomerisation upon RIPK3-mediated activation of MLKL (Davies KA et al. 2018). RIPK3-mediated phosphorylation is thought to trigger a conformational change within the pseudokinase of MLKL that promotes 4HB domain exposure, enabling MLKL to form oligomers, which are trafficked to the plasma membrane where cell permeabilization occurs (Sun L et al. 2012; Wang H et al. 2014; Petrie EJ et al. 2020; Samson AL et al. 2020). Even though the Reactome annotation shows that 4 molecules of MLKL bind to the RIPK1:RIPK3 oligomer, the exact stoichiometry of the binding and the oligomerization of MLKL has been highly debated (Chen X et al. 2014; Cai Z et al. 2014; Davies KA et al. 2018; Petrie EJ et al. 2018; Petrie EJ 2017). While trimers, tetramers, hexamers were reported in studies with the recombinant MLKL protein, single-cell imaging approaches revealed that endogenous human phosphorylated MLKL assembles into higher order species that are heterogeneous in MLKL stoichiometry (Samson AL et al. 2020). The mechanisms of necroptosis regulation and execution downstream of MLKL remain elusive.

Preceded by: RIPK3 is phosphorylated, RIPK1:RIPK3 oligomerizes to form amyloid-like fibrils

Followed by: RIPK3 phosphorylates MLKL

Literature references

Sun, L., Wang, H., Wang, Z., He, S., Chen, S., Liao, D. et al. (2012). Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. *Cell, 148*, 213-27. ↗

Zhao, J., Jitkaew, S., Cai, Z., Choksi, S., Li, Q., Luo, J. et al. (2012). Mixed lineage kinase domain-like is a key receptor interacting protein 3 downstream component of TNF-induced necrosis. *Proc. Natl. Acad. Sci. U.S.A., 109*, 5322-7. ↗

Editions

2013-12-20	Authored	Shamovsky, V.
2014-10-31	Reviewed	Gillespie, ME.
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2015-02-15	Reviewed	Chan, FK.
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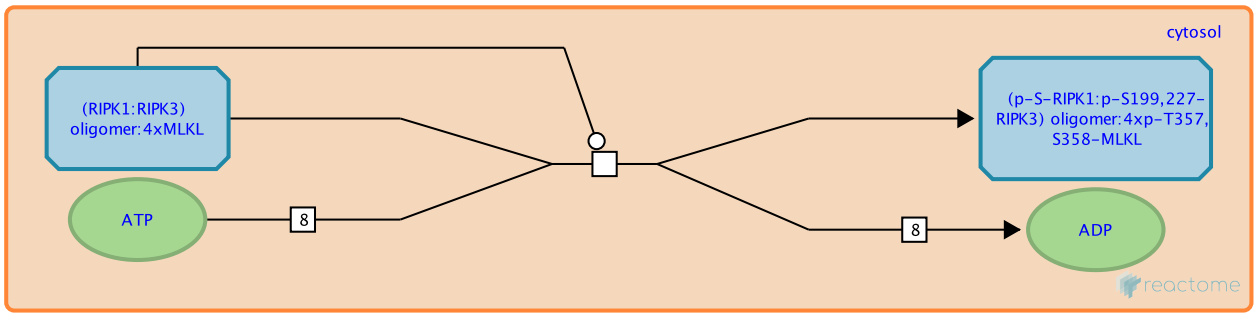
RIPK3 phosphorylates MLKL ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5218906

Type: transition

Compartments: cytosol



Receptor-interacting serine/threonine-protein kinase 3 (RIPK3) was shown to activate mixed lineage kinase domain-like protein (MLKL) by phosphorylation of the threonine 357 (T357) and serine 358 (S358) residues within the kinase-like domain in human MLKL and S345 in mouse MLKL (Sun L et al. 2012: Wang H et al. 2014; Murphy JM et al. 2013; Tanzer MC et al. 2015; Rodriguez DA et al. 2016). The precise mechanism of MLKL activation by RIPK3 is incompletely understood and may vary across species (Davies KA et al. 2020; reviewed by Murphy JM 2020). The pseudokinase domain (psKD) of MLKL is known to engage the kinase domain (KD) of RIPK3, stably in the case of the human system (Sun L et al. 2012; Davies KA et al. 2018; Petrie EJ et al. 2018, 2019a), but transiently in the mouse system (Tanzer MC et al. 2015; Rodriguez DA et al. 2016; Petrie EJ et al. 2019b). The kinase-dead RIPK3 mutants were unable to bind MLKL or mediate TNF-induced necroptosis in human and mouse cells (Sun L et al. 2012; Zhao J et al. 2012; Murphy JM et al. 2013; Chen W et al. 2013). Studies involving knockout of endogenous MLKL in human histiocytic lymphoma U937 and adenocarcinoma HT-29 cells support the idea that activation of MLKL relies on the RIPK3-mediated phosphorylation of T357 and S358 in human MLKL (Petrie EJ et al. 2018). While wild-type human MLKL could reconstitute the necroptotic signaling, both the T357E/S358E phosphomimic and the T357A/S358A phospho-ablating human MLKL constructst blocked necroptosis in MLKL-/- U937 and HT-29 cell lines in the presence of necroptosis stimuli (Petrie EJ et al. 2018). Furthermore, introduction of constructs harboring mutations within the human MLKL pseudoactive site, such as those observed in colon, lung, and endometrial carcinomas and melanoma specimens, into MLKL-/- U937 cells did not promote MLKL's killing activity, but rather delayed the kinetics of cell death following treatment with a necroptosis stimulus (Petrie EJ et al. 2018). Biophysical data suggest that defective MLKL variants are locked in a monomeric conformation, which hampers assembly into higher order oligomers that are responsible for cell death (Petrie EJ et al. 2018). Although wild-type human MLKL robustly bound human RIPK3 kinase domain, no binding was detected for the human MLKL T357E/S358E constructsts (Petrie et al. 2018). These data support the idea that human MLKL activation relies on recruitment to human RIPK3 in cells as a precursor to its activation (Petrie EJ et al. 2019). RIPK3-mediated phosphorylation of human MLKL is thought to trigger a conformational change within the pseudokinase of MLKL that promotes the N-terminal four-helix bundle (4HB) domain exposure, enabling MLKL to form higher order MLKL assemblies which are trafficked to the plasma membrane (Sun L et al. 2012; Wang H et al. 2014; Petrie EJ et al. 2017,2018, 2019; 2020; Samson AL et al. 2020). The phosphorylation of MLKL may induce disengagement of MLKL from RIPK3 followed by translocation to the the plasma membrane where cell permeabilization occurs (Davies KA et al. 2020; Murphy JM 2020). Important to note that the assembly of MLKL into higher order species and the translocation of MLKL oligomers to the plasma membrane are hallmarks of necroptosis (Davies KA et al. 2020; Petrie EJ et al. 2020; Samson AL et

al. 2020). This Reactome event shows that 4 molecules of MLKL are bound to RIPK1:RIPK3 oligomer, however the exact stoichiometry of MLKL binding remains unclear (Chen X et al. 2014; Cai Z et al. 2014; Davies KA et al. 2018; Petrie EJ et al. 2018; reviewed by Petrie EJ 2017). Single-cell imaging approaches revealed that endogenous human MLKL assembles on necrosomes into higher order species that are heterogeneous in MLKL stoichiometry (Samson AL et al. 2020). The mechanisms of necroptosis regulation and execution downstream of MLKL remain elusive.

Preceded by: RIPK1:RIPK3 oligomer binds MLKL

Followed by: MLKL oligomerizes

Literature references

Sun, L., Wang, H., Wang, Z., He, S., Chen, S., Liao, D. et al. (2012). Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. *Cell, 148*, 213-27. ↗

Wang, H., Sun, L., Su, L., Rizo, J., Liu, L., Wang, LF. et al. (2014). Mixed lineage kinase domain-like protein MLKL causes necrotic membrane disruption upon phosphorylation by RIP3. *Mol. Cell, 54*, 133-46. ↗

Editions

2013-12-20	Authored	Shamovsky, V.
2014-10-31	Reviewed	Gillespie, ME.
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2015-02-15	Reviewed	Chan, FK.
2020-08-28	Reviewed	Murphy, JM.

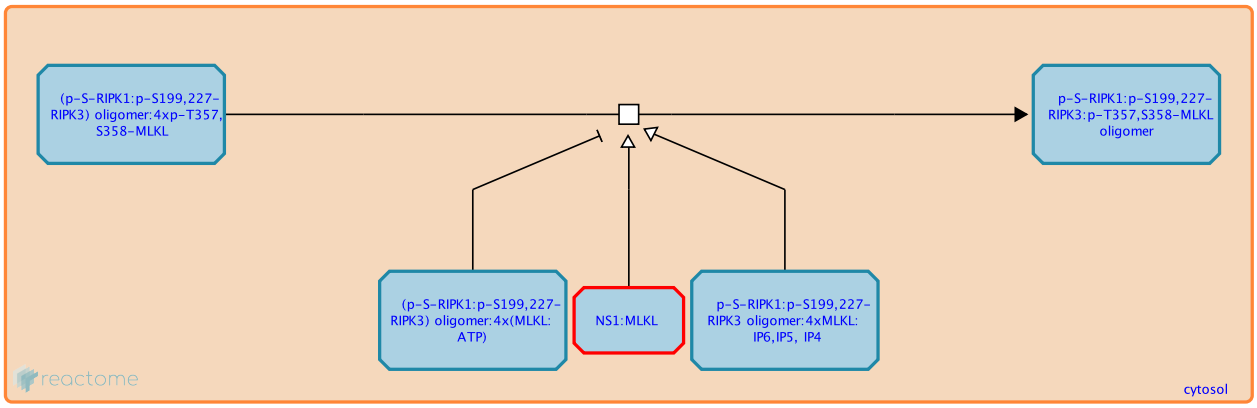
MLKL oligomerizes ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5357927

Type: transition

Compartments: cytosol



Mixed lineage kinase domain-like protein (MLKL) was found to form oligomers that translocate to and mediate permeabilisation of plasma membrane (Hildebrand JM et al. 2014; Davies KA et al. 2018; Petrie EJ et al. 2018; Samson AL et al. 2020). The oligomerization of MLKL was observed in a variaty of human (colon adenocarcinoma HT-29, FADD-null Jurkat cells, leukemic monocyte lymphoma U937) and mouse cells upon necroptosis induced by (TNF+Smac mimetic+caspase inhibitor z-VAD-FMK) (Cai Z et al. 2014; Chen X et al. 2014; Davies KA et al. 2018; Petrie EJ et al. 2018). The precise oligomeric form of MLKL that mediates plasma membrane disruption has been highly debated (Chen X et al. 2014; Cai Z et al. 2014; Davies KA et al. 2018; Petrie EJ et al. 2018; reviewed by Petrie EJ 2017). Native mass spectrometry (MS) defined the human MLKL oligomer as a tetramer (Petrie EJ et al. 2018). Low-resolution techniques including cross-linking and deuterium exchange MS and small angle X-ray scattering (SAXS) showed that MLKL exists in equilibrium between a monomer and a daisy chain tetramer with the N-terminal four‐helix bundle (4HB) of one monomer binding to the pseudokinase domain (psKD) of another monomer (Petrie EJ et al. 2018). Cys-oxidation under nonreducing conditions and crosslinking analyses detected tetramers and octamers in L929 murine fibroblast and HEK293 cells undergoing TNF-mediated necroptosis, although the relationship of these disulfide crosslinks to MLKL's killer function remains unknown (Huang D et al. 2017). While trimers, tetramers, hexamers were reported in studies with the recombinant MLKL protein (Cai Z et al. 2014; Chen X et al. 2014; Dondelinger Y et al. 2014; Wang H et al. 2014; Petrie EJ et al. 2018), single-cell imaging approaches revealed that endogenous human phosphorylated MLKL assembles on necrosomes into higher order species that are heterogeneous in MLKL stoichiometry (Samson AL et al. 2020). RIPK3-mediated phosphorylation of MLKL's pseudokinase domain leads to MLKL switching from an inert to activated state, where exposure of 4HB 'executioner' domain leads to cell death (Hildebrand JM et al 2014; Petrie EJ et al. 2018). Following activation, toggling within the MLKL pseudokinase domain promotes 4HB domain disengagement from the pseudokinase domain αC helix and pseudocatalytic loop, to enable formation of a necroptosis-inducing tetramer (Petrie EJ et al. 2018). Despite lacking catalytic activity, the pseudokinase domain of MLKL has retained the ability to bind ATP (Murphy JM et al. 2013, 2014; Petrie EJ et al. 2018). The ATP binding has been shown to negatively regulate MLKL-mediated membrane permeabilization by destabilizing the MLKL tetramers and shifting the tetramer:monomer equilibrium toward the monomeric state (Petrie EJ et al. 2018). The two interdomain helices, termed the 'brace' helices, contribute to MLKL oligomerization by connecting phosphorylation of the pseudokinase domain to the release or activation of the 4HB domain executioner

function to enable its participation in membrane localisation, permeabilization and cell death (Davies KA et al. 2018). In addition, the autoinhibited N-terminal 4HB of human MLKL is activated by inositol phosphate metabolites IP4, IP5 and IP6 produced by inositol phosphate multikinase (IPMK), inositol tetrakisphosphate kinase 1 (ITPK1) and inositol pentakisphosphate 2-kinase (IPPK) (Dovey CM et al. 2018; McNamara DE et al. 2019). These inositol phosphates promote MLKL-mediated necroptosis through directly binding 4HB domain of MLKL and dissociating its auto-inhibitory region (McNamara DE et al. 2019). Oligomers of MLKL translocate to membrane compartments (Cai Z et al. 2014; Dondelinger Y et al. 2014; Wang H et al. 2014; Hildebrand JM et al. 2014; Davies KA et al. 2018; Petrie EJ et al. 2020; Samson AL et al. 2020). MLKL oligomerization and membrane translocation are hallmarks of the necroptosis pathway, which plays a crucial role in the host defense response against many pathogens (Upton JW et al. 2017). In response, pathogens have developed different strategies to target the host necroptosis machinery (Upton JW et al. 2017; Pearson JC et al. 2017; Petrie EJ et al. 2019; Gaba A et al. 2019).

Even though the stoichiometry of the MLKL oligomerization in the Reactome event depicts MLKL homotetramer, the endogenous MLKL was shown to assemble on necrosomes into higher order species that are heterogeneous in MLKL stoichiometry (Samson AL et al. 2020).

Preceded by: RIPK3 phosphorylates MLKL

Followed by: MLKL binds PIPs

Literature references

Cai, Z., Jitkaew, S., Zhao, J., Chiang, HC., Choksi, S., Liu, J. et al. (2014). Plasma membrane translocation of trimerized MLKL protein is required for TNF-induced necroptosis. *Nat. Cell Biol., 16*, 55-65. ↗

Wang, H., Sun, L., Su, L., Rizo, J., Liu, L., Wang, LF. et al. (2014). Mixed lineage kinase domain-like protein MLKL causes necrotic membrane disruption upon phosphorylation by RIP3. *Mol. Cell, 54*, 133-46. ↗

Petrie, EJ., Sandow, JJ., Jacobsen, AV., Smith, BJ., Griffin, MDW., Lucet, IS. et al. (2018). Conformational switching of the pseudokinase domain promotes human MLKL tetramerization and cell death by necroptosis. *Nat Commun, 9*, 2422. ↗

Samson, AL., Zhang, Y., Geoghegan, ND., Gavin, XJ., Davies, KA., Mlodzianoski, MJ. et al. (2020). MLKL trafficking and accumulation at the plasma membrane control the kinetics and threshold for necroptosis. *Nat Commun, 11*, 3151. ↗

Editions

2013-12-20	Authored	Shamovsky, V.
2014-10-31	Reviewed	Gillespie, ME.
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2015-02-15	Reviewed	Chan, FK.
2020-08-28	Reviewed	Murphy, JM.

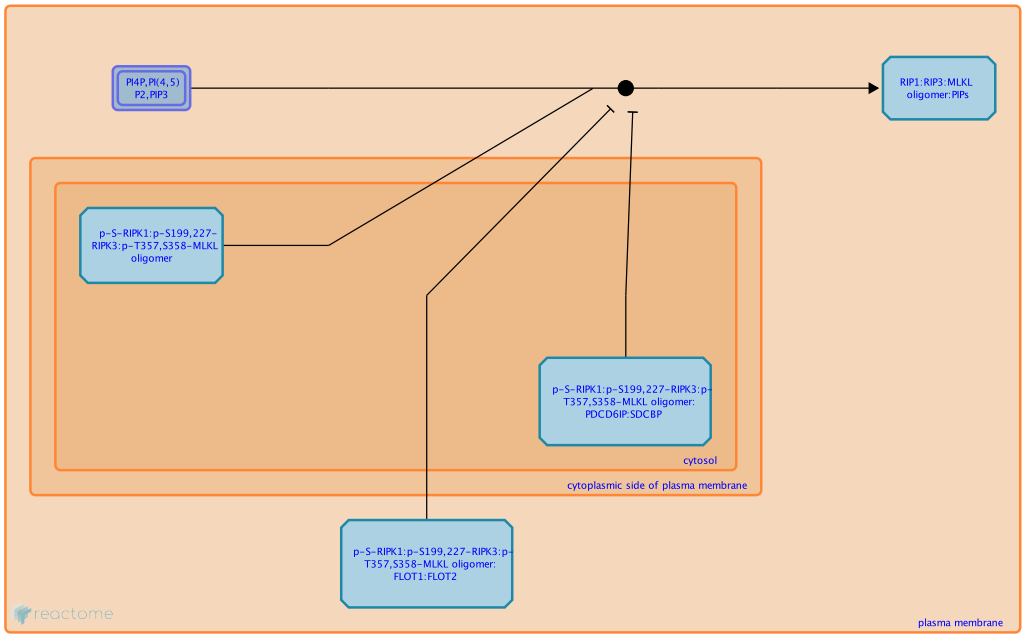
MLKL binds PIPs ↗

Location: RIPK1-mediated regulated necrosis

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).

Preceded by: MLKL oligomerizes

Literature references

Dondelinger, Y., Declercq, W., Montessuit, S., Roelandt, R., Goncalves, A., Bruggeman, I. et al. (2014). MLKL compromises plasma membrane integrity by binding to phosphatidylinositol phosphates. *Cell Rep, 7*, 971-81. ↗

Cai, Z., Jitkaew, S., Zhao, J., Chiang, HC., Choksi, S., Liu, J. et al. (2014). Plasma membrane translocation of trimerized MLKL protein is required for TNF-induced necroptosis. *Nat. Cell Biol., 16*, 55-65. ↗

Wang, H., Sun, L., Su, L., Rizo, J., Liu, L., Wang, LF. et al. (2014). Mixed lineage kinase domain-like protein MLKL causes necrotic membrane disruption upon phosphorylation by RIP3. *Mol. Cell, 54*, 133-46. ↗

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2013-12-20	Authored	Shamovsky, V.
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2015-02-15	Reviewed	Chan, FK.
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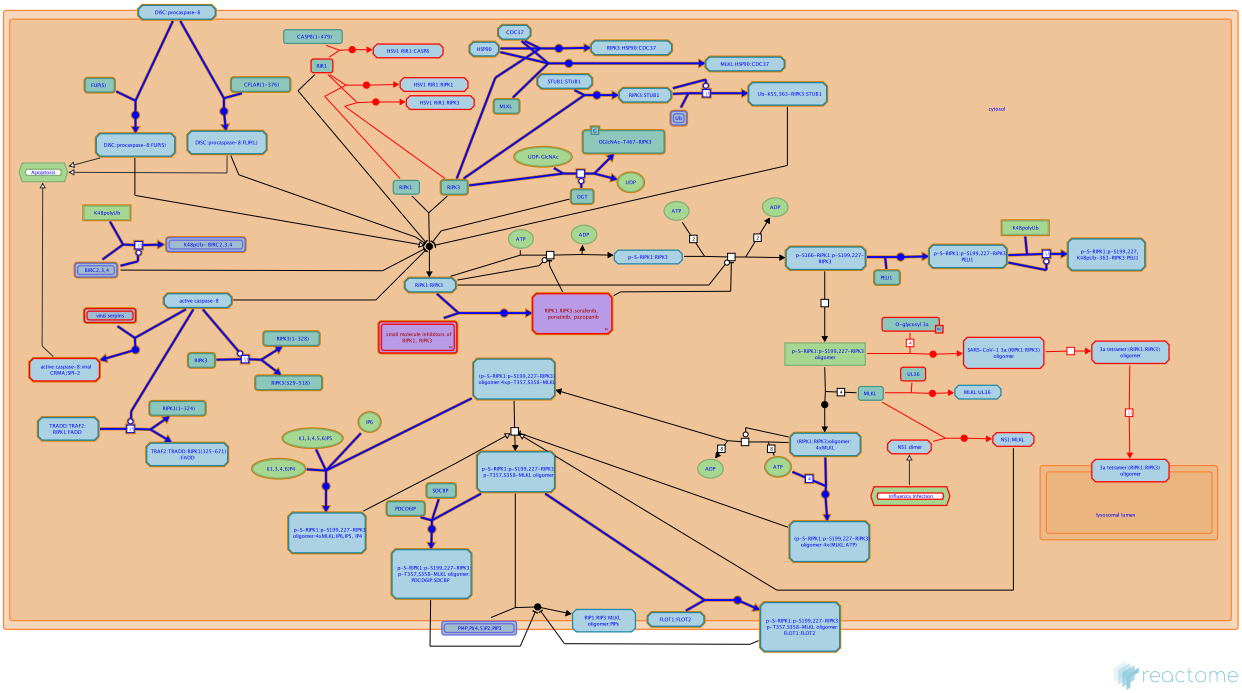
Regulation of necroptotic cell death ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-5675482



A regulated balance between cell survival and cell death is essential for normal development and homeostasis of multicellular organisms. Defects in control of this balance may contribute to autoimmune disease, neurodegeneration, ischemia/reperfusion injury, non alcoholic steatohepatitis (NASH) and cancer.

Literature references

Vittori, D., Vota, D., Callero, M., Chamorro, ME., Nesse, A. (2010). c-FLIP is involved in erythropoietin-mediated protection of erythroid-differentiated cells from TNF-alpha-induced apoptosis. *Cell Biol. Int., 34*, 621-30. ↗

Chang, DW., Xing, Z., Pan, Y., Algeciras-Schimnich, A., Barnhart, BC., Yaish-Ohad, S. et al. (2002). c-FLIP(L) is a dual function regulator for caspase-8 activation and CD95-mediated apoptosis. *EMBO J., 21*, 3704-14. ↗

Golks, A., Brenner, D., Fritsch, C., Krammer, PH., Lavrik, IN. (2005). c-FLIPR, a new regulator of death receptor-induced apoptosis. *J. Biol. Chem., 280*, 14507-13. ↗

Varfolomeev, E., Goncharov, T., Fedorova, AV., Dynek, JN., Zobel, K., Deshayes, K. et al. (2008). c-IAP1 and c-IAP2 are critical mediators of tumor necrosis factor alpha (TNFalpha)-induced NF-kappaB activation. *J. Biol. Chem., 283*, 24295-9. ↗

Bertrand, MJ., Milutinovic, S., Dickson, KM., Ho, WC., Boudreault, A., Durkin, J. et al. (2008). cIAP1 and cIAP2 facilitate cancer cell survival by functioning as E3 ligases that promote RIP1 ubiquitination. *Mol. Cell, 30*, 689-700. ↗

Editions

2015-02-10	Authored	Shamovsky, V.
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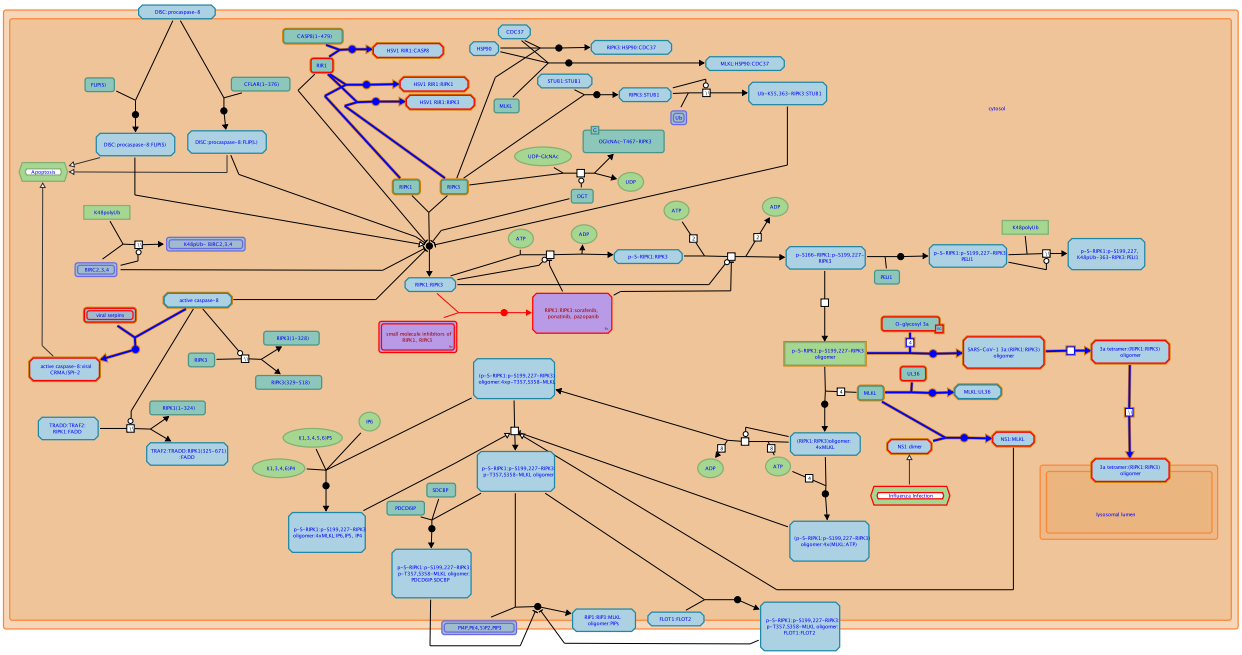
Microbial modulation of RIPK1-mediated regulated necrosis ↗

Location: RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9686347

Diseases: bacterial infectious disease, viral infectious disease



Activation of receptor-interacting serine/threonine protein (RIP) kinases RIPK1 and RIPK3 coordinate an immunogenic form of programmed cell death known as regulated necrosis or necroptosis (Upton JW et al. 2017). This form of necrosis leads to anti-viral inflammation in host through cell death-associated release of damage-associated molecular patterns (DAMPs) (Nailwal H & Ka-Ming Chan F 2019; Upton JW et al. 2017). Microbial pathogens are able to modulate host regulated necrosis through different triggers and pathways. The promotion and inhibition of host cell death vary and depend on the microbe types, virulence, and phenotypes (Upton JW et al. 2010, 2012, 2017; Jaclyn S Pearson JS et al. 2017; Petrie EJ et al. 2019; Fletcher-Etherington A et al. 2020; Nailwal H & Ka-Ming Chan F 2019;).

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2020-05-21	Authored	Shamovsky, V.
2020-06-26	Reviewed	D'Eustachio, P.
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