RIPK3 binds RIPK1

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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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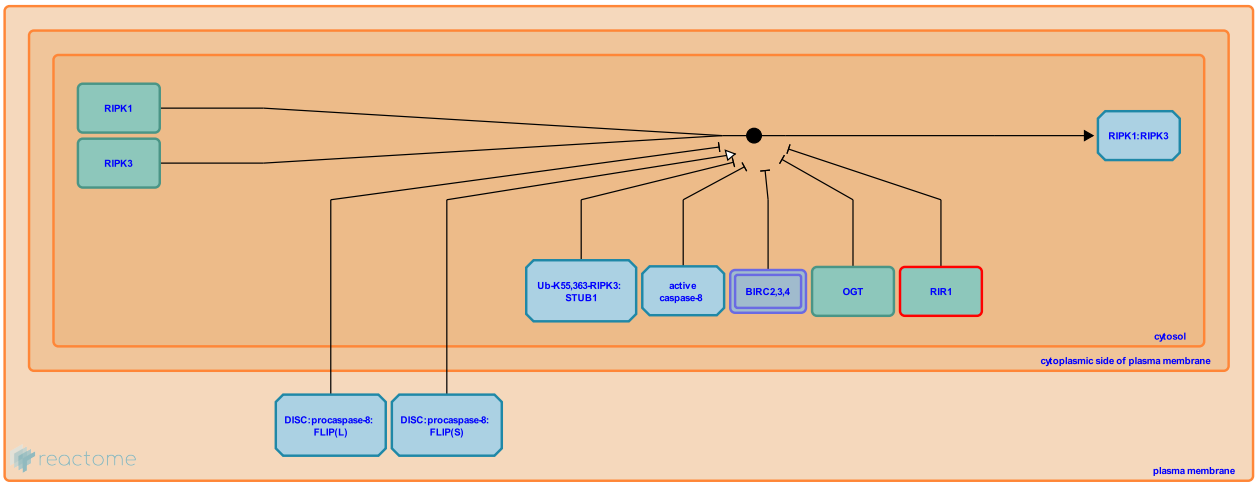
Stable identifier: R-HSA-5213462

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 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). 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.

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Editions

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