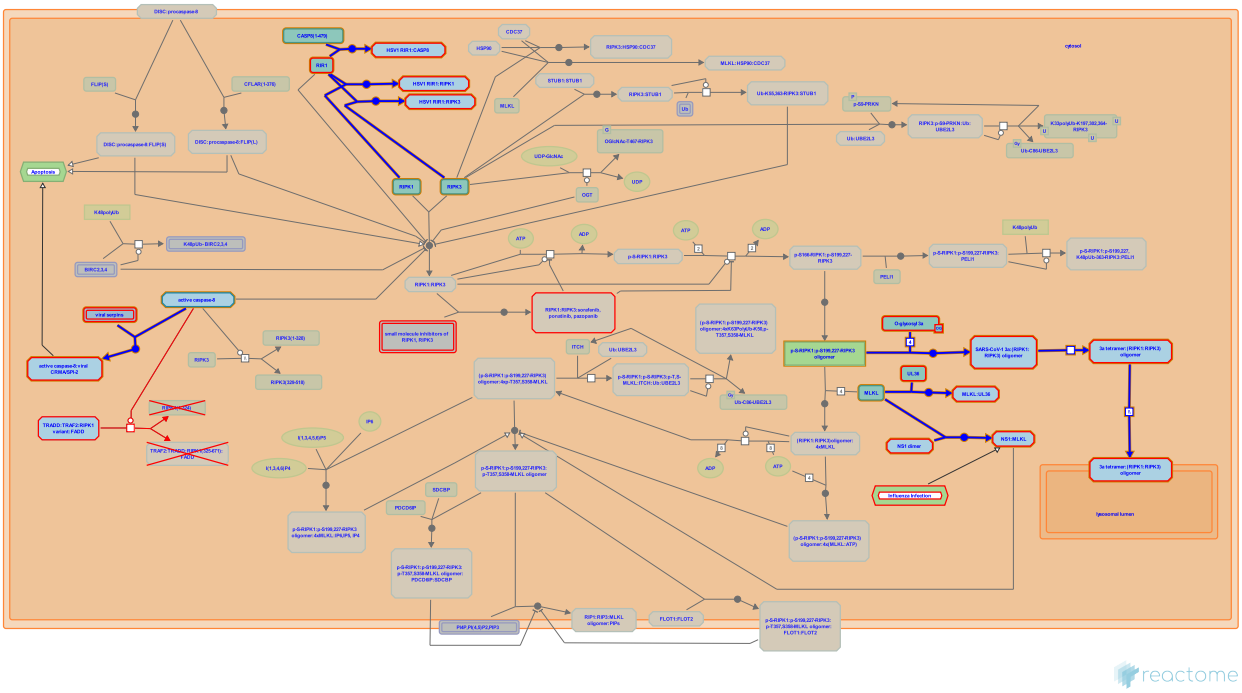
Microbial modulation of RIPK1-mediated regulated necrosis



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

29/04/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

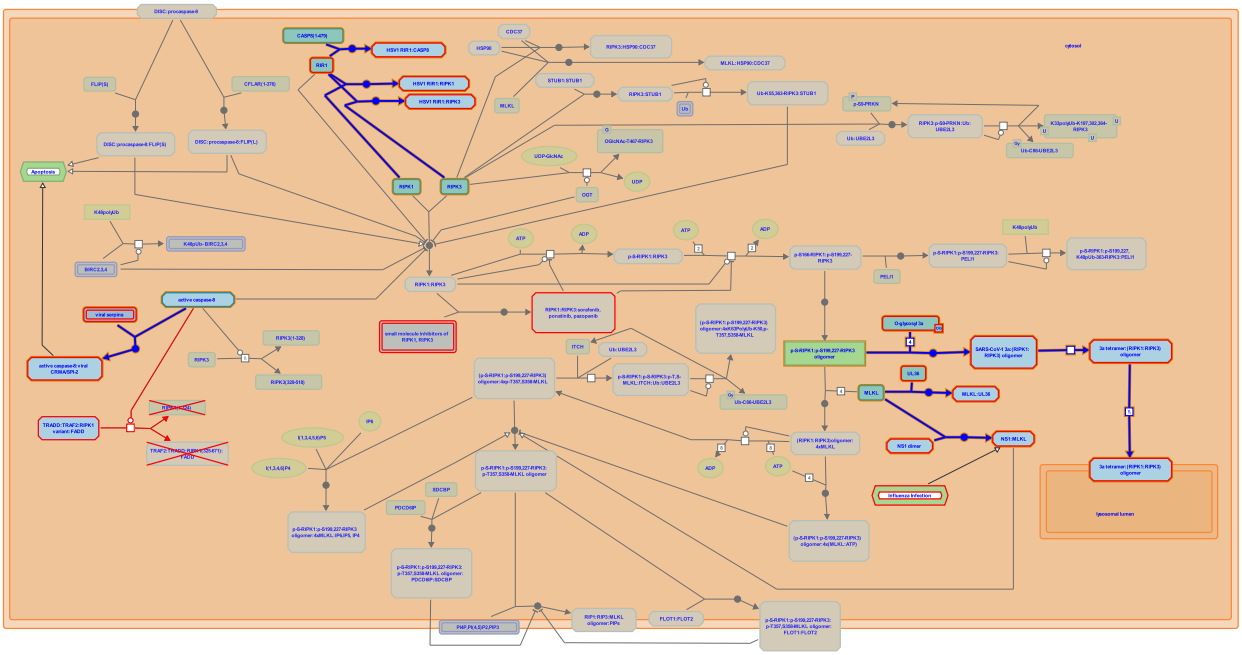
Reactome database release: 88

This document contains 1 pathway and 9 reactions (see Table of Contents)

Microbial modulation of 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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SARS-CoV-1 3a binds RIPK1:RIPK3 oligomer ↗

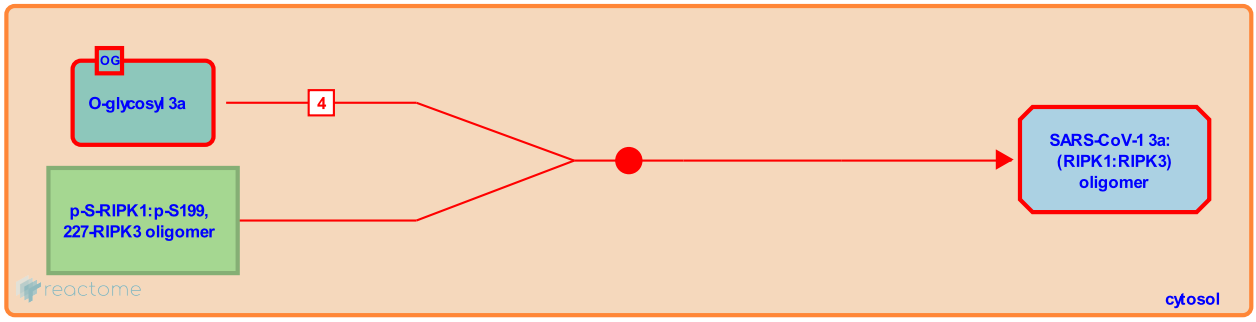
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9686345

Type: binding

Compartments: cytosol

Diseases: severe acute respiratory syndrome



Severe acute respiratory syndrome-associated coronavirus type 1 (SARS-CoV-1) 3a protein was shown to interact with receptor interacting protein kinase 3 (RIPK3) by immunoprecipitation analysis upon co-expression of viral 3a and RIPK3 in human embryonic kidney 293 (HEK293) cells (Yue Y et al. 2018). Mapping of the interaction between RIPK3 and 3a showed that the kinase domain of RIPK3 (1–326) interacted with SARS-CoV-1 3a, but that the RIP homotypic interaction motif (RHIM) containing C-terminus (327–518) interacted very weakly. Time-lapse confocal microscopy using Cherry-tagged RIP3 in HeLa cells expressing SARS-CoV-1 3a-GFP showed that expression of RIPK3 drives cell death in the presence of SARS 3a. Further, RIPK3-induced oligomerization of SARS-CoV-1 3a (studied with the oligomerization-deficient viral 3a-flag C133A mutant) helped drive necrotic cell death in RIPK3-expressing HEK293, HeLa and 5-Aza-2′-deoxycytidine (5-AD)-treated human alveolar epithelial A549 cells (Yue Y et al. 2018). The A549 cell line is resistant to the traditional necroptotic stimuli, but treatment with hypomethylating agents such as 5-AD induced RIPK3 expression (Yue Y et al. 2018). The results of the study suggest that SARS-Cov-1 3a does not induce cell death in the absence of RIPK3, but induces significant oligomerization-dependent death in the presence of endogenous RIPK3. (Yue Y et al. 2018).

During tumor necrosis factor (TNF)-induced necroptosis, RIPK3 and RIPK1 associate with each other through their RHIM domains into heteromeric RIPK1:RIPK3 complexes that further polymerize into filamentous β-amyloid structures promoting the activation of RIPK3 kinase (Cho Y et al. 2009; Li J et al. 2012). Functionally active RIPK3 activates mixed-lineage kinase domain-like pseudokinase (MLKL), the membrane-disrupting effector of programmed necrosis (Sun L et al. 2012; Murphy JM et al. 2013; Wang H et al. 2014). Other RHIM-containing proteins, such as the TLR3/TLR4 adaptor TRIF (also known as TICAM1) and the DNA sensor DAI/ZBP can form the necroptotic signaling platforms to support activation of RIPK3 and its interaction with MLKL (Kaiser W et al. 2013; Lin J et al. 2016).

This Reactome event shows a scaffolding role of RIPK3 bound to RIPK1 in supporting the formation of SARS-CoV-1 3a oligomers.

Followed by: SARS-CoV-1 3a oligomerizes

Literature references

Shi, CS., Hwang, IY., Kehrl, JH., Xiao, X., Kamenyeva, O., Nabar, NR. et al. (2018). SARS-Coronavirus Open Reading Frame-3a drives multimodal necrotic cell death. *Cell Death Dis, 9*, 904. ↗

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SARS-CoV-1 3a oligomerizes ↗

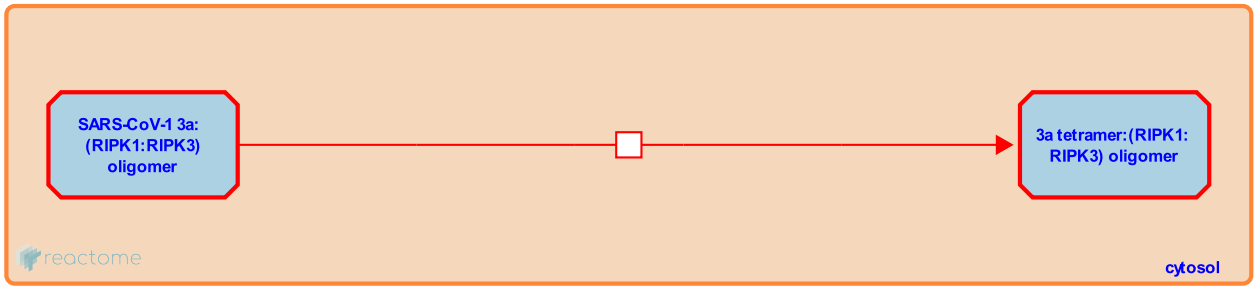
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9686336

Type: transition

Compartments: cytosol

Diseases: severe acute respiratory syndrome



Receptor interacting serine/threonine protein kinase 3 (RIPK3) was found to induce oligomerization of severe acute respiratory syndrome-associated coronavirus type 1 (SARS-CoV-1) 3a (studied with the oligomerization-deficient viral 3a-flag C133A mutant) in human embryonic kidney 293 (HEK293) that do not express endogenous RIPK3 or MLKL, after co-transfection of viral 3a and RIPK3 (Yue Y et al. 2018). RIPK3-induced oligomerization of viral 3a helped drive necrotic cell death in RIPK3-expressing HEK293 and 5-Aza-2′-deoxycytidine (5-AD)-treated human alveolar epithelial A549 cells (Yue Y et al. 2018). The A549 cell line is resistant to the traditional necroptotic stimuli, but treatment with hypomethylating agents such as 5-AD induced RIPK3 expression (Yue Y et al. 2018). The results of the study suggest that SARS-Cov-1 3a does not induce cell death in the absence of RIPK3, but induces significant oligomerization-dependent death in the presence of endogenous RIPK3. (Yue Y et al. 2018). RIPK3 kinase activity was dispensable for the RIPK3-driven oligomerization of 3a (Yue Y et al. 2018). Further, a disulfide bond formation at cysteine-133 was found to mediate the oligomerization of 3a (Lu W et al. 2006) and the addition of DTT to cell lysates from HEK293 cells after co-transfection of viral 3a and RIPK3 completely erased the oligomerization 3a, confirming its disulfide bond dependence (Yue Y et al. 2018). SARS-CoV-1 3a formed homodimer and homotetramer complexes in 3a-cDNA-transfected HEK 293 cells (Lu W et al. 2006). The tetrameric pattern is a very common feature of a protein involved in ion channel formation (Shi N et al. 2006).

Preceded by: SARS-CoV-1 3a binds RIPK1:RIPK3 oligomer

Followed by: SARS-CoV-1 3a binds the lysosomal membrane

Literature references

Shi, CS., Hwang, IY., Kehrl, JH., Xiao, X., Kamenyeva, O., Nabar, NR. et al. (2018). SARS-Coronavirus Open Reading Frame-3a drives multimodal necrotic cell death. *Cell Death Dis, 9*, 904. ↗

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SARS-CoV-1 3a binds the lysosomal membrane ↗

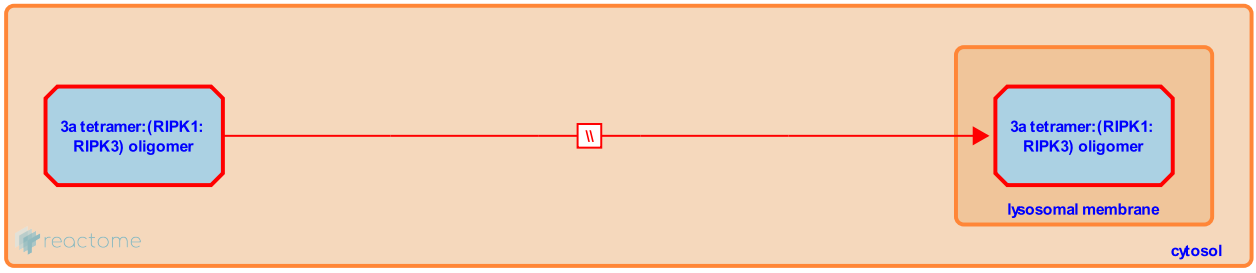
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9686338

Type: omitted

Compartments: cytosol, lysosomal membrane

Diseases: severe acute respiratory syndrome



Severe acute respiratory syndrome-associated coronavirus type 1 (SARS-CoV-1) open reading frame-3a has been implicated in host cell death pathways. Receptor interacting serine/threonine protein kinase 3 (RIPK3) was found to induce oligomerization of SARS-CoV-1 3a after co-transfection of viral 3a and RIPK3 in human embryonic kidney 293 (HEK293) that do not express endogenous RIPK3 or MLKL (Yue Y et al. 2018). Confocal imaging showed that co-expressed SARS-CoV-1 3a and RIPK3 co-localized with lysosomal-associated membrane protein 1 (LAMP1) in HeLa cells (Yue Y et al. 2018). Quantification of colocalization revealed that 3a likely targets RIPK3 to lysosomes. Further, a lysosomal galectin puncta assay showed that SARS-CoV-1 3a caused lysosomal membrane permeabilization. In addition, the SARS-CoV-1 3a-mediated release of cathepsins from lysosomes in HEK293 cells (Yue Y et al. 2018). Thus, RIPK3 is thought to induce oligomerization of SARS-CoV-1 3a, which facilitates membrane insertion and ion channel functionality of SARS-CoV-1 3a (Yue Y et al. 2018).

Preceded by: SARS-CoV-1 3a oligomerizes

Literature references

Shi, CS., Hwang, IY., Kehrl, JH., Xiao, X., Kamenyeva, O., Nabar, NR. et al. (2018). SARS-Coronavirus Open Reading Frame-3a drives multimodal necrotic cell death. *Cell Death Dis, 9*, 904. ↗

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IAV NS1 binds MLKL ↗

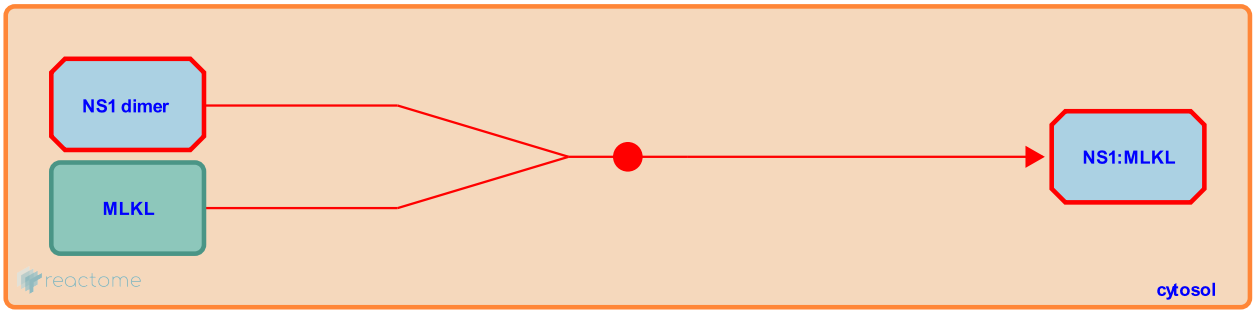
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9686343

Type: binding

Compartments: cytosol

Diseases: influenza



Co-immunoprecipitation assays in influenza A virus (IAV)-infected human leukemia monocytic THP1 cell, as well as NS1-transfected human embryonic kidney (HEK293) cells showed that viral NS1 interacts with mixed-lineage kinase domain-like protein (MLKL) in an RNA-dependent manner (Gaba A et al. 2019). The second brace helix of MLKL is responsible for interacting with NS1 (Gaba A et al. 2019). The interaction of NS1 with MLKL is thought to increased MLKL membrane translocation. Moreover, the MLKL:NS1 interaction enhanced NLRP3 inflammasome activation and increases IL-1β processing and secretion (Gaba A et al. 2019).

Literature references

Zhou, Y., Liu, G., Lu, Y., Park, HS., Xu, F., Gaba, A. (2019). The NS1 Protein of Influenza A Virus Participates in Necroptosis by Interacting with MLKL and Increasing Its Oligomerization and Membrane Translocation. *J. Virol., 93*. ↗

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HSV1 RIR1 binds RIPK1 ↗

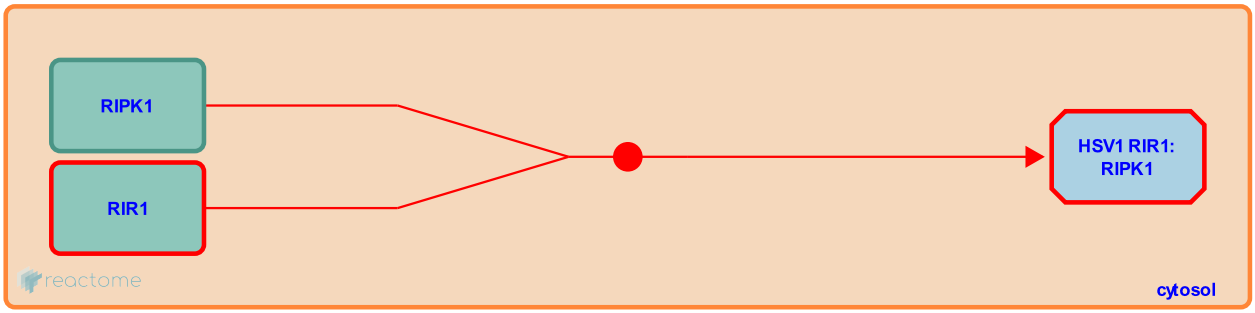
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9687465

Type: binding

Compartments: cytosol

Diseases: viral infectious disease



Necroptosis complements apoptosis as a host defense pathway to stop virus infection. During infection in human cells, herpes simplex virus (HSV)-1 and HSV-2 modulate cell death pathways using the large subunit (R1) of viral ribonucleotide reductase (RIR1 or UL39) (Dufour F et al. 2011; Guo H et al. 2015; Yu X et al. 2016; Ali M et al.2019). The N-terminal region of RIR1 protein carrying the RIP homotypic interaction motif (RHIM)-like element is sufficient for RHIM-dependent interaction with receptor-interacting protein kinase 1 (RIPK1) and receptor-interacting protein kinase 3 (RIPK3) thus inhibiting the interaction between RIPK1 and RIPK3 (Guo H et al. 2015; Yu X et al. 2015). An intact RHIM is required for the interaction between RIPK1 and RIPK3 that occurs downstream of tumour necrosis factor receptor 1 (TNFR1) activation during the programmed cell death response known as necroptosis (Sun X et al. 2002). In addition, the large carboxyl-terminal region of HSV RIR1 protein mediates the binding to caspase 8 (CASP8) (Dufour F et al. 2011; Guo H et al. 2015). HSV RIR1 is thought to block necroptosis in infected human cells by interactions with RIPK1, RIPK3 and CASP8 (Guo H et al. 2015; Mocarski ES et al. 2015).

Literature references

Zheng, C., Yu, X., Yang, C., Li, Y., Jiang, X., Chen, Q. et al. (2016). Herpes Simplex Virus 1 (HSV-1) and HSV-2 Mediate Species-Specific Modulations of Programmed Necrosis through the Viral Ribonucleotide Reductase Large Subunit R1. *J. Virol., 90*, 1088-95. ↗

Mocarski, ES., Finger, JN., Omoto, S., Kaiser, WJ., Guo, H., Bertin, J. et al. (2015). Herpes simplex virus suppresses necroptosis in human cells. *Cell Host Microbe, 17*, 243-51. ↗

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HSV1 RIR1 binds RIPK3 ↗

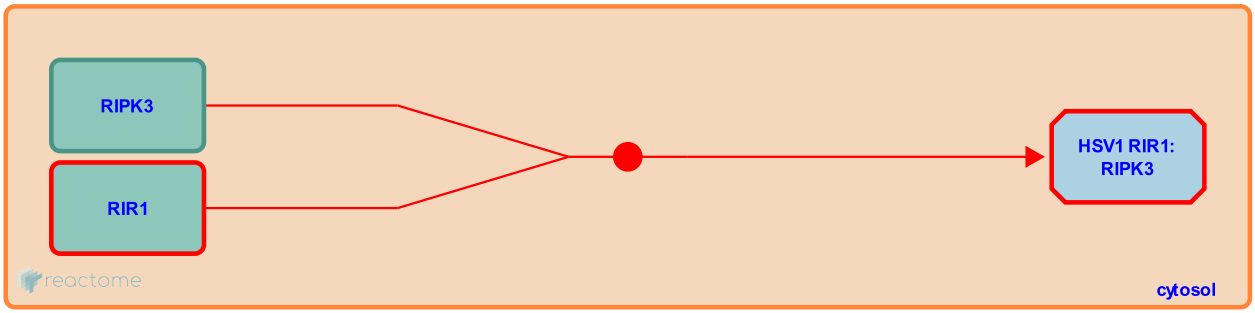
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9687455

Type: binding

Compartments: cytosol

Diseases: viral infectious disease



During infection in human cells, herpes simplex virus (HSV)-1 and HSV-2 modulate cell death pathways using the large subunit (R1) of viral ribonucleotide reductase (RIR1 or UL39) (Dufour F et al. 2011; Guo H et al. 2015; Yu X et al. 2016; Ali M et al.2019). The N-terminal region of RIR1 protein carrying the RIP homotypic interaction motif (RHIM)-like element is sufficient for RHIM-dependent interaction with receptor-interacting protein kinase 1 (RIPK1) and receptor-interacting protein kinase 3 (RIPK3) thus inhibiting the interaction between RIPK1 and RIPK3 (Guo H et al. 2015; Yu X et al. 2015). An intact RHIM is required for the interaction between RIPK1 and RIPK3 that occurs downstream of tumour necrosis factor receptor 1 (TNFR1) activation during the programmed cell death response known as necroptosis (Sun X et al. 2002). In addition, the large carboxyl-terminal region of HSV RIR1 protein mediates the binding to caspase 8 (CASP8) (Dufour F et al. 2011; Guo H et al. 2015). HSV RIR1 is thought to block necroptosis in infected human cells by interactions with RIPK1, RIPK3 and CASP8 (Guo H et al. 2015; Mocarski ES et al. 2015).

Literature references

Zheng, C., Yu, X., Yang, C., Li, Y., Jiang, X., Chen, Q. et al. (2016). Herpes Simplex Virus 1 (HSV-1) and HSV-2 Mediate Species-Specific Modulations of Programmed Necrosis through the Viral Ribonucleotide Reductase Large Subunit R1. *J. Virol., 90*, 1088-95. ↗

Mocarski, ES., Finger, JN., Omoto, S., Kaiser, WJ., Guo, H., Bertin, J. et al. (2015). Herpes simplex virus suppresses necroptosis in human cells. *Cell Host Microbe, 17*, 243-51. ↗

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HSV1 RIR1 binds CASP8

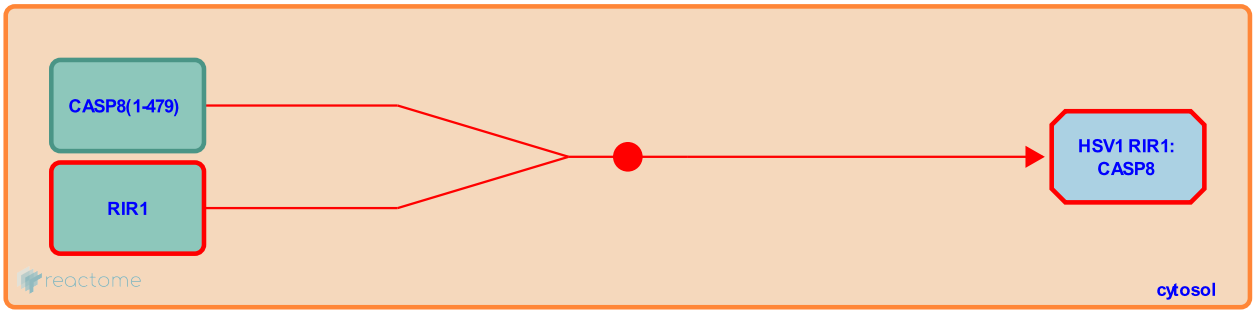
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9687458

Type: binding

Compartments: cytosol

Diseases: viral infectious disease



During infection in human cells, herpes simplex virus 1 (HSV1) and HSV2 modulate cell death pathways using the large subunit (R1) of viral ribonucleotide reductase (RIR1 or UL39) proteins (Dufour F et al. 2011; Guo H et al. 2015; Yu X et al. 2016; Ali M et al. 2019). The HSV1 and HSV2 RIR1 proteins suppress death receptor-dependent apoptosis by interacting with death effector domains of caspase 8 (CASP8) via a conserved C-terminal ribonucleotide reductase (RNR) domain (Dufour F et al. 2011). The ability of HSV1 RIR1 and HSV2 RIR1 to bind CASP8 is integral to their suppression activity against necroptosis in human cells. Necroptosis complements apoptosis as a host defense pathway to stop virus infection and is mediated by the interaction between receptor-interacting protein kinase 1 (RIPK1) and RIPK3 that occurs downstream of tumor necrosis factor receptor 1 (TNFR1) activation during the programmed cell death response (Sun X et al. 2002). The N-terminal region of HSV1 and HSV2 RIR1 proteins carrying the RIP homotypic interaction motif (RHIM)-like element is sufficient for RHIM-dependent interaction with RIPK1 and RIPK3 thus inhibiting the interaction between RIPK1 and RIPK3 (Guo H et al. 2015; Yu X et al. 2015). HSV1 RIR1 and HSV2 RIR1 are thought to block the programmed cell death responses in infected human cells by interactions with RIPK1, RIPK3 and CASP8 (Guo H et al. 2015; Mocarski ES et al. 2015).

Literature references

Mocarski, ES., Finger, JN., Omoto, S., Kaiser, WJ., Guo, H., Bertin, J. et al. (2015). Herpes simplex virus suppresses necroptosis in human cells. *Cell Host Microbe, 17*, 243-51.

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Viral serpin blocks caspase-8 activity ↗

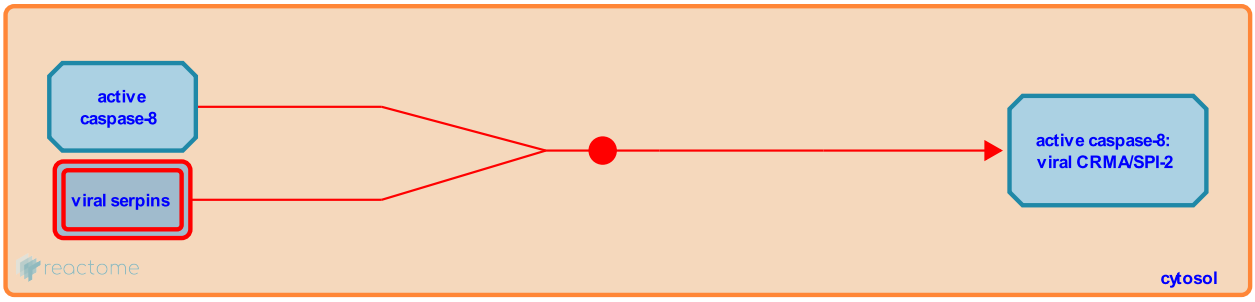
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-2672196

Type: binding

Compartments: cytosol

Diseases: viral infectious disease



SPI-2/CrmA (cytokine response modifier A) is a poxvirus gene product with homology to members of the serpin (serine protease inhibitor) superfamily. Cowpox virus-derived and vaccinia virus-derived CrmA cDNAs transfected into cells inhibit apoptosis induced by Fas-ligation and activation of TNFR1 (Tewari M and Dixit VM 1995; Miura M et al, 1995; Kettle S et al. 1997). Cowpox virus-derived CrmA was shown to selectively inhibit caspases in Fas-mediated apoptosis, showing the highest affinity for interleukin-1 beta-converting enzyme (ICE) and a similarly high affinity for caspase-8, Ki = 0.95 nM (Zhou Q et al. 1997).

Literature references

Snipas, S., Zhou, Q., Muzio, M., Dixit, VM., Orth, K., Salvesen, GS. (1997). Target protease specificity of the viral serpin CrmA. Analysis of five caspases. *J. Biol. Chem., 272*, 7797-800. ↗

Khanna, A., Alcamí, A., Jassoy, C., Kettle, S., Smith, GL., Ehret, R. (1997). Vaccinia virus serpin B13R (SPI-2) inhibits interleukin-1beta-converting enzyme and protects virus-infected cells from TNF- and Fas-mediated apoptosis, but does not prevent IL-1beta-induced fever. *J. Gen. Virol., 78*, 677-85. ↗

Friedlander, RM., Yuan, J., Miura, M. (1995). Tumor necrosis factor-induced apoptosis is mediated by a CrmA-sensitive cell death pathway. *Proc. Natl. Acad. Sci. U.S.A., 92*, 8318-22. ↗

Tewari, M., Dixit, VM. (1995). Fas- and tumor necrosis factor-induced apoptosis is inhibited by the poxvirus crmA gene product. *J. Biol. Chem., 270*, 3255-60. ↗

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HCMV UL36 binds MLKL ↗

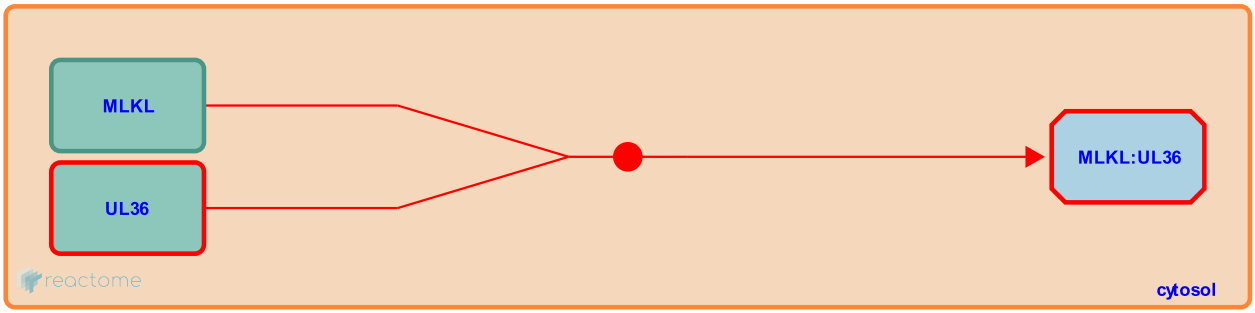
Location: Microbial modulation of RIPK1-mediated regulated necrosis

Stable identifier: R-HSA-9698677

Type: binding

Compartments: cytosol

Diseases: viral infectious disease



Human cytomegalovirus (HCMV) protein pUL36 was found to bind mixed lineage kinase domain-like protein (MLKL) and target MLKL for degradation in HCMV-infected TERT-immortalized primary human fetal foreskin fibroblasts (HFFF-TERTs) (Fletcher-Etherington A et al. 2020). Furthermore, mutation of pUL36 Cys131 abrogated MLKL degradation and restored necroptosis in HFFF-TERTs. The same residue was also required for pUL36-mediated inhibition of apoptosis by preventing proteolytic activation of procaspase-8, suggesting that pUL36 acts as a multifunctional inhibitor of both apoptotic and necroptotic cell death (Fletcher-Etherington A et al. 2020; Skaletskaya A et al. 2001).

Literature references

Stanton, RJ., Nightingale, K., Davison, AJ., Nichols, J., Nobre, L., Weekes, MP. et al. (2020). Human cytomegalovirus protein pUL36: A dual cell death pathway inhibitor. *Proc. Natl. Acad. Sci. U.S.A., 117*, 18771-18779. ↗

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Table of Contents