RIPK1 is cleaved by CASP8

Gillespie, ME., Lalaoui, N., Murphy, JM., Shamovsky, V., Wajant, H.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

08/05/2024

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. ↗

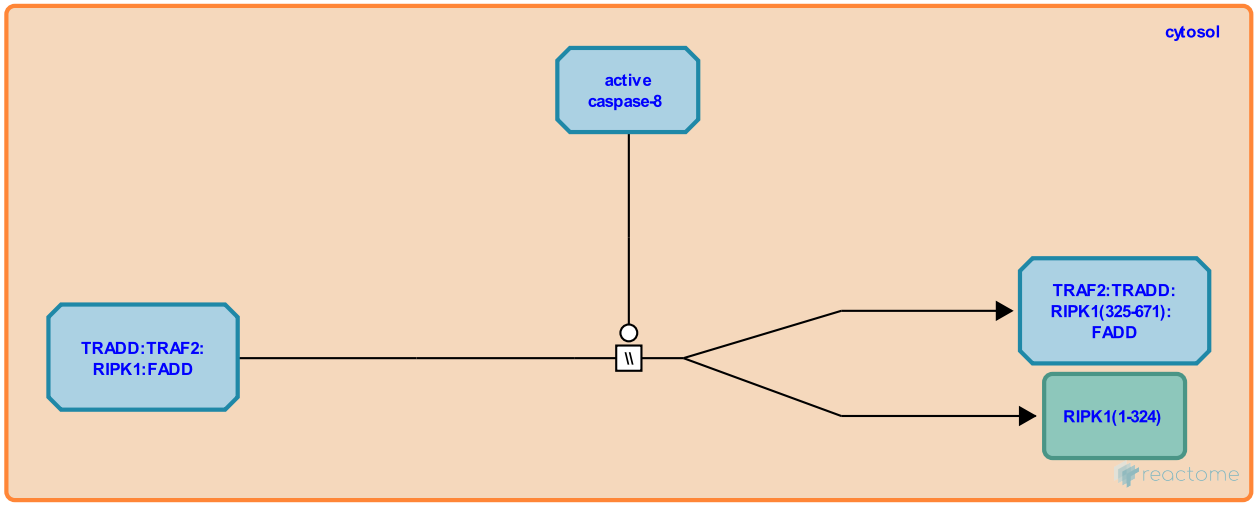
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

RIPK1 is cleaved by CASP8 ↗

Stable identifier: R-HSA-5357828

Type: omitted

Compartments: cytosol



Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) can be a part of cell death and survival signaling complexes. Whether RIPK1 functions in apoptosis, necroptosis or NFκB signaling is dependent on autocrine/paracrine signals, on the cellular context and tightly regulated by posttranslational modifications of RIP1 itself. The pro-survival function of RIPK1 is achieved by polyubiquitination which is required for recruitment of signaling molecules/complexes such as the IKK complex and the TAB2:TAK1 complex to mediate activation of NFκB signaling (Ea CK et al. 2006). CYLD-mediated deubiquitination of RIPK1 switches its pro-survival function to caspase-mediated pro-apoptotic signaling (Fujikura D et al. 2012; Moquin DM et al. 2013). Caspase-8 (CASP8) in human and rodent cells facilitates the cleavage of kinases RIPK1 and RIPK3 and prevents RIPK1/RIPK3-dependent necroptosis (Lin Y et al. 1999; Hopkins-Donaldson S et al. 2000; Newton K et al. 2019; Zhang X et al. 2019; Lalaoui N et al. 2020). CASP8-mediated cleavage of human RIPK1 after D324 (D325 in mice) separates the amino-terminal kinase domain from the carboxy-terminal part of the molecule preventing RIPK1 kinase activation through dimerization via the carboxy-terminal death domain and leads to the dissociation of the complex TRADD:TRAF2:RIP1:FADD:CASP8 (Lin Y et al. 1999; Meng H et al. 2018). The lack of CASP8 proteolytic activity in the presence of viral (e.g. CrmA and vICA) or pharmacological caspase inhibitors results in necroptosis induction via RIPK1 and RIPK3 (Tewari M & Dixit VM 1995; Fliss PM & Brune W 2012; Hopkins-Donaldson S et al. 2000). Cellular FLICE-like inhibitory protein (cFLIP), which is an NF-κB target gene, form heterodimer with procaspase-8 and inhibits activation of CASP8 within the the TRADD:TRAF2:RIP1:FADD:CASP8:FLIP complex (Yu JW et al. 2009; Pop C et al. 2011). The presence of cFLIP (long form) limits CASP8 to cleave CASP3/7 but allow cleavage of RIPK1 to cause the dissociation of the TRADD:TRAF2:RIP1:FADD:CASP8, thereby inhibiting both apoptosis and necroptosis (Boatright KM et al. 2004; Yu JW et al. 2009; Pop C et al. 2011; Feoktistova M et al. 2011). Mice that lack CASP8 or knock-in mice that express catalytically inactive CASP8 (C362A) die in a RIPK3- and MLKL-dependent manner during embryogenesis (Kaiser WJ et al. 2011; Newton K et al. 2019). Studies using mice that express RIPK1(D325A), in which the CASP8 cleavage site Asp325 had been mutated, further confirmed that cleavage of RIPK1 by CASP8 is a mechanism for dismantling death-inducing complexes for limiting aberrant cell death in response to stimuli (Newton K et al. 2019; Lalaoui N et al. 2020). Disrupted cleavage of RIPK1 variants with mutations at D324 by CASP8 in humans leads to an autoinflammatory response by promoting the activation of RIPK1 (Tao P et al. 2020; Lalaoui N et al. 2020).

Literature references

Devin, A., Liu, ZG., Lin, Y., Rodriguez, Y. (1999). Cleavage of the death domain kinase RIP by caspase-8 prompts TNF-induced apoptosis. *Genes Dev., 13*, 2514-26. ↗

Newton, K., Webster, JD., Roose-Girma, M., Dugger, DL., Komuves, L., Wickliffe, KE. et al. (2019). Cleavage of RIPK1 by caspase-8 is crucial for limiting apoptosis and necroptosis. *Nature, 574*, 428-431. ↗

Editions

2015-02-15	Edited	Shamovsky, V.
2015-03-12	Reviewed	Gillespie, ME.
2015-05-12	Authored	Shamovsky, V.
2015-08-25	Reviewed	Wajant, H.
2020-08-19	Edited	Shamovsky, V.
2020-08-20	Reviewed	Lalaoui, N.
2020-08-28	Reviewed	Murphy, JM.