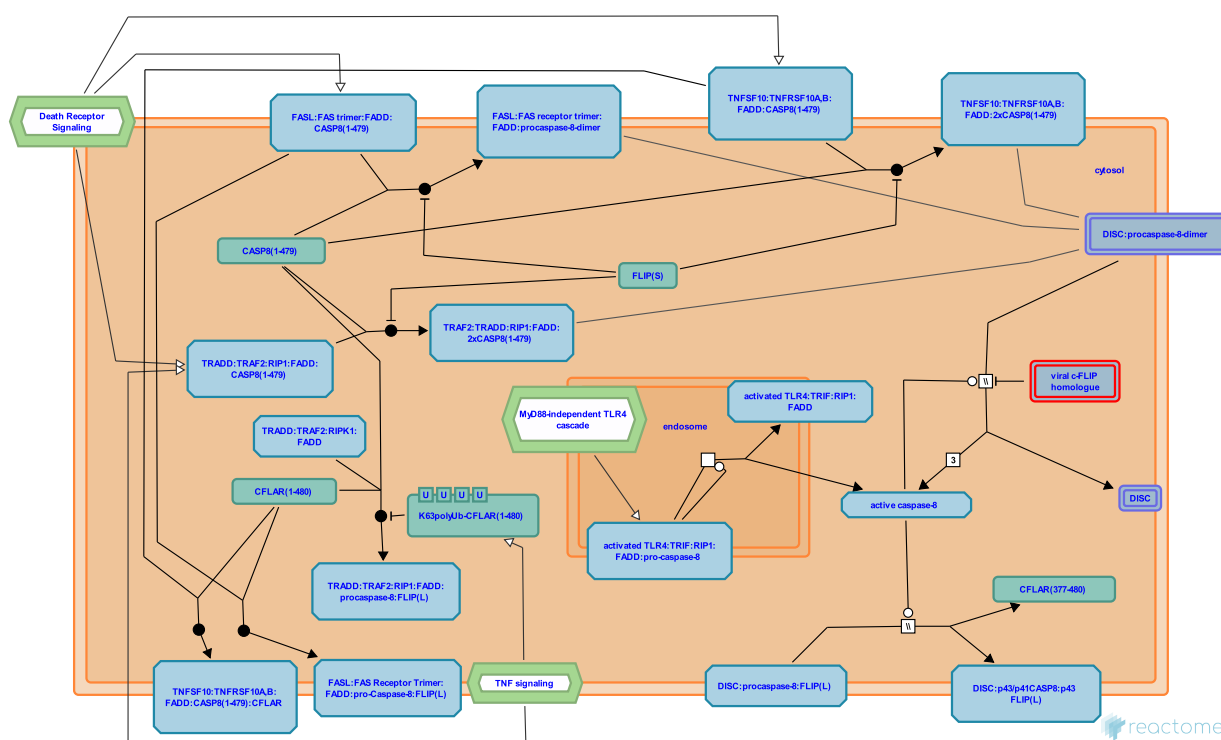


Caspase activation via Death Receptors in the presence of ligand



Fitzgerald, KA., Gillespie, ME., Pop, C., Salvesen, GS., Shamovsky, V.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/about/faq).

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](https://reactome.org/textbook).

03/04/2024

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. [↗](#)

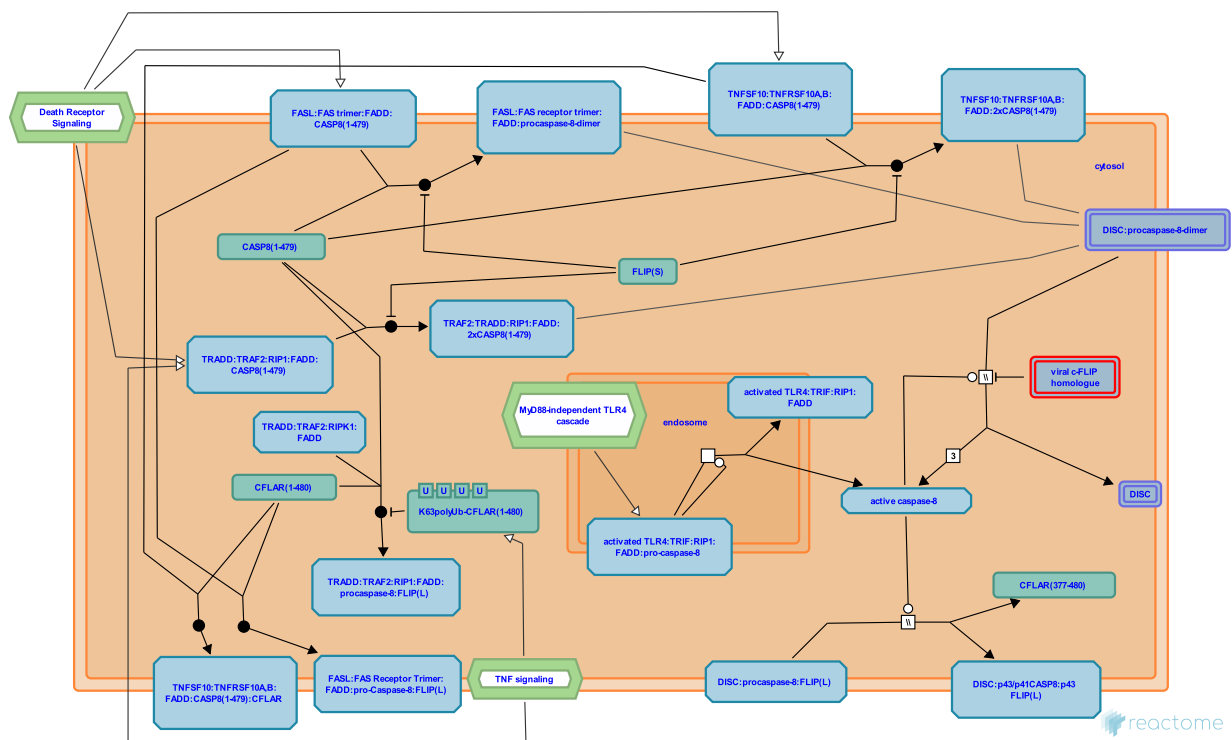
Reactome database release: 88

This document contains 3 pathways and 2 reactions ([see Table of Contents](#))

Caspase activation via Death Receptors in the presence of ligand ↗

Stable identifier: R-HSA-140534

Compartments: cytosol



Caspase-8 is synthesized as zymogen (procaspase-8) and is formed from procaspase-8 as a cleavage product. However, the cleavage itself appears not to be sufficient for the formation of an active caspase-8. Only the coordinated dimerization and cleavage of the zymogen produce efficient activation in vitro and apoptosis in cellular systems [Boatright KM and Salvesen GS 2003; Keller N et al 2010; Oberst A et al 2010].

The caspase-8 zymogens are present in the cells as inactive monomers, which are recruited to the death-inducing signaling complex (DISC) by homophilic interactions with the DED domain of FADD. The monomeric zymogens undergo dimerization and the subsequent conformational changes at the receptor complex, which results in the formation of catalytically active form of procaspase-8.[Boatright KM et al 2003; Donepudi M et al 2003; Keller N et al 2010; Oberst A et al 2010].

Literature references

- Blais, V., Oberst, A., Denault, JB., Green, DR., Salvesen, GS., Tremblay, AG. et al. (2010). Inducible dimerization and inducible cleavage reveal a requirement for both processes in caspase-8 activation. *J Biol Chem*, 285, 16632-42. ↗
- Grütter, MG., Briand, C., Mac Sweeney, A., Donepudi, M. (2003). Insights into the regulatory mechanism for caspase-8 activation. *Mol. Cell*, 11, 543-9. ↗
- Salvesen, GS., Boatright, KM. (2003). Mechanisms of caspase activation. *Curr Opin Cell Biol*, 15, 725-31. ↗
- Grütter, MG., Keller, N., Zerbe, O. (2010). Studies of the molecular mechanism of caspase-8 activation by solution NMR. *Cell Death Differ.*, 17, 710-8. ↗
- Sperandio, S., Shin, H., Ricci, JE., Scott, FL., Renatus, M., Sutherlin, DP. et al. (2003). A unified model for apical caspase activation. *Mol Cell*, 11, 529-41. ↗

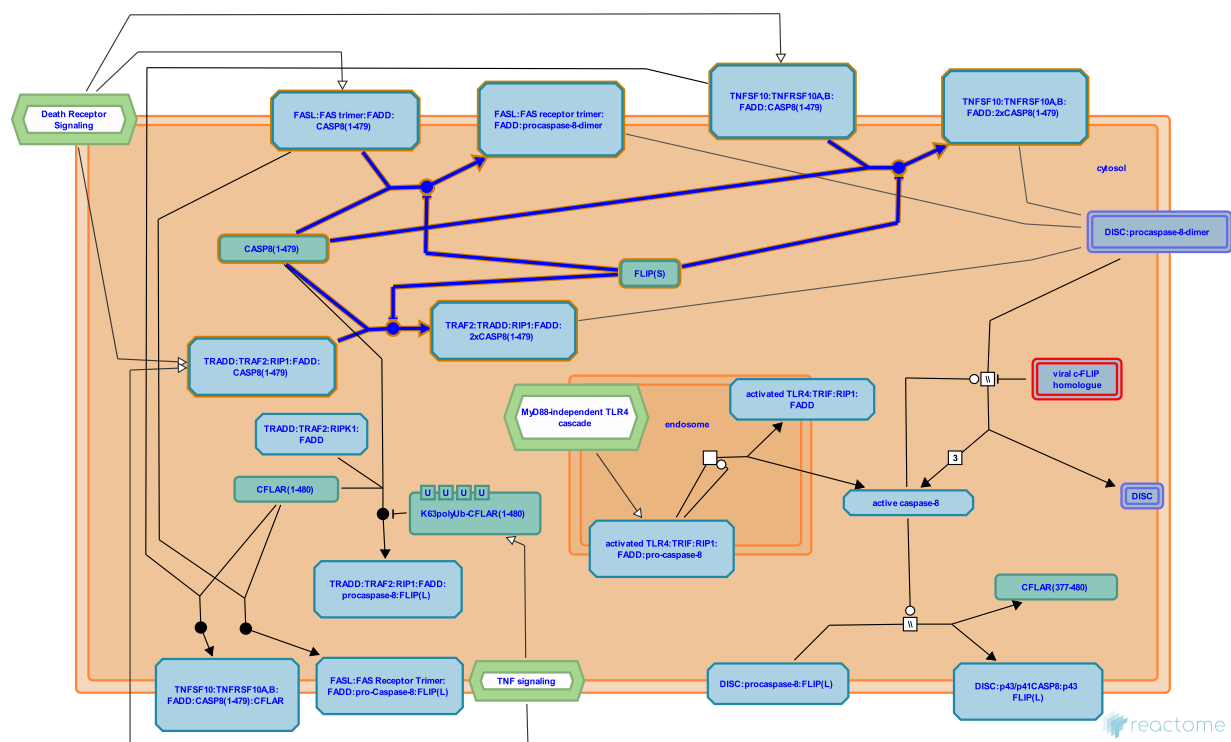
Editions

2012-11-19	Reviewed	Gillespie, ME.
2013-05-18	Edited	Shamovsky, V.
2013-05-22	Reviewed	Salvesen, GS., Pop, C.
2015-01-12	Revised	Shamovsky, V.

Dimerization of procaspase-8 ↗

Location: Caspase activation via Death Receptors in the presence of ligand

Stable identifier: R-HSA-69416



Procaspase-8 monomers undergo dimerization. The dimerization event occurs at death-inducing signaling complex (DISC) and results in a reposition of the procaspase-8 inter-subunit linker to become accessible for intermolecular processing by the associated procaspase-8 molecule [Keller N et al 2010; Oberst A et al 2010].

Literature references

Blais, V., Oberst, A., Denault, JB., Green, DR., Salvesen, GS., Tremblay, AG. et al. (2010). Inducible dimerization and inducible cleavage reveal a requirement for both processes in caspase-8 activation. *J Biol Chem*, 285, 16632-42. ↗

Grütter, MG., Briand, C., Mac Sweeney, A., Donepudi, M. (2003). Insights into the regulatory mechanism for caspase-8 activation. *Mol. Cell*, 11, 543-9. ↗

Grütter, MG., Keller, N., Zerbe, O. (2010). Studies of the molecular mechanism of caspase-8 activation by solution NMR. *Cell Death Differ.*, 17, 710-8. ↗

Editions

2012-11-19	Reviewed	Gillespie, ME.
2013-05-18	Edited	Shamovsky, V.
2013-05-22	Reviewed	Salvesen, GS., Pop, C.

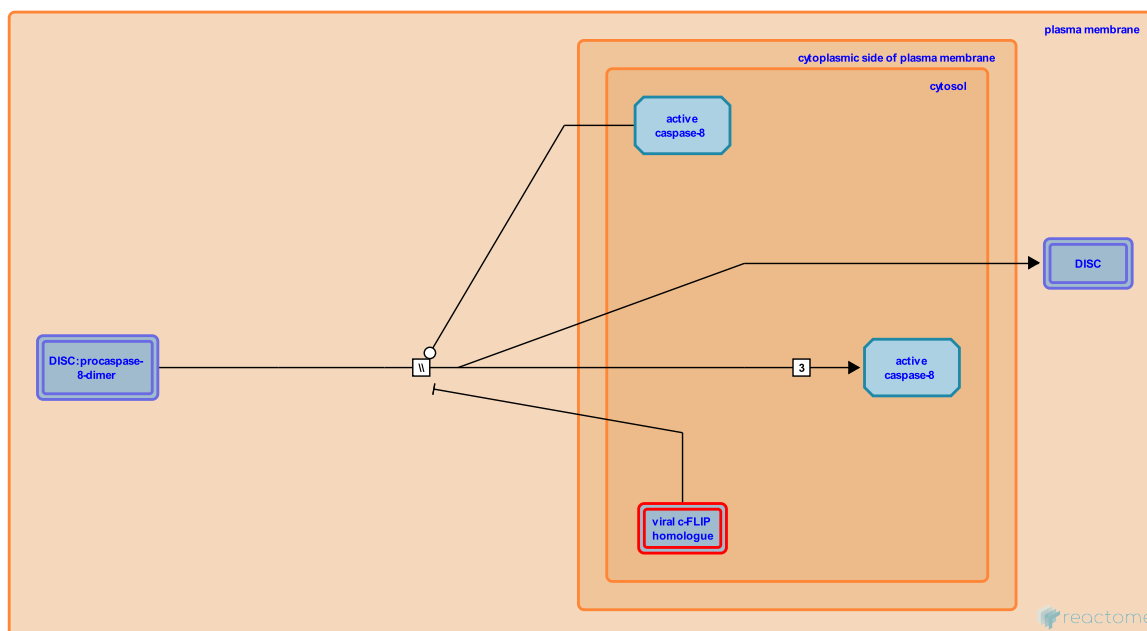
Caspase-8 processing in the DISC [↗](#)

Location: Caspase activation via Death Receptors in the presence of ligand

Stable identifier: R-HSA-139952

Type: omitted

Compartments: plasma membrane, cytosol



Caspase-8 zymogens are present in the cells as inactive monomers, containing a large N-terminal prodomain with two death effector domains (DED), and a C-terminal catalytic subunit composed of small and a large domains separated by a smaller linker region [Donepudi M et al 2003; Keller N et al 2009]. Dimerization is required for the caspase-8 activation [Donepudi M et al 2003]. Once dimerized, caspase-8 zymogen undergoes a series of autoproteolytic cleavage events at aspartic acid residues in their interdomain linker regions. A second cleavage event between the the N-terminal prodomain and the catalytic domain releases the active caspase from the activation complex into the cytosol. The resulting fully active enzyme is a homodimer of catalytic domains, where each domain is composed of a large p18 and a small p10 subunit [Keller N et al 2009; Oberst A et al 2010].

Literature references

- Zerbe, O., Keller, N., Grütter, MG., Mares, J. (2009). Structural and biochemical studies on procaspase-8: new insights on initiator caspase activation. *Structure*, 17, 438-48. [↗](#)
- Blais, V., Oberst, A., Denault, JB., Green, DR., Salvesen, GS., Tremblay, AG. et al. (2010). Inducible dimerization and inducible cleavage reveal a requirement for both processes in caspase-8 activation. *J Biol Chem*, 285, 16632-42. [↗](#)
- Grütter, MG., Briand, C., Mac Sweeney, A., Donepudi, M. (2003). Insights into the regulatory mechanism for caspase-8 activation. *Mol. Cell*, 11, 543-9. [↗](#)

Editions

2012-11-19	Reviewed	Gillespie, ME.
2013-05-18	Edited	Shamovsky, V.
2013-05-22	Reviewed	Salvesen, GS., Pop, C.

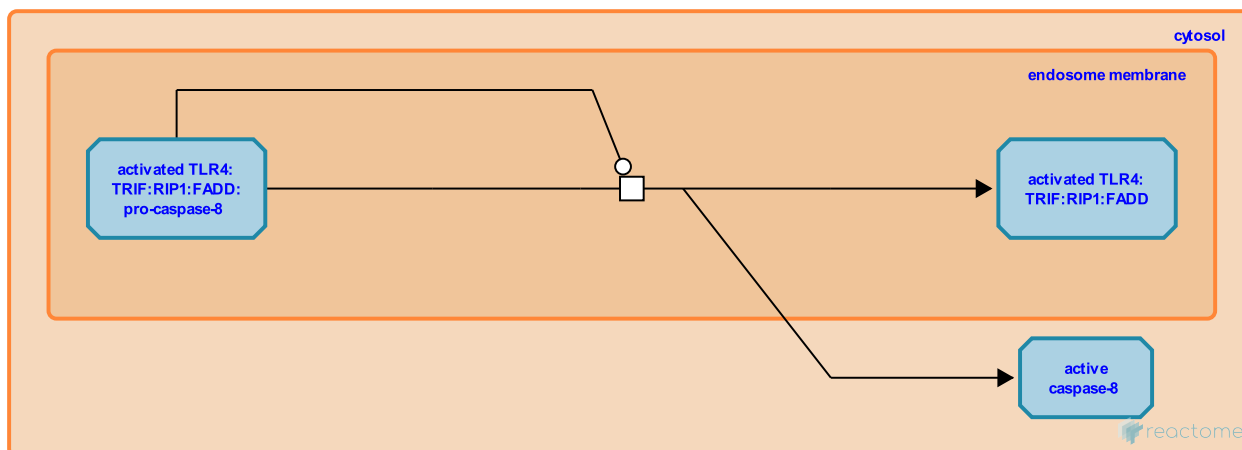
Caspase-8 processing within TLR4 complex ↗

Location: [Caspase activation via Death Receptors in the presence of ligand](#)

Stable identifier: R-HSA-2562564

Type: transition

Compartments: endosome membrane, cytosol



TLR4 and TLR3 signaling pathways were shown to mediate apoptosis in various human cell lines in the FADD:caspase-8-dependent manner [Kalai M et al 2002; Kaiser WJ and Offermann MK 2005; Estornes Y et al 2012]. Caspase-8 zymogens (procaspase-8) are present in the cells as inactive monomers, containing a large N-terminal prodomain with two death effector domains (DED), and a C-terminal catalytic subunit composed of small and a large domains separated by a smaller linker region [Donepudi M et al 2003; Keller N et al 2009]. Dimerization is required for caspase-8 activation [Donepudi M et al 2003]. The dimerization event occurs at the receptor signaling complex. Once dimerized, caspase-8 zymogen undergoes a series of autoproteolytic cleavage events at aspartic acid residues in their interdomain linker regions. A second cleavage event between the the N-terminal prodomain and the catalytic domain releases the active caspase from the activation complex into the cytosol. The resulting fully active enzyme is a homodimer of catalytic domains, where each domain is compsed of a large p18 and a small p10 subunit [Keller N et al 2009; Oberst A et al 2010].

Literature references

- Zerbe, O., Keller, N., Grütter, MG., Mares, J. (2009). Structural and biochemical studies on procaspase-8: new insights on initiator caspase activation. *Structure*, 17, 438-48. ↗
- Offermann, MK., Kaiser, WJ. (2005). Apoptosis induced by the toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. *J Immunol*, 174, 4942-52. ↗
- Blais, V., Oberst, A., Denault, JB., Green, DR., Salvesen, GS., Tremblay, AG. et al. (2010). Inducible dimerization and inducible cleavage reveal a requirement for both processes in caspase-8 activation. *J Biol Chem*, 285, 16632-42. ↗
- Grütter, MG., Briand, C., Mac Sweeney, A., Donepudi, M. (2003). Insights into the regulatory mechanism for caspase-8 activation. *Mol. Cell*, 11, 543-9. ↗
- Kalai, M., Van Loo, G., Vandenabeele, P., Burm, W., Meeus, A., Vanden Berghe, T. et al. (2002). Tipping the balance between necrosis and apoptosis in human and murine cells treated with interferon and dsRNA. *Cell Death Differ.*, 9, 981-94. ↗

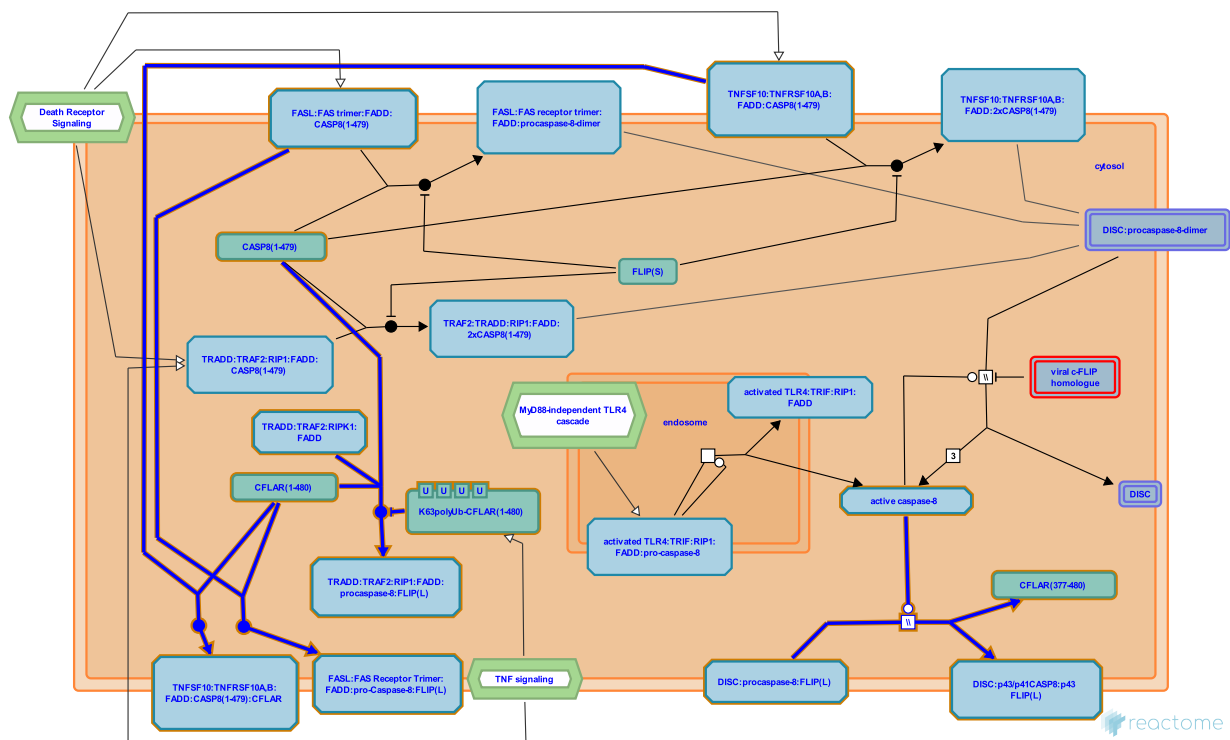
Editions

2012-05-15	Authored	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-19	Edited	Shamovsky, V.

Regulation by c-FLIP ↗

Location: Caspase activation via Death Receptors in the presence of ligand

Stable identifier: R-HSA-3371378



c-FLIP proteins (CASP8 and FADD-like apoptosis regulators or c-FLICE inhibitory proteins) are death effector domain (DED)-containing proteins that are recruited to the death-inducing signaling complex (DISC) to regulate activation of caspases-8. Three out of 13 distinct spliced variants of c-FLIP had been found to be expressed at the protein level, the 26 kDa short form FLIP(S), the 24 kDa form FLIP(R), and the 55 kDa long form FLIP(L) (Irmeler M et al. 1997; Shu HB et al. 1997; Srinivasula SM et al. 1997; Scaffidi C et al. 1999; Golks A et al. 2005; Haag C et al. 2011)

All c-FLIP proteins carry two DEDs at their N termini, which can bind FADD and procaspase-8. In addition to two DEDs, FLIP(L) contains a large (p20) and a small (p12) caspase-like domain without catalytic activity. FLIP(S) and FLIP(R) consist of two DEDs and a small C terminus. Depending on its level of expression FLIP(L) may function as an anti-apoptotic or pro-apoptotic factor, while FLIP(S) and FLIP(R) protect cells from apoptosis by blocking the processing of caspase-8 at the receptor level (Scaffidi C et al. 1999; Golks A et al. 2005; Toivonen HT et al. 2011; Fricker N et al. 2010).






Literature references

- Shi, Y., Jeffrey, PD., Yu, JW. (2009). Mechanism of procaspase-8 activation by c-FLIPL. *Proc. Natl. Acad. Sci. U.S.A.*, 106, 8169-74. ↗
- Drag, M., Van Raam, BJ., Oberst, A., Green, DR., Riedl, SJ., Salvesen, GS. et al. (2011). FLIP(L) induces caspase 8 activity in the absence of interdomain caspase 8 cleavage and alters substrate specificity. *Biochem J*, 433, 447-57. ↗
- Schneider, P., Tschopp, J., Bodmer, JL., Steiner, V., Hahne, M., French, LE. et al. (1997). Inhibition of death receptor signals by cellular FLIP. *Nature*, 388, 190-5. ↗

Editions

2013-05-13	Authored	Shamovsky, V.
2013-05-18	Edited	Shamovsky, V.
2013-05-22	Reviewed	Salvesen, GS., Pop, C.

Table of Contents

Introduction	1
 Caspase activation via Death Receptors in the presence of ligand	2
 Dimerization of procaspase-8	4
 Caspase-8 processing in the DISC	5
 Caspase-8 processing within TLR4 complex	6
 Regulation by c-FLIP	7
Table of Contents	8