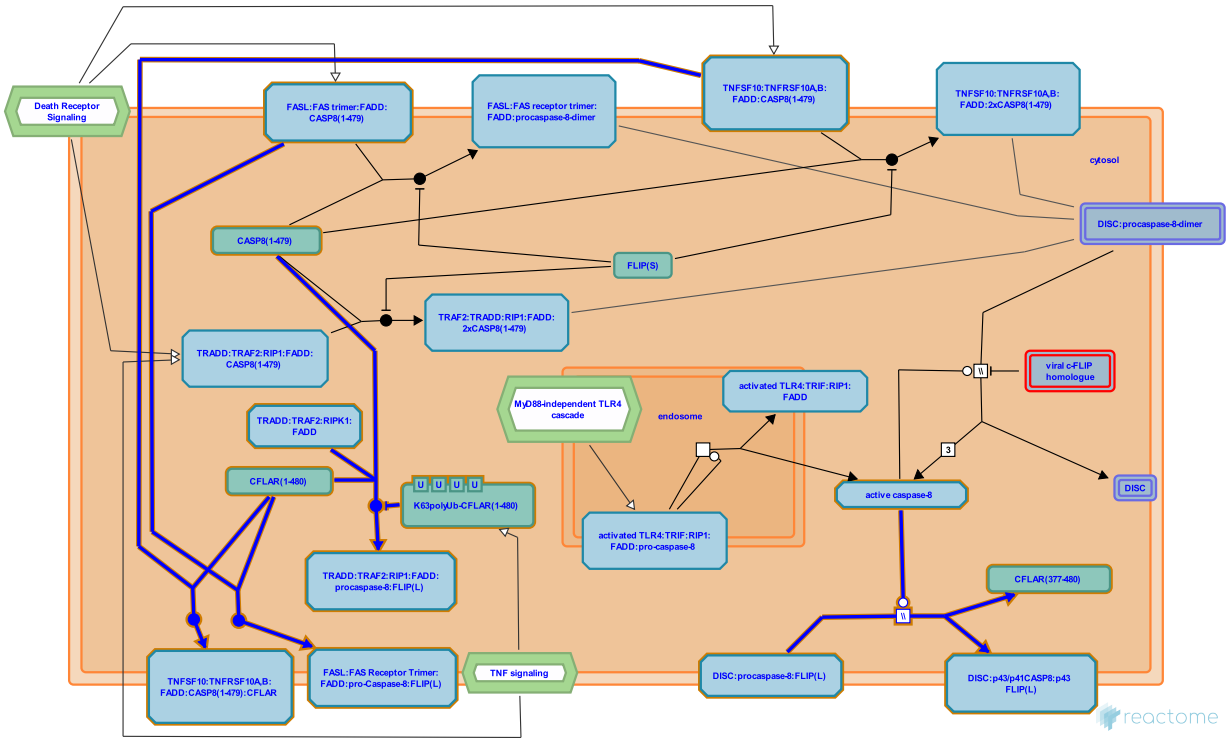
Regulation by c-FLIP



Lalaoui, N., Pop, C., Salvesen, GS., Shamovsky, V., Tu, H.

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

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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.
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).

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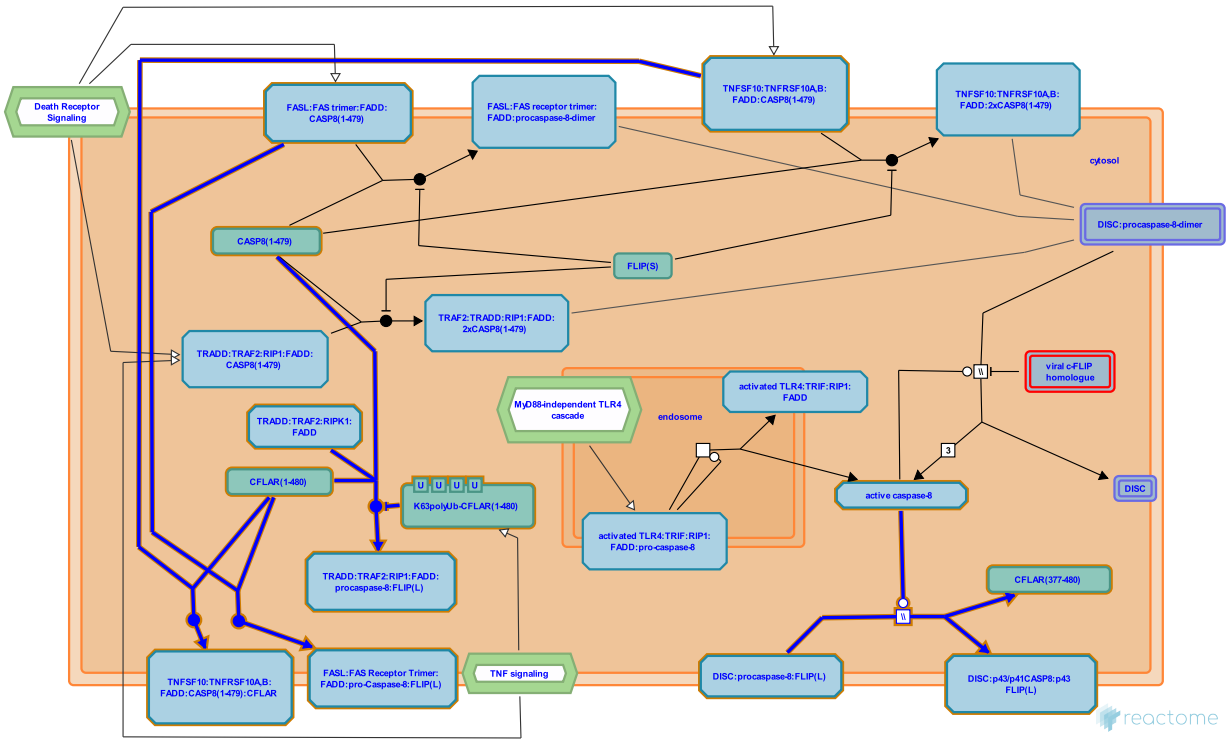
Regulation by c-FLIP ↗

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) (Irmler 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. ↗

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Editions

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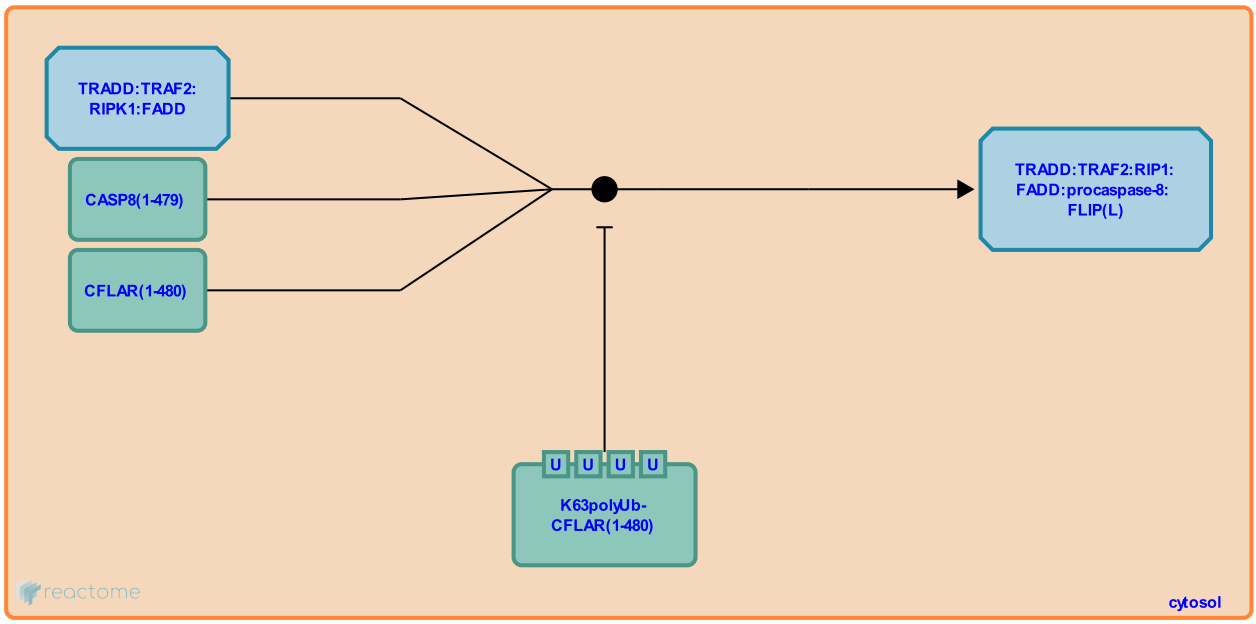
FLIP(L) and procaspase-8 form heterodimer in TNF signaling ↗

Location: Regulation by c-FLIP

Stable identifier: R-HSA-3371360

Type: binding

Compartments: cytosol



Following recruitment to the death-inducing signaling complex (DISC) and called complex II in the TNFR1 signalling pathway, cellular FLICE-like inhibitory protein (cFLIP) forms a heterodimer with procaspase-8. The presence of cFLIP in complex II determines if and how cells die. cFLIP is encoded by the CFLAR gene and is expressed in two major isoforms cFLIP long (FLIP(L)) and cFLIP short (FLIP(S)). While both FLIP(L) and FLIP(S) form heterodimers with procaspase-8, they differentially control caspase-8 activation. FLIP(L) interacts with procaspase-8 through both death effector domain (DED) and caspase-like domain (CLD). The procaspase-8 catalytic domain prefers heterodimerization with the CLD of FLIP(L) over homodimerization with catalytic domains of other procaspase-8 molecules (Boatright KM et al. 2004; Yu JW et al. 2009). Heterodimerization to FLIP(L) rearranges the catalytic site of procaspase-8, producing a conformation that renders the heterodimer highly active even in the absence of proteolytic processing of either caspase-8 or cFLIPL (Micheau O et al. 2002; Yu JW et al. 2009; reviewed in Tummers B & Green DR 2017). In addition, FLIP(L) can also regulate TNFR1 signaling via interaction with the DED of FADD (Majkut J et al. 2014). However, other studies showed that FLIP(L) is only weakly able to bind FADD (Hughes MA et al. 2016; Fu TM et al. 2016; Schleich K et al. 2016). The regulatory function of FLIP(L) has been found to differ depending on its expression levels. FLIP(L) was shown to inhibit death receptor (DR)-mediated apoptosis only when expressed at high levels, while low cell levels of FLIP(L) enhanced DR signaling to apoptosis (Boatright KM et al. 2004; Okano H et al. 2003; Yerbes R et al. 2011; Hughes MA et al. 2016). The FLIP(S) protein lacks CLD and contains only two tandem DEDs and a short C-terminal tail. FLIP(S) blocks DISC-dependent procaspase-8 activation. The expression levels of cFLIP proteins were shown to be regulated by NFkappaB signaling pathway (Micheau O et a. 2001; Kreuz S et al 2001).

Followed by: Caspase-8 and FLIP(L) processing at DISC

Literature references

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Editions

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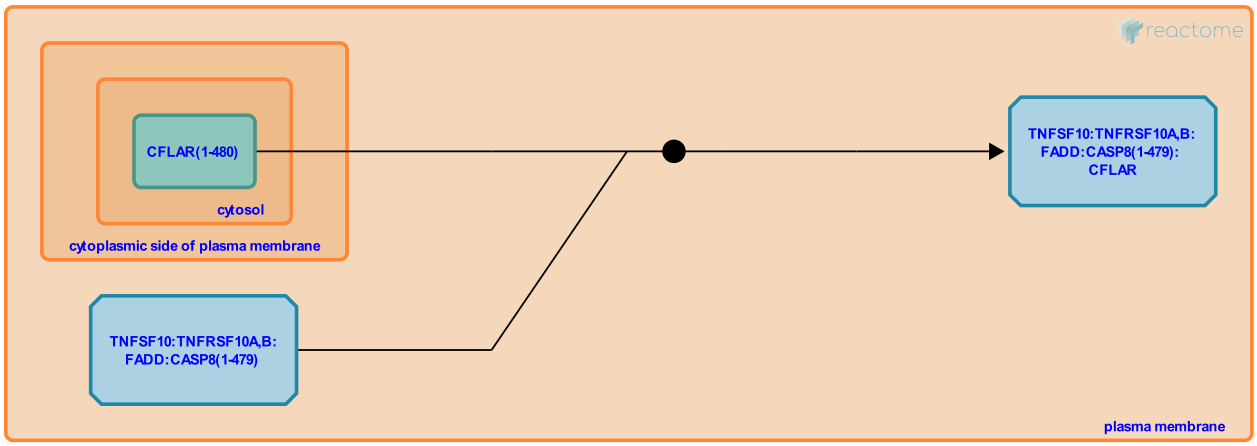
FLIP(L) and procaspase-8 form heterodimer in TRAIL signaling ↗

Location: Regulation by c-FLIP

Stable identifier: R-HSA-3371359

Type: binding

Compartments: plasma membrane, cytosol



Pro-caspase-8 and FLIP(L) are recruited to the DISC. Following recruitment to the DISC, FLIP-L forms a heterodimer with caspase-8 through both death effector domain (DED) and caspase-like domain (CLD). In addition, FLIP(L) can also regulate signaling via interaction with the DED of FADD. The regulatory function of FLIP(L) has been found to differ depending on its expression levels. FLIP(L) was shown to inhibit death receptor (DR)-mediated apoptosis only when expressed at high levels, while low cell levels of FLIP(L) enhanced DR signaling to apoptosis (Sharp DA et al. 2005; Siegmund D et al. 2002; Boatright KM et al. 2004; Okano H et al. 2003; Yerbes R et al. 2011). The expression levels of c-FLIP proteins were shown to be regulated by NFkappaB signaling pathway (Micheau O et a. 2001; Kreuz S et al 2001).

Followed by: Caspase-8 and FLIP(L) processing at DISC

Literature references

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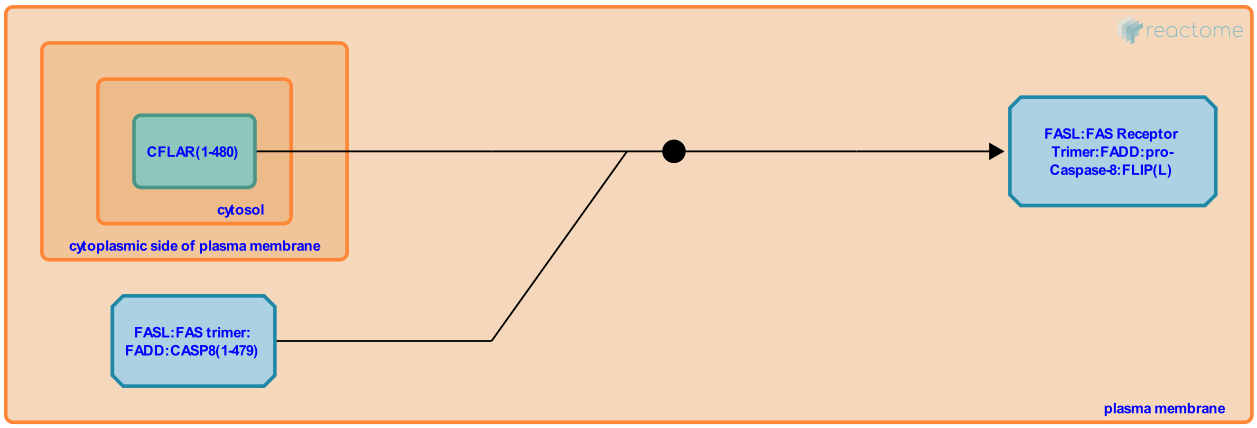
FLIP(L) and procaspase-8 form heterodimer in FasL/CD95 signaling ↗

Location: Regulation by c-FLIP

Stable identifier: R-HSA-3465459

Type: binding

Compartments: plasma membrane, cytosol



Pro-caspase-8 and FLIP(L) are recruited to FAS/CD95 receptor complex where FLIP(L) forms a heterodimer with caspase-8 through both death effector domain (DED) and caspase-like domain (CLD). In addition, FLIP(L) can also regulate signaling via interaction with the DED of FADD. The regulatory function of FLIP(L) has been found to differ depending on its expression levels. FLIP(L) was shown to inhibit death receptor (DR)-mediated apoptosis only when expressed at high levels, while low cell levels of FLIP-L enhanced DR signaling to apoptosis (Chang DW et al. 2002; Fricker N et al. 2010; Toivonen HT et al. 2011; Boatright KM et al. 2004; Okano H et al. 2003). The expression levels of c-FLIP proteins were shown to be regulated by NFkappaB signaling pathway (Micheau O et a. 2001; Kreuz S et al 2001).

Followed by: Caspase-8 and FLIP(L) processing at DISC

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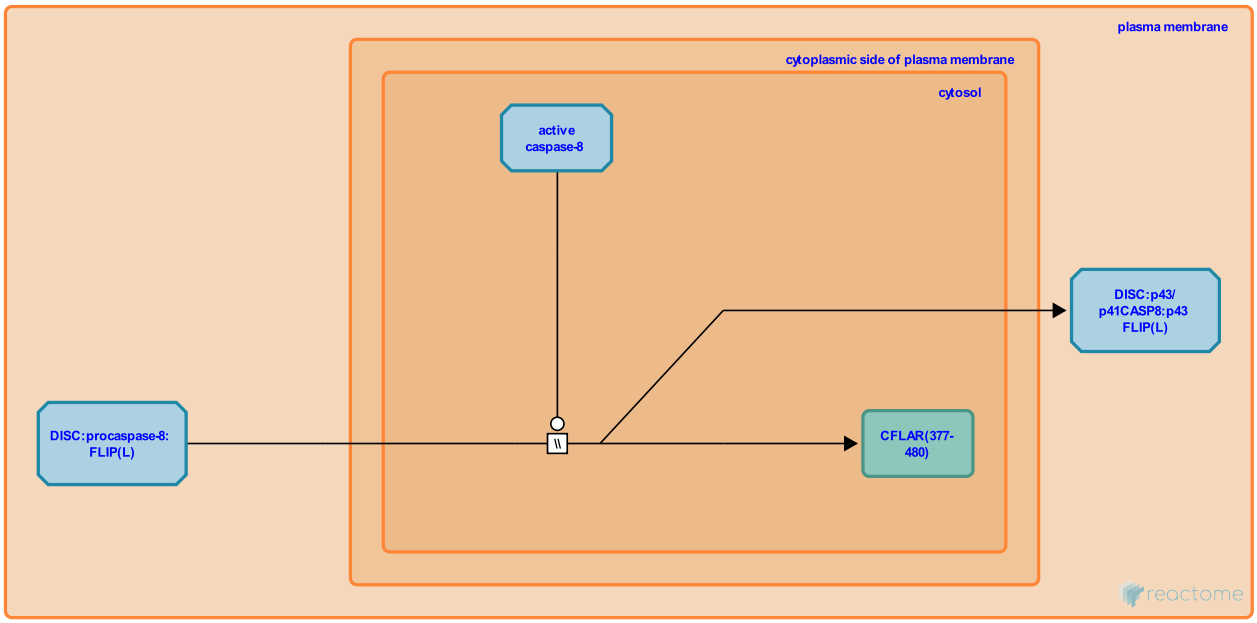
Caspase-8 and FLIP(L) processing at DISC ↗

Location: Regulation by c-FLIP

Stable identifier: R-HSA-3465448

Type: omitted

Compartments: cytosol



In the presence of FLIP(L), both caspase-8 and FLIP(L) are recruited and partially processed at the death-inducing signaling complex (DISC). The partially processed proteins stay bound to the DISC.

The long cellular FLIP (FLIP(L) or c-FLIPL) has two death effector domains (DED) and a caspase-like domain that lacks catalytic activity due to absence of a cysteine residue. Processing of FLIP(L) occurs at the DISC and depends on caspase-8 activity (zymogen and mature form). Upon activation FLIP(L) is cleaved to generate N-terminal FLIP(p43) and C-terminal FLIP(p12)(Irmler M et al. 1997; Jong WY et al. 2009). Processed FLIP(L) can enhance the proteolytic activity of procaspase-8 (Chang DW et al. 2002; Jong WY et al. 2009; Pop C et al. 2011). However, the increased FLIP(L) protein levels in cells have been found to limit caspase-8 activity and inhibit apoptotic signaling pathway,

Preceded by: FLIP(L) and procaspase-8 form heterodimer in TRAIL signaling, FLIP(L) and procaspase-8 form heterodimer in FasL/CD95 signaling, FLIP(L) and procaspase-8 form heterodimer in TNF signaling

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