Caspase-8 and FLIP(L) processing at TNFR signaling complex

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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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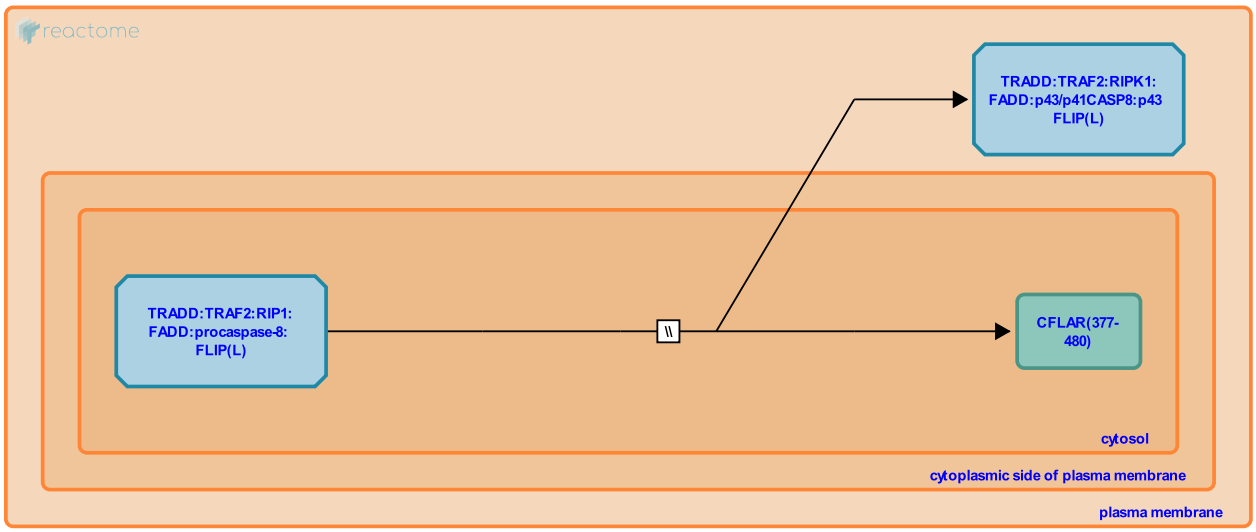
Stable identifier: R-HSA-9697747

Type: omitted

Compartments: cytosol



The balance between caspase-dependent apoptosis and RIPK-dependent necroptosis was found to depend on the levels of FADD-like interleukin-1 beta converting enzyme (FLICE)-inhibitory protein isoforms (cFLIP, encoded by the CFLAR gene) (reviewed in Tummers B & Green DR 2017). cFLIP exists in two main isoforms: long FLIP(L) and short FLIP(S) forms. Both FLIP(L) and FLIP(S) dimerize with procaspase-8 at the death-inducing signaling complex (DISC) such as TRADD:TRAF2:RIPK1: FADD:CASP8:FLIP(L), however they differentially regulate CASP8 activation (Pop C et al. 2011; Oberst A et al. 2011; Hughes MA et al. 2009, 2016). The heterodimers of FLIP(L):CASP8 inhibit CASP8 activity limiting the cleavage of CASP3/7 but allowing the cleavage of RIPK1 to cause the dissociation of the TRADD:TRAF2:RIPK1:FADD:CASP8 complex, thereby inhibiting both apoptosis and necroptosis (Pop C et al. 2011; Oberst A et al. 2011; Hughes MA et al. 2009; Lalaoui N et al 2020). Processing of FLIP(L) also occurs at the DISC and depends on CASP8 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; Chang DW et al. 2002; Yu JW et al. 2009; Pop C et al. 2011). FLIP(S) is a truncated version of procaspase-8 containing tandem DEDs only. FLIP(S) acts purely as an antagonist of CASP8 activity inhibiting apoptosis. FLIP(S) has also been proposed to induce necroptosis in conditions when RIPK1 is deubiquitylated and when FLIP(L) is absent (Feoktistova M et al. 2011). Important to note that the latest statement has been shown in the context of the TLR3 signalling pathway.

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Editions

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