Caspase activation via Death Receptors in the presence of ligand

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

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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.

17/11/2022

https://reactome.org
**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**


Reactome database release: 82

This document contains 3 pathways and 2 reactions (see Table of Contents)
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**


## Editions

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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


Editions

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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].

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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 (pro-caspase-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 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**


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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 pro-caspase-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**


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.
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