Caspase activation via extrinsic apoptotic signalling pathway

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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.

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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**


Reactome database release: 83

This document contains 3 pathways (see Table of Contents)

[https://reactome.org](https://reactome.org)
Caspases, a family of cysteine proteases, execute apoptotic cell death. Caspases exist as inactive zymogens in cells and undergo a cascade of catalytic activation at the onset of apoptosis. Initiation of apoptosis occurs through either a cell-intrinsic or cell-extrinsic pathway. Extrinsic pathway cell death signals originate at the plasma membrane where:

- An extracellular ligand (e.g., FasL) binds to its cell surface transmembrane “death receptor” (e.g., Fas receptor), inducing oligomerization of the receptor (Trauth et al. 1989; Itoh and Nagata 1993; Danial and Korsmeyer 2004). The "death receptors" are specialized cell-surface receptors including Fas/CD95, tumor necrosis factor-alpha (TNF-alpha) receptor 1, and two receptors, DR4 and DR5, that bind to the TNF-alpha related apoptosis-inducing ligand (TRAIL). Ligand binding promotes clustering of proteins that bind to the intracellular domain of the receptor (e.g., FADD, or Fas-associated death domain-containing protein), which then binds to the prodomain of initiator caspases (e.g., caspase-8 or -10) to promote their dimerization and activation. Active caspase-8/-10 can then directly cleave and activate effector caspases, such as caspase-3 or it can cleave Bid, which facilitates mitochondrial cytochrome c release.

- Unique group of proteins termed dependence receptors (DpRs) transduce positive (often prosurvival or progrowth) signals when engaged by ligand, but emit proapoptotic signals in the absence of ligand (Goldschneider and Mehlen 2010). DpR family includes p75 neurotrophin receptor (p75NTR), deleted in colon cancer (DCC), and UNC5 homologs, among others. cell-surface membrane receptors.

**Literature references**

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https://reactome.org
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**


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Caspase activation via Dependence Receptors in the absence of ligand

Location: Caspase activation via extrinsic apoptotic signalling pathway

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In the presence of Netrin1, DCC and UNC5 generate attractive and repulsive signals to growing axons. In the absence of Netrin-1, DCC induces cell death signaling initiated via caspase cleavage of DCC and the interaction of caspase-9. Recent reports have shown that UNC5 receptors similarly induce apoptosis in the absence of Netrin-1. These reactions proceed without a requirement for cytochrome c release from mitochondria or interaction with apoptotic protease activating factor 1 (APAF1). DCC thus regulates an apoptosome-independent pathway for caspase activation. DCC and UNC-5 are hence defined as dependence receptors. Dependence receptors exhibit dual functions depending on the availability of ligand. They create cellular states of dependence on their respective ligands by either inducing apoptosis when unoccupied by the ligand, or inhibiting apoptosis in the presence of the ligand.

Literature references


Editions

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