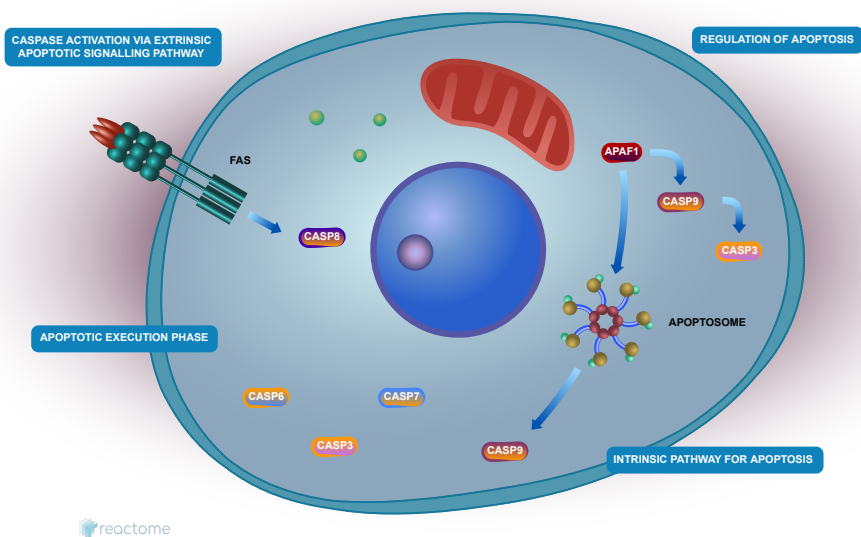


Apoptosis



Alnemri, E., Chang, E., Gillespie, ME., Gopinathrao, G., Hardwick, JM., Hengartner, M., Jakobi, R., Joshi-Tope, G., Matthews, L., Ranganathan, S., Shamovsky, V., Tschopp, J., Tsujimoto, Y., Vaux, DL.

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

26/04/2024

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.

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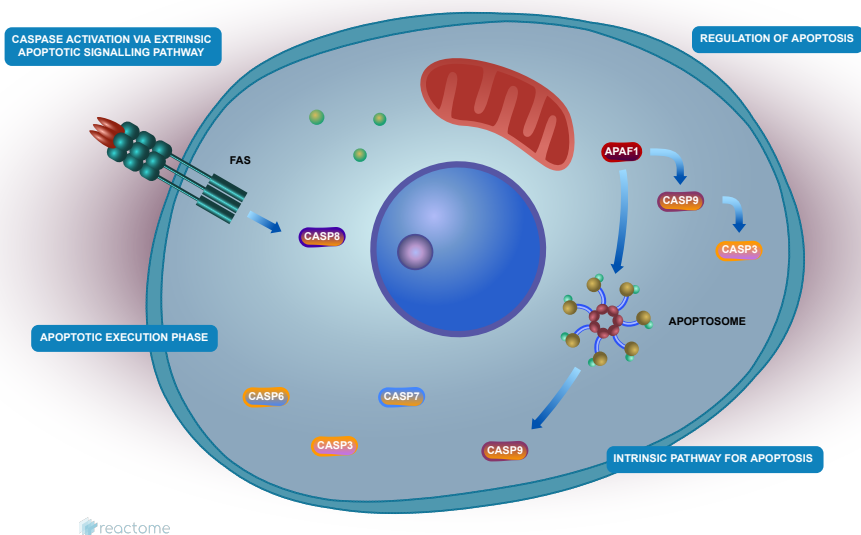
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Reactome database release: 88

This document contains 5 pathways ([see Table of Contents](#))

Apoptosis ↗

Stable identifier: R-HSA-109581



Apoptosis is a distinct form of cell death that is functionally and morphologically different from necrosis. Nuclear chromatin condensation, cytoplasmic shrinking, dilated endoplasmic reticulum, and membrane blebbing characterize apoptosis in general. Mitochondria remain morphologically unchanged. In 1972 Kerr et al introduced the concept of apoptosis as a distinct form of "cell-death", and the mechanisms of various apoptotic pathways are still being revealed today.

The two principal pathways of apoptosis are (1) the Bcl-2 inhibitable or intrinsic pathway induced by various forms of stress like intracellular damage, developmental cues, and external stimuli and (2) the caspase 8/10 dependent or extrinsic pathway initiated by the engagement of death receptors

The caspase 8/10 dependent or extrinsic pathway is a death receptor mediated mechanism that results in the activation of caspase-8 and caspase-10. Activation of death receptors like Fas/CD95, TNFR1, and the TRAIL receptor is promoted by the TNF family of ligands including FASL (APO1L OR CD95L), TNF, LT-alpha, LT-beta, CD40L, LIGHT, RANKL, BLYS/BAFF, and APO2L/TRAIL. These ligands are released in response to microbial infection, or as part of the cellular, humoral immunity responses during the formation of lymphoid organs, activation of dendritic cells, stimulation or survival of T, B, and natural killer (NK) cells, cytotoxic response to viral infection or oncogenic transformation.

The Bcl-2 inhibitable or intrinsic pathway of apoptosis is a stress-inducible process, and acts through the activation of caspase-9 via Apaf-1 and cytochrome c. The rupture of the mitochondrial membrane, a rapid process involving some of the Bcl-2 family proteins, releases these molecules into the cytoplasm. Examples of cellular processes that may induce the intrinsic pathway in response to various damage signals include: auto reactivity in lymphocytes, cytokine deprivation, calcium flux or cellular damage by cytotoxic drugs like taxol, deprivation of nutrients like glucose and growth factors like EGF, anoikis, transactivation of target genes by tumor suppressors including p53.

In many non-immune cells, death signals initiated by the extrinsic pathway are amplified by connections to the intrinsic pathway. The connecting link appears to be the truncated BID (tBID) protein a proteolytic cleavage product mediated by caspase-8 or other enzymes.

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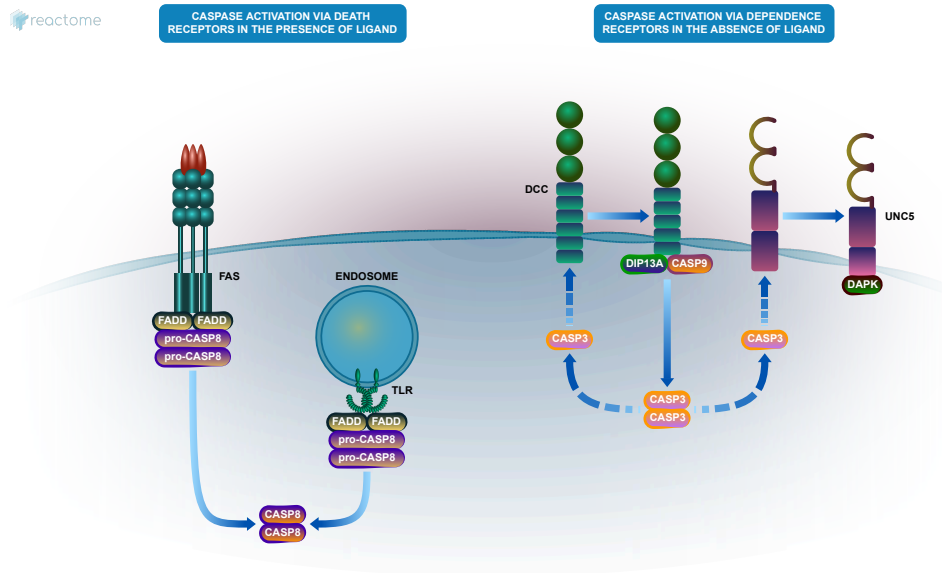
Editions

2004-01-16	Authored	Tsujimoto, Y., Hengartner, M., Alnemri, E., Hardwick, JM., Tschopp, J.
2013-11-25	Edited	Gillespie, ME., Gopinathrao, G., Matthews, L., Joshi-Tope, G.
2024-03-06	Reviewed	Hengartner, M., Vaux, DL., Ranganathan, S.

Caspase activation via extrinsic apoptotic signalling pathway ↗

Location: Apoptosis

Stable identifier: R-HSA-5357769



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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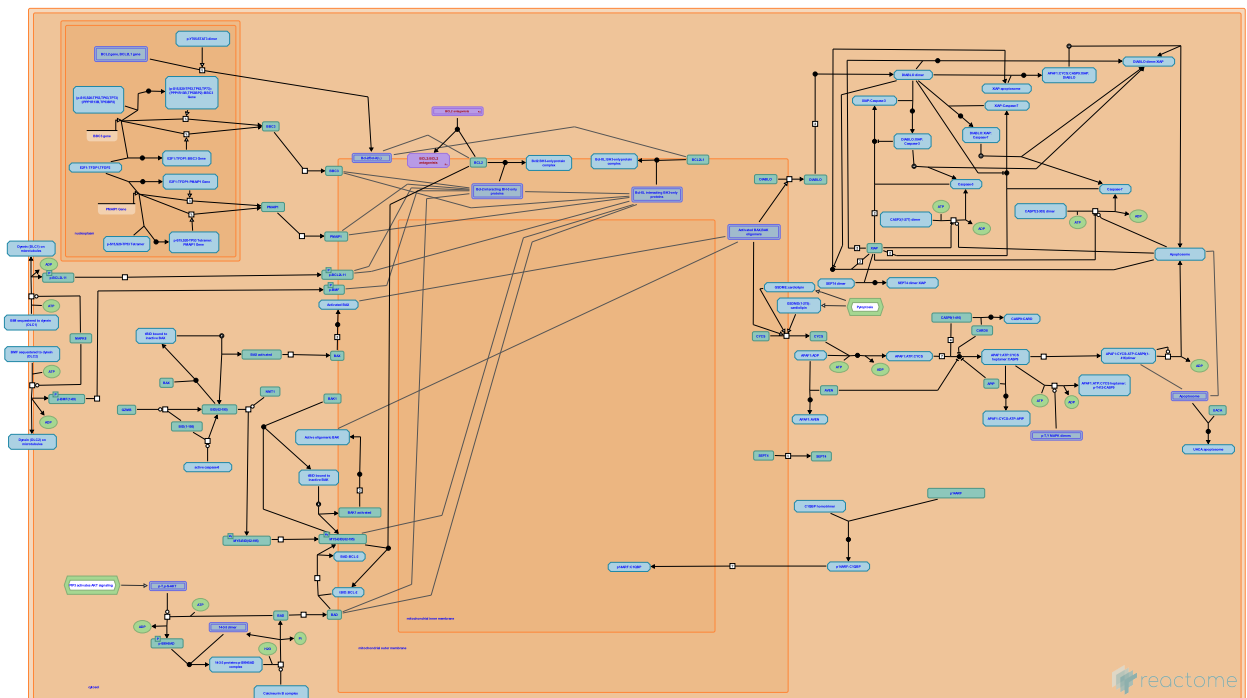
Editions

2014-03-26	Authored	Shamovsky, V.
2015-02-06	Reviewed	Gillespie, ME.
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Intrinsic Pathway for Apoptosis ↗

Location: Apoptosis

Stable identifier: R-HSA-109606



The intrinsic (Bcl-2 inhibitable or mitochondrial) pathway of apoptosis functions in response to various types of intracellular stress including growth factor withdrawal, DNA damage, unfolding stresses in the endoplasmic reticulum and death receptor stimulation. Following the reception of stress signals, proapoptotic BCL-2 family proteins are activated and subsequently interact with and inactivate antiapoptotic BCL-2 proteins. This interaction leads to the destabilization of the mitochondrial membrane and release of apoptotic factors. These factors induce the caspase proteolytic cascade, chromatin condensation, and DNA fragmentation, ultimately leading to cell death. The key players in the Intrinsic pathway are the Bcl-2 family of proteins that are critical death regulators residing immediately upstream of mitochondria. The Bcl-2 family consists of both anti- and proapoptotic members that possess conserved alpha-helices with sequence conservation clustered in BCL-2 Homology (BH) domains. Proapoptotic members are organized as follows:

1. "Multidomain" BAX family proteins such as BAX, BAK etc. that display sequence conservation in their BH1-3 regions. These proteins act downstream in mitochondrial disruption.
2. "BH3-only" proteins such as BID,BAD, NOXA, PUMA,BIM, and BMF have only the short BH3 motif. These act upstream in the pathway, detecting developmental death cues or intracellular damage. Anti-apoptotic members like Bcl-2, Bcl-XL and their relatives exhibit homology in all segments BH1-4. One of the critical functions of BCL-2/BCL-XL proteins is to maintain the integrity of the mitochondrial outer membrane.

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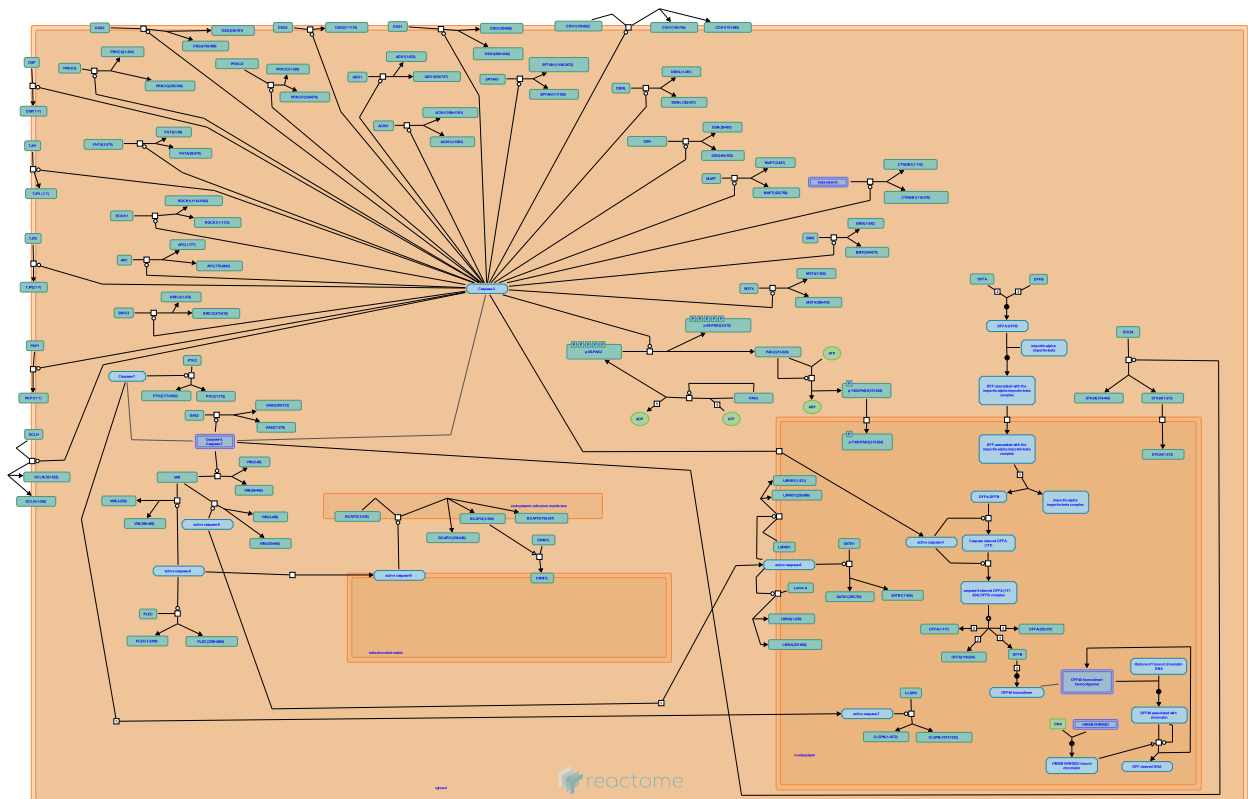
Authored

Matthews, L.

Apoptotic execution phase ↗

Location: Apoptosis

Stable identifier: R-HSA-75153



In the execution phase of apoptosis, effector caspases cleave vital cellular proteins leading to the morphological changes that characterize apoptosis. These changes include destruction of the nucleus and other organelles, DNA fragmentation, chromatin condensation, cell shrinkage and cell detachment and membrane blebbing (reviewed in Fischer et al., 2003).

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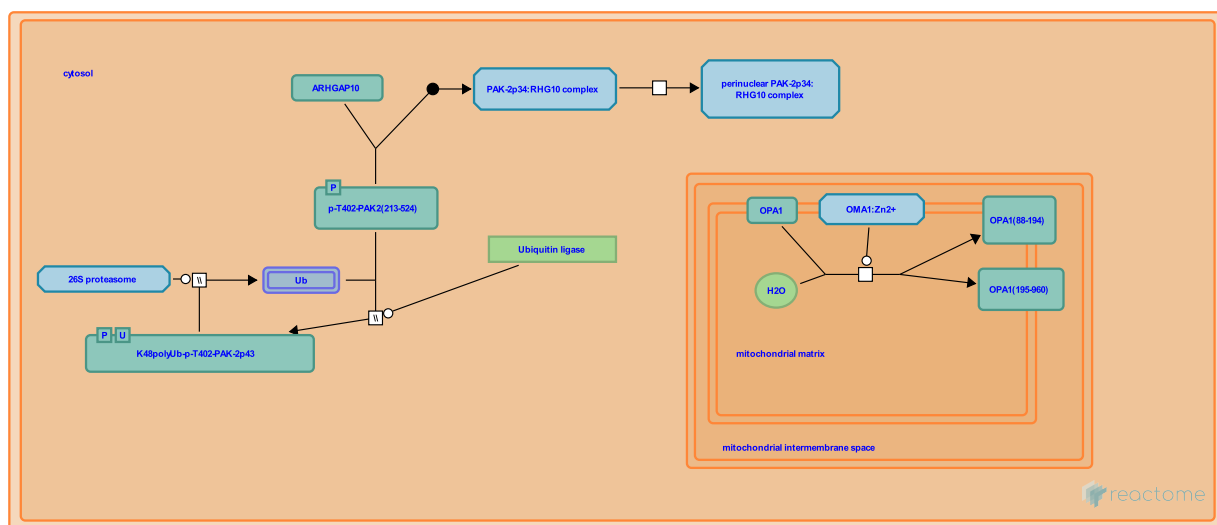
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2004-02-17	Authored	Alnemri, E.
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Regulation of Apoptosis ↗

Location: Apoptosis

Stable identifier: R-HSA-169911



A regulated balance between cell survival and apoptosis is essential for normal development and homeostasis of multicellular organisms (see Matsuzawa, 2001). Defects in control of this balance may contribute to autoimmune disease, neurodegeneration and cancer. Protein ubiquitination and degradation is one of the major mechanisms that regulate apoptotic cell death (reviewed in Yang and Yu 2003).

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