Intrinsic Pathway for Apoptosis

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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: 79

This document contains 7 pathways (see Table of Contents)
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. Antiapoptotic 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.

**Literature references**


BID may promote cell death by activating BAX and BAK while inactivating anti-apoptotic proteins. The engagement of cell surface receptors activates the caspase-8, a heterodimer, that cleaves BID in its amino terminal region. This particular event may act as a link between Extrinsic (caspase 8/10 dependent) and Intrinsic (Bcl-2 inhibitable) pathways although some evidences from mouse genetic experiments suggest the contrary. It has been suggested that the death signals from the extrinsic or death receptor pathway may get amplified by the mechanisms of intrinsic pathway and that this functional loop may be enabled by the molecules like tBID (truncated BID).

Cleavage of BID to tBID can also be achieved by Granzyme B. The truncated protein is myristoylated and translocates to mitochondria.

Literature references


Editions

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Activation of BH3-only proteins

Location: Intrinsic Pathway for Apoptosis

Stable identifier: R-HSA-114452

Compartments: cytosol

The BH3-only members act as sentinels that selectively trigger apoptosis in response to developmental cues or stress-signals like DNA damages. Widely expressed mammalian BH3-only proteins are thought to act by binding to and neutralizing their pro-survival counterparts. Activation of BH3-only proteins directly or indirectly results in the activation of proapoptotic BAX and BAK to trigger cell death. Anti-apoptotic BCL-2 or BCL-XL may bind and sequester BH3-only molecules to prevent BAX, BAK activation. The individual BH3-only members are held in check by various mechanisms within the cells. They are recruited for death duties in response to death cues by diverse activation processes. The mechanisms involved in activation and release of BH3-only proteins for apoptosis will be discussed in this section.

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Literature references


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BH3-only proteins associate with and inactivate anti-apoptotic BCL-2 members

**Location:** Intrinsic Pathway for Apoptosis

**Stable identifier:** R-HSA-111453

**Compartments:** mitochondrial outer membrane

Bcl-2 interacts with tBid (Yi et al. 2003), BIM (Puthalakath et al. 1999), PUMA (Nakano and Vousden 2001), NOXA (Oda et al. 2000), BAD (Yang et al. 2005), BMF (Puthalakath et al. 2001), resulting in inactivation of BCL2. Binding of BCL2 to tBID inhibits BID-induced cytochrome C release and apoptosis (Yi et al. 2003). BH3 only proteins associate with and inactivate anti-apoptotic BCL-XL.
Activation, translocation and oligomerization of BAX

Location: Intrinsic Pathway for Apoptosis

Stable identifier: R-HSA-114294

As a result of binding to Bid, Bax oligomerizes and integrates in the outer mitochondrial membrane, triggering cytochrome c release. Bax mitochondrial membrane insertion triggered by Bid may represent a key step in pathways leading to apoptosis (Eskes et al., 2000).

Literature references


tBID binds to its mitochondrial partner BAK to release cytochrome c. Activated tBID results in an allosteric activation of BAK. This may induce its intramembranous oligomerization into a pore for cytochrome c efflux.
In response to apoptotic signals, mitochondrial proteins are released into the cytosol and activate both caspase-dependent and -independent cell death pathways. Cytochrome c induces apoptosome formation, AIF and endonuclease G function in caspase independent apoptotic nuclear DNA damage. Smac/DIABLO and HtrA2/OMI promote both caspase activation and caspase-independent cytotoxicity (Saelens et al., 2004).

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