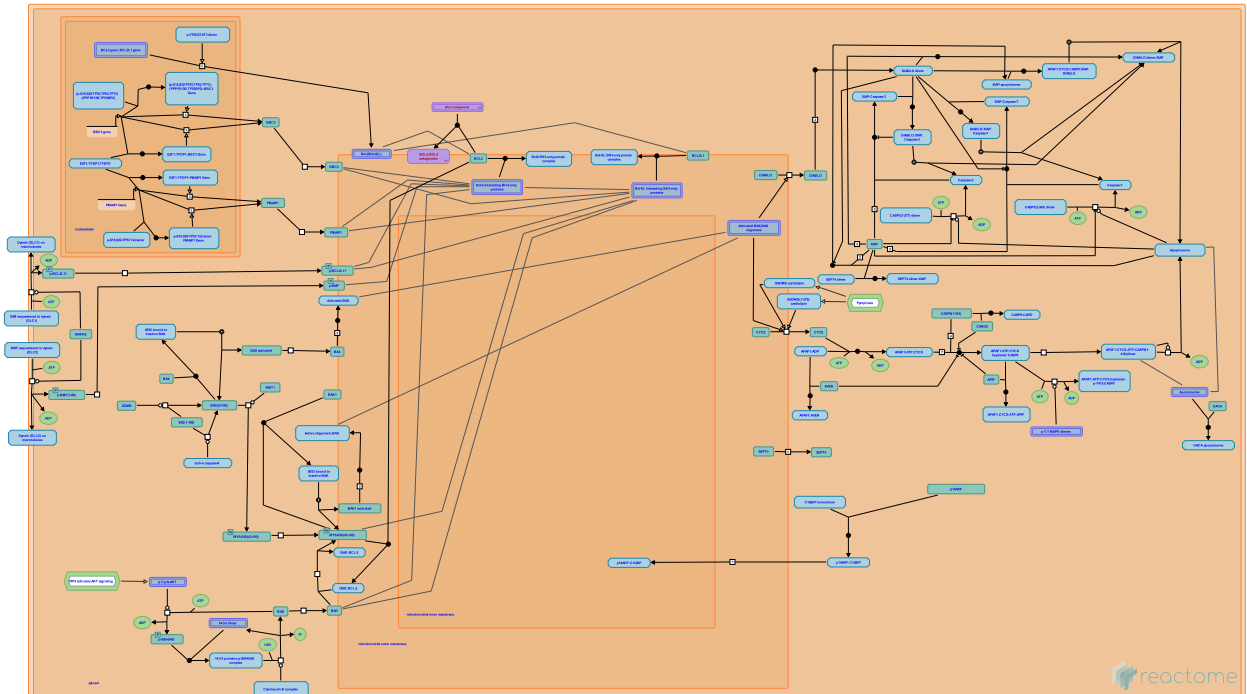


# Intrinsic Pathway for Apoptosis



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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/).

27/04/2024

## 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.

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

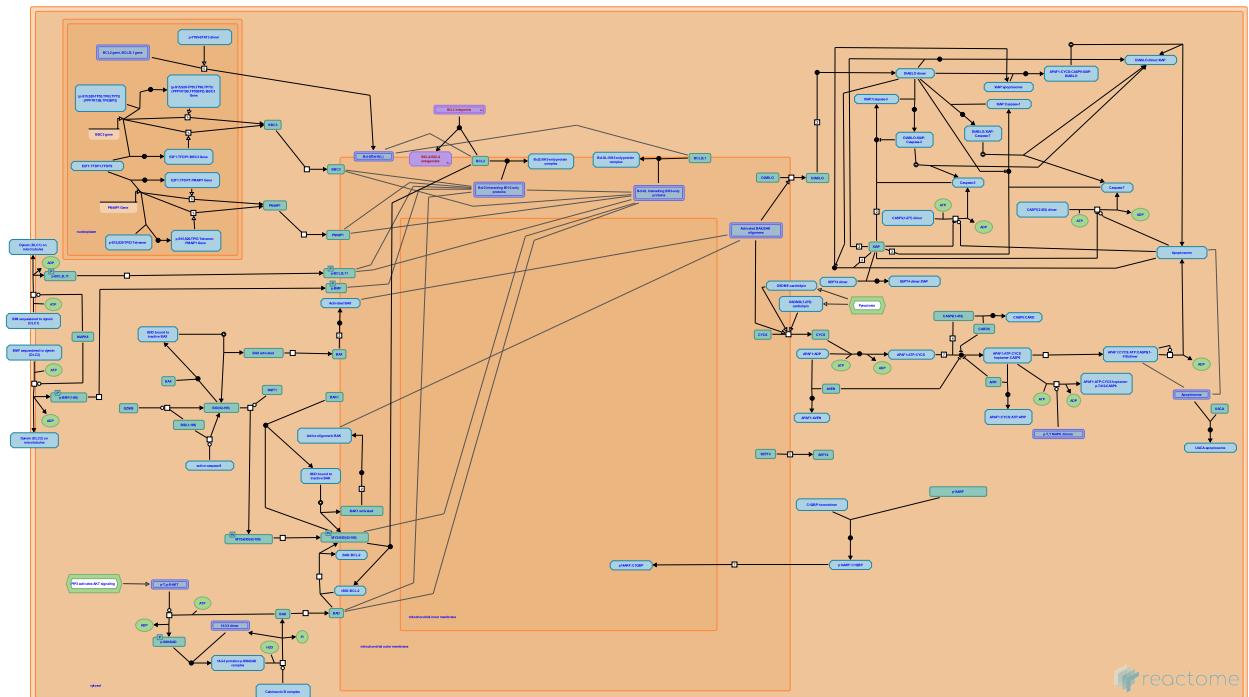
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 7 pathways ([see Table of Contents](#))

# Intrinsic Pathway for 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.

## Literature references

van Loo, G., van Gurp, M., Vandenabeele, P., Saelens, X., Vande Walle, L., Festjens, N. (2004). Toxic proteins released from mitochondria in cell death. *Oncogene*, 23, 2861-74. ↗

Wang, X. (2001). The expanding role of mitochondria in apoptosis. *Genes Dev*, 15, 2922-33. ↗

Salvesen, GS., Duckett, CS. (2002). IAP proteins: blocking the road to death's door. *Nat Rev Mol Cell Biol*, 3, 401-10. ↗

## Editions

2004-08-06

Authorred

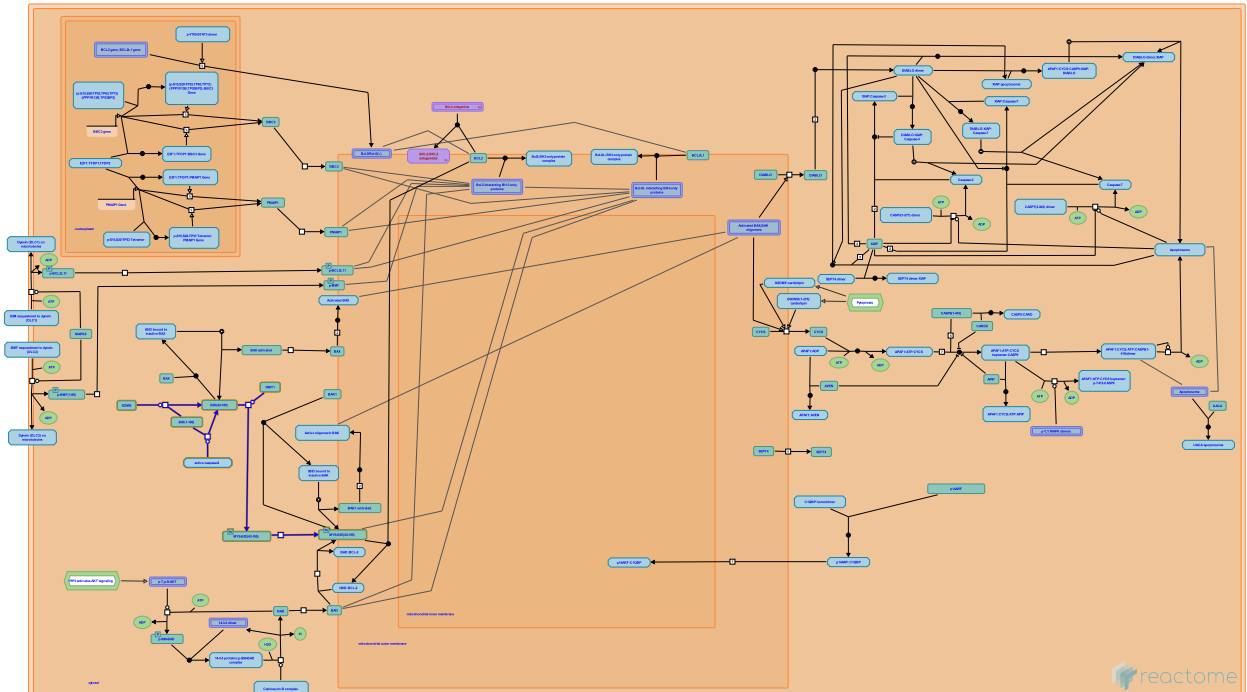
Matthews, L.

# Activation, myristoylation of BID and translocation to mitochondria ↗

**Location:** Intrinsic Pathway for Apoptosis

**Stable identifier:** R-HSA-75108

**Compartments:** cytosol



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

Xu, CJ., Li, H., Yuan, J., Zhu, H. (1998). Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell*, 94, 491-501. ↗

Adams, JM., Huang, DC., Cory, S. (2003). The Bcl-2 family: roles in cell survival and oncogenesis. *Oncogene*, 22, 8590-607. ↗

## Editions

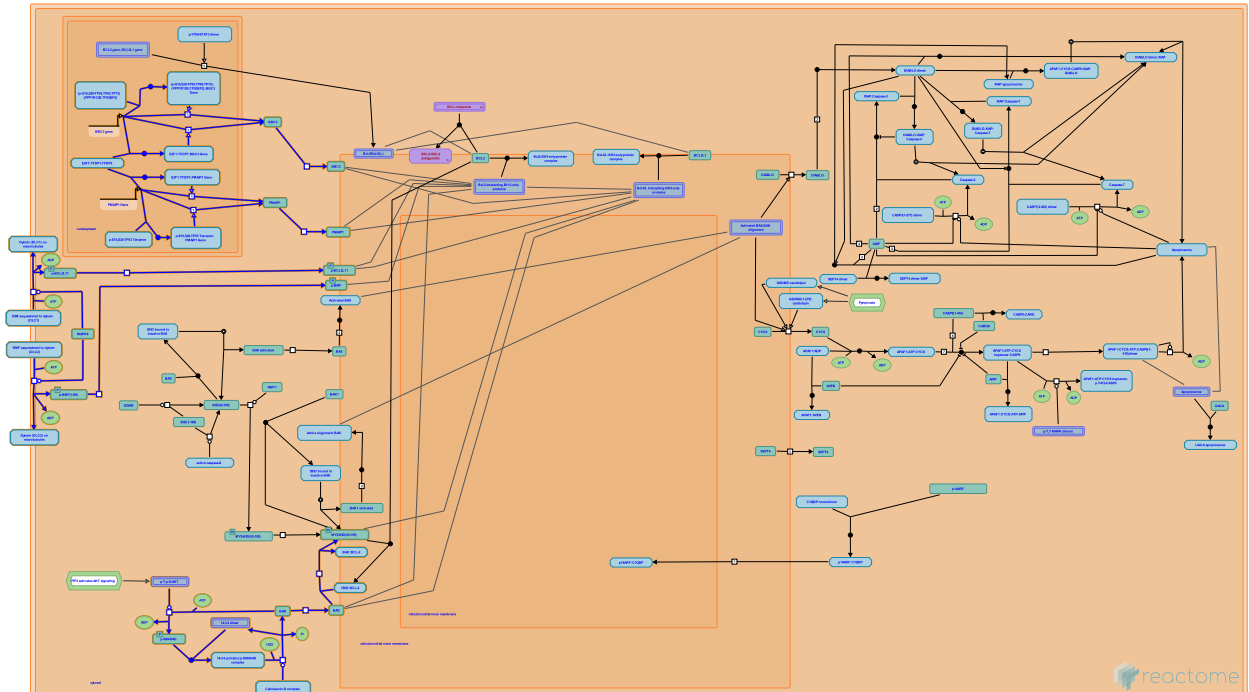
2004-08-20	Authored	Gopinathrao, G.
2024-03-06	Reviewed	Vaux, DL.

## 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

Adams, JM., Huang, DC., Cory, S. (2003). The Bcl-2 family: roles in cell survival and oncogenesis. *Oncogene*, 22, 8590-607. ↗

Adams, JM., Cory, S. (2002). The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer*, 2, 647-56. ↗

### Editions

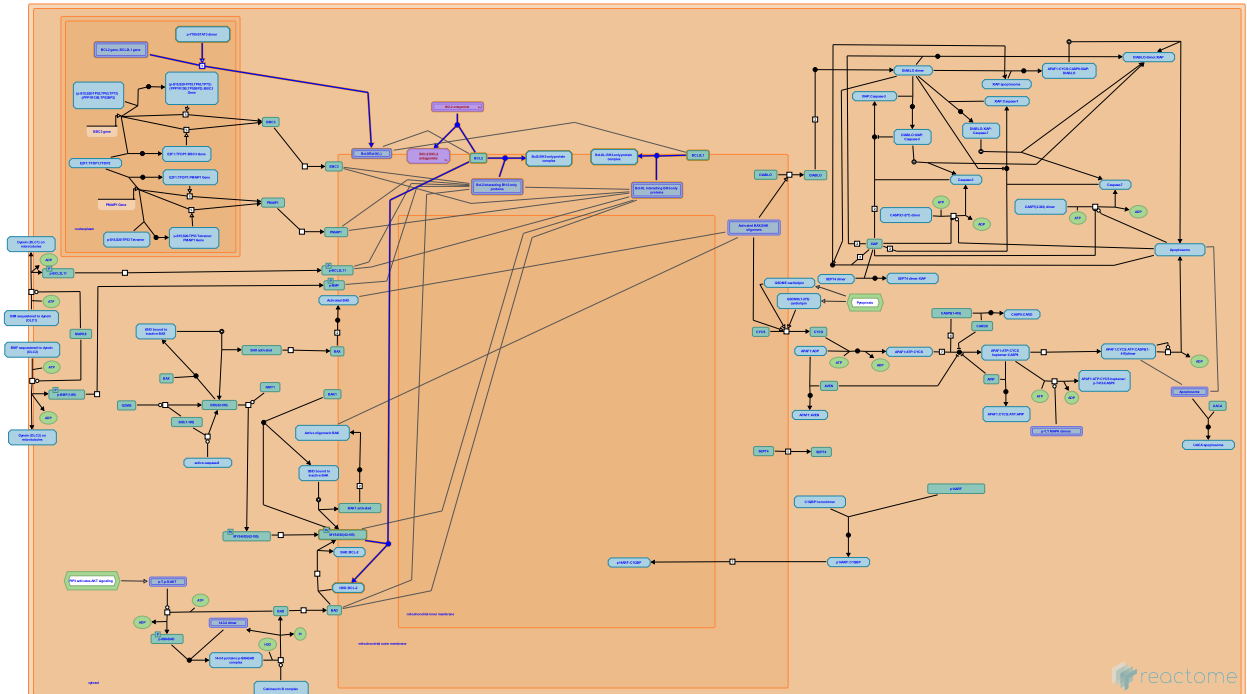
2004-08-20	Authored	Gopinathrao, G.
2024-03-06	Reviewed	Vaux, DL.

## 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

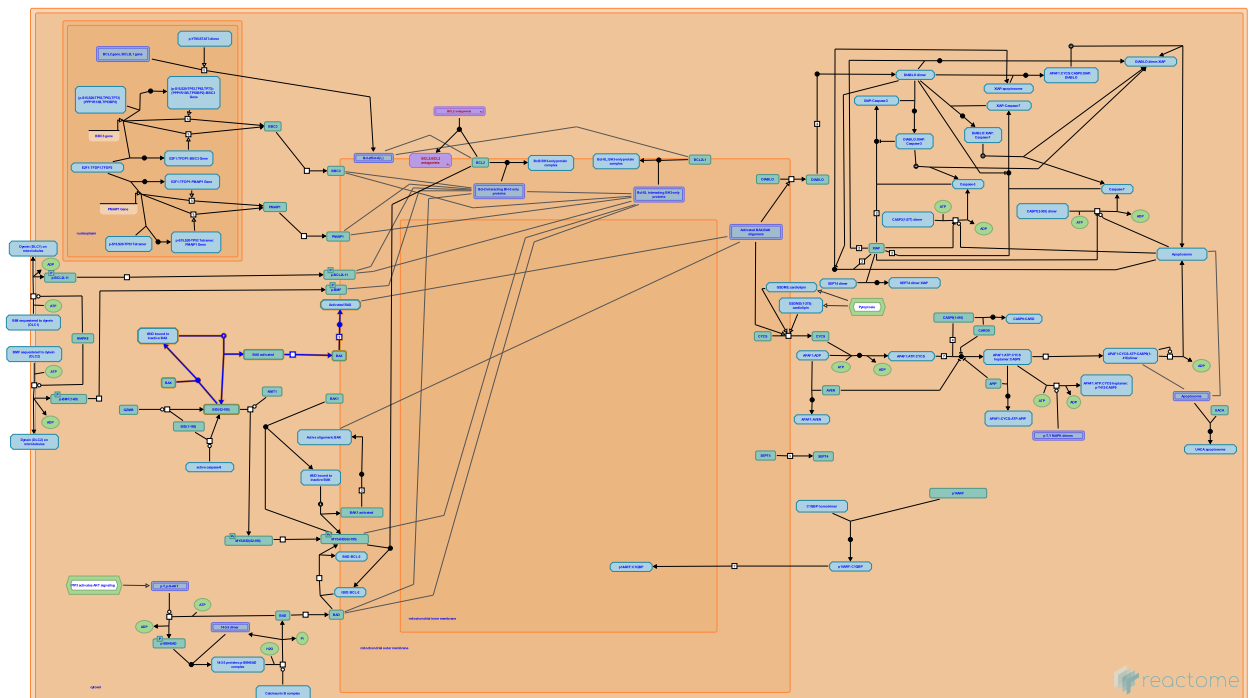


Bcl-2 interacts with tBid (Yi et al. 2003), BIM (Puthalakath et al. 1999), PUMA (Nakano and Vousden 2001), NOXA (Oda et al. 2000), BAD (Yang et al. 2005), BMF (Puthalakath et al. 2001), resulting in inactivation of BCL2. Binding of BCL2 to tBID inhibits BID-induced cytochrome C release and apoptosis (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

Martinou, J.C., Antonsson, B., Montessuit, S., Sanchez, B. (2001). Bax is present as a high molecular weight oligomer/complex in the mitochondrial membrane of apoptotic cells. *J Biol Chem*, 276, 11615-23. ↗

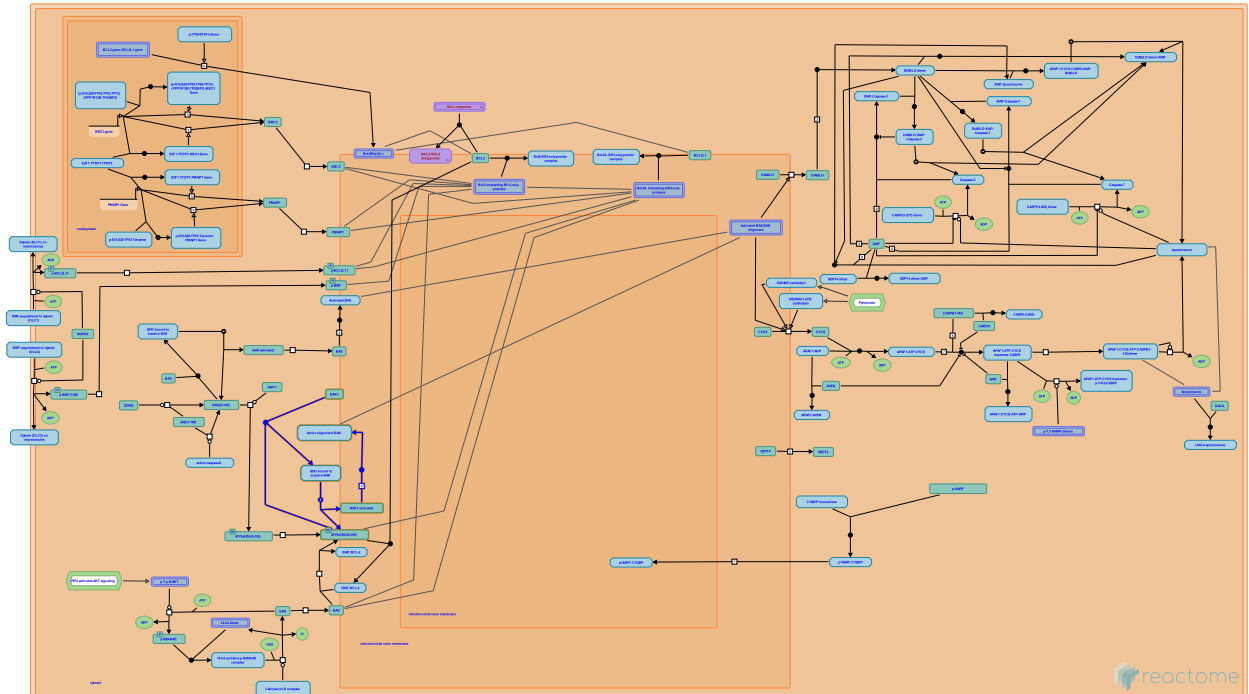
Roucou, X., Martinou, J.C., Antonsson, B., Montessuit, S. (2002). Bax oligomerization in mitochondrial membranes requires tBid (caspase-8-cleaved Bid) and a mitochondrial protein. *Biochem J*, 368, 915-21. ↗

## Activation and oligomerization of BAK protein ↗

**Location:** Intrinsic Pathway for Apoptosis

**Stable identifier:** R-HSA-111452

**Compartments:** mitochondrial outer membrane



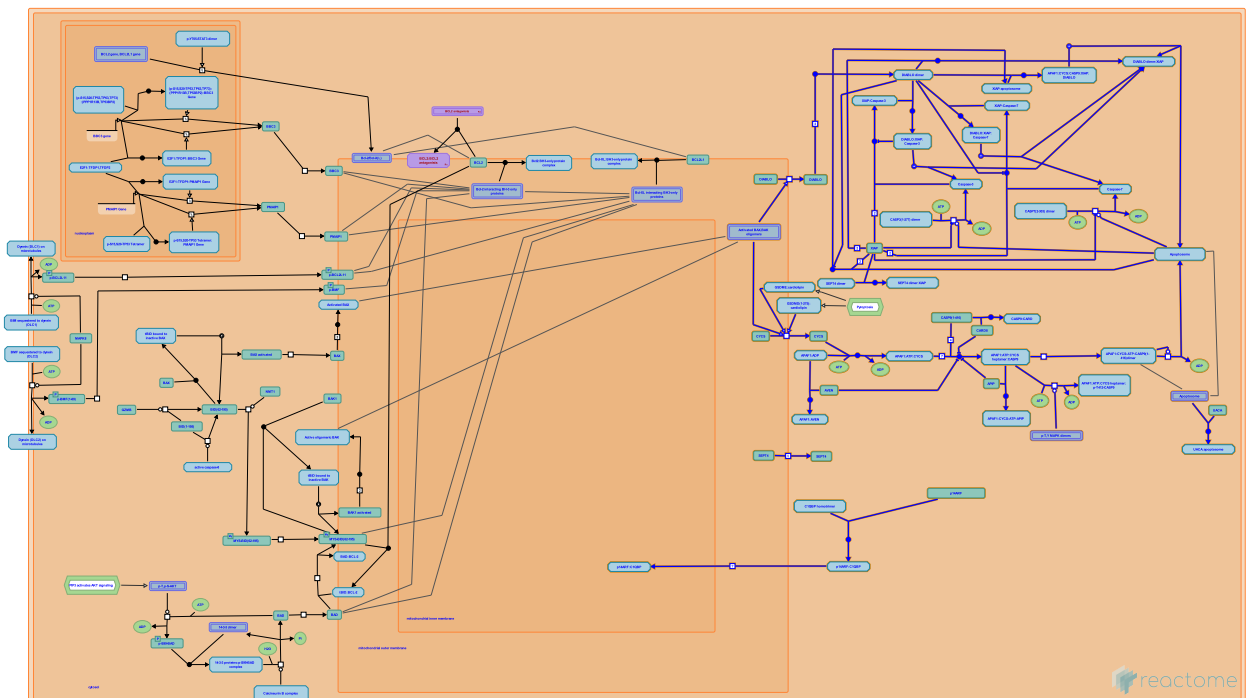
tBID binds to its mitochondrial partner BAK to release cytochrome c. Activated tBID results in an allosteric activation of BAK. This may induce its intramembraneous oligomerization into a pore for cytochrome c efflux.



# Apoptotic factor-mediated response ↗

**Location:** [Intrinsic Pathway for Apoptosis](#)

**Stable identifier:** R-HSA-111471



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).

## Literature references

van Loo, G., van Gurp, M., Vandenabeele, P., Saelens, X., Vande Walle, L., Festjens, N. (2004). Toxic proteins released from mitochondria in cell death. *Oncogene*, 23, 2861-74. ↗

Salvesen, GS., Duckett, CS. (2002). IAP proteins: blocking the road to death's door. *Nat Rev Mol Cell Biol*, 3, 401-10. ↗

## Editions

2017-07-26	Authored	Shamovsky, V.
2018-11-02	Edited, Revised	Shamovsky, V.
2018-11-05	Reviewed	Matthews, L.

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