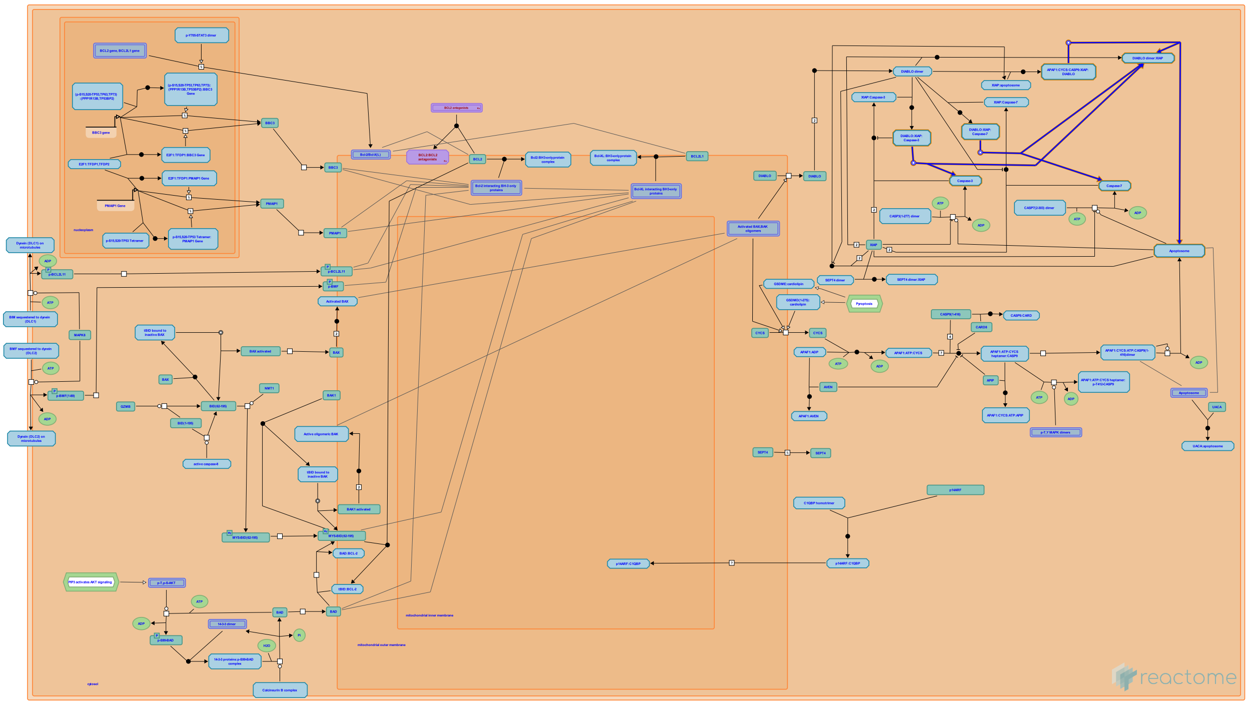
SMAC(DIABLO)-mediated dissociation of IAP:caspase complexes



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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.

15/05/2024

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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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. ↗

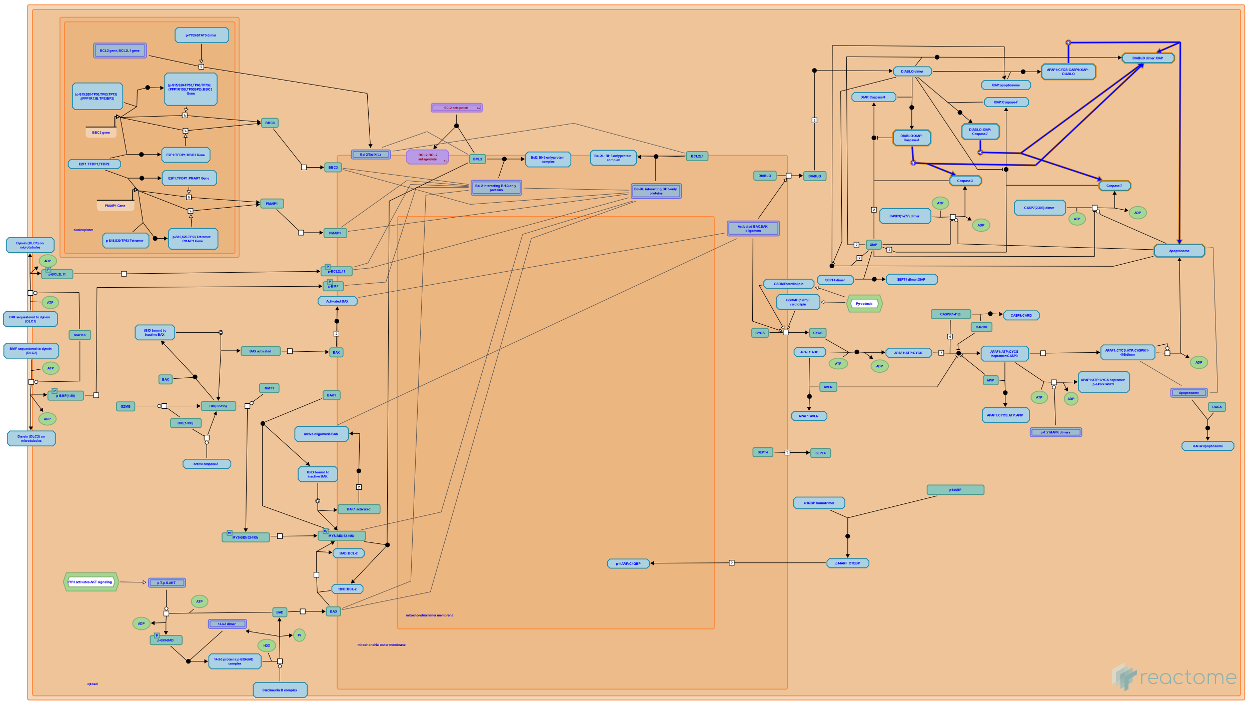
Reactome database release: 88

This document contains 1 pathway and 3 reactions (see Table of Contents)

SMAC(DIABLO)-mediated dissociation of IAP:caspase complexes ↗

Stable identifier: R-HSA-111464

Compartments: cytosol



Second mitochondria derived activator of caspase/direct inhibitor of apoptosis binding protein with low pI (SMAC, also known as DIABLO) regulates XIAP function and potentiates caspase-3, -7 and -9 activity by disrupting the interaction of caspases with XIAP. Residues 56-59 of SMAC (DIABLO) are homologous to the amino-terminal motif that is used by caspase-9 (CASP9) to bind to the BIR3 domain of XIAP. SMAC (DIABLO) competes with CASP9 for binding to BIR3 domain of XIAP promoting the release of XIAP from the CASP9:apoptosome complex (Srinivasula SM et al. 2001; Salvesen et al. 2002). The binding of SMAC to the BIR2 and BIR3 regions of XIAP creates a steric hindrance that is essential for preventing binding of XIAP linker region with effector caspases CASP3 and CASP7 thus achieving neutralization of XIAP inhibition. The strong affinity for XIAP allows SMAC (DIABLO) to displace caspase-3, -7 from the XIAP:caspase complexes (Wu G et al. 2000; Chai J et al. 2001; Huang Y et al. 2003; Abhari BA & Davoodi J 2008).

Literature references

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

Editions

2018-03-02	Reviewed	Matthews, L.
2018-11-02	Edited	Shamovsky, V.

Dissociation of Caspase-3 from DIABLO:XIAP:Caspase-3 ↗

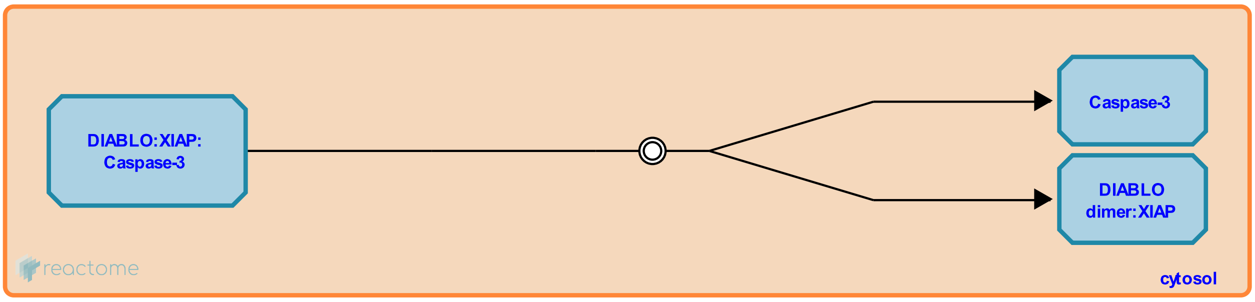
Location: SMAC(DIABLO)-mediated dissociation of IAP:caspase complexes

Stable identifier: R-HSA-114419

Type: dissociation

Compartments: cytosol

Inferred from: Dissociation of Caspase-7 from DIABLO:XIAP:Caspase-7 (Homo sapiens)



The linker region preceding BIR2 of XIAP is responsible for the inhibition of caspase-3 and -7, which is further stabilized by interaction with the BIR2 domain itself (Scott et al. 2005). Binding of DIABLO (SMAC) to BIR2 domain of XIAP can destabillize the XIAP:CASP3 interaction promoting the liberation of active caspase-3 from its complex with XIAP (Kashkar et al. 2003). Furthermore, SMAC (DIABLO) interacted with the BIR3 and then BIR2 domains of XIAP sequentially, and such dynamic interaction cooperatively neutralized inhibition of caspase-3 by the linker region of XIAP (Gao Z et al. 2007).

Literature references

Kronke, M., Jurgensmeier, JM., Hamilton-Dutoit, SJ., Kashkar, H., Haefs, C., Salvesen, GS. et al. (2003). XIAP-mediated caspase inhibition in Hodgkin's lymphoma-derived B cells. *J. Exp. Med., 198*, 341-7. ↗

Editions

2004-02-17	Authored	Alnemri, E.
2018-11-02	Edited	Shamovsky, V.
2018-11-05	Reviewed	Matthews, L.

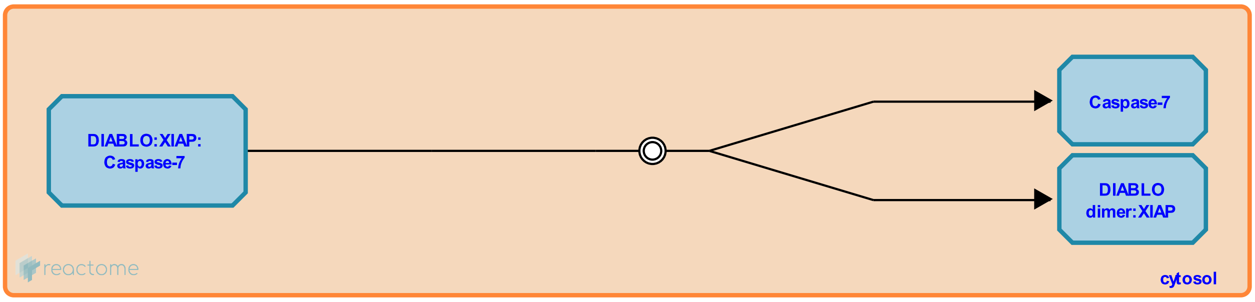
Dissociation of Caspase-7 from DIABLO:XIAP:Caspase-7 ↗

Location: SMAC(DIABLO)-mediated dissociation of IAP:caspase complexes

Stable identifier: R-HSA-114392

Type: dissociation

Compartments: cytosol



The linker region preceding BIR2 of XIAP is responsible for the inhibition of caspase-3 and -7, which is further stabilized by interaction with the BIR2 domain itself (Scott et al. 2005). Binding of a dimeric SMAC (DIABLO) N-terminal peptide with the BIR2 domain of XIAP effectively antagonized inhibition of caspase-7 by XIAP (Wu G et al. 2000; Chai J et al. 2000). As DIABLO has a higher affinity for the BIR2 domain than caspase-7, DIABLO (SMAC) binding to XIAP results in the liberation of caspase-7 (Huang et al. 2001).

Literature references

Huang, Y., Wu, H., Rich, RL., Park, YC., Myszka, DG., Segal, D. (2001). Structural basis of caspase inhibition by XIAP: differential roles of the linker versus the BIR domain. *Cell, 104*, 781-90. ↗

Editions

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2018-11-05	Reviewed	Matthews, L.

Dissociation of DIABLO:XIAP from the apoptosome complex ↗

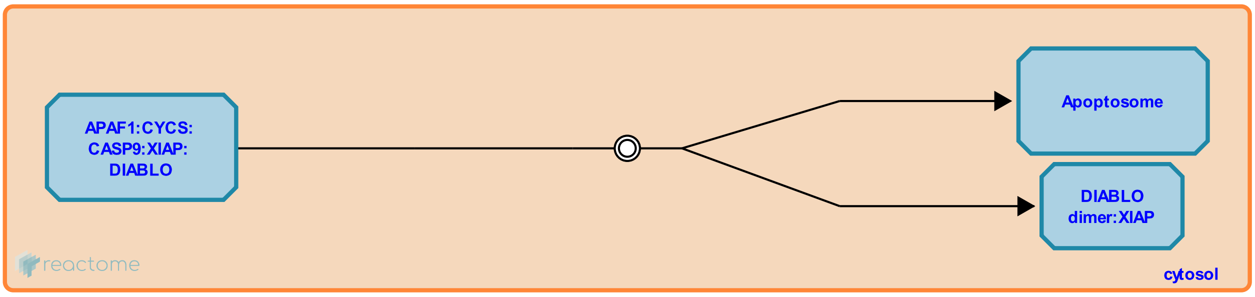
Location: SMAC(DIABLO)-mediated dissociation of IAP:caspase complexes

Stable identifier: R-HSA-114440

Type: dissociation

Compartments: cytosol

Inferred from: Dissociation of Caspase-7 from DIABLO:XIAP:Caspase-7 (Homo sapiens)



X linked inhibitor of apoptosis protein (XIAP) associates with the active caspase 9 (CASP9) within APAF1 apoptosome complex. Binding of DIABLO (SMAC) to XIAP promotes the release of caspase-9 from XIAP (Du et al. 2000). XIAP consists of three baculoviral IAP repeat (BIR) domains and a COOH terminal RING domain (Duckett CS et al. 1996). The BIR3 region binds to the amino terminus of the linker peptide on the small subunit of CASP9, which becomes exposed after proteolytic processing of procaspase 9 at Asp315 (Srinivasula SM et al. 2001). SMAC (DIABLO) competes with CASP9 for binding to BIR3 domain of XIAP promoting the release of XIAP from the CASP9:apoptosome complex (Du et al. 2000; Srinivasula SM et al. 2001).

Literature references

Wang, X., Li, L., Du, C., Fang, M., Li, Y. (2000). Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition. *Cell, 102*, 33-42. ↗

Editions

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