SMAC (DIABLO) binds to IAPs

Matthews, L., Shamovsky, V.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

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.

26/12/2022

https://reactome.org
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


Reactome database release: 83

This document contains 1 pathway and 4 reactions (see Table of Contents)
**SMAC (DIABLO) binds to IAPs**

**Stable identifier:** R-HSA-111463

**Compartments:** cytosol

Second mitochondriaderived activator of caspases protein (SMAC, also known as direct IAP binding protein with low pl or DIABLO) in its dimeric form interacts and antagonizes X-linked inhibitor of apoptosis protein (XIAP) by concurrently targeting both BIR2 and BIR3 domains of XIAP (Chai J et al. 2000; Liu Z et al. 2000; Burke SP & Smith JB 2010). XIAP inhibits apoptosis by binding to and inhibiting the effectors caspase83 and 87 and an initiator caspase89 (Deveraux QL et al. 1997; Paulsen M et al. 2008). During apoptosis, SMAC (DIABLO) is released from the mitochondria (Du C et al. 2000). In the cytosol, SMAC binds to XIAP displacing it from caspase:XIAP complexes liberating the active caspases (Wu G et al. 2000; Abhari BA & Davoodi J 2008).

**Literature references**

Second mitochondria derived activator of caspase/direct inhibitor of apoptosis binding protein with low pI (SMAC, also known as DIABLO) is normally a mitochondrial protein but is released into the cytosol when cells undergo apoptosis (Du C et al. 2000). Mitochondrial import and cleavage of its signal peptide are required for SMAC to gain its apoptotic activity (Du C et al. 2000). In vitro studies revealed that dimerization was required for its function, while monomerization of cytosolic mature SMAC attenuated interaction with XIAP (Chai J et al. 2000; Burke SP & Smith JB 2010). Moreover, SMAC dimer showed high stability in vitro as measured by high hydrostatic pressure, low and high temperatures, and chemical denaturation (Goncalves RB et al. 2008). Binding of SMAC (DIABLO) to the BIR3 region of X linked inhibitor of apoptosis protein (XIAP) competitively inhibits binding of XIAP to caspase 9, while binding to the BIR2 region sterically hinders the interaction of XIAP with CASP3 and CASP7 (Srinivasula SM et al. 2001; Abhari BA & Davoodi J 2008).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-07-26</td>
<td>Authored</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2018-11-02</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2018-11-05</td>
<td>Reviewed</td>
<td>Matthews, L.</td>
</tr>
</tbody>
</table>

https://reactome.org
SMAC binds XIAP:Caspase-3

Location: SMAC (DIABLO) binds to IAPs

Stable identifier: R-HSA-114306

Type: binding

Compartments: cytosol

Inferred from: SMAC binds XIAP:Caspase-7 (Homo sapiens)

Binding of a dimeric SMAC (DIABLO) N-terminal peptide with the BIR2 domain of XIAP effectively antagonizes inhibition of caspase3 by XIAP (Wu G et al. 2000; Chai J et al. 2000). SMAC (DIABLO) interacts with the BIR3 and then BIR2 domains of XIAP sequentially, and such dynamic interaction cooperatively neutralizes inhibition of caspase3 by the linker region of XIAP (Gao Z et al. 2007).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-11-05</td>
<td>Reviewed</td>
<td>Matthews, L.</td>
</tr>
<tr>
<td>2018-11-07</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
</tbody>
</table>
SMAC binds XIAP:Caspase-7

Location: SMAC (DIABLO) binds to IAPs

Stable identifier: R-HSA-114354

Type: binding

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).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-11-05</td>
<td>Reviewed</td>
<td>Matthews, L.</td>
</tr>
<tr>
<td>2018-11-07</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
</tbody>
</table>
SMAC binds XIAP within apoptosome

Location: SMAC (DIABLO) binds to IAPs

Stable identifier: R-HSA-114361

Type: binding

Compartments: cytosol

Inferred from: SMAC binds XIAP:Caspase-7 (Homo sapiens)

X linked inhibitor of apoptosis protein (XIAP) associates with the active caspase 9 (CASP9) within the APAF1 apoptosome complex. XIAP consists of three baculoviral IAP repeat (BIR) domains and a COOH terminal RING domain (Duckett CS et al. 1996). The BIR3 region of XIAP 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; Liu Z et al. 2000; Srinivasula SM et al. 2001).

Literature references


Editions

<table>
<thead>
<tr>
<th>Editions</th>
<th>Reviewed</th>
<th>Edited</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-11-05</td>
<td>2018-11-07</td>
<td></td>
</tr>
<tr>
<td>Matthews, L.</td>
<td>Shamovsky, V.</td>
<td></td>
</tr>
</tbody>
</table>
## Table of Contents

- Introduction
- SMAC (DIABLO) binds to IAPs
  - SMAC (DIABLO) binds XIAP
  - SMAC binds XIAP:Caspase-3
  - SMAC binds XIAP:Caspase-7
  - SMAC binds XIAP within apoptosome

Table of Contents