NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

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28/06/2020
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: 73

This document contains 1 pathway and 5 reactions (see Table of Contents)
NF-κB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

**Stable identifier:** R-HSA-933543

**Compartments:** mitochondrial outer membrane

Fas-AssociatedDeathDomain (FADD) and receptor interacting protein 1 (RIP1) are death domain containing molecules that interact with the C-terminal portion of IPS-1 and induce NF-κB through interaction and activation of initiator caspases (caspase-8 and -10). Caspases are usually involved in apoptosis and inflammation but they also exhibit nonapoptotic functions. These nonapoptotic caspase functions involve prodomain-mediated activation of NF-κB. Processed caspases (caspase-8/10) encoding the DED (death effector domain) strongly activate NF-κB. The exact mechanism by which caspases mediate NF-κB activation is unclear, but the prodomains of caspase-8/10 may act as a scaffolding and allow the recruitment of the IKK complex in association with other signaling molecules.

**Literature references**


**Editions**

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MAVS interacts with RIPK1 and FADD

Location: NF-κB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

Stable identifier: R-HSA-168934

Type: binding

Compartments: cytosol, mitochondrial outer membrane

Receptor-interacting protein 1 (RIP1) and Fas-Associated Death Domain (FADD) are death domain (DD)-containing proteins. These proteins interact with IPS-1 and activate NF-κB through interaction and activation of caspase-8 and caspase-10.

Followed by: Recruitment of caspase-8 and -10 to FADD complex

Literature references


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Recruitment of caspase-8 and -10 to FADD complex

Location: NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

Stable identifier: R-HSA-933526

Type: binding

Compartments: cytosol, mitochondrial outer membrane

Caspase-8 (CASP8) and caspase-10 (CASP10) are involved in RIG-I/MDA5-dependent antiviral immune responses. Caspase-8/10 activation contributes to NF-kB activation in response to viral dsRNA.

Caspase-8/10 are synthesized as zymogens (procaspases), containing a large N-terminal prodomain with two death effector domains (DED), and a C-terminal catalytic subunit composed of small and a large domain separated by a smaller linker region. FADD plays a crucial role in the recruitment and activation of procaspase-8/10. The two DED domains of procaspase-8/10 interacts with DED domain of FADD.

Preceded by: MAVS interacts with RIPK1 and FADD

Followed by: Dimerzation of procaspase-8, procaspase-10

Literature references


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Dimerzation of procaspase-8, procaspase-10

Location: NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

Stable identifier: R-HSA-933523

Type: binding

Compartments: cytosol, mitochondrial outer membrane

Procaspase-8/10 undergo dimerization and the subsequent conformational changes at the receptor complex results in the formation of catalytic active caspase dimers.

Preceded by: Recruitment of caspase-8 and -10 to FADD complex

Followed by: Processing of caspases

Literature references


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https://reactome.org
Processing of caspases

Location: NF-kB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

Stable identifier: R-HSA-933532

Type: transition

Compartments: cytosol, mitochondrial outer membrane

Processing of caspases is required for activation of downstream signaling and dsRNA stimulation induces the processing of these caspases. The nonapoptotic caspase function of both caspase-8 and -10 does not require the protease activity and the DED-containing prod domains are sufficient for NF-kB activation.

Preceded by: Dimerzation of procaspase-8, procaspase-10

Followed by: Recruitment of IKK complex

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Recruitment of IKK complex

**Location:** NF-κB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10

**Stable identifier:** R-HSA-933539

**Type:** binding

**Compartments:** cytosol, mitochondrial outer membrane

The molecular mechanisms by which caspase-8/10 attribute to NF-κB signaling is unclear. Caspase-8 might act as a scaffolding protein by bringing the IKK-complex in close proximity to its activator TAK1. The prodomain of Caspase-8 could interact with IKK2 in the IKK complex whereas the protease homology domain failed to do so. These results indicate that the interaction of the DEDs-containing prodomain of caspase-8 with the IKKs may be crucial for the NF-κB induction by caspase-8.

**Preceded by:** Processing of caspases

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</table>
# Table of Contents

- Introduction 1
- NF-κB activation through FADD/RIP-1 pathway mediated by caspase-8 and -10 2
  - MAVS interacts with RIPK1 and FADD 3
  - Recruitment of caspase-8 and -10 to FADD complex 4
  - Dimerzation of pro-caspase-8, pro-caspase-10 5
  - Processing of caspases 6
  - Recruitment of IKK complex 7

Table of Contents 8