Cytochrome c-mediated apoptotic response

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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: 72

This document contains 3 pathways (see Table of Contents)
Cytochrome c-mediated apoptotic response

Stable identifier: R-HSA-111461

Compartments: cytosol

Upon its release from the mitochondrial intermembrane space, cytochrome c (CYSC) binds to and causes an ATP-mediated conformational change in the cytoplasmic adaptor protein apoptotic protease-activating factor 1 (APAF1). This conformational change triggers the formation of procaspase-9-activating oligomeric protein complex named apoptosome. The active caspase9 holoenzyme activates downstream effector caspases3 and 7. The activated effector caspases then cleave various cellular proteins.

Literature references


Editions

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The apoptosome is a cytoplasmic protein complex of two major components: the adapter protein apoptotic protease activating factor 1 (APAF1) and the pro tease caspase9 (CASP9) which interact with each other through their caspase recruitment domains (CARD) (Qin et al. 1999; Yuan S et al. 2010; Yuan S & Akey CW 2013). The function of the apoptosome is to assemble a multimeric complex between APAF1 and procaspase-9 CARDs to facilitate CASP9 activation (Jiang X and Wang X 2000; Srinivasrula SM et al. 2001; Shiozaki EN et al. 2002). The apoptosome is assembled upon APAF1 interaction with cytochrome c (CYCS), which is released from the mitochondrial intermembrane space during apoptosis (Zou H et al. 1997; Yuan S et al. 2013; Shakeri R et al. 2017). CYCS-bound APAF1 undergoes ATP-mediated conformational changes and in the presence of CARD of CASP9 oligomerizes into a heptameric complex, which activates procaspase 9 (Zou H et al. 1997; Bratton SB et al. 2010; Acehan D et al. 2002; Yu X et al. 2005; Yuan S et al. 2010; Su TW et al. 2017). In the apoptosome, recruitment of caspase-9 may occur before oligomerization in the CARD disk, which presumably brings the caspase domain into proximity for their dimerization and activation (Su TW et al. 2017; Hu Q et al. 2014; Cheng TC et al. 2016). Once activated, CASP9 activates downstream effector caspases3 and 7. The activated effector caspases then cleave various cellular proteins.

Different models have been proposed to explain CASP9 activation: the “proximity-driven dimerization model” and the “induced conformation model”. The first models states that upon binding to heptameric APAF1, monomers of procaspase9 are brought into close proximity at a high concentration (Acehan et al. 2002; Renatus et al. 2001). This induces dimerization which is sufficient for CASP9 activation whereas autoprocessing within the apoptosome complex merely stabilizes CASP9 dimer (Boatright KM et al. 2003; Pop C et al. 2006). The “induced conformation model” is based on the observation that CASP9 has a much higher level of catalytic activity when it's bound to the apoptosome. The model suggests that a conformational change occurs at the active site of CASP9 upon binding to APAF1 thus inducing CASP9 homodimerization and stabilizing it in the catalytically active conformation (Shiozaki EN et al. 2002). CASP9 activa-
tion may also involve formation of a multimeric CARD:CARD assembly between APAF1 and procaspase-9 (Hu Q et al. 2014).

**Literature references**


**Editions**

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Activation of caspases through apoptosome-mediated cleavage

Location: Cytochrome c-mediated apoptotic response

Stable identifier: R-HSA-111459

Compartments: cytosol

Procaspses-3 and 7 are cleaved by the apoptosome.

Literature references


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