Cytosolic iron-sulfur cluster assembly

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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.

12/11/2022
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: 82

This document contains 1 pathway and 3 reactions (see Table of Contents)
Cytosolic iron-sulfur cluster assembly

Stable identifier: R-HSA-2564830

Compartment: cytosol

Iron-sulfur clusters containing 4 atoms of iron and 4 atoms of sulfur (4Fe-4S clusters) are assembled in the cytosol on a heterotetrameric scaffold composed of NUBP2 and NUBP1 subunits (reviewed in Lill et al. 2012, Rouault et al. 2012, Sharma et al. 2010, Lill and Muhlenhoff 2006). The sources of iron and sulfur are uncertain but the process requires a sulfur-containing compound exported from mitochondria via ABCB7 (ABC7). Newly synthesized 4Fe-4S are transferred to apoproteins such as XPD and POLD1 via the CIA targeting complex, composed of NARFL, CIAO1, FAM96B, and MMS19.

Literature references


Editions

2012-11-07 Authored Lill, R.
2012-11-07 Edited May, B.
2013-02-05 Reviewed Uiringa, EJ.
NADPH reduces NDOR1:CIAPIN1

Location: Cytosolic iron-sulfur cluster assembly

Stable identifier: R-HSA-2564824

Type: dissociation

Compartments: cytosol

Inferred from: NADPH reduces TAH18:DRE2 (Saccharomyces cerevisiae)

Cytosolic Fe/S protein biogenesis depends on the electron transfer chain from NAD(P)H to the Fe/S protein (CIAPIN1 in humans, DRE2 in yeast) via the flavoprotein NDOR1 (TAH18 in yeast). The precise role of electrons in the assembly process is unclear but in the absence of the electron chain the stable [4Fe-4S] cluster of NUBP1 is not assembled. CIAPIN1 binds two Fe/S clusters of the [2Fe-2S] and the [4Fe-4S] type. The [2Fe-2S] cluster is reduced by NDOR1-NADPH.

Followed by: 4Fe-4S cluster assembles on NUBP2:NUBP1 scaffold

Literature references


Editions

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4Fe-4S cluster assembles on NUBP2:NUBP1 scaffold

**Location:** Cytosolic iron-sulfur cluster assembly

**Stable identifier:** R-HSA-2564826

**Type:** omitted

**Compartments:** cytosol

**Inferred from:** 4Fe-4S cluster assembles on CFD1:NBP35 scaffold (Saccharomyces cerevisiae)

Mitochondria export via a mitochondrial ABC transporter (yeast ATM1, human ABCB7) a still unknown, sulfur-containing compound which is essential for Fe/S cluster assembly in the cytosol. As inferred from the yeast homolog Atm1p, the compound may be a 2Fe-2S cluster complexed with glutathione (Li and Cowan 2015).

A [4Fe-4S] cluster is assembled on a scaffold composed of the P-loop NTPases NUBP2 (CFD1 in yeast) and NUBP1 (Nbp35 in yeast) in a nucleotide-dependent fashion. The two proteins form a heterotetramer which transiently binds the [4Fe-4S] cluster in a bridged form between two subunits of the complex. The Fe/S cluster is bound to two highly conserved Cys residues in the C-termini of each of these proteins. NUBP1 contains an additional, stably associated [4Fe-4S] cluster at its N-terminus which is essential for function.

Mitochondria play a crucial role in cytosolic and nuclear Fe/S protein biogenesis. They export via a mitochondrial ABC transporter (yeast ATM1, human ABCB7) a still unknown, sulfur-containing compound which is essential for Fe/S cluster assembly in the cytosol.

The general cytosolic iron donor, the multi-domain monothiol glutaredoxin (human GRX3 or PICOT, yeast Grx3-Grx4) plays a crucial role in cytosolic-nuclear Fe/S protein biogenesis. The precise molecular function of the glutaredoxin is still unclear.

**Preceded by:** NADPH reduces NDOR1:CIAPIN1

**Followed by:** CIA Targeting Complex transfers 4Fe-4S cluster to apoproteins

https://reactome.org
Literature references


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A complex of four proteins termed CIA targeting complex is involved in the delivery of the NUBP1-NUBP2-bound Fe/S cluster to specific target apoproteins. NARFL (IOP1, Nar1 in yeast) is similar in sequence to iron-only hydrogenases and binds two [4Fe-4S] clusters. These cofactors are essential for biogenesis but their molecular function is unknown. The WD40 domain protein CIAO1 (Cia1 in yeast) forms a propeller-like structure which may serve as a docking site for the other members of the CIA targeting complex. The role of FAM96B (YHR122W, CIA2 in yeast) and MMS19 is still unclear, but they show some specificity for the delivery of Fe/S clusters into certain target apoproteins. They directly interact with numerous Fe/S target proteins including many proteins involved in nuclear DNA integrity and maintenance such as DNA polymerases (POLD1), helicases of the DNA repair pathway (XPD or FANCl) or of telomere maintenance (RTEL1), and primases. Cells with mutated MMS19 are hypersensitive to DNA damage and have elongated telomeres therefore these target proteins are relevant to various cancer-related diseases and aging.

**Preceded by:** 4Fe-4S cluster assembles on NUBP2:NUBP1 scaffold

**Literature references**


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