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: 82

This document contains 1 pathway and 8 reactions (see Table of Contents)
Choline catabolism

Stable identifier: R-HSA-6798163

Choline is an essential water-soluble nutrient in humans, serving as a precursor of phospholipids and the neurotransmitter acetylcholine. It is often associated with B vitamins based on its chemical structure but it isn't an official B vitamin. Its oxidation to betaine provides a link to folate-dependent, one-carbon metabolism where betaine is a methyl donor in the methionine cycle. Betaine is further metabolised to dimethylglycine which is cleared by the kidney (Ueland 2011, Hollenbeck 2012).

Literature references


Editions

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SLC44A1 transports Cho from cytosol to mitochondrial matrix

**Location:** Choline catabolism

**Stable identifier:** R-HSA-6797956

**Type:** transition

**Compartments:** mitochondrial matrix, cytosol, mitochondrial outer membrane

The choline transporter-like protein 1 (SLC44A1) as an important mediator of choline transport across both the plasma membrane and the mitochondrial membrane. It is an essential step in the oxidation of Cho to betaine, which occurs in the mitochondrial matrix (Michel & Bakovic 2009).

**Followed by:** CHDH oxidises Cho to BETALD

**Literature references**


**Editions**

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CHDH oxidises Cho to BETALD ➔

**Location:** Choline catabolism

**Stable identifier:** R-HSA-6797961

**Type:** transition

**Compartments:** mitochondrial inner membrane, mitochondrial matrix

Mitochondrial choline dehydrogenase (CHDH), located on the inner mitochondrial membrane, catalyses the oxidation of choline (Cho) to betaine aldehyde (BETALD). Human CHDH activity is inferred from rat Chdh (Huang & Lin 2003). While CHDH is associated with FAD, and plausible electron transfer schemes from FADH2 have been hypothesized for this reaction (e.g., Packer et al. 1960), direct experimental evidence for FAD as the hydrogen acceptor in this reaction is lacking and so it is annotated here with a generic acceptor and donor.

**Preceded by:** SLC44A1 transports Cho from cytosol to mitochondrial matrix

**Followed by:** ALDH7A1 oxidises BETALD to BET

**Literature references**


**Editions**

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https://reactome.org
Alpha-aminoadipic semialdehyde dehydrogenase (ALDH7A1) is a multifunctional enzyme present in mitochondria, nucleus and the cytosol and plays an important role in protecting against hyperosmotic stress and metabolising toxic aldehydes. It is able to oxidise the osmolyte precursor betaine aldehyde (BETALD) to betaine (BET) (as well as the intermediate lysine degradation product, alpha-aminoadipic semialdehyde, not shown here) (Brocker et al. 2010). The mitochondrial isoform of ALDH7A1 is shown here.

**Preceded by:** CHDH oxidises Cho to BETALD

**Followed by:** BET translocates from mitochondrial matrix to cytosol

**Literature references**


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Betaine (BET) is further metabolised in the cytosol and needs to translocate from the mitochondrial matrix to the cytosol. From rat studies, the process is suggested to be simple diffusion (Porter et al. 1993).

**Preceded by:** ALDH7A1 oxidises BETALD to BET

**Followed by:** BHMT tetramer transfers CH3 group from BET to HCYS to form DMGLY

**Literature references**

BHMT tetramer transfers CH3 group from BET to HCYS to form DMGLY

Location: Choline catabolism

Stable identifier: R-HSA-1614654

Type: transition

Compartments: cytosol

Remethylation of homocysteine (HCYS) to methionine (L-Met) can also proceed by using betaine (BET) as a methyl donor, which is oxidised to dimethylglycine (DMGLY). This reaction is also part of choline catabolism, thereby providing a link to folate-dependent, one-carbon metabolism (Li et al. 2008).

Preceded by: BET translocates from mitochondrial matrix to cytosol

Literature references


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DMGLY translocates from cytosol to mitochondrial matrix

Location: Choline catabolism

Stable identifier: R-HSA-6797962

Type: uncertain

Compartments: mitochondrial matrix, cytosol

Dimethylglycine (DMGLY) is either cleared by the kidneys or is further metabolised in the mitochondrion. Cytosolic DMGLY translocates to the mitochondrial matrix possibly by simple diffusion but the mechanism is unknown (Porter et al. 1993).

Followed by: DMGDH:FAD oxidatively demethylates DMGLY to SARC

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Mitochondrial dimethylglycine dehydrogenase (DMGDH) is an enzyme involved in the choline catabolic pathway, mediating the oxidative demethylation of dimethylglycine (DMGLY) to form sarcosine (SARC, aka methylglycine, MeGly) and formaldehyde (CH2O), an active 1-carbon unit (Binzak et al. 2000). DMGDH covalently binds one FAD cofactor per monomer. Defects in DMGDH cause DMGDH deficiency (DMGDHD; MIM:605850), a disorder characterised by a fishy odour and muscle fatigue with increased serum creatine kinase. Biochemically, increased levels of DMGLY are detected in the serum and urine (Binzak et al. 2001).

Preceded by: DMGLY translocates from cytosol to mitochondrial matrix

Followed by: SARDH:FAD oxidatively demethylates SARC to Gly

Literature references


Mitochondrial sarcosine dehydrogenase (SARDH) oxidatively demethylates sarcosine (SARC, aka methylglycine) to glycine (Gly) and formaldehyde (CH2O), an active 1-carbon unit (Eschenbrenner & Jorns 1999, ). SARDH requires one FAD as cofactor, which is reduced during the reaction. Defects in SARDH cause sarcosinemia (SARCOS; MIM:268900), a disorder characterised by an increased concentration of sarcosine in plasma and increased sarcosine excretion in urine. The clinical phenotypes of sarcosinemia are diverse, ranging from normal (most common) to ones associated with mental retardation, growth delay and muscular abnormalities (Bar-joseph et al. 2012).

**Preceded by:** DMGDH:FAD oxidatively demethylates DMGLY to SARC

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</tbody>
</table>
## Table of Contents

- **Introduction**  
  1
- **Choline catabolism**  
  2
  - SLC44A1 transports Cho from cytosol to mitochondrial matrix  
  3
  - CHDH oxidises Cho to BETALD  
  4
  - ALDH7A1 oxidises BETALD to BET  
  5
  - BET translocates from mitochondrial matrix to cytosol  
  6
  - BHMT tetramer transfers CH3 group from BET to HCYS to form DMGLY  
  7
  - DMGLY translocates from cytosol to mitochondrial matrix  
  8
  - DMGDH:FAD oxidatively demethylates DMGLY to SARC  
  9
  - SARDH:FAD oxidatively demethylates SARC to Gly  
  10

Table of Contents  
11