Carnitine metabolism

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20/09/2021
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: 77

This document contains 1 pathway and 9 reactions (see Table of Contents)

https://reactome.org
The mitochondrial carnitine system catalyzes the transport of long-chain fatty acids into the mitochondrial matrix where they undergo beta oxidation. This transport system consists of the malonyl-CoA sensitive carnitine palmitoyltransferase I (CPT-I) localized in the mitochondrial outer membrane, the carnitine:acylcarnitine translocase, an integral inner membrane protein, and carnitine palmitoyltransferase II localized on the matrix side of the inner membrane. (Kerner and Hoppel, 2000).

**Literature references**


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OCTN2 / SLC22A5 transports CAR from extracellular space to cytosol

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-165026

**Type:** transition

**Compartments:** plasma membrane

OCTN2 (organic cation transporter novel 2, encoded by the SLC22A5 gene) mediates the sodium-dependent transport of CAR (carnitine) from the extracellular space into the cytosol.

While humans are capable of synthesizing carnitine de novo, the enzyme that catalyzes the last reaction of the biosynthetic pathway is found only in liver and kidney cells, and at very low levels in brain cells. Other tissues that require carnitine, such as muscle, are dependent on transport systems that mediate its export from the liver and uptake by other tissues (Kerner & Hoppel 1998). The specific transport systems responsible for liver export have been characterized biochemically in model organisms but specific transport proteins have not yet been identified. OCTN2 is the major transporter responsible for carnitine uptake in extrahepatic tissues, as demonstrated both by the biochemical characterization of overexpressed recombinant human protein (Tamai et al. 1998) and by the appearance of symptoms of carnitine deficiency in humans lacking a functional SLC22A5 gene (Seth et al. 1999; reviewed by Longo et al. 2016).

**Followed by:** CAR translocates from the cytosol to the mitochondrial intermembrane space

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CAR translocates from the cytosol to the mitochondrial intermembrane space

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-8949399

**Type:** omitted

**Compartments:** cytosol, mitochondrial intermembrane space

CAR (carnitine) diffuses across the mitochondrial outer membrane from the cytosol to the mitochondrial intermembrane space, presumably via porin channels in the outer membrane (Bay & Court 2002).

**Preceded by:** OCTN2 / SLC22A5 transports CAR from extracellular space to cytosol

**Followed by:** CPT1A,B transfers PALM to CAR

**Literature references**


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Carnitine palmitoyl transferase 1 (CPT1) associated with the inner mitochondrial membrane, catalyzes the reaction of palmitoyl-CoA (PALM-CoA) from the cytosol with carnitine (CAR) in the mitochondrial intermembrane space to form palmitoylcarnitine (L-PCARN) and CoA-SH. Three CPT1 isoforms exist; CPT1A, B and C. In the body, CPT1A is most abundant in liver while CPT1B is abundant in muscle. CPT1C is mainly expressed in neurons and localises to the ER and not to the mitochondria. It has little or no enzymatic activity in fatty acid oxidation. Both CPT1A and CPT1B are inhibited by malonyl-CoA (Morillas et al. 2002, 2004; Zammit et al. 2001; Zhu et al. 1997). Mutations in CPT1A are associated with defects in fatty acid metabolism and fasting intolerance, consistent with the role assigned to CPT1 from studies in vitro and in animal models (IJlst et al. 1998; Gobin et al. 2003).

In the nucleus, cellular retinoic acid-binding protein 1 or 2 (CRABP1 or 2), bound to all-trans-retinoic acid (atRA), directly binds to the heterodimeric complex of retinoic acid receptor alpha RXRA) and peroxisome proliferator-activated receptor delta (PPARD). When bound to PPARD, atRA can significantly increase the expression of proteins involved in fatty acid oxidation such as CPT1A via its induction of PPARD (Amengual et al. 2012).

Preceded by: CAR translocates from the cytosol to the mitochondrial intermembrane space

Followed by: Exchange of palmitoylcarnitine and carnitine across the inner mitochondrial membrane

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Exchange of palmitoylcarnitine and carnitine across the inner mitochondrial membrane

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-200424

**Type:** transition

**Compartment:** mitochondrial intermembrane space, mitochondrial inner membrane, mitochondrial matrix

The carnitine-acylcarnitine transporter (SLC25A20 / CACT), embedded in the inner mitochondrial membrane, mediates the exchange of palmitoyl-carnitine (and other acylcarnitine esters) and carnitine across the inner mitochondrial membrane (Huizing et al., 1997).

**Preceded by:** CPT1A,B transfers PALM to CAR

**Followed by:** palmitoylcarnitine + CoASH => palmitoyl-CoA + carnitine

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palmitoylcarnitine + CoASH => palmitoyl-CoA + carnitine

Location: Carnitine metabolism

Stable identifier: R-HSA-200410

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix

CPT2, associated with the inner mitochondrial membrane, catalyzes the reaction of palmitoylcarnitine and CoASH to form palmitoyl-CoA and carnitine (Verderio et al. 1995).

Preceded by: Exchange of palmitoylcarnitine and carnitine across the inner mitochondrial membrane

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MID1IP1 binds THRSP

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-8866941

**Type:** binding

**Compartments:** cytosol

Mid1-interacting protein 1 (MID1IP1, aka MIG12, SPOT14R, S14R) plays a role in the regulation of lipogenesis in the liver. It is rapidly upregulated by processes that induce lipogenesis (enhanced glucose metabolism, thyroid hormone administration) (Tsatsos et al. 2008). MID1IP1 forms a heterodimer with thyroid hormone-inducible hepatic protein (THRSP, aka SPOT14, S14), proposed to play the same role in lipogenesis as MID1IP1 (Aipoalani et al. 2010). This complex can polymerise acetyl-CoA carboxylases 1 and 2 (ACACA and ACACB), the first committed enzymes in fatty acid (FA) synthesis. Polymerisation enhances ACACA and ACACB enzyme activities (Kim et al. 2010, Park et al. 2013).

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**Btn-ACACA:2Mn2+ polymer carboxylates Ac-CoA to form Mal-CoA**

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-75851

**Type:** transition

**Compartments:** cytosol

Cytosolic acetyl-CoA carboxylase 1 (ACACA) catalyzes the reaction of bicarbonate, ATP, and acetyl-CoA to form malonyl-CoA, ADP, and orthophosphate. The reaction is positively regulated by citrate. The human ACACA cDNA has been cloned (Abu-Elheiga et al. 1995) and the biochemical properties of the human enzyme have recently been described (Cheng et al. 2007; Locke et al. 2008). Four ACACA isoforms generated by alternative splicing have been identified as mRNAs - the protein product of the first has been characterized experimentally. ACACA uses biotin (Btn) and two Mn2+ ions per subunit as cofactors and its activity is increased by polymerisation (Kim et al. 2010, Ingaramo & Beckett 2012). Cytosolic ACACA is thought to maintain regulation of fatty acid synthesis in all tissues but especially lipogenic tissues such as adipose tissue and lactating mammary glands.

Mid1-interacting protein 1 (MID1IP1, aka MIG12, SPOT14R, S14R) plays a role in the regulation of lipogenesis in the liver. It is rapidly upregulated by processes that induce lipogenesis (enhanced glucose metabolism, thyroid hormone administration) (Tsatsos et al. 2008). MID1IP1 forms a heterodimer with thyroid hormone-inducible hepatic protein (THRSP, aka SPOT14, S14), proposed to play the same role in lipogenesis as MID1IP1 (Aipoalani et al. 2010). This complex can polymerise acetyl-CoA carboxylases 1 and 2 (ACACA and B), the first committed enzymes in fatty acid (FA) synthesis. Polymerisation enhances ACACA and ACACB enzyme activities (Kim et al. 2010).

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Btn-ACACB:2Mn2+ polymer carboxylates Ac-CoA to form Mal-CoA

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-8876889

**Type:** transition

**Compartments:** cytosol, mitochondrial outer membrane

Mitochondrial acetyl-CoA carboxylase 2 (ACACB, ACC2) (Kim et al. 2007) catalyses the reaction of bicarbonate, ATP, and acetyl-CoA to form malonyl-CoA, ADP, and orthophosphate. The reaction is positively regulated by citrate. ACACB uses biotin (Btn) and two Mn2+ ions per subunit as cofactors and its activity is increased by polymerisation (Kim et al. 2010, Ingaramo & Beckett 2012). ACACB is located on the outer mitochondrial membrane and is involved in the regulation of mitochondrial fatty acid oxidation through the inhibition of carnitine palmitoyltransferase 1 by its product malonyl-CoA (Abu-Elheiga et al. 2000).

Mid1-interacting protein 1 (MID1IP1, aka MIG12, SPOT14R, S14R) plays a role in the regulation of lipogenesis in the liver. It is rapidly upregulated by processes that induce lipogenesis (enhanced glucose metabolism, thyroid hormone administration) (Tsatsos et al. 2008). MID1IP1 forms a heterodimer with thyroid hormone-inducible hepatic protein (THRSP, aka SPOT14, S14), proposed to play the same role in lipogenesis as MID1IP1 (Aipoalani et al. 2010). This complex can polymerise acetyl-CoA carboxylases 1 and 2 (ACACA and B), the first committed enzymes in fatty acid (FA) synthesis. Polymerisation enhances ACACA and ACACB enzyme activities (Kim et al. 2010).

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pAMPK inactivates ACACB, inhibiting malonyl-CoA synthesis

**Location:** Carnitine metabolism

**Stable identifier:** R-HSA-200423

**Type:** transition

**Compartments:** cytosol, mitochondrial outer membrane

Acetyl-CoA carboxylase 2 (ACACB, ACC2) is involved in the regulation of mitochondrial fatty acid oxidation through the inhibition of carnitine palmitoyltransferase 1 by its product malonyl-CoA. Phosphorylated AMPK inactivates ACACB in muscle cells by phosphorylation. This results in decreased levels of malonyl CoA, contributing to the homeostasis of mitochondrial beta oxidation (Ruderman & Prentki 2004).

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    - pAMPK inactivates ACACB, inhibiting malonyl-CoA synthesis

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