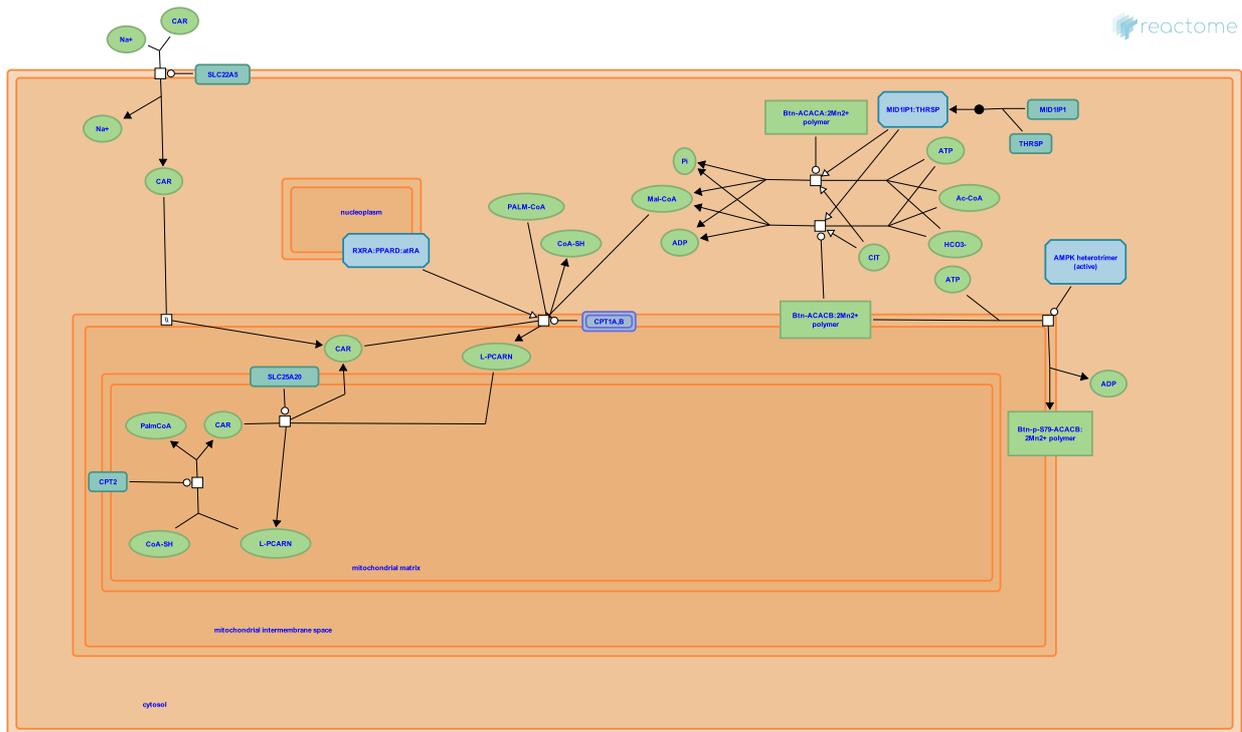


Import of palmitoyl-CoA into the mitochondrial matrix



D'Eustachio, P., Gopinathrao, G., Jassal, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://creativecommons.org/licenses/by/4.0/).

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

- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

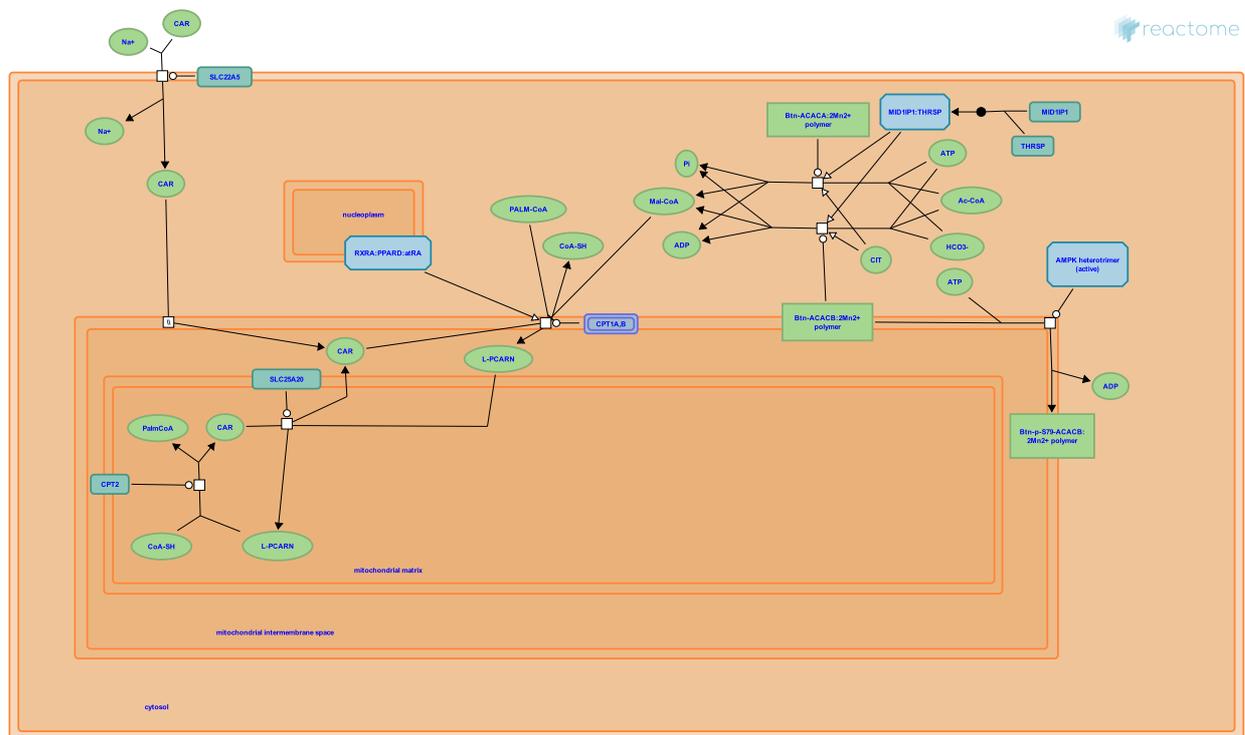
Reactome database release: 70

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

Import of palmitoyl-CoA into the mitochondrial matrix ↗

Stable identifier: R-HSA-200425

Compartments: mitochondrion, cytosol



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

Ramsay, RR., Gandour, RD., van der Leij, FR. (2001). Molecular enzymology of carnitine transfer and transport. *Biochim Biophys Acta*, 1546, 21-43. ↗

Editions

2007-07-29	Authored, Edited	Gopinathrao, G.
2007-07-31	Reviewed	D'Eustachio, P.

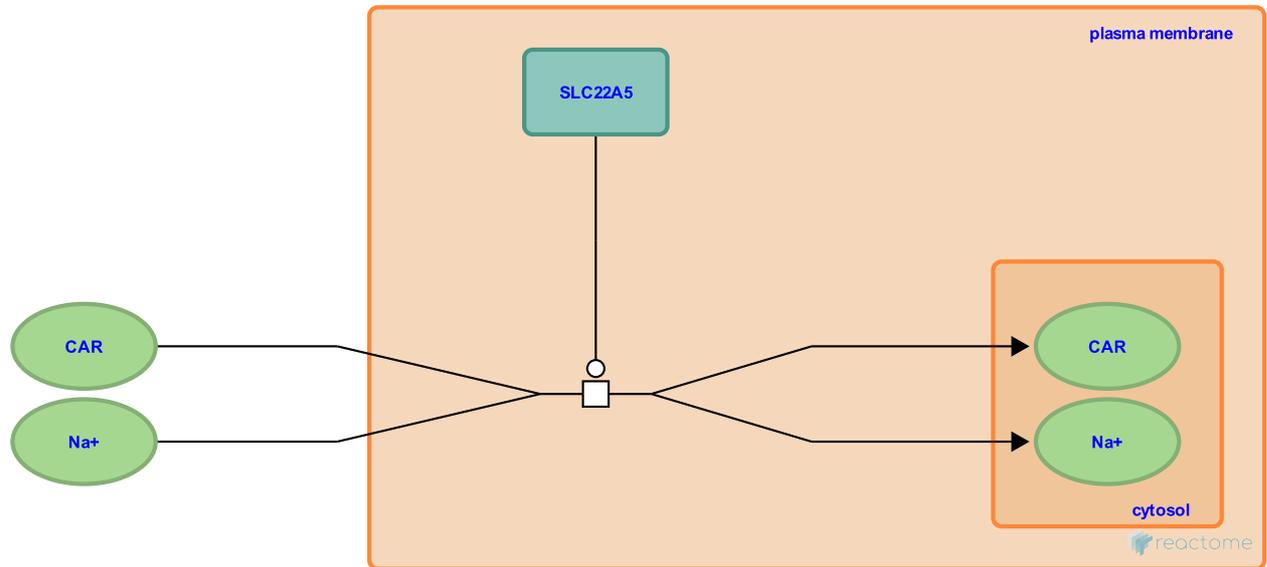
OCTN2 / SLC22A5 transports CAR from extracellular space to cytosol ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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](#)

Literature references

Kerner, J., Hoppel, C. (1998). Genetic disorders of carnitine metabolism and their nutritional management. *Annu Rev Nutr*, 18, 179-206. ↗

Longo, N., Frigeni, M., Pasquali, M. (2016). Carnitine transport and fatty acid oxidation. *Biochim. Biophys. Acta*, 1863, 2422-35. ↗

Seth, P., Wu, X., Huang, W., Leibach, FH., Ganapathy, V. (1999). Mutations in novel cation transporter (OCTN2), an organic cation/carnitine transporter, with differential effects on the organic cation transport function and the carnitine transport function. *J Biol Chem*, 274, 33388-33392. ↗

Tamai, I., Ohashi, R., Nezu, J., Yabuuchi, H., Oku, A., Shimane, M. et al. (1998). Molecular and functional identification of sodium ion-dependent, high-affinity human carnitine transporter OCTN2. *J Biol Chem*, 273, 20378-20382. ↗

Editions

2005-07-26	Authored	D'Eustachio, P.
2016-12-23	Reviewed	Jassal, B.
2019-08-16	Edited	D'Eustachio, P.

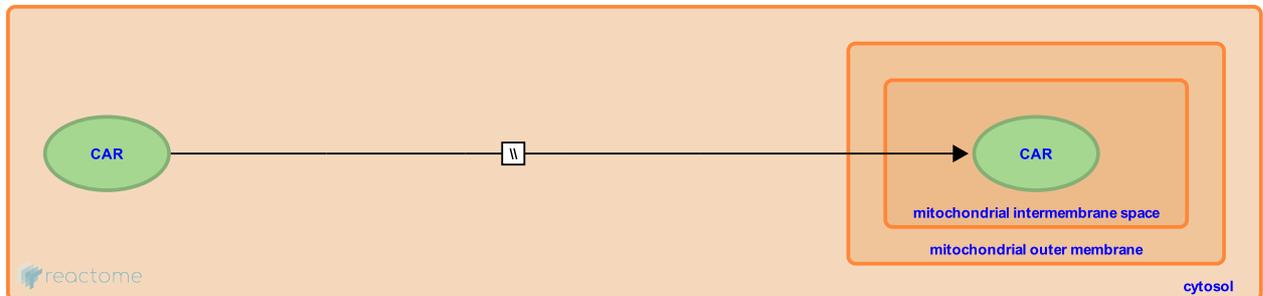
CAR translocates from the cytosol to the mitochondrial intermembrane space ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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

Bay, DC., Court, DA. (2002). Origami in the outer membrane: the transmembrane arrangement of mitochondrial porins. *Biochem. Cell Biol.*, 80, 551-62. ↗

Editions

2016-11-23	Authored, Edited	D'Eustachio, P.
2016-12-23	Reviewed	Jassal, B.

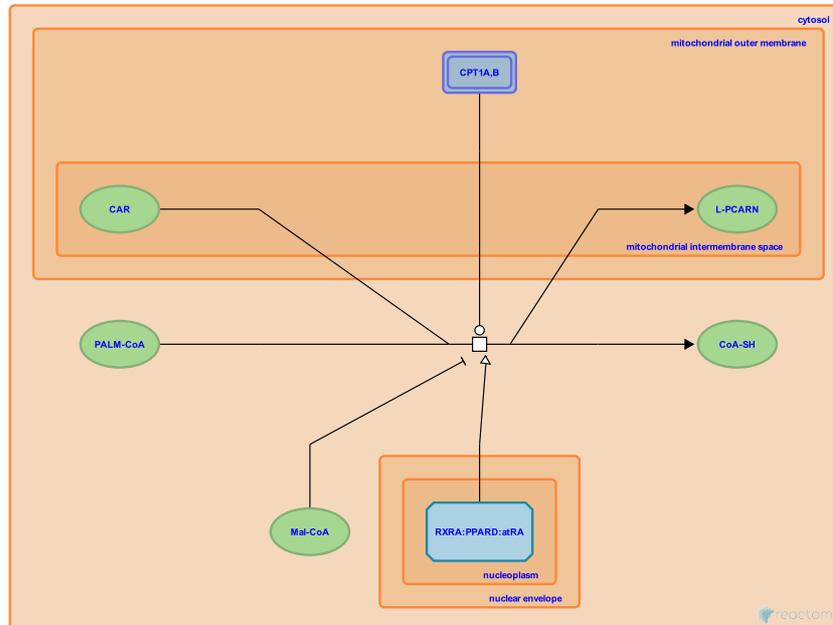
CPT1A,B transfers PALM to CAR ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

Stable identifier: R-HSA-200406

Type: transition

Compartments: cytosol, mitochondrial outer membrane, mitochondrial intermembrane space



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](#)

Literature references

- Gobin, S., Thuillier, L., Jogl, G., Faye, A., Tong, L., Chi, M. et al. (2003). Functional and structural basis of carnitine palmitoyltransferase 1A deficiency. *J Biol Chem*, 278, 50428-34. ↗
- IJlst, L., Mandel, H., Oostheim, W., Ruiter, JP., Gutman, A., Wanders, RJ. (1998). Molecular basis of hepatic carnitine palmitoyltransferase I deficiency. *J Clin Invest*, 102, 527-31. ↗

Morillas, M., Gomez-Puertas, P., Rubi, B., Clotet, J., Arino, J., Valencia, A. et al. (2002). Structural model of a malonyl-CoA-binding site of carnitine octanoyltransferase and carnitine palmitoyltransferase I: mutational analysis of a malonyl-CoA affinity domain. *J Biol Chem*, 277, 11473-80. [↗](#)

Morillas, M., López-Viñas, E., Valencia, A., Serra, D., Gomez-Puertas, P., Hegardt, FG. et al. (2004). Structural model of carnitine palmitoyltransferase I based on the carnitine acetyltransferase crystal. *Biochem J*, 379, 777-84. [↗](#)

Zammit, VA., Price, NT., Fraser, F., Jackson, VN. (2001). Structure-function relationships of the liver and muscle isoforms of carnitine palmitoyltransferase I. *Biochem Soc Trans*, 29, 287-92. [↗](#)

Editions

2007-07-18	Edited	Gopinathrao, G.
2007-07-29	Authored	Gopinathrao, G.
2007-07-31	Reviewed	D'Eustachio, P.
2014-05-08	Revised	Jassal, B.

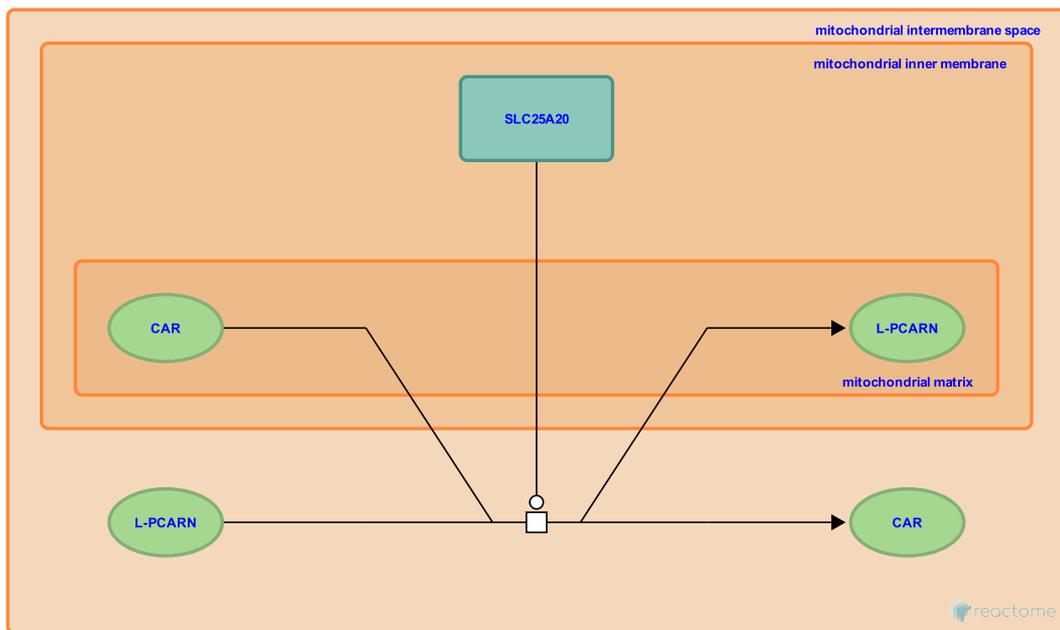
Exchange of palmitoylcarnitine and carnitine across the inner mitochondrial membrane ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

Stable identifier: R-HSA-200424

Type: transition

Compartments: 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](#)

Literature references

Huizing, M., Iacobazzi, V., IJlst, L., Savelkoul, P., Ruitenbeek, W., van den Heuvel, L. et al. (1997). Cloning of the human carnitine-acylcarnitine carrier cDNA and identification of the molecular defect in a patient. *Am J Hum Genet*, 61, 1239-45. ↗

Editions

2007-07-29	Authored	Gopinathrao, G.
2007-07-31	Reviewed	D'Eustachio, P.

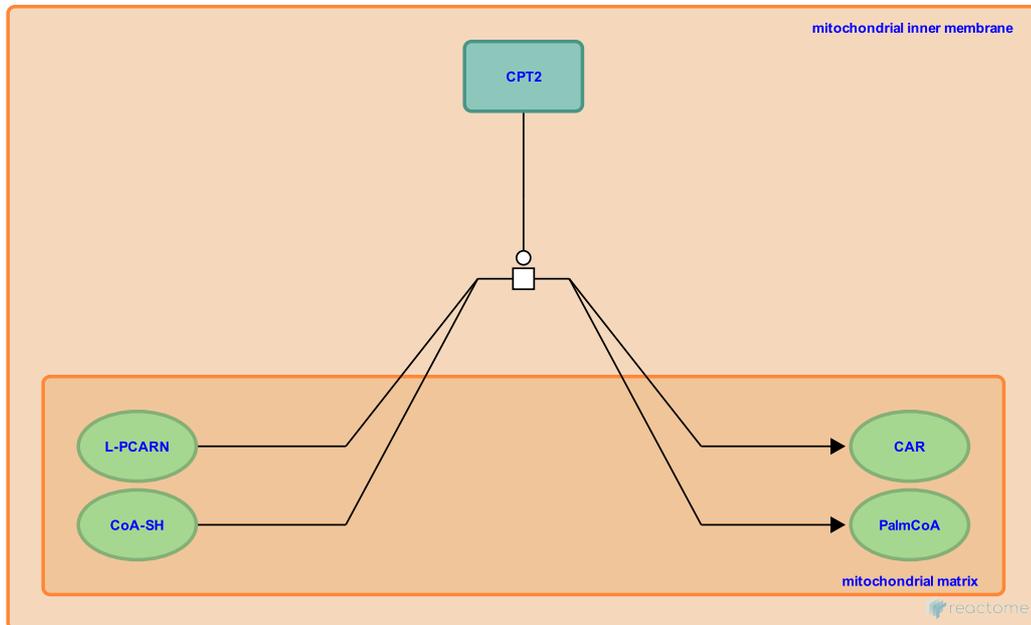
palmitoylcarnitine + CoASH => palmitoyl-CoA + carnitine ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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](#)

Literature references

Verderio, E., Cavadini, P., Montermini, L., Wang, H., Lamantea, E., Finocchiaro, G. et al. (1995). Carnitine palmitoyl-transferase II deficiency: structure of the gene and characterization of two novel disease-causing mutations. *Hum Mol Genet*, 4, 19-29. ↗

Editions

2007-07-29	Authored	Gopinathrao, G.
2007-07-31	Reviewed	D'Eustachio, P.

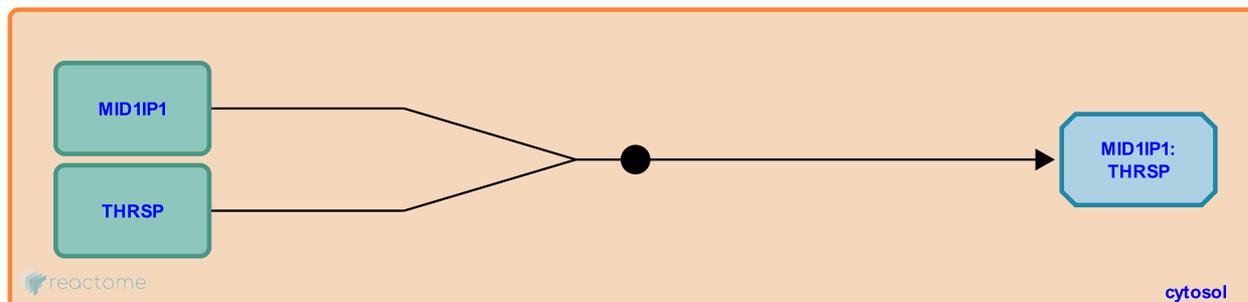
MID1IP1 binds THRSP ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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 B), the first committed enzymes in fatty acid (FA) synthesis. Polymerisation enhances ACACA and ACACB enzyme activities (Kim et al. 2010, Park et al. 2013).

Literature references

Tsatsos, NG., Augustin, LB., Anderson, GW., Towle, HC., Mariash, CN. (2008). Hepatic expression of the SPOT 14 (S14) paralog S14-related (Mid1 interacting protein) is regulated by dietary carbohydrate. *Endocrinology*, 149, 5155-61. ↗

Aipoalani, DL., O'Callaghan, BL., Mashek, DG., Mariash, CN., Towle, HC. (2010). Overlapping roles of the glucose-responsive genes, S14 and S14R, in hepatic lipogenesis. *Endocrinology*, 151, 2071-7. ↗

Park, S., Hwang, IW., Makishima, Y., Perales-Clemente, E., Kato, T., Niederländer, NJ. et al. (2013). Spot14/Mig12 heterocomplex sequesters polymerization and restrains catalytic function of human acetyl-CoA carboxylase 2. *J. Mol. Recognit.*, 26, 679-88. ↗

Editions

2016-04-05	Authored, Edited	Jassal, B.
2016-07-15	Reviewed	D'Eustachio, P.

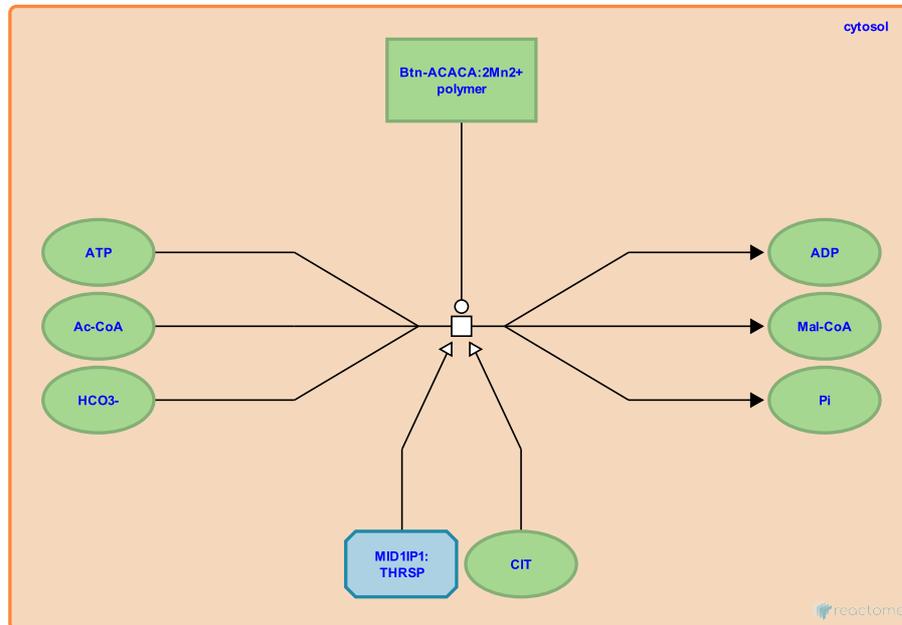
Btn-ACACA:2Mn2+ polymer carboxylates Ac-CoA to form Mal-CoA ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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).

Literature references

- Kim, KW., Yamane, H., Zondlo, J., Busby, J., Wang, M. (2007). Expression, purification, and characterization of human acetyl-CoA carboxylase 2. *Protein Expr Purif*, 53, 16-23. ↗
- Abu-Elheiga, L., Almarza-Ortega, DB., Baldini, A., Wakil, SJ. (1997). Human acetyl-CoA carboxylase 2. Molecular cloning, characterization, chromosomal mapping, and evidence for two isoforms. *J Biol Chem*, 272, 10669-77. ↗
- Brinkley, WR., Zhong, L., Woldegiorgis, G., Wakil, SJ. (2000). The subcellular localization of acetyl-CoA carboxylase 2. *Proc Natl Acad Sci U S A*, 97, 1444-9. ↗

Kim, CW., Moon, YA., Park, SW., Cheng, D., Kwon, HJ., Horton, JD. (2010). Induced polymerization of mammalian acetyl-CoA carboxylase by MIG12 provides a tertiary level of regulation of fatty acid synthesis. *Proc. Natl. Acad. Sci. U.S.A.*, 107, 9626-31. [↗](#)

Ingaramo, M., Beckett, D. (2012). Selectivity in post-translational biotin addition to five human carboxylases. *J. Biol. Chem.*, 287, 1813-22. [↗](#)

Editions

2007-07-29	Authored	Gopinathrao, G.
2007-07-31	Reviewed	D'Eustachio, P.
2016-06-17	Edited, Revised	Jassal, B.

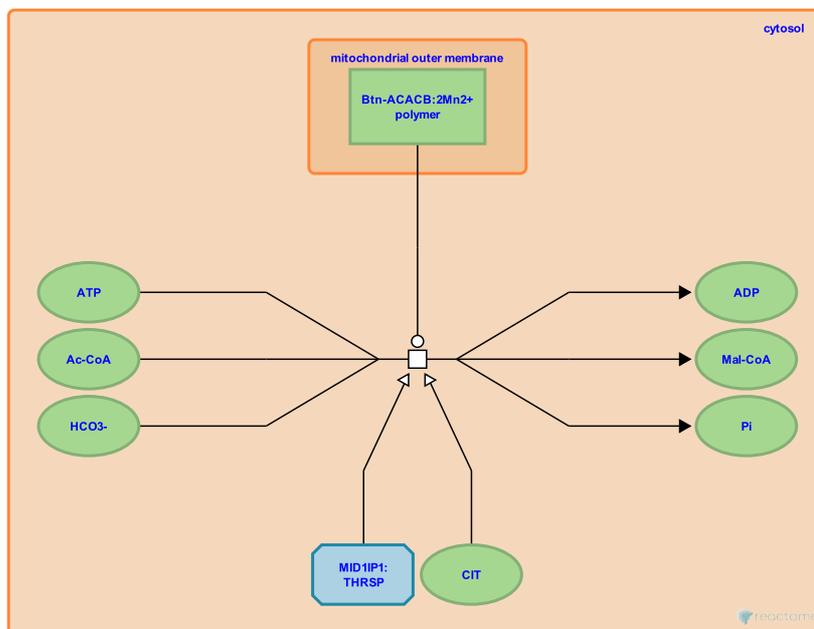
Btn-ACACB:2Mn²⁺ polymer carboxylates Ac-CoA to form Mal-CoA ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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).

Literature references

- Kim, KW., Yamane, H., Zondlo, J., Busby, J., Wang, M. (2007). Expression, purification, and characterization of human acetyl-CoA carboxylase 2. *Protein Expr Purif*, 53, 16-23. ↗
- Brinkley, WR., Zhong, L., Woldegiorgis, G., Wakil, SJ. (2000). The subcellular localization of acetyl-CoA carboxylase 2. *Proc Natl Acad Sci U S A*, 97, 1444-9. ↗
- Kim, CW., Moon, YA., Park, SW., Cheng, D., Kwon, HJ., Horton, JD. (2010). Induced polymerization of mammalian acetyl-CoA carboxylase by MIG12 provides a tertiary level of regulation of fatty acid synthesis. *Proc. Natl. Acad. Sci. U.S.A.*, 107, 9626-31. ↗
- Ingaramo, M., Beckett, D. (2012). Selectivity in post-translational biotin addition to five human carboxylases. *J. Biol. Chem.*, 287, 1813-22. ↗

Tsatsos, NG., Augustin, LB., Anderson, GW., Towle, HC., Mariash, CN. (2008). Hepatic expression of the SPOT 14 (S14) paralog S14-related (Mid1 interacting protein) is regulated by dietary carbohydrate. *Endocrinology*, 149, 5155-61. [↗](#)

Editions

2016-06-17	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

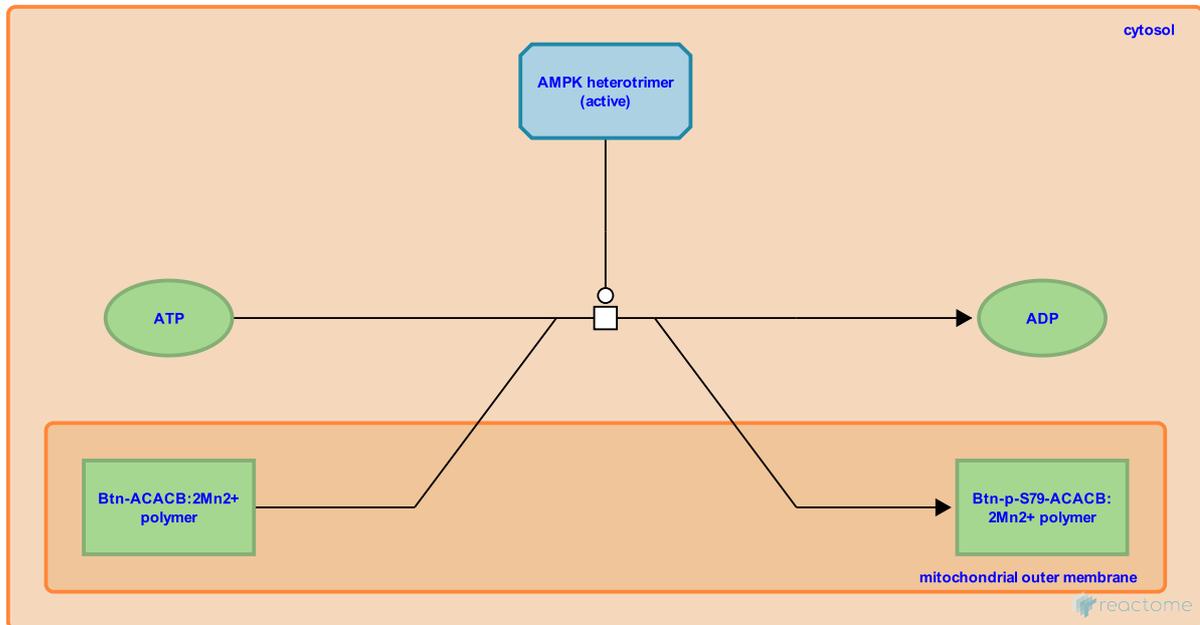
pAMPK inactivates ACACB, inhibiting malonyl-CoA synthesis ↗

Location: [Import of palmitoyl-CoA into the mitochondrial matrix](#)

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).

Literature references

Ruderman, N., Prentki, M. (2004). AMP kinase and malonyl-CoA: targets for therapy of the metabolic syndrome. *Nat Rev Drug Discov*, 3, 340-51. ↗

Editions

2007-07-29	Authored	Gopinathrao, G.
2007-07-31	Reviewed	D'Eustachio, P.
2016-06-17	Edited, Revised	Jassal, B.

Table of Contents

Introduction	1
❏ Import of palmitoyl-CoA into the mitochondrial matrix	2
↳ OCTN2 / SLC22A5 transports CAR from extracellular space to cytosol	3
↳ CAR translocates from the cytosol to the mitochondrial intermembrane space	5
↳ CPT1A,B transfers PALM to CAR	6
↳ Exchange of palmitoylcarnitine and carnitine across the inner mitochondrial membrane	8
↳ palmitoylcarnitine + CoASH => palmitoyl-CoA + carnitine	9
↳ MID1IP1 binds THRSP	10
↳ Btn-ACACA:2Mn ²⁺ polymer carboxylates Ac-CoA to form Mal-CoA	11
↳ Btn-ACACB:2Mn ²⁺ polymer carboxylates Ac-CoA to form Mal-CoA	13
↳ pAMPK inactivates ACACB, inhibiting malonyl-CoA synthesis	15
Table of Contents	16