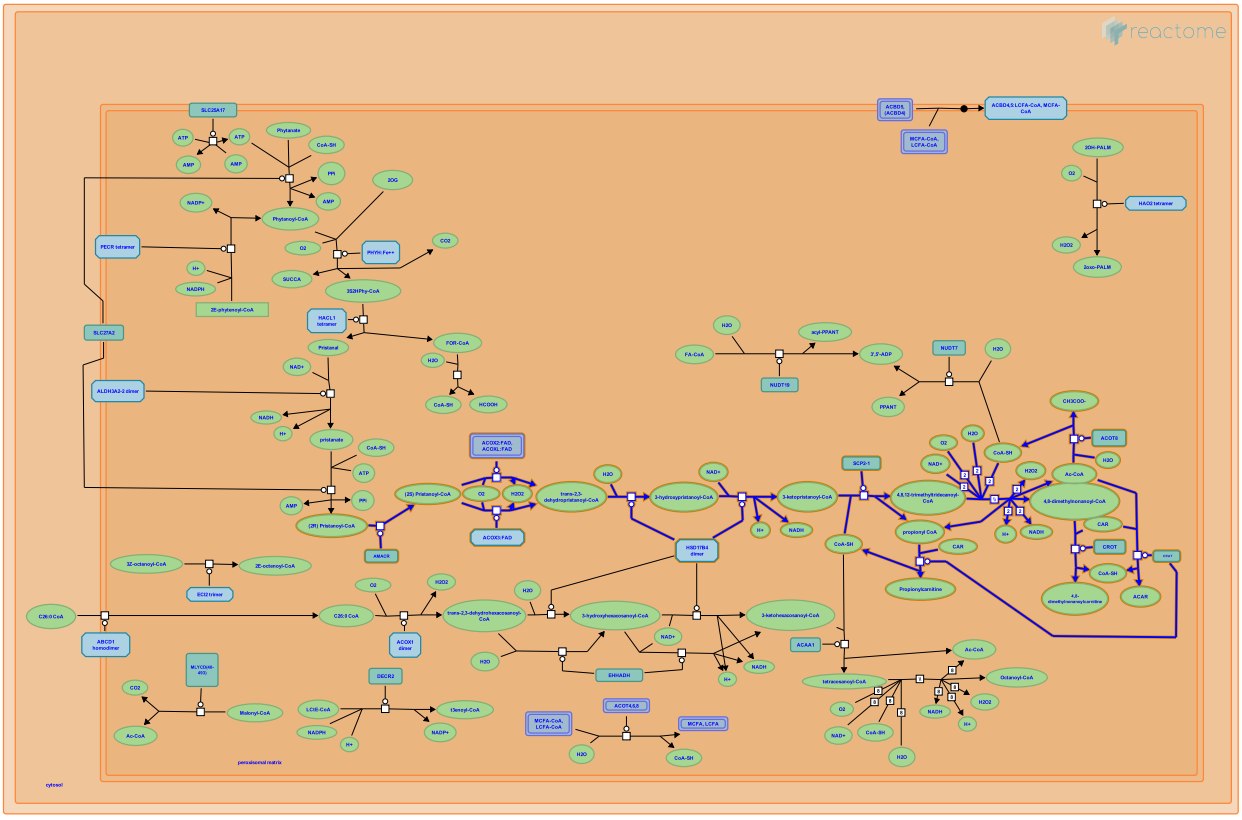
Beta-oxidation of pristanoyl-CoA



D'Eustachio, P., Jassal, B.

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

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19/04/2021

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

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. ↗

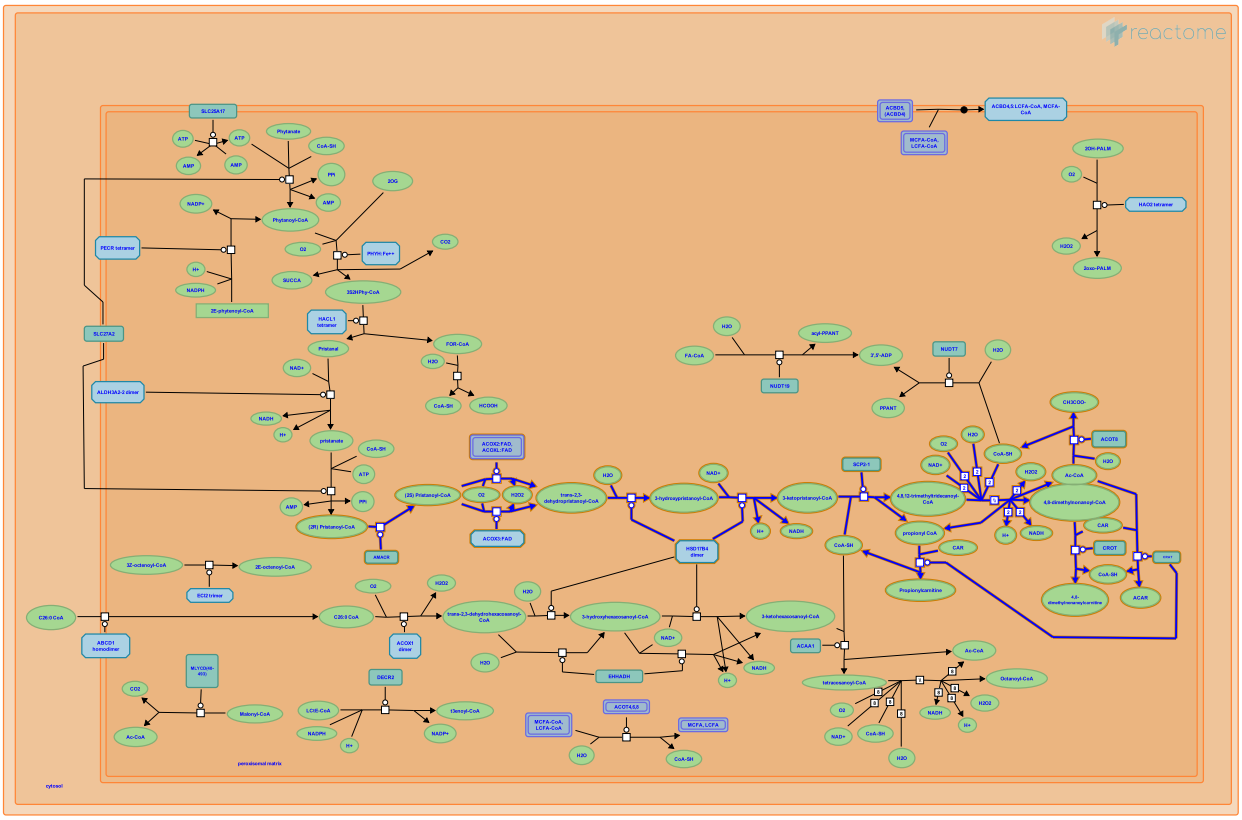
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Beta-oxidation of pristanoyl-CoA ↗

Stable identifier: R-HSA-389887

Compartments: peroxisomal matrix



Pristanoyl-CoA, generated in the peroxisome by alpha-oxidation of dietary phytanic acid, is further catabolized by three cycles of peroxisomal beta-oxidation to yield 4,8-dimethylnonanoyl-CoA, acetyl-CoA and two molecules of propionyl-CoA. These molecules in turn are converted to carnitine conjugates, which can be transported to mitochondria (Wanders and Waterham 2006, Verhoeven et al. 1998, Ferdinandusse et al. 1999).

Literature references

Verhoeven, NM., Roe, DS., Kok, RM., Wanders, RJ., Jakobs, C., Roe, CR. (1998). Phytanic acid and pristanic acid are oxidized by sequential peroxisomal and mitochondrial reactions in cultured fibroblasts. *J Lipid Res, 39*, 66-74. ↗

Ferdinandusse, S., Mulders, J., IJlst, L., Denis, S., Dacremont, G., Waterham, HR. et al. (1999). Molecular cloning and expression of human carnitine octanoyltransferase: evidence for its role in the peroxisomal beta-oxidation of branched-chain fatty acids. *Biochem Biophys Res Commun, 263*, 213-8. ↗

Wanders, RJ., Waterham, HR. (2006). Biochemistry of mammalian peroxisomes revisited. *Annu Rev Biochem, 75*, 295-332. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

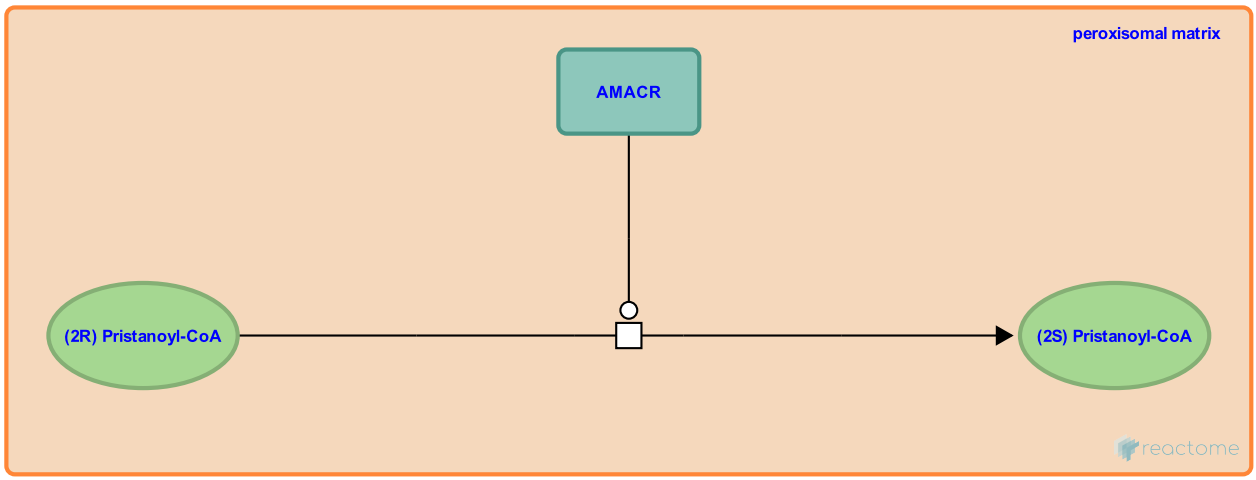
Isomerization of (2R)-pristanoyl-CoA to (2S)-pristanoyl-CoA ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-389897

Type: transition

Compartments: peroxisomal matrix



Peroxisomal 2-methylacyl-CoA racemase (AMACR) catalyzes the isomerization of (2R)-pristanoyl-CoA to form (2S)-pristanoyl-CoA. The active form of the enzyme is a monomer (Schmitz et al. 1995; Amery et al. 2000; Ferdinandusse et al. 2000).

Followed by: (2S)-pristanoyl-CoA + O2 => trans-2,3-dehydropristanoyl-CoA + H2O2 (ACOX3), ACOX2:FAD, ACOXL:FAD oxidise (2S)-pristanoyl-CoA to trans-2,3-dehydropristanoyl-CoA

Literature references

Schmitz, W., Albers, C., Fingerhut, R., Conzelmann, E. (1995). Purification and characterization of an alpha-methylacyl-CoA racemase from human liver. *Eur J Biochem, 231*, 815-22. ↗

Amery, L., Fransen, M., De Nys, K., Mannaerts, GP., Van Veldhoven, PP. (2000). Mitochondrial and peroxisomal targeting of 2-methylacyl-CoA racemase in humans. *J Lipid Res, 41*, 1752-9. ↗

Ferdinandusse, S., Denis, S., IJlst, L., Dacremont, G., Waterham, HR., Wanders, RJ. (2000). Subcellular localization and physiological role of alpha-methylacyl-CoA racemase. *J Lipid Res, 41*, 1890-6. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

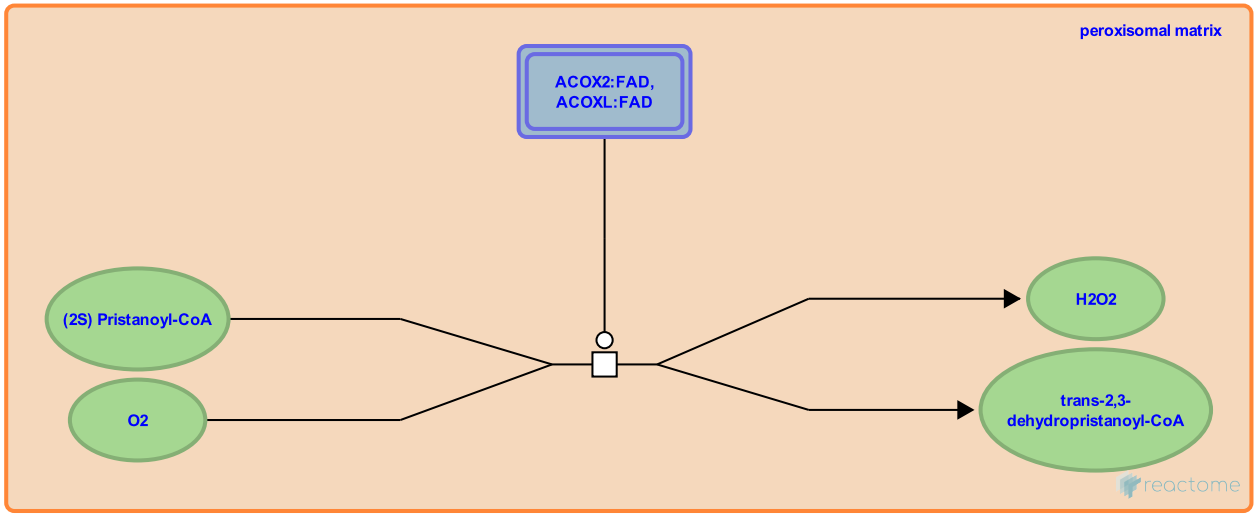
ACOX2:FAD, ACOXL:FAD oxidise (2S)-pristanoyl-CoA to trans-2,3-dehydro-pristanoyl-CoA ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-389889

Type: transition

Compartments: peroxisomal matrix



In human liver and kidney tissue, monomeric peroxisomal ACOX2 (bound to FAD cofactor) catalyzes the reaction of (2S)-pristanoyl-CoA and O2 to form trans-2,3-dehydropristanoyl-CoA and H2O2 (Vanhove et al. 1993; Baumgart et al. 1996). A putative acyl-coenzyme A oxidase-like protein ACOXL could catalyse this type of reaction but its activity has not yet been determined.

Preceded by: Isomerization of (2R)-pristanoyl-CoA to (2S)-pristanoyl-CoA

Followed by: trans-2,3-dehydropristanoyl-CoA + H2O => 3-hydroxypristanoyl-CoA

Literature references

Vanhove, GF., Van Veldhoven, PP., Fransen, M., Denis, S., Eyssen, HJ., Wanders, RJ. et al. (1993). The CoA esters of 2-methyl-branched chain fatty acids and of the bile acid intermediates di- and trihydroxycoprostanic acids are oxidized by one single peroxisomal branched chain acyl-CoA oxidase in human liver and kidney. *J Biol Chem, 268* , 10335-44. ↗

Baumgart, E., Vanhooren, JC., Fransen, M., Marynen, P., Puype, M., Vandekerckhove, J. et al. (1996). Molecular characterization of the human peroxisomal branched-chain acyl-CoA oxidase: cDNA cloning, chromosomal assignment, tissue distribution, and evidence for the absence of the protein in Zellweger syndrome. *Proc Natl Acad Sci U S A, 93*, 13748-53. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.
2015-12-09	Revised	Jassal, B.

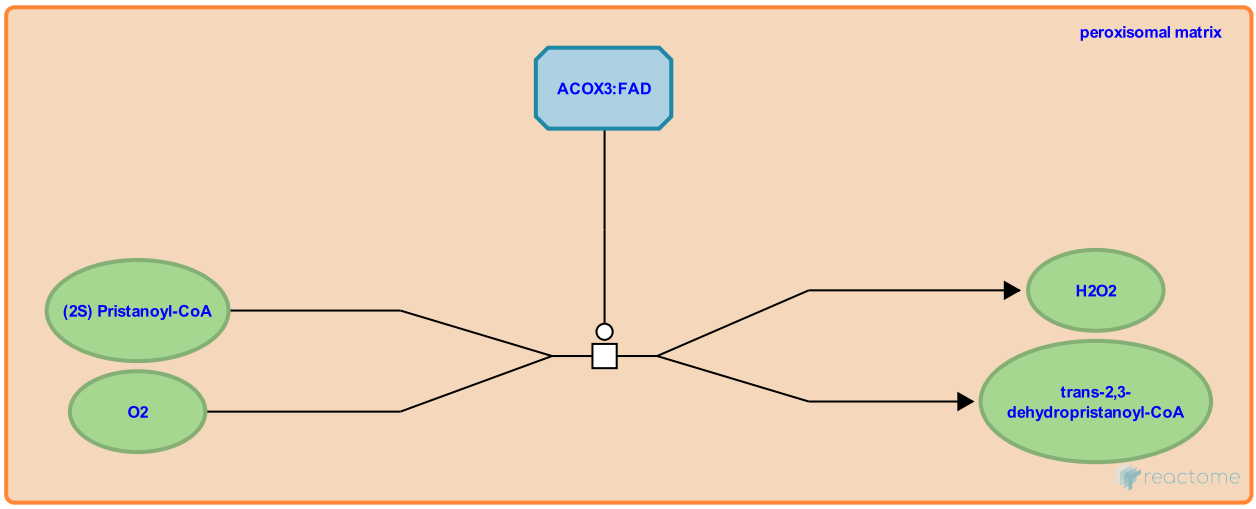
(2S)-pristanoyl-CoA + O2 => trans-2,3-dehydropristanoyl-CoA + H2O2 (ACOX3)

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-389891

Type: transition

Compartments: peroxisomal matrix



Peroxisomal ACOX3 catalyzes the reaction of (2S)-pristanoyl-CoA and O2 to form trans-2,3-dehydro-pristanoyl-CoA and H2O2. ACOX3 protein and enzyme activity have been observed in prostate tumors, but are undetectable in normal prostate tissue as well as in liver and kidney (where ACOX2 catalyzes the oxidation of pristanoyl-CoA) (Zha et al. 2005; Vanhooren et al. 1997). The physiological consequences of this differential gene expression are unknown.

Preceded by: Isomerization of (2R)-pristanoyl-CoA to (2S)-pristanoyl-CoA

Followed by: trans-2,3-dehydropristanoyl-CoA + H2O => 3-hydroxypristanoyl-CoA

Literature references

Zha, S., Ferdinandusse, S., Hicks, JL., Denis, S., Dunn, TA., Wanders, RJ. et al. (2005). Peroxisomal branched chain fatty acid beta-oxidation pathway is upregulated in prostate cancer. *Prostate, 63*, 316-23.

Vanhooren, JC., Marynen, P., Mannaerts, GP., Van Veldhoven, PP. (1997). Evidence for the existence of a pristanoyl-CoA oxidase gene in man. *Biochem J, 325*, 593-9.

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

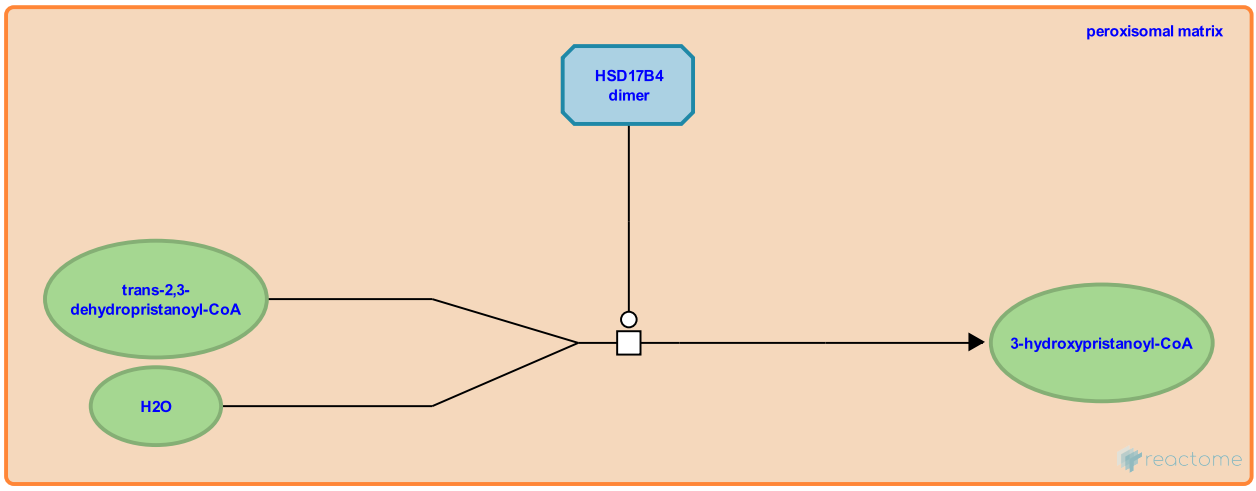
trans-2,3-dehydropristanoyl-CoA + H2O => 3-hydroxypristanoyl-CoA ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-389986

Type: transition

Compartments: peroxisomal matrix



Peroxisomal HSD17B4 dimer catalyzes the reaction of trans-2,3-dehydropristanoyl-CoA and H2O to form 3-hydroxypristanoyl-CoA. The enzyme is bifunctional - an aminoterminal domain catalyzes the dehydrogenation of a variety of 3-hydroxyacyl-CoA's and a carboxyterminal domain catalyzes the hydration of a variety of trans-2,3-dehydroacyl-CoA's, the reaction annotated here (Jiang et al. 1996, 1997). Defects in the enzyme are associated with a severe disorder of peroxisomal fatty acid metabolism in humans (Ferdinandusse et al. 2006).

Preceded by: ACOX2:FAD, ACOXL:FAD oxidise (2S)-pristanoyl-CoA to trans-2,3-dehydropristanoyl-CoA, (2S)-pristanoyl-CoA + O2 => trans-2,3-dehydropristanoyl-CoA + H2O2 (ACOX3)

Followed by: 3-hydroxypristanoyl-CoA + NAD+ => 3-ketoxypristanoyl-CoA + NADH + H+

Literature references

Ferdinandusse, S., Ylianttila, MS., Gloerich, J., Koski, MK., Oostheim, W., Waterham, HR. et al. (2006). Mutational spectrum of D-bifunctional protein deficiency and structure-based genotype-phenotype analysis. *Am J Hum Genet, 78*, 112-24. ↗

Jiang, LL., Kobayashi, A., Matsuura, H., Fukushima, H., Hashimoto, T. (1996). Purification and properties of human D-3-hydroxyacyl-CoA dehydratase: medium-chain enoyl-CoA hydratase is D-3-hydroxyacyl-CoA dehydratase. *J Biochem (Tokyo), 120*, 624-32. ↗

Jiang, LL., Miyazawa, S., Souri, M., Hashimoto, T. (1997). Structure of D-3-hydroxyacyl-CoA dehydratase/D-3-hydroxyacyl-CoA dehydrogenase bifunctional protein. *J Biochem, 121*, 364-9. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

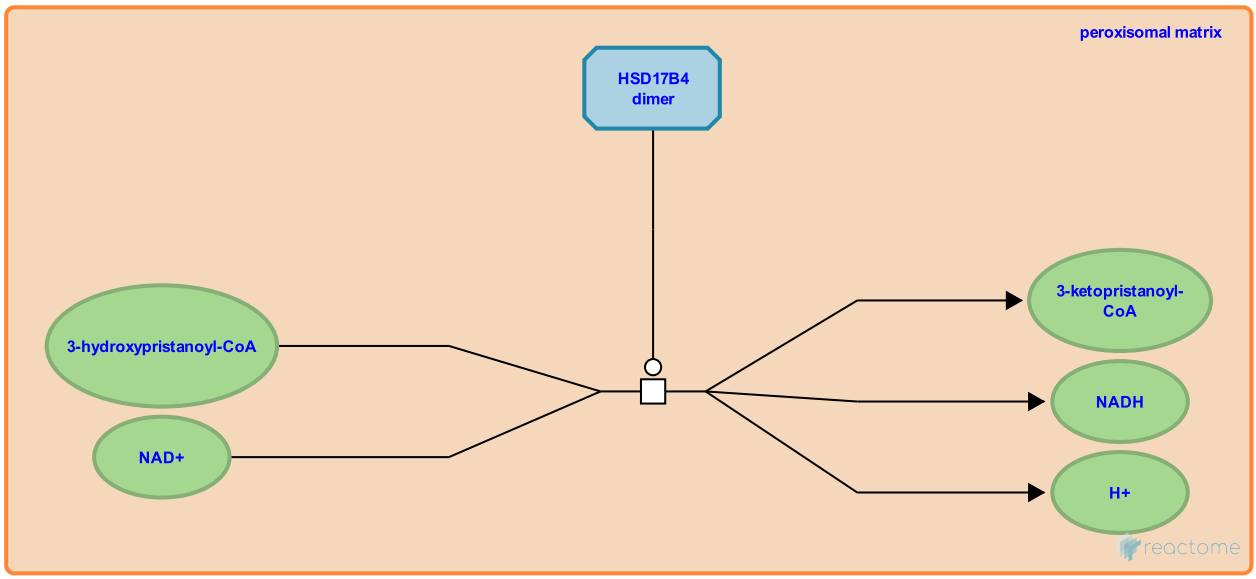
3-hydroxypristanoyl-CoA + NAD+ => 3-ketoxypristanoyl-CoA + NADH + H+ ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-389995

Type: transition

Compartments: peroxisomal matrix



Peroxisomal HSD17B4 dimer catalyzes the reaction of 3-hydroxypristanoyl-CoA and NAD+ to form 3-ketoxypristanoyl-CoA and NADH + H+. The enzyme is bifunctional - an aminoterminal domain catalyzes the dehydrogenation of a variety of 3-hydroxyacyl-CoA's, the reaction annotated here, and a carboxyterminal domain catalyzes the hydration of a variety of trans-2,3-dehydroacyl-CoA's (Jiang et al. 1996, 1997). Defects in the enzyme are associated with a severe disorder of peroxisomal fatty acid metabolism in humans (Ferdinandusse et al. 2006).

Preceded by: trans-2,3-dehydropristanoyl-CoA + H2O => 3-hydroxypristanoyl-CoA

Followed by: 3-ketopristanoyl-CoA + CoASH => 4,8,12-trimethyltridecanoyl-CoA + propionyl-CoA

Literature references

Ferdinandusse, S., Ylianttila, MS., Gloerich, J., Koski, MK., Oostheim, W., Waterham, HR. et al. (2006). Mutational spectrum of D-bifunctional protein deficiency and structure-based genotype-phenotype analysis. *Am J Hum Genet, 78*, 112-24. ↗

Jiang, LL., Kobayashi, A., Matsuura, H., Fukushima, H., Hashimoto, T. (1996). Purification and properties of human D-3-hydroxyacyl-CoA dehydratase: medium-chain enoyl-CoA hydratase is D-3-hydroxyacyl-CoA dehydratase. *J Biochem (Tokyo), 120*, 624-32. ↗

Jiang, LL., Miyazawa, S., Souri, M., Hashimoto, T. (1997). Structure of D-3-hydroxyacyl-CoA dehydratase/D-3-hydroxyacyl-CoA dehydrogenase bifunctional protein. *J Biochem, 121*, 364-9. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

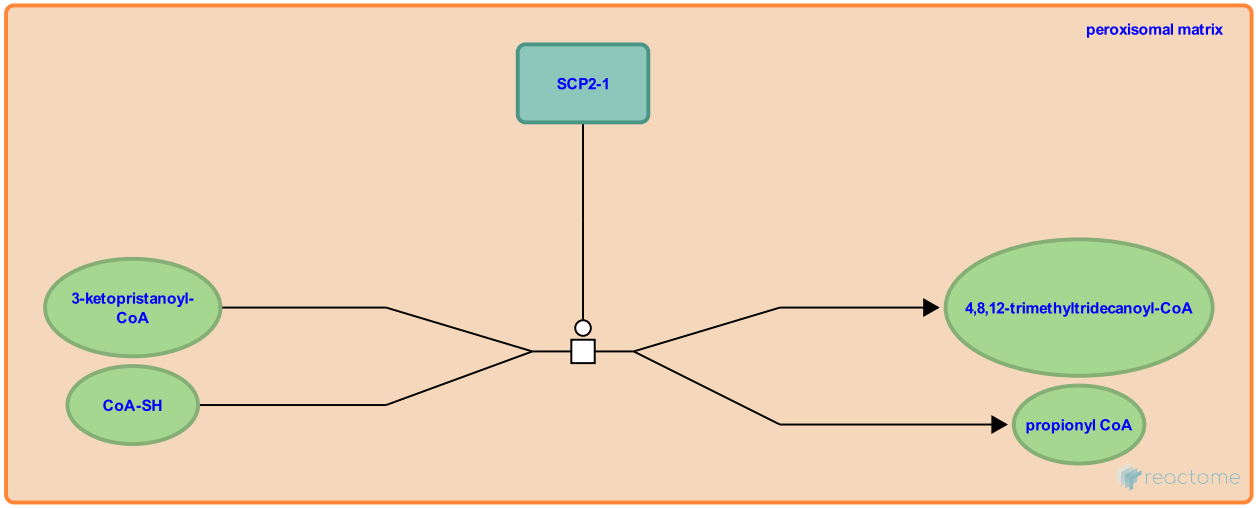
3-ketopristanoyl-CoA + CoASH => 4,8,12-trimethyltridecanoyl-CoA + propionyl-CoA

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-390224

Type: transition

Compartments: peroxisomal matrix



Peroxisomal SCPx (Non-specific lipid transfer protein; SCP2) catalyzes the reaction of 3-ketopristanoyl-CoA and CoASH to form 4,8,12-trimethyltridecanoyl-CoA and propionyl-CoA. Both intact SCPx and an SCPx fragment corresponding to approximately the 430 aminoterminal residues of the protein are catalytically active in vitro; the latter form may predominate in vivo. Consistent with the role of SCPx in the beta-oxidation of branched-chain fatty acids in vitro, mutations in the protein are associated with elevated levels of pristanic acid in the blood in vivo and the development of neurological defects (Ferdinandusse et al. 2000, 2006).

Preceded by: 3-hydroxypristanoyl-CoA + NAD+ => 3-ketoxypristanoyl-CoA + NADH + H+

Followed by: propionyl-CoA + carnitine => propionylcarnitine + CoASH, 4,8,12-trimethyltridecanoyl-CoA + 2 O2 + 2 H2O + 2 NAD+ + 2 CoASH => 4,8-dimethylnonanoyl-CoA + 2 H2O2 + 2 NADH + 2 H+ + acetyl-CoA + propionyl-CoA

Literature references

Ferdinandusse, S., Denis, S., van Berkel, E., Dacremont, G., Wanders, RJ. (2000). Peroxisomal fatty acid oxidation disorders and 58 kDa sterol carrier protein X (SCPx). Activity measurements in liver and fibroblasts using a newly developed method. *J Lipid Res, 41*, 336-42.

Ferdinandusse, S., Kostopoulos, P., Denis, S., Rusch, H., Overmars, H., Dillmann, U. et al. (2006). Mutations in the gene encoding peroxisomal sterol carrier protein X (SCPx) cause leukencephalopathy with dystonia and motor neuropathy. *Am J Hum Genet, 78*, 1046-52.

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

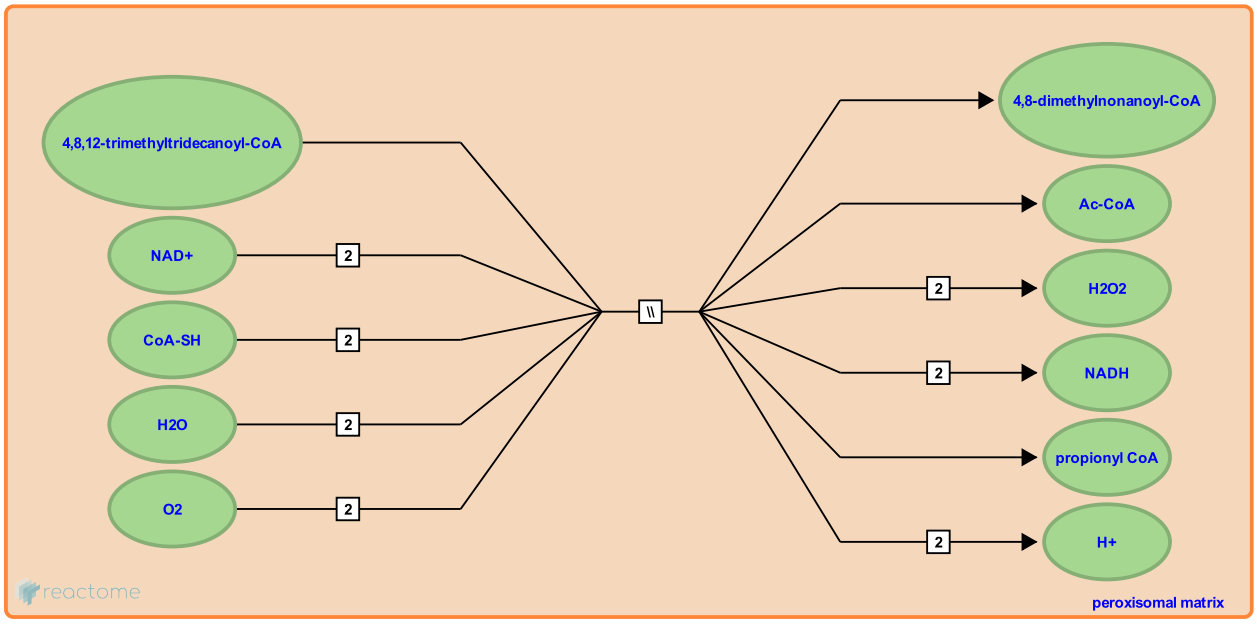
4,8,12-trimethyltridecanoyl-CoA + 2 O2 + 2 H2O + 2 NAD+ + 2 CoASH => 4,8-dimethylnonanoyl-CoA + 2 H2O2 + 2 NADH + 2 H+ + acetyl-CoA + propionyl-CoA ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-390276

Type: omitted

Compartments: peroxisomal matrix



In two cycles of beta-oxidation mediated by the same enzyme activities responsible for the conversion of pristanoyl-CoA to 4,8,12-trimethyltridecanoyl-CoA, the latter molecule is converted to 4,8-dimethylnonanoyl-CoA. Two molecules each of O2, H2O, NAD+, and CoASH are consumed in the process and two molecules of H2O2 and NADH + H+ are generated, together with single molecules of acetyl-CoA and propionyl-CoA (Verhoeven et al. 1998).

Preceded by: 3-ketopristanoyl-CoA + CoASH => 4,8,12-trimethyltridecanoyl-CoA + propionyl-CoA

Followed by: 4,8-dimethylnonanoyl-CoA + carnitine => 4,8-dimethylnonanoylcarnitine + CoASH, propionyl-CoA + carnitine => propionylcarnitine + CoASH, acetyl-CoA + carnitine => acetylcarnitine + CoASH, acetyl-CoA + H2O => acetate + CoASH

Literature references

Verhoeven, NM., Roe, DS., Kok, RM., Wanders, RJ., Jakobs, C., Roe, CR. (1998). Phytanic acid and pristanic acid are oxidized by sequential peroxisomal and mitochondrial reactions in cultured fibroblasts. *J Lipid Res, 39*, 66-74. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.

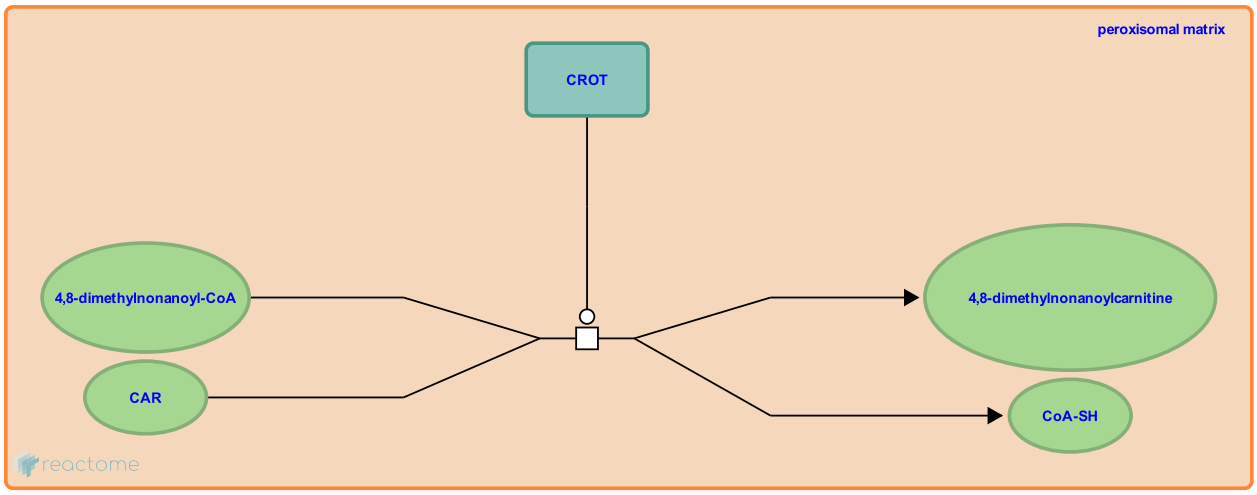
4,8-dimethylnonanoyl-CoA + carnitine => 4,8-dimethylnonanoylcarnitine + CoASH ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-390281

Type: transition

Compartments: peroxisomal matrix



Peroxisomal CROT catalyzes the reaction of 4,8-dimethylnonanoyl-CoA and carnitine to form 4,8-dimethylnonanoylcarnitine and CoASH (Ferdinandusse et al. 1999).

Preceded by: 4,8,12-trimethyltridecanoyl-CoA + 2 O2 + 2 H2O + 2 NAD+ + 2 CoASH => 4,8-dimethylnonanoyl-CoA + 2 H2O2 + 2 NADH + 2 H+ + acetyl-CoA + propionyl-CoA

Literature references

Ferdinandusse, S., Mulders, J., IJlst, L., Denis, S., Dacremont, G., Waterham, HR. et al. (1999). Molecular cloning and expression of human carnitine octanoyltransferase: evidence for its role in the peroxisomal beta-oxidation of branched-chain fatty acids. *Biochem Biophys Res Commun, 263*, 213-8. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

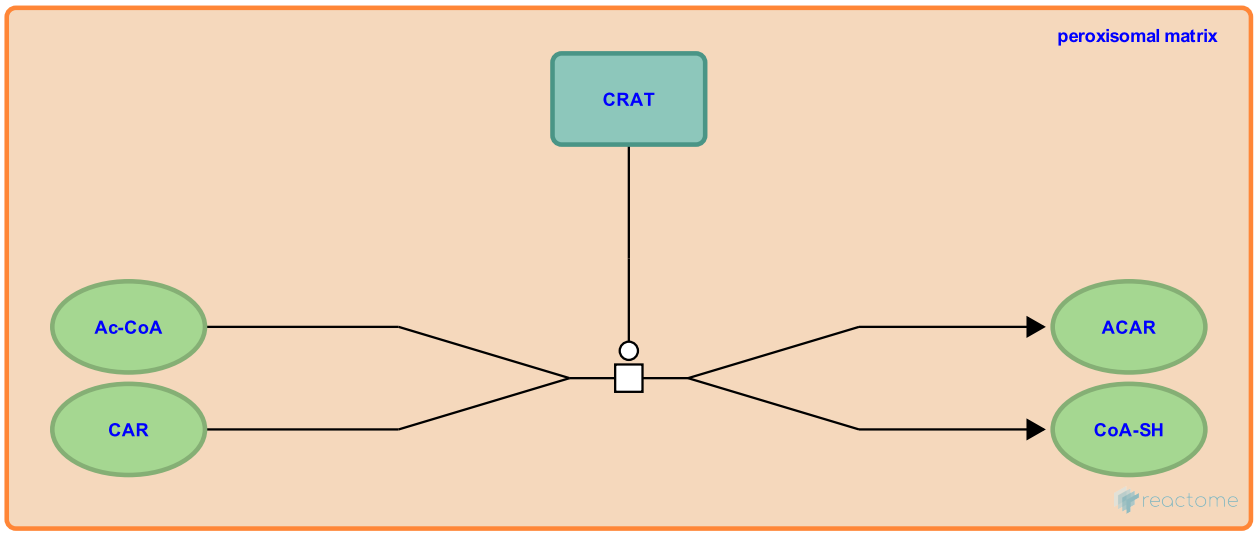
acetyl-CoA + carnitine => acetylcarnitine + CoASH ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-390291

Type: transition

Compartments: peroxisomal matrix



Peroxisomal carnitineacetyltransferase (CRAT) catalyzes the reaction of acetyl-CoA and carnitine to form acetylcarnitine and CoASH. The active form of the enzyme is a monomer (Bloisi et al. 1990; Wu et al. 2003).

Preceded by: 4,8,12-trimethyltridecanoyl-CoA + 2 O2 + 2 H2O + 2 NAD+ + 2 CoASH => 4,8-dimethylnonanoyl-CoA + 2 H2O2 + 2 NADH + 2 H+ + acetyl-CoA + propionyl-CoA

Literature references

Bloisi, W., Colombo, I., Garavaglia, B., Giardini, R., Finocchiaro, G., DiDonato, S. (1990). Purification and properties of carnitine acetyltransferase from human liver. *Eur J Biochem, 189*, 539-46. ↗

Wu, D., Govindasamy, L., Lian, W., Gu, Y., Kukar, T., Agbandje-McKenna, M. et al. (2003). Structure of human carnitine acetyltransferase. Molecular basis for fatty acyl transfer. *J Biol Chem, 278*, 13159-65. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

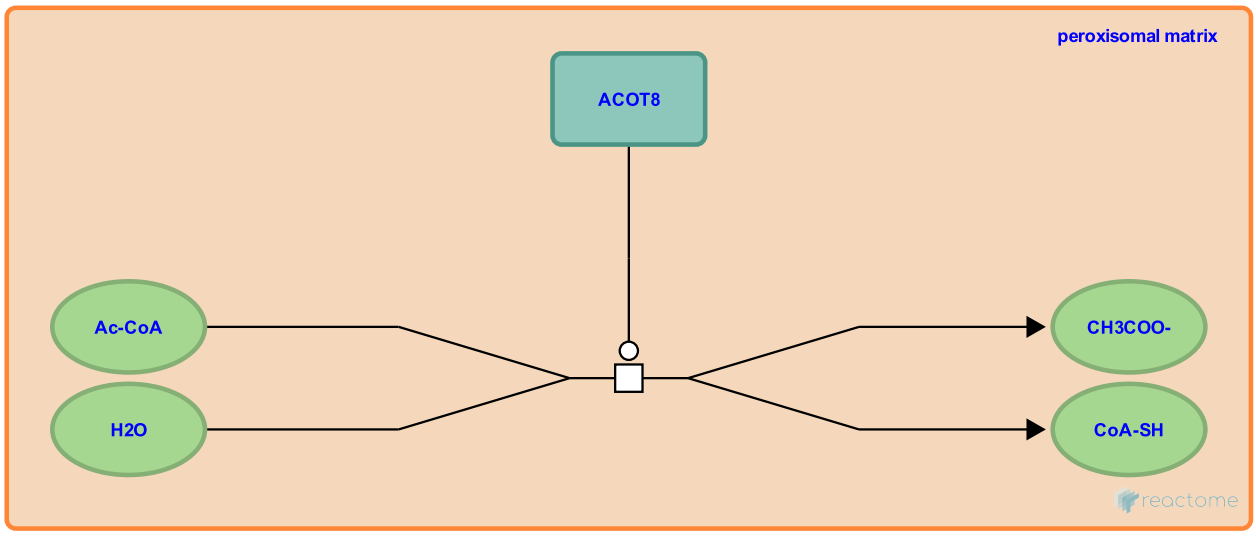
acetyl-CoA + H2O => acetate + CoASH ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-390304

Type: transition

Compartments: peroxisomal matrix



Peroxisomal ACOT8 catalyzes the hydrolysis of acetyl-CoA to form acetate and CoASH (Jones et al. 1999; Wanders and Waterham 2006).

Preceded by: 4,8,12-trimethyltridecanoyl-CoA + 2 O2 + 2 H2O + 2 NAD+ + 2 CoASH => 4,8-dimethylnonanoyl-CoA + 2 H2O2 + 2 NADH + 2 H+ + acetyl-CoA + propionyl-CoA

Literature references

Jones, JM., Nau, K., Geraghty, MT., Erdmann, R., Gould, SJ. (1999). Identification of peroxisomal acyl-CoA thioesterases in yeast and humans. *J Biol Chem, 274*, 9216-23. ↗

Wanders, RJ., Waterham, HR. (2006). Biochemistry of mammalian peroxisomes revisited. *Annu Rev Biochem, 75*, 295-332. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

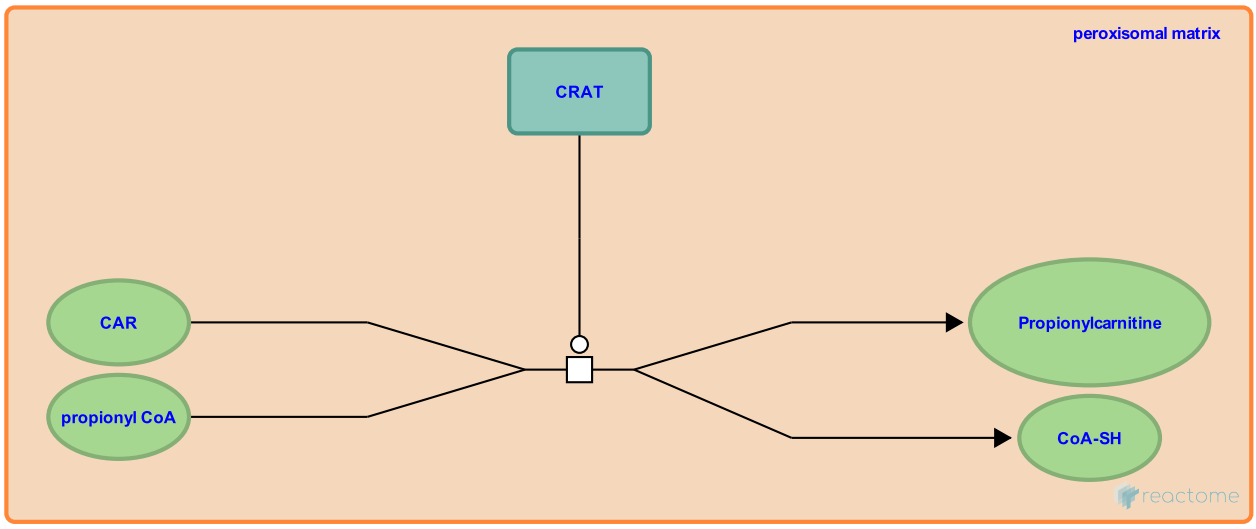
propionyl-CoA + carnitine => propionylcarnitine + CoASH ↗

Location: Beta-oxidation of pristanoyl-CoA

Stable identifier: R-HSA-390284

Type: transition

Compartments: peroxisomal matrix



Peroxisomal carnitineacetyltransferase (CRAT) catalyzes the reaction of propionyl-CoA and carnitine to form propionylcarnitine and CoASH. The active form of the enzyme is a monomer (Bloisi et al. 1990; Wu et al. 2003).

Preceded by: 3-ketopristanoyl-CoA + CoASH => 4,8,12-trimethyltridecanoyl-CoA + propionyl-CoA, 4,8,12-trimethyltridecanoyl-CoA + 2 O2 + 2 H2O + 2 NAD+ + 2 CoASH => 4,8-dimethylnonanoyl-CoA + 2 H2O2 + 2 NADH + 2 H+ + acetyl-CoA + propionyl-CoA

Literature references

Bloisi, W., Colombo, I., Garavaglia, B., Giardini, R., Finocchiaro, G., DiDonato, S. (1990). Purification and properties of carnitine acetyltransferase from human liver. *Eur J Biochem, 189*, 539-46. ↗

Wu, D., Govindasamy, L., Lian, W., Gu, Y., Kukar, T., Agbandje-McKenna, M. et al. (2003). Structure of human carnitine acetyltransferase. Molecular basis for fatty acyl transfer. *J Biol Chem, 278*, 13159-65. ↗

Editions

2009-02-27	Reviewed	Jassal, B.
2009-03-16	Authored	D'Eustachio, P.
2009-03-18	Edited	D'Eustachio, P.

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