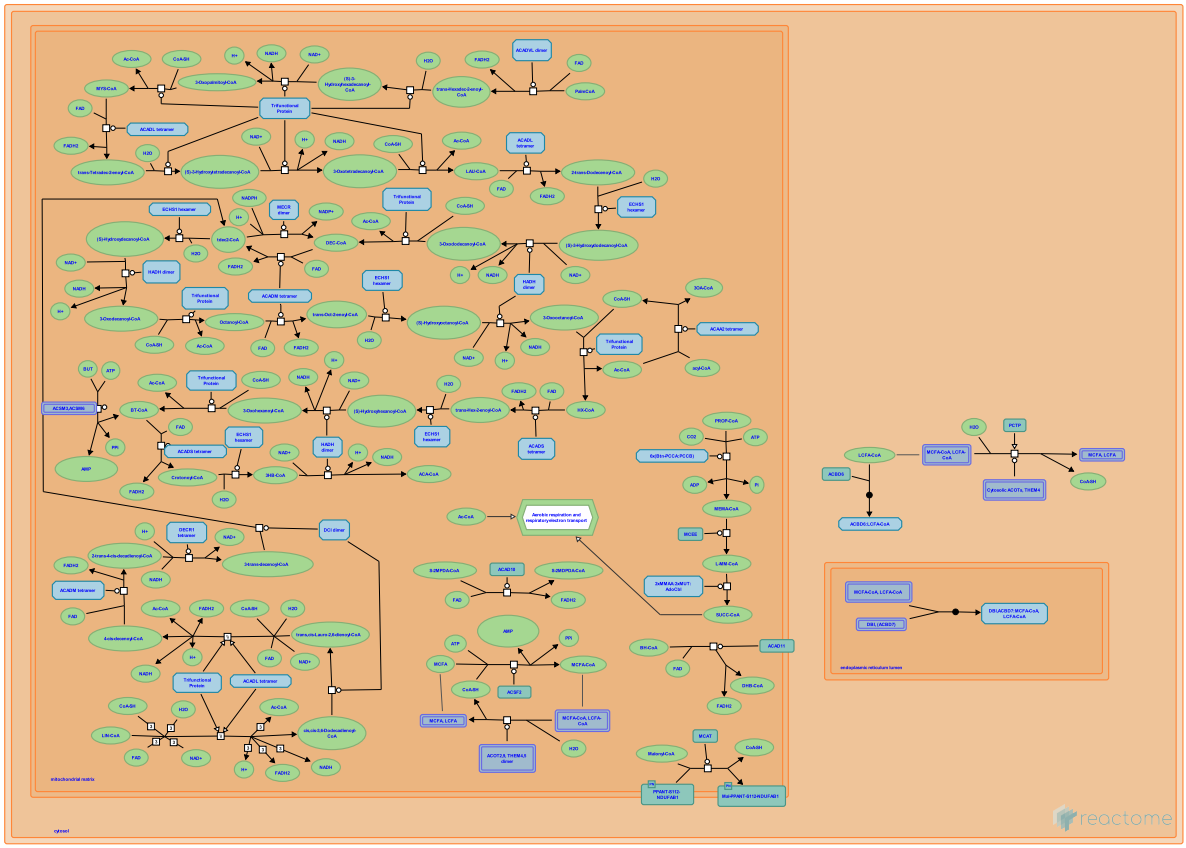
Mitochondrial Fatty Acid Beta-Oxidation



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27/04/2024

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. ↗

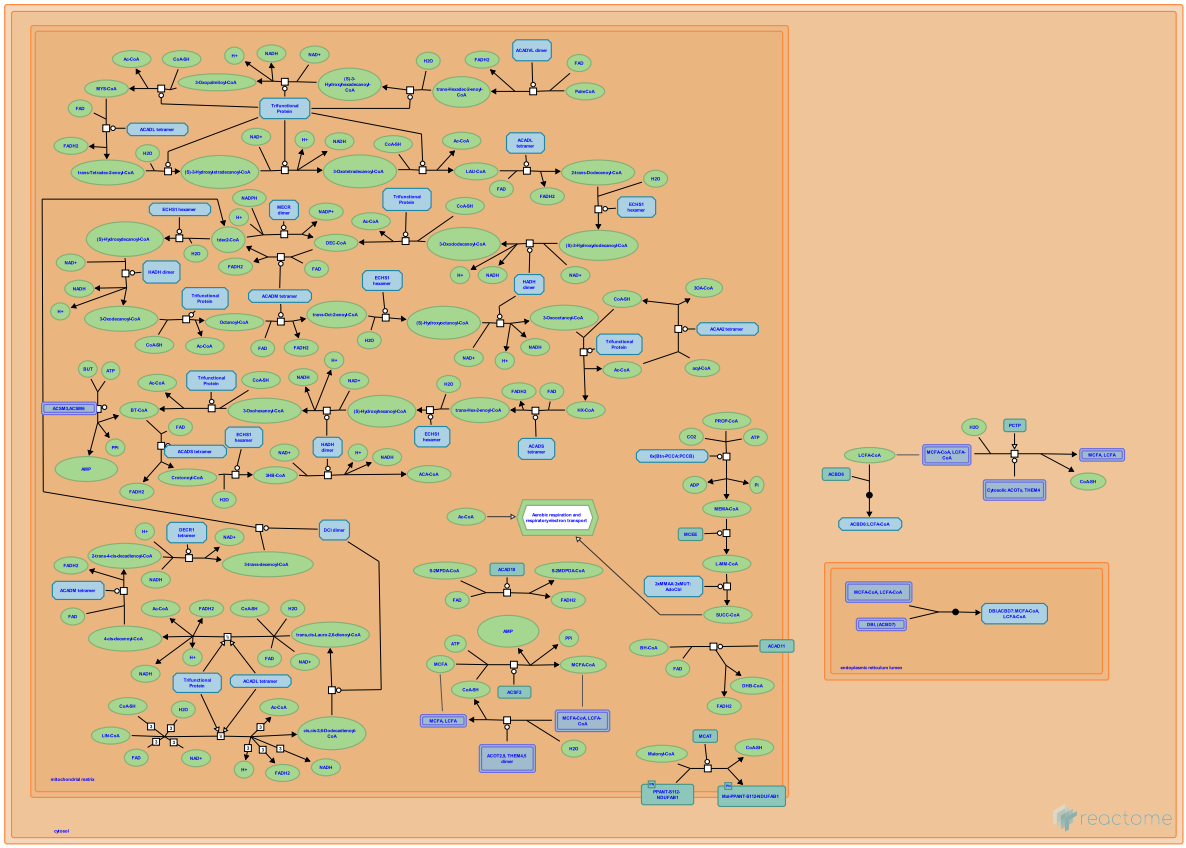
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Mitochondrial Fatty Acid Beta-Oxidation ↗

Stable identifier: R-HSA-77289

Compartments: mitochondrial matrix



Beta-oxidation begins once fatty acids have been imported into the mitochondrial matrix by carnitine acyltransferases. The beta-oxidation spiral of fatty acids metabolism involves the repetitive removal of two carbon units from the fatty acyl chain. There are four steps to this process: oxidation, hydration, a second oxidation, and finally thiolysis. The last step releases the two-carbon acetyl-CoA and a ready primed acyl-CoA that takes another turn down the spiral. In total each turn of the beta-oxidation spiral produces one NADH, one FADH2, and one acetyl-CoA.

Further oxidation of acetyl-CoA via the tricarboxylic acid cycle generates additional FADH2 and NADH. All reduced cofactors are used by the mitochondrial electron transport chain to form ATP. The complete oxidation of a fatty acid molecule produces numerous ATP molecules. Palmitate, used as the model here, produces 129 ATPs.

Beta-oxidation pathways differ for saturated and unsaturated fatty acids. The beta-oxidation of saturated fatty acids requires four different enzymatic steps. Beta-oxidation produces and consumes intermediates with a trans configuration; unsaturated fatty acids that have bonds in the cis configuration require three separate enzymatic steps to prepare these molecules for the beta-oxidation pathway.

Literature references

Coates, PM., Tanaka, K. (1992). Molecular basis of mitochondrial fatty acid oxidation defects. *J Lipid Res, 33*, 1099-110 . ↗

Rinaldo, P., Bennett, MJ., Matern, D. (2002). Fatty acid oxidation disorders. *Annu Rev Physiol, 64*, 477-502. ↗

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Mitochondrial fatty acid oxidation disorders, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 2297-2326.

Roe, CR., Roe, DS. (2000). Recent developments in the investigation of inherited metabolic disorders using cultured human cells. *Mol Genet Metab, 68*, 243-57. ↗

Hale, DE., Stanley, CA. (1994). Genetic disorders of mitochondrial fatty acid oxidation. *Curr Opin Pediatr, 6*, 476-81. ↗

Editions

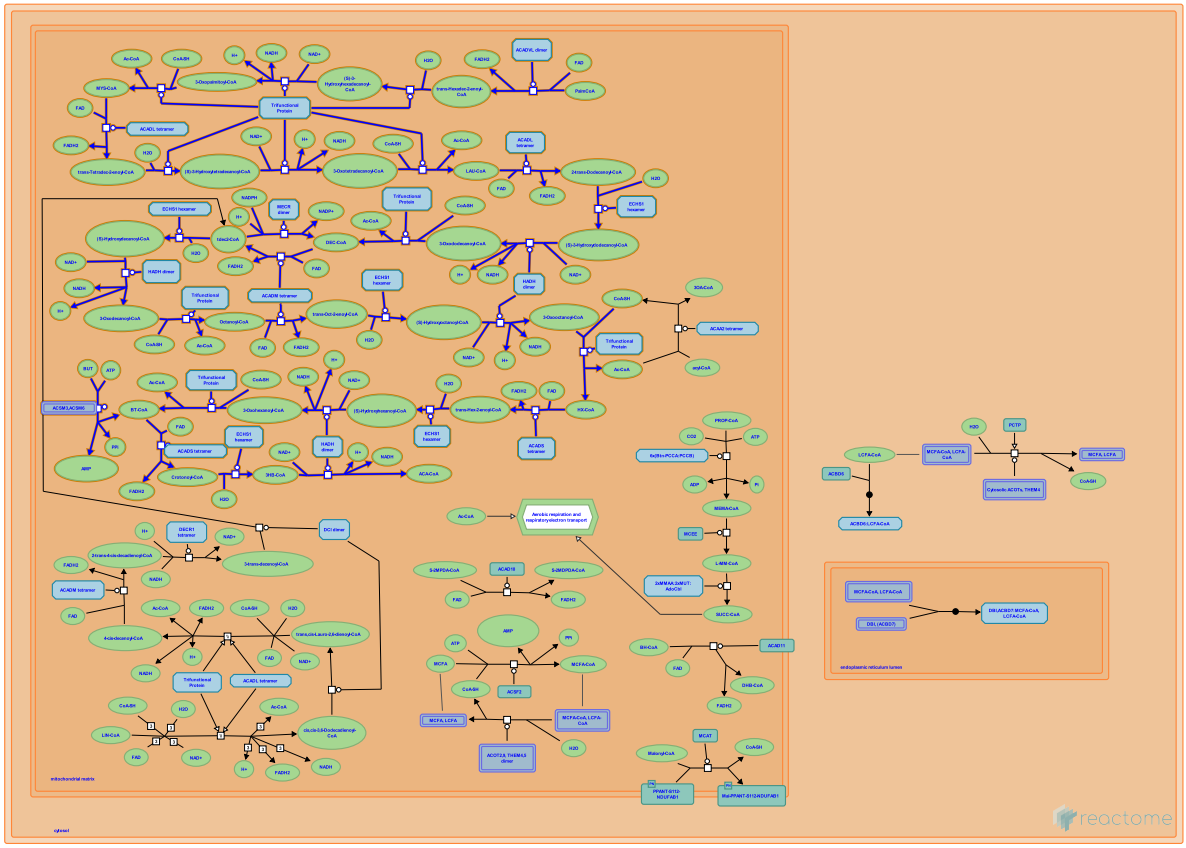
2003-09-19	Authored	Gillespie, ME.
2024-03-06	Edited	Gillespie, ME.

mitochondrial fatty acid beta-oxidation of saturated fatty acids ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-77286

Compartments: mitochondrial matrix



Once fatty acids have been imported into the mitochondrial matrix by the carnitine acyltransferases, the beta-oxidation spiral begins. Each turn of this spiral concludes with the repetitive removal of two carbon units from the fatty acyl chain. beta-oxidation of saturated fatty acids (fatty acids with even numbered carbon chains and no double bonds) involves four different enzymatic steps: oxidation, hydration, a second oxidation, and a concluding thiolysis step, resulting in the two-carbon acetyl-CoA and a newly CoA primed acyl-CoA for the next turn of the spiral.

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Mitochondrial fatty acid oxidation disorders, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 2297-2326.

Editions

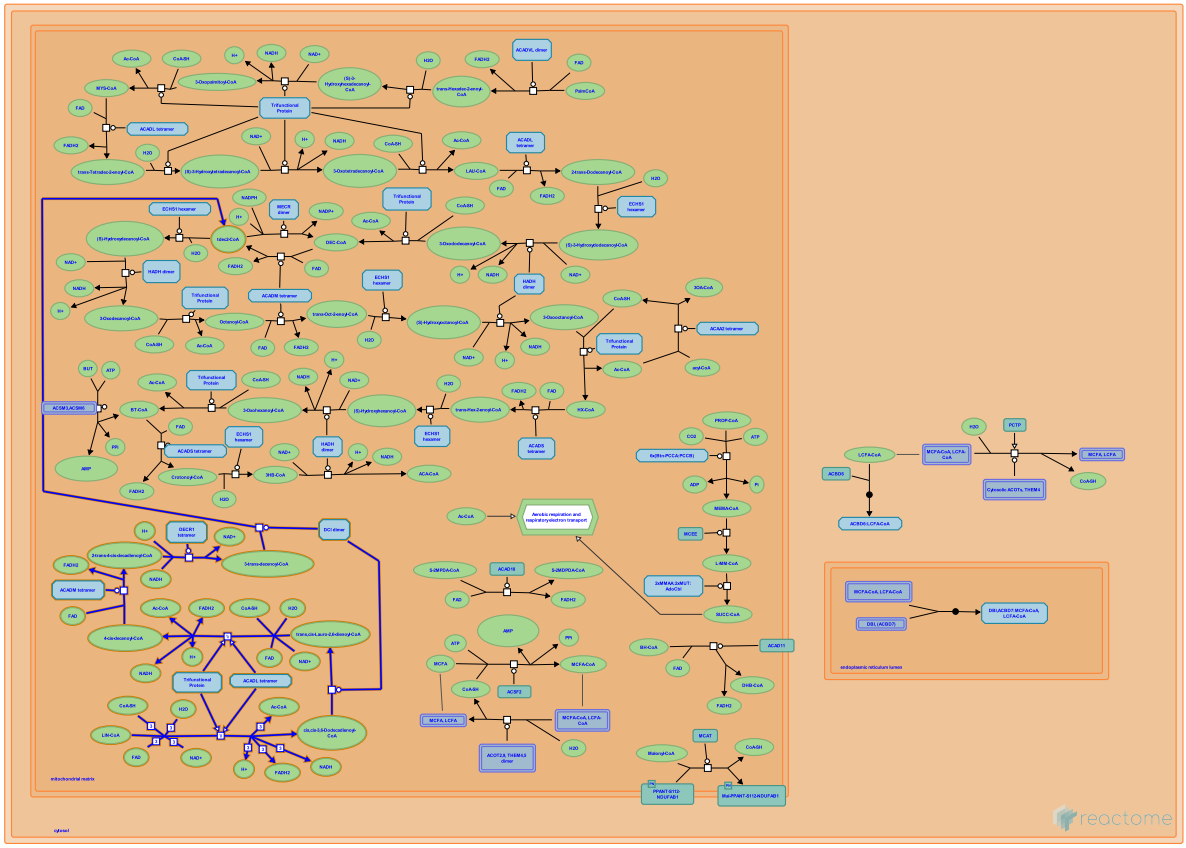
2003-09-19	Authored	Gillespie, ME.
2024-03-06	Edited	Gillespie, ME.

mitochondrial fatty acid beta-oxidation of unsaturated fatty acids ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-77288

Compartments: mitochondrial matrix



The complete beta-oxidation spiral produces and consumes intermediates with a trans configuration. Mitochondrial beta-oxidation of unsaturated fatty acids leads to intermediates not compatible with the four enzymatic steps responsible for the beta-oxidation of saturated fatty acids. Unsaturated fatty acids that have bonds in the cis configuration require three separate enzymatic steps to prepare these molecules for the beta-oxidation pathway. The further processing of these intermediates requires additional enzymes, depending on the position of the double bonds in the original fatty acids. Described here is the beta-oxidation of linoleoyl-CoA.

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Mitochondrial fatty acid oxidation disorders, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 2297-2326.

Editions

2003-10-25	Authored	Gillespie, ME.
2024-03-06	Edited	Gillespie, ME.

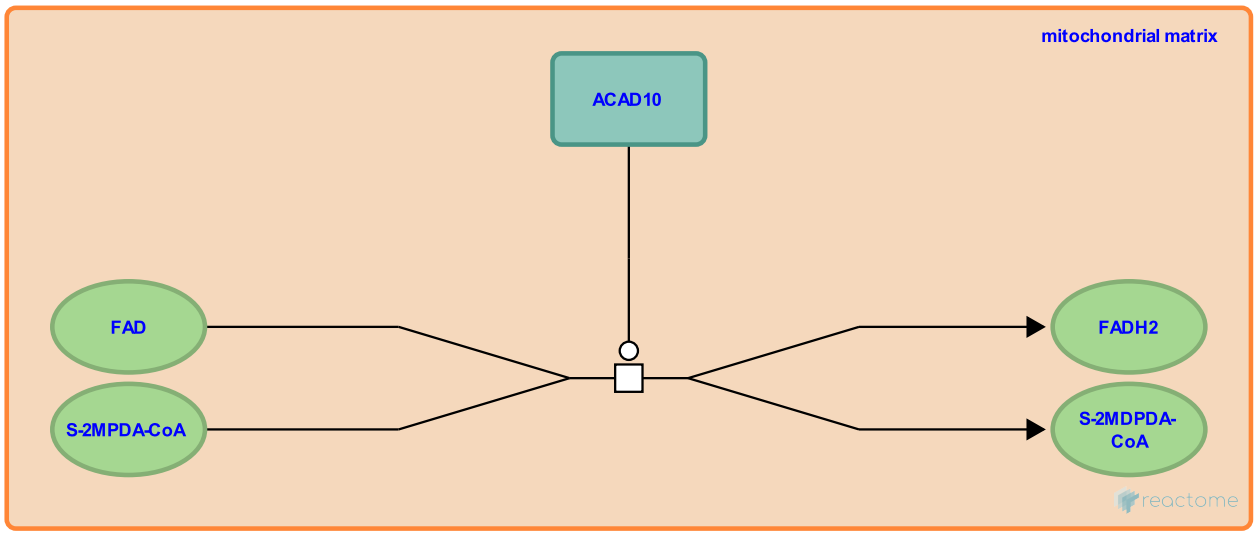
ACAD10 dehydrogenates S-2MPDA-CoA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-5695980

Type: transition

Compartments: mitochondrial matrix



Acyl-CoA dehydrogenase family member 10 (ACAD10) is a mitochondrial enzyme that can catalyse the alpha, beta-dehydrogenation of acyl-CoA esters. ACAD10 shows highest expression in foetal brain and is shown to be active only on S-2-methylpentadecenoyl-CoA (S-2MPDA-CoA), a C15 acyl-CoA. The S isomer is dehydrogenated to its respective 2,3-dehydroacyl-CoA product, S-2methyl-2,3-dehydropentadecenoyl-CoA (S-2MDPDA) (He et al. 2011).

Literature references

Murdoch, G., Mohsen, AW., Watkins, P., Ensenauer, R., He, M., Van Veldhoven, PP. et al. (2011). Identification and characterization of new long chain acyl-CoA dehydrogenases. *Mol. Genet. Metab., 102*, 418-29. ↗

Editions

2015-05-26	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

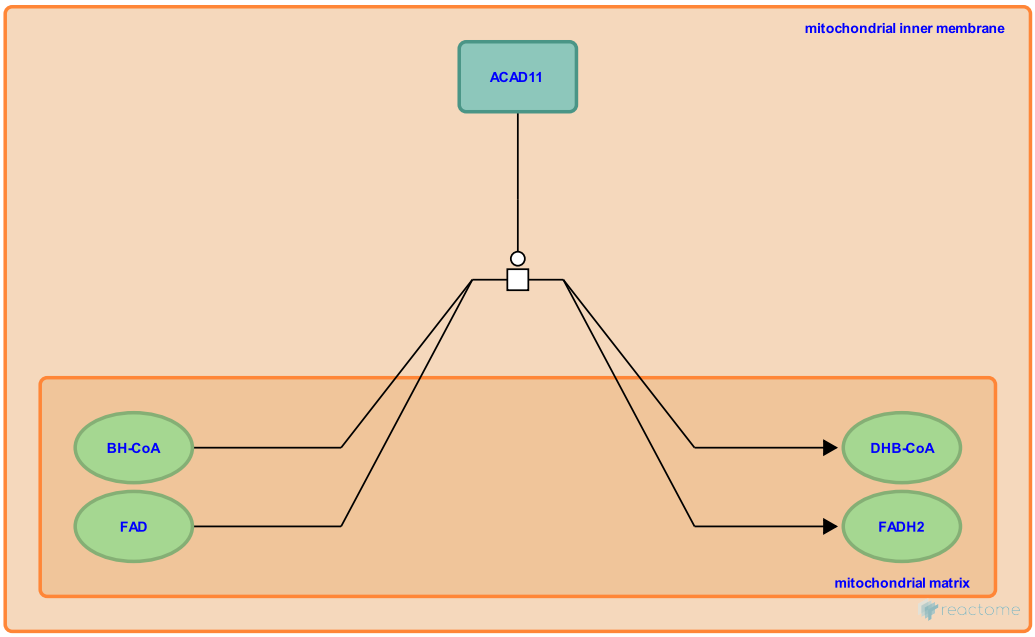
ACAD11 dehydrogenates BH-CoA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-5695989

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



Acyl-CoA dehydrogenase family member 11 (ACAD11) is a mitochondrial membrane-bound enzyme that can catalyse the alpha, beta-dehydrogenation of acyl-CoA esters. ACAD11 shows highest expression in the brain and is shown to dehydrogenate the C22 acyl-CoA behenoyl-CoA (BH-CoA) to 2,3-dehydrobehenoyl-CoA (DBH-CoA) (He et al. 2011).

Literature references

Murdoch, G., Mohsen, AW., Watkins, P., Ensenauer, R., He, M., Van Veldhoven, PP. et al. (2011). Identification and characterization of new long chain acyl-CoA dehydrogenases. *Mol. Genet. Metab., 102*, 418-29. ↗

Editions

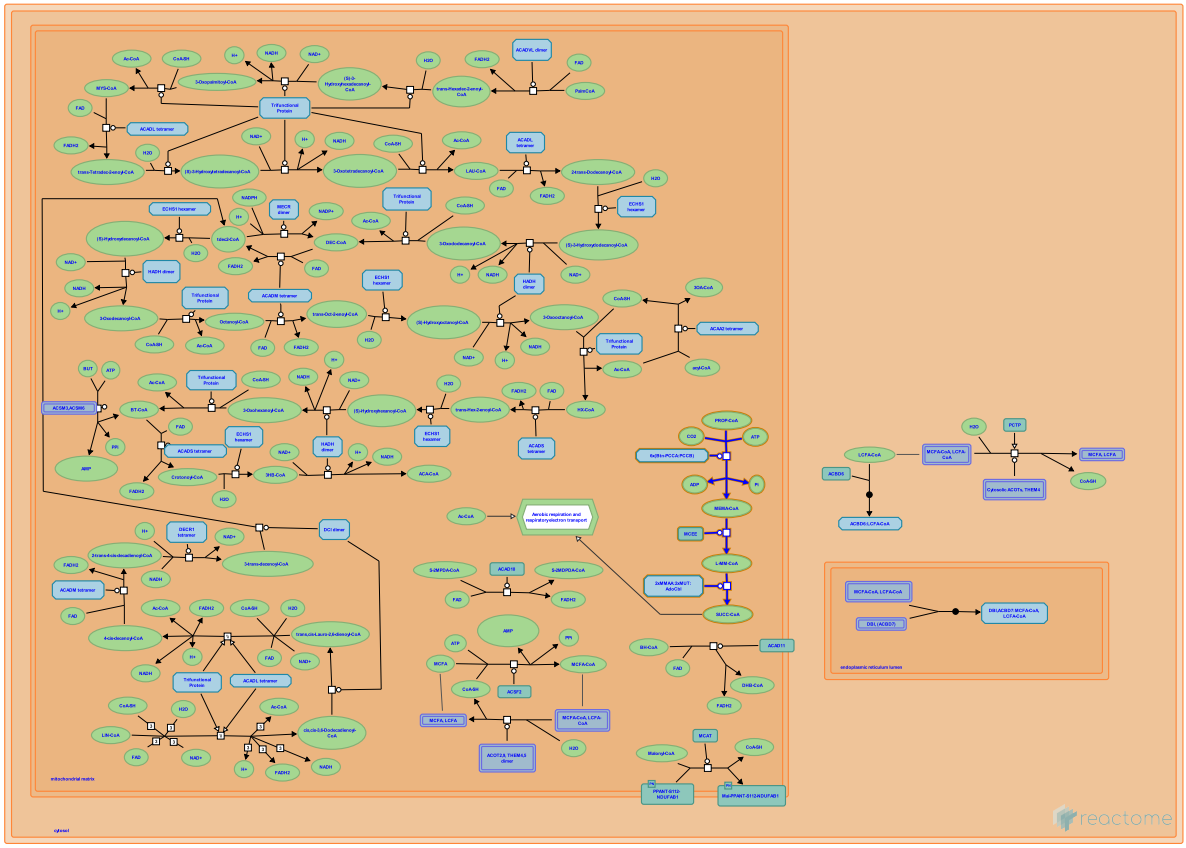
2015-05-26	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

Propionyl-CoA catabolism ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-71032

Compartments: mitochondrial matrix



Propionyl-CoA is a product of the catabolism of the amino acids, leucine, methionine, and threonine, and of the beta-oxidation of fatty acids with odd numbers of carbon atoms. The three reactions of this pathway convert propionyl-CoA to succinyl-CoA, an intermediate of the citric acid cycle. Through these reactions, carbon atoms from these sources can be fully oxidized to produce energy, or can be directed to gluconeogenesis. The three reactions of propionyl-CoA catabolism take place in the mitochondrial matrix.

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Disorders of propionate and methylmalonate metabolism, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 2165-2193.

Editions

2024-03-06	Edited	D'Eustachio, P.

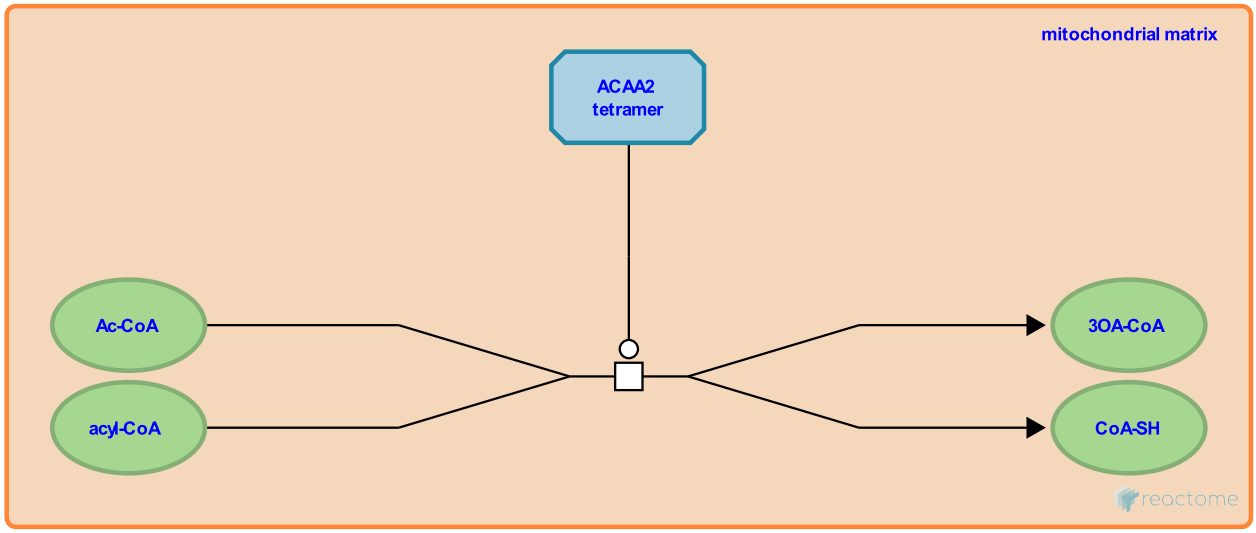
ACAA2 tetramer transfers acyl group from Ac-CoA to acyl-CoA forming 3OA-CoA and CoA-SH ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-8874745

Type: transition

Compartments: mitochondrial matrix



Mitochondrial 3-ketoacyl-CoA thiolase (ACAA2) is a mitochondrial matrix enzyme involved in fatty acid beta-oxidation, transferring the acyl group from acyl-CoA (acyl-CoA) to acetyl-CoA (Ac-CoA) to form 3-oxyoacyl-CoA (3OA-CoA) and CoA-SH (Abe et al. 1993, Middleton 1973).

Literature references

Abe, H., Suzuki, Y., Takayanagi, M., Sakuraba, H., Ohtake, A., Takiguchi, M. et al. (1993). Cloning and sequence analysis of a full length cDNA encoding human mitochondrial 3-oxoacyl-CoA thiolase. *Biochim. Biophys. Acta, 1216*, 304-6. ↗

Middleton, B. (1973). The oxoacyl-coenzyme A thiolases of animal tissues. *Biochem. J., 132*, 717-30. ↗

Editions

2016-05-27	Authored, Edited	Jassal, B.
2016-07-15	Reviewed	D'Eustachio, P.

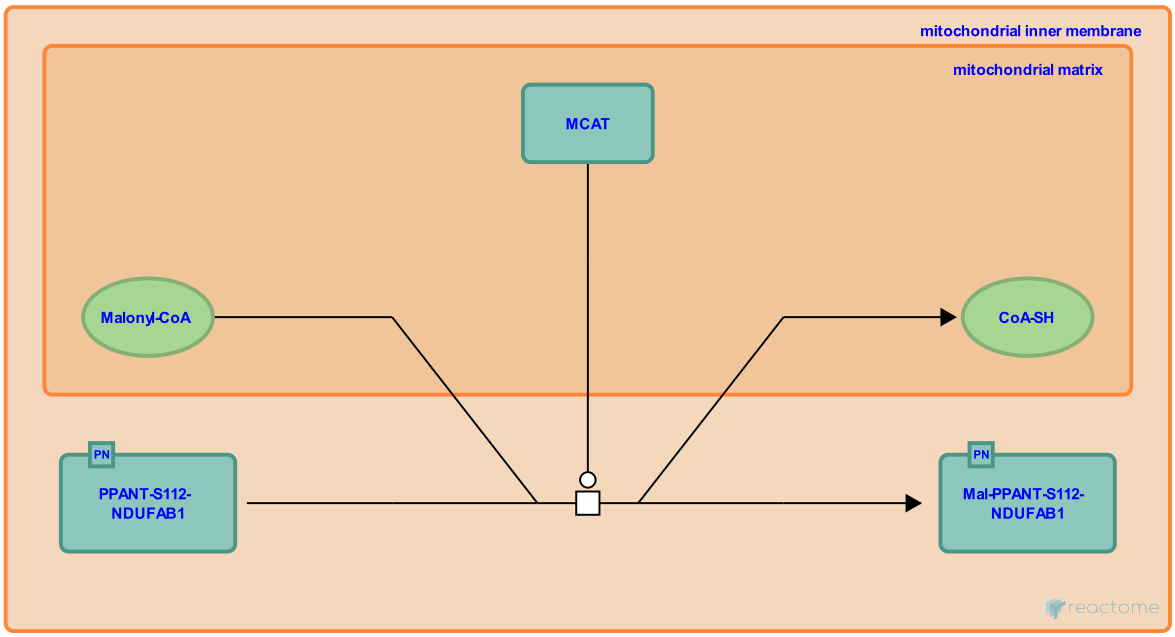
MCAT transfers Mal from Mal-CoA to NDUFAB1 ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-8933547

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix



The ACP (acyl carrier protein) NDUFAB1 is the cofactor protein that covalently binds all fatty acyl intermediates via a phosphopantetheine linkage during the synthesis of fatty acids. Mitochondrial malonyl-CoA-acyl carrier protein transacylase (MCAT, MT) catalyses the transfer of a malonyl moiety from malonyl-CoA (Mal-CoA) to the free thiol group of the phosphopantetheine arm of NDUFAB1, suggesting a possible role in fatty acid biosynthesis in the mitochondrion (Zhang et al. 2003).

Literature references

Joshi, AK., Zhang, L., Smith, S. (2003). Cloning, expression, characterization, and interaction of two components of a human mitochondrial fatty acid synthase. Malonyltransferase and acyl carrier protein. *J. Biol. Chem., 278*, 40067-74. ↗

Editions

2016-08-05	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

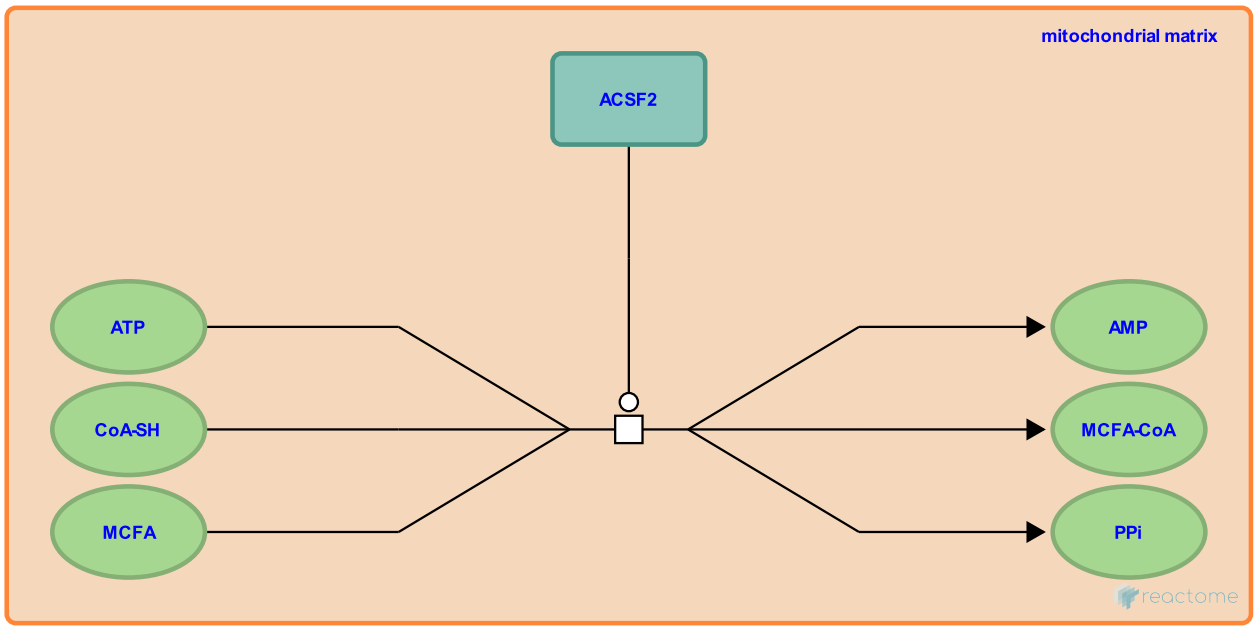
ACSF2 ligates CoA-SH to MCFA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-5696004

Type: transition

Compartments: mitochondrial matrix



Acyl-coenzyme A synthetases (ACSs) catalyse the activation of fatty acids by thioesterification to CoA, the fundamental initial reaction in fatty acid metabolism. Mitochondrial acyl-CoA synthetase family member 2 (ACSF2) preferentially ligates CoA-SH to medium-chain fatty acids (MCFA), around C8 in length (Watkins et al. 2007).

Literature references

Pevsner, J., Jia, Z., Watkins, PA., Maiguel, D. (2007). Evidence for 26 distinct acyl-coenzyme A synthetase genes in the human genome. *J. Lipid Res., 48*, 2736-50. ↗

Editions

2015-05-26	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

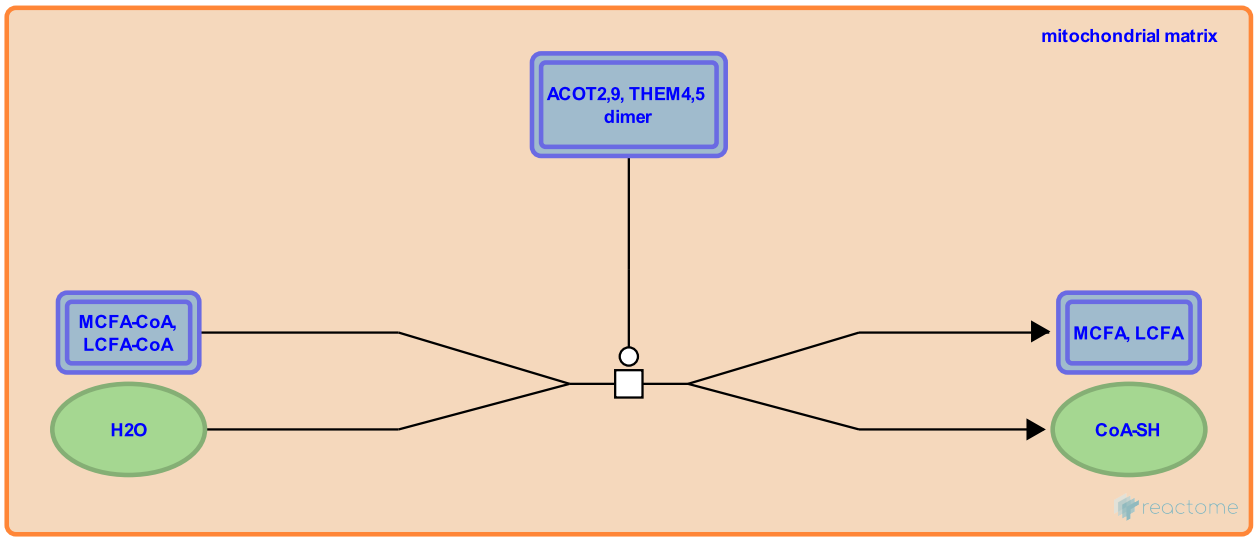
ACOT2,9,THEM4,5 hydrolyse MCFA-CoA, LCFA-CoA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-5690066

Type: transition

Compartments: mitochondrial matrix



The maintenance/regulation of cellular levels of free fatty acids and fatty acyl-CoAs (the activated form of free fatty acids) is extremely important, as imbalances in lipid metabolism can have serious consequences for human health. Acyl-coenzyme A thioesterases (ACOTs) hydrolyse the thioester bond in medium- to long-chain fatty acyl-CoAs (of C12-C18 lengths) (MCFA-CoA, LCFA-CoA) to their free fatty acids (MCFA, LCFA) (Cohen 2013, Hunt et al. 2012, Kirkby et al. 2010). ACOTs that function in the mitochondrion are ACOT2 (Hunt et al. 2006), ACOT9 (Kirkby et al. 2010), THEM4 dimer (Zhuravleva et al. 2012, Zhao et al. 2012) and THEM5 dimer (Zhuravleva et al. 2012). THEM4 is also functional in the cytosol and at the plasma membrane (Cohen 2013).

Literature references

Forwood, JK., Kobe, B., Roman, N., Kirkby, B., Kellie, S. (2010). Functional and structural properties of mammalian acyl-coenzyme A thioesterases. *Prog. Lipid Res., 49*, 366-77. ↗

Westin, MA., Alexson, SE., Svensson, LT., Rautanen, A., Hunt, MC. (2006). Analysis of the mouse and human acyl-CoA thioesterase (ACOT) gene clusters shows that convergent, functional evolution results in a reduced number of human peroxisomal ACOTs. *FASEB J., 20*, 1855-64. ↗

Dummler, B., Zhuravleva, E., Marcellin, D., Gut, H., Esposti, MD., Cron, P. et al. (2012). Acyl coenzyme A thioesterase Them5/Acot15 is involved in cardiolipin remodeling and fatty liver development. *Mol. Cell. Biol., 32*, 2685-97. ↗

Alexson, SE., Siponen, MI., Hunt, MC. (2012). The emerging role of acyl-CoA thioesterases and acyltransferases in regulating peroxisomal lipid metabolism. *Biochim. Biophys. Acta, 1822*, 1397-410. ↗

Cohen, DE. (2013). New players on the metabolic stage: How do you like Them Acots?. *Adipocyte, 2*, 3-6. ↗

Editions

2015-04-27	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

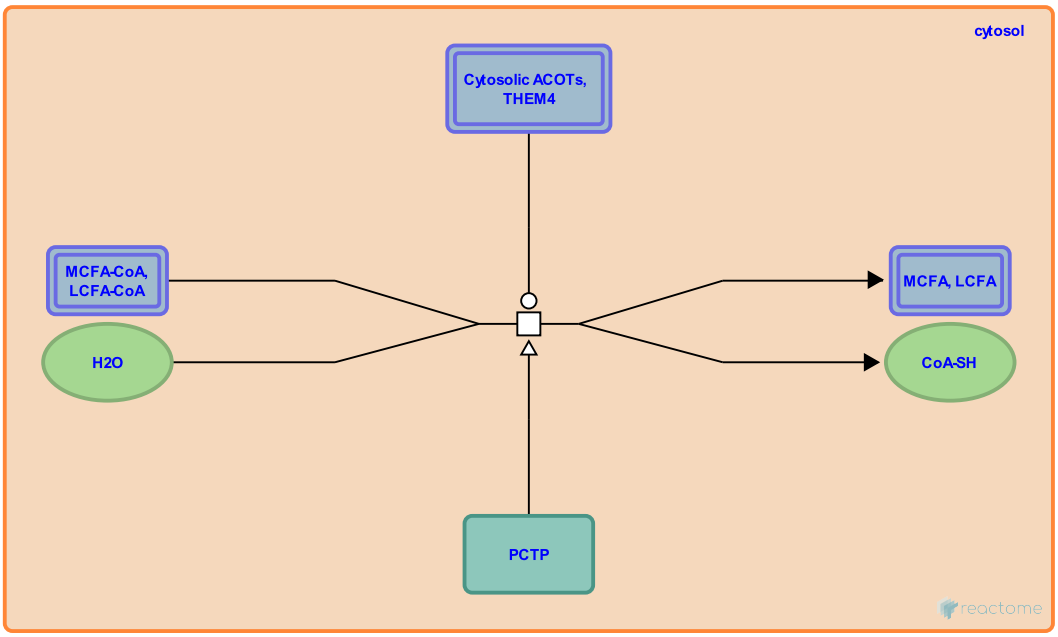
Cytosolic ACOTs hydrolyse MCFA-CoA, LCFA-CoA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-5690043

Type: transition

Compartments: cytosol



The maintenance/regulation of cellular levels of free fatty acids and fatty acyl-CoAs (the activated form of free fatty acids) is extremely important, as imbalances in lipid metabolism can have serious consequences for human health. Free fatty acids can act as detergents to disrupt membranes so their generation is normally tightly regulated to states where they will be rapidly consumed or sequestered. Acyl-coenzyme A thioesterases (ACOTs) hydrolyse the thioester bond in medium- to long-chain fatty acyl-CoAs (of C12-C18 lengths) (MCFA-CoA, LCFA-CoA) to their free fatty acids (MCFA, LCFA) (Cohen 2013, Hunt et al. 2012, Kirkby et al. 2010). ACOTs that function in the cytosol are ACOT1 (Hunt et al. 2005), ACOT11 (Adams et al. 2001), ACOT12 trimer (Swarbrick et al. 2014), ACOT13 tetramer (Cao et al. 2009, Cheng et al. 2006), ACOT7 hexamer (Hunt et al. 2005b) and ACOT7L dimer (Jiang et al. 2006).

Recent mouse studies reveals a key regulatory role for PCTP in lipid and glucose metabolism. Phosphatidylcholine transfer protein (PCTP aka STARD2) is a member of the steroidogenic acute regulatory protein (StAR)-related lipid transfer (START) domain superfamily, a functionally diverse group of proteins that share a unique structural motif for binding lipids. PCTP appears to limit access of fatty acids to mitochondria by binding to (Ersoy et al. 2013) and stimulating the activity of acyl-coenzyme A thioesterase 13 (ACOT13, aka Acyl-CoA thioesterase 13, THEM2), an enzyme that catalyses the hydrolysis of acyl-CoAs to their free fatty acids (Kawano et al. 2014). Ultimately, insulin signaling is downregulated (Kang et al. 2010).

Literature references

Chen, LZ., Feng, BJ., Yu, XJ., Feng, QS., Chen, HK., Zhang, RH. et al. (2006). A functional variant in the transcriptional regulatory region of gene LOC344967 cosegregates with disease phenotype in familial nasopharyngeal carcinoma. *Cancer Res., 66*, 693-700. ↗

Ersoy, BA., Ukomadu, C., Tarun, A., Cohen, DE., D'Aquino, K., Manning, BD. et al. (2013). Phosphatidylcholine transfer protein interacts with thioesterase superfamily member 2 to attenuate insulin signaling. *Sci Signal, 6*, ra64. ↗

Cheng, Z., Song, F., Wang, Y., Wei, Z., Gong, W., Shan, X. et al. (2006). Crystal structure of human thioesterase superfamily member 2. *Biochem. Biophys. Res. Commun., 349*, 172-7. ↗

Adams, SH., Lewin, DA., Yu, XX., Schilbach, SL., Colman, S., Chui, C. et al. (2001). BFIT, a unique acyl-CoA thioesterase induced in thermogenic brown adipose tissue: cloning, organization of the human gene and assessment of a potential link to obesity. *Biochem. J., 360*, 135-42. ↗

Zhao, H., Gong, W., Dunaway-Mariano, D., Xu, H., Cao, J. (2009). The mechanisms of human hotdog-fold thioesterase 2 (hTHEM2) substrate recognition and catalysis illuminated by a structure and function based analysis. *Biochemistry, 48*, 1293-304. ↗

Editions

2015-04-27	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

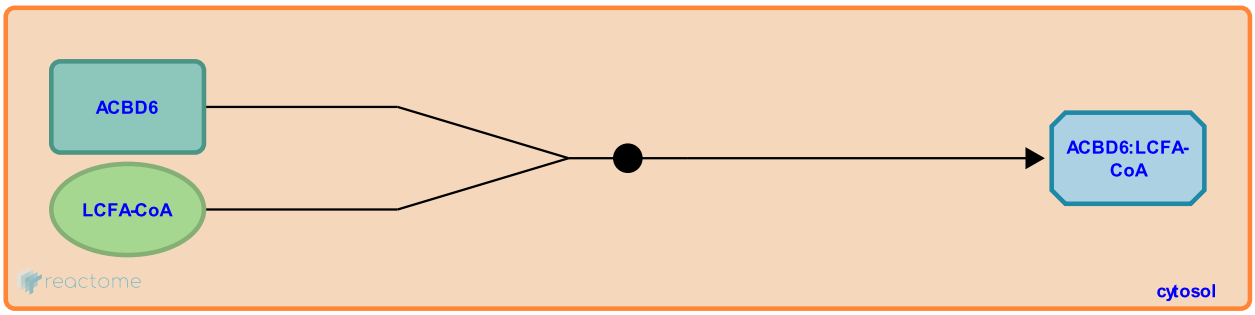
ACBD6 binds LCFA-CoA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-8848250

Type: binding

Compartments: cytosol



Acyl-CoA-binding domain-containing protein 6 (ACBD6) has an acyl-CoA binding domain at its N terminus and two ankyrin motifs at its C terminus. ACBD6 binds long-chain acyl-CoAs (LCFA-CoA) with a strong preference for unsaturated, C18:1-CoA and C20:4-CoA, over saturated, C16:0-CoA substrates. ACBD6 is expressed in tissues and progenitor cells with functions in blood and vessel development (Soupene et al. 2008). A possible role of ACBD6 could be to protect membrane systems from the detergent nature of free acyl-CoAs by controlling their release to acyl-CoA-utilising enzymes (Soupene & Kuypers 2015).

Literature references

Kuypers, FA., Soupene, E. (2015). Ligand binding to the ACBD6 protein regulates the acyl-CoA transferase reactions in membranes. *J. Lipid Res., 56*, 1961-71. ↗

Kuypers, FA., Soupene, E., Serikov, V. (2008). Characterization of an acyl-coenzyme A binding protein predominantly expressed in human primitive progenitor cells. *J. Lipid Res., 49*, 1103-12. ↗

Editions

2015-12-07	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

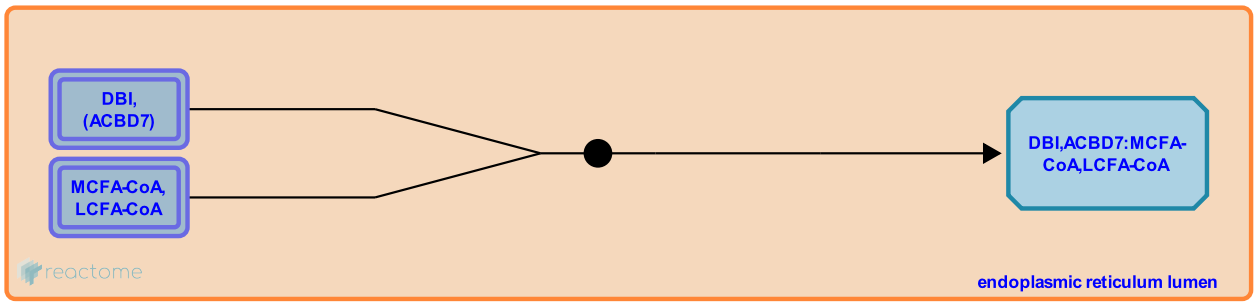
DBI, ACBD7 bind MCFA-CoA and LCFA-CoA ↗

Location: Mitochondrial Fatty Acid Beta-Oxidation

Stable identifier: R-HSA-8848246

Type: binding

Compartments: endoplasmic reticulum lumen



Acyl-CoA-binding protein (DBI, aka ACBP) can bind medium- and long-chain acyl-CoA esters (MCFA-CoA, LCFA-CoA) with very high affinity. It is localised to the ER (and Golgi) and may function as an intracellular carrier of acyl-CoA esters (Hansen et al. 2008, Bloksgaard et al. 2014). Acyl-CoA-binding domain-containing protein 7 (ACBD7) shares around 60% sequence homology with DBI and is proposed to also bind fatty acyl-CoAs but its function is yet to be determined.

Literature references

Kragelund, BB., Faergeman, NJ., Hansen, JS., Knudsen, J. (2008). Acyl-CoA-binding protein (ACBP) localizes to the endoplasmic reticulum and Golgi in a ligand-dependent manner in mammalian cells. *Biochem. J., 410*, 463-72. ↗

Færgeman, NJ., Neess, D., Mandrup, S., Bloksgaard, M. (2014). Acyl-CoA binding protein and epidermal barrier function. *Biochim. Biophys. Acta, 1841*, 369-76. ↗

Editions

2015-12-07	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

Table of Contents