



# Fatty acyl-CoA biosynthesis

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17/09/2024

## 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

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- 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. *オ*

This document contains 2 pathways and 13 reactions (see Table of Contents)

## Fatty acyl-CoA biosynthesis *▼*

#### Stable identifier: R-HSA-75105

#### Compartments: cytosol, endoplasmic reticulum membrane



Fatty acyl-CoA biosynthesis involves following steps:

-Palmitate synthesis catalyzed by Acetyl-CoA carboxylase and Fatty acid synthase

-Conversion of palmitic acid to long chain fatty acids and

-Conversion of long chain fatty acids to fatty acyl-CoA by acyl-CoA synthases.

## Literature references

Beld, J., Lee, DJ., Burkart, MD. (2015). Fatty acid biosynthesis revisited: structure elucidation and metabolic engineering. *Mol Biosyst*, 11, 38-59. 7

2003-10-03	Authored, Edited	Gopinathrao, G.
2024-02-28	Reviewed	Matthews, L.

## ACLY tetramer transforms CIT to Ac-CoA 7

Location: Fatty acyl-CoA biosynthesis

#### Stable identifier: R-HSA-75848

#### Type: transition

Compartments: cytosol

![](_page_3_Figure_5.jpeg)

While fatty acid synthesis from acetyl CoA (Ac-CoA) proceeds in the cytosol, most Ac-CoA in the cell is generated within the mitochondria by oxidative decarboxylation of the pyruvate derived from glycolysis, as well as from several reactions of amino acid catabolism. Mitochondrial Ac-CoA is transported to the cytosol as citrate (CIT) to participate in fatty acid biosynthesis (for a review, see, e.g., Arnold & Finley, 2023). Cytosolic ATP-citrate synthase (ACLY), in tetrameric form, catalyzes the transformation of CIT to Ac-CoA and plays an essential role in lipogenesis, adipogenesis, and differentiation of 3T3-L1 preadipocyte cells (Elshourbagy et al. 1992, Sun et al., 2011; Lin et al. 2013). Cytosolic MORC family CW-type zinc finger protein 2 (MORC2) positively regulates the activity of ACLY. Thus, it could mediate lipogenesis, adipogenic differentiation, and lipid homeostasis (Sanchez-Solana et al. 2014). High glucose leads to overexpression and nuclear localization of ACLY, subsequently increasing histone acetylation (reviewed by Bradshaw, 2021). SLC25A1 citrate export and acetyl-CoA production by ACLY are sometimes called the citrate-malate shuttle (for a review, see Guo et al., 2023).

Followed by: Formation of Malonyl-CoA from Acetyl-CoA (liver)

## Literature references

- Bradshaw, PC. (2021). Acetyl-CoA Metabolism and Histone Acetylation in the Regulation of Aging and Lifespan. Antioxidants (Basel), 10. 7
- Kumar, R., Sánchez-Solana, B., Li, DQ. (2014). Cytosolic functions of MORC2 in lipogenesis and adipogenesis. Biochim. Biophys. Acta, 1843, 316-26.
- Meng, Y., Lu, Z., Luo, S., Guo, D., He, H. (2023). Determiners of cell fates: the tricarboxylic acid cycle versus the citrate-malate shuttle. *Protein Cell*, 14, 162-164.
- Arnold, PK., Finley, LWS. (2023). Regulation and function of the mammalian tricarboxylic acid cycle. J Biol Chem, 299, 102838. 7
- Xiong, Y., Guan, KL., Zhou, X., Gao, X., Lei, QY., Lin, R. et al. (2013). Acetylation stabilizes ATP-citrate lyase to promote lipid biosynthesis and tumor growth. *Mol. Cell*, *51*, 506-18. 7

2003-10-03	Authored	Gopinathrao, G.
2017-01-09	Edited, Revised	Jassal, B.

## SLC27A2 ligates CoA to bempedoic acid to form ETC-1002-CoA 7

**Location:** Fatty acyl-CoA biosynthesis

#### Stable identifier: R-HSA-9734535

#### Type: transition

Compartments: cytosol

![](_page_5_Figure_5.jpeg)

Bempedoic acid (ETC-1002) is first-in-class ATP-citrate lyase (ACLY) inhibitor used once a day for reducing LDL cholesterol levels in statin-refractory patients. ETC-1002 itself is a prodrug, which is converted to the active metabolite ETC-1002–CoA by endogenous liver acyl-CoA synthetase (SLC27A2, ACSVL1) activity (Pinkosky et al. 2016).

Followed by: ACLY tetramer binds ETC-1002-CoA

## Literature references

Steinberg, GR., Pinkosky, SL., Day, EA., Newton, RS., Smith, BK., Birch, CM. et al. (2016). Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*, *7*, 13457.

2021-06-17	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

## ACLY tetramer binds ETC-1002-CoA ↗

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-9734540

#### Type: binding

Compartments: cytosol

![](_page_6_Figure_5.jpeg)

Cytosolic ATP-citrate synthase (ACLY) is an important enzyme with significant effects on fatty acid and cholesterol metabolism. It is highly expressed in lipogenic tissues such as the liver and white adipose tissue and links energy metabolism from carbohydrates to the production of fatty acids through catalyzing acetyl CoA synthesis, the fundamental substrate for the biosynthesis of both fatty acids and cholesterol. Elevated LDL-C levels are a well-established risk factor for atherosclerotic cardiovascular disease (ACSVD) and hypercholesterolemia. Its crucial role in lipid biosynthesis makes ACLY a potential target for lipid-lowering intervention.

Bempedoic acid (ETC-1002) is first-in-class adenosine triphosphate-citrate lyase (ACLY) inhibitor used once a day for reducing LDL cholesterol levels in statin-refractory patients. ETC-1002 itself is a prodrug, which is converted to an active metabolite (ETC-1002–CoA) by endogenous liver acyl-CoA synthetase activity (Pinkosky et al. 2016), which then inhibits ACLY (Pinkosky et al. 2013, 2016).

By inhibiting cholesterol synthesis in the liver, ETC-1002 induces upregulation of the LDL receptor and stimulates the uptake of LDL particles by the liver, which contributes to reductions of LDL-C levels in the blood. Also, because the prodrug is converted to the active drug specifically in the liver, this may avoid potential adverse muscle effects as seen with cholesterol inhibition by statins in muscle (Susekov et al. 2021).

Preceded by: SLC27A2 ligates CoA to bempedoic acid to form ETC-1002-CoA

## Literature references

- Cramer, CT., Naples, M., Baker, C., Pinkosky, SL., Newton, RS., Brant, AF. et al. (2013). AMP-activated protein kinase and ATP-citrate lyase are two distinct molecular targets for ETC-1002, a novel small molecule regulator of lipid and carbohydrate metabolism. J Lipid Res, 54, 134-51. ↗
- Steinberg, GR., Pinkosky, SL., Day, EA., Newton, RS., Smith, BK., Birch, CM. et al. (2016). Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*, *7*, 13457.

2021-06-17	Authored, Edited	Jassal, B.
2024-04-12	Reviewed	Hill, DP.

## Formation of Malonyl-CoA from Acetyl-CoA (liver) 7

Location: Fatty acyl-CoA biosynthesis

#### Stable identifier: R-HSA-200555

#### Type: transition

Compartments: cytosol

![](_page_7_Figure_5.jpeg)

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 polymerization (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 polymerizes in fatty acid (FA) synthesis. Polymerization enhances ACACA and ACACB enzyme activities (Kim et al. 2010).

#### Preceded by: ACLY tetramer transforms CIT to Ac-CoA

Followed by: Conversion of malonyl-CoA and acetyl-CoA to palmitate

#### Literature references

- Feder, JN., Chu, CH., Locke, GA., An, Y., Cheng, D., Tamura, JK. et al. (2007). Expression, purification, and characterization of human and rat acetyl coenzyme A carboxylase (ACC) isozymes. *Protein Expr Purif*, *51*, 11-21. *¬*
- Jayakumar, A., Wakil, SJ., Chirala, SS., Baldini, A., Abu-Elheiga, L. (1995). Human acetyl-CoA carboxylase: characterization, molecular cloning, and evidence for two isoforms. *Proc Natl Acad Sci U S A*, 92, 4011-5. *¬*
- Haque, T., Carney, RF., Locke, GA., Rendina, AR., Cheng, D., Tamura, JK. et al. (2008). Differential activation of recombinant human acetyl-CoA carboxylases 1 and 2 by citrate. *Arch Biochem Biophys*, 475, 72-9. A

2003-10-03	Authored	Gopinathrao, G.
2024-04-12	Reviewed	Hill, DP.

## Formation of fatty acid synthase (FAS) dimer 7

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-163756

Type: transition

Compartments: cytosol

![](_page_9_Figure_5.jpeg)

Association of cytosolic FAS into multimers is linked to increased catalytic activity (Locke et al. 2008).

Followed by: Conversion of malonyl-CoA and acetyl-CoA to palmitate

## Literature references

Haque, T., Carney, RF., Locke, GA., Rendina, AR., Cheng, D., Tamura, JK. et al. (2008). Differential activation of recombinant human acetyl-CoA carboxylases 1 and 2 by citrate. *Arch Biochem Biophys*, 475, 72-9.

## **Editions**

2024-04-12

Reviewed

Hill, DP.

## Conversion of malonyl-CoA and acetyl-CoA to palmitate 7

**Location:** Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-75872

#### Type: transition

Compartments: cytosol

![](_page_10_Figure_5.jpeg)

Cytosolic fatty acid synthase (FAS) complex catalyzes the reaction of acetyl-CoA with 7 malonyl-CoA and 14 NADHP + 14 H+ to form a molecule of palmitate and 7 CO2, 14 NADP+, 8 CoASH, and 6 H2O. The process proceeds via the successive condensations of malonyl groups onto the growing acyl chain, each followed by loss of CO2 and three steps of reduction (Jayakumar et al. 1995; Smith et al. 2003).

**Preceded by:** Formation of fatty acid synthase (FAS) dimer, Formation of Malonyl-CoA from Acetyl-CoA (liver)

## Literature references

Jayakumar, A., Wakil, SJ., Huang, WY., Hsu, M., Chirala, SS., al-Feel, W. et al. (1995). Human fatty acid synthase: properties and molecular cloning. *Proc Natl Acad Sci U S A*, 92, 8695-9. *¬* 

Joshi, AK., Witkowski, A., Smith, S. (2003). Structural and functional organization of the animal fatty acid synthase. *Prog Lipid Res, 42,* 289-317. 7

#### Editions

2003-10-23

Authored

Joshi-Tope, G.

## OLAH hydrolyzes decanoyl-FASN dimer to DECA and FASN dimer 7

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-5655955

Type: transition

Compartments: cytosol

Inferred from: Olah hydrolyzes decanoyl-Fasn dimer to decanoate and Fasn dimer (Rattus norvegicus)

![](_page_11_Figure_6.jpeg)

OLAH, a monomeric cytosolic thiolase, catalyzes the hydrolysis of FASN (fatty acid synthase) charged with decanoyl fatty acyl moieties to yield FASN and decanoate (DECA). OLAH expression is confined to the lactating mammary gland, and its catalytic activity enables the early termination of a portion of fatty acid biosynthesis to produce the medium chain-length fatty acids (annotated here as DECA) found in milk (Insull & Ahrens 1959; Breckenridge et al. 1969). OLAH is known only as an open reading frame identified in the human genome and as an mRNA observed in gene expression screening studies. Its biological properties are inferred from those of its well-studied rat ortholog (Libertini & Smith 1978; Mikkelsen et al. 1987).

## Literature references

- Insull, W., Ahrens, EH. (1959). The fatty acids of human milk from mothers on diets taken ad libitum. *Biochem. J.*, 72, 27-33. ↗
- Kuksis, A., Marai, L., Breckenridge, WC. (1969). Triglyceride structure of human milk fat. *Can. J. Biochem., 47*, 761-9.
- Witkowski, A., Mikkelsen, J., Smith, S. (1987). Interaction of rat mammary gland thioesterase II with fatty acid synthetase is dependent on the presence of acyl chains on the synthetase. J. Biol. Chem., 262, 1570-4.
- Libertini, LJ., Smith, S. (1978). Purification and properties of a thioesterase from lactating rat mammary gland which modifies the product specificity of fatty acid synthetase. J. Biol. Chem., 253, 1393-401.

2015-01-29	Reviewed	Jassal, B.
2024-04-12	Reviewed	Hill, DP.

## Synthesis of very long-chain fatty acyl-CoAs ↗

**Location:** Fatty acyl-CoA biosynthesis

#### Stable identifier: R-HSA-75876

#### Compartments: endoplasmic reticulum membrane, cytosol

![](_page_12_Figure_4.jpeg)

Very long-chain fatty acids (VLCFA), ones with more than 20 carbon atoms, have diverse physiological roles, notably as components of ceramides in membrane lipids and as precursors of the eicosanoid hormones that play central roles in the generation and resolution of inflammatory responses. Saturated and monounsaturated VLCFAs can be synthesized by elongation of palmitic acid synthesized de novo or derived from the diet. Polyunsaturated VLCFAs are synthesized from dietary linoleic and linolenic acids - humans lack the desaturase enzymes to synthesize these molecules from stearate.

Chemically, the elongation process that yields VLCFA parallels the one by which palmitate (16 carbons) or stearate (18 carbons) are synthesized de novo from acetate. The starting fatty acid is activated by conjugation with coenzyme A (CoA-SH), condensed with malonyl-CoA to form a 3-oxoacyl CoA containing two more carbon atoms than the starting long chain fatty acyl CoA and CO2, reduced with NADPH to a 3-hydroxyacyl CoA, dehydrated to a trans 2,3-enoyl-CoA, and reduced with NADPH to yield a fatty acyl-CoA two carbons longer than the starting one.

The process differs from the de novo one in that the enzymatic activities resposible for each step are expressed by different proteins associated with the endoplasmic reticulum membrane, not by separate domains of a single multifunctional cytosolic protein. In humans, activation is catalyzed by one of five acyl-CoA synthetase long-chain (ACSL) enzymes, conjugation by one of seven elongation of very long chain fatty acids (ELOVL) proteins, reduction by one of two HSB17B estradiol dehydrogenases, dehydration by one of four protein tyrosine phosphatase-like / 3-hydroxyacyl-CoA dehydratase (PTPL / HACD) proteins, and reduction by one of two trans-2,3-enoyl-CoA reductase (TECR) proteins. Members of the four enzyme families differ in their tissue-specific expression patterns and in their substrate preferences (chain length, degree of saturation), leading to tissue-specific complements of VLCA (Jakobsson et al. 2006; Kihara 2012; Nugteren 1965; Sassa & Kihara 2014).

Here the full two-carbon elongation cycle to form stearate from palmitate is annotated, as well as the activation and condensation steps for elongation of arachidonate, the 20-carbon unsaturated fatty acid that plays a central role in the synthesis of prostaglandins and related hormones.

## Literature references

- Kihara, A. (2012). Very long-chain fatty acids: elongation, physiology and related disorders. J. Biochem., 152, 387-95.
- Jakobsson, A., Jacobsson, A., Westerberg, R. (2006). Fatty acid elongases in mammals: their regulation and roles in metabolism. *Prog Lipid Res, 45*, 237-49.
- Sassa, T., Kihara, A. (2014). Metabolism of very long-chain Fatty acids: genes and pathophysiology. *Biomol Ther* (Seoul), 22, 83-92. ↗

2003-03-10	Authored, Edited	Gopinathrao, G.
2010-03-15	Revised	D'Eustachio, P.
2015-02-19	Revised	Jassal, B.
2015-02-22	Reviewed	D'Eustachio, P.

## SCD desaturates ST-CoA to OLE-CoA 7

**Location:** Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-5690565

#### Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

![](_page_14_Figure_5.jpeg)

Acyl-CoA desaturase (SCD), located on the ER membrane, is the terminal enzyme of the liver microsomal stearyl-CoA desaturase system and is the rate-limiting enzyme in the cellular synthesis of monounsaturated fatty acids (MUFAs) from saturated fatty acids. SCD utilises O2 and electrons from reduced ferrocytochrome b5 (Fe(2+)Cb5) to catalyse the insertion of a double bond into a range of fatty acyl-CoA substrates. This example shows stearoyl-CoA (ST-CoA) desaturation to oleoyl-CoA (OLE-CoA) (Li et al. 1994, Zhang et al. 1999). Studies of tagged recombinant enzyme overexpressed in transiently transfected cells suggest that the enzyme forms dimers and higher oligomers (Zhang et al. 2005).

## Literature references

- Shi, Y., Yang, Y., Zhang, S. (2005). Characterization of human SCD2, an oligomeric desaturase with improved stability and enzyme activity by cross-linking in intact cells. *Biochem. J.*, 388, 135-42. 🛪
- Wood, CB., Gilmour, RS., Fermor, BF., Li, J., Ding, SF., Habib, NA. (1994). Partial characterization of a cDNA for human stearoyl-CoA desaturase and changes in its mRNA expression in some normal and malignant tissues. *Int J Cancer, 57*, 348-52. *¬*

Zhang, L., Stenn, K., Prouty, SM., Parimoo, S., Ge, L. (1999). Human stearoyl-CoA desaturase: alternative transcripts generated from a single gene by usage of tandem polyadenylation sites. *Biochem. J.*, 340, 255-64.

2015-04-29	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.

## SCD5 desaturates ST-CoA to OLE-CoA 7

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-8847579

#### Type: transition

Compartments: endoplasmic reticulum membrane, cytosol

![](_page_15_Figure_5.jpeg)

Stearoyl-CoA desaturase 5 (SCD5, also known as acyl-CoA desaturase 4), located on the ER membrane, utilises O2 and electrons from reduced ferrocytochrome b5 (Fe(2+)Cb5) to catalyse the insertion of a double bond into a range of fatty acyl-CoA substrates. SCD5 is most abundant in brain and pancreas. The reaction annotated here shows stearoyl-CoA (ST-CoA) desaturation to oleoyl-CoA (OLE-CoA). Studies of tagged recombinant enzyme overexpressed in transiently transfected cells suggest that the enzyme forms dimers and higher oligomers (Wang et al. 2005; Zhang et al. 2005).

## Literature references

- Shi, Y., Yang, Y., Zhang, S. (2005). Characterization of human SCD2, an oligomeric desaturase with improved stability and enzyme activity by cross-linking in intact cells. *Biochem. J.*, 388, 135-42. 7
- Cao, G., Wang, J., Su, C., Yu, L., Huang, X., Schmidt, RE. et al. (2005). Characterization of HSCD5, a novel human stearoyl-CoA desaturase unique to primates. *Biochem. Biophys. Res. Commun.*, 332, 735-42.

2015-12-01	Authored, Edited	D'Eustachio, P.
2016-01-29	Reviewed	Jassal, B.

## PPT1 hydrolyses palmitoylated proteins 7

**Location:** Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-5690517

#### Type: transition

#### Compartments: lysosomal lumen

![](_page_16_Figure_5.jpeg)

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) (MCFAcylCoA, LCFAcylCoA) to their free fatty acids (MCFA, LCFA) (Cohen 2013, Hunt et al. 2012, Kirkby et al. 2010). Lysosomal thioesterase PPT1 is able to specifically hydrolyse palmitic acid (PALM) from palmitoylated proteins (PALM:protein) (Camp & Hofmann 1993, Camp et al. 1994).

## 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. *¬*
- Camp, LA., Hofmann, SL., Slaughter, CA., Verkruyse, LA., Afendis, SJ. (1994). Molecular cloning and expression of palmitoyl-protein thioesterase. J. Biol. Chem., 269, 23212-9. 7
- Camp, LA., Hofmann, SL. (1993). Purification and properties of a palmitoyl-protein thioesterase that cleaves palmitate from H-Ras. J. Biol. Chem., 268, 22566-74. 🛪
- 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. 7

Cohen, DE. (2013). New players on the metabolic stage: How do you like Them Acots?. Adipocyte, 2, 3-6. 7

2015-04-29	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2024-04-12	Reviewed	Hill, DP.

## PPT2 hydrolyses PALMCoA to PALM ↗

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-5690046

#### Type: transition

#### Compartments: lysosomal lumen

![](_page_17_Figure_5.jpeg)

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) (MCFAcylCoA, LCFAcylCoA) to their free fatty acids (MCFA, LCFA) (Cohen 2013, Hunt et al. 2012, Kirkby et al. 2010). Lysosomal thioesterase PPT2 is able to specifically hydrolyse palmitoyl-CoA (PALM-CoA) to palmitic acid (PALM) (Soyombo & Hofmann 1997).

## 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. 7
- Soyombo, AA., Hofmann, SL. (1997). Molecular cloning and expression of palmitoyl-protein thioesterase 2 (PPT2), a homolog of lysosomal palmitoyl-protein thioesterase with a distinct substrate specificity. J. Biol. Chem., 272, 27456-63. *¬*
- 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. 🛪

2015-04-27	Authored, Edited	Jassal, B.
2015-06-26	Reviewed	D'Eustachio, P.
2024-04-12	Reviewed	Hill, DP.

## 2xHSD17B8:2xCBR4 reduces 3OA-ACP to 3HA-ACP 7

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-8862152

#### Type: transition

#### Compartments: mitochondrial matrix

![](_page_18_Figure_5.jpeg)

Estradiol 17-beta-dehydrogenase 8 (HSD17B8) (Ohno et al. 2008) forms a heterotetramer with carbonyl reductase family member 4 (CBR4) (Chen et al. 2009, Zhang et al. 2005). The heterotetramer has NADPH-dependent 3-ketoacyl-acyl carrier protein reductase activity which is suggested to play a role in biosynthesis of fatty acids in mitochondria (Venkatesan et al. 2014).

## Literature references

- Prus, P., Venkatesan, R., Awoniyi, LO., Sah-Teli, SK., Wierenga, RK., Hiltunen, JK. et al. (2014). Insights into mitochondrial fatty acid synthesis from the structure of heterotetrameric 3-ketoacyl-ACP reductase/3R-hydroxyacyl-CoA dehydrogenase. *Nat Commun, 5*, 4805. *¬*
- Miinalainen, IJ., Hiltunen, JK., Wierenga, RK., Rajaram, V., Kastaniotis, AJ., Chen, Z. (2009). 17beta-hydroxysteroid dehydrogenase type 8 and carbonyl reductase type 4 assemble as a ketoacyl reductase of human mitochondrial FAS. *FASEB J.*, 23, 3682-91.
- Joshi, AK., Hofmann, J., Schweizer, E., Zhang, L., Smith, S. (2005). Cloning, expression, and characterization of the human mitochondrial beta-ketoacyl synthase. Complementation of the yeast CEM1 knock-out strain. J. Biol. Chem., 280, 12422-9. 7
- Nakajin, S., Ohno, S., Nishikawa, K., Honda, Y. (2008). Expression in E. coli and tissue distribution of the human homologue of the mouse Ke 6 gene, 17beta-hydroxysteroid dehydrogenase type 8. *Mol. Cell. Biochem.*, 309, 209-15.

2016-02-25	Authored, Edited	Jassal, B.
2016-04-05	Reviewed	D'Eustachio, P.

## RPP14 (HTD2) dehydrates 3HA-CoA to t2E-CoA ↗

Location: Fatty acyl-CoA biosynthesis

Stable identifier: R-HSA-8957389

#### Type: transition

#### Compartments: mitochondrial matrix

![](_page_19_Figure_5.jpeg)

Polycistronic transcripts, where a single mRNA can encode several different polypeptide chains, are common in prokaryotes. In humans, only 3 bicistronic transcripts have been characterised to date. Human cDNAs encoding both RPP14 of the RNase P complex and mitochondrial 3-hydroxyacyl thioester dehydratase (HTD2) have been isolated. HTD2 functions in the mitochondrial fatty acid synthesis (FAS) pathway, dehydrating (3R)-hydroxyacyl-CoA (3HA-CoA) to trans-2-enoyl-CoA (t2E-CoA) (Autio et al. 2008).

## Literature references

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2017-01-25	Authored, Edited	Jassal, B.
2017-01-30	Reviewed	D'Eustachio, P.

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