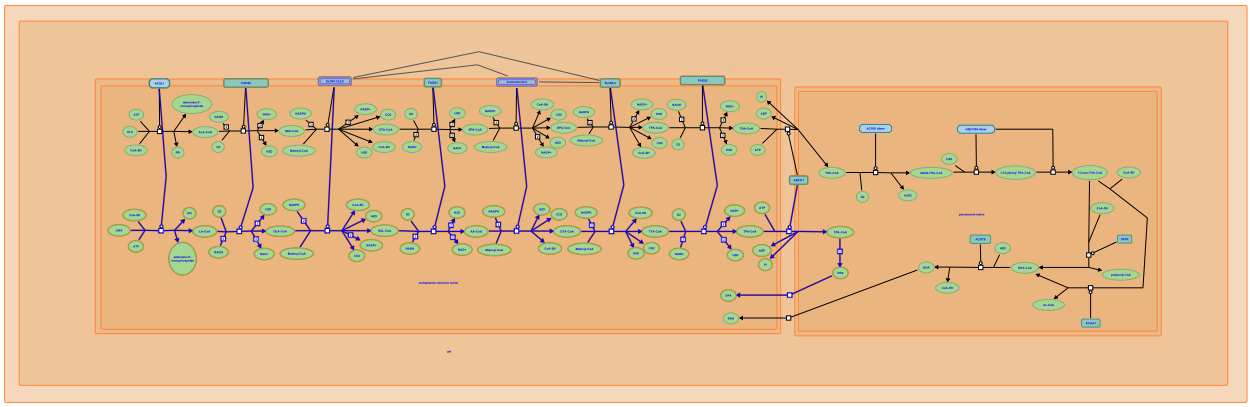
Linoleic acid (LA) metabolism



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22/10/2020

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. ↗

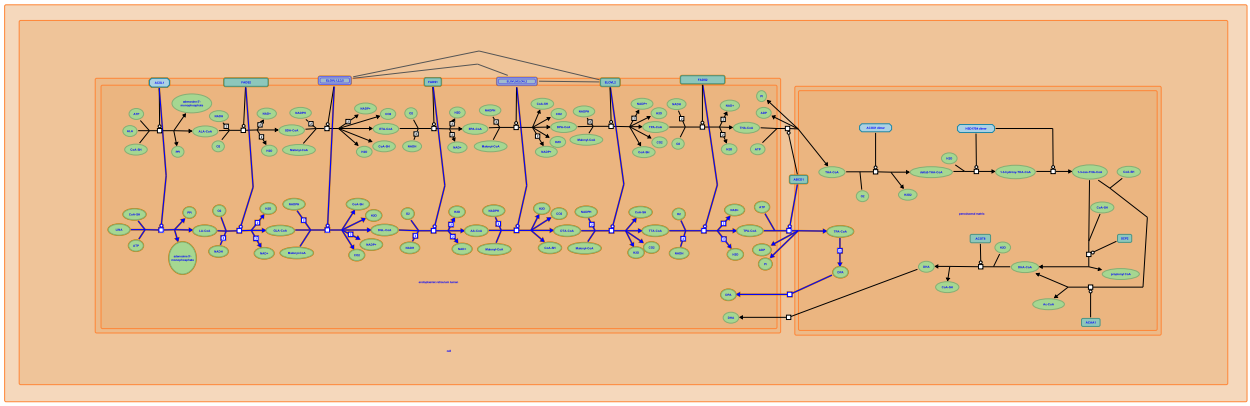
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Linoleic acid (LA) metabolism ↗

Stable identifier: R-HSA-2046105

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane, peroxisomal matrix, peroxisomal membrane



Linoleic acid (LA, 18:2(n-6)) is an omega-6 fatty acid obtained through diet, mainly from vegetable oils. Omega-6 fatty acids helps stimulate skin and hair growth, maintain bone health, regulate metabolism, and maintain the reproductive system. All the desaturation and elongation steps occur in the endoplasmic reticulum (ER) except for the final step which requires translocation to peroxisomes for partial beta-oxidation. The linoleic acid pathway involves the following steps: 18:2(n-6)-->18:3(n-6)--> 20:3(n-6)-->20:4(n-6)-->22:4(n-6)-->24:4(n-6)-->24:5(n-6)-->22:5(n-6). Two desaturation enzymes are involved in this process: delta-6 desaturase which converts 18:2(n-6) to 18:3 (n-6) and 24:4(n-6) to 24:5(n-6) respectively, and delta-5 desaturase which converts 20:3(n-6) to 20:4(n-6). (Sprecher 2002).

Literature references

Sprecher, H. (2000). Metabolism of highly unsaturated n-3 and n-6 fatty acids. *Biochim Biophys Acta, 1486*, 219-31. ↗

Leonard, AE., Pereira, SL., Sprecher, H., Huang, YS. (2004). Elongation of long-chain fatty acids. *Prog Lipid Res, 43*, 36-54. ↗

Kapoor, R., Huang, YS. (2006). Gamma linolenic acid: an antiinflammatory omega-6 fatty acid. *Curr Pharm Biotechnol , 7*, 531-4. ↗

Chilton-Lopez, T., Surette, ME., Swan, DD., Fonteh, AN., Johnson, MM., Chilton, FH. (1996). Metabolism of gammalinolenic acid in human neutrophils. *J Immunol, 156*, 2941-7. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

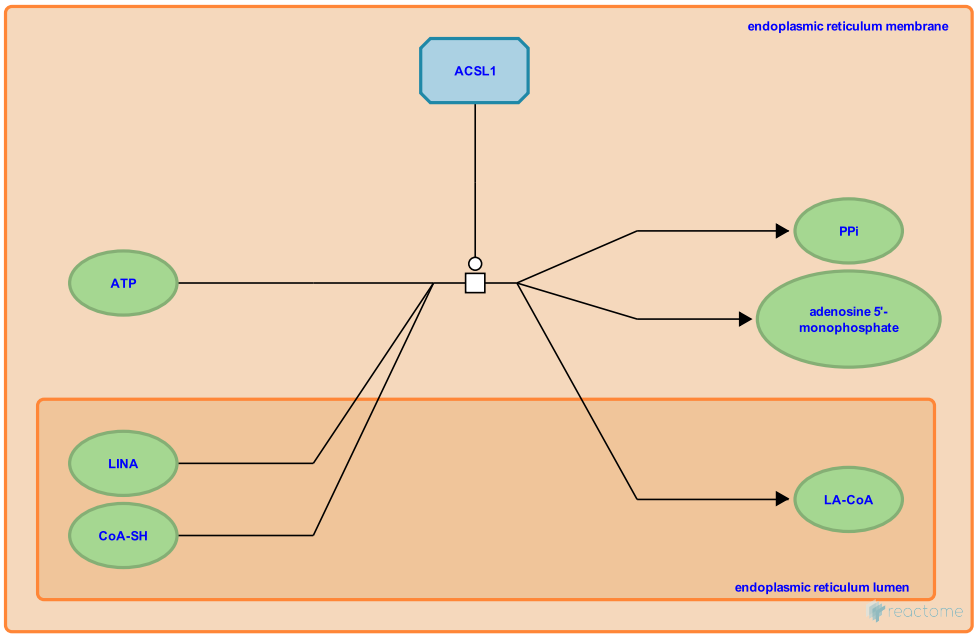
Activation of linoleic acid to linoleoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046098

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



The dietary essential fatty acid (EFA) linoleic acid (LA) is activated to a high energy form known as linoleoyl-CoA by the action of long-chain acyl-CoA synthetases (ACSLs). Thioesterification of long-chain fatty acids into their acyl-CoA derivatives is considered to be the first committed step in fatty acid metabolism. Formation of acyl-CoA allows an otherwise non-reactive fatty acid to participate in biosynthetic or catabolic pathways. This acyl CoA form is converted to its longer-chain polyunsaturated products by a series of desaturation and elongation reactions (Ellis et al. 2010, Watkins 2008).

Followed by: Desaturation of Linoleoyl-CoA to gamma-linolenoyl-CoA

Literature references

Biosketch, M. (2003). Docosahexaenoic acid, Nutrient Metabolism. *Elsevier Science Ltd*, 164-175.

Wilson, DB., Prescott, SM., Majerus, PW. (1982). Discovery of an arachidonoyl coenzyme A synthetase in human platelets. *J Biol Chem, 257*, 3510-5. ↗

Editions

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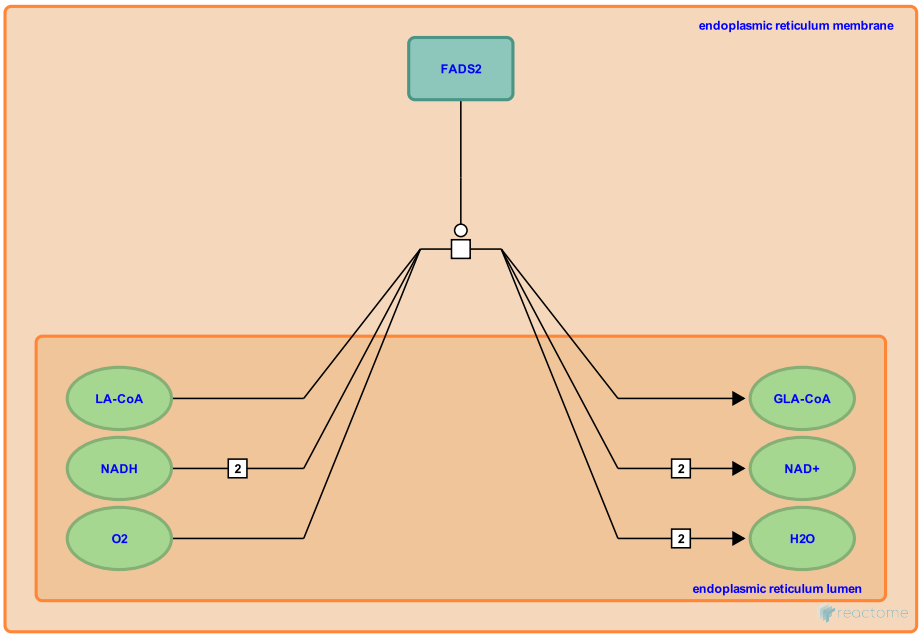
Desaturation of Linoleoyl-CoA to gamma-linolenoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046096

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



The first major step in the metabolism of linoleic acid (LA) is desaturation of delta 9,12-octadecadienoyl CoA/linoleoyl CoA (LA-CoA) to delta 6,9,12-octodecatrienoyl CoA/gamma-lenoleoyl CoA (GLA-CoA). This step is catalyzed by delta-6-destaurase (fatty acid desaturase-2, FADS2) which introduces a cis-double bond between carbons 6 and 7. This is the rate limiting step in LA metabolism (Horrobin 1993).

Preceded by: Activation of linoleic acid to linoleoyl-CoA

Followed by: Elongation of gamma-lenolenoyl-CoA to dihomo-gamma-lenolenoyl-CoA

Literature references

Ge, L., Gordon, JS., Hsuan, C., Stenn, K., Prouty, SM. (2003). Identification of the delta-6 desaturase of human sebaceous glands: expression and enzyme activity. *J Invest Dermatol, 120*, 707-14. ↗

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d'Andréa, S., Guillou, H., Jan, S., Catheline, D., Thibault, JN., Bouriel, M. et al. (2002). The same rat Delta6-desaturase not only acts on 18- but also on 24-carbon fatty acids in very-long-chain polyunsaturated fatty acid biosynthesis. *Biochem J, 364*, 49-55. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

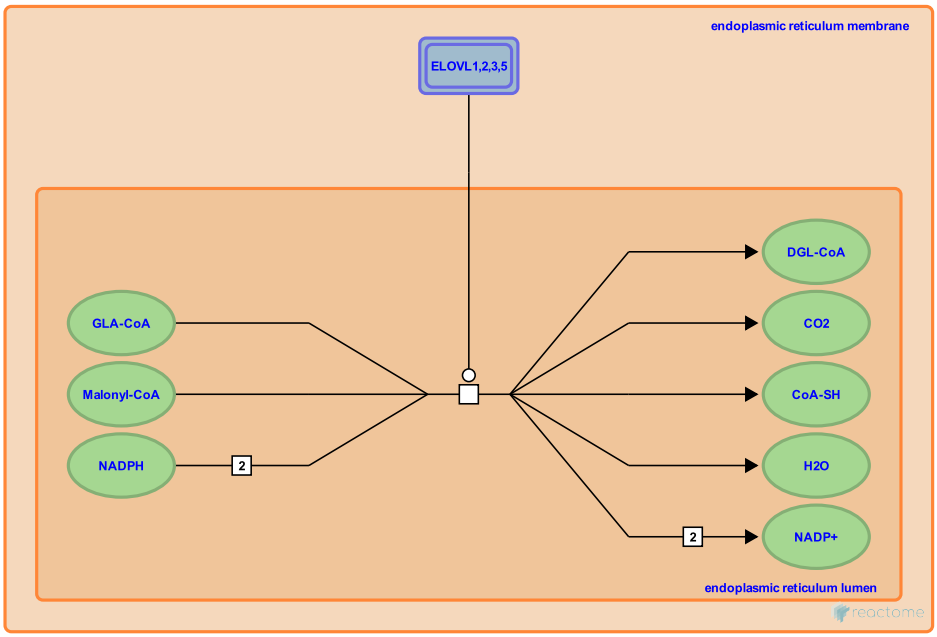
Elongation of gamma-lenolenoyl-CoA to dihomo-gamma-lenolenoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046094

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Gamma-linolenoyl-CoA (6,9,12-20:3(n-6)) is rapidly elongated to dihomo-gamma-linolenoyl-CoA (DGL-CoA; 8,11,14-20:3(n-6)) by the action of C18-PUFA-specific elongase 5 (ELOVL5). Two carbon atoms are added during this reaction. DGL-CoA later undergoes desaturation to form arachidonic acid (AA, 5,8,11,14-20:4(n-6)).

Depending on the cell type, DGL-CoA can also be metabolized by cyclooxygenases and lipoxygenases to produce anti-inflammatory eicosanoids (prostaglandins of series 1 (PGE1) and 15-hydroxyeico- satrienoic acid (15-HETrE)). GLA and these two oxidative metabolites exert clinical effects in a variety of diseases, including suppression of chronic inflammation, vasodilation and lowering of blood pressure, inhibition of platelet aggregation and thrombosis. (Fan et al. 2001, Fan & Chapkin 1998, Kapoor & Huang. 2006)

Preceded by: Desaturation of Linoleoyl-CoA to gamma-linolenoyl-CoA

Followed by: Desaturation of dihomo-gamma-lenolenoyl-CoA to arachidonoyl-CoA

Literature references

Chilton-Lopez, T., Surette, ME., Swan, DD., Fonteh, AN., Johnson, MM., Chilton, FH. (1996). Metabolism of gammalinolenic acid in human neutrophils. *J Immunol, 156*, 2941-7. ↗

Fan, YY., Chapkin, RS. (1998). Importance of dietary gamma-linolenic acid in human health and nutrition. *J Nutr, 128*, 1411-4. ↗

Leonard, AE., Bobik, EG., Dorado, J., Kroeger, PE., Chuang, LT., Thurmond, JM. et al. (2000). Cloning of a human cDNA encoding a novel enzyme involved in the elongation of long-chain polyunsaturated fatty acids. *Biochem J, 350*, 765-70. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

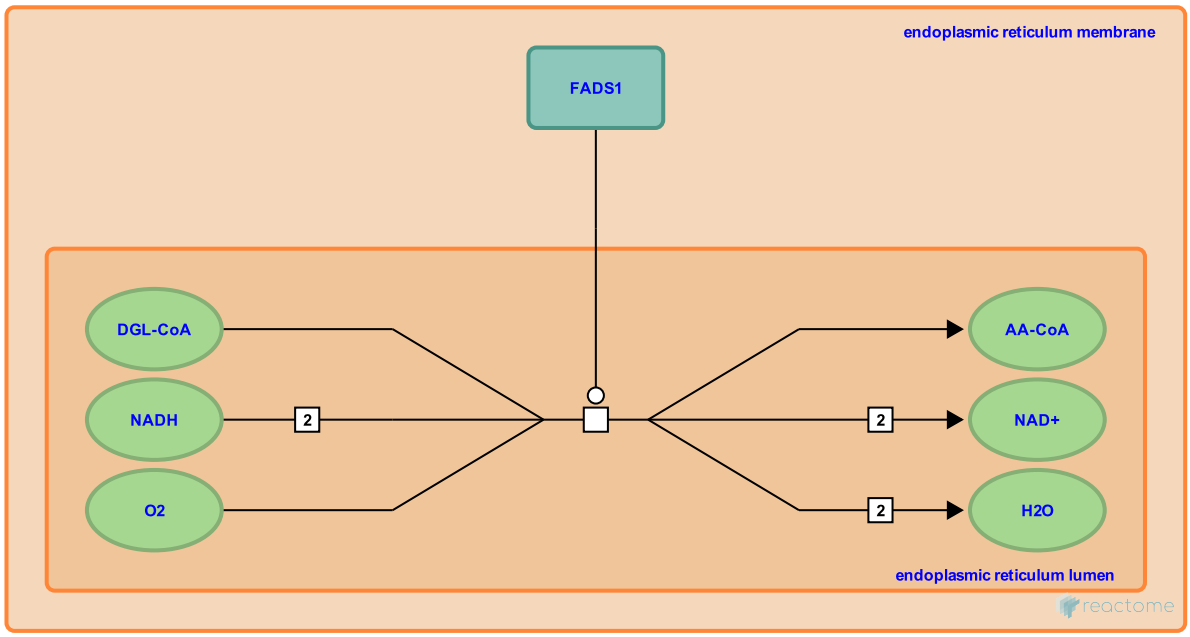
Desaturation of dihomo-gamma-lenolenoyl-CoA to arachidonoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046092

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



DGL-CoA (8,11,14-eicosatrienoyl-CoA) undergoes desaturation by delta 5-desaturase (D5-desaturase) forming arachidonoyl-CoA (AA-CoA, 5,8,11,14-Eicosatetraenoic acid). D5-desaturase has 62% sequence identity with D6-desaturase but desaturates a different carbon atom, adding a double bond at position C5 in arachidonoyl-CoA (AA-CoA). AA can be metabolized by variety of oxygenases (including cyclo-oxygenase and lipoxygenase systems) to form a family of varying products known as eicosanoids, prostaglandins, leukotrines and thromboxanes thus playing important role in inflamation response.

Preceded by: Elongation of gamma-lenolenoyl-CoA to dihomo-gamma-lenolenoyl-CoA

Followed by: Elongation of arachidonyl-CoA to docosatetraenoyl-CoA

Literature references

Cho, HP., Nakamura, M., Clarke, SD. (1999). Cloning, expression, and fatty acid regulation of the human delta-5 desaturase. *J Biol Chem, 274*, 37335-9. ↗

Leonard, AE., Kelder, B., Bobik, EG., Chuang, LT., Parker-Barnes, JM., Thurmond, JM. et al. (2000). cDNA cloning and characterization of human Delta5-desaturase involved in the biosynthesis of arachidonic acid. *Biochem J, 347* , 719-24. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

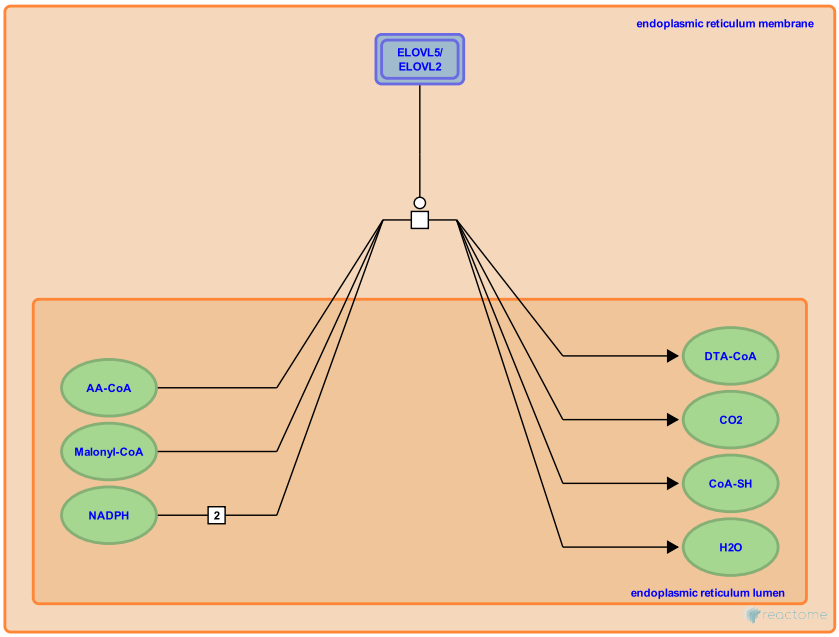
Elongation of arachidonyl-CoA to docosatetraenoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046083

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Arachidonyl-CoA undergoes a two-carbon chain elongation on the carboxyl end to form docosatetraenoyl-CoA (DTA-CoA/Adrenic acid/7,10,13,16-docosatetraenoic acid (7,10,13,16-22:4(n-6)). This reaction is catalyzed by the enzymes ELOVL5 or ELOVL2. Malanoyl-CoA provides the additional two carbons required for elongation. Docosatetraenoyl-CoA is further metabolized by cyclooxygenases (COX), lipoxygenases (LO) and cytochrome P450s (CYP450s) to dihomo (DH) eicosanoids (Kopf et al. 2010, Leonard et al. 2004).

Preceded by: Desaturation of dihomo-gamma-lenolenoyl-CoA to arachidonoyl-CoA

Followed by: Elongation of docosatetraenoyl-CoA to tetracosatetraenoyl-CoA

Literature references

Leonard, AE., Bobik, EG., Dorado, J., Kroeger, PE., Chuang, LT., Thurmond, JM. et al. (2000). Cloning of a human cDNA encoding a novel enzyme involved in the elongation of long-chain polyunsaturated fatty acids. *Biochem J, 350*, 765-70. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

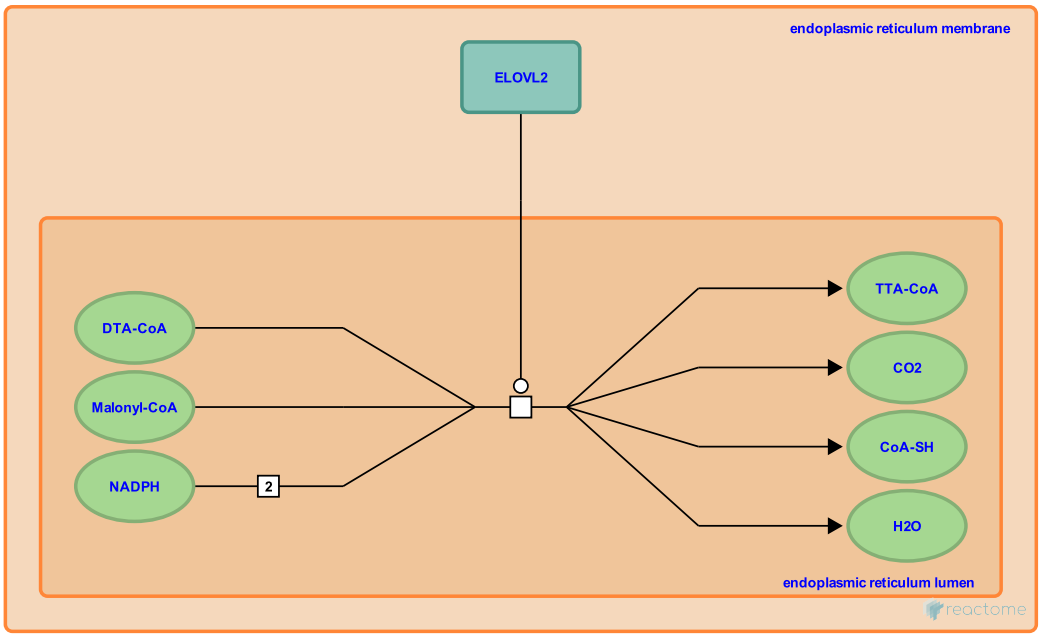
Elongation of docosatetraenoyl-CoA to tetracosatetraenoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046095

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Docosatetraenoyl-CoA is elongated to tetracosatetraenoyl-CoA (TTA-CoA, 9,12,15,18-tetracosatetraenoic acid, 9,12,15,18-24:4(n-6)) by the elongase enzyme ELOVL2.

Preceded by: Elongation of arachidonyl-CoA to docosatetraenoyl-CoA

Followed by: Desaturation of tetracosatetraenoyl-CoA to tetracosapentaenoyl-CoA

Literature references

Bridges, RB., Coniglio, JG. (1970). The biosynthesis of delta-9,12,15,18-tetracosatetraenoic and of delta-6,9,12,15,18-tetracosapentaenoic acids by rat testes. *J Biol Chem, 245*, 46-9. ↗

Leonard, AE., Pereira, SL., Sprecher, H., Huang, YS. (2004). Elongation of long-chain fatty acids. *Prog Lipid Res, 43*, 36-54. ↗

Ayala, S., Gaspar, G., Brenner, RR., Peluffo, RO., Kunau, W. (1973). Fate of linoleic, arachidonic, and docosa-7,10,13,16-tetraenoic acids in rat testicles. *J Lipid Res, 14*, 296-305. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

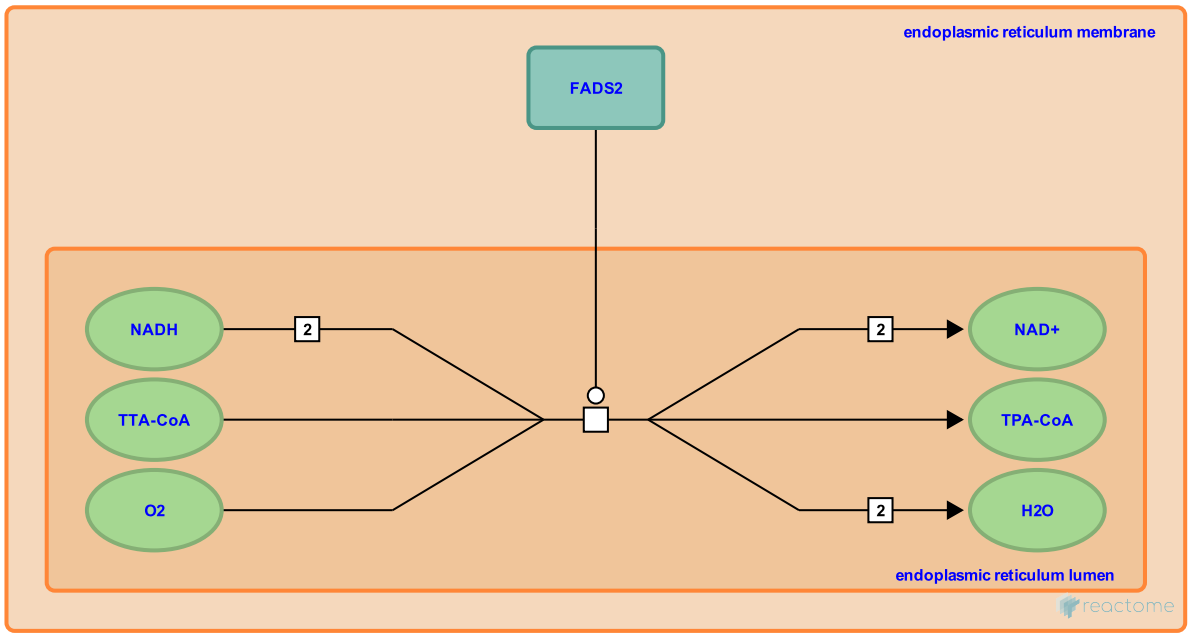
Desaturation of tetracosatetraenoyl-CoA to tetracosapentaenoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046097

Type: transition

Compartments: endoplasmic reticulum lumen, endoplasmic reticulum membrane



Tetracosatetraenoyl-CoA is further desaturated by delta 6-desaturase (FADS2) to tetracosapentaenoyl-CoA (TPA-CoA, 6,9,12,15,18-24:5(n-6)).

Preceded by: Elongation of docosatetraenoyl-CoA to tetracosatetraenoyl-CoA

Followed by: Translocation of tetracosapentaenoyl-CoA to peroxisomes

Literature references

Voss, A., Reinhart, M., Sankarappa, S., Sprecher, H. (1991). The metabolism of 7,10,13,16,19-docosapentaenoic acid to 4,7,10,13,16,19-docosahexaenoic acid in rat liver is independent of a 4-desaturase. *J Biol Chem, 266*, 19995-20000. ↗

d'Andréa, S., Guillou, H., Jan, S., Catheline, D., Thibault, JN., Bouriel, M. et al. (2002). The same rat Delta6-desaturase not only acts on 18- but also on 24-carbon fatty acids in very-long-chain polyunsaturated fatty acid biosynthesis. *Biochem J, 364*, 49-55. ↗

Editions

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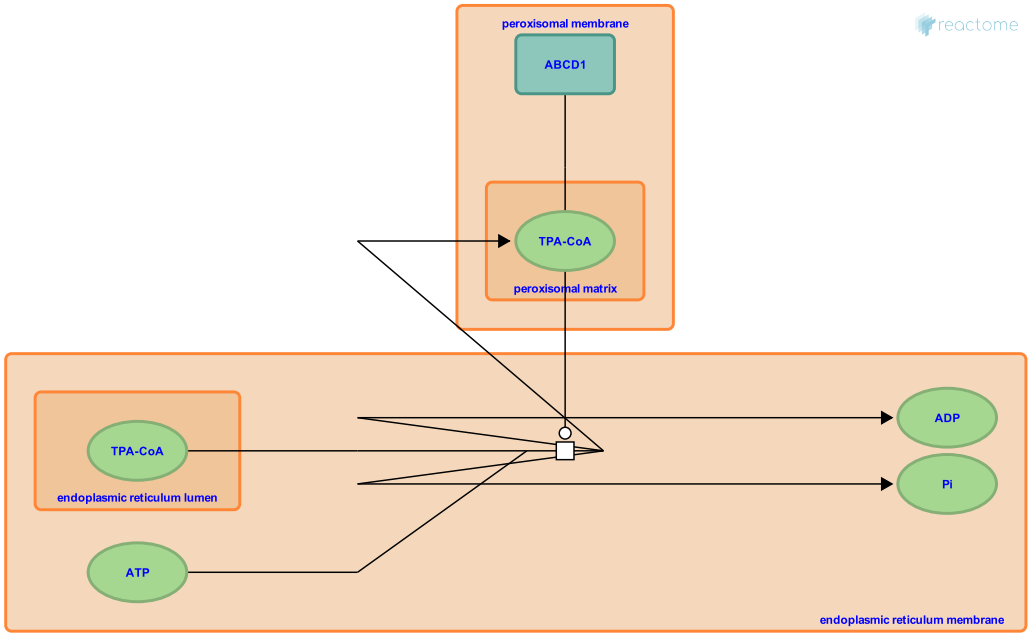
Translocation of tetracosapentaenoyl-CoA to peroxisomes ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046093

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen, peroxisomal membrane, peroxisomal matrix



Prior to this reaction all the enzymes involved in the desaturation and elongation of linoleic acid are located in the ER, but for this last step tetracosapentaenoyl-CoA must be transferred to the peroxisomes for partial beta-oxidation to docosapentaenoyl-CoA (DPA-CoA, 4,7,10,13,16-22:5(n-6)) (Su et al. 2001).

Preceded by: Desaturation of tetracosatetraenoyl-CoA to tetracosapentaenoyl-CoA

Followed by: Peroxisomal beta-oxidation of tetracosapentaenoyl-CoA to Docosapentaenoyl-CoA

Literature references

Infante, JP., Huszagh, VA. (1998). Analysis of the putative role of 24-carbon polyunsaturated fatty acids in the biosynthesis of docosapentaenoic (22:5n-6) and docosahexaenoic (22:6n-3) acids. *FEBS Lett, 431*, 1-6. ↗

Su, HM., Moser, AB., Moser, HW., Watkins, PA. (2001). Peroxisomal straight-chain Acyl-CoA oxidase and D-bifunctional protein are essential for the retroconversion step in docosahexaenoic acid synthesis. *J Biol Chem, 276*, 38115-20. ↗

Ferdinandusse, S., Denis, S., Dacremont, G., Wanders, RJ. (2003). Studies on the metabolic fate of n-3 polyunsaturated fatty acids. *J Lipid Res, 44*, 1992-7. ↗

Editions

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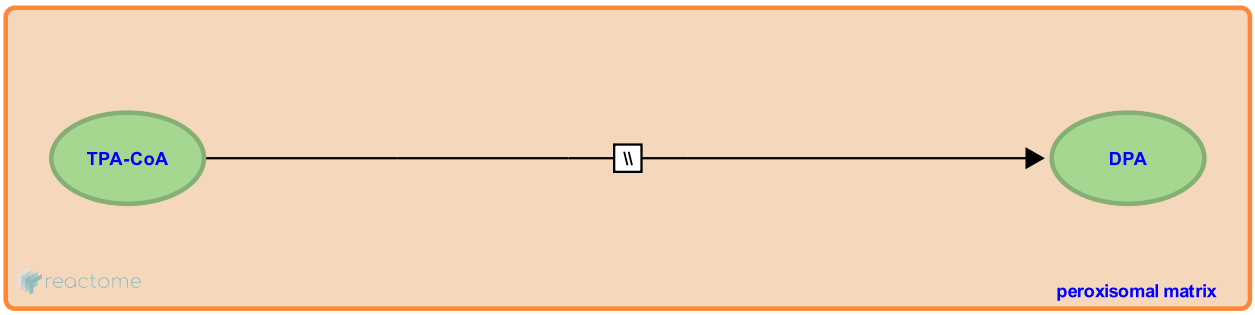
Peroxisomal beta-oxidation of tetracosapentaenoyl-CoA to Docosapentaenoyl-CoA ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2046101

Type: omitted

Compartments: peroxisomal matrix



One cycle of peroxisomal beta-oxidation shortens C24:5(n-6) to C22:5(n-6), releasing one molecules of acetyl-CoA. Peroxisomal acyl-coenzyme A oxidase 1 (AOX), D-bifunctional protein (DBP/MFE2), and either peroxisomal 3-oxoacyl-CoA thiolase (Th) or SCPx thiolase (SCPx) enzymes have been proposed to be responsible for this partial beta-oxidation (Infante & Huszagh 1998, Su et al. 2001).

Preceded by: Translocation of tetracosapentaenoyl-CoA to peroxisomes

Followed by: Translocation of DPA to the ER

Literature references

Infante, JP., Huszagh, VA. (1998). Analysis of the putative role of 24-carbon polyunsaturated fatty acids in the biosynthesis of docosapentaenoic (22:5n-6) and docosahexaenoic (22:6n-3) acids. *FEBS Lett, 431*, 1-6. ↗

Editions

2012-01-11	Authored, Edited	Garapati, P V.

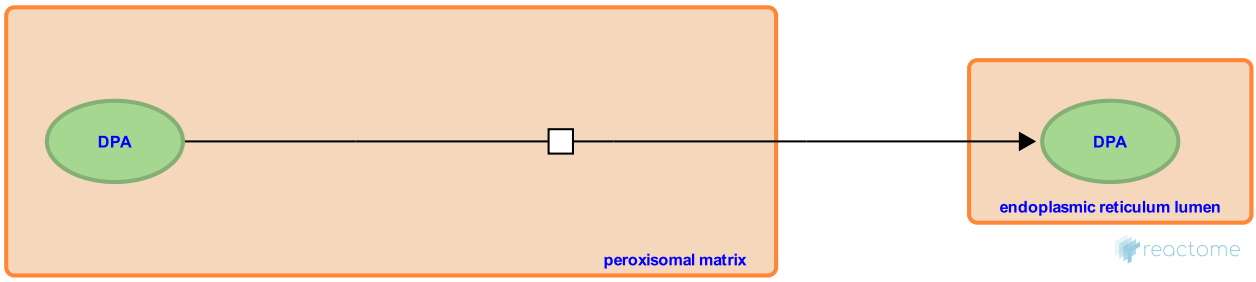
Translocation of DPA to the ER ↗

Location: Linoleic acid (LA) metabolism

Stable identifier: R-HSA-2066782

Type: transition

Compartments: peroxisomal matrix, endoplasmic reticulum lumen



The resulted free DPA is transported back to ER, where it is incorporated into membrane lipids.

Preceded by: Peroxisomal beta-oxidation of tetracosapentaenoyl-CoA to Docosapentaenoyl-CoA

Literature references

Ellis, JM., Frahm, JL., Li, LO., Coleman, RA. (2010). Acyl-coenzyme A synthetases in metabolic control. *Curr Opin Lipidol, 21*, 212-7. ↗

Su, HM., Moser, AB., Moser, HW., Watkins, PA. (2001). Peroxisomal straight-chain Acyl-CoA oxidase and D-bifunctional protein are essential for the retroconversion step in docosahexaenoic acid synthesis. *J Biol Chem, 276*, 38115-20. ↗

Editions

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