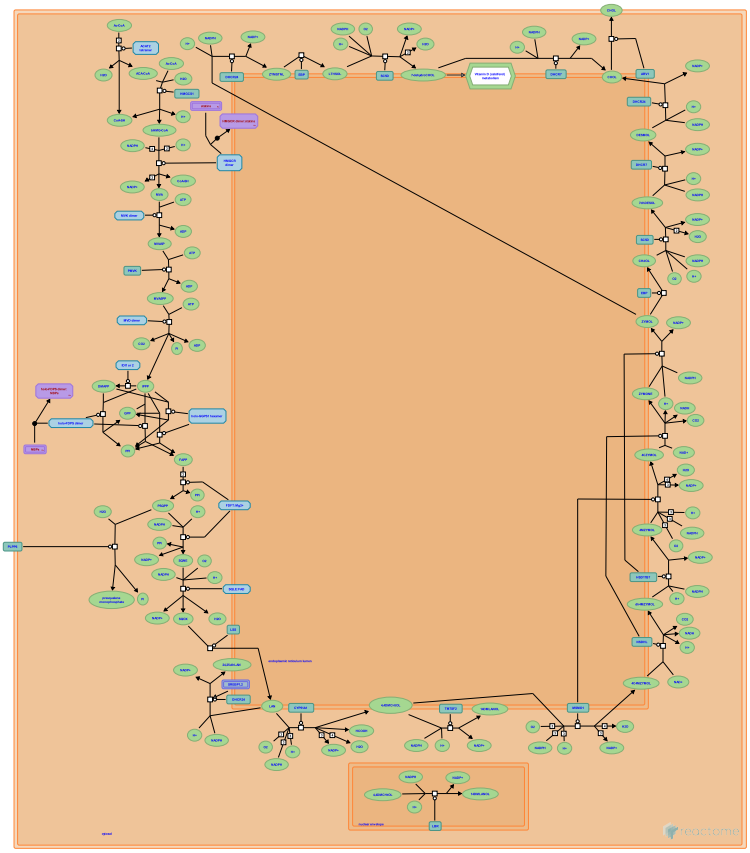
Cholesterol biosynthesis



Brown, AJ., D'Eustachio, P., Huddart, R., Jassal, B., Jupe, S., Levy, BD., Matthews, L., Rozman, D J., Sturley, SL.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

03/04/2024

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. ↗

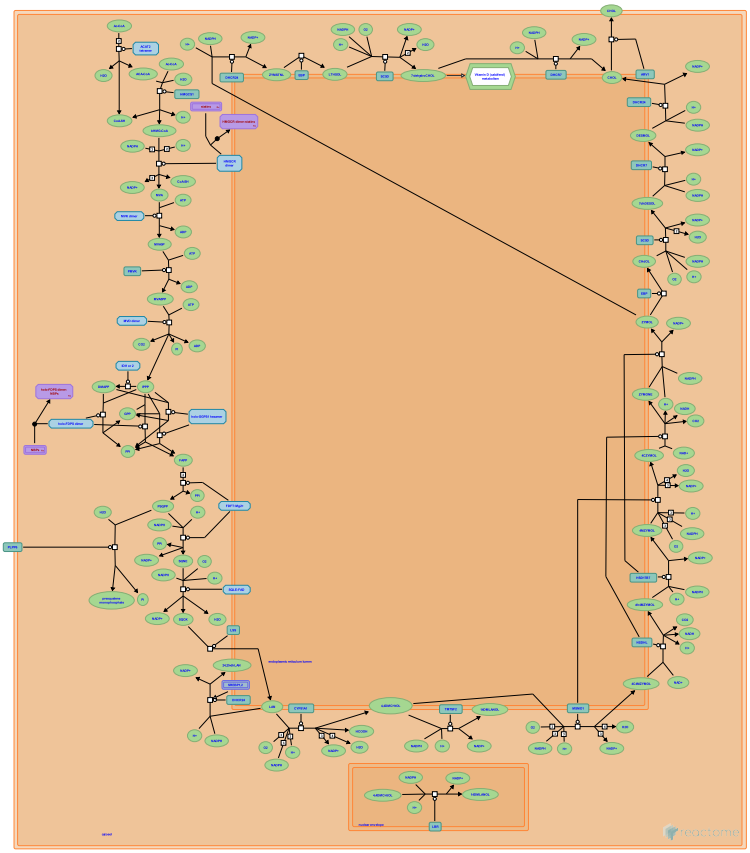
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways and 29 reactions (see Table of Contents)

Cholesterol biosynthesis ↗

Stable identifier: R-HSA-191273



Cholesterol is synthesized de novo from acetyl CoA. The overall synthetic process is outlined in the attached illustration. Enzymes whose regulation plays a major role in determining the rate of cholesterol synthesis in the body are highlighted in red, and connections to other metabolic processes are indicated. The transformation of zymosterol into cholesterol can follow either of routes, one in which reduction of the double bond in the isooctyl side chain is the final step (cholesterol synthesis via desmosterol, also known as the Bloch pathway) and one in which this reduction is the first step (cholesterol biosynthesis via lathosterol, also known as the Kandutsch-Russell pathway). The former pathway is prominent in the liver and many other tissues while the latter is prominent in skin, where it may serve as the source of the 7-dehydrocholesterol that is the starting point for the synthesis of D vitamins. Defects in several of the enzymes involved in this process are associated with human disease and have provided useful insights into the regulatory roles of cholesterol and its synthetic intermediates in human development (Gaylor 2002; Herman 2003; Kandutsch & Russell 1960; Mitsche et al. 2015; Song et al. 2005).

Literature references

Song, BL., DeBose-Boyd, RA., Javitt, NB. (2005). Insig-mediated degradation of HMG CoA reductase stimulated by lanosterol, an intermediate in the synthesis of cholesterol. *Cell Metab, 1*, 179-89. ↗

Gaylor, JL. (2002). Membrane-bound enzymes of cholesterol synthesis from lanosterol. *Biochem Biophys Res Commun, 292*, 1139-46. ↗

Herman, GE. (2003). Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. *Hum Mol Genet, 12*, R75-88. ↗

Rudney, H., Sexton, RC. (1986). Regulation of cholesterol biosynthesis. *Annu Rev Nutr, 6*, 245-72. ↗

Russell, DW. (1992). Cholesterol biosynthesis and metabolism. *Cardiovasc Drugs Ther, 6*, 103-10. ↗

Editions

2007-01-22	Edited, Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.
2015-11-02	Revised	D'Eustachio, P.
2015-11-02	Reviewed	Jassal, B.
2021-11-23	Revised	Rozman, D J.

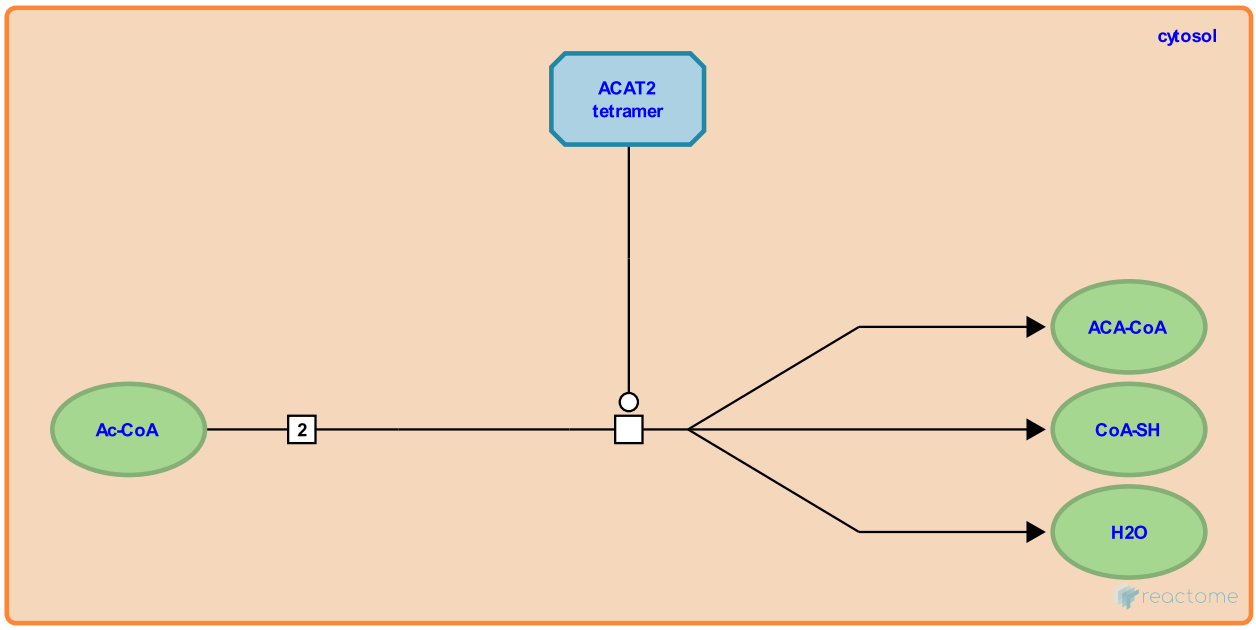
ACAT2 condenses 2 Ac-CoA to form ACA-CoA ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-8848215

Type: transition

Compartments: cytosol



Three human enzymes can utilise ketone bodies for energy production. Two mitochondrial enzymes function in ketolysis whereas a cytosolic enzyme is implicated in cytosolic cholesterol biosynthesis. Cytosolic acetyl-CoA acetyltransferase tetramer (ACAT2 tetramer) (Song et al. 1994) catalyses the condensation of two acetyl-CoA (Ac-CoA) molecules to form acetoacetyl-CoA (ACA-CoA). This is the first step in the biosynthesis of cholesterol (Fukao et al. 1997).

Followed by: HMGCS1 condenses Ac-CoA and ACA-CoA to form bHMG-CoA

Literature references

Sukegawa, K., Orii, T., Mitchell, GA., Kondo, N., Yamaguchi, S., Fukao, T. et al. (1997). Enzymes of ketone body utilization in human tissues: protein and messenger RNA levels of succinyl-coenzyme A (CoA):3-ketoacid CoA transferase and mitochondrial and cytosolic acetoacetyl-CoA thiolases. *Pediatr. Res., 42*, 498-502. ↗

Hashimoto, T., Orii, T., Yamaguchi, S., Fukao, T., Miyazawa, S., Song, XQ. (1994). Molecular cloning and nucleotide sequence of complementary DNA for human hepatic cytosolic acetoacetyl-coenzyme A thiolase. *Biochem. Biophys. Res. Commun., 201*, 478-85. ↗

Editions

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

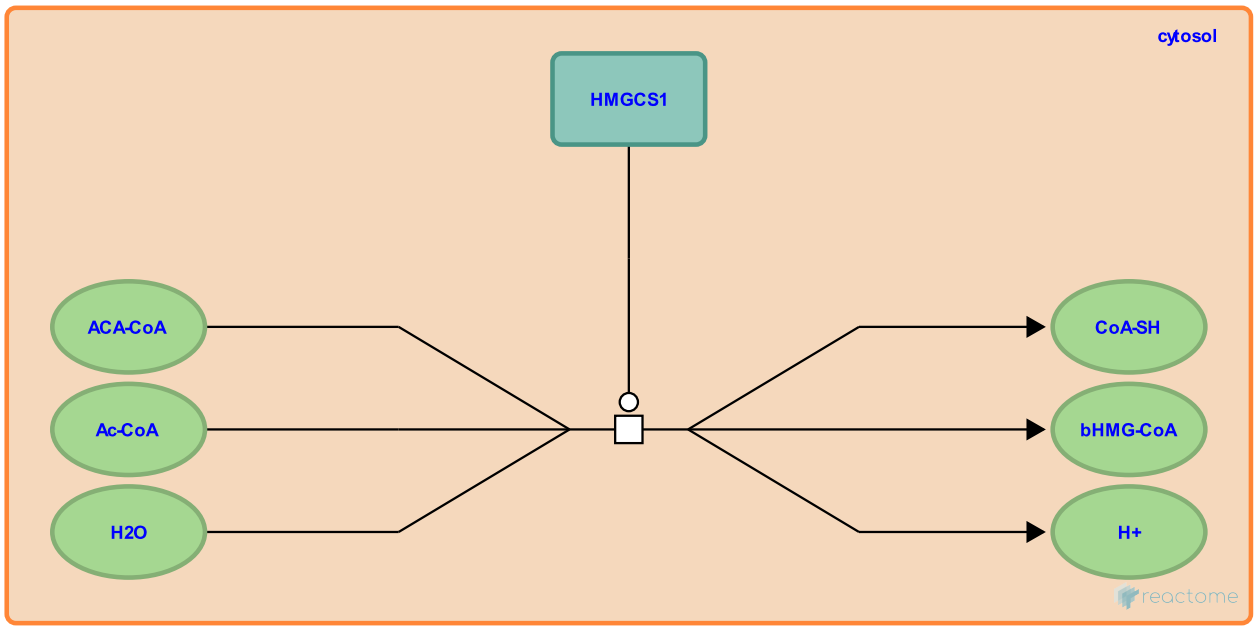
HMGCS1 condenses Ac-CoA and ACA-CoA to form bHMG-CoA ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191323

Type: transition

Compartments: cytosol



3-hydroxy-3-methylglutaryl Coenzyme A synthase (HMG-CoA synthase) catalyzes the condensation of acetyl CoA with acetoacetyl CoA to produce HMG-CoA. There are two forms of this enzyme, cytosolic and mitochondrial. The cytosolic form is ubiquitous in the body and is involved in cholesterol biosynthesis and synthesis of other isoprenoid products. The mitochondrial form, found solely in the liver and kidney, is involved in the ketogenic pathway.

Preceded by: ACAT2 condenses 2 Ac-CoA to form ACA-CoA

Followed by: HMGCR dimer reduces bHMG-CoA to MVA

Literature references

Butkiewicz, EA., Sanyal, G., Rokosz, LL., Cueto, MA., Lachance, PA., Boulton, DA. et al. (1994). Human cytoplasmic 3-hydroxy-3-methylglutaryl coenzyme A synthase: expression, purification, and characterization of recombinant wild-type and Cys129 mutant enzymes. *Arch Biochem Biophys, 312*, 1-13. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.
2021-06-30	Revised	D'Eustachio, P.

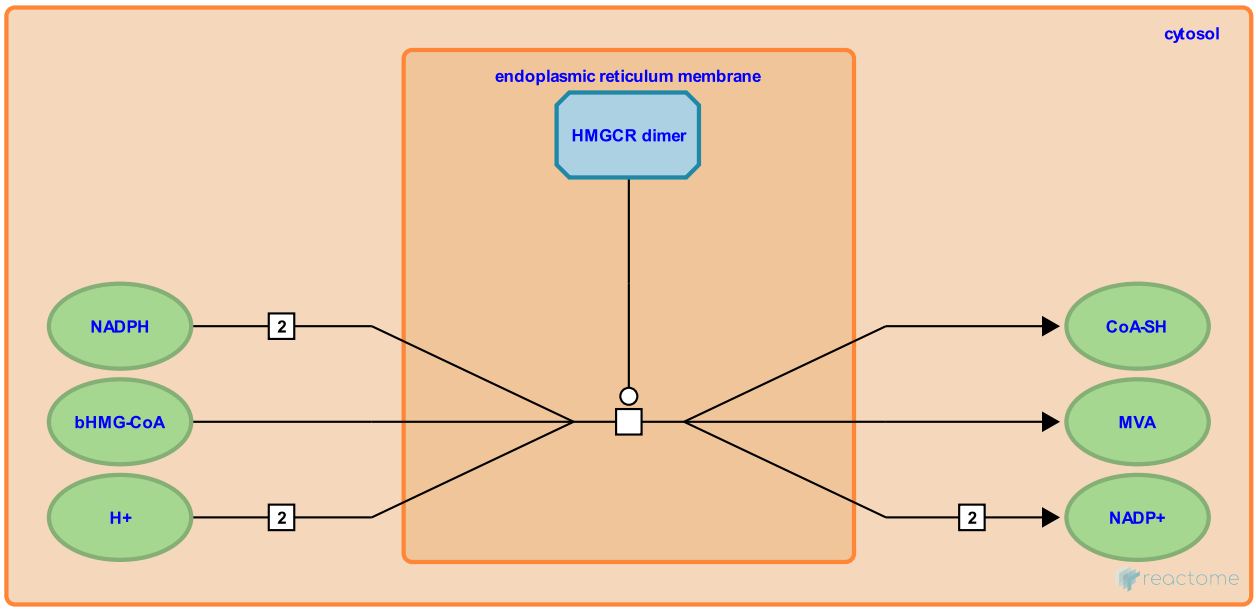
HMGCR dimer reduces bHMG-CoA to MVA ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191352

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Dimeric 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR dimer) catalyzes the four-electron reduction of beta-hydroxy-beta-methylglutaryl-CoA (bHMG-CoA) to mevalonate (MVA). MVA concentrations in the cell are tightly controlled through the activity of HMGCR dimer, which is one of the most highly regulated enzymes in metabolism (Goldstein & Brown 1990).

Preceded by: HMGCS1 condenses Ac-CoA and ACA-CoA to form bHMG-CoA

Followed by: Mevalonate is phosphorylated to mevalonate-5-phosphate

Literature references

Deisenhofer, J., Istvan, ES., Buchanan, SK., Palnitkar, M. (2000). Crystal structure of the catalytic portion of human HMG-CoA reductase: insights into regulation of activity and catalysis. *EMBO J, 19*, 819-30. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

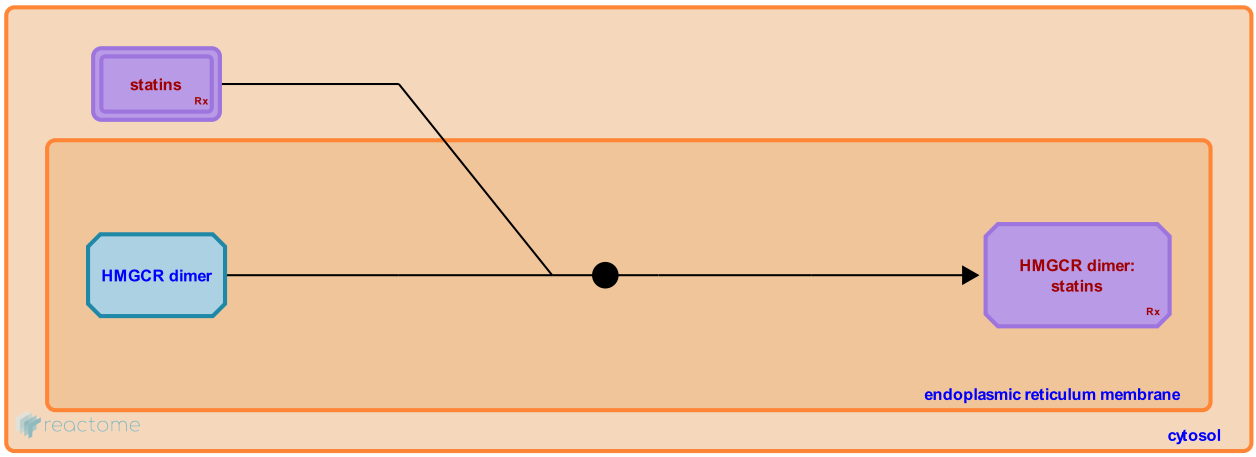
HMGCR dimer binds statins ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-9705584

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol



Dimeric 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR dimer) is the key enzyme in the cholesterol biosynthetic pathway and catalyzes the committed step of the reduction of beta-hydroxy-3-methylglutaryl CoA (bHMG-CoA) to mevalonate. HMGCR is regarded as one of the most important drug targets in the treatment of hypercholesterolemia. HMGCR inhibitors, commonly referred to as statins, are among the most widely prescribed drugs in the world. Statins work by their similarity to the substrate (bHMG-CoA), leading to competition towards the HMG binding site on the enzyme between substrate and statins (Istvan & Deisenhofer 2001). As statins also block the access of the substrate to the binding site, the affinity of HMGCR for statins is slightly higher than its affinity for the substrate (Istvan 2002, Carbonell & Ernesto Freire 2005, Gesto et al. 2020). Statins can be divided in two types, according to their origin. Type I statins e.g. lovastatin, pravastatin and simvastatin, are natural fungal products and Type II statins e.g. atorvastatin, rosuvastatin and fluvastatin, are fully synthetic.

Literature references

Istvan, ES. (2002). Structural mechanism for statin inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Am Heart J, 144*, S27-32. ↗

Freire, E., Carbonell, T. (2005). Binding thermodynamics of statins to HMG-CoA reductase. *Biochemistry, 44*, 11741-8. ↗

Istvan, ES., Deisenhofer, J. (2001). Structural mechanism for statin inhibition of HMG-CoA reductase. *Science, 292*, 1160-4. ↗

Editions

2020-10-27	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

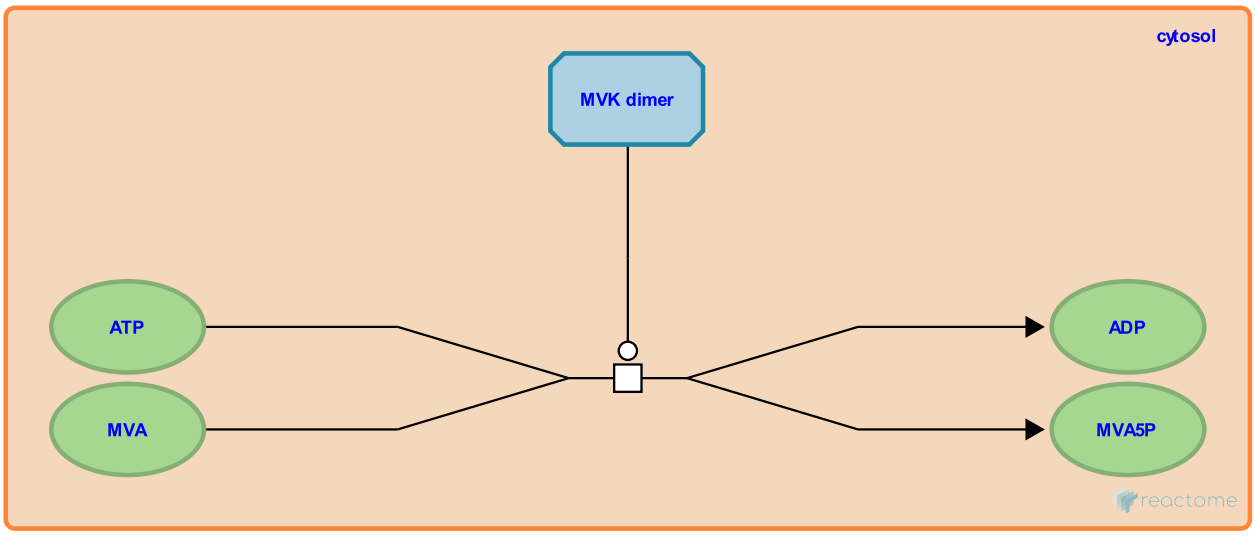
Mevalonate is phosphorylated to mevalonate-5-phosphate ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191380

Type: transition

Compartments: cytosol



Mevalonate kinase (MK) catalyzes the phosphorylation of mevalonate to mevalonate-5-phosphate.

Preceded by: HMGCR dimer reduces bHMG-CoA to MVA

Followed by: Mevalonate-5-phosphate is further phosphorylated.

Literature references

Mosley, ST., Bishop, RW., Schafer, BL., Kalinowski, SS., Kratunis, VJ., Gibson, KM. et al. (1992). Molecular cloning of human mevalonate kinase and identification of a missense mutation in the genetic disease mevalonic aciduria. *J Biol Chem, 267*, 13229-38. ↗

Koster, J., Tuyp, JJ., Wanders, RJA., Espeel, M., Waterham, HR., Hogenboom, S. (2004). Mevalonate kinase is a cytosolic enzyme in humans. *J Cell Sci, 117*, 631-9. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

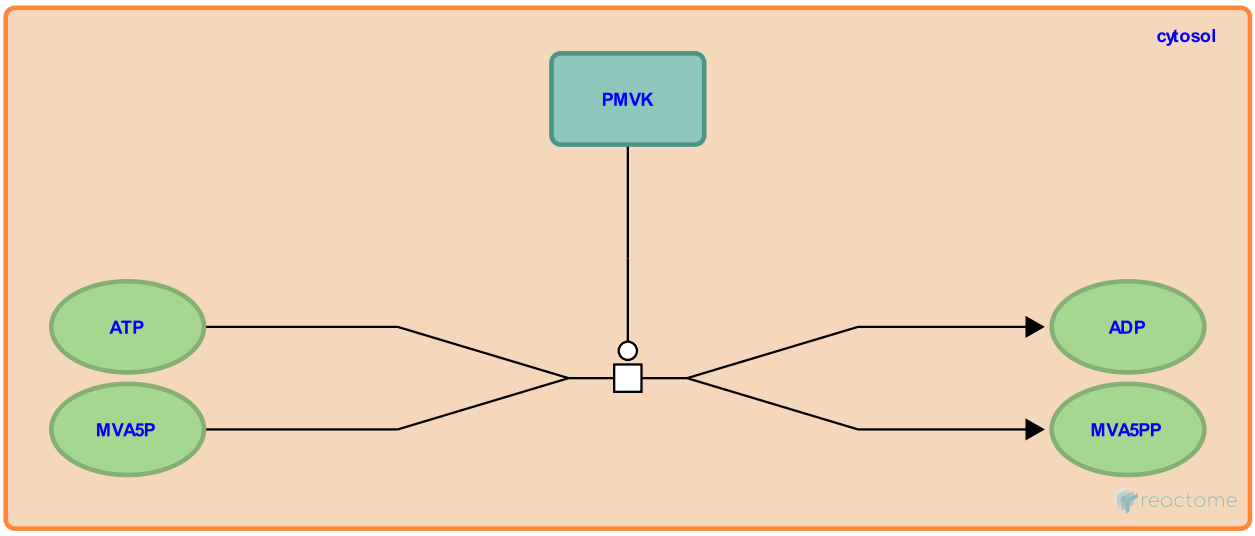
Mevalonate-5-phosphate is further phosphorylated. ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191422

Type: transition

Compartments: cytosol



Phosphomevalonate kinase (PMK) catalyzes the reversible, ATP-dependent phosphorylation of mevalonate-5-phosphate, producing mevalonate-5-pyrophosphate.

Preceded by: Mevalonate is phosphorylated to mevalonate-5-phosphate

Followed by: MVD decarboxylates MVA5PP to IPPP

Literature references

Koster, J., Tuyp, JJ., Wanders, RJA., Espeel, M., Waterham, HR., Hogenboom, S. (2004). Phosphomevalonate kinase is a cytosolic protein in humans. *J Lipid Res, 45*, 697-705. ↗

Herdendorf, TJ., Miziorko, HM. (2006). Phosphomevalonate kinase: functional investigation of the recombinant human enzyme. *Biochemistry, 45*, 3235-42. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

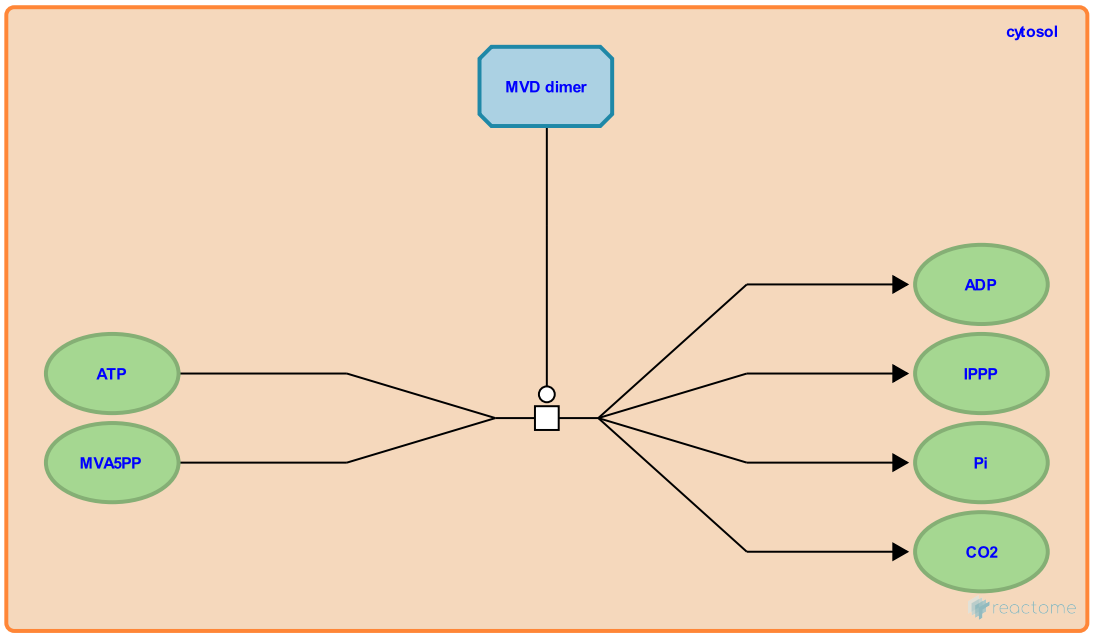
MVD decarboxylates MVA5PP to IPPP ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191414

Type: transition

Compartments: cytosol



Mevalonate pyrophosphate decarboxylase (MPD) decarboxylates mevalonate-5-pyrophosphate (MVA5PP) into isopentenyl pyrophosphate (IPPP) while hydrolysing ATP to ADP and orthophosphate (Toth & Huwyler 1996).

Preceded by: Mevalonate-5-phosphate is further phosphorylated.

Followed by: Isopentenyl pyrophosphate rearranges to dimethylallyl pyrophosphate

Literature references

Huwyler, L., Toth, MJ. (1996). Molecular cloning and expression of the cDNAs encoding human and yeast mevalonate pyrophosphate decarboxylase. *J Biol Chem, 271*, 7895-8. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored, Edited	Jassal, B.

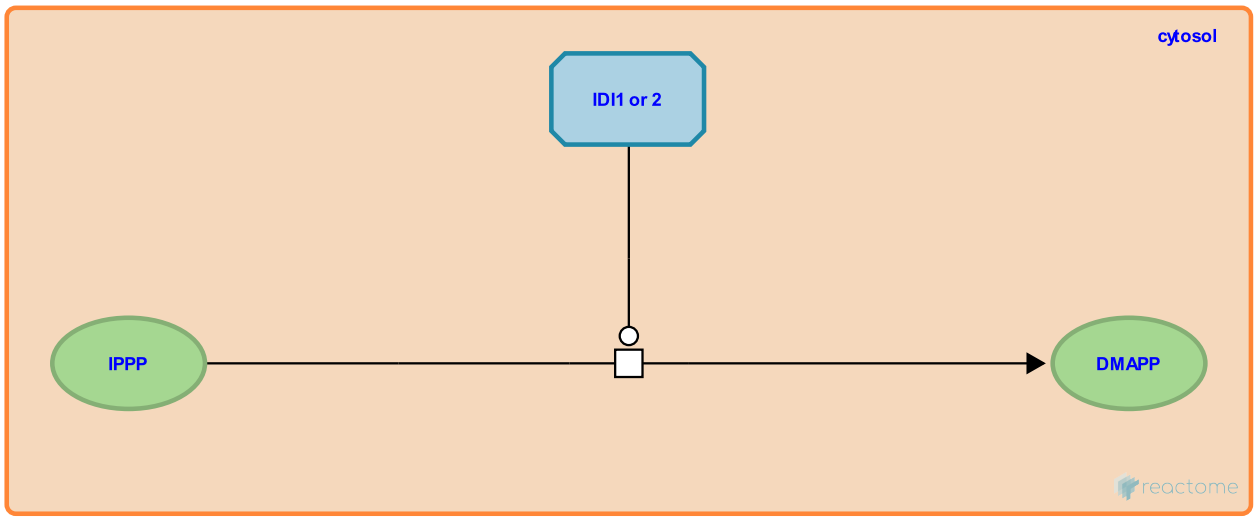
Isopentenyl pyrophosphate rearranges to dimethylallyl pyrophosphate ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191382

Type: transition

Compartments: cytosol



Cytosolic isopentenyl diphosphate isomerase (IPP isomerase) catalyzes an essential activation step in the isoprenoid biosynthetic pathway. It rearranges isopentenyl pyrophosphate into its highly electrophilic isomer, dimethylallyl pyrophosphate (DMAPP). IPP isomerase may also be located in human peroxisomes but it's function there is not clear.

Preceded by: MVD decarboxylates MVA5PP to IPPP

Followed by: FDPS dimer transfers IPPP to DMAPP, GGPS1 hexamer transfers IPPP to DMAPP

Literature references

Xuan, JW., Chambers, AF., Poulter, CD., Hahn, FM. (1996). Human isopentenyl diphosphate: dimethylallyl diphosphate isomerase: overproduction, purification, and characterization. *Arch Biochem Biophys, 332*, 30-4. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

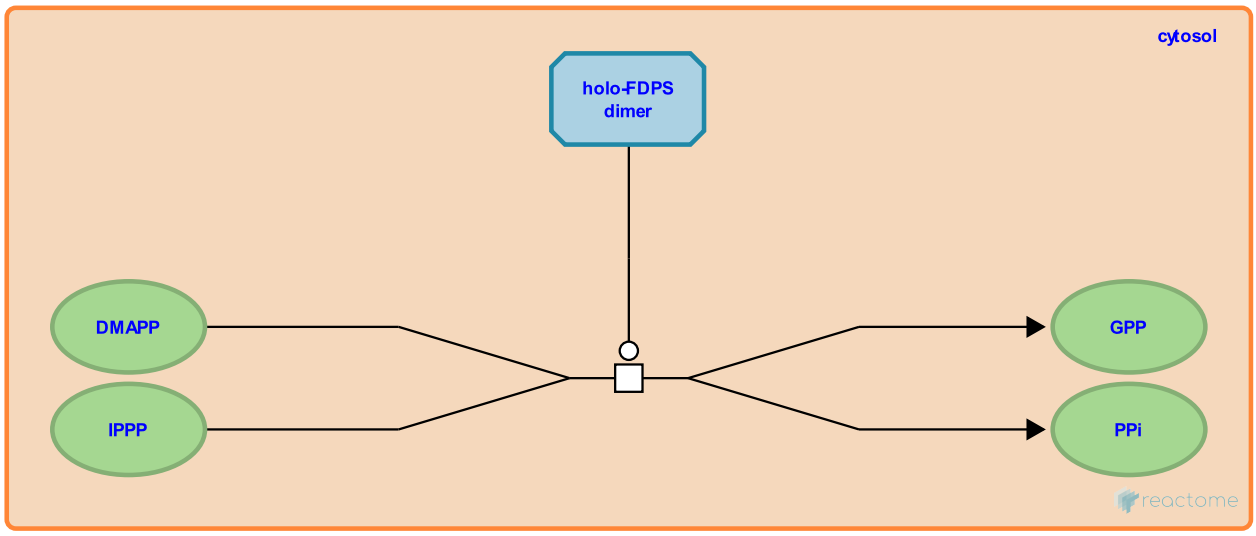
FDPS dimer transfers IPPP to DMAPP ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191322

Type: transition

Compartments: cytosol



The family of enzymes called prenyltransferases is involved in the biosynthesis of isoprenoids. Two members of this family are known to catalyse the sequential condensation of isopentenyl pyrophosphate (IPPP) to DMAPP: farnesyl pyrophosphate synthase dimer (FPPS dimer) and geranylgeranyl pyrophosphate synthetase hexamer (GGPPS hexamer) (Kavanaugh et al, 2006). Both enzymes utlise Mg2+ as cofactor (Chang et al. 2021).

Preceded by: Isopentenyl pyrophosphate rearranges to dimethylallyl pyrophosphate

Followed by: FDPS dimer transfers IPPP to GPP

Literature references

Wang, AH., Chang, HY., Cheng, TH. (2021). Structure, catalysis, and inhibition mechanism of prenyltransferase. *IUBMB Life, 73*, 40-63. ↗

Edwards, PA., Shell, BK., Greene, JM., Ericsson, J., Florence, C., Carter, KC. et al. (1998). Human geranylgeranyl diphosphate synthase: isolation of the cDNA, chromosomal mapping and tissue expression. *J Lipid Res, 39*, 1731-9. ↗

Knapp, S., Russell, RG., Guo, K., Oppermann, U., Ebetino, FH., Kavanagh, KL. et al. (2006). The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci U S A, 103*, 7829-34. ↗

Sagami, I., Kuzuguchi, T., Morita, Y., Sagami, H., Ogura, K. (1999). Human geranylgeranyl diphosphate synthase. cDNA cloning and expression. *J Biol Chem, 274*, 5888-94. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored, Edited	Jassal, B.

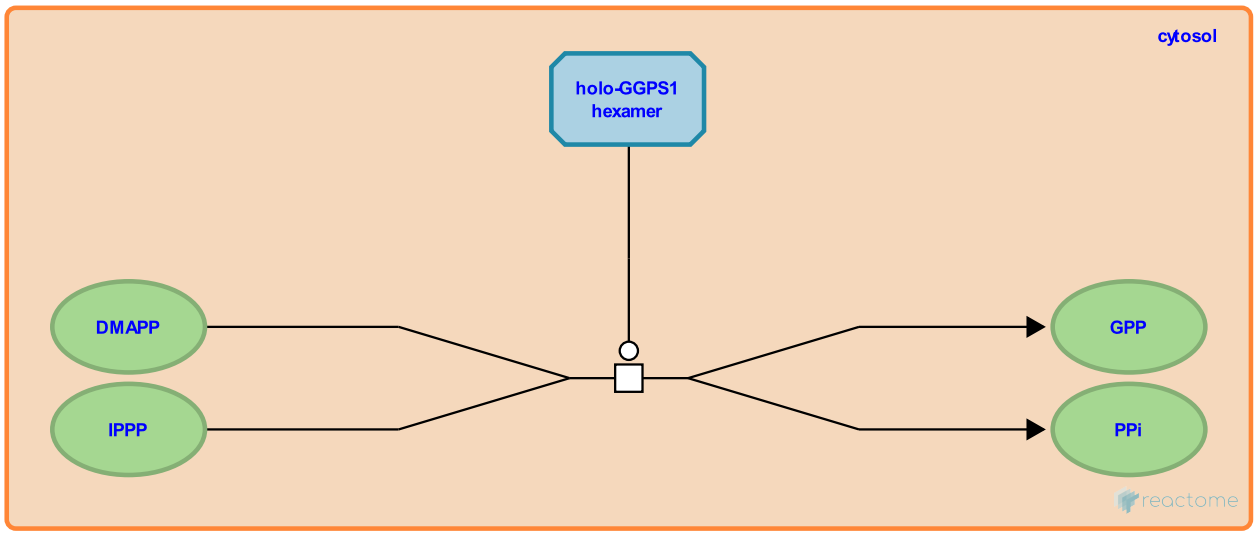
GGPS1 hexamer transfers IPPP to DMAPP ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-9717834

Type: transition

Compartments: cytosol



The family of enzymes called prenyltransferases is involved in the biosynthesis of isoprenoids. Two members of this family are known to catalyse the sequential condensation of isopentenyl pyrophosphate (IPPP) to DMAPP: farnesyl pyrophosphate synthase dimer (FPPS dimer) and geranylgeranyl pyrophosphate synthetase hexamer (GGPPS hexamer) (Kavanaugh et al, 2006). Both enzymes utlise Mg2+ as cofactor (Chang et al. 2021).

Preceded by: Isopentenyl pyrophosphate rearranges to dimethylallyl pyrophosphate

Followed by: GGPS1 hexamer transfers IPPP to GPP

Literature references

Wang, AH., Chang, HY., Cheng, TH. (2021). Structure, catalysis, and inhibition mechanism of prenyltransferase. *IUBMB Life, 73*, 40-63. ↗

Edwards, PA., Shell, BK., Greene, JM., Ericsson, J., Florence, C., Carter, KC. et al. (1998). Human geranylgeranyl diphosphate synthase: isolation of the cDNA, chromosomal mapping and tissue expression. *J Lipid Res, 39*, 1731-9. ↗

Knapp, S., Russell, RG., Guo, K., Oppermann, U., Ebetino, FH., Kavanagh, KL. et al. (2006). The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci U S A, 103*, 7829-34. ↗

Sagami, I., Kuzuguchi, T., Morita, Y., Sagami, H., Ogura, K. (1999). Human geranylgeranyl diphosphate synthase. cDNA cloning and expression. *J Biol Chem, 274*, 5888-94. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored, Edited	Jassal, B.

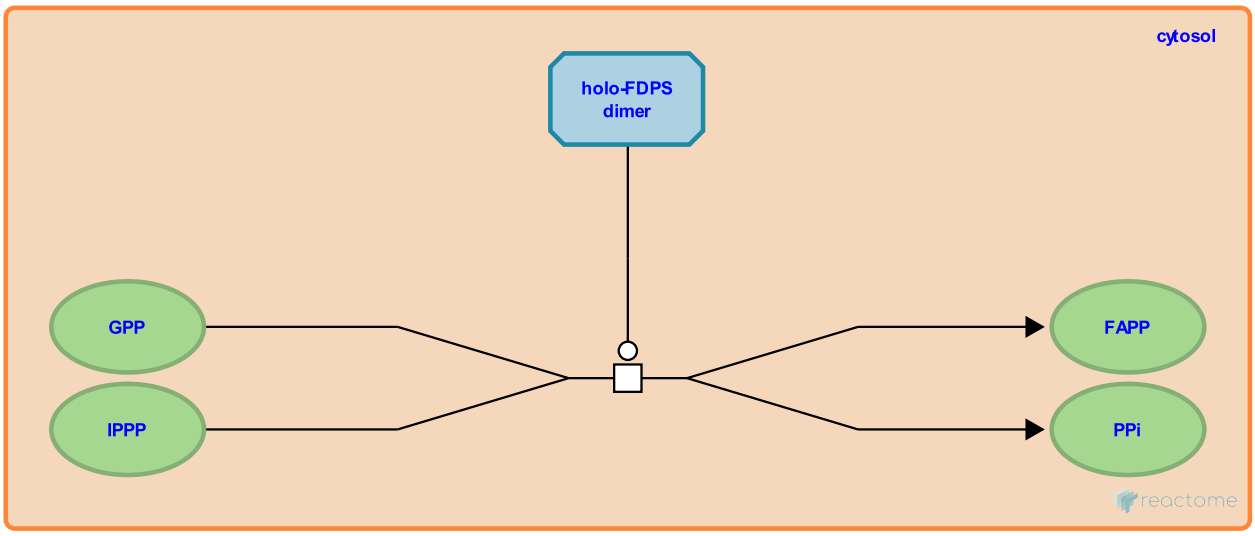
FDPS dimer transfers IPPP to GPP ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191303

Type: transition

Compartments: cytosol



Further condensation of an isopentenyl pyrophosphate (IPPP) with geranyl pyrophosphate (GPP) to form farnesyl pyrophosphate (FAPP) is catalyzed by the prenyltransferases FPP synthase and GGPP synthase (Kavanagh et al, 2006).

Preceded by: FDPS dimer transfers IPPP to DMAPP

Followed by: Two FPP molecules dimerize to form presqualene diphosphate

Literature references

Edwards, PA., Shell, BK., Greene, JM., Ericsson, J., Florence, C., Carter, KC. et al. (1998). Human geranylgeranyl diphosphate synthase: isolation of the cDNA, chromosomal mapping and tissue expression. *J Lipid Res, 39*, 1731-9. ↗

Knapp, S., Russell, RG., Guo, K., Oppermann, U., Ebetino, FH., Kavanagh, KL. et al. (2006). The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci U S A, 103*, 7829-34. ↗

Sagami, I., Kuzuguchi, T., Morita, Y., Sagami, H., Ogura, K. (1999). Human geranylgeranyl diphosphate synthase. cDNA cloning and expression. *J Biol Chem, 274*, 5888-94. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored, Edited	Jassal, B.

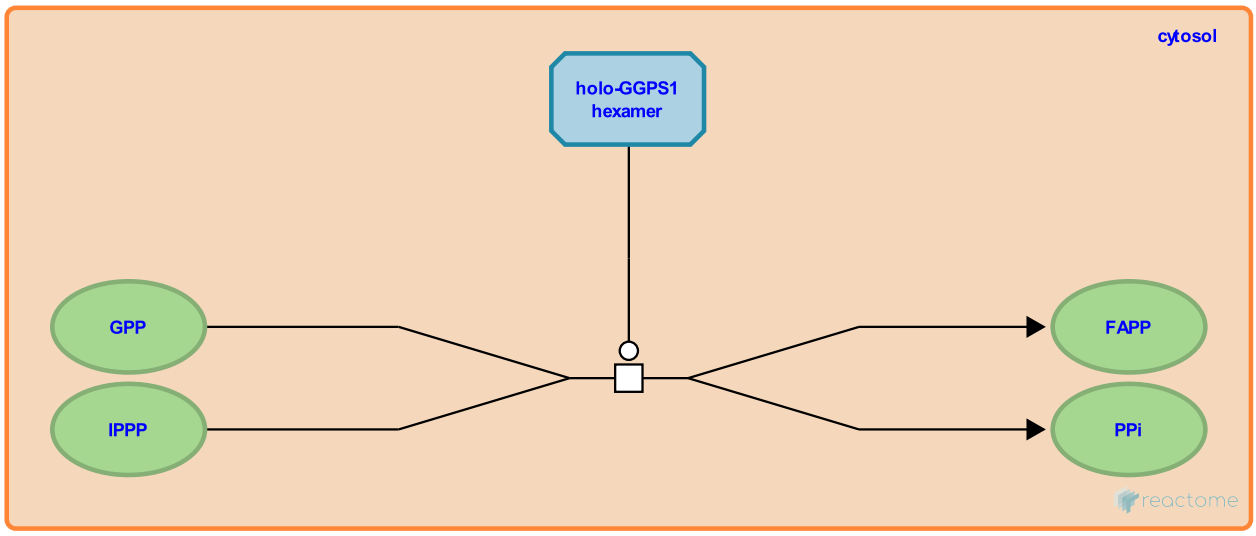
GGPS1 hexamer transfers IPPP to GPP ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-9717830

Type: transition

Compartments: cytosol



Further condensation of an isopentenyl pyrophosphate (IPPP) with geranyl pyrophosphate (GPP) to form farnesyl pyrophosphate (FAPP) is catalyzed by the prenyltransferases FPP synthase and GGPP synthase (Kavanagh et al, 2006).

Preceded by: GGPS1 hexamer transfers IPPP to DMAPP

Followed by: Two FPP molecules dimerize to form presqualene diphosphate

Literature references

Edwards, PA., Shell, BK., Greene, JM., Ericsson, J., Florence, C., Carter, KC. et al. (1998). Human geranylgeranyl diphosphate synthase: isolation of the cDNA, chromosomal mapping and tissue expression. *J Lipid Res, 39*, 1731-9. ↗

Knapp, S., Russell, RG., Guo, K., Oppermann, U., Ebetino, FH., Kavanagh, KL. et al. (2006). The molecular mechanism of nitrogen-containing bisphosphonates as antiosteoporosis drugs. *Proc Natl Acad Sci U S A, 103*, 7829-34. ↗

Sagami, I., Kuzuguchi, T., Morita, Y., Sagami, H., Ogura, K. (1999). Human geranylgeranyl diphosphate synthase. cDNA cloning and expression. *J Biol Chem, 274*, 5888-94. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored, Edited	Jassal, B.

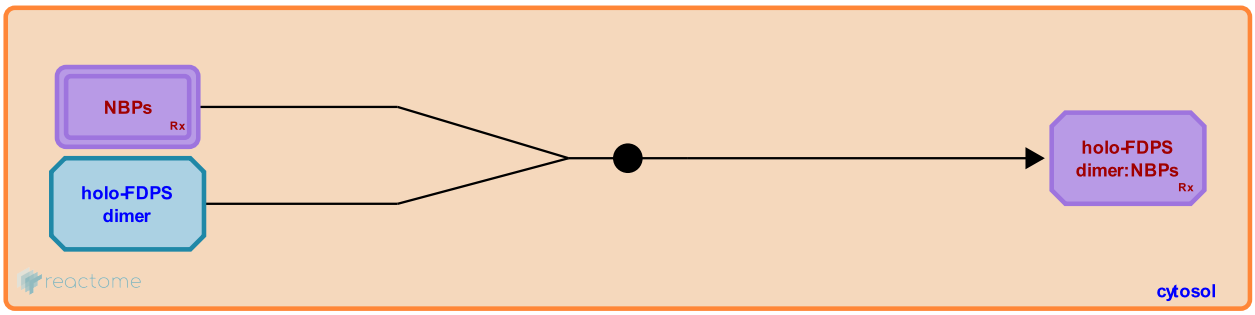
holo-FDPS dimer binds NBPs ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-9717841

Type: binding

Compartments: cytosol



The mevalonate pathway is responsible for the biosynthesis of all isoprenoids, metabolites that are vital for normal cellular functions. Two key isoprenoids, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) are responsible for the post-translational prenylation of small GTP-binding proteins, and serve as the biosynthetic precursors to numerous other biomolecules. The downstream metabolite of FPP and GGPP is squalene, the precursor to steroids, bile acids, lipoproteins, and vitamin D.

Nitrogen-containing bisphosphonates (NBPs) are drugs used to treat diseases characterized by excessive bone resorption such as Paget's disease of bone, bone metastases, multiple myeloma (Simoni et al. 2008), and osteoporosis. NBPs act by inhibiting farnesyl pyrophosphate synthase (FDPS) involved in the mevalonate pathway (Bergstrom et al. 2000, Dunford et al. 2001, Dunford et al. 2008, Räikkönen et al. 2011). Inhibition of FDPS in osteoclasts prevents the biosynthesis of the isoprenoid lipids FPP and GGPP, which are essential for the post-translational farnesylation and geranylgeranylation of small GTPase signalling proteins. Loss of bone-resorptive activity and osteoclast apoptosis is primarily due to the loss of geranylgeranylated small GTPases (Review - Cremers et al. 2019). Approved NBPs include the second generation NBPs pamidronic acid and alendronic acid and the third generation NBPs ibandronic acid, zoledronic acid, minodronic acid and risedronate.

Literature references

Luckman, SP., Dunford, JE., Ebetino, FH., Thompson, K., Poulter, CD., Rogers, MJ. et al. (2001). Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J. Pharmacol. Exp. Ther., 296*, 235-42. ↗

Russell, RG., Kwaasi, AA., Barnett, BL., Dunford, JE., Oppermann, U., Rogers, MJ. et al. (2008). Structure-activity relationships among the nitrogen containing bisphosphonates in clinical use and other analogues: time-dependent inhibition of human farnesyl pyrophosphate synthase. *J. Med. Chem., 51*, 2187-95. ↗

Provera, S., Limongelli, V., Dieli, F., Kwaasi, A., Invidiata, FP., Marchioro, C. et al. (2008). Design, synthesis, and biological evaluation of novel aminobisphosphonates possessing an in vivo antitumor activity through a gammadelta-T lymphocytes-mediated activation mechanism. *J. Med. Chem., 51*, 6800-7. ↗

Kirsten, ML., Dunford, JE., Baron, RA., McKenna, CE., Ebetino, FH., Stewart, CA. et al. (2010). Synthesis, chiral high performance liquid chromatographic resolution and enantiospecific activity of a potent new geranylgeranyl transferase inhibitor, 2-hydroxy-3-imidazo[1,2-a]pyridin-3-yl-2-phosphonopropionic acid. *J Med Chem, 53*, 3454-64. ↗

Räikkönen, J., Mönkkönen, H., Dunford, JE., Mönkkönen, J., Taskinen, M., Auriola, S. (2011). Correlation between time-dependent inhibition of human farnesyl pyrophosphate synthase and blockade of mevalonate pathway by nitrogen-containing bisphosphonates in cultured cells. *Biochem Biophys Res Commun, 407*, 663-7. ↗

Editions

2021-03-15	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.

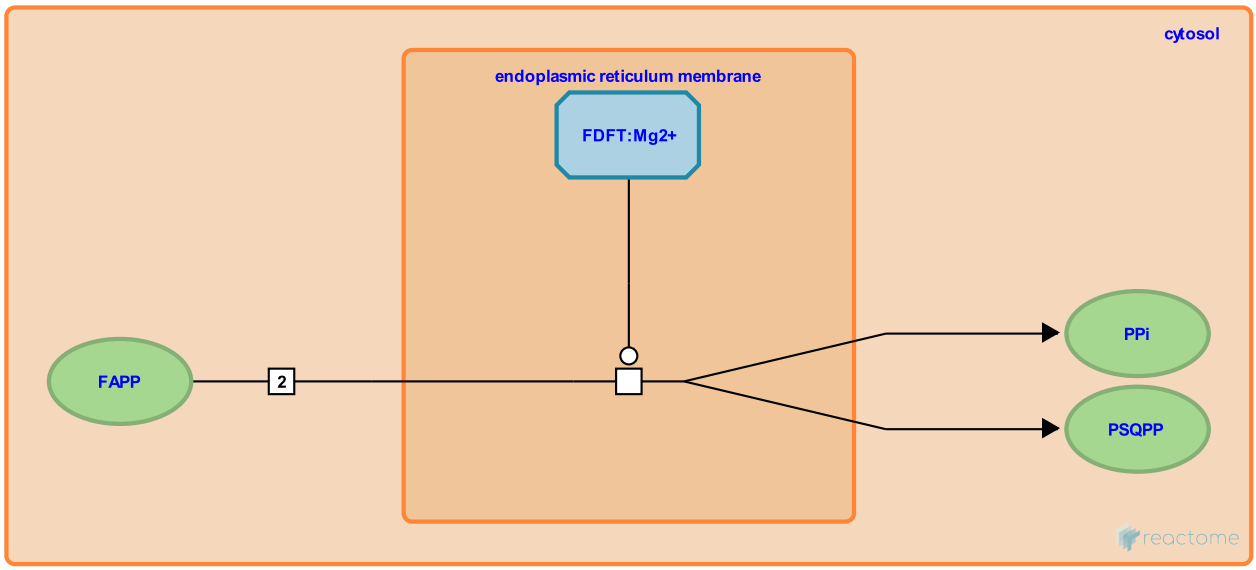
Two FPP molecules dimerize to form presqualene diphosphate ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191405

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Farnesyl diphosphate farnesyltransferase (FDFT; squalene synthase) catalyzes the reductive dimerization of two farnesyl diphosphate (FPP) molecules to form squalene. This happens in two distinct steps. The first step of dimerization forms presqualene diphosphate (Pandit et al. 2000).

Preceded by: FDPS dimer transfers IPPP to GPP, GGPS1 hexamer transfers IPPP to GPP

Followed by: Reduction of presqualene diphosphate to form squalene

Literature references

Danley, DE., Harwood HJ, Jr., Hamanaka, ES., Schulte, GK., Pandit, J., Mazzalupo, S. et al. (2000). Crystal structure of human squalene synthase. A key enzyme in cholesterol biosynthesis. *J Biol Chem, 275*, 30610-7. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

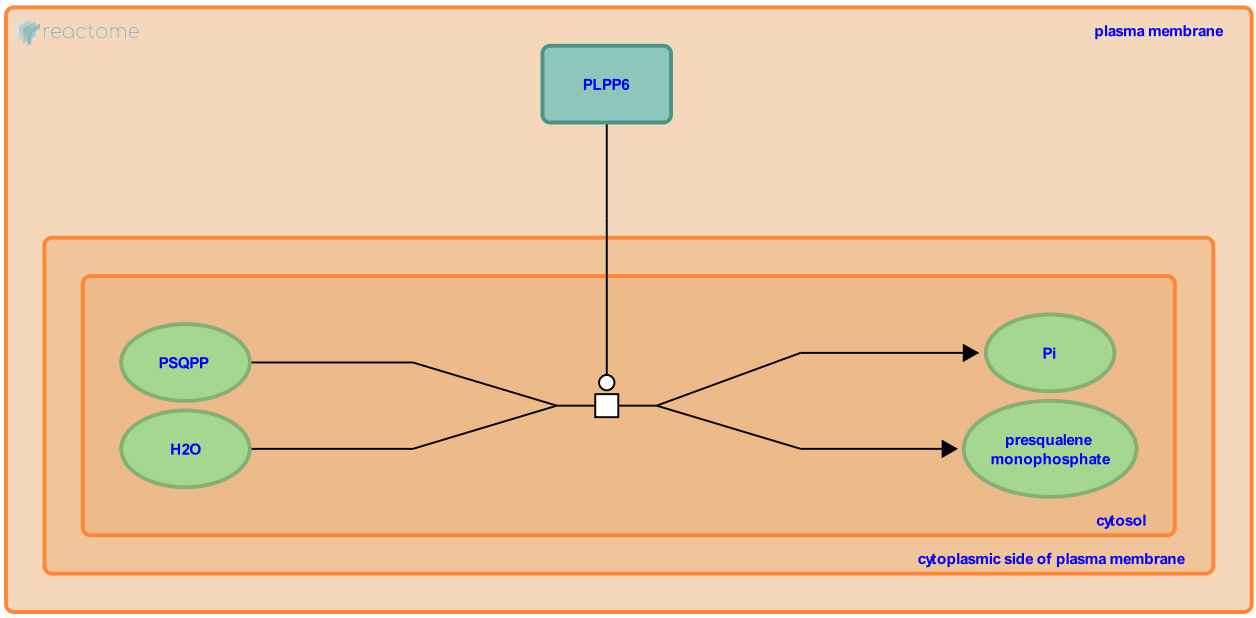
Phospholipid phosphatase 6 hydrolyses Presqualene diphosphate to presqualene monophosphate ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-8952137

Type: transition

Compartments: cytosol



Phospholipid phosphatase 6 (PLPP6) dephosphorylates presqualene diphosphate (PSQPP) to presqualene monophosphate (PSMP). It may be indirectly involved in innate immunity, as PSDP is a bioactive lipid that rapidly remodels to presqualene monophosphate PSMP upon cell activation. PLPP6 displays diphosphate phosphatase activity with a substrate preference PSDP > FDP > phosphatidic acid.

Literature references

Arita, M., Morris, AJ., Levy, BD., Fukunaga, K., Pfeffer, M., Takahashi, M. (2006). Identification and functional characterization of a presqualene diphosphate phosphatase. *J. Biol. Chem., 281*, 9490-7. ↗

Editions

2016-12-13	Authored	Jupe, S.
2017-01-13	Edited	Jupe, S.
2017-01-23	Reviewed	Levy, BD.

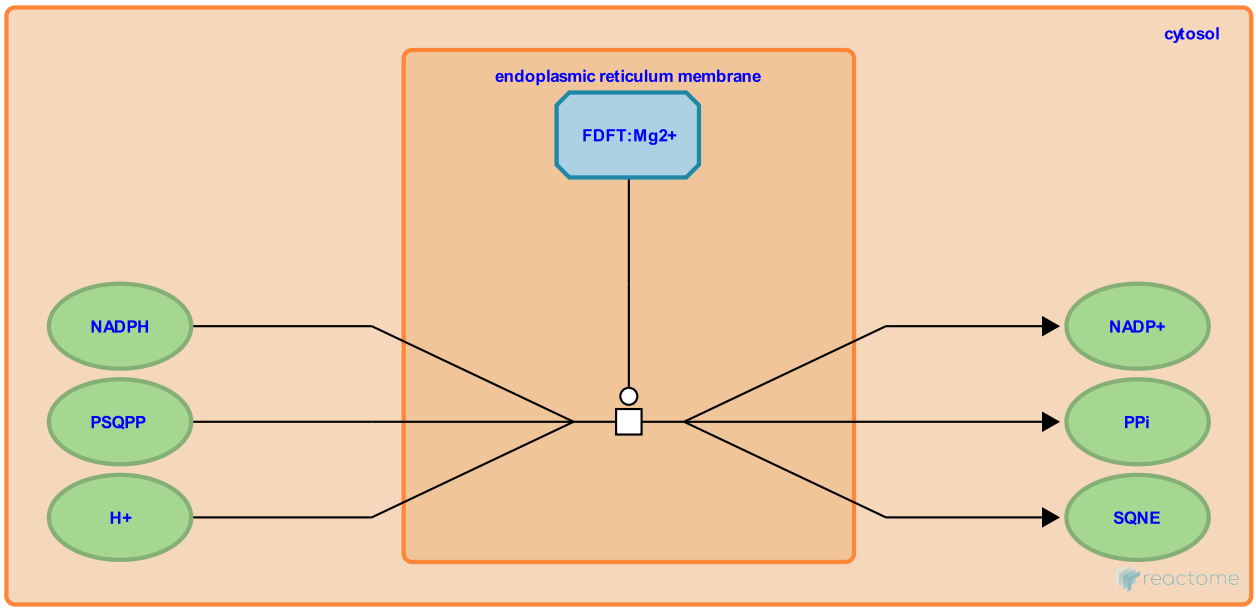
Reduction of presqualene diphosphate to form squalene ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191402

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



In the second step, FDFT catalyzes the reduction of presqualene diphosphate to squalene (Pandit et al. 2000).

Preceded by: Two FPP molecules dimerize to form presqualene diphosphate

Followed by: Squalene is oxidized to its epoxide

Literature references

Danley, DE., Harwood HJ, Jr., Hamanaka, ES., Schulte, GK., Pandit, J., Mazzalupo, S. et al. (2000). Crystal structure of human squalene synthase. A key enzyme in cholesterol biosynthesis. *J Biol Chem, 275*, 30610-7. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

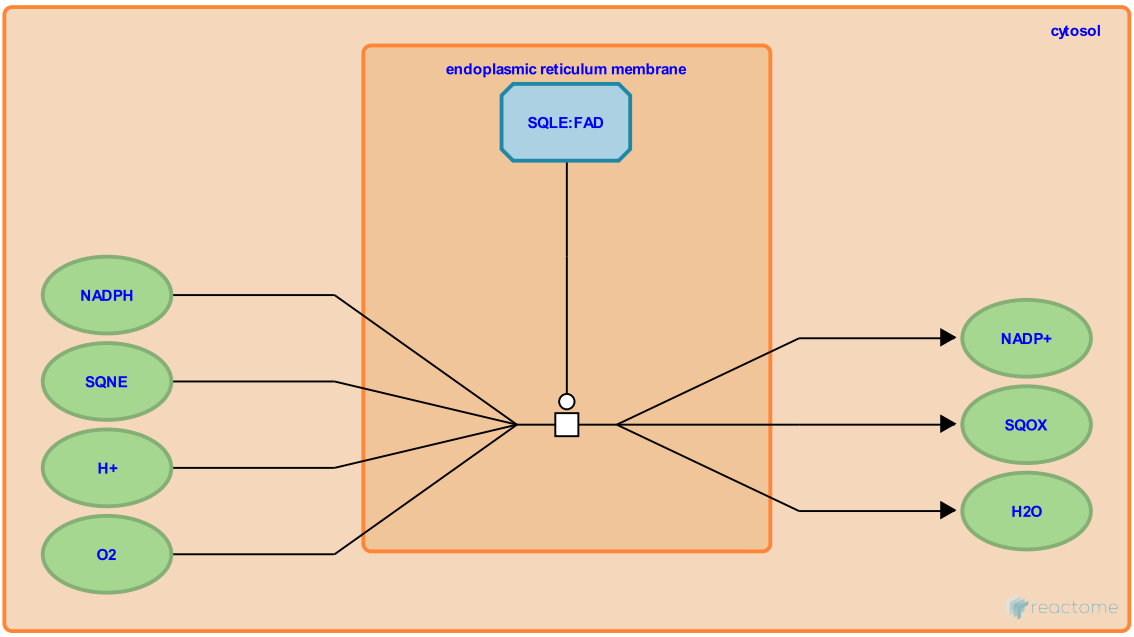
Squalene is oxidized to its epoxide ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191299

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Squalene monooxygenase (squalene epoxidase, SE) is located on the endoplamic reticulum. It catalyzes the oxidation of squalene to squalene 2,3-epoxide. SE seems to be an important rate-limiting enzyme in cholesterol biosynthesis.

Preceded by: Reduction of presqualene diphosphate to form squalene

Followed by: Squalene 2,3-epoxide cyclizes, forming lanosterol

Literature references

Tang, Y., Laden, BP., Porter, TD. (2000). Cloning, heterologous expression, and enzymological characterization of human squalene monooxygenase. *Arch Biochem Biophys, 374*, 381-8. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

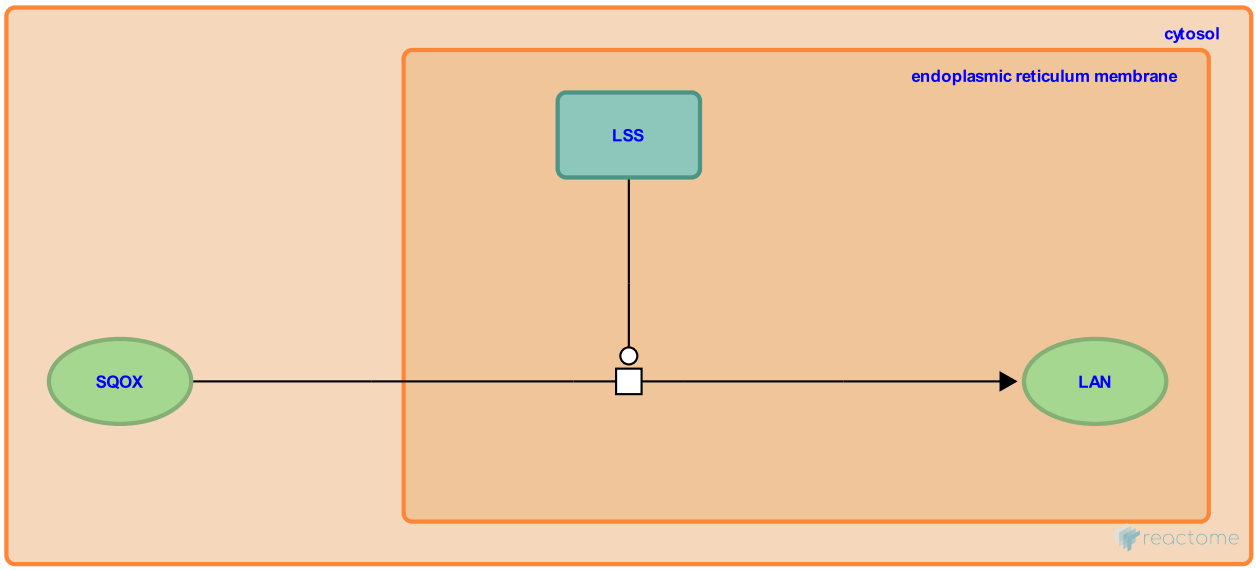
Squalene 2,3-epoxide cyclizes, forming lanosterol ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-191366

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Lanosterol synthase (LSS) catalyzes the cyclization of squalene 2,3-epoxide to lanosterol, a reaction that forms the sterol nucleus. LSS is located on the ER membrane and is active in monomeric form (Ruf et al. 2004).

Preceded by: Squalene is oxidized to its epoxide

Followed by: DHCR24 reduces LAN to 24,25-dhLAN, Cholesterol biosynthesis via desmosterol, CYP51A1 demethylates LNSOL

Literature references

Sankawa, U., Shibuya, M., Ebizuka, Y., Sung, CK. (1995). Molecular cloning of cDNA encoding human lanosterol synthase. *Biol Pharm Bull, 18*, 1459-61. ↗

Van Tamelen, EE., Willett, JD., Clayton, RB., Lord, KE. (1966). Enzymic conversion of squalene 2,3-oxide to lanosterol and cholesterol. *J Am Chem Soc, 88*, 4752-4. ↗

Editions

2007-01-22	Reviewed	D'Eustachio, P.
2007-01-24	Authored	Jassal, B.

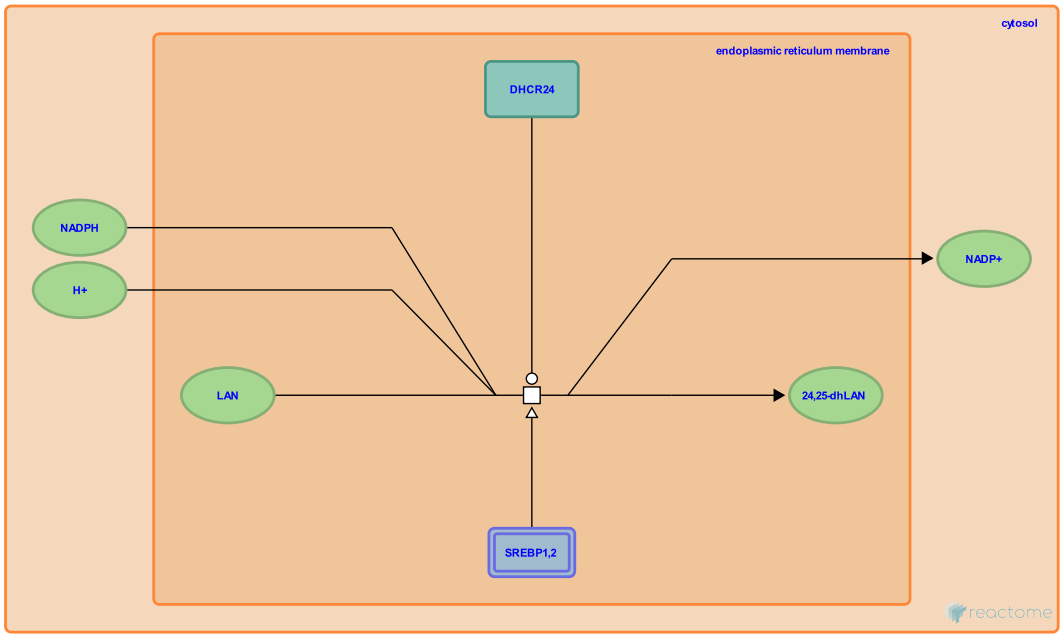
DHCR24 reduces LAN to 24,25-dhLAN ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-9755937

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



DHCR24 (delta(24)-sterol reductase) (review Zerenturk et al. 2013) associated with the endoplasmic reticulum membrane catalyzes the reduction of lanosterol (LAN) to 24,25-dihydrolanosterol (24,25-dhLAN) (Kandutsch & Russell 1960). Like most cholesterol synthesis enzymes, DHCR24 is transcriptionally regulated by the SREBP family of transcription factors and hence, is subject to negative regulation by cholesterol (Zerenturk et al. 2012).

Preceded by: Squalene 2,3-epoxide cyclizes, forming lanosterol

Literature references

Crespo, L., Rodríguez-Acebes, S., Lasunción, MA., Daimiel, LA., Martínez-Botas, J., Gómez-Coronado, D. et al. (2012). Promoter analysis of the DHCR24 (3β-hydroxysterol Δ(24)-reductase) gene: characterization of SREBP (sterol-regulatory-element-binding protein)-mediated activation. *Biosci Rep, 33*, 57-69. ↗

Russell, AE., Kandutsch, AA. (1960). Preputial gland tumor sterols. 3. A metabolic pathway from lanosterol to cholesterol. *J. Biol. Chem., 235*, 2256-61. ↗

Editions

2021-10-11	Edited	Jassal, B.
2021-10-15	Reviewed	Brown, AJ.
2021-11-23	Authored	Rozman, D J.

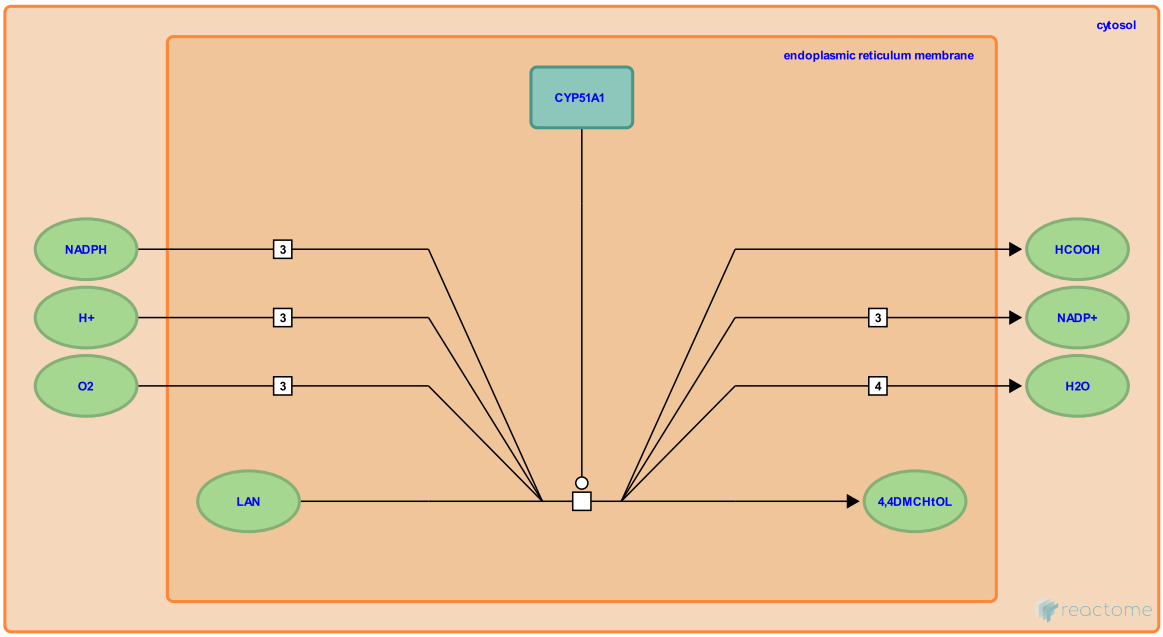
CYP51A1 demethylates LNSOL ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194678

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Lanosterol 14-alpha demethylase (CYP51A1) catalyses oxidative C14-demethylation of lanosterol (LNSOL) to 4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol (4,4DMCHOLtrienol). Although the reaction is annotated here as a single concerted event, studies with purified rat enzyme indicate that the methyl group is converted successively to an alcohol and an aldehyde before being released as formate (Stromstedt et al. 1996, Strushkevich et al. 2010).

Preceded by: Squalene 2,3-epoxide cyclizes, forming lanosterol

Followed by: 4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol is reduced to 4,4-dimethylcholesta-8(9),24-dien-3beta-ol [TM7SF2], 4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol is reduced to 4,4-dimethylcholesta-8(9),24-dien-3beta-ol [LBR]

Literature references

Park, HW., Usanov, SA., Strushkevich, N. (2010). Structural basis of human CYP51 inhibition by antifungal azoles. *J. Mol. Biol., 397*, 1067-78. ↗

Stromstedt, M., Waterman, MR., Rozman, D. (1996). The ubiquitously expressed human CYP51 encodes lanosterol 14 alpha-demethylase, a cytochrome P450 whose expression is regulated by oxysterols. *Arch Biochem Biophys, 329*, 73-81. ↗

Editions

2007-04-21	Edited	D'Eustachio, P.
2008-05-19	Authored	Jassal, B.
2008-05-28	Reviewed	D'Eustachio, P.
2014-06-23	Revised	Jassal, B.

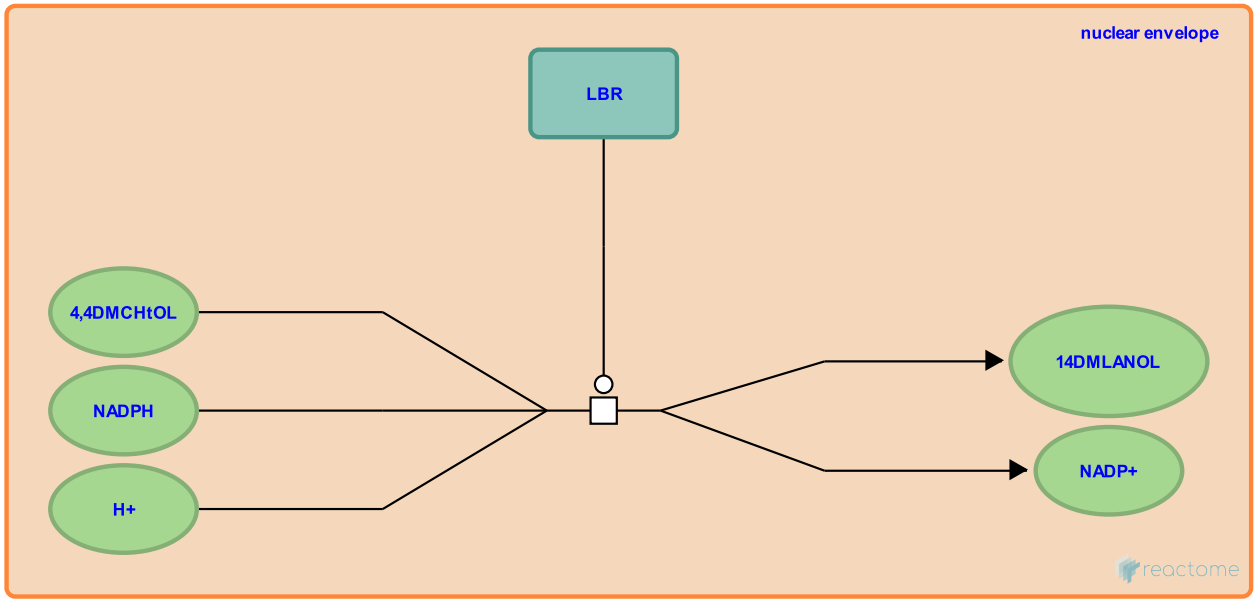
4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol is reduced to 4,4-dimethylcholesta-8(9),24-dien-3beta-ol [LBR]

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194674

Type: transition

Compartments: nuclear envelope



4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol and NADPH + H+ react to form 4,4-dimethylcholesta-8(9),24-dien-3beta-ol and NADP+, catalyzed by LBR in the nuclear envelope. LBR protein spans the inner nuclear envelope, has an aminoterminal region with properties of a laminin receptor and a carboxyterminal domain with sequence similarity to sterol delta14-reductases (Holmer et al. 1998). Studies of material from an individual with HEM/Greenberg skeletal dysplasia indicate that LBR catalyzes the sterol delta14-reductase step of cholesterol biosynthesis in vivo. DNA sequencing revealed homozygosity for a mutant LBR allele encoding a truncated protein in the affected individual, and cells from the individual accumulated cholesta-8,14-dien-3beta-ol in culture. Transfection of wild-type LBR into the cultured cells reversed the accumulation of cholesta-8,14-dien-3beta-ol (Waterham et al. 2003). This observation is surprising because a second gene, TM7SF2, encodes an efficient sterol delta14-reductase that is localized to the endoplasmic reticulum whose expression is up-regulated in response to sterol depletion (Bennati et al. 2006). The physiological roles of LBR and TM7SF2 in vivo remain to be determined.

Preceded by: CYP51A1 demethylates LNSOL

Followed by: 4,4-dimethylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol

Literature references

Wilcox, WR., van Noort, G., Oosterwijk, JC., Hennekam, RC., Koster, J., Mooyer, P. et al. (2003). Autosomal recessive HEM/Greenberg skeletal dysplasia is caused by 3 beta-hydroxysterol delta 14-reductase deficiency due to mutations in the lamin B receptor gene. *Am J Hum Genet, 72*, 1013-7.

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

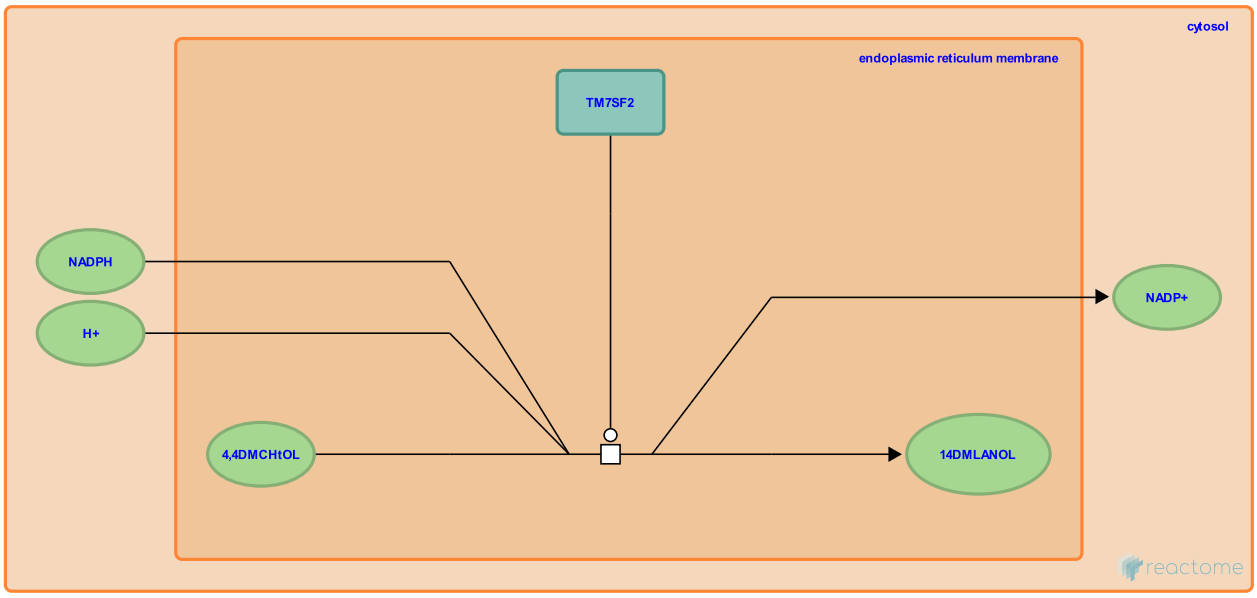
4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol is reduced to 4,4-dimethylcholesta-8(9),24-dien-3beta-ol [TM7SF2]

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194698

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol and NADPH + H+ react to form 4,4-dimethylcholesta-8(9),24-dien-3beta-ol and NADP+, catalyzed by TM7SF2 in the endoplasmic reticulum. TM7SF2 protein has sterol delta14-reductase activity in vitro, and expression of the gene is induced by sterol starvation in human cells, as expected for a gene involved in sterol biosynthesis (Bennati et al. 2006). However, molecular studies of material from an individual with HEM/Greenberg skeletal dysplasia indicate that LBR, a protein that spans the inner nuclear membrane and has both laminin receptor and sterol delta14-reductase activities, is required for normal sterol 14delta-reductase activity in human cells. It remains to be determined whether both LBR and TM7SF2 catalyze this reaction in vivo, and whether the role of TM7SF2 is essential (Waterham et al. 2003).

Preceded by: CYP51A1 demethylates LNSOL

Followed by: 4,4-dimethylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol

Literature references

Roberti, R., Castelli, M., Bennati, AM., Caruso, D., Servillo, G., Beccari, T. et al. (2006). Sterol dependent regulation of human TM7SF2 gene expression: role of the encoded 3beta-hydroxysterol Delta14-reductase in human cholesterol biosynthesis. *Biochim Biophys Acta, 1761*, 677-85.

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

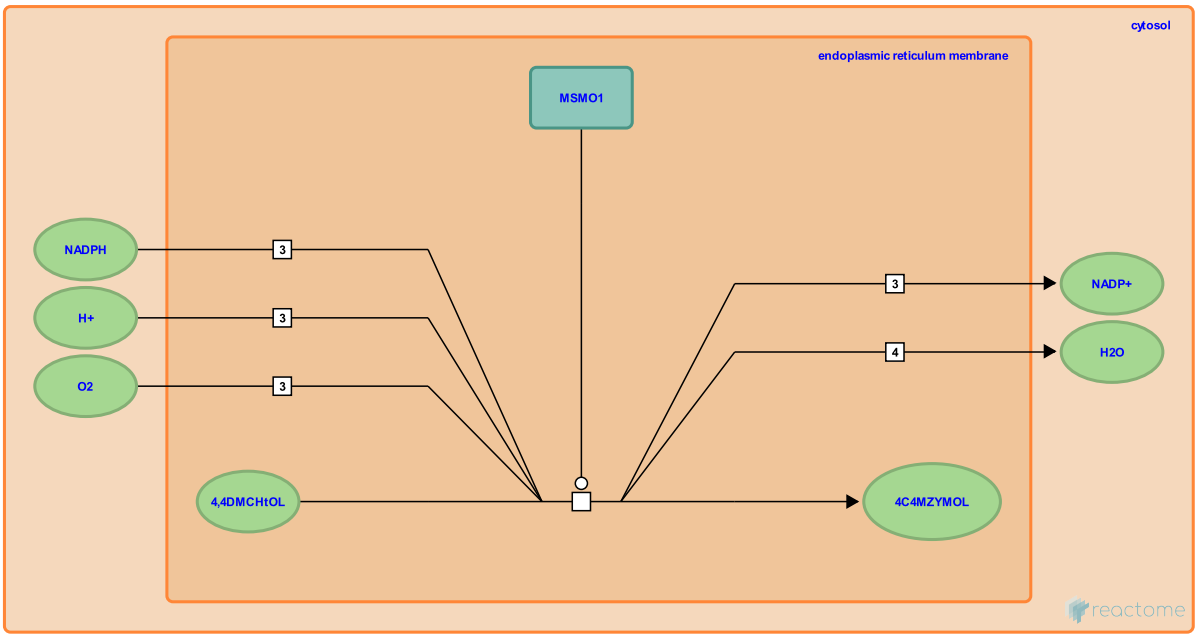
4,4-dimethylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194641

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



4,4-dimethylcholesta-8(9),24-dien-3beta-ol, NADPH + H+, and O2 react to form 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol, NADP+, and H2O. This reaction, in the endoplasmic reticulum, is catalyzed by SC4MOL (C-4 methylsterol oxidase). The human enzyme has been identified based on its sequence similarity to yeast methyl sterol oxidase (ERG25) and the ability of the cloned human gene to rescue ERG25-deficient yeast cells (Li and Kaplan 1996). The mechanism and stoichiometry of the reaction have been inferred from studies of partially purified rat enzyme (Gaylor et al. 1975; Fukushima et al. 1981).

Preceded by: 4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol is reduced to 4,4-dimethylcholesta-8(9),24-dien-3beta-ol [TM7SF2], 4,4-dimethylcholesta-8(9),14,24-trien-3beta-ol is reduced to 4,4-dimethylcholesta-8(9),24-dien-3beta-ol [LBR]

Followed by: 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form 4-methylcholesta-8(9),24-dien-3-one

Literature references

Li, L., Kaplan, J. (1996). Characterization of yeast methyl sterol oxidase (ERG25) and identification of a human homologue. *J Biol Chem, 271*, 16927-33. ↗

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

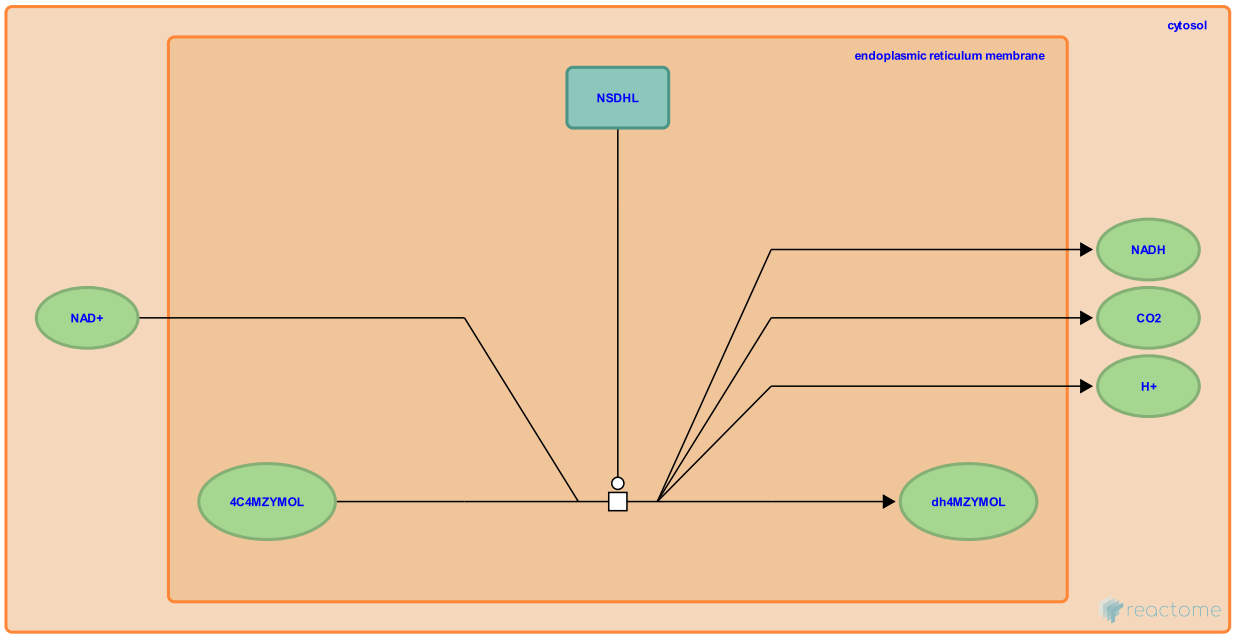
4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form 4-methylcholesta-8(9),24-dien-3-one ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194642

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol and NAD+ react to form 4-methylcholesta-8(9),24-dien-3-one, CO2, and NADH + H+. This reaction occurs in the endoplasmic reticulum, catalyzed by NSDHL (Caldas and Herman 2003). Defects in this enzyme are associated with CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform nevus and Limb Defects) (Konig et al. 2000), but cholesterol biosynthesis in cells and tissues from affected individuals has not been characterized. Instead, the mechanism and stoichiometry of the reaction are inferred from biochemical studies of partially purified rat enzyme (Rahimtula and Gaylor 1972).

Preceded by: 4,4-dimethylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol

Followed by: 4-methylcholesta-8(9),24-dien-3-one is reduced to 4-methylcholesta-8(9),24-dien-3beta-ol

Literature references

Herman, GE., Caldas, H. (2003). NSDHL, an enzyme involved in cholesterol biosynthesis, traffics through the Golgi and accumulates on ER membranes and on the surface of lipid droplets. *Hum Mol Genet, 12*, 2981-91. ↗

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

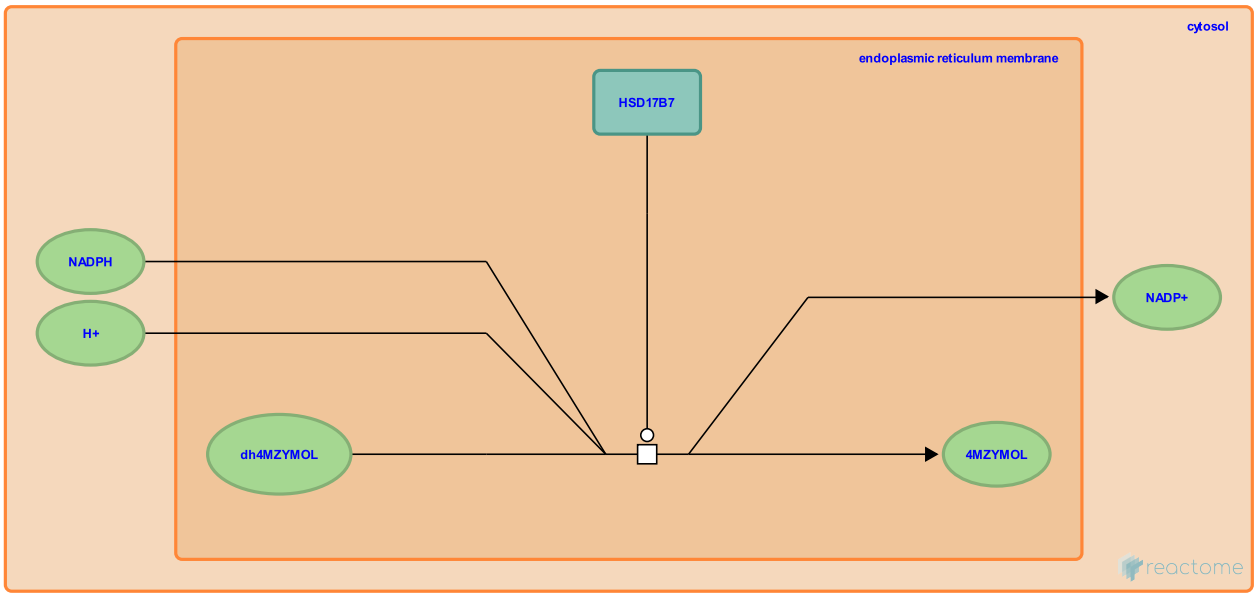
4-methylcholesta-8(9),24-dien-3-one is reduced to 4-methylcholesta-8(9),24-dien-3beta-ol ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194689

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



4-methylcholesta-8(9),24-dien-3-one and NADPH + H+ react to form 4-methylcholesta-8(9),24-dien-3beta-ol and NADP+. This reaction takes place in the endoplasmic reticulum, catalyzed by HSD17B7. Two isoforms of the enzyme due to alternative splicing have been identified but only the first has been tested for enzymatic activity (Marijanovic et al. 2003). The human enzyme has not been studied extensively; molecular details of the reaction are inferred from those worked out in studies of material from rat liver (Gaylor 2002).

Preceded by: 4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form 4-methylcholesta-8(9),24-dien-3-one

Followed by: 4-methylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-carboxycholesta-8(9),24-dien-3beta-ol

Literature references

Breitling, R., Marijanovic, Z., Moller, G., Adamski, J., Gege, C., Husen, B. et al. (2003). Closing the gap: identification of human 3-ketosteroid reductase, the last unknown enzyme of mammalian cholesterol biosynthesis. *Mol. Endocrinol., 17,* 1715-25. ↗

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

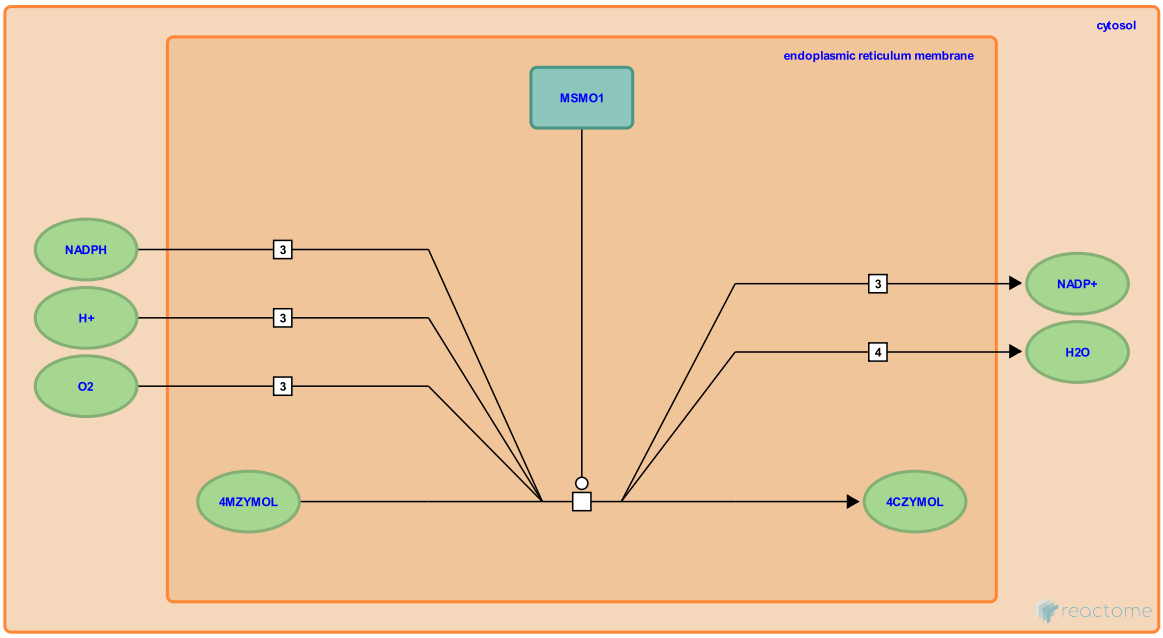
4-methylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-carboxycholesta-8(9),24-dien-3beta-ol ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194669

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



4-methylcholesta-8(9),24-dien-3beta-ol, NADPH + H+, and O2 react to form 4-carboxycholesta-8(9),24-dien-3beta-ol, NADP+, and H2O. This reaction, in the endoplasmic reticulum, is catalyzed by SC4MOL (C-4 methylsterol oxidase). The human enzyme has been identified based on its sequence similarity to yeast methyl sterol oxidase (ERG25) and the ability of the cloned human gene to rescue ERG25-deficient yeast cells (Li and Kaplan 1996). The mechanism and stoichiometry of the reaction have been inferred from studies of partially purified rat enzyme (Gaylor et al. 1975; Fukushima et al. 1981).

Preceded by: 4-methylcholesta-8(9),24-dien-3-one is reduced to 4-methylcholesta-8(9),24-dien-3beta-ol

Followed by: 4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form cholesta-8(9),24-dien-3-one (zymosterone)

Literature references

Li, L., Kaplan, J. (1996). Characterization of yeast methyl sterol oxidase (ERG25) and identification of a human homologue. *J Biol Chem, 271*, 16927-33. ↗

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

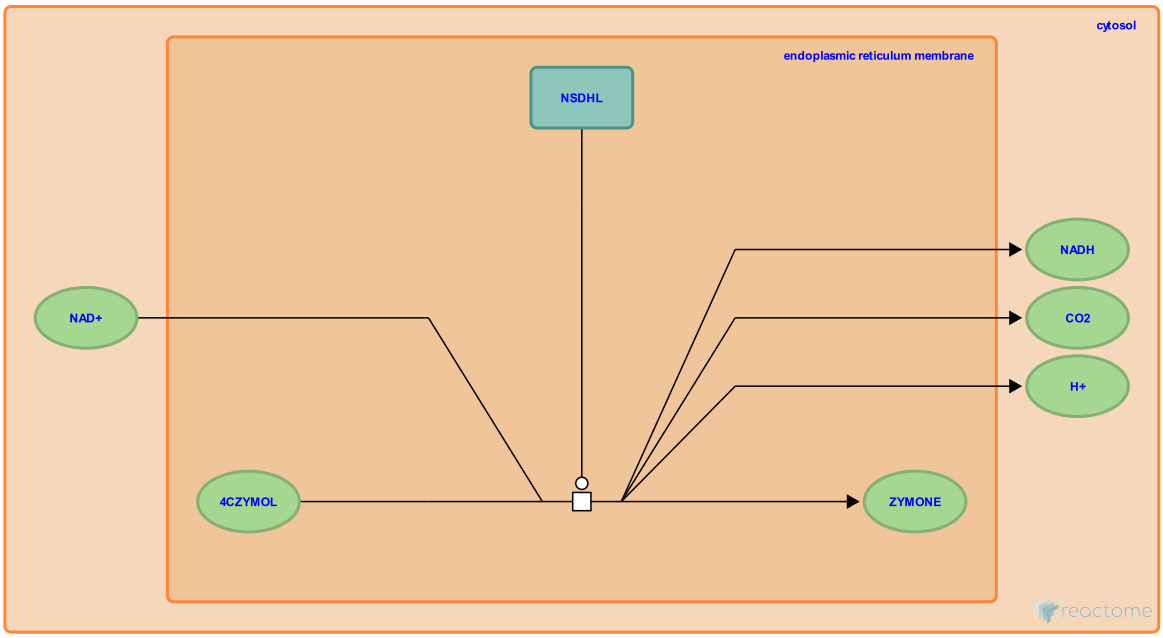
4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form cholesta-8(9),24-dien-3-one (zymosterone)

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194718

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



4-carboxycholesta-8(9),24-dien-3beta-ol and NAD+ react to form zymosterone (cholesta-8(9),24-dien-3-one), CO2, and NADH + H+. This reaction occurs in the endoplasmic reticulum, catalyzed by NSDHL (Caldas and Herman 2003). Defects in this enzyme are associated with CHILD syndrome (Congenital Hemidysplasia with Ichthyosiform nevus and Limb Defects) (Konig et al. 2000), but cholesterol biosynthesis in cells and tissues from affceted individuals has not been characterized. Instead, the mechanism and stoichiometry of the reaction are inferred from biochemical studies of partially purified rat enzyme (Rahimtula and Gaylor 1972).

Preceded by: 4-methylcholesta-8(9),24-dien-3beta-ol is oxidized to 4-carboxycholesta-8(9),24-dien-3beta-ol

Followed by: Zymosterone (cholesta-8(9),24-dien-3-one) is reduced to zymosterol (cholesta-8(9),24-dien-3beta-ol)

Literature references

Herman, GE., Caldas, H. (2003). NSDHL, an enzyme involved in cholesterol biosynthesis, traffics through the Golgi and accumulates on ER membranes and on the surface of lipid droplets. *Hum Mol Genet, 12*, 2981-91.

Editions

2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

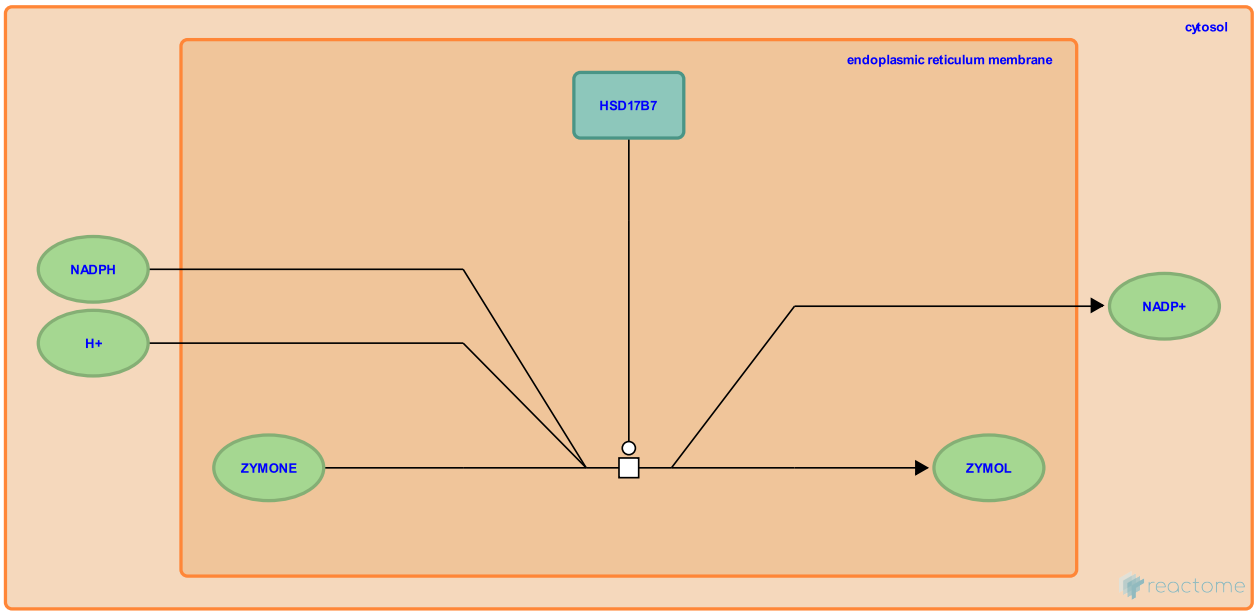
Zymosterone (cholesta-8(9),24-dien-3-one) is reduced to zymosterol (cholesta-8(9),24-dien-3beta-ol) ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-194632

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Zymosterone (cholesta-8(9),24-dien-3-one) and NADPH + H+ react to form zymosterol (cholesta-8(9),24-dien-3beta-ol) and NADP+. This reaction takes place in the endoplasmic reticulum, catalyzed by HSD17B7. Two isoforms of the enzyme due to alternative splicing have been identified but only the first has been tested for enzymatic activity (Marijanovic et al. 2003). The human enzyme has not been studied extensively; molecular details of the reaction are inferred from those worked out in studies of material from rat liver (Gaylor 2002).

Preceded by: 4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form cholesta-8(9),24-dien-3-one (zymosterone)

Followed by: Cholesterol biosynthesis via lathosterol

Literature references

Breitling, R., Marijanovic, Z., Moller, G., Adamski, J., Gege, C., Husen, B. et al. (2003). Closing the gap: identification of human 3-ketosteroid reductase, the last unknown enzyme of mammalian cholesterol biosynthesis. *Mol. Endocrinol., 17*, 1715-25. ↗

Editions

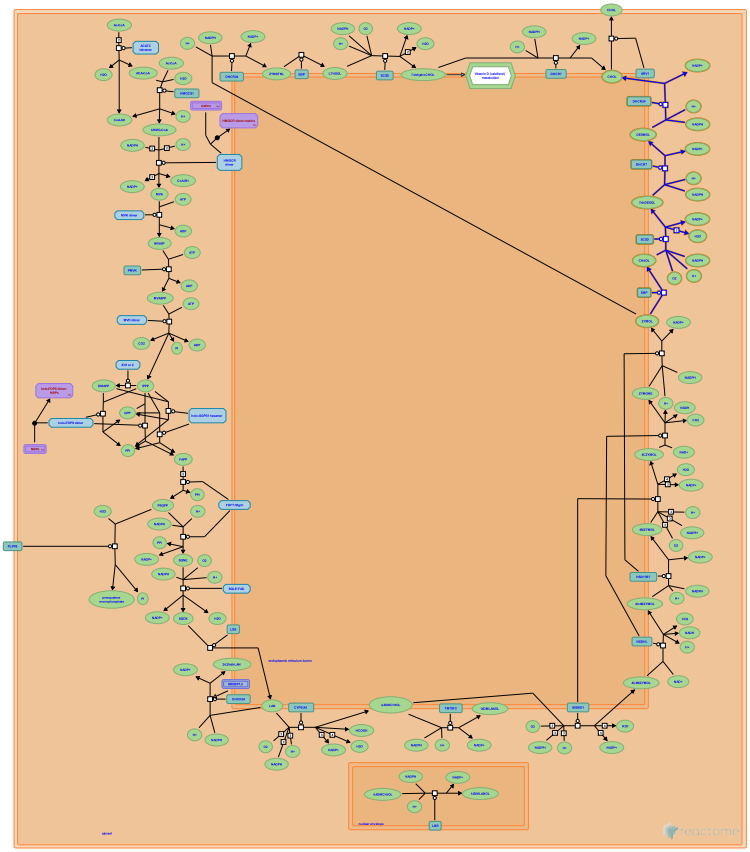
2007-04-21	Authored, Edited	D'Eustachio, P.
2007-04-21	Reviewed	Jassal, B.

Cholesterol biosynthesis via desmosterol ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-6807047

Compartments: endoplasmic reticulum membrane, cytosol



The transformation of zymosterol into cholesterol can follow either of routes, one in which reduction of the double bond in the isooctyl side chain is the final step (cholesterol synthesis via desmosterol, also known as the Bloch pathway) and one in which this reduction is the first step (cholesterol biosynthesis via lathosterol, also known as the Kandutsch-Russell pathway). The former pathway is prominent in the liver and many other tissues while the latter is prominent in skin, where it may serve as the source of the 7-dehydrocholesterol that is the starting point for the synthesis of D vitamins (Mitsche et al. 2015).

Literature references

Hobbs, HH., Mitsche, MA., Cohen, JC., McDonald, JG. (2015). Flux analysis of cholesterol biosynthesis in vivo reveals multiple tissue and cell-type specific pathways. *Elife, 4*, e07999. ↗

Editions

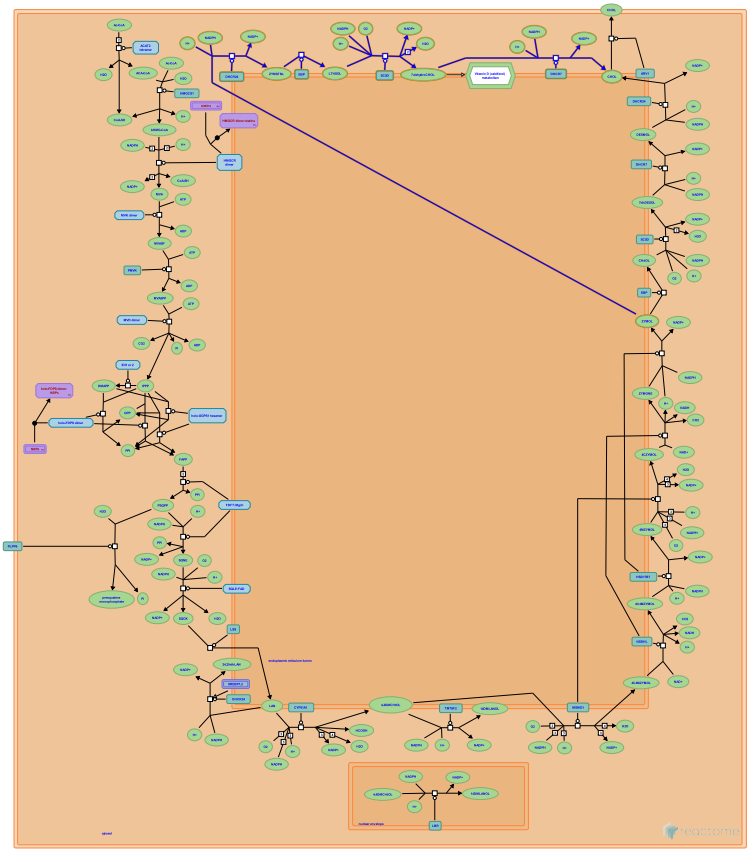
2015-11-02	Authored, Edited	D'Eustachio, P.
2015-11-02	Reviewed	Jassal, B.

Cholesterol biosynthesis via lathosterol ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-6807062

Compartments: endoplasmic reticulum membrane, cytosol



The transformation of zymosterol into cholesterol can follow either of routes, one in which reduction of the double bond in the isooctyl side chain is the final step (cholesterol synthesis via desmosterol, also known as the Bloch pathway) and one in which this reduction is the first step (cholesterol biosynthesis via lathosterol, also known as the Kandutsch-Russell pathway). The former pathway is prominent in the liver and many other tissues while the latter is prominent in skin, where it may serve as the source of the 7-dehydrocholesterol that is the starting point for the synthesis of D vitamins (Kandutsch & Russell 1960; Mitsche et al. 2015).

Literature references

Russell, AE., Kandutsch, AA. (1960). Preputial gland tumor sterols. 3. A metabolic pathway from lanosterol to cholesterol. *J. Biol. Chem., 235*, 2256-61. ↗

Hobbs, HH., Mitsche, MA., Cohen, JC., McDonald, JG. (2015). Flux analysis of cholesterol biosynthesis in vivo reveals multiple tissue and cell-type specific pathways. *Elife, 4*, e07999. ↗

Editions

2015-11-02	Authored, Edited	D'Eustachio, P.
2015-11-02	Reviewed	Jassal, B.

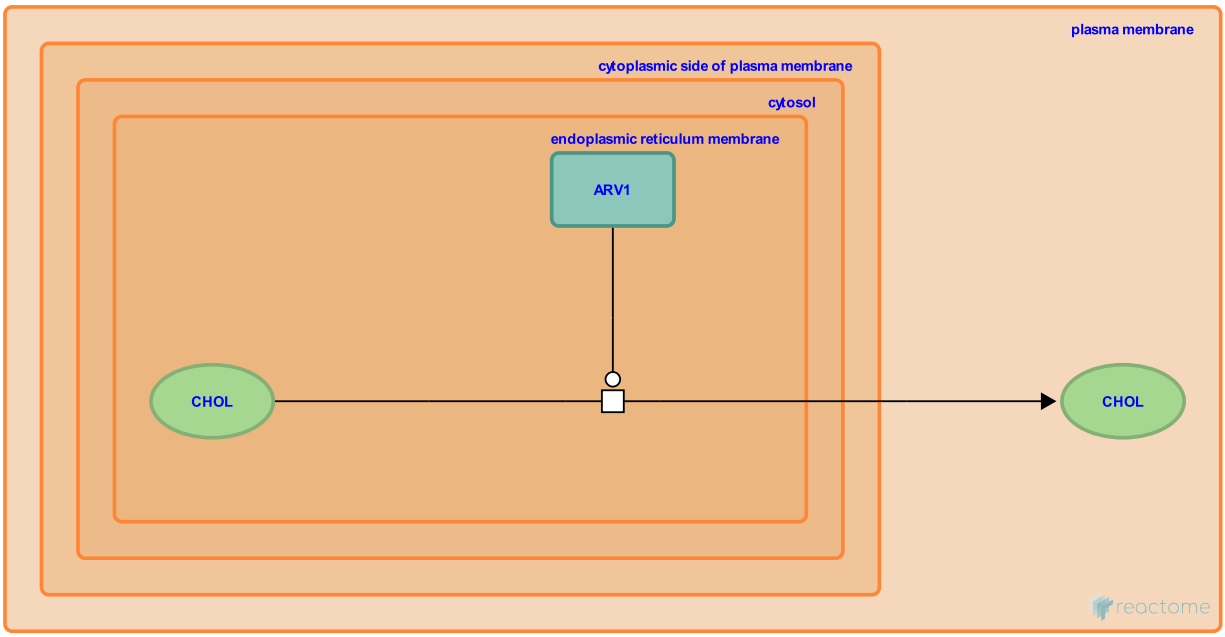
ARV1 transports CHOL from ER membrane to plasma membrane ↗

Location: Cholesterol biosynthesis

Stable identifier: R-HSA-5250531

Type: transition

Compartments: endoplasmic reticulum membrane, plasma membrane, endoplasmic reticulum lumen



Sterols such as cholesterol (CHOL) synthesised in the endoplasmic reticulum (ER) need to be efficiently transported to the plasma membrane, where 90% of the free sterol pool resides. Conversely, sterols taken up from outside the cell need to be transported back to the ER for esterification to sterol esters. The mechanisms that control this bi-directional movement of sterols are still poorly understood but a likely candidate is protein ARV1 (ARV1). Studies with mutant yeast Arv1 indicate altered intracellular sterol distribution and subsequent defects in sphingolipid metabolism. Human ARV1, a predicted sequence ortholog of yeast Arv1, complements the defects seen associated with deletion of yeast Arv1 (Tinkelenberg et al. 2000, Swain et al. 2002).

Literature references

Liu, Y., Nickels, JT., McDonough, V., Sturley, SL., Stukey, J., Swain, E. et al. (2002). Yeast cells lacking the ARV1 gene harbor defects in sphingolipid metabolism. Complementation by human ARV1. *J. Biol. Chem., 277*, 36152-60. ↗

Alcantara, F., Liu, Y., Tinkelenberg, AH., Bard, M., Guo, Z., Sturley, SL. et al. (2000). Mutations in yeast ARV1 alter intracellular sterol distribution and are complemented by human ARV1. *J. Biol. Chem., 275*, 40667-70. ↗

Editions

2014-01-27	Authored, Edited	Jassal, B.
2014-10-03	Reviewed	Sturley, SL.
2015-02-11	Revised	Jassal, B.

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