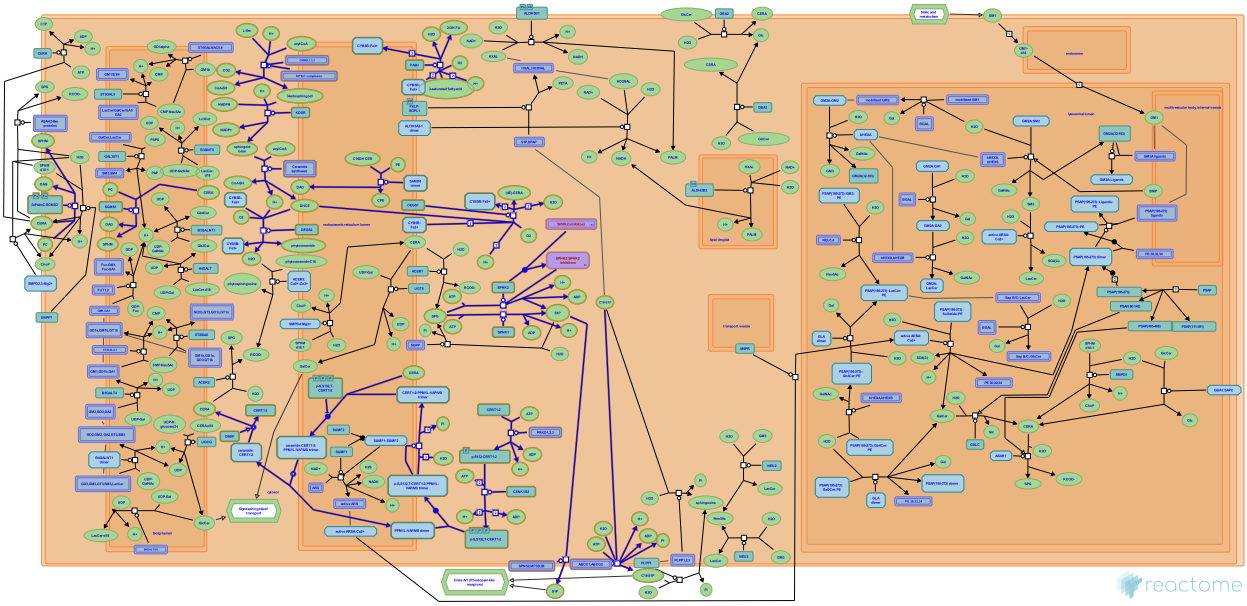
Sphingolipid de novo biosynthesis



D'Eustachio, P., Hannun, YA., Huddart, R., Jassal, B., Luberto, C., Matthews, L., Stephan, R.

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.

07/05/2024

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.
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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. ↗

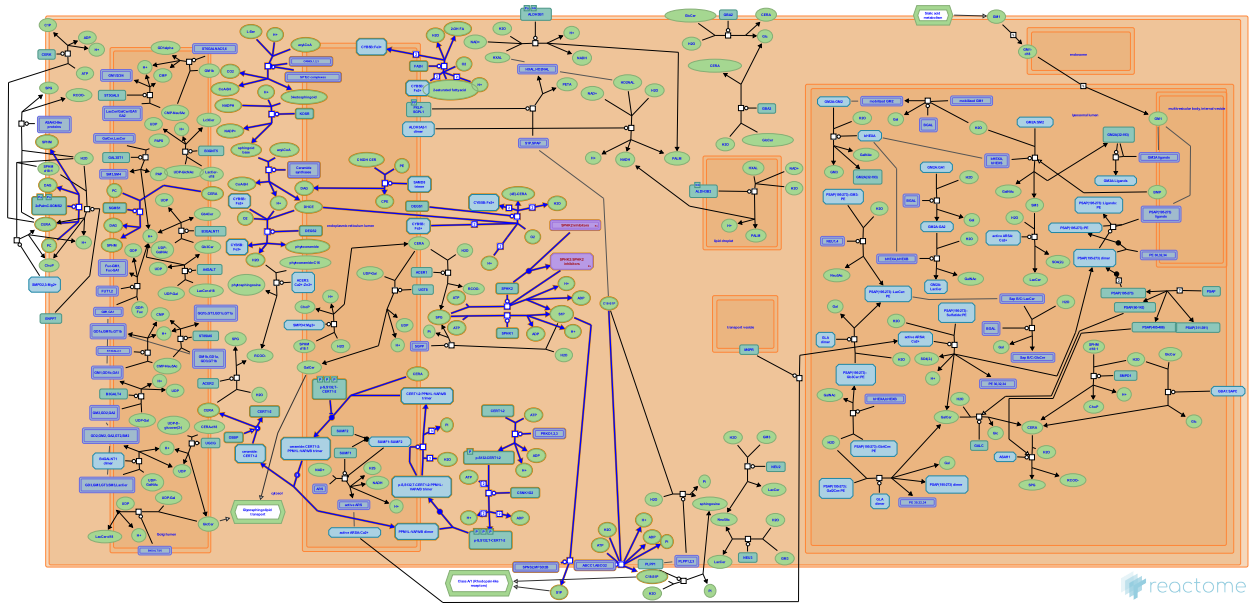
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Sphingolipid de novo biosynthesis ↗

Stable identifier: R-HSA-1660661

Compartments: cytosol, endoplasmic reticulum lumen, endoplasmic reticulum membrane



Glycosphingolipid biosynthesis is based on salvage of sphingolipids and de novo sphingolipid synthesis. Sphingoid-1-phosphate signalling molecules are synthesized through the same pathway, which starts with the transfer of a fatty acid onto serine. The diversity of products results from later dehydrogenation or hydroxylation of fatty acid moieties, as well as the usage of fatty acids of different lengths. Biosynthesis takes place in the endoplasmic reticulum lumen and the cytosol. Lipophilic products are transported to other membranes via a specialized transporter (CERT1) or the secretory pathway. Soluble sphingoid-1-phosphates are exported by multiple transporters in the plasma membrane (reviewed by Merrill 2002, Gault et al. 2010).

Literature references

Gault, CR., Hannun, YA., Obeid, LM. (2010). An overview of sphingolipid metabolism: from synthesis to breakdown. *Adv Exp Med Biol, 688*, 1-23. ↗

Merrill AH, Jr. (2002). De novo sphingolipid biosynthesis: a necessary, but dangerous, pathway. *J Biol Chem, 277*, 25843-6. ↗

Editions

2009-08-21	Authored	D'Eustachio, P.
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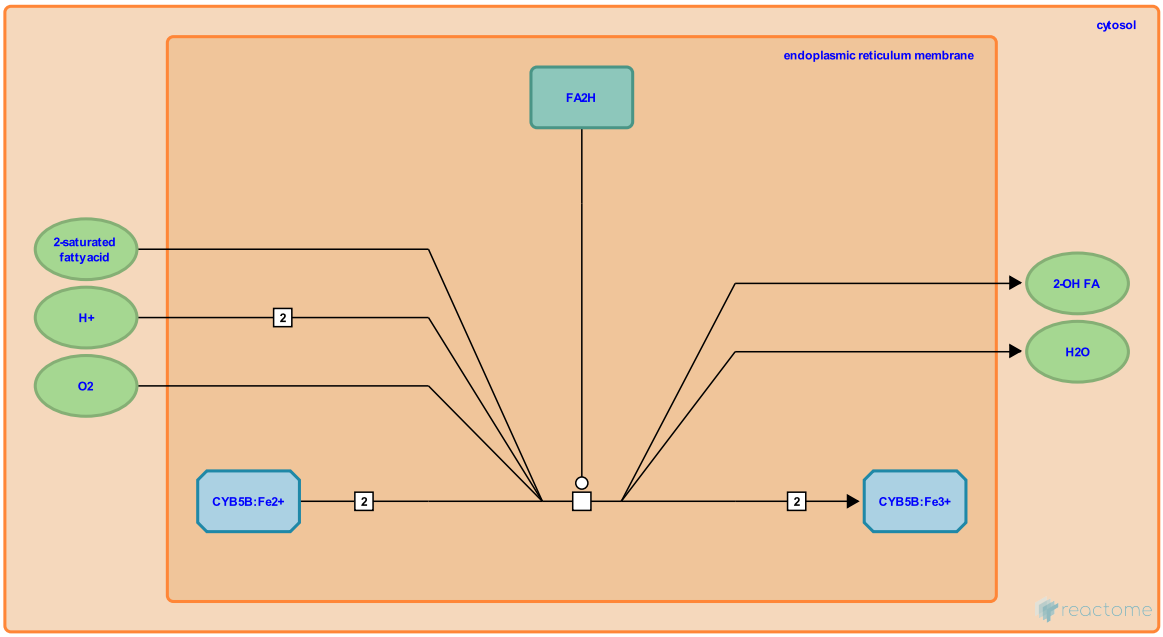
FA2H hydroxylates 1,2-saturated fatty acids ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-5693761

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Fatty acid 2-hydroxylase (FA2H), an ER membrane-associated enzyme, catalyzes the cytochrome b5-dependent hydroxylation of free fatty acids on the saturated C2 position. 2-Hydroxylation of free fatty acids occurs before de novo ceramide synthesis. In mammals, 2-hydroxysphingolipids are abundant in the brain as components of the myelin lipids galactosylceramides and sulfatides (Alderson et al., 2004; Uchida et al., 2007; Guo et al., 2012; reviewed by Hama, 2009). Deficiency in FA2H causes a form of spastic paraplegia (SPG35, MIM:612319). A low expression level of FA2H correlates with a poor prognosis in many cancers (reviewed by Eckhardt, 2023).

Literature references

Hama, H. (2010). Fatty acid 2-Hydroxylation in mammalian sphingolipid biology. *Biochim Biophys Acta, 1801*, 405-14. ↗

Zhang, X., Guo, L., Zhou, D., Su, X., Okunade, AL. (2012). Stereospecificity of fatty acid 2-hydroxylase and differential functions of 2-hydroxy fatty acid enantiomers. *J Lipid Res, 53*, 1327-35. ↗

Eckhardt, M. (2023). Fatty Acid 2-Hydroxylase and 2-Hydroxylated Sphingolipids: Metabolism and Function in Health and Diseases. *Int J Mol Sci, 24*. ↗

Holleran, WM., Hama, H., Alderson, NL., Crumrine, DA., Wang, Y., Elias, PM. et al. (2007). Fatty acid 2-hydroxylase, encoded by FA2H, accounts for differentiation-associated increase in 2-OH ceramides during keratinocyte differentiation. *J. Biol. Chem., 282*, 13211-9. ↗

Hama, H., Alderson, NL., Bielawski, J., Walla, MD., Rembiesa, BM., Bielawska, A. (2004). The human FA2H gene encodes a fatty acid 2-hydroxylase. *J. Biol. Chem., 279*, 48562-8. ↗

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2015-05-18	Authored, Edited	Jassal, B.
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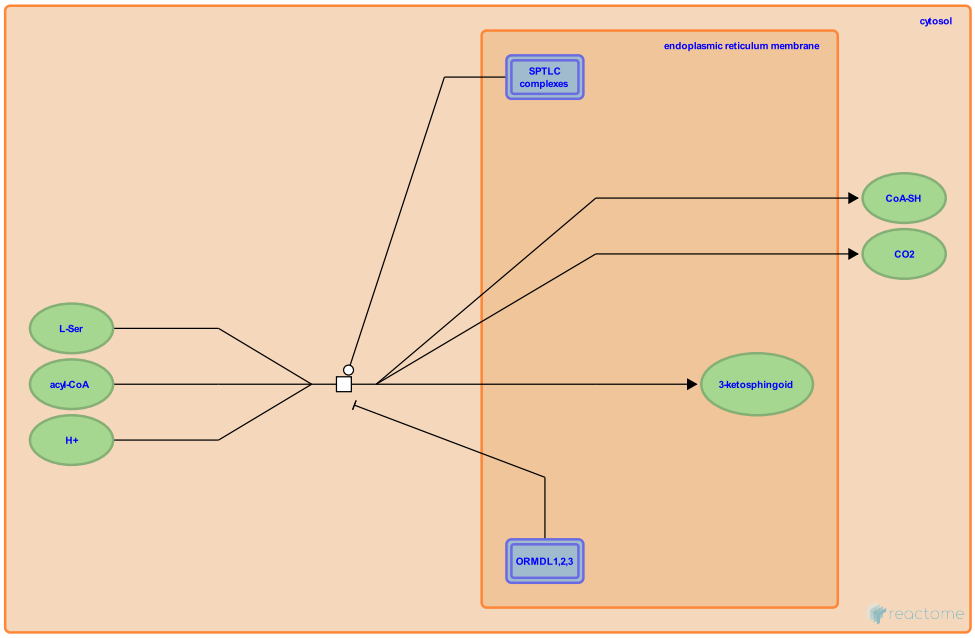
SPTLC complexes transfer acyl-CoA onto serine ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-428127

Type: transition

Compartments: cytosol, endoplasmic reticulum membrane



SPTLC (serine palmitoyltransferase) enzyme complexes associated with the endoplasmic reticulum membrane catalyze the reaction of acyl-CoA and serine to form a 3-ketosphingoid. Quantitatively, the most common ligand is palmitoyl-CoA (C16), but different isoforms of the complexes have specific activity toward the C12, C14, and C18 species (Han et al., 2009; Suzuki et al., 2022). SPTLC2 and SPTLC3 polypeptides exhibit enzyme activity when either is complexed with SPTLC1. SPTLC1 and 2 are abundant and widely expressed in human tissues, while SPTLC3 is expressed only in a smaller group of tissues and at variable levels. Analyses of complexes from cultured human cells and placenta suggested that the SPTLC heterodimers might associate with larger complexes (Hanada et al., 2000; Weiss and Stoffel, 1997; Hornemann et al. 2006, 2007; reviewed by Ikushiro & Hayashi, 2011; Lowther et al., 2012). Two novel small subunits (SPTSSA and SPTSSB) were identified, both of which enhance SPTLC activity >10-fold when bound to either of the SPTLC heterodimers (Han et al. 2009). Orosomucoid (ORM) proteins, first identified in yeast, associate with and negatively regulate SPTLC activity (Breslow et al. 2010; Han et al. 2010). The three human ORM proteins similarly bind and negatively regulate SPTLC activity (Breslow et al., 2010; reviewed by Davis et al., 2018). In particular, dysregulation of SPT activity by ORML3 appears to be involved with forms of obesity (reviewed by Brown & Spiegel, 2023). In serine deficiency, SPTLC transfers acyl-CoA onto alanine, and the resulting 1-deoxysphingoids ultimately get processed to 1-deoxyceramides (reviewed by Duan & Merrill, 2015).

Followed by: KDSR reduces 3-ketosphingoid

Literature references

Hayashi, H., Ikushiro, H. (2011). Mechanistic enzymology of serine palmitoyltransferase. *Biochim Biophys Acta, 1814*, 1474-80. ↗

Naismith, JH., Campopiano, DJ., Dunn, TM., Lowther, J. (2012). Structural, mechanistic and regulatory studies of serine palmitoyltransferase. *Biochem Soc Trans, 40*, 547-54. ↗

Richard, S., Wei, Y., Rutti, MF., Hornemann, T., von Eckardstein, A. (2006). Cloning and initial characterization of a new subunit for mammalian serine-palmitoyltransferase. *J Biol Chem, 281*, 37275-81. ↗

Stoffel, W., Weiss, B. (1997). Human and murine serine-palmitoyl-CoA transferase--cloning, expression and characterization of the key enzyme in sphingolipid synthesis. *Eur J Biochem, 249*, 239-47. ↗

Schneiter, R., Chang, A., Han, S., Lone, MA. (2010). Orm1 and Orm2 are conserved endoplasmic reticulum membrane proteins regulating lipid homeostasis and protein quality control. *Proc. Natl. Acad. Sci. U.S.A., 107,* 5851-6. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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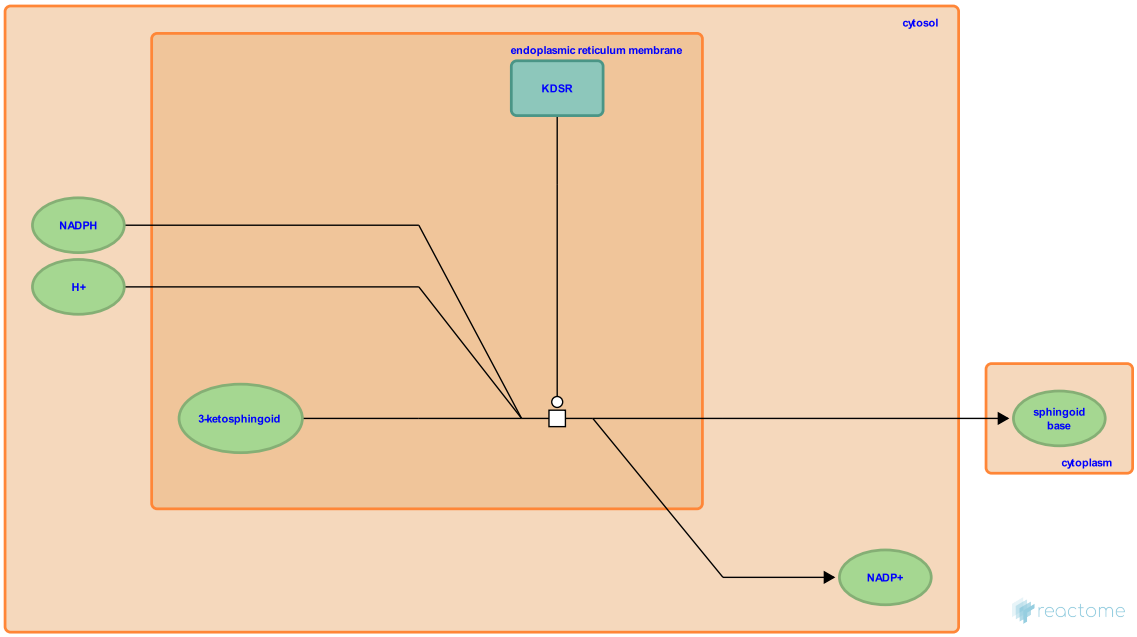
KDSR reduces 3-ketosphingoid ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-428123

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



KDSR (3-ketodihydrosphingosine reductase) enzyme associated with the cytosolic face of the endoplasmic reticulum membrane catalyzes the reduction of 3-ketosphingoid by NADPH to form sphingoid (Kihara and Igarashi 2004). Defects in KDSR or missing activity causes Erythrokeratodermia (EKVP4, MIM:617526), associated with sphingolipid dysregulation (Boyden et al., 2017). While there is no data on substrates other than 3-ketosphinganine, it is probable that KDSR has activity toward 3-ketosphingoids with other chain lengths than C16.

Preceded by: SPTLC complexes transfer acyl-CoA onto serine

Followed by: SPHK2 phosphorylates sphingoid, SPHK1 phosphorylates sphingoid, Ceramide synthases transfer acyl-CoA onto sphingoid

Literature references

Igarashi, Y., Kihara, A. (2004). FVT-1 is a mammalian 3-ketodihydrosphingosine reductase with an active site that faces the cytosolic side of the endoplasmic reticulum membrane. *J Biol Chem, 279*, 49243-50. ↗

Diaz, LA., Craiglow, BG., Boyden, LM., Choate, KA., Baserga, SJ., Rosman, IS. et al. (2017). Mutations in KDSR Cause Recessive Progressive Symmetric Erythrokeratoderma. *Am J Hum Genet, 100*, 978-984. ↗

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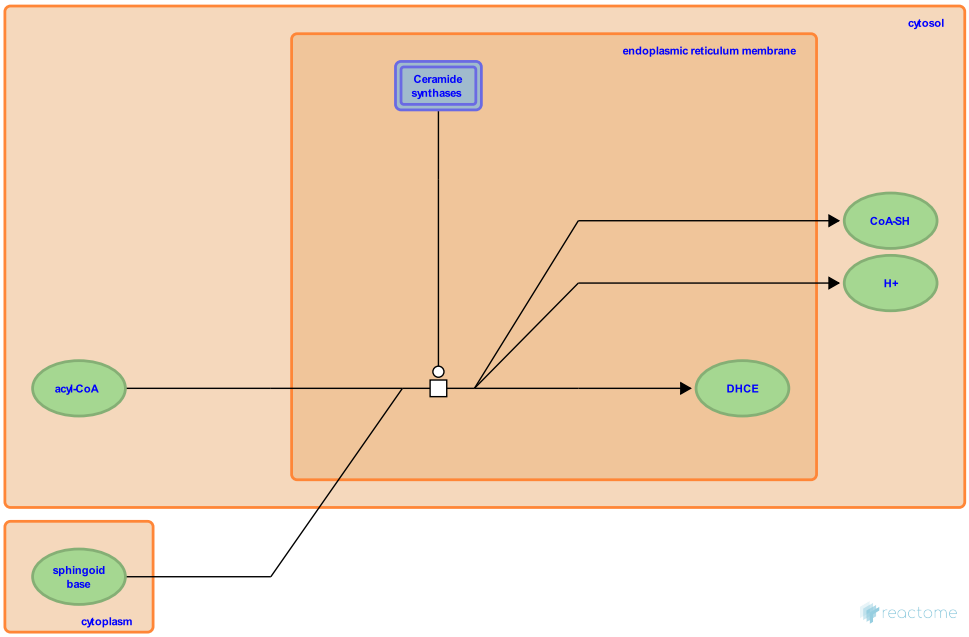
Ceramide synthases transfer acyl-CoA onto sphingoid ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-428185

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Ceramide synthase enzymes (CerS, LASS) associated with the endoplasmic reticulum membrane catalyze the reaction of a sphingoid and a long-chain fatty acyl CoA such as stearyl-CoA to form a dihydroceramide and CoASH (Pewzner-Jung et al. 2006). Six human CerS genes have been identified; they differ in the identities of the fatty acyl CoAs that they use most efficiently as substrates (Lahiri and Futerman, 2005; Laviad et al., 2008; reviewed in Stiban et al., 2010; Mullen et al., 2012; Cingolani et al., 2016). Ceramide synthases have regulatory roles in the progression of many cancers and chemoresistance (reviewed in Brachtendorf et al., 2019; Zhang et al., 2023). As ceramides with different acyl chain lengths have specific functions in neuronal membranes, and the six CerS have different activities toward different acyl chain lengths, CerS expression patterns are involved in neurologic conditions (reviewed by Ben-David and Futerman, 2010). Missing CERS1 activity is the cause of progressive myoclonic epilepsy (EPM8, MIM:616230) (Vanni et al., 2014). Defects in CERS3 can cause a form of autosomal recessive congenital ichthyosis (ARCI9, MIM:615023) (Radner et al., 2013).

Preceded by: KDSR reduces 3-ketosphingoid

Followed by: DEGS1 dehydrogenates dihydroceramide, DEGS2 oxygenates dihydroceramide

Literature references

Bramanti, P., Sander, T., Bielawski, J., Vanni, N., Minetti, C., Fruscione, F. et al. (2014). Impairment of ceramide synthesis causes a novel progressive myoclonus epilepsy. *Ann Neurol, 76*, 206-12. ↗

El-Hindi, K., Brachtendorf, S., Grösch, S. (2019). Ceramide synthases in cancer therapy and chemoresistance. *Prog Lipid Res, 74*, 160-185. ↗

Casas, J., Cingolani, F., Futerman, AH. (2016). Ceramide synthases in biomedical research. *Chem Phys Lipids, 197*, 25-32. ↗

Schempp, W., Kirchmeier, P., Lathrop, M., Ribierre, F., Leipoldt, M., Turki, H. et al. (2013). Mutations in CERS3 cause autosomal recessive congenital ichthyosis in humans. *PLoS Genet, 9*, e1003536. ↗

Ben-Dor, S., Pewzner-Jung, Y., Futerman, AH. (2006). When do Lasses (longevity assurance genes) become CerS (ceramide synthases)?: Insights into the regulation of ceramide synthesis. *J Biol Chem, 281*, 25001-5. ↗

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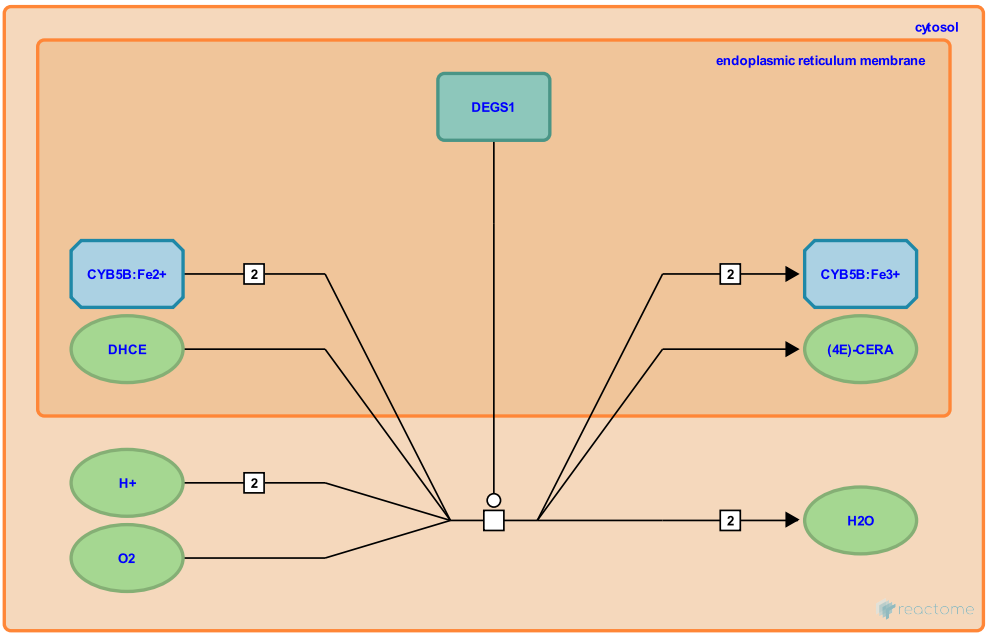
DEGS1 dehydrogenates dihydroceramide ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-428259

Type: transition

Compartments: cytosol, endoplasmic reticulum membrane



DEGS1 (DES1, sphingolipid delta(4)-desaturase 1 / "degenerative spermatocyte homolog 1") enzyme associated with the cytosolic face of the endoplasmic reticulum catalyzes the desaturation of dihydroceramide to form ceramide (Cadena et al. 1997; Ternes et al. 2002). The stoichiometry and cofactor requirements of the reaction are inferred from those observed in studies of ceramide synthesis in vitro catalyzed by rat liver microsomes (Michel et al. 1997). Apparently, DEGS1 is part of an enzyme complex, together with non-heme cytochrome b5 carrying Fe2+, that provides the reduction equivalent, which is subsequently refreshed by NADH (Geeraert et al., 1997; reviewed by Fabrias et al., 2011). The reaction is necessary as a step in ceramide biosynthesis, dihydroceramides and their downstream products like dihydrosphingomyelins are biologically active, for example, as part of lipid rafts, and inhibition of DEGS1 is a therapeutic target in cancer treatment (reviewed by Fabrias et al., 2011; Tzou et al., 2023). Mutations in DEGS1 cause hypomyelinating leukodystrophy (HLD18, MIM:618404) (reviewed by Wong et al., 2023).

Preceded by: Ceramide synthases transfer acyl-CoA onto sphingoid

Followed by: SAMD8 transfers phosphatidyl from PE onto C16DH CER, CERT1-2 complex binds ceramide

Literature references

Tzou, FY., Hornemann, T., Huang, SY., Yeh, JY. (2023). The pathophysiological role of dihydroceramide desaturase in the nervous system. *Prog Lipid Res, 91*, 101236. ↗

Zahringer, U., Franke, S., Ternes, P., Heinz, E., Sperling, P. (2002). Identification and characterization of a sphingolipid delta 4-desaturase family. *J Biol Chem, 277*, 25512-8. ↗

Kurten, RC., Cadena, DL., Gill, GN. (1997). The product of the MLD gene is a member of the membrane fatty acid desaturase family: overexpression of MLD inhibits EGF receptor biosynthesis. *Biochemistry, 36*, 6960-7. ↗

Wang, E., Merrill AH, Jr., Michel, C., van Echten-Deckert, G., Sandhoff, K., Rother, J. (1997). Characterization of ceramide synthesis. A dihydroceramide desaturase introduces the 4,5-trans-double bond of sphingosine at the level of dihydroceramide. *J Biol Chem, 272*, 22432-7. ↗

Mannaerts, GP., Geeraert, L., Van Veldhoven, PP. (1997). Conversion of dihydroceramide into ceramide: involvement of a desaturase. *Biochem J, 327*, 125-32. ↗

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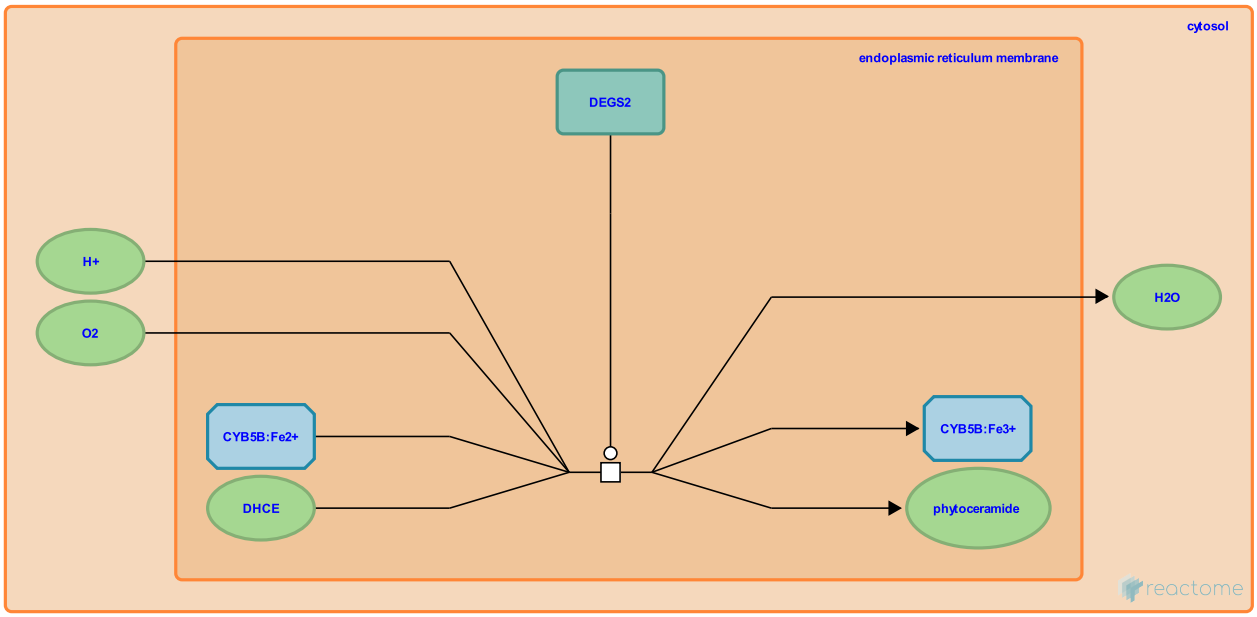
DEGS2 oxygenates dihydroceramide ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-428260

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



DEGS2 (sphingolipid C4-hydroxylase 2 / “degenerative spermatocyte homolog 2”) enzyme associated with the cytosolic face of the endoplasmic reticulum catalyzes the hydroxylation of dihydroceramide to form phytoceramide (Mizutani et al. 2004). DEGS2 appears not to be essential, with another unknown enzyme catalyzing the same reaction. The highest activity of DEGS2 is on long-chain (>= C21) dihydroceramides. DEGS2 also catalyzes the C4-dehydrogenation of dihydroceramide, but this activity is minor (Ota et al., 2023).

Preceded by: Ceramide synthases transfer acyl-CoA onto sphingoid

Literature references

Igarashi, Y., Kihara, A., Mizutani, Y. (2004). Identification of the human sphingolipid C4-hydroxylase, hDES2, and its up-regulation during keratinocyte differentiation. *FEBS Lett, 563*, 93-7. ↗

Nojiri, K., Matsuda, J., Ota, A., Jojima, K., Kihara, A., Miyamoto, M. et al. (2023). Bifunctional DEGS2 has higher hydroxylase activity toward substrates with very-long-chain fatty acids in the production of phytosphingosine ceramides. *J Biol Chem, 299*, 104603. ↗

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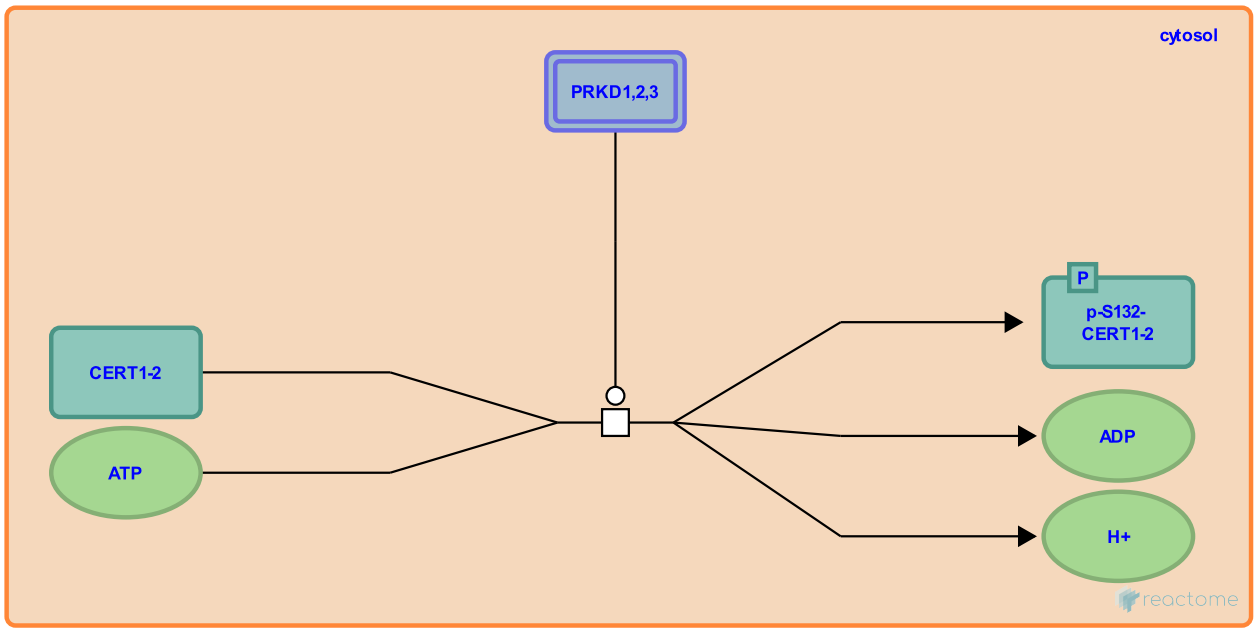
PRKD1,2,3 phosphorylates CERT1-2 ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429698

Type: transition

Compartments: cytosol



Cytosolic PRKD1, 2, and 3 (protein kinase D1, D2, and D3) catalyze the phosphorylation of serine residue 132 of isoform 2 of ceramide transfer protein (CERT1-2, aka COL4A3BP-2). Protein kinase D (PRKD) is a crucial regulator of secretory transport at the trans-Golgi network (TGN). Phosphorylation of COL4A3BP-2 reduces its ceramide transfer activity. PRKDs may, therefore, act as regulators of lipid homeostasis (Fugmann et al., 2007; Kumagai et al., 2014; Shimasaki et al., 2022; reviewed by Olayioye & Hausser, 2011; Kumagai & Hanada, 2019).

Preceded by: CERT1-2 complex dissociates

Followed by: CSNK1G2 phosphorylates p-CERT1-2

Literature references

Yamaji, T., Sakai, S., Shimasaki, K., Hanada, K., Kumagai, K. (2022). Hyperosmotic Stress Induces Phosphorylation of CERT and Enhances Its Tethering throughout the Endoplasmic Reticulum. *Int J Mol Sci, 23*. ↗

Kawano-Kawada, M., Hanada, K., Kumagai, K. (2014). Phosphoregulation of the ceramide transport protein CERT at serine 315 in the interaction with VAMP-associated protein (VAP) for inter-organelle trafficking of ceramide in mammalian cells. *J Biol Chem, 289*, 10748-10760. ↗

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

Schoffler, P., Olayioye, MA., Hausser, A., Pfizenmaier, K., Fugmann, T., Schmid, S. (2007). Regulation of secretory transport by protein kinase D-mediated phosphorylation of the ceramide transfer protein. *J Cell Biol, 178*, 15-22. ↗

Hausser, A., Olayioye, MA. (2012). Integration of non-vesicular and vesicular transport processes at the Golgi complex by the PKD-CERT network. *Biochim Biophys Acta, 1821*, 1096-103. ↗

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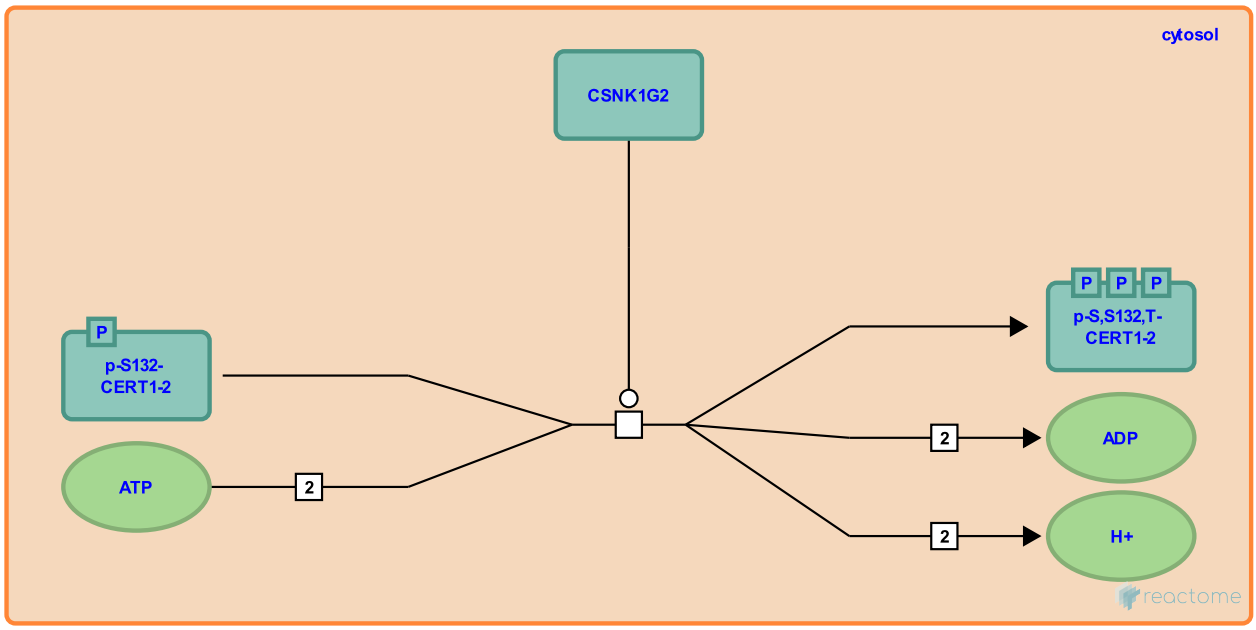
CSNK1G2 phosphorylates p-CERT1-2 ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429714

Type: transition

Compartments: cytosol



Cytosolic CSNK1G2 (casein kinase 1, gamma 2) catalyzes the phosphorylation of multiple serine and threonine residues of "CERT" (ceramide transfer protein) already phosphorylated on serine-132 (Tomishige et al. 2009). This reaction has the effect of inhibiting ceramide transport from the endoplasmic reticulum to the Golgi apparatus as multiphospho-CERT is unable to bind ceramides or associate with the Golgi membrane (reviewed by Kumagai & Hanada, 2019).

Preceded by: PRKD1,2,3 phosphorylates CERT1-2

Followed by: Multiphospho-CERT1-2 binds PPM1L, VAPA/B

Literature references

Hanada, K., Kusuda, J., Kumagai, K., Tomishige, N., Nishijima, M. (2009). Casein kinase I{gamma}2 down-regulates trafficking of ceramide in the synthesis of sphingomyelin. *Mol Biol Cell, 20*, 348-57. ↗

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

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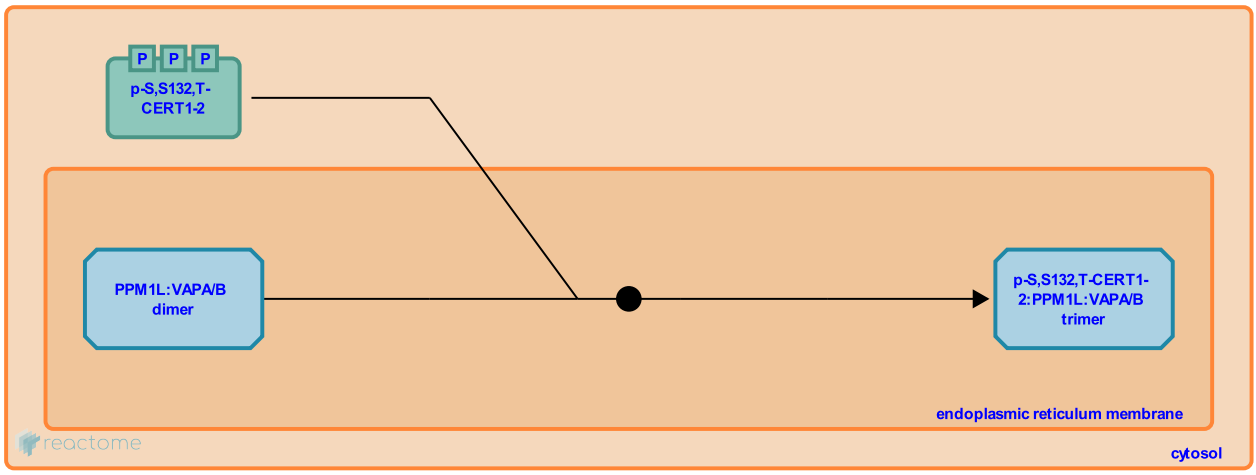
Multiphospho-CERT1-2 binds PPM1L, VAPA/B ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429732

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol



Multiphospho-CERT retains its affinity for VAPA or VAPB (VAMP-associated proteins A or B) and PPM1L (protein phosphatase 1-like) in the endoplasmic reticulum membrane, and can associate with them to form a membrane-associated complex (Kawano et al., 2006; Saito et al. 2008; reviewed by Kumagai & Hanada, 2019).

Preceded by: CERT1-2 complex dissociates, CSNK1G2 phosphorylates p-CERT1-2

Followed by: PPM1L dephosphorylates multiphospho-CERT1-2

Literature references

Tamura, S., Saito, S., Kobayashi, T., Echigo, S., Kawano, M., Matsui, H. et al. (2008). Protein phosphatase 2Cepsilon is an endoplasmic reticulum integral membrane protein that dephosphorylates the ceramide transport protein CERT to enhance its association with organelle membranes. *J Biol Chem, 283*, 6584-93. ↗

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

Kawano, M., Hanada, K., Kumagai, K., Nishijima, M. (2006). Efficient trafficking of ceramide from the endoplasmic reticulum to the Golgi apparatus requires a VAMP-associated protein-interacting FFAT motif of CERT. *J Biol Chem , 281*, 30279-88. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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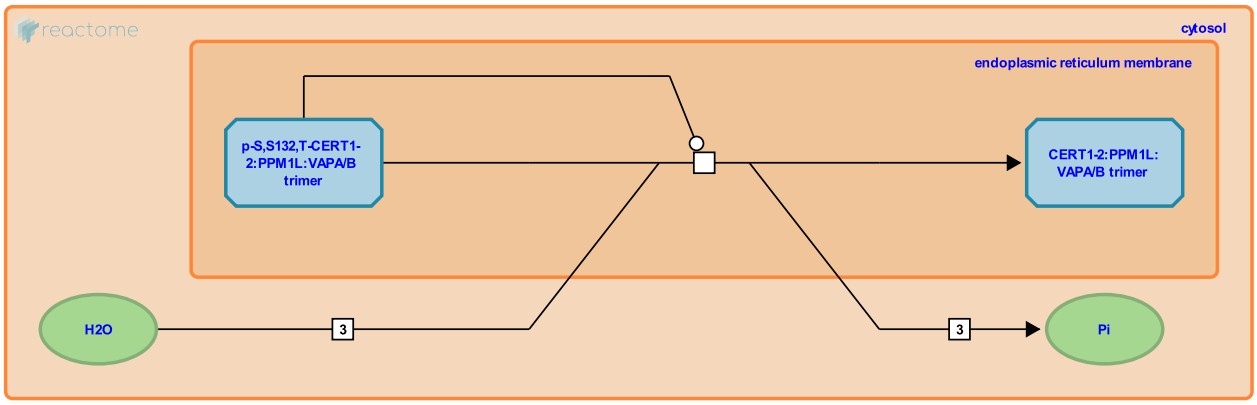
PPM1L dephosphorylates multiphospho-CERT1-2 ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429730

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



PPM1L (protein phosphatase 1-like) catalyzes the dephosphorylation of multiphospho-"CERT" (ceramide transfer protein) that is complexed with it in the endoplasmic reticulum membrane (Saito et al. 2008; reviewed by Kumagai & Hanada, 2019). This reinstates binding of ceramide to and its transport by CERT.

Preceded by: Multiphospho-CERT1-2 binds PPM1L, VAPA/B

Followed by: CERT1-2 complex binds ceramide

Literature references

Tamura, S., Saito, S., Kobayashi, T., Echigo, S., Kawano, M., Matsui, H. et al. (2008). Protein phosphatase 2Cepsilon is an endoplasmic reticulum integral membrane protein that dephosphorylates the ceramide transport protein CERT to enhance its association with organelle membranes. *J Biol Chem, 283*, 6584-93. ↗

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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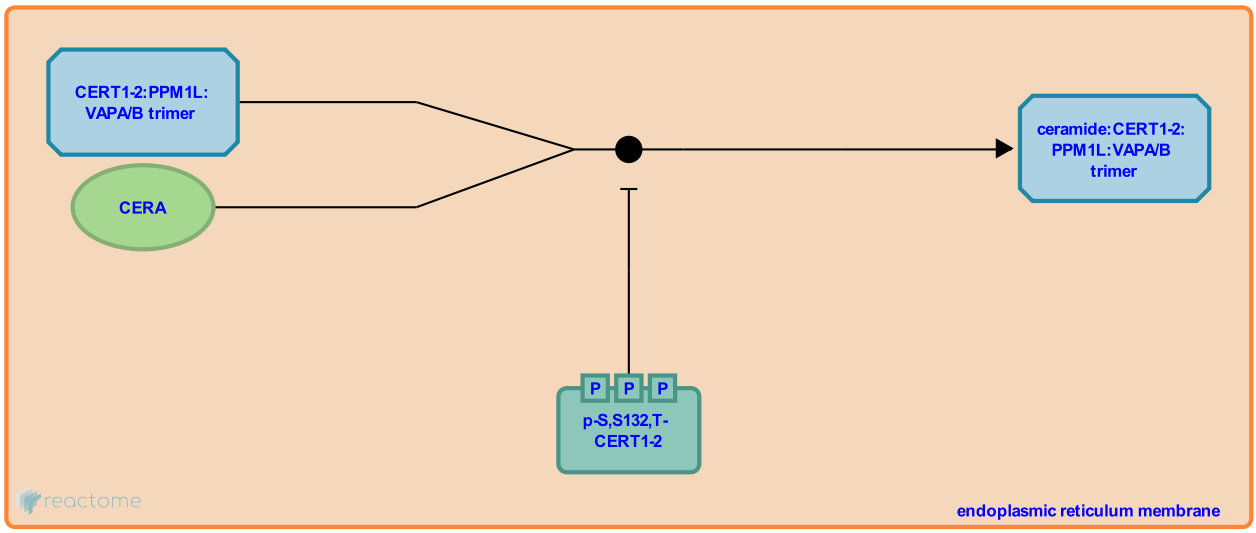
CERT1-2 complex binds ceramide ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429699

Type: binding

Compartments: endoplasmic reticulum membrane



CERT1-2 (ceramide transfer protein, isoform 2), an isoform of COL4A3BP, mediates the translocation of ceramides from the endoplasmic reticulum (ER) membrane to the membrane of the Golgi apparatus at the ER-Golgi membrane contact sites (MCS). Immunoprecipitation experiments suggest that CERT1-2 is associated with the ER membrane as part of a complex with PPM1L (protein phosphatase 1-like) (Saito et al. 2008) and VAPA or VAPB (VAMP-associated proteins A or B) (Kawano et al. 2006). The carboxyterminal START domain of CERT1-2 protein specifically binds ceramides (Hanada et al. 2003; Kudo et al. 2008). Non-vesicular transport of ceramide from endoplasmic reticulum to Golgi membranes is essential for cellular lipid homeostasis (reviewed by Olaiyoye et al., 2012; Kumagai & Hanada, 2019). While there is no direct support for the transfer of other ceramides than Cer(d18:1/16:0), it makes sense to assume other ceramides are transported, as well.

Preceded by: DEGS1 dehydrogenates dihydroceramide, PPM1L dephosphorylates multiphospho-CERT1-2

Followed by: CERT1-2 releases its bound ceramide into the membrane of the Golgi apparatus, CERT1-2 complex dissociates

Literature references

Tamura, S., Saito, S., Kobayashi, T., Echigo, S., Kawano, M., Matsui, H. et al. (2008). Protein phosphatase 2Cepsilon is an endoplasmic reticulum integral membrane protein that dephosphorylates the ceramide transport protein CERT to enhance its association with organelle membranes. *J Biol Chem, 283*, 6584-93. ↗

Wakatsuki, S., Kato, R., Yamaji, T., Hanada, K., Tomishige, N., Kumagai, K. et al. (2008). Structural basis for specific lipid recognition by CERT responsible for nonvesicular trafficking of ceramide. *Proc Natl Acad Sci U S A, 105*, 488-93. ↗

Yasuda, S., Miura, Y., Kawano, M., Fukasawa, M., Kumagai, K., Hanada, K. et al. (2003). Molecular machinery for non-vesicular trafficking of ceramide. *Nature, 426*, 803-9. ↗

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

Hausser, A., Olayioye, MA. (2012). Integration of non-vesicular and vesicular transport processes at the Golgi complex by the PKD-CERT network. *Biochim Biophys Acta, 1821*, 1096-103. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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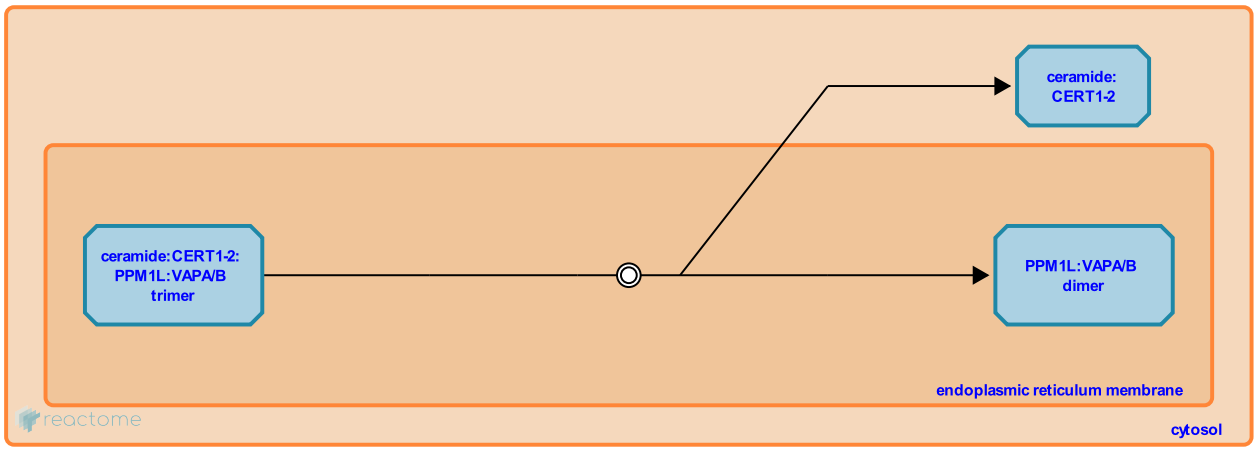
CERT1-2 complex dissociates ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429694

Type: dissociation

Compartments: endoplasmic reticulum membrane, cytosol



CERT1-2 (ceramide transfer protein, isoform 2) can dissociate from its complex in the endoplasmic reticulum membrane with VAPA or VAPB (VAMP-associated proteins A or B) and PPM1L (protein phosphatase 1-like) and is released into the cytosol (Kawano et al. 2006; reviewed by Kumagai & Hanada, 2019).

Preceded by: CERT1-2 complex binds ceramide

Followed by: Multiphospho-CERT1-2 binds PPM1L, VAPA/B, PRKD1,2,3 phosphorylates CERT1-2

Literature references

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

Kawano, M., Hanada, K., Kumagai, K., Nishijima, M. (2006). Efficient trafficking of ceramide from the endoplasmic reticulum to the Golgi apparatus requires a VAMP-associated protein-interacting FFAT motif of CERT. *J Biol Chem , 281*, 30279-88. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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2009-11-19	Reviewed	Hannun, YA., Luberto, C.
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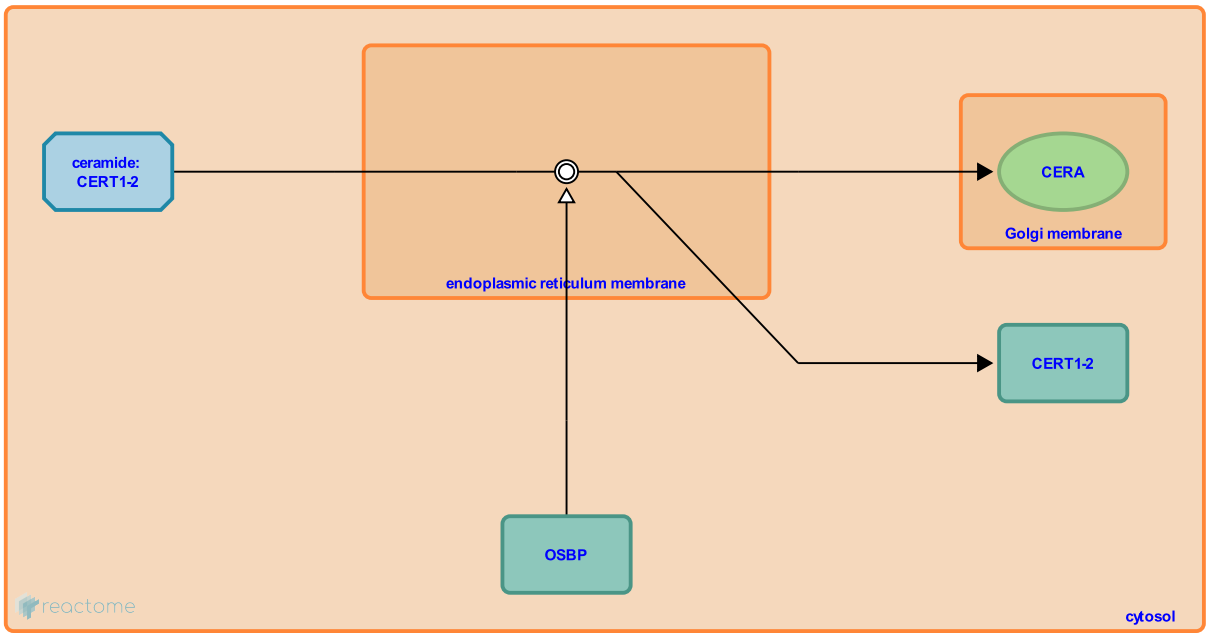
CERT1-2 releases its bound ceramide into the membrane of the Golgi apparatus ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429683

Type: dissociation

Compartments: endoplasmic reticulum membrane



CERT1-2 (ceramide transfer protein, isoform 2), associated with the cytosolic face of the endoplasmic reticulum (ER) in a complex with VAPA or VAPB (VAMP-associated proteins A or B) (Kawano et al. 2006) and PPM1L (protein phosphatase 1-like) (Saito et al. 2008), can bridge the gap between the ER and the Golgi apparatus via its PH domain and transfer a molecule of ceramide extracted from the ER membrane to the Golgi at the ER-Golgi membrane contact sites (MCS) (Hanada et al. 2003; Saito et al. 2008). CERT1-2-mediated ceramide transfer is positively regulated by OSBP (oxysterol binding protein), apparently through accumulation of phosphatidylinositol 4-phosphate (PI-4P) at MCS (Perry and Ridgway 2006; Goto et al., 2016). Non-vesicular transport of ceramide from endoplasmic reticulum to Golgi membranes is essential for cellular lipid homeostasis (reviewed by Olaiyoye et al., 2012; Kumagai & Hanada, 2019).

Preceded by: CERT1-2 complex binds ceramide

Followed by: SGMS1 transfers phosphocholine onto ceramide

Literature references

Ridgway, ND., Perry, RJ. (2006). Oxysterol-binding protein and vesicle-associated membrane protein-associated protein are required for sterol-dependent activation of the ceramide transport protein. *Mol Biol Cell, 17*, 2604-16. ↗

Tamura, S., Saito, S., Kobayashi, T., Echigo, S., Kawano, M., Matsui, H. et al. (2008). Protein phosphatase 2Cepsilon is an endoplasmic reticulum integral membrane protein that dephosphorylates the ceramide transport protein CERT to enhance its association with organelle membranes. *J Biol Chem, 283*, 6584-93. ↗

Yasuda, S., Miura, Y., Kawano, M., Fukasawa, M., Kumagai, K., Hanada, K. et al. (2003). Molecular machinery for non-vesicular trafficking of ceramide. *Nature, 426*, 803-9. ↗

Goto, A., Charman, M., Ridgway, ND. (2016). Oxysterol-binding Protein Activation at Endoplasmic Reticulum-Golgi Contact Sites Reorganizes Phosphatidylinositol 4-Phosphate Pools. *J Biol Chem, 291*, 1336-47. ↗

Hanada, K., Kumagai, K. (2019). Structure, functions and regulation of CERT, a lipid-transfer protein for the delivery of ceramide at the ER-Golgi membrane contact sites. *FEBS Lett, 593*, 2366-2377. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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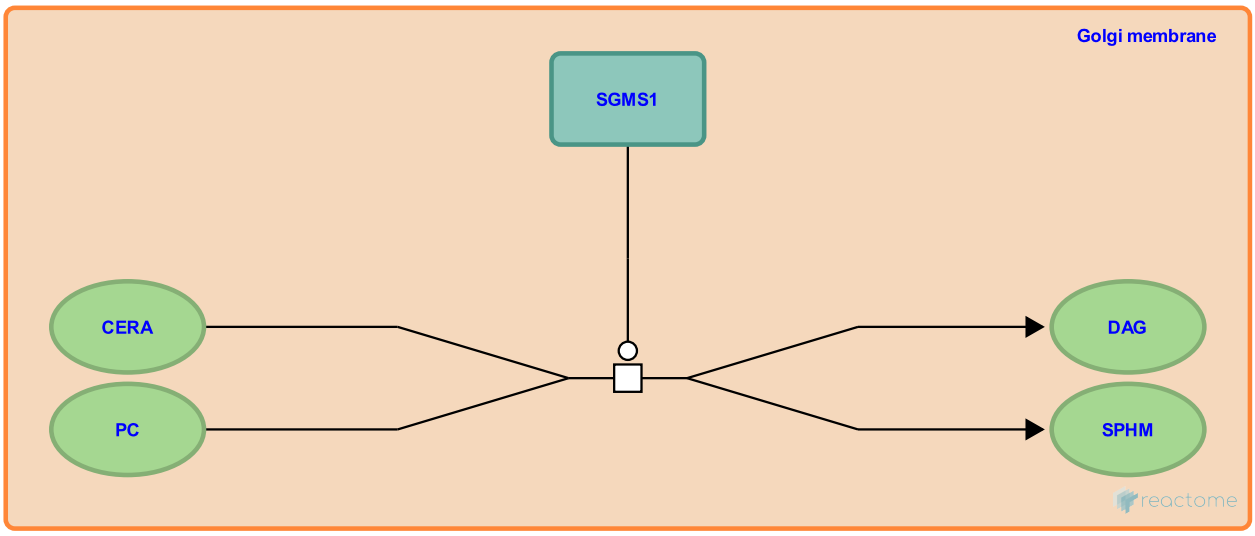
SGMS1 transfers phosphocholine onto ceramide ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429798

Type: transition

Compartments: Golgi membrane



SGMS1 (sphingomyelin synthase 1) associated with the membrane of the Golgi apparatus catalyzes the reversible reaction of phosphatidylcholine and ceramide to form sphingomyelin and diacylglycerol. Phosphatidylcholine was identified as the source of the phosphocholine moiety donated to ceramide in this reaction in studies of the mouse enzyme in the 1970s (Diringer et al. 1972; Ullman and Radin 1974). SGMS1 is widely expressed in the body, and studies of cultured cells indicate that this reaction provides the primary source of cellular sphingomyelin (Yamaoka et al., 2004; Huitema et al., 2004; Tafesse et al., 2007; reviewed by Chen & Cao, 2017).

Preceded by: CERT1-2 releases its bound ceramide into the membrane of the Golgi apparatus

Literature references

Chen, Y., Cao, Y. (2017). The sphingomyelin synthase family: proteins, diseases, and inhibitors. *Biol Chem, 398*, 1319-1325. ↗

Radin, NS., Ullman, MD. (1974). The enzymatic formation of sphingomyelin from ceramide and lecithin in mouse liver. *J Biol Chem, 249*, 1506-12. ↗

Koch, MA., Diringer, H., Anderer, FA., Marggraf, WD. (1972). Evidence for a new biosynthetic pathway of sphingomyelin in SV 40 transformed mouse cells. *Biochem Biophys Res Commun, 47*, 1345-52. ↗

van der Poel, S., Uphoff, A., Tafesse, FG., Huitema, K., Hermansson, M., Holthuis, JC. et al. (2007). Both sphingomyelin synthases SMS1 and SMS2 are required for sphingomyelin homeostasis and growth in human HeLa cells. *J Biol Chem, 282*, 17537-47. ↗

Kitano, T., Umehara, H., Yamaoka, S., Okazaki, T., Miyaji, M. (2004). Expression cloning of a human cDNA restoring sphingomyelin synthesis and cell growth in sphingomyelin synthase-defective lymphoid cells. *J Biol Chem, 279*, 18688-93. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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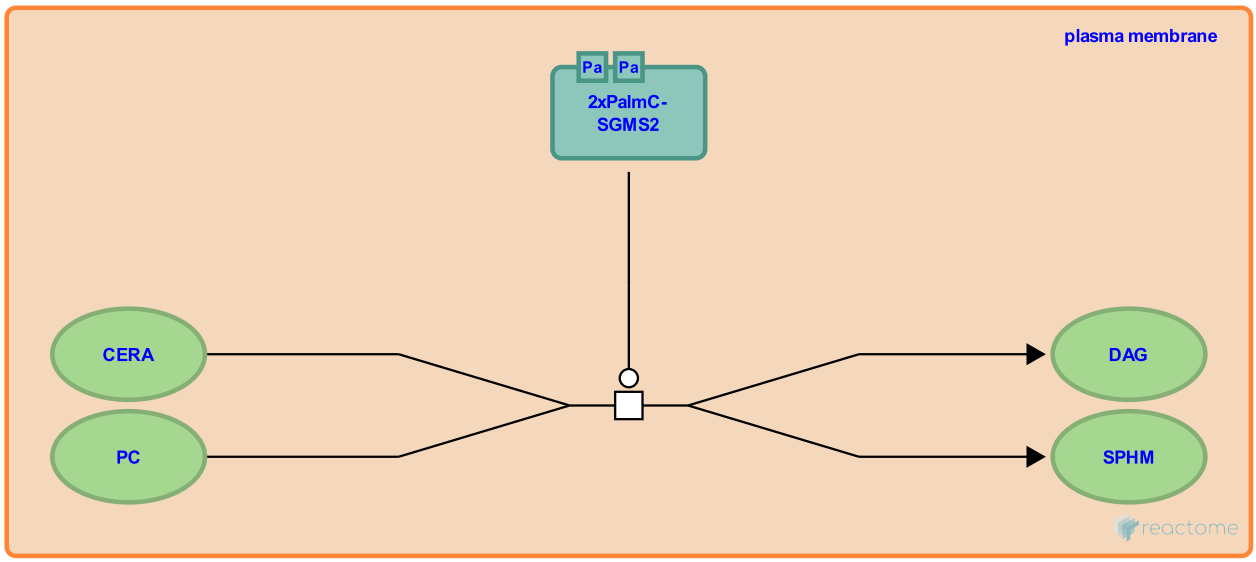
SGMS2 transfers phosphocholine onto ceramide ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-429786

Type: transition

Compartments: plasma membrane



SGMS2 (sphingomyelin synthase 2) catalyzes the reversible reaction of phosphatidylcholine and ceramide to form sphingomyelin and diacylglycerol. Most SGMS2 activity is associated with the plasma membrane, although active enzyme is also present in the Golgi apparatus (Tafesse et al. 2007; Villani et al. 2008; Ding et al. 2008). Phosphatidylcholine was identified as the source of the phosphocholine moiety donated to ceramide in this reaction in studies of the mouse enzyme in the 1970s (Diringer et al., 1972; Ullman and Radin, 1974). The association of SGMS2 with the plasma membrane appears to require palmitoylation of at least two cysteine residues near the carboxy terminus (Tani and Kuge, 2009). SGMS2 is widely expressed in the body, and while studies of cultured cells indicate that this is a minor source of cellular sphingomyelin, blockage of SGMS2 activity inhibits cell growth. SGMS2 deficiency causes forms of osteoporosis (CDL, MIM:126550; CDLSMD, MIM:126550) (Huitema et al., 2004; Tafesse et al., 2007; reviewed by Chen & Cao, 2017).

Literature references

Chen, Y., Cao, Y. (2017). The sphingomyelin synthase family: proteins, diseases, and inhibitors. *Biol Chem, 398*, 1319-1325. ↗

Radin, NS., Ullman, MD. (1974). The enzymatic formation of sphingomyelin from ceramide and lecithin in mouse liver. *J Biol Chem, 249*, 1506-12. ↗

Koch, MA., Diringer, H., Anderer, FA., Marggraf, WD. (1972). Evidence for a new biosynthetic pathway of sphingomyelin in SV 40 transformed mouse cells. *Biochem Biophys Res Commun, 47*, 1345-52. ↗

van der Poel, S., Uphoff, A., Tafesse, FG., Huitema, K., Hermansson, M., Holthuis, JC. et al. (2007). Both sphingomyelin synthases SMS1 and SMS2 are required for sphingomyelin homeostasis and growth in human HeLa cells. *J Biol Chem, 282*, 17537-47. ↗

Tani, M., Kuge, O. (2009). Sphingomyelin synthase 2 is palmitoylated at the COOH-terminal tail, which is involved in its localization in plasma membranes. *Biochem Biophys Res Commun, 381*, 328-32. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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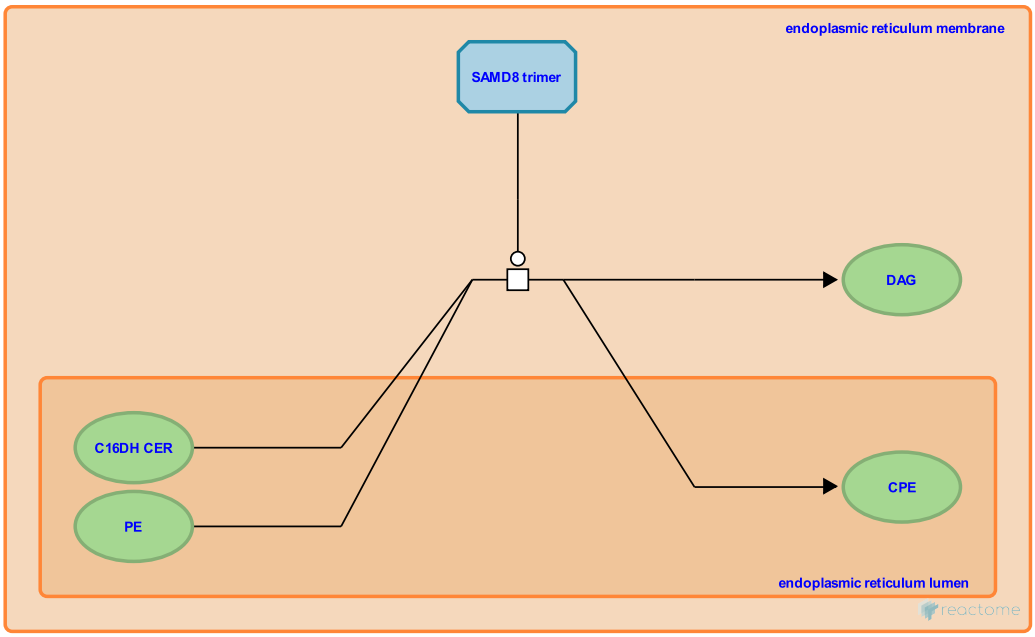
SAMD8 transfers phosphatidyl from PE onto C16DH CER ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-8959462

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Sphingolipids such as sphingomyelin (SM) are essential components of cellular membranes and dynamic regulators of many cellular processes in most organisms. Ceramides constitute the backbone of all sphingolipids and are synthesized on the cytosolic surface of the endoplasmic reticulum (ER) and then transported to the Golgi for conversion to SM. The ER-membrane resident protein sphingomyelin synthase-related protein 1 (SAMD8) catalyzes the synthesis of the SM analog ceramide phosphoethanolamine (CPE) in the ER lumen. SAMD8 only produces trace amounts of CPE, but blocking its catalytic activity causes a substantial rise in ER ceramide levels and a structural collapse of the early secretory pathway. SAMD8 is, therefore, a key regulator of ceramide homeostasis, functioning as a sensor rather than a converter of ceramides in the ER (Vacaru et al., 2009). SAMD8 self-associates into ER-resident trimers and hexamers (Cabukusta et al., 2017). The biological role of the produced CPE in humans needs to be better defined. However, it is the main sphingolipid in arthropods and some protozoa and bacteria (see review by Panewska et al., 2019).

Preceded by: DEGS1 dehydrogenates dihydroceramide

Literature references

Cabukusta, B., Bickert, A., Holthuis, JC., Mina, JG., Kol, M., Hilderink, A. et al. (2017). ER residency of the ceramide phosphoethanolamine synthase SMSr relies on homotypic oligomerization mediated by its SAM domain. *Sci Rep, 7*, 41290. ↗

Rabouille, C., Kondylis, V., Holthuis, JC., Ternes, P., Vacaru, AM., Brouwers, JF. et al. (2009). Sphingomyelin synthase-related protein SMSr controls ceramide homeostasis in the ER. *J. Cell Biol., 185*, 1013-27. ↗

Sepčić, K., Maček, P., Skočaj, M., Panevska, A., Križaj, I. (2019). Ceramide phosphoethanolamine, an enigmatic cellular membrane sphingolipid. *Biochim Biophys Acta Biomembr, 1861*, 1284-1292. ↗

Editions

2017-01-26	Authored, Edited	Jassal, B.
2017-01-30	Reviewed	D'Eustachio, P.
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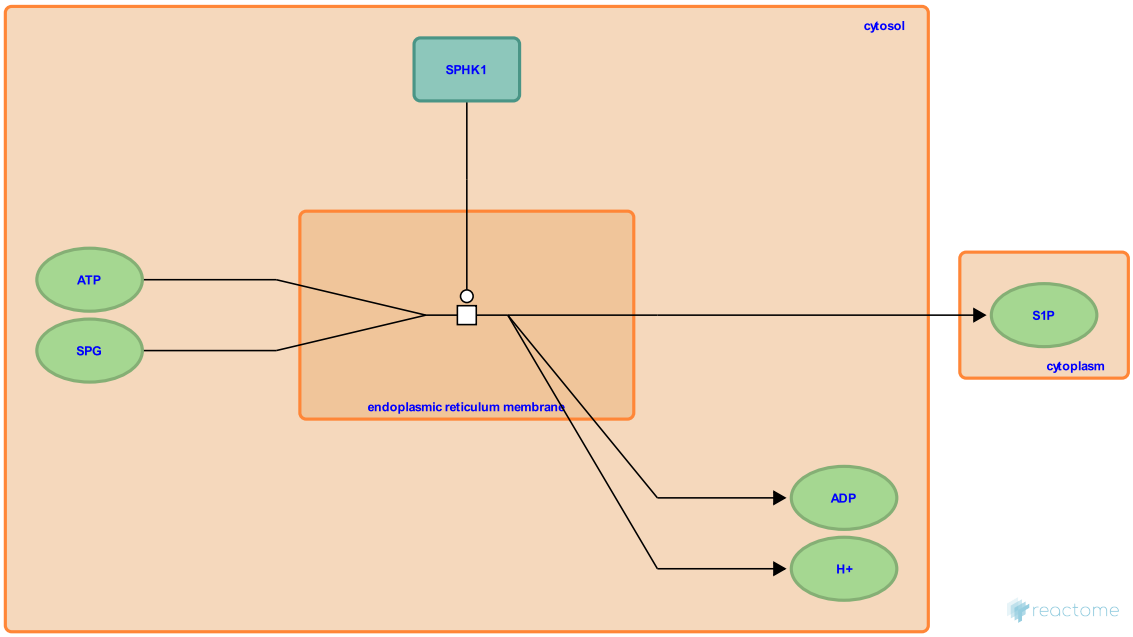
SPHK1 phosphorylates sphingoid ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-428273

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



The cytosolic enzyme sphingosine kinase 1 (SPHK1) catalyzes the phosphorylation of sphingoids (SPG) to sphingoid 1-phosphate (S1P). The main product is sphingosine 1-phoshate, a bioactive lipid that acts extracellularly on G protein-coupled receptors of the S1P1/EDG-1 subfamily (Nava et al., 2000; Pitson et al., 2000; Wang et al., 2013; reviewed by Siow & Wattenberg, 2011). The isoforms SK1a, SK1b, and SK1c are produced through alternative splicing and show functional differences in their activity (reviewed by Hatoum et al., 2017). SPHK1 is regulated transcriptionally by transcription factors, cytokines, and micro-RNAs (reviewed by Bonica et al., 2020). Its activity is also modulated by posttranslational modifications and interactions with other proteins (reviewed by Pulkoski-Gross & Obeid, 2018). Through its product S1P, which is a multifunctional signaling lipid, SPHK1 is essential in inflammation processes (reviewed by Rauch, 2014). SPHK1 was also shown to be associated with cancer genesis, progression, and metastasic processes (Zhang et al., 2014).

Preceded by: KDSR reduces 3-ketosphingoid

Followed by: ABCC1,ABCG2 transport C18-S1P to extracellular region, SPNS2,MFSD2B transport S1P from cytosol to extracellular region

Literature references

Sugiura, M., Poulton, S., Liu, H., Nava, VE., Spiegel, S., Kohama, T. et al. (2000). Functional characterization of human sphingosine kinase-1. *FEBS Lett, 473*, 81-4. ↗

Hatoum, D., McGowan, EM., Nassif, NT., Lin, Y., Haddadi, N. (2017). Mammalian sphingosine kinase (SphK) isoenzymes and isoform expression: challenges for SphK as an oncotarget. *Oncotarget, 8*, 36898-36929. ↗

Romanow, W., Walker, N., Dai, J., Xiao, SH., Johnstone, S., Thibault, S. et al. (2013). Molecular basis of sphingosine kinase 1 substrate recognition and catalysis. *Structure, 21*, 798-809. ↗

Rauch, BH. (2014). Sphingosine 1-phosphate as a link between blood coagulation and inflammation. *Cell Physiol Biochem, 34*, 185-96. ↗

Pulkoski-Gross, MJ., Obeid, LM. (2018). Molecular mechanisms of regulation of sphingosine kinase 1. *Biochim Biophys Acta Mol Cell Biol Lipids, 1863*, 1413-1422. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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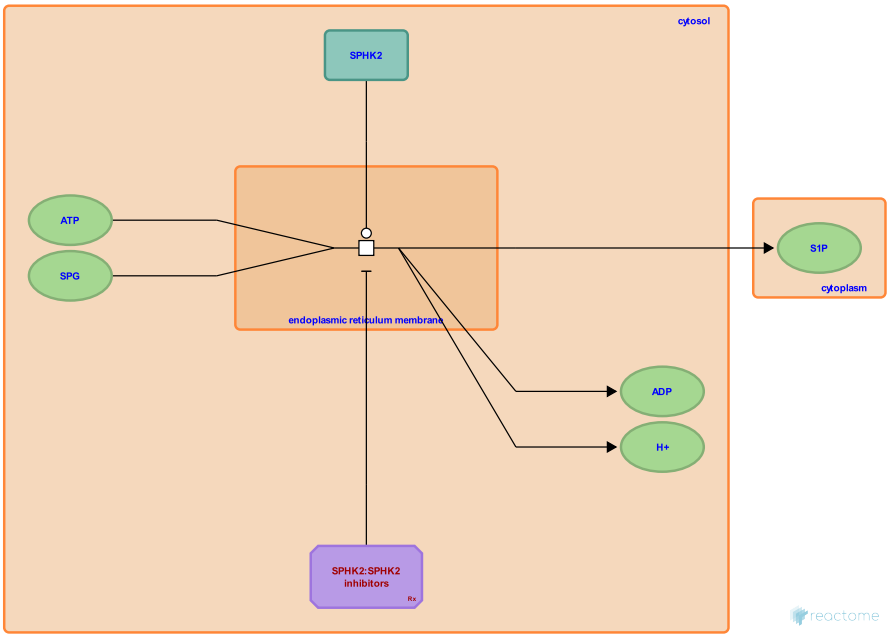
SPHK2 phosphorylates sphingoid ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-9695949

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



The cytosolic enzyme sphingosine kinase 2 (SPHK2) catalyzes the phosphorylation of sphingoids (SPG) to sphingoid 1-phosphate (S1P). The main product is sphingosine 1-phosphate, a bioactive lipid that acts extracellularly on G protein-coupled receptors of the S1P1/EDG-1 subfamily (Liu et al., 2000; reviewed by Siow & Wattenberg, 2011). Through alternative splicing, the isoforms of SK2a and SK2b are produced that show functional differences in their activity (reviewed by Hatoum et al., 2017). In contrast to pro-survival SPHK1, the BH3-only protein SPHK2 inhibits cell growth and enhances apoptosis (Maceyka et al., 2005).

Preceded by: KDSR reduces 3-ketosphingoid

Followed by: ABCC1,ABCG2 transport C18-S1P to extracellular region, SPNS2,MFSD2B transport S1P from cytosol to extracellular region

Literature references

Hatoum, D., McGowan, EM., Nassif, NT., Lin, Y., Haddadi, N. (2017). Mammalian sphingosine kinase (SphK) isoenzymes and isoform expression: challenges for SphK as an oncotarget. *Oncotarget, 8*, 36898-36929. ↗

Maceyka, M., Zhang, M., Liu, H., Spiegel, S., Merrill, AH., Collier, C. et al. (2005). SphK1 and SphK2, sphingosine kinase isoenzymes with opposing functions in sphingolipid metabolism. *J. Biol. Chem., 280*, 37118-29. ↗

Sugiura, M., Edsall, LC., Poulton, S., Nava, VE., Liu, H., Spiegel, S. et al. (2000). Molecular cloning and functional characterization of a novel mammalian sphingosine kinase type 2 isoform. *J Biol Chem, 275*, 19513-20. ↗

Siow, D., Wattenberg, B. (2011). The compartmentalization and translocation of the sphingosine kinases: mechanisms and functions in cell signaling and sphingolipid metabolism. *Crit Rev Biochem Mol Biol, 46*, 365-75. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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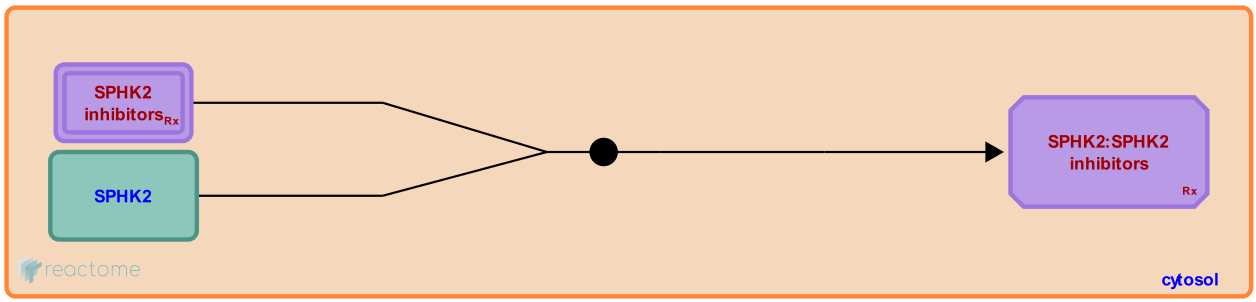
SPHK2 binds SPHK2 inhibitors ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-9695917

Type: binding

Compartments: cytosol



The bioactive sphingolipids ceramide, sphingosine and sphingosine-1-phosphate (S1P) are important signalling molecules whose balances can dictate cell fate. Ceramide and sphingosine enhance apoptosis and S1P promotes cell survival and proliferation. The sphingosine kinases (SPHKs) catalyse the production of S1P from sphingosine and are therefore central regulators of the sphingolipid rheostat. SPHKs are overexpressed in a variety of human cancers, making these enzymes potential molecular targets for cancer therapy.

Opaganib (ABC294640) selectively inhibits SPHK2 activity in vitro, attenuates S1P formation in intact cells and, in tissue culture, it suppresses the proliferation of a broad panel of tumor cell lines (Gao et al. 2012, French et al. 2010). Both isoforms of SPHK have been shown to regulate the replication or pathogenicity of many viruses (Wolf et al. 2019).

Other investigational SPHK2 inhibitors include ROMe (Lim et al. 2011), MP-A08 (Pitman et al. 2015) and SLM6071469 (Compound 10) (Sibley et al. 2020).

Literature references

Ebert, LM., Pitson, SM., Coolen, C., Powell, JA., Finnie, JW., Don, AS. et al. (2015). A selective ATP-competitive sphingosine kinase inhibitor demonstrates anti-cancer properties. *Oncotarget, 6*, 7065-83. ↗

Lim, KG., Bittman, R., Pyne, NJ., Sun, C., Pyne, S. (2011). (R)-FTY720 methyl ether is a specific sphingosine kinase 2 inhibitor: Effect on sphingosine kinase 2 expression in HEK 293 cells and actin rearrangement and survival of MCF-7 breast cancer cells. *Cell. Signal., 23*, 1590-5. ↗

Kharel, Y., Sibley, CD., Bevan, DR., Morris, EA., Brown, AM., Lynch, KR. et al. (2020). Discovery of a Small Side Cavity in Sphingosine Kinase 2 that Enhances Inhibitor Potency and Selectivity. *J. Med. Chem., 63*, 1178-1198. ↗

Studstill, CJ., Hahm, B., Wolf, JJ. (2019). Emerging Connections of S1P-Metabolizing Enzymes with Host Defense and Immunity During Virus Infections. *Viruses, 11*. ↗

Smith, RA., Smith, CD., Peterson, YK., Gao, P. (2012). Characterization of isoenzyme-selective inhibitors of human sphingosine kinases. *PLoS ONE, 7*, e44543. ↗

Editions

2020-07-16	Authored, Edited	Jassal, B.
2022-03-01	Reviewed	Huddart, R.
2022-05-10	Edited	Matthews, L.
2023-10-24	Reviewed	D'Eustachio, P.

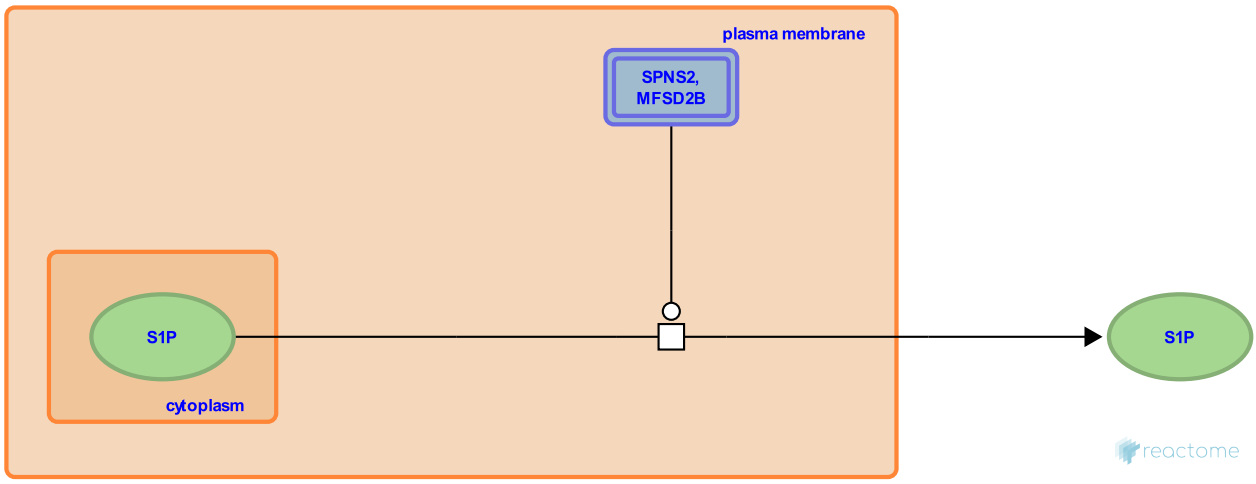
SPNS2,MFSD2B transport S1P from cytosol to extracellular region ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-9695890

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Several different transporters catalyze the secretion of sphingosine 1-phosphate (S1P). S1P is a signaling molecule that regulates many physiological processes in development and the immune system. S1P is produced inside cells, so it must be secreted to exert its effects through its receptors. Protein spinster homolog 2 (SPNS2) is an S1P transporter involved in S1P secretion and regulation of its levels in the lymph, thereby playing a role in lymphocyte trafficking (Nagahashi et al., 2013; Chen et al., 2023; reviewed by Spiegel et al., 2019). MFSD2A exports S1P and is mainly expressed in erythrocytes and platelets, having the function, together with SPNS2, of maintaining the blood-brain barrier (Kobayashi et al., 2018; reviewed by Ghaderi & Levkau, 2023). There is evidence in rats of S1P export by rat homologs of ABCA1, ABCA7, and ABCC1 (reviewed by Reitsema et al., 2014).

Preceded by: SPHK2 phosphorylates sphingoid, SPHK1 phosphorylates sphingoid

Literature references

Levkau, B., Ghaderi, S. (2023). An erythrocyte-centric view on the MFSD2B sphingosine-1-phosphate transporter. *Pharmacol Ther, 249*, 108483. ↗

Kawasaki-Nishi, S., Yamaguchi, A., Hisano, Y., Kobayashi, N., Nishi, T., Otsuka, M. (2018). MFSD2B is a sphingosine 1-phosphate transporter in erythroid cells. *Sci Rep, 8*, 4969. ↗

Kok, JW., Bouma, H., Reitsema, V. (n.d.). Sphingosine-1-phosphate transport and its role in immunology. Retrieved from https://doi.org/10.3934/MOLSCI.2014.4.183

Ramachandran, S., Yamada, A., Maceyka, M., Nagahashi, M., Spiegel, S., Allegood, JC. et al. (2013). Spns2, a transporter of phosphorylated sphingoid bases, regulates their blood and lymph levels, and the lymphatic network. *FASEB J., 27*, 1001-11. ↗

Kim, JH., Chen, H., Ahmed, S., Li, X., Dai, Y., Elghobashi-Meinhardt, N. et al. (2023). Structural and functional insights into Spns2-mediated transport of sphingosine-1-phosphate. *Cell, 186*, 2644-2655.e16. ↗

Editions

2020-07-16	Authored, Edited	Jassal, B.
2020-07-17	Reviewed	D'Eustachio, P.
2023-10-24	Reviewed	D'Eustachio, P.

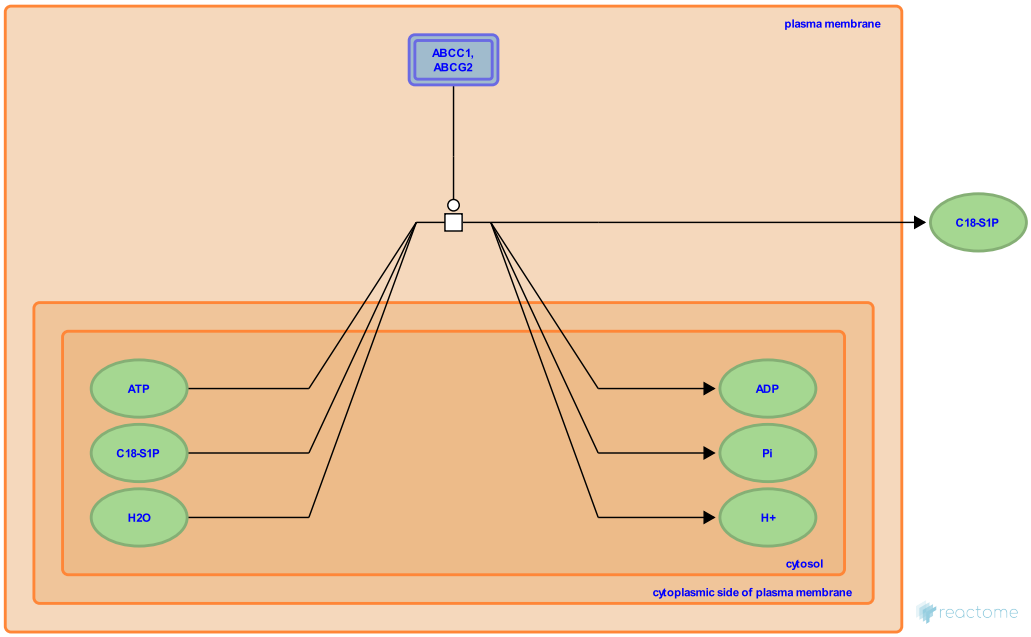
ABCC1,ABCG2 transport C18-S1P to extracellular region ↗

Location: Sphingolipid de novo biosynthesis

Stable identifier: R-HSA-9843721

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The proton pumps ABCC1, ABCG2 transport sphing-4-enine 1-phosphate (sphingosine-1-phosphate, C18-S1P) out of cells. ABCC1 is mainly expressed in mast cells, fibroblasts, and endothelial cells (Mitra et al., 2006; Nieuwenhuis et al., 2009). Export of C18-S1P by ABCG2 has been shown in MCF-7 epithelial cells (Takabe et al., 2010). These processes support a role of C18-S1P secretion in mast cell migration, cytoprotection, maintenance of epithelial barriers, and cancer/multidrug resistance (reviewed by Reitsema et al., 2014).

Preceded by: SPHK2 phosphorylates sphingoid, SPHK1 phosphorylates sphingoid

Literature references

Lüth, A., Pfeilschifter, J., Nieuwenhuis, B., Huwiler, A., Schäfer-Korting, M., Kleuser, B. et al. (2009). Involvement of the ABC-transporter ABCC1 and the sphingosine 1-phosphate receptor subtype S1P(3) in the cytoprotection of human fibroblasts by the glucocorticoid dexamethasone. *J Mol Med (Berl), 87*, 645-57. ↗

Kok, JW., Bouma, H., Reitsema, V. (n.d.). Sphingosine-1-phosphate transport and its role in immunology. Retrieved from https://doi.org/10.3934/MOLSCI.2014.4.183

Oskeritzian, CA., Beaven, MA., Milstien, S., Mitra, P., Spiegel, S., Payne, SG. (2006). Role of ABCC1 in export of sphingosine-1-phosphate from mast cells. *Proc Natl Acad Sci U S A, 103*, 16394-9. ↗

Ramachandran, S., Kim, RH., Harikumar, KB., Nagahashi, M., Allegood, JC., Milstien, S. et al. (2010). Estradiol induces export of sphingosine 1-phosphate from breast cancer cells via ABCC1 and ABCG2. *J Biol Chem, 285*, 10477-86. ↗

Editions

2023-09-09	Authored	Stephan, R.
2023-10-23	Edited	Stephan, R.
2023-10-24	Reviewed	D'Eustachio, P.

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