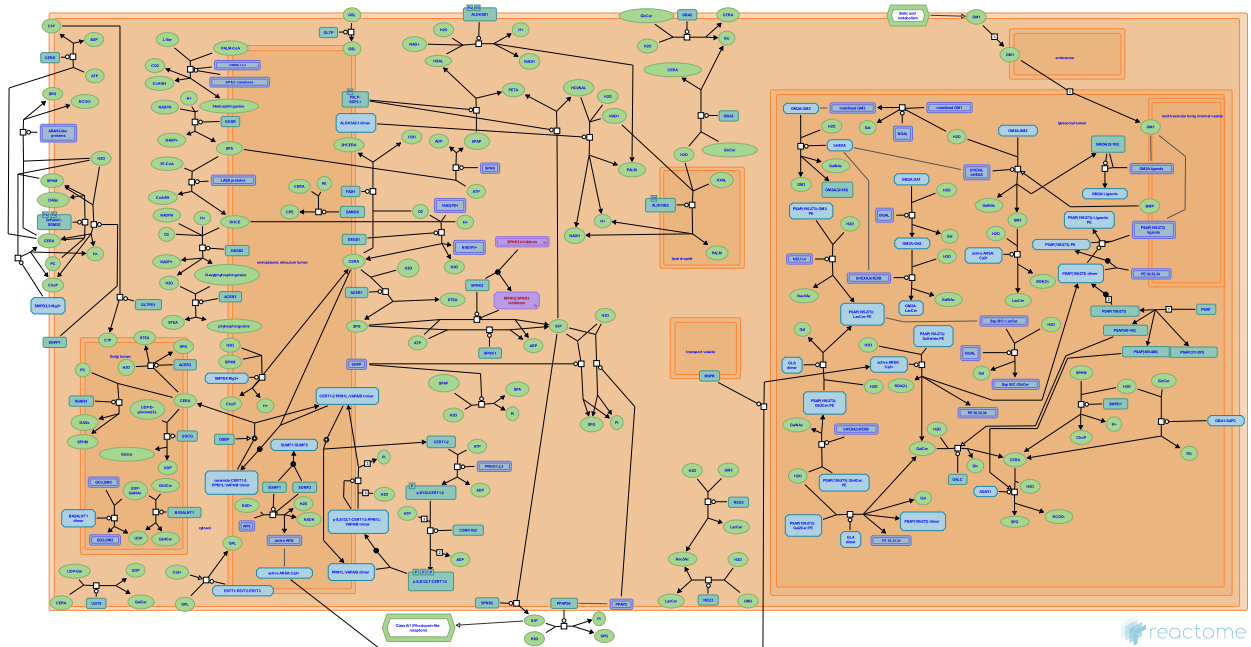


Sphingolipid metabolism



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

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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](https://reactome.org/textbook/).

25/11/2023

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

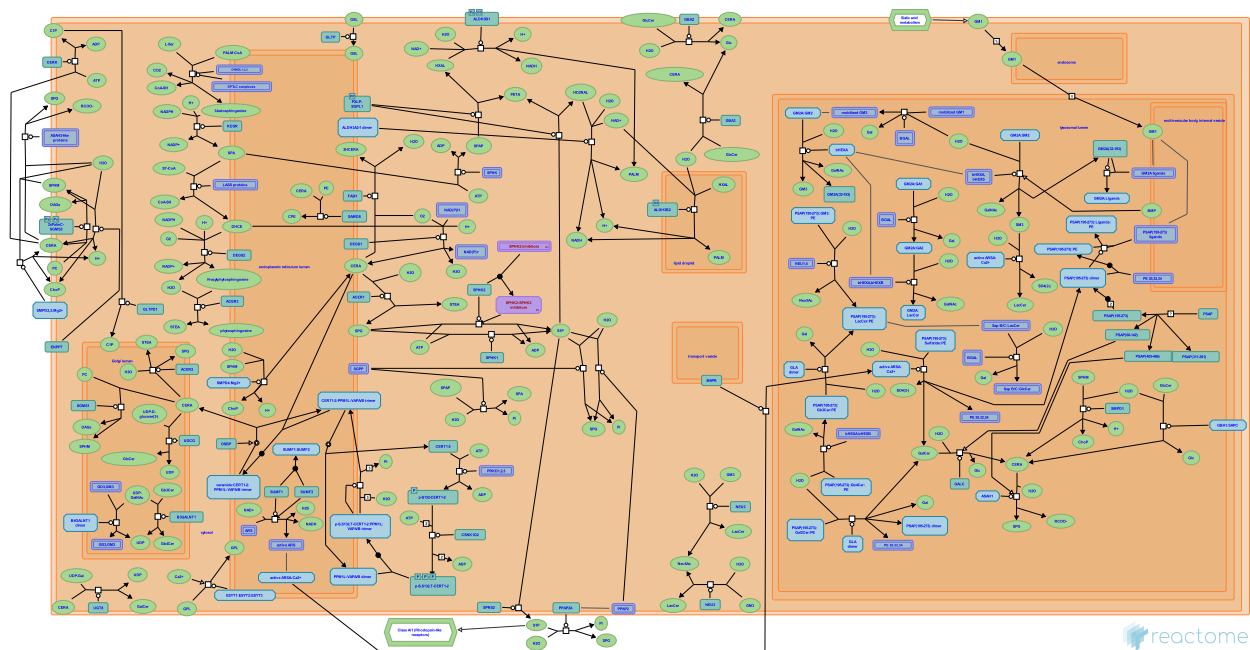
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Reactome database release: 86

This document contains 3 pathways and 12 reactions ([see Table of Contents](#))

Sphingolipid metabolism ↗

Stable identifier: R-HSA-428157



Sphingolipids are derivatives of long chain sphingoid bases such as sphingosine (trans-1,3-dihydroxy 2-amino-4-octadecene), an 18-carbon unsaturated amino alcohol which is the most abundant sphingoid base in mammals. Amide linkage of a fatty acid to sphingosine yields ceramides. Esterification of phosphocholine to ceramides yields sphingomyelin, and ceramide glycosylation yields glycosylceramides. Introduction of sialic acid residues yields gangliosides. These molecules appear to be essential components of cell membranes, and intermediates in the pathways of sphingolipid synthesis and breakdown modulate processes including apoptosis and T cell trafficking.

While sphingolipids are abundant in a wide variety of foodstuffs, these dietary molecules are mostly degraded by the intestinal flora and intestinal enzymes. The body primarily depends on de novo synthesis for its sphingolipid supply (Hannun and Obeid 2008; Merrill 2002). De novo synthesis proceeds in four steps: the condensation of palmitoyl-CoA and serine to form 3-ketosphinganine, the reduction of 3-ketosphinganine to sphinganine, the acylation of sphinganine with a long-chain fatty acyl CoA to form dihydroceramide, and the desaturation of dihydroceramide to form ceramide.

Other sphingolipids involved in signaling are derived from ceramide and its biosynthetic intermediates. These include sphinganine (dihydrosphingosine) 1-phosphate, phytoceramide, sphingosine, and sphingosine 1-phosphate.

Sphingomyelin is synthesized in a single step in the membrane of the Golgi apparatus from ceramides generated in the endoplasmic reticulum (ER) membrane and transferred to the Golgi by CERT (ceramide transfer protein), an isoform of COL4A3BP that is associated with the ER membrane as a complex with PPM1L (protein phosphatase 1-like) and VAPA or VAPB (VAMP-associated proteins A or B). Sphingomyelin synthesis appears to be regulated primarily at the level of this transport process through the reversible phosphorylation of CERT (Saito et al. 2008).

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. ↗

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

Hannun, YA., Obeid, LM. (2008). Principles of bioactive lipid signalling: lessons from sphingolipids. *Nat Rev Mol Cell Biol*, 9, 139-50. [↗](#)

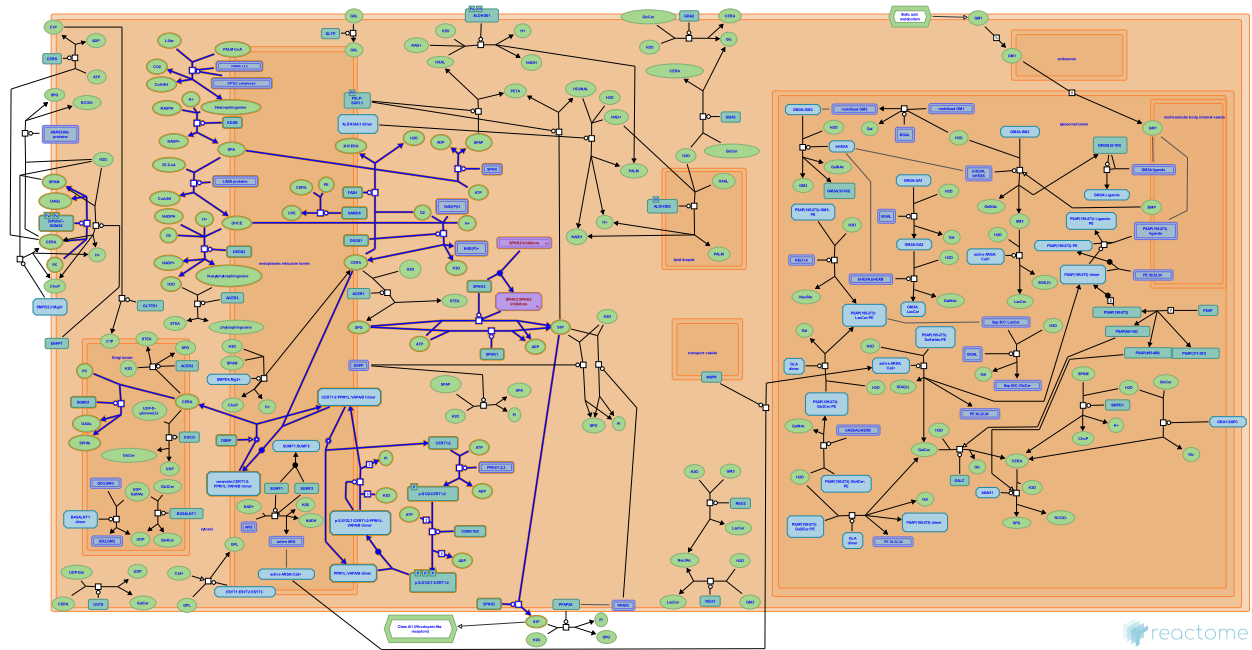
Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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2009-11-19	Reviewed	Hannun, YA., Luberto, C.
2023-08-17	Reviewed	D'Eustachio, P.

Spingolipid de novo biosynthesis ↗

Location: Spingolipid metabolism

Stable identifier: R-HSA-1660661



The main steps involved in de novo sphingolipid synthesis are annotated here (Merrill 2002, Gault et al. 2010).

Literature references

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

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

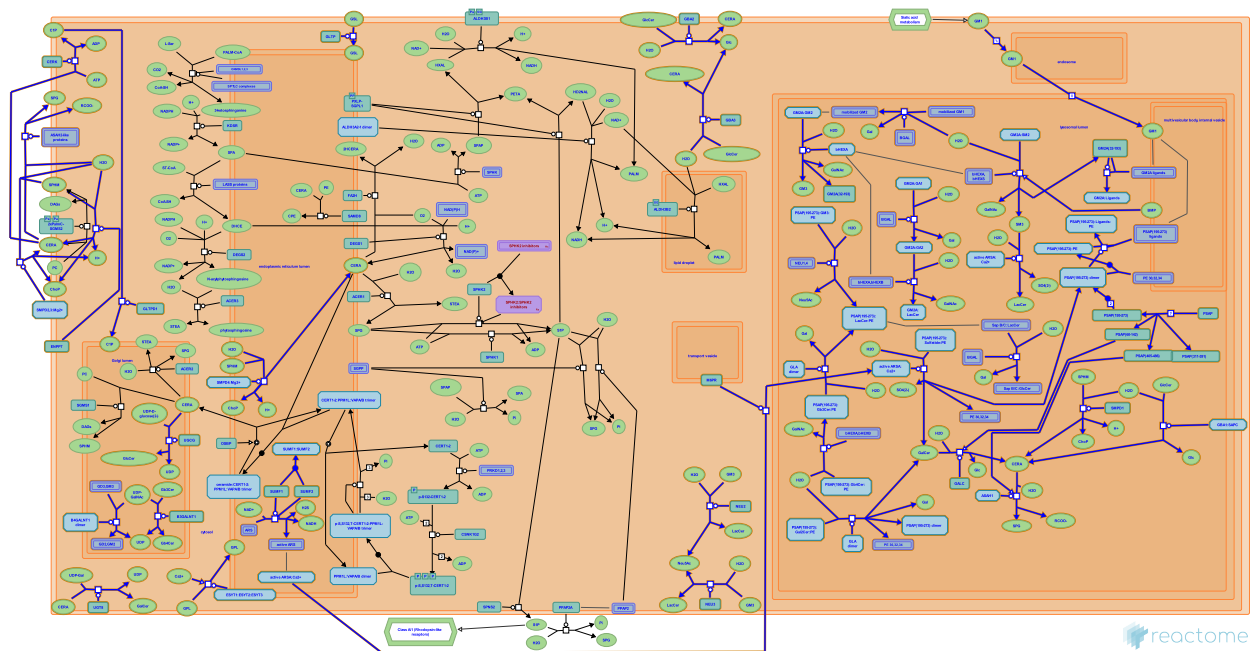
Editions

2009-08-21	Authored	D'Eustachio, P.
2011-10-14	Edited	Jassal, B.
2023-08-17	Reviewed	D'Eustachio, P.

Glycosphingolipid metabolism ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-1660662



The steps involved in the synthesis and degradation of glycosphingolipids (sphingolipids with one or more sugars attached) are annotated here (the topic is reviewed by Gault et al. 2010; Sandhoff & Sandhoff, 2018; Sandhoff et al, 2018).

Literature references

Sandhoff, R., Sandhoff, K. (2018). Emerging concepts of ganglioside metabolism. *FEBS Lett*, 592, 3835-3864. ↗

Schulze, H., Sandhoff, R., Sandhoff, K. (2018). Ganglioside Metabolism in Health and Disease. *Prog Mol Biol Transl Sci*, 156, 1-62. ↗

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

Editions

2011-10-14	Authored, Edited	Jassal, B.
2011-10-31	Reviewed	Stephan, R.
2012-05-15	Revised	Jassal, B.
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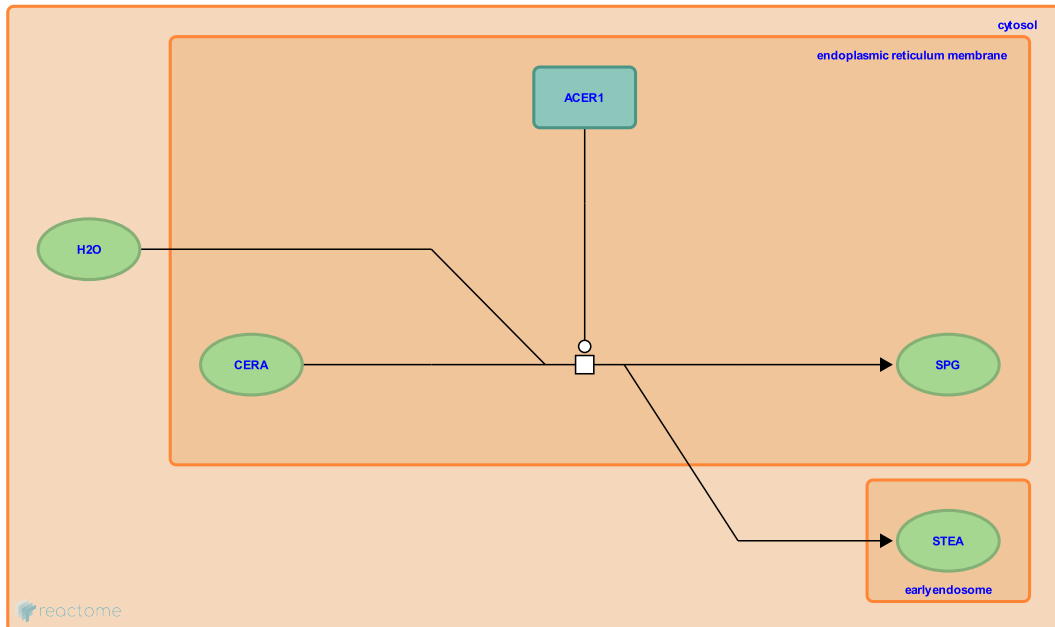
ceramide + H2O <=> stearate + sphingosine [endoplasmic reticulum] ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428231

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



ACER1 (alkaline ceramidase 1), associated with the endoplasmic reticulum membrane, catalyzes the reversible hydrolysis of ceramide to yield a free fatty acid (annotated here as stearate) and sphingosine (Sun et al. 2008).

Literature references

Thiers, BH., Mao, C., Crellin, HA., Sun, W., Hu, W., Jin, J. et al. (2008). Upregulation of the human alkaline ceramidase 1 and acid ceramidase mediates calcium-induced differentiation of epidermal keratinocytes. *J Invest Dermatol*, 128, 389-97. ↗

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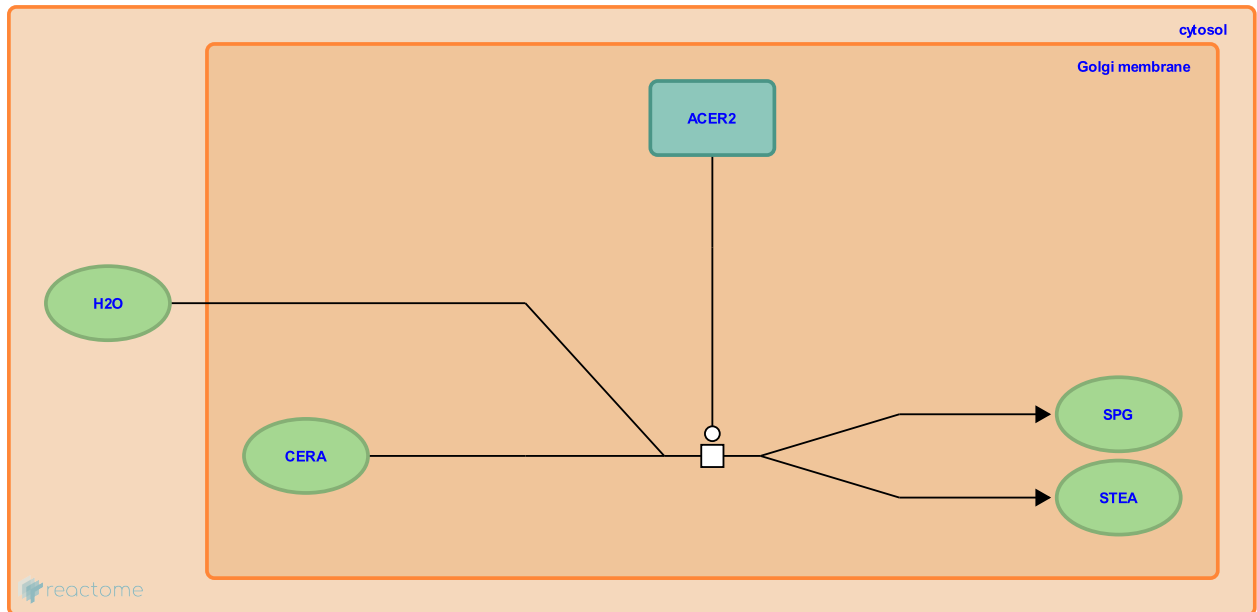
ceramide + H2O => stearate + sphingosine [Golgi] ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428205

Type: transition

Compartments: Golgi membrane, cytosol



ACER2 (alkaline ceramidase 2), associated with the membrane of the Golgi apparatus, catalyzes the hydrolysis of ceramide to yield a free fatty acid (annotated here as stearate) and sphingosine. ACER2 mRNA is widely expressed in the body, although only at low levels except in placenta (Xu et al. 2006).

Literature references

Mao, C., Sun, W., Hu, W., Jin, J., Taha, T., Bielawski, J. et al. (2006). Golgi alkaline ceramidase regulates cell proliferation and survival by controlling levels of sphingosine and S1P. *FASEB J*, 20, 1813-25. ↗

Editions

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2009-08-21	Reviewed	Jassal, B.
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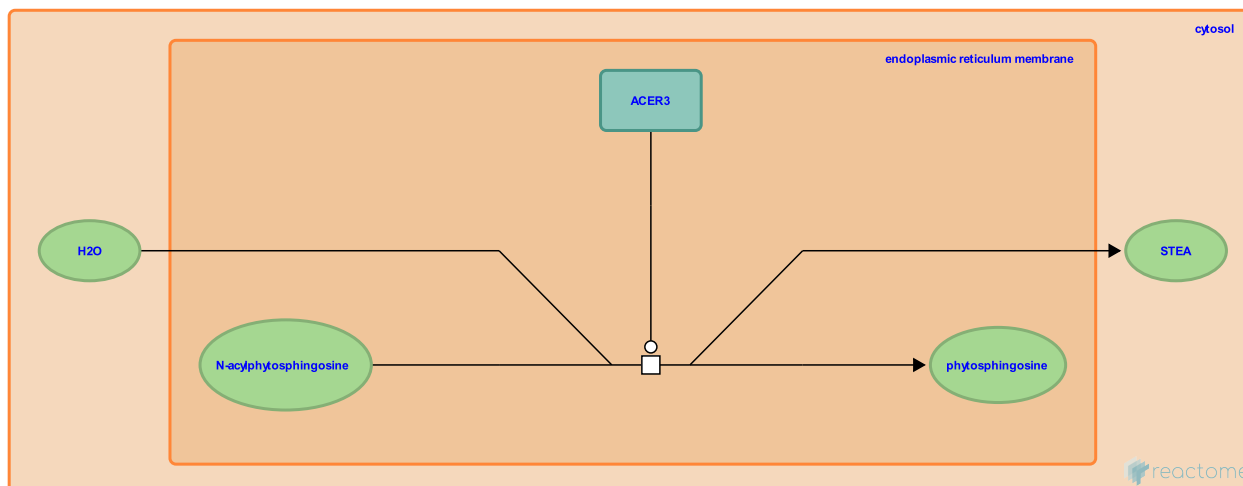
phytoceramide + H2O => stearate + phytosphingosine ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428262

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



ACER3 (alkaline ceramidase 3) catalyzes the hydrolysis of phytoceramide to yield a free fatty acid (annotated here as stearate) and phytosphingosine. ACER3 mRNA is widely expressed in the body, although most abundant in placenta. Immunofluorescence studies of cultured cells over-expressing GFP-tagged protein suggest its localization to membranes of the endoplasmic reticulum (annotated here) and also the Golgi apparatus (Mao et al. 2001).

Literature references

Mao, C., Xu, R., Obeid, LM., Bielawska, A., Galadari, SH., Szulc, ZM. (2001). Cloning and characterization of a novel human alkaline ceramidase. A mammalian enzyme that hydrolyzes phytoceramide. *J Biol Chem*, 276, 26577-88. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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2009-11-19	Reviewed	Hannun, YA., Luberto, C.

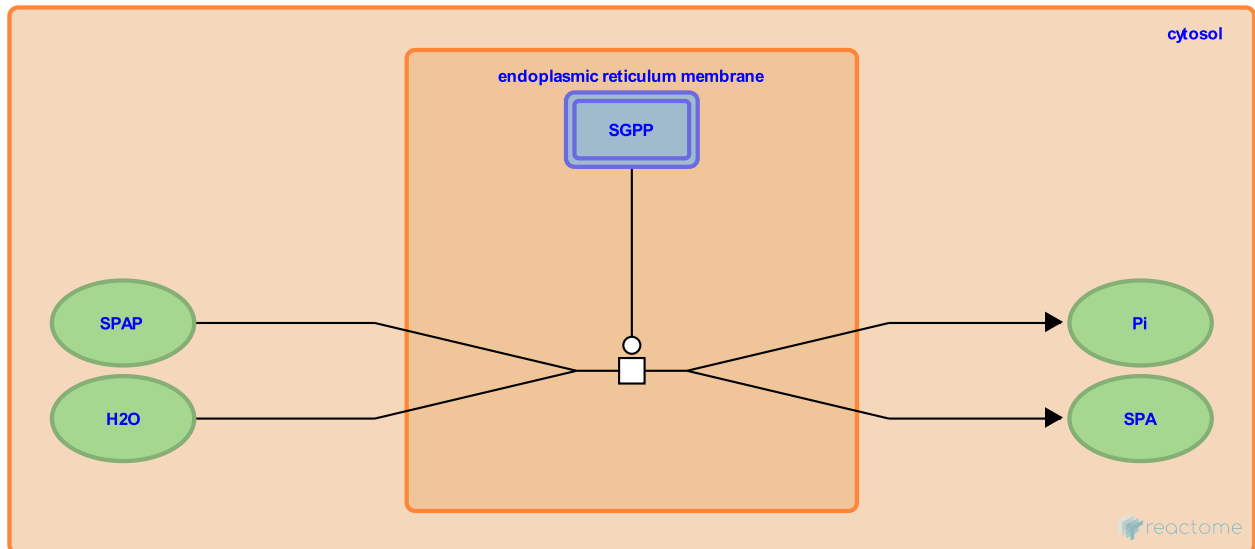
sphinganine 1-phosphate + H2O => sphinganine + orthophosphate ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428664

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



SGPP1 and 2 (sphingosine-1-phosphate phosphatase 1 and 2) enzymes associated with the endoplasmic reticulum membrane catalyze the hydrolysis of cytosolic sphinganine 1-phosphate to form sphinganine (dihydrosphingosine) and orthophosphate (Johnson et al. 2003; Ogawa et al. 2003).

Literature references

Ogawa, C., Gokoh, M., Igarashi, Y., Kihara, A. (2003). Identification and characterization of a novel human sphingosine-1-phosphate phosphohydrolase, hSPP2. *J Biol Chem*, 278, 1268-72. ↗

Mao, C., Johnson, KR., Bielawski, J., Obeid, LM., Becker, KP., Johnson, KY. (2003). Role of human sphingosine-1-phosphate phosphatase 1 in the regulation of intra- and extracellular sphingosine-1-phosphate levels and cell viability. *J Biol Chem*, 278, 34541-7. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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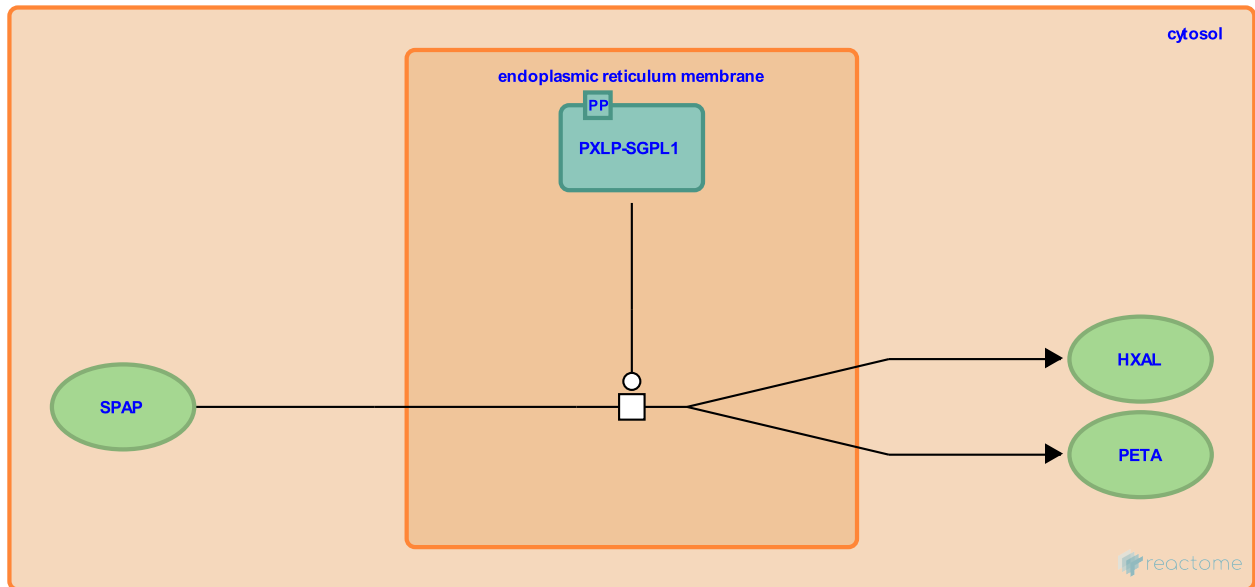
sphinganine 1-phosphate => phosphoethanolamine + hexadecanal ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428681

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



SGPL1 (sphingosine-1-phosphate lyase 1), associated with the endoplasmic reticulum membrane, catalyzes the cleavage of cytosolic sphinganine (dihydro sphingosine) 1-phosphate to form phosphoethanolamine and hexadecanal (Van Veldhoven et al. 2000; Fyrst and Saba 2008).

Followed by: [ALDH3B1 oxidises HXAL to PALM](#), [ALDH3B2 oxidises HXAL to PALM](#)

Literature references

Brys, V., Vermeesch, JR., Van Veldhoven, PP., Mannaerts, GP., Gijssbers, S. (2000). Human sphingosine-1-phosphate lyase: cDNA cloning, functional expression studies and mapping to chromosome 10q22(1). *Biochim Biophys Acta*, 1487, 128-34. ↗

Fyrst, H., Saba, JD. (2008). Sphingosine-1-phosphate lyase in development and disease: sphingolipid metabolism takes flight. *Biochim Biophys Acta*, 1781, 448-58. ↗

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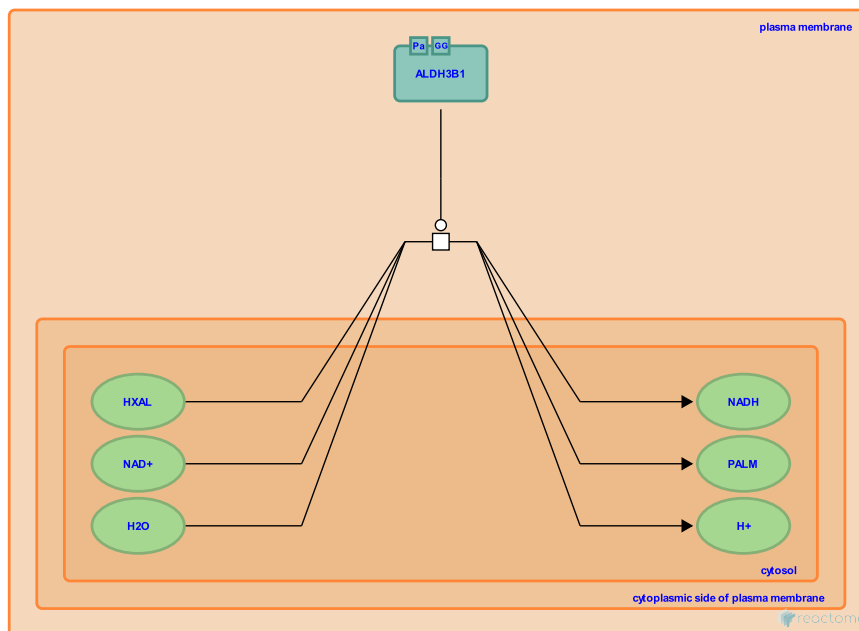
ALDH3B1 oxidises HXAL to PALM ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-5696080

Type: transition

Compartments: plasma membrane, cytosol



Aldehyde dehydrogenases (ALDHs) detoxify toxic aldehydes by oxidation to the corresponding carboxylic acids. Long-chain aliphatic aldehydes are largely produced by catabolic metabolism of several lipids, including ether glycerolipids, fatty alcohols, sphingolipids and wax esters. Some medium-chain aliphatic aldehydes, such as hexanal, octanal and 4-hydroxy-2-nonenal (4HNE) are produced via lipid peroxidation during oxidative stress. Aldehyde dehydrogenase family 3 member B1 (ALDH3B1) is able to oxidise both medium- and long-chain aldehydes. C16 aldehydes such as hexadecanal (HXAL) generated through sphingolipid metabolism on the plasma membrane can be oxidised to palmitic acid (PALM) (Kitamura et al. 2013). 4HNE, amongst other reactive medium-chain aldehydes, can be detoxified by oxidation to 4-hydroxynonenic acid (4HNA) by ALDH3B1, suggesting a potential physiological role for ALDH3B1 against oxidative stress (not shown here) (Marchitti et al. 2010).

Preceded by: [sphinganine 1-phosphate => phosphoethanolamine + hexadecanal](#)

Literature references

Abe, K., Nakahara, K., Ohno, Y., Kitamura, T., Kihara, A., Naganuma, T. (2013). Substrate specificity, plasma membrane localization, and lipid modification of the aldehyde dehydrogenase ALDH3B1. *Biochim. Biophys. Acta*, 1831, 1395-401. ↗

Orlicky, DJ., Brocker, C., Vasiliou, V., Marchitti, SA. (2010). Molecular characterization, expression analysis, and role of ALDH3B1 in the cellular protection against oxidative stress. *Free Radic. Biol. Med.*, 49, 1432-43. ↗

Editions

2015-05-27	Authored, Edited	Jassal, B.
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sphingosine 1-phosphate + H₂O => sphingosine + orthophosphate [cytosolic - PPAP]

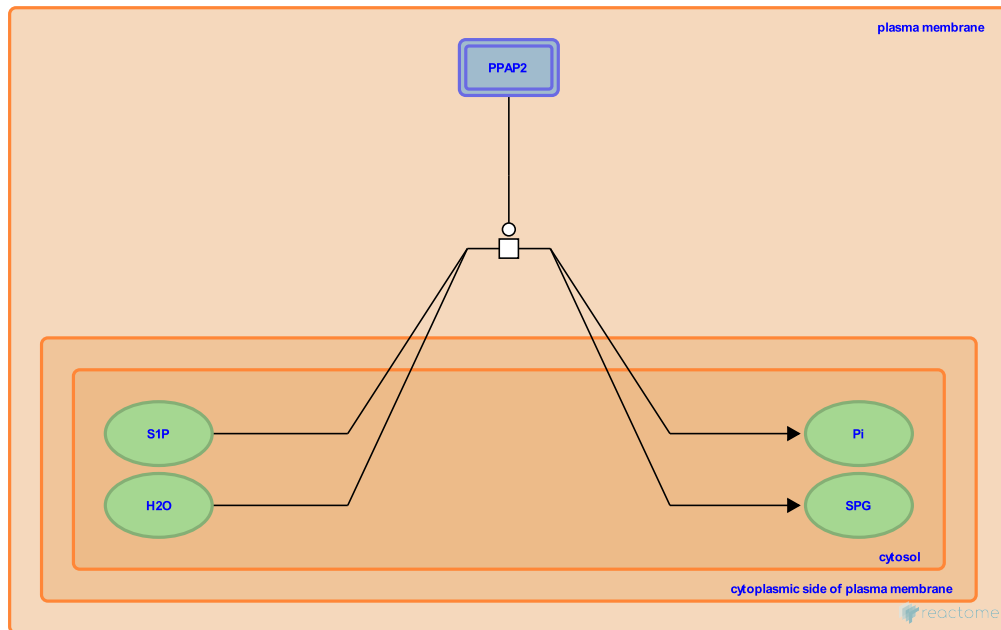
↗

Location: Sphingolipid metabolism

Stable identifier: R-HSA-428696

Type: transition

Compartments: plasma membrane, cytosol



PPAP2A, B, and C (phosphatidate phosphohydrolase type 2A, B, and C) enzymes associated with the plasma membrane catalyze the hydrolysis of cytosolic sphingosine 1-phosphate to form sphingosine and orthophosphate (Roberts et al 1998).

Literature references

Morris, AJ., Roberts, R., Sciorra, VA. (1998). Human type 2 phosphatidic acid phosphohydrolases. Substrate specificity of the type 2a, 2b, and 2c enzymes and cell surface activity of the 2a isoform. *J Biol Chem*, 273, 22059-67. ↗

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sphingosine 1-phosphate + H2O => sphingosine + orthophosphate [cytosolic - SGPP]

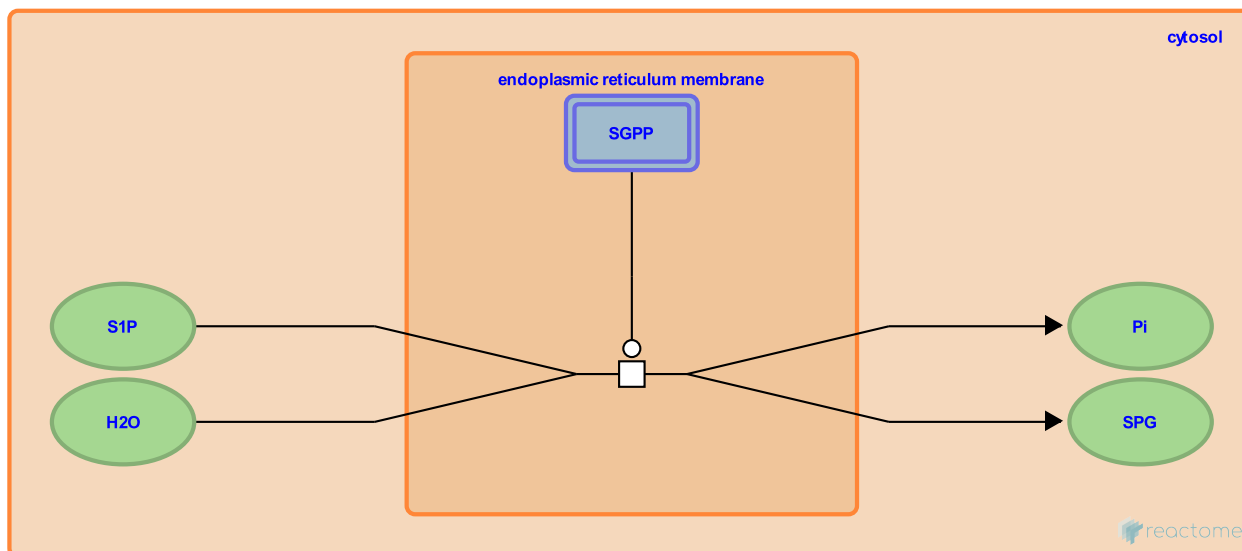


Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428701

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



SGPP1 and 2 (sphingosine-1-phosphate phosphatase 1 and 2) enzymes associated with the endoplasmic reticulum membrane catalyze the hydrolysis of cytosolic sphingosine 1-phosphate to form sphingosine and orthophosphate (Johnson et al. 2003; Ogawa et al. 2003).

Literature references

- Ogawa, C., Gokoh, M., Igarashi, Y., Kihara, A. (2003). Identification and characterization of a novel human sphingosine-1-phosphate phosphohydrolase, hSPP2. *J Biol Chem*, 278, 1268-72. [↗](#)
- Mao, C., Johnson, KR., Bielawski, J., Obeid, LM., Becker, KP., Johnson, KY. (2003). Role of human sphingosine-1-phosphate phosphatase 1 in the regulation of intra- and extracellular sphingosine-1-phosphate levels and cell viability. *J Biol Chem*, 278, 34541-7. [↗](#)

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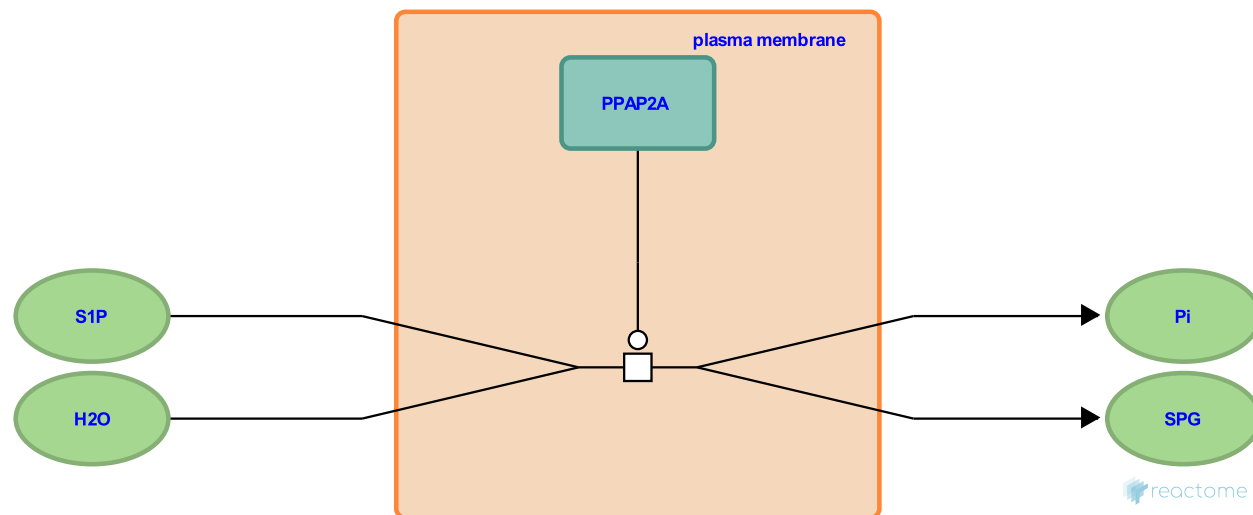
sphingosine 1-phosphate + H₂O => sphingosine + orthophosphate [extracellular] ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428690

Type: transition

Compartments: plasma membrane, extracellular region



PPAP2A (phosphatidate phosphohydrolase type 2A) enzyme associated with the plasma membrane catalyzes the hydrolysis of extracellular sphingosine 1-phosphate to form sphingosine and orthophosphate (Roberts et al 1998).

Literature references

Morris, AJ., Roberts, R., Sciorra, VA. (1998). Human type 2 phosphatidic acid phosphohydrolases. Substrate specificity of the type 2a, 2b, and 2c enzymes and cell surface activity of the 2a isoform. *J Biol Chem*, 273, 22059-67. ↗

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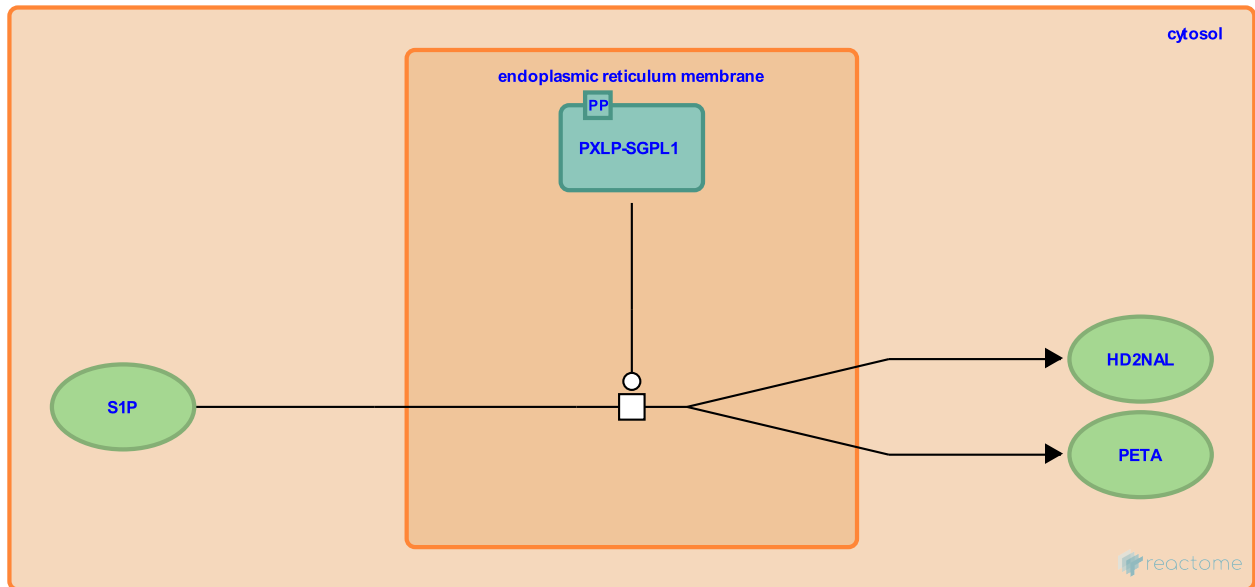
sphingosine 1-phosphate => phosphoethanolamine + hexadec-2-enal ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-428676

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



SGPL1 (sphingosine-1-phosphate lyase 1), associated with the endoplasmic reticulum membrane, catalyzes the cleavage of cytosolic sphingosine 1-phosphate (S1P) to form phosphoethanolamine (PETA) and hexadec-2-enal (HD2NAL) (Van Veldhoven et al. 2000; Fyrst and Saba 2008).

Followed by: [ALDH3A2-1 oxidises HD2NAL to PALM](#)

Literature references

Brys, V., Vermeesch, JR., Van Veldhoven, PP., Mannaerts, GP., Gijssbers, S. (2000). Human sphingosine-1-phosphate lyase: cDNA cloning, functional expression studies and mapping to chromosome 10q22(1). *Biochim Biophys Acta*, 1487, 128-34. ↗

Fyrst, H., Saba, JD. (2008). Sphingosine-1-phosphate lyase in development and disease: sphingolipid metabolism takes flight. *Biochim Biophys Acta*, 1781, 448-58. ↗

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2009-11-19	Reviewed	Hannun, YA., Luberto, C.

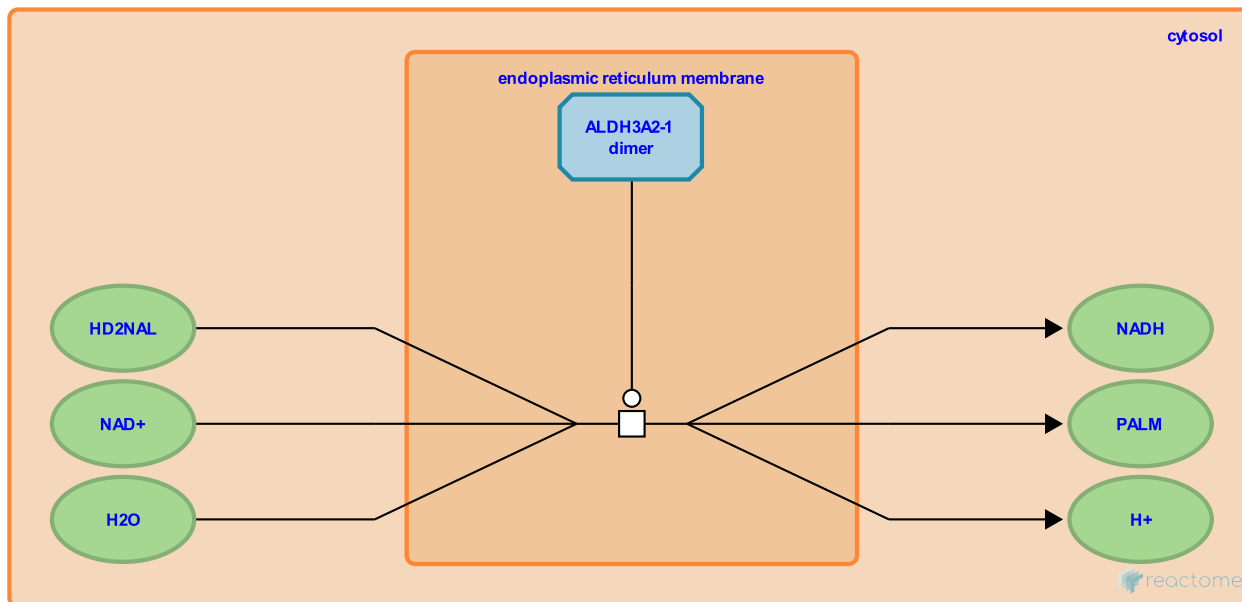
ALDH3A2-1 oxidises HD2NAL to PALM ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-5692261

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Fatty aldehyde dehydrogenase family 3 member A2, isoform 1 (ALDH3A2-1) in the endoplasmic reticulum membrane can catalyse the oxidation of long-chain aliphatic aldehydes to fatty acids (Kelson et al. 1997; Rizzo et al. 2001). Structural studies suggest that the enzyme is a homodimer (Keller et al. 2010), and expression studies of the homologous mouse proteins in cultured cells indicate that ALDH3A2 isoform 1 is localized to the endoplasmic reticulum while isoform 2 is localized to peroxisomes (Ashibe et al. 2007). The sphingosine 1-phosphate (S1P) degradation product hexadec-2-enal (HD2NAL) can be oxidised to hexadecenoic acid (palmitic acid, PALM) (Nakahara et al. 2012). Defective ALDH3A2 results in Sjogren-Larsson syndrome (SLS; MIM:270200), a neurocutaneous disorder characterised by a combination of severe mental retardation, spastic di- or tetraplegia and congenital ichthyosis. Accumulation of the S1P metabolite HD2NAL contributes to the pathogenesis of SLS (De Laurenzi et al. 1996, Sillen et al. 1998).

Preceded by: [sphingosine 1-phosphate => phosphoethanolamine + hexadec-2-enal](#)

Literature references

- Hirai, T., Ashibe, B., Motojima, K., Higashi, K., Sekimizu, K. (2007). Dual subcellular localization in the endoplasmic reticulum and peroxisomes and a vital role in protecting against oxidative stress of fatty aldehyde dehydrogenase are achieved by alternative splicing. *J. Biol. Chem.*, 282, 20763-73. ↗
- Abe, K., Ohkuni, A., Nakahara, K., Zoeller, RA., Ohno, Y., Kitamura, T. et al. (2012). The Sjögren-Larsson syndrome gene encodes a hexadecenal dehydrogenase of the sphingosine 1-phosphate degradation pathway. *Mol. Cell*, 46, 461-71. ↗
- Lindner, HH., Werner-Felmayer, G., Werner, ER., Golderer, G., Keller, MA., Maglione, M. et al. (2010). Monitoring of fatty aldehyde dehydrogenase by formation of pyrenedecanoic acid from pyrenedecanal. *J. Lipid Res.*, 51, 1554-9. ↗
- Rizzo, WB., Steinert, PM., Markova, N., Rogers, GR., Hamrock, DJ., Compton, JG. et al. (1996). Sjögren-Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nat. Genet.*, 12, 52-7. ↗

Lin, Z., Rizzo, WB., Carney, G. (2001). Fatty aldehyde dehydrogenase: genomic structure, expression and mutation analysis in Sjögren-Larsson syndrome. *Chem. Biol. Interact.*, 130, 297-307. [↗](#)

Editions

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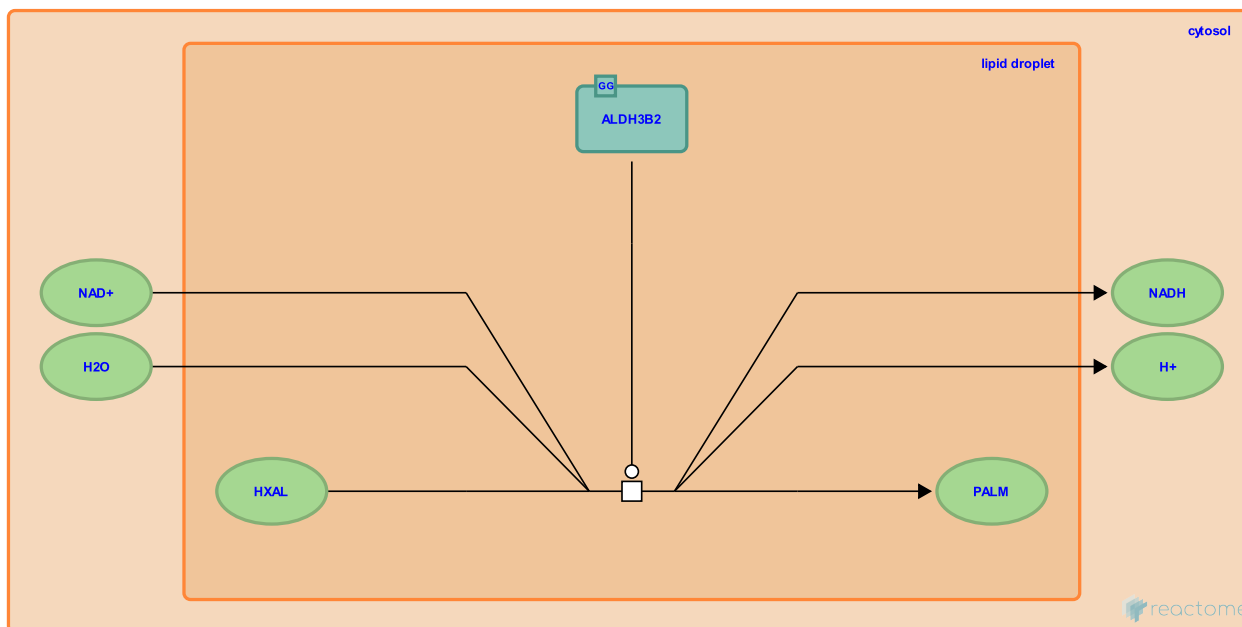
ALDH3B2 oxidises HXAL to PALM ↗

Location: [Sphingolipid metabolism](#)

Stable identifier: R-HSA-6808464

Type: transition

Compartments: lipid droplet, cytosol



ALDH3B2 (aldehyde dehydrogenase family 3 member B2), associated with cytosolic lipid droplets, catalyzes the NAD-dependent oxidation of HXAL (hexadecanal) to PALM (palmitate). A geranylgeranylated cysteine residue mediates the enzyme's association with the lipid droplet (Kitamura et al. 2013, 2015).

Preceded by: [sphinganine 1-phosphate => phosphoethanolamine + hexadecanal](#)

Literature references

Abe, K., Nakahara, K., Ohno, Y., Kitamura, T., Kihara, A., Naganuma, T. (2013). Substrate specificity, plasma membrane localization, and lipid modification of the aldehyde dehydrogenase ALDH3B1. *Biochim. Biophys. Acta*, 1831, 1395-401. ↗

Takagi, S., Kitamura, T., Kihara, A., Naganuma, T. (2015). Mouse aldehyde dehydrogenase ALDH3B2 is localized to lipid droplets via two C-terminal tryptophan residues and lipid modification. *Biochem. J.*, 465, 79-87. ↗

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