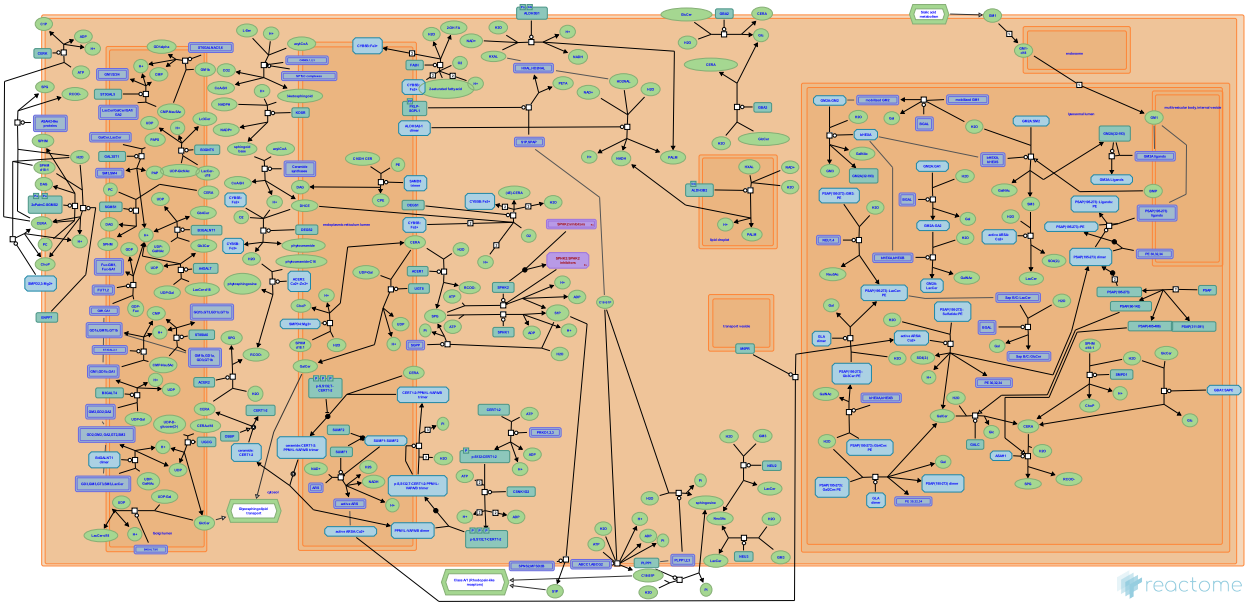
Sphingolipid metabolism



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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.

26/04/2024

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. ↗

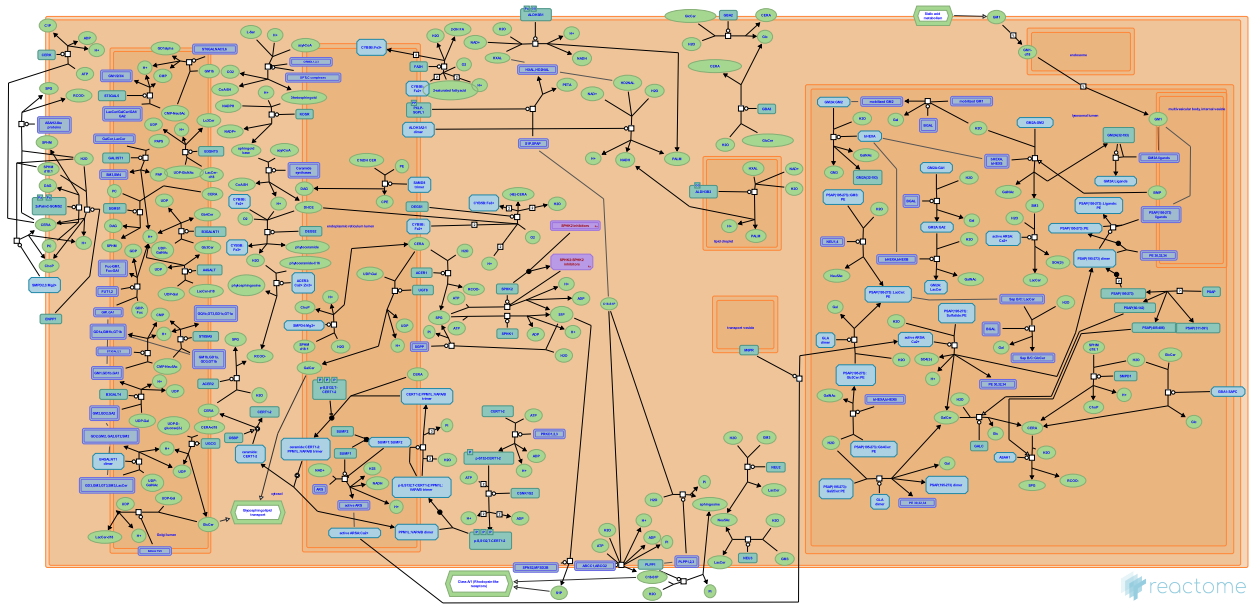
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

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. ↗

Delannoy, P., Groux-Degroote, S., Guérardel, Y. (2017). Gangliosides: Structures, Biosynthesis, Analysis, and Roles in Cancer. *Chembiochem, 18*, 1146-1154. ↗

Editions

2009-08-21	Authored, Edited	D'Eustachio, P.
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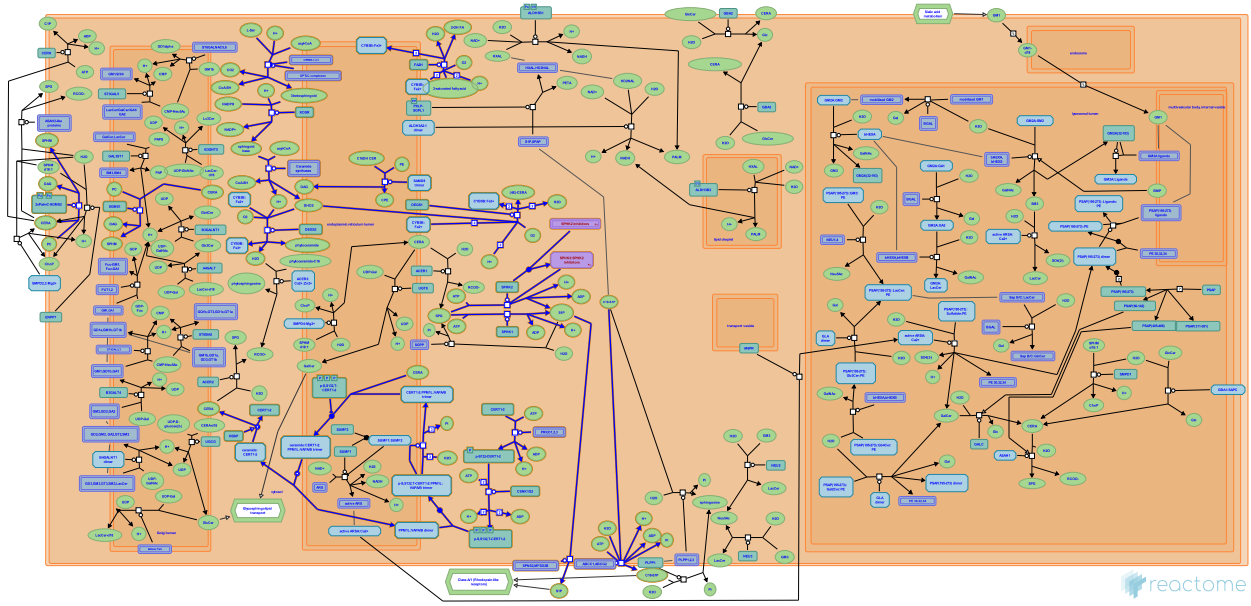
Sphingolipid de novo biosynthesis ↗

Location: Sphingolipid metabolism

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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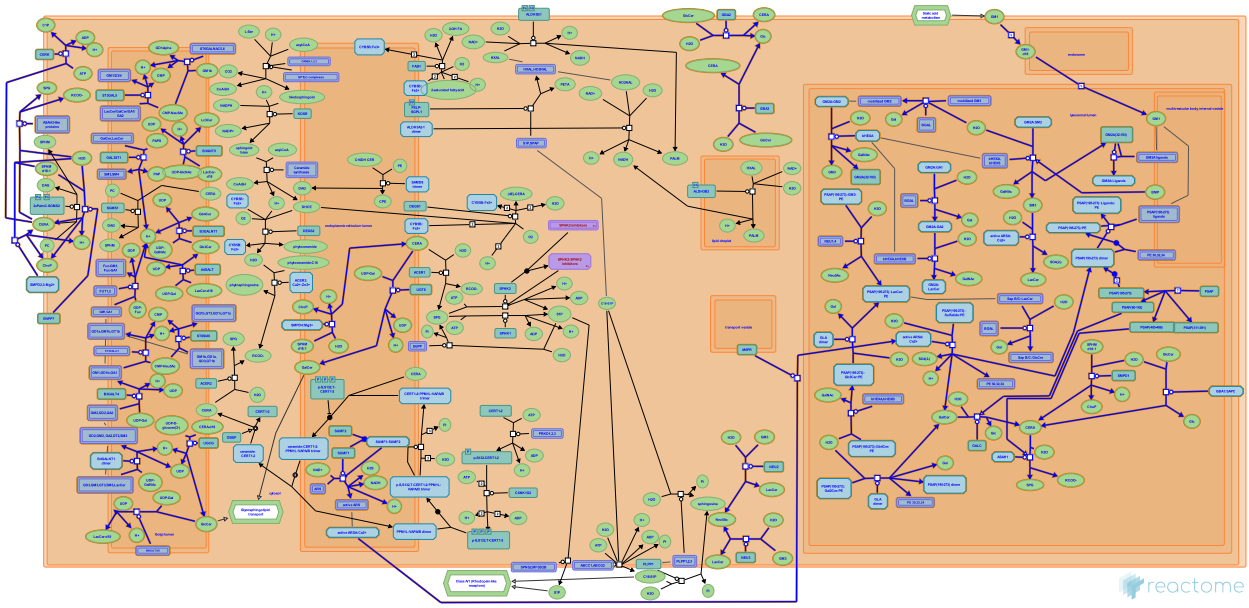
Glycosphingolipid metabolism ↗

Location: Sphingolipid metabolism

Stable identifier: R-HSA-1660662

Compartments: endoplasmic reticulum membrane, plasma membrane, Golgi membrane, Golgi lumen, multivesicular body, internal vesicle membrane, lysosomal lumen, multivesicular body, internal vesicle, endoplasmic reticulum lumen, multivesicular body lumen, lysosomal membrane



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

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2023-10-24	Reviewed	D'Eustachio, P.
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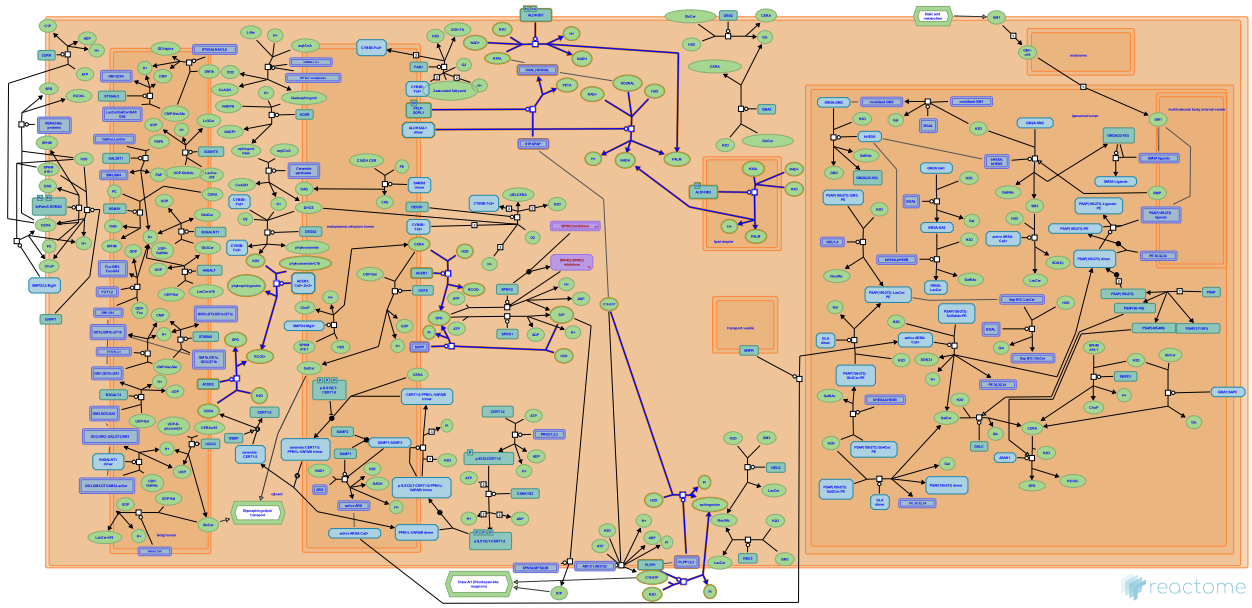
Sphingolipid catabolism ↗

Location: Sphingolipid metabolism

Stable identifier: R-HSA-9845614

Compartments: endoplasmic reticulum membrane, Golgi membrane, Golgi lumen, endoplasmic reticulum lumen



The main steps involved in de novo sphingolipid synthesis are annotated here (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. ↗

Editions

2023-10-05	Authored	Stephan, R.
2023-10-23	Edited	Stephan, R.
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