

Ceramide turnover in GtoPdb v.2021.3

Anthony H. Futerman¹

1. Weizmann Institute of Science, Israel

Abstract

Ceramides are a family of sphingophospholipids synthesized in the endoplasmic reticulum, which mediate cell stress responses, including apoptosis, autophagy and senescence, Serine palmitoyltransferase generates 3-ketosphinganine, which is reduced to dihydrosphingosine. N-Acylation allows the formation of dihydroceramides, which are subsequently reduced to form ceramides. Once synthesized, ceramides are trafficked from the ER to the Golgi bound to the ceramide transfer protein, CERT (*COL4A3BP*, *Q9Y5P4*). Ceramide can be metabolized via multiple routes, ensuring tight regulation of its cellular levels. Addition of phosphocholine generates sphingomyelin while carbohydrate is added to form glucosyl- or galactosylceramides. Ceramidase reforms sphingosine or sphinganine from ceramide or dihydroceramide. Phosphorylation of ceramide generates ceramide phosphate. The determination of accurate kinetic parameters for many of the enzymes in the sphingolipid metabolic pathway is complicated by the lipophilic nature of the substrates.

Contents

This is a citation summary for Ceramide turnover in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [4].

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

Ceramide turnover

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=767>

Serine palmitoyltransferase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=788>

Enzymes

[SPT1\(serine palmitoyltransferase long chain base subunit 1\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2509>

[SPT2\(serine palmitoyltransferase long chain base subunit 2\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2510>

[SPT3\(serine palmitoyltransferase long chain base subunit 3\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2511>

[SPTSSA\(serine palmitoyltransferase small subunit A\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2512>

[SPTSSB\(serine palmitoyltransferase small subunit B\)](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2513>

3-ketodihydrosphingosine reductase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=791>

Enzymes

3-ketodihydrosphingosine reductase

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2463>

Ceramide synthase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=789>

Enzymes

CERS1(ceramide synthase 1)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2474>

CERS2(ceramide synthase 2)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2475>

CERS3(ceramide synthase 3)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2476>

CERS4(ceramide synthase 4)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2477>

CERS5(ceramide synthase 5)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2478>

CERS6(ceramide synthase 6)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2479>

Sphingolipid Δ^4 -desaturase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=790>

Enzymes

delta 4-desaturase, sphingolipid 1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2484>

delta 4-desaturase, sphingolipid 2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2485>

Sphingomyelin synthase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=774>

Introduction to Sphingomyelin synthase

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=774>

Enzymes

sphingomyelin synthase 1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2520>

sphingomyelin synthase 2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2521>

sterile alpha motif domain containing 8

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2525>

Sphingomyelin phosphodiesterase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=773>

Enzymes

sphingomyelin phosphodiesterase 1

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2514>

sphingomyelin phosphodiesterase 2

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2515>

sphingomyelin phosphodiesterase 3

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2516>

sphingomyelin phosphodiesterase 4

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2517>

sphingomyelin phosphodiesterase acid-like 3A

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2518>

sphingomyelin phosphodiesterase acid-like 3B

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2519>

Neutral sphingomyelinase coupling factors

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=772>

Enzymes

embryonic ectoderm development

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2487>

neutral sphingomyelinase activation associated factor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2495>

Ceramide glucosyltransferase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=775>

Enzymes

UDP-glucose ceramide glucosyltransferase

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2528>

Acid ceramidase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=769>

Enzymes

[N-acylsphingosine amidohydrolase 1](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2491>

Neutral ceramidases

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=770>

Enzymes

[N-acylsphingosine amidohydrolase 2](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2492>

[N-acylsphingosine amidohydrolase 2B](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2493>

Alkaline ceramidases

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=768>

Enzymes

[alkaline ceramidase 1](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2468>

[alkaline ceramidase 2](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2469>

[alkaline ceramidase 3](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2470>

Ceramide kinase

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=771>

Enzymes

[ceramide kinase](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2473>

References

1. Adam-Klages S, Adam D, Wiegmann K, Struve S, Kolanus W, Schneider-Mergener J and Krönke M. (1996) FAN, a novel WD-repeat protein, couples the p55 TNF-receptor to neutral sphingomyelinase. *Cell* **86**: 937-47 [PMID:8808629]
2. Beauchamp E, Tekpli X, Marteil G, Lagadic-Gossmann D, Legrand P and Rioux V. (2009) N-Myristoylation targets dihydroceramide Delta4-desaturase 1 to mitochondria: partial involvement in the apoptotic effect of myristic acid. *Biochimie* **91**: 1411-9 [PMID:19647031]
3. Bourque E, Celatka C, Hirth B, Metz M, Zhao Z, Skerlj R, Xiang Y, Jancsics K, Marshall J and Cheng S *et al.*. (2014) Glucosylceramide synthase inhibitors Patent number: WO2012129084A2.
4. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
5. Butters TD, van den Broek LAGM, Fleet GWJ, Krulle TM, Wormald MR, Dwek RA and Platt FM. (2000) Molecular requirements of imino sugars for the selective control of N-linked glycosylation and glycosphingolipid biosynthesis. *Tetrahedron: Assymetry* **11**: 113-124
6. Camacho L, Simbari F, Garrido M, Abad JL, Casas J, Delgado A and Fabriàs G. (2012) 3-Deoxy-3,4-dehydro analogs of XM462. Preparation and activity on sphingolipid metabolism and cell fate. *Bioorg Med Chem* **20**: 3173-9 [PMID:22537678]
7. Chan HM, Gu X-JJ, Huang Y, Li L, Mi Y, Qi W, Sendzik M, Sun Y, Wang L and Yu Z *et al.*. (2016) Triazolopyrimidine compounds and uses thereof Patent number: WO2016103155A1.
8. Chen Y and Cao Y. (2017) The sphingomyelin synthase family: proteins, diseases, and inhibitors. *Biol Chem* **398**: 1319-1325 [PMID:28742512]
9. Cingolani F, Casasampere M, Sanllehí P, Casas J, Bujons J and Fabrias G. (2014) Inhibition of dihydroceramide desaturase activity by the sphingosine kinase inhibitor SKI II. *J Lipid Res* **55**: 1711-20 [PMID:24875537]
10. Coant N, Sakamoto W, Mao C and Hannun YA. (2017) Ceramidases, roles in sphingolipid metabolism and in health and disease. *Adv Biol Regul* **63**: 122-131 [PMID:27771292]
11. Deng X, Lin F, Zhang Y, Li Y, Zhou L, Lou B, Li Y, Dong J, Ding T and Jiang X *et al.*. (2014) Identification of small molecule sphingomyelin synthase inhibitors. *Eur J Med Chem* **73**: 1-7 [PMID:24374347]
12. Efremov IV, Kazmirski S, Li q, Thompson LA III, Wallace OW, Johnstone SD, Zhou F and Rahl P. (2020) MACROCYCLIC AZOLOPYRIDINE DERIVATIVES AS EED AND PRC2 MODULATORS Patent number: WO2020190754.
13. Fabrias G, Muñoz-Olaya J, Cingolani F, Signorelli P, Casas J, Gagliostro V and Ghidoni R. (2012) Dihydroceramide desaturase and dihydrosphingolipids: debutant players in the sphingolipid arena. *Prog Lipid Res* **51**: 82-94 [PMID:22200621]
14. Graf C, Klumpp M, Habig M, Rovina P, Billich A, Baumruker T, Oberhauser B and Bornancin F. (2008) Targeting ceramide metabolism with a potent and specific ceramide kinase inhibitor. *Mol Pharmacol* **74**: 925-32 [PMID:18612076]

15. Han G, Gupta SD, Gable K, Niranjanakumari S, Moitra P, Eichler F, Brown Jr RH, Harmon JM and Dunn TM. (2009) Identification of small subunits of mammalian serine palmitoyltransferase that confer distinct acyl-CoA substrate specificities. *Proc Natl Acad Sci USA* **106**: 8186-91 [PMID:19416851]
16. He Y, Selvaraju S, Curtin ML, Jakob CG, Zhu H, Comess KM, Shaw B, The J, Lima-Fernandes E and Szewczyk MM *et al.*. (2017) The EED protein-protein interaction inhibitor A-395 inactivates the PRC2 complex. *Nat Chem Biol* **13**: 389-395 [PMID:28135237]
17. Hoch DG, Abegg D, Hannich JT, Pechalrieu D, Shuster A, Dwyer BG, Wang C, Zhang X, You Q and Riezman H *et al.*. (2020) Combined Omics Approach Identifies Gambogic Acid and Related Xanthenes as Covalent Inhibitors of the Serine Palmitoyltransferase Complex. *Cell Chem Biol* **27**: 586-597.e12 [PMID:32330443]
18. Houben E, Holleran WM, Yaginuma T, Mao C, Obeid LM, Rogiers V, Takagi Y, Elias PM and Uchida Y. (2006) Differentiation-associated expression of ceramidase isoforms in cultured keratinocytes and epidermis. *J Lipid Res* **47**: 1063-70 [PMID:16477081]
19. Jiang X-C, Yeang C, Li Z, Chakraborty M, Zhang H and Fan Y.. (2009) Sphingomyelin biosynthesis: its impact on lipid metabolism and atherosclerosis. *Clinical Lipidology* **4**: 595-609
20. Koch J, Gärtner S, Li CM, Quintern LE, Bernardo K, Levrán O, Schnabel D, Desnick RJ, Schuchman EH and Sandhoff K. (1996) Molecular cloning and characterization of a full-length complementary DNA encoding human acid ceramidase. Identification Of the first molecular lesion causing Farber disease. *J Biol Chem* **271**: 33110-5 [PMID:8955159]
21. Lahiri S and Futerman AH. (2005) LASS5 is a bona fide dihydroceramide synthase that selectively utilizes palmitoyl-CoA as acyl donor. *J Biol Chem* **280**: 33735-8 [PMID:16100120]
22. Laviad EL, Albee L, Pankova-Kholmyansky I, Epstein S, Park H, Merrill Jr AH and Futerman AH. (2008) Characterization of ceramide synthase 2: tissue distribution, substrate specificity, and inhibition by sphingosine 1-phosphate. *J Biol Chem* **283**: 5677-84 [PMID:18165233]
23. Li YL, Qi XY, Jiang H, Deng XD, Dong YP, Ding TB, Zhou L, Men P, Chu Y and Wang RX *et al.*. (2015) Discovery, synthesis and biological evaluation of 2-(4-(N-phenethylsulfamoyl)phenoxy)acetamides (SAPAs) as novel sphingomyelin synthase 1 inhibitors. *Bioorg Med Chem* **23**: 6173-84 [PMID:26314925]
24. Li Z, Fan Y, Liu J, Li Y, Huan C, Bui HH, Kuo MS, Park TS, Cao G and Jiang XC. (2012) Impact of sphingomyelin synthase 1 deficiency on sphingolipid metabolism and atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* **32**: 1577-84 [PMID:22580896]
25. Li Z, Zhang H, Liu J, Liang CP, Li Y, Li Y, Teitelman G, Beyer T, Bui HH and Peake DA *et al.*. (2011) Reducing plasma membrane sphingomyelin increases insulin sensitivity. *Mol Cell Biol* **31**: 4205-18 [PMID:21844222]
26. Liu J, Huan C, Chakraborty M, Zhang H, Lu D, Kuo MS, Cao G and Jiang XC. (2009) Macrophage sphingomyelin synthase 2 deficiency decreases atherosclerosis in mice. *Circ Res* **105**: 295-303 [PMID:19590047]
27. Mao C, Xu R, Szulc ZM, Bielawska A, Galadari SH and Obeid LM. (2001) Cloning and characterization of a novel human alkaline ceramidase. A mammalian enzyme that hydrolyzes phytoceramide. *J Biol Chem* **276**: 26577-88 [PMID:11356846]
28. Mao C, Xu R, Szulc ZM, Bielawski J, Becker KP, Bielawska A, Galadari SH, Hu W and Obeid LM. (2003) Cloning and characterization of a mouse endoplasmic reticulum alkaline ceramidase: an enzyme that preferentially regulates metabolism of very long chain ceramides. *J Biol Chem* **278**: 31184-91 [PMID:12783875]
29. Miyake Y, Kozutsumi Y, Nakamura S, Fujita T and Kawasaki T. (1995) Serine palmitoyltransferase is the primary target of a sphingosine-like immunosuppressant, ISP-1/myriocin. *Biochem Biophys Res Commun* **211**: 396-403 [PMID:7794249]
30. Mizutani Y, Kihara A and Igarashi Y. (2005) Mammalian Lass6 and its related family members regulate synthesis of specific ceramides. *Biochem J* **390**: 263-71 [PMID:15823095]
31. Mlinar B and Corradetti R. (2003) Endogenous 5-HT, released by MDMA through serotonin transporter- and secretory vesicle-dependent mechanisms, reduces hippocampal excitatory synaptic transmission by preferential activation of 5-HT1B receptors located on CA1 pyramidal neurons. *Eur J Neurosci* **18**: 1559-71 [PMID:14511335]
32. Mo M, Yang J, Jiang XC, Cao Y, Fei J, Chen Y, Qi X, Chu Y, Zhou L and Ye D. (2018) Discovery of 4-Benzyloxybenzoyl diisoxazole-3-amine Derivatives as Highly Selective and Orally Efficacious Human Sphingomyelin Synthase 2 Inhibitors that Reduce Chronic Inflammation in db/db Mice. *J Med Chem* **61**: 8241-8254 [PMID:30074791]
33. Philipp S, Puchert M, Adam-Klages S, Tchikov V, Winoto-Morbach S, Mathieu S, Deerberg A, Kolker L, Marchesini N and Kabelitz D *et al.*. (2010) The Polycomb group protein EED couples TNF receptor 1 to neutral sphingomyelinase. *Proc Natl Acad Sci USA* **107**: 1112-7 [PMID:20080539]
34. Rabionet M, van der Spoel AC, Chuang CC, von Tümpling-Radosta B, Litjens M, Bouwmeester D, Hellbusch CC, Körner C, Wiegandt H and Gorgas K *et al.*. (2008) Male germ cells require polyenoic sphingolipids with complex glycosylation for completion of meiosis: a link to ceramide

- synthase-3. *J Biol Chem* **283**: 13357-69 [PMID:18308723]
35. Riebeling C, Allegood JC, Wang E, Merrill Jr AH and Futerman AH. (2003) Two mammalian longevity assurance gene (LAG1) family members, trh1 and trh4, regulate dihydroceramide synthesis using different fatty acyl-CoA donors. *J Biol Chem* **278**: 43452-9 [PMID:12912983]
 36. Sun W, Xu R, Hu W, Jin J, Crellin HA, Bielawski J, Szulc ZM, Thiers BH, Obeid LM and Mao C. (2008) Upregulation of the human alkaline ceramidase 1 and acid ceramidase mediates calcium-induced differentiation of epidermal keratinocytes. *J Invest Dermatol* **128**: 389-97 [PMID:17713573]
 37. Tani M, Iida H and Ito M. (2003) O-glycosylation of mucin-like domain retains the neutral ceramidase on the plasma membranes as a type II integral membrane protein. *J Biol Chem* **278**: 10523-30 [PMID:12499379]
 38. Tani M and 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 [PMID:19233134]
 39. Venkataraman K, Riebeling C, Bodennec J, Riezman H, Allegood JC, Sullards MC, Merrill Jr AH and Futerman AH. (2002) Upstream of growth and differentiation factor 1 (uog1), a mammalian homolog of the yeast longevity assurance gene 1 (LAG1), regulates N-stearoyl-sphinganine (C18-(dihydro)ceramide) synthesis in a fumonisin B1-independent manner in mammalian cells. *J Biol Chem* **277**: 35642-9 [PMID:12105227]
 40. Wang K, Xu R, Snider AJ, Schrandt J, Li Y, Bialkowska AB, Li M, Zhou J, Hannun YA and Obeid LM *et al.*. (2016) Alkaline ceramidase 3 deficiency aggravates colitis and colitis-associated tumorigenesis in mice by hyperactivating the innate immune system. *Cell Death Dis* **7**: e2124 [PMID:26938296]
 41. Xu R, Jin J, Hu W, Sun W, Bielawski J, Szulc Z, Taha T, Obeid LM and Mao C. (2006) Golgi alkaline ceramidase regulates cell proliferation and survival by controlling levels of sphingosine and S1P. *FASEB J* **20**: 1813-25 [PMID:16940153]
 42. Yang K, Nong K, Gu Q, Dong J and Wang J. (2018) Discovery of N-hydroxy-3-alkoxybenzamides as direct acid sphingomyelinase inhibitors using a ligand-based pharmacophore model. *Eur J Med Chem* **151**: 389-400 [PMID:29649738]
 43. Yang K, Yu J, Nong K, Wang Y, Niu A, Chen W, Dong J and Wang J. (2020) Discovery of Potent, Selective, and Direct Acid Sphingomyelinase Inhibitors with Antidepressant Activity. *J Med Chem* **63**: 961-974 [PMID:31944697]
 44. Yokomatsu T, Murano T, Akiyama T, Koizumi J, Shibuya S, Tsuji Y, Soeda S and Shimeno H. (2003) Synthesis of non-competitive inhibitors of sphingomyelinases with significant activity. *Bioorg Med Chem Lett* **13**: 229-36 [PMID:12482429]
 45. Young SA, Mina JG, Denny PW and Smith TK. (2012) Sphingolipid and ceramide homeostasis: potential therapeutic targets. *Biochem Res Int* **2012**: 248135 [PMID:22400113]