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Supplementary information S3. Sphingolipid metabolizing enzymes

Gene	Protein Alternative name; catalytic activity Topology	Alteration linked to disease	Disease	Reference
SPTLC	Serine palmitoyltransferase (SPT) Palmitoyl-CoA: L-serine C-palmitoyltransferase; condensation of serine and palmitoyl CoA to generate 3-ketodihydrosphingosine Endoplasmic reticulum	Mutation of *SPT1* and *SPT2* subunits	Hereditary Sensory and Autonomic Neuropathy Type I (HSANI).	(1-8)
KDSR	3-Ketodihydrosphingosine reductase (KDHR) 3-oxosphinganine: NADPH oxidoreductase; reduction of 3-ketodihydrosphingosine to dihydrosphingosine Endoplasmic reticulum	--	--	(9,10)
LASS1-6	(Dihydro)ceramide synthase (CerS1-6) Acyl-CoA:(dihydro)sphingosine-N-acyltransferase; N-acylation of	Frameshift (*fln*) and point mutation (*to*) in *CerS1* gene encoding CerS1 protein (mouse brain)	Progressive degeneration of cerebellar Purkinje neurons and widespread lipofuscin accumulation.	(2,11-19)
		CerS1 null mice	Altered cerebellum size due to significant atrophy of	(20,21)

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	(dihydro)sphingosine and generation of dihydroceramide Endoplasmic reticulum, nuclear envelope, mitochondria, mitochondrial-associated membrane		cerebellar hemispheres between 6 and 12 months postnatally. Abnormal cerebellar foliation pattern during postnatal development.	
		*CerS*2 null mice	Severe non-zonal hepatopathy from about 30 days of age, and increased rates of hepatocyte apoptosis and proliferation. Extensive and pronounced hepatocellular anisocytosis with extensive formation of nodules of regenerative hepatocellular hyperplasia in older mice. Progressive hepatomegaly and noninvasive hepatocellular carcinoma at approximately 10 months of age. Hepatic insulin resistance, defects in myelin in the central nervous system, and biophysical alterations in the properties of membrane lipids. Perivascular inflammation in the lungs from adult mice (3 months or older), accumulation of foamy alveolar macrophages in the airspaces and increase in airflow resistance. Development of pheochromocytoma.	(22-28)
		Missense encoding single-nucleotide in CERS2 gene (variant rs267738) in humans	Associated to rhegmatogenous retinal detachment (RRD).	(29)
		*CerS*3 null mice	Dysfunction on epidermal barrier characteristics and structure.	(18,30)
		Mutation resulting in a codon exchange Trp15Arg in human CerS3	Autosomal recessive congenital ichthyosis (ARCI).	(31)

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		*CerS*4 null mice	Altered epidermal stem/progenitor cell homeostasis and hair follicle cycling resulting in hair loss in older mice.	(32,33)
		High CerS5 expression in colorectal cancer (CRC) patients	Activation of autophagy which correlates with poor prognosis in patients with CRC.	(34)
		CerS6 null mice	Impaired neuromotoric function, such as clasping phenotype of hind limbs, poor performance in the horizontal wire test in null mice as compared to wild-type. Behavioral abnormality presenting higher levels of agitation and exploratory activity in the open field.	(35)
		Elevated mRNA levels of LASS2, LASS4, LASS5, LASS6 and ceramides in malignant and benign tissue as compared with normal tissue	Breast cancer progression.	(36)
		Overexpression of CerS4 and CerS6 in breast cancer cells (MCF-7) and colon cancer cells (HCT-116)	Increased apoptosis and reduced colony formation.	(37)
DES1	Dihydroceramide desaturase (DES) Dihydroceramide Δ^4 desaturation; introduction of (E) double bond between C4 and C-5 in the sphingosine backbone to generate ceramide Endoplasmic Reticulum	*Des1* null mice	Skin and hair defects, tremors, hematological disorders, aberrant liver function, fail to gain weight and death 8–10 weeks after birth.	(38-41)
		Des1−/− mouse embryonic fibroblasts (MEFs)	Increased autophagy	(42)
		Dihydroceramide desaturase inhibitors in T98G and U87MG glioblastoma cell lines	Cytoprotective autophagy.	(43)

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SGMS1-2	Sphingomyelin synthase (SMS1-2) Phosphatidylcholine: ceramide cholinephosphotransferase; transfer of phosphocholine from phosphatidylcholine (PC) to C-1 position of ceramide and generation of sphingomyelin and diacylglycerol (DAG) Trans-Golgi (SMS1) apparatus, plasma membrane (SMS2)	*Sms1* gene null mice	Moderate neonatal lethality, reduced body weight, loss of fat tissues mass, β cell mitochondrial dysfunction, and insulin secretion inhibition.	(44-47)
		Sms1$^{-/-}$→*Ldlr*$^{-/-}$ macrophages	Decrease in atherosclerosis in *Ldlr*$^{-/-}$ mice fed a western diet for 3 months.	(48)
		Adenovirus-mediated overexpression of SMS1 and SMS2 in mice	Increased lipoprotein atherogenic potential	(49)
SMPD1, SMPD3	Acid sphingomyelinase (aSMase) Sphingomyelin phosphodiesterase; hydrolysis of sphingomyelin to ceramide	Acid sphingomyelinase deficiency (ASMD) caused by *SMPD1* mutations including missense, nonsense, frameshift mutations and splice variants in humans	Niemann-Pick Disease type A (NPD A) and Niemann-Pick Disease type B (NPD B).	(50,51)
	Lysosome (L-SMase) Extracellular; secreted (S-SMase)	*Asm* knockout mice	Niemann-Pick Disease type A (NPD A) and Niemann-Pick Disease type B (NPD B). Defect in radiation-induced apoptosis. Progressive degeneration of cerebellar Purkinje cells, neuronal degeneration. Loss of lung metastasis in mice injected with B16F10 melanoma cells.	(52-59)

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		Asm−/−; *Apoe*−/− mice *Asm*−/−; *Ldlr* −/− mice	Smaller foam cell lesions and decrease in lipoprotein retention within aortic root lesions in chow-fed *Asm*−/−; *Apoe*−/− mice. Less sub-endothelial lipoprotein retention Smaller aortic root lesions in Western diet-fed *Asm*−/−; *Ldlr*−/− mice. Reduction in lipoprotein retention within early lesions in both the chow-fed and Western diet-fed mice models of atherosclerosis.	(60-63)
		Lymphoblast cell lines from Niemann-Pick Disease patients. ASM knockout (ASMKO) mice	Defect in radiation-induced apoptosis.	(63)
	Neutral sphingomyelinase 2 (nSMase2) Outer leaflet of the plasma membrane, cytosol, golgi apparatus	Increased activity of nSMase induced by Aβ25–35 peptide	Alzheimer's disease (AD).	(64,65)
		Smpd3-null mouse	Retarded maturation of chondrocytes and ossification in the epiphyseal growth plate, which leads to dwarfism and severe skeletal chondrodysplasia.	(66)
		Recessive mutation fragilitas ossium (fro) in *Smpd3* gene in mice	Osteogenesis imperfecta. Smaller mice at birth, deformities, multiple fractures of ribs and long bones. Elevated mortality. Parathyroid hormone is elevated and bone osteonectin is decreased by 30% in adult mice. Lung anomalies.	(67-69)
	Mitochondrial neutral sphingomyelinase (MA-nSMase) Mitochondria	--	--	(70,71)

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CGT	Ceramide galactosyltransferase (CGT) UDP-Glucose: N-Acylsphingosine D-Glucosyltransferase; transfer of galactose to ceramide to generate galactosylceramide Endoplasmic reticulum	*Cgt* null mutant mice	Disruption of lipid bilayer of the myelin membrane of the central nervous system (CNS) and the peripheral nervous system (PNS). Growth retardation. Whole body tremor, increased loss of locomotor activity and evident gait pattern. Minute activity showed in the open field test. Increasing weakness of their front and hind legs, resulting in severe paralysis around day 21.	(72-77)
UGCG	Glucosylceramide synthase (GCS) UDP-Glucose: N-Acylsphingosine D-Glucosyltransferase; glycosylation of ceramide to generate glucosylceramide Cis/medial-Golgi apparatus	*Ugcg* null mice	Embryonic lethality occurring at gastrulation due to massive apoptosis.	(78-81)
		GCS overexpression in several cancer and leukemia cell lines	Multidrug-resistance (MDR). Lymph node invasion, reduced mean overall 5-year survival and reduced mean disease-free survival times in bladder cancer.	(81-83)
		$Ugcg^{\Delta EX7Neo/\Delta EX7Hydro\ (-/-)}$ mutant teratoma	Poorly differentiated epithelial tissue and small focus of bronchial epithelium.	(80)
		Regular chow-fed or western diet-fed *Apoe*−/− mice plus D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (D-PDMP). Wester-fed rabbit plus D-PDMP.	Ameliorated aortic wall thickening, arterial stiffness and pulse wave velocity in atherosclerotic mice.	(84-86)
B4GALT6	Lactosylceramide synthase (LCS) UDP-Galactose: Beta-N-Acetylglucosamine Beta-1,4-Galactosyltransferase; transfer of galactose from UDP-galactose to glucosylceramide and generation of lactosylceramide Trans-Golgi apparatus		Ameliorated hyperlipidemia and atherosclerotic plaque buildup and lumen volume in western diet-fed *Apoe*−/− mice. Prevention of cardiac hypertrophy in *ApoE-/-* mice fed a high fat and high cholesterol (HFHC) diet.	(87,88)

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GBA1	Acid β-glucosylceramidase (GBA1) D-Glucosyl-N-Acylsphingosine Glucohydrolase; hydrolysis of glucocerebroside into glucose and ceramide Lysosomal membrane	Pathogenic mutations in GBA gene which includes point mutations, insertions, deletions, frameshift changes, splice site alterations, and recombinant alleles	Gaucher disease (GD), parkinsonian symptoms, development of Lewy body disorders. Increased occurrence of B-cell or plasma cell malignancy as multiple myeloma (MM), acute or chronic leukemia, Hodgkin's disease, cancer.	(81,89-95)
		GBA mutation carriers	Increased susceptibility to alpha-synucleinopathies: Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy.	(95-97)
CERKL	Ceramide kinase (CERK) ATP: ceramide 1-phosphotransferase; phosphorylation of ceramide to form ceramide 1-phosphate Trans-Golgi apparatus, cytosol, nucleus, plasma membrane	Loss-of-function mutation in *CERKL* in humans	Retinitis Pigmentosa (RP).	(98-103)
		CerK-null C57BL/6J mice	Abnormal neuronal functions involving emotional behavior.	(104)
		CerK-null BALB/c mice	Reduced circulating neutrophils and impaired defense against pneumonia.	(105)
		CerK-/- mice	Decreased MCP-1/CCR2 signaling in macrophages infiltrating adipose tissue, resulting in the prevention of obesity and diabetes.	(106)
ASAH1	Acid ceramidase (ACDase) N-Acylsphingosine amidohydrolase; hydrolysis of ceramide into the sphingosine backbone and a fatty acid Lysosomes	Mutations of acid ceramidase in humans	Farber's disease.	(52,107-110)
		Increased expression of AC in tumor cells. Overexpression of AC induced by radiation.	Cell proliferation and cancer resistance.	(111-115)
		Asah1-/- null mice *Asah1+/-* mice	Embryonic lethality in homozygotes and progressive lipid storage disease in heterozygotes	(116)

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ASAH2, 2B, 2C	Neutral ceramidase (NCDase) Plasma membrane	*nCDase−/−* null mice	Improved brain function recovery and lessened brain contusion volume after traumatic brain injury (TBI). Increased inflammation in dextran sulfate sodium (DSS)-induced colitis model.	(117-119)
		nCDase inhibition in colon cancer cells and a colon cancer xenograft mouse model *nCDase−/−* mice	Decreased survival, increased apoptosis, and autophagy of colon cancer. Delayed tumor growth and decreased tumor cell proliferation in xenograft model. *nCDase−/−* mice showed protection from tumor protection.	(120)
		nCDase-/ - MEF cells	Protection from nutrient deprivation-induced necroptosis.	(121)
		Asah2 mutant mice	Defective digestion of dietary sphingolipids.	(122)
		Overexpression of neutral CDase in primary hepatocytes.	Inhibition of TNF-α-induced apoptosis.	(123)
ACER1-3	Alkaline ceramidase (alkCDase) Endoplasmic reticulum (ACER1), Golgi apparatus (ACER2)	*Acer1-/-* mice *Acer1-/-* skin	Alterations in infundibulum and sebaceous gland architecture. Disrupted skin homeostasis and whole-body energy homeostasis.	(124-126)
		Acer3−/− mice	Aggravated dextran sulfate sodium (DSS)-induced colitis and colitis-associated colorectal cancer (CAC). Purkinje cell degeneration and cerebellar ataxia.	(127)
		Inhibition of ACER3 expression by shRNA-encoding lentivirus system in human acute myeloid leukemia (AML) cells	Decreased cell growth and colony formation, and elevated apoptosis.	(128,129)
		Point mutation E33G in the human ACER3 gene resulting in enzyme inactivation	Childhood leukodystrophy.	(130)

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SPHK1, 2	Sphingosine kinases (SK1, SK2) ATP: sphingoid base 1-phosphotransferase; phosphorylation of sphingosine to sphingosine-1-phosphate Cytosol, plasma membrane (SK1)	Overexpression of mRNA transcript and/or SK1 protein	Associated to acute myeloid leukemia (AML) and increased tumor progression, chemo-resistance and poor prognosis.	(131)
		Knockdown of SK1 protein or inhibition of SK1 activity. Dominant-negative SK1 mutant in cells	Decreased cytokine-induced pro-inflammatory proteins.	(132-140)
		Sphk1-/- knockout mice in AOM/DSS-induced colon carcinogenesis	Decreased aberrant crypt foci (ACF) formation and significantly reduced colon cancer development.	(141-144)
		p53–SK1 double knockout mice	Increased survival and decreased tumor burden.	(145)
		Murine pancreatic cancer cells are implanted in the abdominal cavities of *SphK1-/-* mice	Reduced tumor burden of pancreatic cancer peritoneal carcinomatosis (PC).	(146-148)
		Sphk1-/- knockout mice or inhibition of SK1 activity	Protection from dextran sulfate sodium (DSS)-induced colitis.	(149)
		Mice with Lyve-1 CRE-mediated ablation of *Sphk1* and lacking *Sphk2*	Loss of S1P in lymph while maintaining normal plasma S1P and subsequently block of T and B cell egress from lymph nodes.	(150)
		Knockdown of SK1 or SK2 in arthritis mouse model	Decreased incidence and severity of arthritis in $SK1^{-/-}$ mice but increased disease severity and incidence in $SK2^{-/-}$ mice.	(151)
	Sphingosine kinases (SK1, SK2) Nucleus, endoplasmic reticulum, and mitochondria (SK2)			(152-155)
		Sphk2−/− mice in a colitis and colitis-associated cancer model	Increased expression of *SphK1* and *S1PR1* resulting in exacerbated acute colitis and colitis-associated cancer (CAC).	(152,156)

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		Knockdown SK2 expression in multiple myeloma (MM) cells. Inhibition of SK2 activity in MM cells	Decreased cell growth, increased cell death.	(157)
		Inhibition of SK2 in a lupus nephritis mouse model (MRL/lpr mice)	Reduced progression of glomerular disease.	(158-164)
SGPP1,2	Sphingosine-1-phosphate phosphatases (SPP1, SPP2) (Dihydro)sphingosine-1-phosphate phosphohydrolase: dephosphorylation of sphingosine-1-phosphate back to sphingosine Endoplasmic reticulum	siRNA knockdown of hSPPase1 in MCF-7 cells	Increased resistance to cytotoxic agents.	(165)
		Both *in vivo* and *in vitro* overexpression of mRNA transcript and/or SPP2 protein in human gastric cancer cells	Associated to cell proliferation and cell migration.	(166)
SGPL1	Sphingosine-1-phosphate lyase (SPL) Sphinganine-1-phosphate palmitaldehyde-lyase: breaks down sphingosine-1-phosphate to produce phosphoethanolamine and hexadecenal Endoplasmic reticulum	*Sgpl1-/-* knockout mice	Mice do not survive beyond 3–4 weeks after birth and show significant growth failure and anemia, vascular abnormalities, skeletal defects, thoracic malformations of sternum, ribs and vertebrae, and renal abnormalities. Metabolic and immunological alterations. Increased pro-inflammatory response with impaired migration of neutrophils into tissues and therefore abnormal neutrophil homeostatic regulatory loop.	(158-164)
		Intestinal epithelium-specific *Sgpl1-/-* knockout mice	Increased chemically (AOM/DSS treatment or DSS treatment) induced colitis and tumor formation.	(165)

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		SPL loss-of-function mutant mice	Increased hemodynamic recovery from ex vivo Ischemia/Reperfusion-induced heart injury.	(166)
		Downregulation of SPL expression or chemical inhibition of SPL activity in human pulmonary artery endothelial cells (HPAECs)	Increased cell migration and wound healing.	(167)
		Stable overexpression/ knockdown of human SPL in human embryonic kidney (HEK293T)	Elevated apoptosis as compared to control cells in response to IR, whereas knockdown of SPL in conferred resistance to IR treatment.	(168)

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