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Beyond the Cherry-Red Spot: Ocular Manifestations of Sphingolipid-mediated Neurodegenerative and Inflammatory Disorders

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Abstract

Sphingolipids are a ubiquitous membrane lipid present in every cell and found most abundantly in neural tissues. Disorders such as Tay Sachs or Niemann Pick disease are the most familiar examples of dysfunction in sphingolipid metabolism and are typically associated with neurodegeneration and ocular findings such as blindness. More recently, the role of bioactive sphingolipids has been established in a multitude of cellular events, including cell survival, growth, senescence and apoptosis, inflammation, and neovascularization. We discuss our current knowledge and understanding of sphingolipid metabolism and signaling in the pathogenesis of ocular diseases.

Keywords

Retina; retinal degenerations; uveitis; sphingolipid; ceramide; sphingosine; FTY720

I. INTRODUCTION

Sphingolipids are integral components of every cell membrane. In the past two decades significant progress has been made in elucidating the signaling roles of sphingolipids in cellular physiology and diseases. Any imbalance in the level of bioactive sphingolipids, such as ceramide (Cer), sphingosine (Sph), and their respective phosphorylated products--namely ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P)--can alter the signaling for cell survival, cell growth, inflammation, senescence, and apoptosis.[49, 50, 95, 96, 103]

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Deregulation of sphingolipid metabolism may contribute to the pathophysiology of a number of ocular diseases (e.g. diabetic retinopathy and retinal degenerative disorders), neurodegenerative disorders (e.g. Alzheimer's and Parkinson's), cardiovascular diseases, chronic inflammation, and cancer.[12, 29, 48, 49, 71, 77, 97, 114, 133, 138] The recent development of the synthetic sphingosine analog, FTY720, and its application in neuroinflammatory diseases, strengthens the putative role of sphingolipids in inflammatory neural and ocular diseases because FTY720 modulates both biosynthesis of Cer and S1P signaling.[7, 14, 41, 43, 146] Chatterjee,[26] Singh and Hall;[126] Hannun and Obeid,[60] Nixon,[102] Jana et al., [64] and Morales et al.[99] provide broader overviews of the role of sphingolipids in specific cell functions and other systemic diseases.

Nevertheless, there is limited information available on the role of sphingolipid metabolites and their signaling in the pathophysiology of ocular diseases. We review the findings on sphingolipid metabolism-associated ocular pathogenesis in pursuit of a better understanding of the sphingolipids' role in various degenerative, autoimmune, and inflammatory eye diseases.

II. SPHINGOLIPID STRUCTURE AND METABOLISM

Sphingolipid metabolism consists of a complex network of pathways involving hundreds of sphingolipid species within a single cell. For a detailed account of the diversity and metabolism of cellular sphingolipid species see Futerman and Riezman,[47] Lahiri and Futerman,[75] Chen et al.,[28] Gault et al.,[52] and Hannun and Obeid.[59] Sphingosine (Sph), the backbone of all sphingolipids, is a straight, long-chain aminoalcohol with 18–20 carbon atoms. To generate Cer, the key metabolite for cellular sphingolipids, a fatty acid is attached to a Sph molecule through an amide bond.[72, 96] More complex sphingolipids are synthesized from Cer by attaching various head-groups at the C-1 position. For example, the addition of a phosphorylcholine results in sphingomyelin (SM), whereas attachment of a sugar, such as glucose or galactose, generates gluco- or galactosyl ceramide, respectively, which further serves as a precursor for complex glycosphingolipids such as gangliosides (Fig. 1).

Two major, but distinct, pathways exist for intracellular Cer production. The first is the *de novo* biosynthesis of Cer, which begins in the endoplasmic reticulum (ER) (Fig. 2). The Cer generated from this pathway becomes the substrate for synthesizing higher-order sphingolipids, such as sphingomyelin, glucosyl ceramide, galactosyl ceramide, and gangliosides (Fig. 2). The second pathway occurs through recycling and/or degradation of higher-order sphingolipids (e.g. sphingomyelin and gluco- and galactosyl ceramide) in the plasma membrane or in a lysosomal compartment. For example, sphingomyelinase (SMase) hydrolyzes sphingomyelin, into Cer. Ceramidase enzymes catalyze the degradation of Cer to yield Sph (Fig. 2). Both Cer and Sph can then be phosphorylated by specific kinases to form C1P and S1P respectively (Fig. 1). Finally, S1P lyase, located at the cytoplasmic side of the ER, can irreversibly degrade S1P and release it from the sphingolipid cycle (Fig. 2). Alternatively, specific phosphatases at the luminal side of the ER can dephosphorylate S1P and convert it back to Cer for recycling via the salvage pathway.[48]

III. SPHINGOLIPIDS IN THE EYE

Even though sphingolipids were discovered at the end of the 19th century, [35, 92, 111] they were not closely examined until recently. Some bio-active sphingolipids are involved in a multitude of cellular actions and signals.[60, 103, 132] Because of this discovery, there has been a surge of interest in sphingolipids' occurrence, abundance, and role over the past 20 years. New information is accumulating on the roles of sphingolipids in retinal neurons during development and in ocular pathology.[116]

Our group performed the first comprehensive analysis of the sphingolipid content and composition in mammalian (rat and bovine) retinas.[18] We detected that 5.6 – 6.7% of the fatty acids in these retinas are linked to the amide moiety of a sphingosine. Since there is typically only one fatty acid attached to one molecule of sphingolipid (with the exception of O-acylceramides), the mole percentage of retinal sphingolipids ranges from 11.2 – 13.4%. SM is the most abundant sphingolipid species in the retina, comprising 2.40 – 2.53 % of the total retinal lipids.[18] Cer and glycosyl-ceramides (GC) constitute ≤ 1% of the total retinal lipids.[18] On the other hand, gangliosides (GG) that contain sialic acid comprise ~ 3.0% of the total.[18] Retinal sphingolipids have an abundance of saturated fatty acids, especially very long chain saturated fatty acid (VLC-FA); however, very long chain polyunsaturated fatty acids (VLC-PUFA) beyond 24 carbons are lacking. Its two most abundant fatty acid species are 18:0 (44-63%) and 16:0 (11-19%) carbon chains. In contrast, GG contain significant levels of unsaturated and VLC-PUFA.[18] Little information exists on the specific roles, if any, of these sphingolipid species in the retina and other ocular tissues. Sphingolipid metabolic diseases, however, are historically associated with visual dysfunction, suggesting an importance of sphingolipids in ocular function or development.

IV. METABOLIC DISEASES AND THEIR OCULAR PRESENATATION

Lysosomal storage diseases arise from rare genetic defects resulting in total or partial functional loss of specific lysosomal enzymes or co-factors responsible for degradation of sphingolipids. Upstream precursors accumulate, and clinical presentation reflects the amount of residual enzymatic activity, ranging from infantile (little or no enzymatic function) to adolescent/adult (moderate function). The resulting disorders are considered collectively as sphingolipidoses or gangliosidoses, which include GM1 and GM2 (Tay Sachs) gangliosidoses, Niemann-Pick disease, Gaucher disease, Farber disease, Krabbe disease, Fabry disease, and metachromatic leukodystrophy. Each disease includes several types that are named for the lipid substrate that accumulate in each case (for simplicity, the eponymous names above will be used in the remaining discussion).[73, 113] With the exception of X-linked recessive Fabry disease, they share a common autosomal recessive inheritance pattern and have a collective frequency of 1 in 8000 live births.[94] Multiple-organ dysfunction (liver, lung, spleen, heart, and lungs) is common. Since gangliosides are abundantly expressed in the central nervous system, the diseases share clinical findings, including a spectrum of early onset progressive neurodegeneration and a “cherry-red macula” from accumulation of various sphingolipid precursors or byproducts within cells of the retina (Fig. 3).

Despite a clearer understanding of the biochemical and genetic defects that cause most of these disorders, how these defects lead to the pathological features related to the neurodegeneration and visual impairment remains unknown. To date, more than 40 genetically distinct forms of sphingolipid storage disorders have been described. An in-depth examination of each disease is beyond the scope of this review; however, we will explore the ocular findings that are shared by some and unique to others. Additionally, we examine the potential implications of activation of inflammatory pathways by sphingolipid derivatives in the pathogenesis of these diseases.

A. GM1 AND GM2 GANGLIOSIDOSES

GM1 gangliosidosis is an autosomal recessive disorder resulting from a deficiency in beta-galactosidase that leads to the accumulation of GM1-gangliosides within lysosomes and subsequent neuronal apoptosis, demyelination, and gliosis. There are three clinical subtypes defined by age of onset, which often correlates with severity: infantile (most severe), juvenile, and adult. The most common clinical features include coarse facies, hepatosplenomegaly, skeletal dysostosis, and a cherry-red macula.[17] Additional ocular findings include visual inattentiveness, corneal clouding, tortuous retinal vessels, retinal

hemorrhages, and optic atrophy. A cherry-red macula has been reported in 50% of cases (Fig. 3).[10, 88]

The GM2-gangliosidoses involve a deficiency in the alpha (Tay Sachs disease variants) or beta (Sandhoff disease variants) subunits of hexosaminidase. As with GM1 gangliosidoses, the severity of disease and progression reflects the degree of enzymatic dysfunction. Accumulation of GM2 gangliosides in the brain results in early neuronal cell death and progressive neurodegeneration. Clinical features of Tay Sachs include ataxia, muscle wasting with motor degeneration, spasticity, convulsions, deafness, blindness with the classic cherry-red spot, and death by age 3 (Figure 4). Sandhoff disease involves deficiencies in both hexosaminidase A and B, and thus shares similar features with Tay Sachs, including ganglioside accumulation in the cornea, retina, and optic nerve. The most common ocular findings in Tay-Sachs and Sandhoff patients are a pale optic disc and a cherry-red spot in the macula (Figure 3).[80] The cherry-red macula, common to many of the lysosomal storage diseases including GM1 and GM2 gangliosidoses, arise from the accumulation of gangliosides within the retinal ganglion cells, found in highest concentration within the macula. Since the fovea lacks ganglion cells, this allows for a contrast in coloration from the opacified ganglion cells, resulting in the cherry red spot. Long-term follow-up of such patients reveals a decrease in prominence of the cherry red spot as a result of ganglion cell death and resultant gliosis. [101] Thus the lack of a cherry red spot in an older patient may not mean it was never present. Furthermore, this loss of ganglion cells likely parallels progressive loss of visual function over time.[70] Although less commonly reported, ultrastructural examination of the retina and optic nerve reveals abundant pleomorphic storage cytosomes in all neurons of the retina, including the inner segments of the photoreceptor cells and glial cells of the optic nerve.[15]

Interestingly, Jeyakumar et al. also describe an inflammatory component to the pathogenesis of the GM1 and GM2 gangliosidoses--primarily in Sandhoff, late-onset Tay-Sachs, and GM1 mouse models– that is characterized by macrophage activation and enhanced MHC class II expression. This activity leads to microglial activation, an increase in nitric oxide formation, and oxidative damage, which correlates with disease severity. Elevated pro-inflammatory cytokine production (including TNFα, IL1B, and TGFB1) also correlates with disease severity. An elevation in TGFB1 only appeared in late stages and may represent a rescue response to the increased pro-inflammatory signal.[65]

B. GAUCHER DISEASE

Gaucher disease is the most common lysosomal storage disease and can manifest as thrombocytopenia, organomegaly, ocular dysfunction, or even death.[88] It is caused by an autosomal recessive deficiency of the enzyme glucocerebrosidase (Fig. 4) resulting in the accumulation of glucocerebroside (glycolipid glucosylceramide) in the spleen, liver, lungs, bone marrow, and central nervous system. The ocular manifestation of Gaucher patients can range from ocular motor apraxia [39] to corneal opacity.[58] White deposits can be found in the peripheral corneal endothelium, chamber angle and pupillary margin.[121] Conjunctival masses are pathologically infiltrated by Gaucher cells (characteristic lipid-laden cells) beneath normal epithelium.[109] Other findings described in association with Gaucher patients include a uveitic masquerade syndrome,[34] vitreous opacities, and retinal vascular abnormalities.[124] Evaluation of sphingolipids in the vitreous from a patient with Gaucher disease showed an accumulation of glucosylceramide, causing vitreous opacity, followed by infiltration of monocyte–macrophages.[44] These observations may suggest that Cer accumulation (specifically glucosylceramide) is involved in some forms of uveitis.

C. KRABBE DISEASE

Krabbe disease (globoid cell leukodystrophy or galactosyl ceramide lipidosis) is an autosomal recessive disorder arising from a deficiency in β-galactosylceramidase, which catalyzes the formation of Cer from galactosylceramide in the lysosome (Fig. 4). Therefore accumulation of galactosylceramide is expected in the tissue of Krabbe patients; however, it is not galactosylceramide, which in fact decreases in Krabbe brain, but psychosine that accumulates.[137] This paradoxical finding is explained as follows: psychosine (the trivial name for a monoglycosylsphingolipid, which is the non-acylated or lyso form of a cerebroside, normally galactosylsphingosine) is a minor intermediate in the catabolism of monoglycosylceramides and is normally present in tissues in low concentrations. Psychosine is formed either by deacylation of the galactosylceramide or by addition of galactose to sphingosine. Psychosine is also broken down by galactosylceramidase, the enzyme deficient in Krabbe patients, and in its absence psychosine accumulates. Psychosine accumulation causes death of oligodendrocytes. These are the cells that normally synthesize galactosylceramide, so their death would account for the absence of galactosylceramide buildup in Krabbe patients' brain. Accumulation of psychosine disrupts development of the myelin sheath by injuring oligodendrocytes, leading to demyelination and subsequent progressive neurodegeneration with severe motor degeneration.[88] Neuronal degeneration occurs in retrograde fashion, which leads to thinning of the nerve fiber and ganglion cell layers of the retina.[16] Clinically, the disease course follows three stages, beginning with irritability and stiffness, episodic fevers, and seizures, with eventual severe motor and mental deterioration and early demise. Blindness is a significant feature of the later stages of Krabbe disease because of degenerative changes in the afferent visual pathways, both at the optic nerve and optic radiation level.[61] In the postmortem eye, there is a gross reduction in the ganglion cell and nerve fiber layers of the retina.[38] A cherry red macula may also be associated with Krabbe disease.[63]

Neuroinflammation has been shown to be a major component of pathogenesis in Krabbe disease. Animal models have been successfully used to delineate pathogenic roles for multiple proinflammatory molecules, including major histocompatibility complexes,[90] tumor necrosis factor-α, interleukin-6,[79] monocyte chemoattractant protein-1 and interleukin-10.[147] Additional studies have associated inflammatory signaling mediators, such as prostaglandin D (PD) and AMPK, with disease progression. Using a mouse model for Krabbe disease, Mohri et al., demonstrated a PD-mediated interaction between microglia and astrocytes; activated microglia produced an increased amount of PD, which subsequently activated astrocytes that expressed the respective PD receptors. This interaction heightened astrocytic gliosis in association with demyelination and manifested as increased spasticity, reminiscent of both Krabbe disease and multiple sclerosis (MS).[98] Psychosine, a downstream product of galactosylceramide, may also be involved as an inflammatory component of Krabbe disease pathogenesis.[136] Psychosine has been demonstrated to have a potent apoptotic effect on oligodendrocytes. Additionally, Mac 1-positive cells that are found in increased concentrations as the demyelination progresses in this disease express major histocompatibility complex class II (Ia).[136] Whether this signifies either activation of an immune response as a cause for or a byproduct of neurodegeneration remains to be determined. Giri et al., have demonstrated psychosine down-regulation of AMPK activity (part of the anti-inflammatory pathway) in glial cells.[55]

D. NIEMANN-PICK DISEASE

Niemann-Pick disease is a lysosomal storage disease that includes a group of fatal inherited metabolic disorders caused by mutations in the *Sphingomyelin phosphodiesterase (SMPD)* genes (Fig. 4). These mutations cause the complete or partial deficiency of acid sphingomyelinase (ASM) and lead to the accumulation of sphingomyelin (SM), eventually

causing cell death and multiorgan failure. ASM coverts SM into ceramide and phosphorylcholine and accumulation of SM within lysosomes characterizes both Niemann-Pick A and B types. The expanding role of shingolipids signaling at the level of the plasma membrane and cell surface suggests that the pathogenesis of NPD is a result of sphingolipid signaling dysfunction. How this occurs on a molecular level remains unknown.[78] Ledesma et al. review the neurologic consequences in an ASM knockout mouse model, which include not only changes in the lipid structure of neuronal cells, but also possible impaired neuronal signaling that may lead to death of Purkinje cells, altered calcium homeostasis, altered axonal polarity, abnormal endocytosis function, and even impaired microglia functionality leading to increased susceptibility to infection.[78]

Niemann-Pick Type A disease is a severe neurodegenerative disorder of infancy. Death usually occurs between ages 2-4. Niemann-Pick Type B is a milder, non-neuropathic form with later onset and longer survival, sometimes into adulthood. Niemann-Pick Type C is biochemically, genetically, and clinically distinct from both Niemann-Pick Types A and B. In patients with Niemann-Pick Type C, the massive accumulation of glycosphingolipids in the nervous system is linked to structural changes, namely ectopic dendritogenesis and meganeurite formation.[144] A clinical hallmark of Type C is a supranuclear vertical gaze palsy.

Ocular abnormalities in Niemann-Pick disease range from corneal opacification and brown discoloration of the anterior lens capsule to retinal opacification with a macular cherry-red spot in Niemann-Pick Type A (Figure 3).[145] In Niemann-Pick Type B disease, the ocular manifestations are primarily retinal, including macular halos and cherry-red maculae.[83, 93] Histopathologic and microscopic studies have shown the accumulation of lipid deposits in the retinal ganglion cell layer in patients with Type B.[81] Also, spectral domain optical coherence tomography (SD-OCT) reveals focal thickening with high reflectivity in the ganglion cell layer of the fovea, but excluding the foveola.[68]

In Niemann-Pick Type C disease, optic nerve pallor and perimacular gray discoloration are observed clinically as well histologically. Knockout mouse models for Niemann-Pick disease demonstrated a histopathologic enhancement of microglial activity using monoclonal antibody staining and an upregulation of interleukin-1b in astrocytes.[11] Studies of potential anti-inflammatory therapies to treat Niemann-Pick type C also support a key role for inflammation in its pathogenesis.[129]

E. FARBER DISEASE

Farber disease (ceramidase deficiency) is a rare, autosomal recessive lysosomal storage disease in which a mutation in the acid ceramidase gene causes an accumulation of Cer in the joints, liver, throat, CNS (Fig. 4), and even in the retina.[150] Accumulation of Cer in these tissues reportedly activates inflammatory pathways resulting in swollen, tender joints, granuloma formation, and the characteristic hoarse cry in infancy.[37]

Disease onset is typically in early infancy, but may occur later in life. Newborns that have the classic form of Farber disease develop symptoms within the first few weeks of life and may have macular cherry-red spots. Retinal ganglion cells showed the greatest pathologic changes, with gross distention and inclusions.[150, 151]

F. FABRY DISEASE

Fabry disease (also known as alpha-galactosidase A deficiency or angiokeratoma corporis diffusum) is an X-linked recessive lysosomal storage disease that can cause a wide range of systemic symptoms (Fig. 4), but is most associated with early stroke, cardiomyopathy, and

end-stage renal failure. In this disease, a mutation in the Alpha-galactosidase A gene leads to the accumulation of globotriaosylceramide (Gb3) in various tissues and organs, particularly vascular endothelium. Cornea verticillata is the most frequently reported ophthalmic abnormality, which gives Fabry disease its alternate name, angiokeratoma.[130] Other ocular manifestations include conjunctival and/or retinal vessel tortuosity, thinning of the retinal nerve fiber layer, and cataracts.[100, 107, 130] Gb3 deposits have also been detected in conjunctival biopsies of Fabry disease patients by using immunofluorescence microscopy.[117] Variations in expression of interleukin inflammatory genes has been associated with varying effects in Fabry.[118]

G. METACHROMATIC LEUKODYSTROPHY

Metachromatic leukodystrophy is an autosomal recessive disease caused by a deficiency in sulfatide sulfatase (arylsulfatase A). Accumulation of galactosyl-3-sulfate ceramide, among others, causes white matter abnormalities on brain imaging and subsequent progressive neurocognitive and motor degeneration. As the name implies, metachromatic granules are found histologically in various tissues. While ocular findings are less common, demyelination in the optic nerve and, rarely, a cherry red macula may be seen.[10]

V. SPHINGOLIPIDS IN OCULAR DISEASES

A: Association of Sphingolipids in Inflammatory and Autoimmune Eye Diseases

Mounting evidence supports the association of sphingolipids in inflammatory processes, including those described above, and with autoimmune eye diseases such as autoimmune conjunctivitis, corneal transplantation, optic neuritis associated with MS, and uveitis. The pathogenesis of uveitis remains complex, and currently there is no definitive evidence for involvement of sphingolipids. The therapeutic application and effectiveness of fingolimod or FTY720, a sphingolipid analog, in the treatment of MS, experimental uveitis, and other autoimmune eye diseases, however, provide indirect evidence of the involvement of sphingolipids in ocular inflammation.

Up to 50% of patients with MS will develop one or more episodes of optic neuritis, and, for 20-30%, optic neuritis is the presentation. In the 1980s, antibodies against galactocerebroside were widely used to develop models for CNS and optic nerve demyelination.[22, 23, 89,108] Similarly, increased levels of Cer have been detected in the CNS of patients with neurological disorders such as MS and Alzheimer disease. While the significance of these findings is currently undefined, such evidence has stimulated considerable attention toward the potential role of Cer in the pathogenesis of demyelinating and neurodegenerative diseases.[6,33,125] The promising application of FTY720 in treating MS may also reveal a potential pathogenesis of optic neuritis in this setting and could be useful in treating MS-associated optic neuritis.

MS is characteristically known for its immune-mediated demyelination and neurodegeneration; however, the retina is also a target of inflammation in spite of its lack of myelination.[57,139] Animal models suggest that retinal ganglion cells begin to degenerate, alongside activation of retinal microglia, prior to more widespread neurodegenerative damage.[40] Furthermore, the extent of retinal periphlebitis seems to correlate with disease severity.[123] In 2010, the FDA approved Fingolimod (FTY720), a structural analog of Sph that is chemically synthesized from myriocin, an inhibitor of *de novo* ceramide synthesis, for treatment of relapsing MS. *In vivo*, sphingosine kinase 2 phosphorylates FTY720 in a manner similar to the conversion of Sph to S1P (Fig. 2). Despite the small difference in structure, FTY720-phosphate can still bind and inactivate S1P receptor-mediated cellular signals.[87] The exact mechanism of FTY720 as a treatment for MS remains under

investigation, but the expression of S1P receptors in neuronal cells and lymphocytes suggests that FTY720 may affect both.[29] Additionally, FTY720 has been shown to inhibit CerS enzymes and thereby reduce the formation of *de novo* Cer.[13,76] This gives FTY720 the ability to modulate cellular sphingolipid signaling via S1P receptors and sphingolipid (e.g. Cer) synthesis. A delicate balance of signaling sphingolipids is important for cellular homeostasis and signaling, which has been termed the "sphingolipid rheostat".[132] The established role of FTY720 on sphingolipid metabolism and signaling and its overall effect on neuroinflammatory diseases imply sphingolipid signaling is involved in the pathophysiology of these diseases, whether as an activator or inhibitor of sphingolipid-mediated pathways. Nevertheless, there may be additional pathways that are as yet undefined in which FTY720 may be active, and further research is needed in order to better define its role.

Although FTY720 maintains a relatively good safety profile, it has been associated with macular edema, an uncommon and generally reversible side effect in up to 1% of MS patients treated with FTY720, depending on the dose.[30, 67] The most accepted etiology of macular edema in general is nonspecific inflammation, and it is not typically seen clinically in MS in the absence of uveitis or pars planitis. With the aid of higher resolution imaging obtained via SD-OCT, Gelfand et al., observed a 4.7% incidence of microcystic macular edema (MME) in patients with MS, none of who were on FTY720 therapy.[53] They also observed an association between MME and greater overall disability, disease severity, history of optic neuritis, and reduced visual acuity. The presence of MME may indicate local breakdown of the blood-retinal barrier from subtle underlying inflammatory activity.[53] The effects of FTY720 on retina may support the idea that a disturbed sphingolipid rheostat contributes to nonspecific inflammation and macular edema.

Experimental autoimmune uveoretinitis (EAU) is a well-characterized animal model in which proteins from photoreceptors are used as an adjuvant in inoculating the proteins into a different host to induce uveitis.[24] The characteristic inflammatory reaction involves CD4+ T cells that are activated against retinal cells. Previous studies demonstrated FTY720's ability to suppress development of disease in experimental autoimmune models for arthritis and allergic encephalomyelitis, which led to investigation of its effects on EAU model.[74] Subsequent studies have demonstrated its ability to suppress the incidence and intensity of inflammation in a dose-dependent manner.[74] Independent studies found similar results in mouse models when FTY720 was administered 2 days before the onset of EAU. Administration of FTY720 prevented inflammatory cells from infiltrating the retina and suppressed histological disease.[31, 115] Additionally, FTY720 given as an experimental drug suppressed the production of granulocyte monocyte colony stimulating factor (GM-CSF) by T-cell clones (TCC) in Vogt-Koyanagi-Harada (VKH) uveitis patients.[119] The effectiveness of FTY720 in mouse and rat models for uveitis and in human uveitis strongly supports a causal relationship of sphingolipid signaling in inflammatory eye diseases.

The association of Cer with inflammation in the cornea is less clear. Liposomal delivery of short-chain Cer (C_6) was found to be effective in inhibiting inflammation induced by either lipopolysaccharide or *S. aureus* in mouse corneas.[135] Similarly, in rabbit models, Cer can suppress corneal haze caused by exposure to ultraviolet B (UVB) radiation during photorefractive keratectomy (PRK).[69] Oral administration of FTY720 in rats that had undergone orthotopic allogeneic penetrating keratoplasty showed a reduction in infiltrating CD4+, CD8+, CD161+ (NK-cells), and CD25+ (IL2 receptor) cells as well as significantly prolonging corneal allograft survival.[91] FTY720 was also effective in increasing survival rates of corneal transplantation in mouse models, providing potential for its use in corneal allografts.[152]

Finally, sphingolipid signaling has also been shown to participate in the pathophysiology of primary Sjogren syndrome (SS) and allergic conjunctivitis. Sjogren syndrome is an autoimmune eye disease characterized by inflammatory mononuclear cell infiltration and destruction of lacrimal gland epithelial cell. S1P signaling modulates the autoimmune response in this disease.[122] In murine models of experimental allergic conjunctivitis (EC), alpha-galactosylceramide suppressed the pathologic outcome.[45, 46] Moreover, EC can also be suppressed by treatment with FTY720.[134]

B: Association of Sphingolipids in Degenerative Retinal Diseases: Retinitis Pigmentosa and dry Age-related Macular Degeneration (AMD)

Apoptosis of photoreceptors is a hallmark for most retinal degenerative disorders, including retinitis pigmentosa (RP) and age-related macular degeneration (AMD).[21, 25, 110] Cer is a cellular second messenger for inducing apoptosis.[103] The first evidence of Cer involvement in photoreceptor apoptosis came from *Drosophila* studies that detected increased Cer in arrestin2 and phospholipase C mutant photoreceptors.[3] Transgenic over-expression of neutral Ceramidase, an enzyme that reduces Cer into Sph and free fatty acids, prevented Cer-induced photoreceptor cell death.[2,3] More recent *in vitro* studies have established Cer as an essential second messenger in the activation of apoptosis in photoreceptors. German et al., demonstrated in rat retinal neuronal cultures that adding cell-permeable short-chain C_2-Cer triggers photoreceptor apoptosis, whereas inhibiting Cer synthesis protects photoreceptors from oxidative stress (paraquat)-induced apoptosis.[54] In mouse retina-derived 661W cell lines, treatment with sodium nitroprusside, a nitric oxide donor, resulted in increased Cer levels.[120] Retinal cells were protected from oxidative stress-induced apoptosis by desipramine, an inhibitor of SMase enzymes, suggesting a role of Cer in oxidative stress-induced death in photoreceptor cells.[120] In rabbits, *de novo* Cer production has been shown to cause photoreceptor cell death during retinal detachment.[114] Our studies of cell-permeable C8-Cer and BSA-conjugated C16-Cer in 661W cells demonstrated that both of these Cer resulted in dose-dependent cell death.[84] We also observed an increase in Cer in H_2O_2-treated 661W cells (Mandal et al., unpublished data). This provides additional support for the role of Cer as a cell death mediator in retinal cells. Abrahan et al. showed enhanced formation of Cer and its subsequent breakdown into Sph triggered photoreceptor apoptosis when cultured rat retinal neurons were subjected to oxidative stress.[1] This evidence points toward Cer as a common mediator of photoreceptor cell apoptosis.

Cer accumulation has been associated with photoreceptor cell death in Rd10 mouse models of RP, and pharmacologic inhibition of Cer biosynthesis slows the progression of retinal degeneration and preserves the structure and function of photoreceptor cells.[133] In our experience, several inherited and light-induced models of murine retinal degenerations exhibit an association between increased Cer and degeneration of the retina.[85, 86] In humans, mutations in the *Ceramide kinase-like* (*CERKL*) gene have been associated with inherited RP.[5, 141] There has been extensive characterization of this gene and its protein product in mouse models and *in vitro*;[51, 56, 140, 142] however, while the exact function of CERKL is not yet known, it may be involved in the ceramide metabolism pathway. The evidence suggests a link between human retinal neuro-degeneration and ceramide-mediated apoptosis.

Retinal pigment epithelial (RPE) cell atrophy within the macula is characteristic of AMD. In cultured human RPE (hRPE) cells, treatment with the chemical oxidants tri-butyl hydroxyperoxide (tBH) and H_2O_2 resulted in Cer generation and induced RPE apoptosis.[9] Another study demonstrated that laser exposure induced hRPE apoptosis with concomitant Cer production.[8] Studies on the over-expression of sphingomyelin phosphodiesterase-3 (SMPD3), a key enzyme responsible for Cer production from SM (Fig. 2), demonstrated enhanced RPE cell death, arrested cell proliferation, and increased percentage of apoptotic

cells proportionate to the amount of transfected SMPD3 DNA, most likely via increased cellular Cer levels.[154] Interestingly, short-chain C_2 Cer selectively induced apoptosis in non-polarized RPE cultures but not in fully differentiated and polarized RPE cells. Non-polarized RPE cells are found in late age-related macular degeneration lesions, and Cer seems to play a critical role in their apoptosis.[154] Further studies on the mechanisms of Cer-induced RPE apoptosis include the roles of increasing reactive oxygen species production, mitochondrial membrane permeability transition, and caspase-3 activation.[66] As the functional antagonist of Cer, S1P was found to have beneficial effects on protecting RPE cells from Cer-induced apoptosis.[154] In addition to involvement in RPE apoptosis, increased Cer is found in the brains of patients with the juvenile form of Batten disease,[112] in which neuronal apoptosis is thought to be the cause of RP. Finally, Cer is shown to alter the chloride channel activity of the Bestrophin protein, and Cer accumulation may be associated with enhancing inflammation in the retinas of patients with Best vitelliform macular dystrophy.[148]

In summary, both *in vitro* and *in vivo* experiments as well as the associations between Cer modulation and retinal neuronal death underscore the significance of Cer and its metabolites in the pathogenesis of retinal degenerative diseases.

C: Sphingolipids in Neovascular Eye Diseases: Wet AMD and Diabetic Retinopathy

The initiation of neovascularization in the retina occurs from the dysfunction or death of RPE cells, vascular endothelia, and pericytes of the retina. Cer is not only involved in the damage to RPE cells, but also related to the damage and death of vascular endothelium and pericytes. In human umbilical vein endothelial cells exposed to tumor necrosis factor-alpha, Cer mediates the production of rapidly reacting species of oxygen.[32, 128, 131] Recent evidence also shows that Cer alters endothelial cell permeability and induces endothelial cell senescence.[82, 143] Similarly, in cultured bovine retinal pericytes, Cer accumulation leads to increased apoptosis.[36] Furthermore, inhibition of Cer by fumonisin B1 (a ceramide synthase inhibitor) and over-expression of acid ceramidase, which can reduce the level of Cer enzymatically, reversed the pro-apoptotic effect of palmitate.[20]

In vivo studies using animal models reveal that Cer and its metabolites play key roles in the delicate balance of neovascularization in the retina. Although proliferative diabetic retinopathy does not typically manifest in rodent models, streptozotocin-induced diabetic animals exhibit decreased Cer levels and a concomitant increase in GlcCer content in their retinas.[42] Cer-enriched membrane microdomains are the prerequisite for inflammatory cytokine signaling, and SMase activation to generate Cer from sphingomyelin is a key early inducer of cytokine-mediated inflammation in retinal vascular endothelial cells leading to new capillary formation. In human retinal endothelial cells (HRECs), activation of SMase mediates cytokine-induced inflammation.[105] Interestingly, the trophic factor, DHA (docosahexaenoic acid), could potentially inhibit this inflammation by reducing SMase activity.[27,106] In addition, administration of alpha-galactosylceramide into the vitreous cavity of C57BL/6 mice promoted choroidal neovascularization (CNV).[62] In neonatal murine models of ischemia-driven retinopathy, S1P2 receptor deficient mice had no pathologic neovascularization in the vitreous and had reductions in endothelial gaps and inflammatory cell infiltration.[127] In another study on retinal and CNV models, a humanized monoclonal antibody, sonepcizumab, which selectively binds to S1P, injected intraocularly resulted in a significant reduction in the area of the CNV as well as reduction of leakage from the remaining CNV.[149] Similar results were also found in a laser-induced choroidal neovascularization murine model.[19]

These reports support an important role of S1P signaling in retinal neovascularization. S1P is the most widely studied sphingolipid signaling mediator, and is metabolized from Cer in two steps: ceramidases hydrolyze Cer to Sph and free fatty acid. Sphingosine is then

phosphorylated to S1P by specific kinases called sphingosine kinase 1 and 2 (SPHK1 and 2) (Figure 2). S1P signaling is complex: 1) S1P induces cell proliferation and differentiation;[104, 153] 2) S1P is found to be an essential component for TNFα-mediated NFκB activation for inflammatory responses(4) and in the context of retinal neovascularization, and 3) S1P acts as a ligand for 5 known cell surface receptors (S1P1-5) present on endothelial cells and T lymphocytes. Upon activation, these G-protein-coupled receptors induce endothelial cell proliferation and migration and new vessel formation. Industrial researchers quickly realized the role of S1P in retinal neovascular conditions and developed sonepcizumab, as described above, for treatment of neovascular AMD, which has now has moved to human clinical trials. While much of its biochemical pathway and functioning is known, a significant research effort is still needed to understand the role and mechanism of S1P signaling in normal and disease related ocular neovascularization.

VI. CONCLUSION

Lysosomal storage diseases resulting from dysfunction in sphingolipid metabolism have long been associated with various forms of ocular pathogenesis and blindness. As the name implies, storage or accumulation of a metabolic intermediate in the lysosome induces neuronal cell death. Present understanding of the signaling roles of several sphingolipid metabolites warrants a reinvestigation into the pathological mechanism of neuronal or ocular cell death in various sphingolipid storage diseases. This is increasingly relevant as therapeutic interventions targeting sphingolipid metabolism are currently being explored and developed not only for metabolic disorders, but also for many other forms of autoimmune and inflammatory diseases. The consequences of lipid storage and the role of sphingolipids in other biological pathways, such as the function of the retina and other non-neuronal tissues in the eye, have to be more fully elucidated. Alterations in cell death, differentiation, proliferation, and neovascularization, are critical events in major retinal diseases, such as retinitis pigmentosa, AMD, and diabetic retinopathy. Ocular inflammatory and autoimmune diseases also involve activation and migration of endothelial cells, neovascularization, and egress and infiltration of immune cells to the uvea, anterior chamber, and cornea. All of these activities have been linked with sphingolipid signaling, and current investigation has determined these molecules to be important mediators in the pathogenesis of blinding diseases. Deciphering the regulatory role of sphingolipids presents an additional opportunity to pursue them as therapeutic targets.

VII. METHODS OF LITERATURE SEARCH

A search of literature in English language was conducted through Medline, and BioMed Central. For sphingolipids association with retinal and eye diseases, all years from 1950 to the present were included in the search. Search terms included the following in combination with the terms Sphingolipid, ceramide, gangliosides, sphingosine, sphingosine 1-phosphate, lipid storage diseases, sphingolipid metabolic disorders, retina, eye, retinal pigment epithelium, cornea, apoptosis, cell death, inflammation, macula, retinal degeneration, uveitis, AMD, diabetic retinopathy. The references in the relevant articles especially in review articles were also used.

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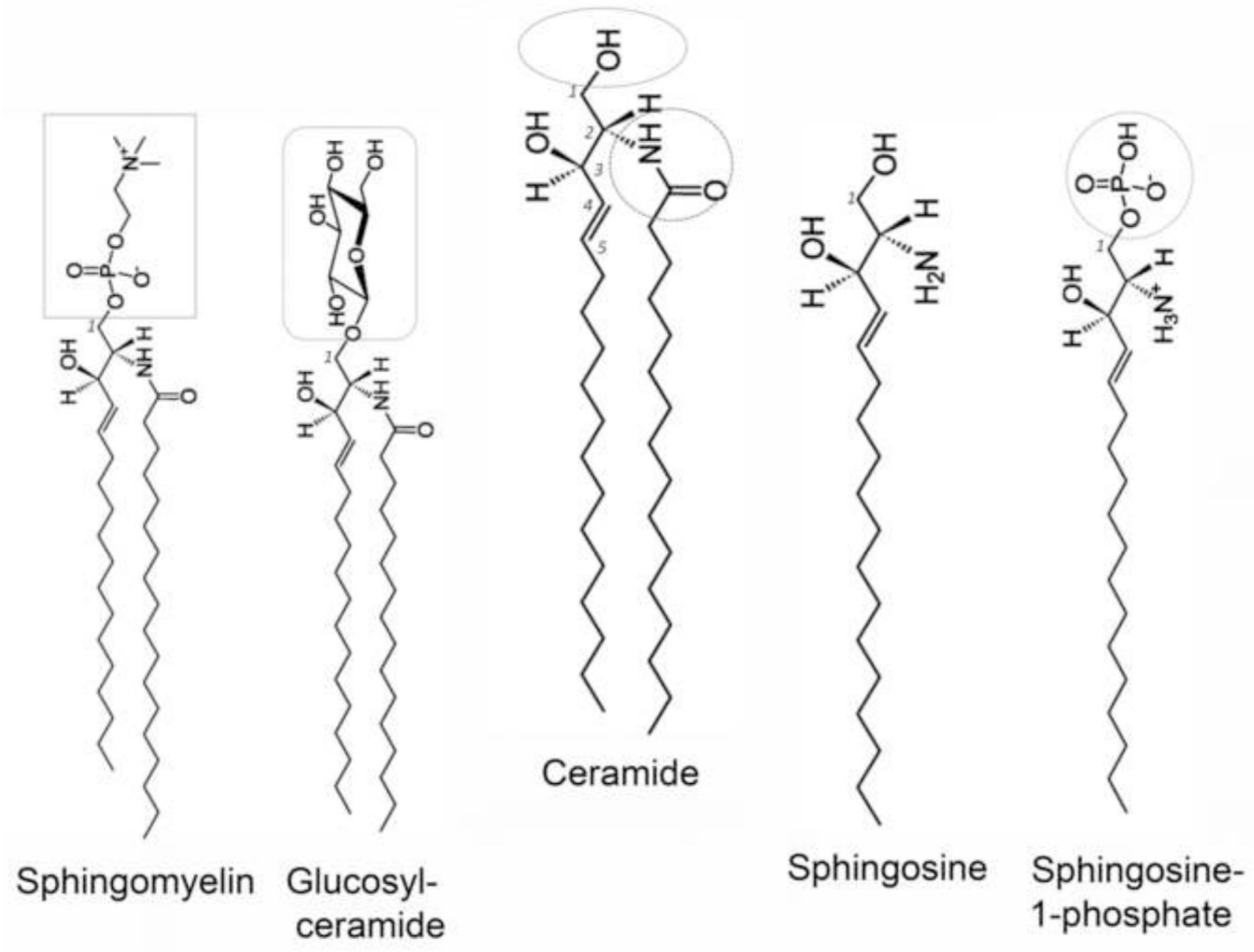

Figure 1. Structure of major sphingolipid species

Ceramide (Cer) is the key metabolite for cellular sphingolipid metabolism, which is the source for other sphingolipids.

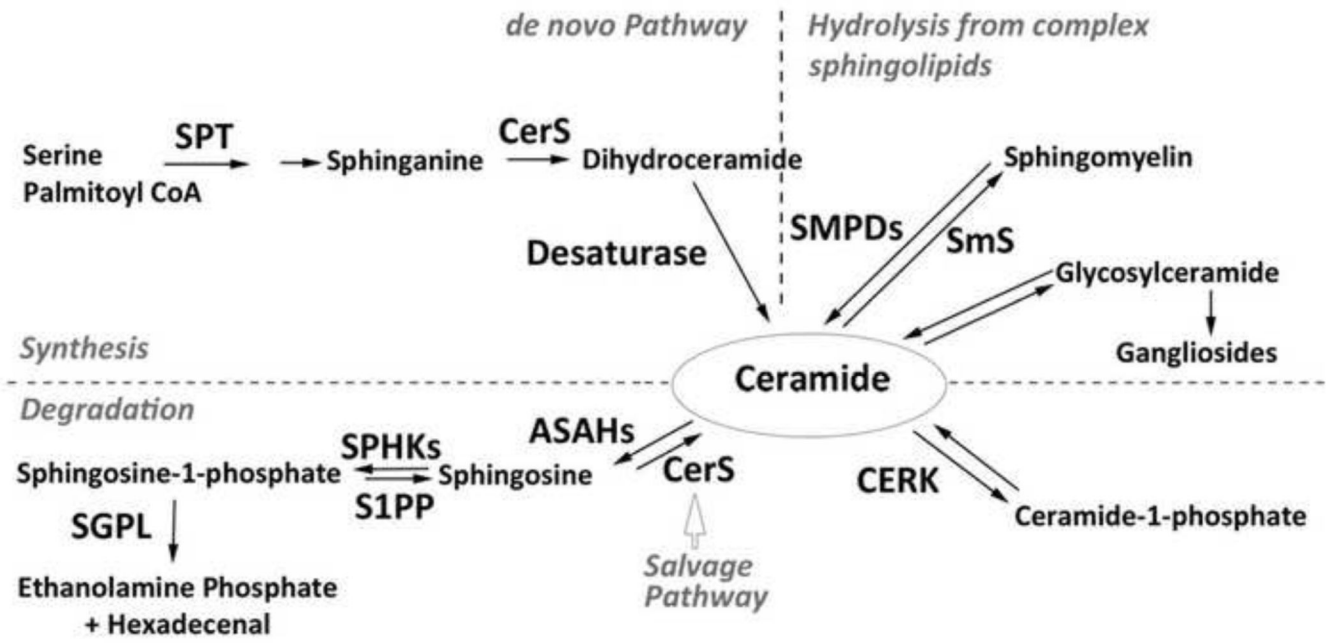

Figure 2. Sphingolipid metabolism in mammalian cells

Cer are the simplest sphingolipids and situated at the center of sphingolipid metabolism. There are two major pathways for Cer synthesis in a cell- de novo biosynthesis and hydrolysis from complex sphingolipids. The transfer of a phosphorylcholine head group from phosphatidylcholine to ceramide yields sphingomyelin. The addition of carbohydrate groups from the sugar donor, UDP-hexose, yields complex glycosphingolipids (cerebrosides, sulfatides, and gangliosides). These compounds can be converted back to Cer by the removal of sugars (glycosidases) or phosphorylcholine by sphingomyelinases. An enzyme (ceramidase) is able to cleave the amide-linked fatty acid of ceramide and free sphingosine. SPT, Serine palmitoyl transferase; CerS, Ceramide synthase; SMPDs, Sphingomyelin phosphodiesterases (sphingomyelinases); SmS, Sphingomyelin synthase; ASAHs, Acyl-sphingosine amidohydrolases (Ceramidases); SPHKs, Sphingosine kinases; S1PP, Sphingosine-1-phosphate phosphatase; SGPL, sphingosine-1-phosphate lyase; CERK, Ceramide kinase.

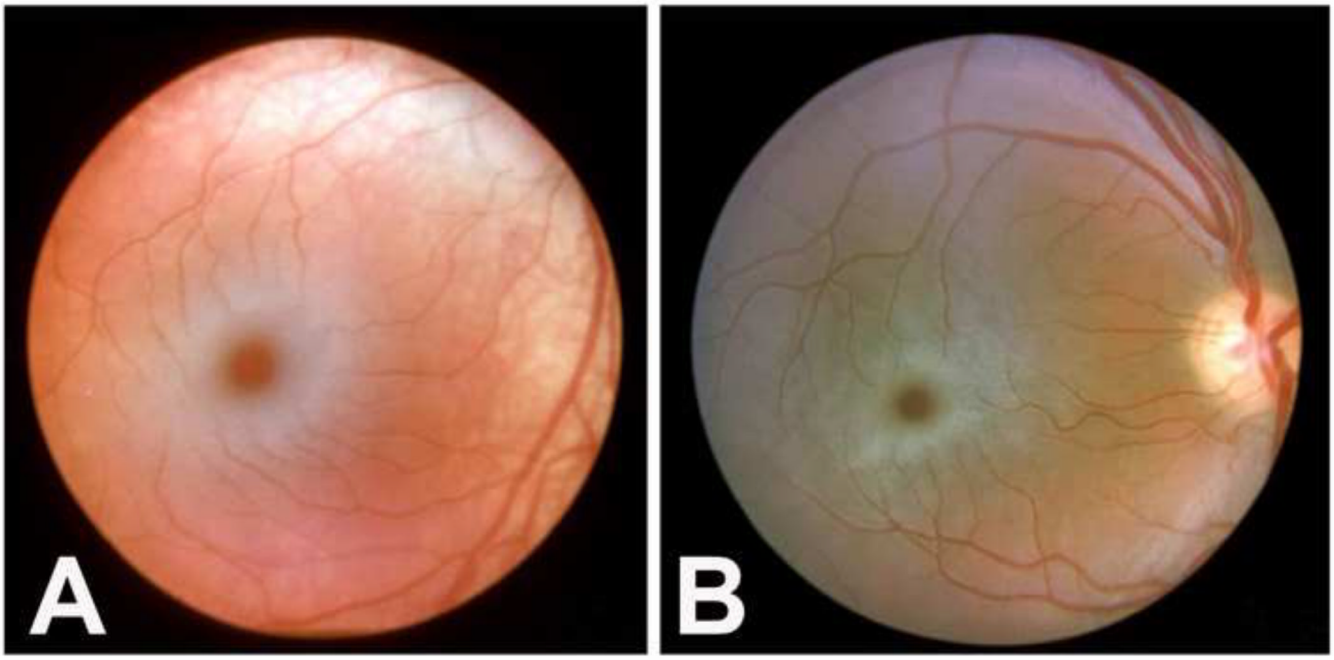

Figure 3. Macular cherry red spots in sphingolipid storage diseases

A macular cherry red spot is the most common retinal pathology observed in sphingolipid storage diseases. A. Macular cherry red spots in Tay Sachs disease; and B. Macular cherry red spots in Niemann Pick disease. The images are obtained from the NOVEL collection at the Spencer S. Eccles Health Sciences Library, University of Utah with permission from North American Neuro-Ophthalmology Association (NANOS).

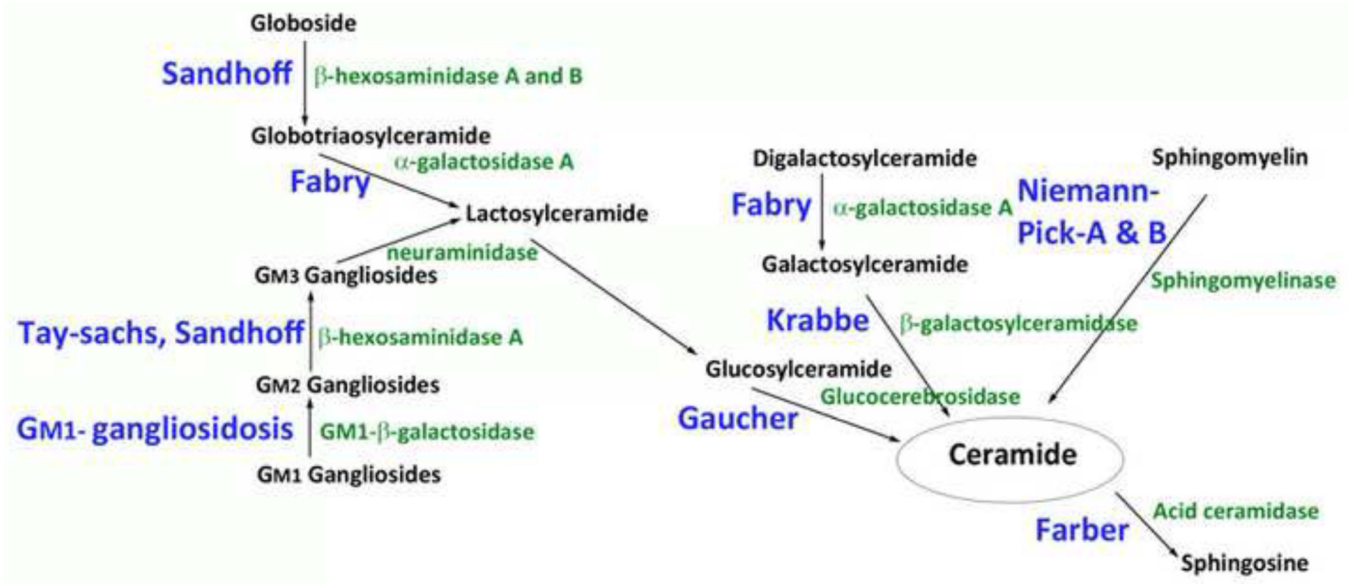

Figure 4. Sphingolipid metabolic disorders

Mutation in genes involved in Cer metabolism cause various forms of severe neurodegenerative diseases. The name of the disorders is presented in blue whereas the enzymes which are deficient or inactive in those particular disorders are presented in green.