# Sphingolipids in Health and Disease

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**SUMMARY**

Sphingolipids are a complex group of lipids that are becoming increasingly important in many aspects of disease and cell physiology. They are composed of a long-chain sphingoid base backbone, a long-chain fatty acid linked by an amide bond, and one or more polar head groups the structures of which are characterized by different sphingolipid subtypes such as ceramide, sphingomyelin, and glycosphingolipids. The metabolism of these lipids plays an integral role in scaling body functions. They take involvement in the membrane domains and signaling, inflammation, cell proliferation, death, migration, and central nervous system development. Due to their discovery as potent messenger and signaling molecules, sphingolipids have lately attracted interest and are now thought to be potential therapeutic targets for a number of diseases. Here, we provide a thorough overview of sphingolipid metabolism and numerous biological functions inside the cell. Additionally, we draw attention to the sphingolipid involvement in a number of diseases, such as cancer, cystic fibrosis, and inflammatory disease, Alzheimer's disease, Parkinson's disease, and diseases related to lysosomal storage.

**KEYWORDS**

*Sphingolipids*; *Sphingosine-1-phosphate*; *Ceramide*; *Glycosphingolipids*; *Diseases*

## Introduction

For almost a century, the sphingolipid (SL) family of lipids was thought to be structural, but during the last 20 years, they have been identified as bioactive molecules with distinct and important physiological roles[1,2]. The first sphingolipids were isolated from brains by Thudicum in the late 19th century. Because of "the many enigmas which it presented to the inquirer", he termed the substance "sphingosin", after Sphinx from the Greek mythology[3]. All sphingolipids share the structural property that their backbones are made up of long-chain amino alcohol, or sphingoid, bases. Sphingosine and sphinganine, commonly known as dihydrosphingosine, are the two most common sphingoid bases in mammals. Other long-chain bases with distinct differences in structure are also known to exist.

Sphingomyelin and glycosphingolipids (GSLs), two categories of complex sphingolipids, were later defined. Research on sphingosine bioactivities began in the mid-1980s, followed by those on ceramides and sphingosine-1-phosphate (S1P). Further research linked ceramide-1-phosphate (C1P), glucosylceramide, lactosylceramide, and a few gangliosides as possible bioactive lipids. Sphingolipids are essential components of the plasma membrane of many different types of cells and play a number of roles in many cellular processes[2].

## Sphingolipid biosynthesis

Many studies have been carried out during the past few decades to determine the intracellular locations of sphingolipid synthesis and degradation, which are found in the lysosome and the endoplasmic reticulum (ER)/Golgi apparatus, respectively[4-6]. *De novo* biosynthesis of sphingolipids begins in the endoplasmic reticulum by condensation of serine and palmitoyl CoA with the enzyme serine palmitoyltransferase[7,8]. The reaction byproduct 3-ketosphinganine is converted to sphinganine[9,10]. Then, sphinganine N-acyl transferase, also referred to as dihydroceramide synthase, acylates sphinganine by adding various chain-length fatty acids to create dihydroceramide. Then, a 4-5 *trans* double bond is added by dihydroceramide desaturase (DES1) to produce ceramide. Ceramide serves as the building block for all complex sphingolipids, which are produced when different head groups are added to the ceramide chain at the C1 position (Fig. 1). To synthesize sphingomyelin (SM), phosphorylcholine is transferred from phosphatidylcholine (PC) to ceramide at the luminal leaflet (i.e., the side facing the Golgi lumen) of the Golgi apparatus[11]. As a

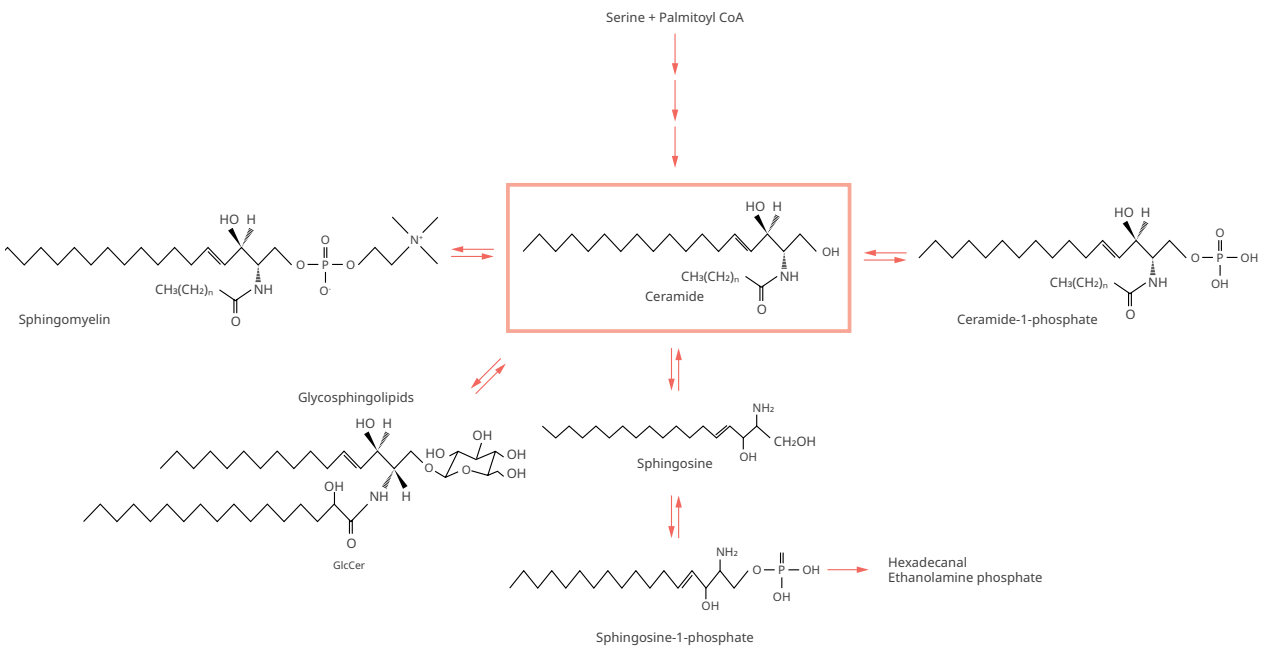


**Fig. 1.** Ceramide synthesis pathways (*de novo* pathway and salvage pathway).

category of complex SLs, the GSLs are structurally most diverse.

They are categorized as neutral (cerebrosides) or acidic (gangliosides). Galactose from a UDP-galactose donor is transferred to ceramide at the luminal leaflet of the endoplasmic reticulum membrane, the side facing the ER lumen, to form galactosylceramide (GalCer)[12,13]. The second destiny of ceramide is glycosylation to glucosylceramide (GlcCer), which occurs on the cytosolic leaflet of the Golgi apparatus[12,14]. Based on the sequential transfer of sugars by specific Golgi apparatus-based enzymes, hundreds of known GSLs are generated from the precursors GalCer and GlcCer[13]. GSLs are transported to the plasma membrane by vesicular transport after synthesis[4]. In order to produce other sphingolipid species such as C1P, ceramide functions as a precursor for ceramide kinase, which is mostly located in the trans-Golgi but is also present in the plasma membrane. Ceramide can be deacylated by ceramidases to produce free fatty acid and sphingosine[15,16]. It is known that various ceramidase isoforms have a specific affinity for ceramides with specific fatty acid chain lengths and can function at acidic, neutral, or alkaline pHs. Sphingosine can be further phosphorylated to form S1P with the enzymes sphingosine kinase 1 and 2 (Sphk1 and 2)[17]. While Sphk1 is primarily a cytosolic enzyme, Sphk2 is present in both the nucleus and the cytosol. Since S1P is a crucial first and second messenger, its level must be regulated. Microsomal S1P-specific phosphatases (SPP) do this, and cytosolic S1P at the endoplasmic reticulum can be dephosphorylated by S1P-phosphatases 1 and 2 (SPP1 and SPP2)[18,19]. However, S1P lyase (SPL) has the ability to convert S1P into two non-SL commodities, hexadecanal and ethanolamine phosphate[20,21].

## Sphingolipid catabolism

Like the stepwise creation of sphingolipids during biosynthesis, their degradation proceeds in the opposite way, with products acting as substrates. Specific lysosomal enzymes degrade complex SL. Sphingolipids are transported from the plasma membrane to the site of their degradation by endocytic pathways[22,23]. Hydrolases that function at neutral or alkaline pH levels can also be used to hydrolyze SLs non-lysosomally[24-26]. Degradation of sphingomyelin yields ceramide and free phosphocholine. It is mediated by three different sphingomyelinases (SMases): neutral, acidic, and alkaline[24,25]. After sugar residues of GSLs have been cut away by lysosomal glycosidases from the nonreducing end, the remaining fatty acids and sphingoid bases are degraded or recycled by the salvage pathway. Since their hydrolyzing enzymes have difficulty accessing GSLs with short carbohydrate chains (four or fewer sugars) in the intralysosomal membrane, lysosomal lipid binding proteins (LLBP) are required for further assistance. These auxiliary proteins include the ganglioside M2 (GM2) activator protein (GM2AP), which is expressed by the *GM2A* gene, and the four saposins (A-D), which are generated by proteolysis from a common precursor protein known as prosaposin (PSAP)[22,27]. The role of GM2AP and saposins is to solubilize and bind GSLs so that the appropriate hydrolases may break them down. Complex sphingolipid degradation results in SL metabolites, some of which can be regenerated back into the SL pathway and used in the SL synthesis salvage process[28,29]. All complex sphingolipids are based on ceramide, which is also the end product of their degradation. Ceramide can be catabolized to sphingosine by ceramidases or phosphorylated by ceramide kinase to form ceramide-1-phosphate[16,30,31]. Sphk1 and 2[32] can phosphorylate sphingosine generated from ceramide to S1P, or it can be recycled *via* the salvage pathway and used again to make ceramide and complex sphingolipids[29].

## Sphingolipid functions

Apart from being the fundamental components of cellular membranes, sphingolipids have various other significant functions. Unique structures of sphingolipid species affect the permeability, structure, and fluidity of the membranes that contain them[33,34]. Numerous studies have demonstrated enrichment of sphingolipids in certain membrane regions, particularly in the plasma membrane. The membrane rafts of nervous system cells contain high quantities of sphingolipids, particularly SM and GSLs[35]. Complex GSLs have a crucial role in cell physiology as they serve as antigens, adaptors of cell adhesion, growth factors and microbial toxin binding agents, and modulators of signal transmission. Ceramides are crucial for structural stability of cell membranes because they are found in large quantities in caveolae and because they are involved in cell signaling. Ceramides are associated with cell differentiation and inflammatory responses, as well as apoptosis and cell cycle arrest[36]. Lipid research has placed a lot of emphasis on ceramide because of the evidence that suggests it is an apoptotic intermediate. Interleukin (IL)-1, IL-1β, nitric oxide, heat shock, ionizing radiation, oxidative stress, and tumor necrosis factor (TNF)-α are a few examples of extrinsic stimuli that raise intracellular ceramide levels and trigger apoptosis. Degradation of complex sphingolipids or *de novo* synthesis can also result in increased ceramide levels within cells[37,38]. Ceramide induces programmed cell death by means of protein phosphatases 1 and 2A, protein kinases (such as protein kinase C), and proteases (such as cathepsin D and caspases)[39,40]. Compared to ceramide, which is primarily thought to be a growth-inhibitory and/or pro-apoptotic lipid, S1P primarily serves as an anti-apoptotic, pro-survival messenger[41]. S1P is released by a variety of cells, such as mast cells, platelets, and monocytes. Since S1P is a charged sphingolipid, it requires the help of membrane transporters for crossing the cell membrane[42]. S1P functions by either interacting with targets within the cell or being exported from the cell for paracrine interaction, typically with members of the G-protein-coupled S1P receptor family[42,43]. S1P is the most interesting SL since it functions as a first and second messenger. As a first messenger, it controls a wide range of functions, including angiogenesis, lymphocyte trafficking, cell migration, and vasculature maturation[44,45,46]. As an intracellular second messenger, S1P controls calcium homeostasis, cell division, carcinogenesis, and suppression of apoptosis[47,48]. It is an essential physiological mediator of homeostasis, particularly in the neurological, vascular, and immune systems[49]. In many of the pathways in which it is implicated, particularly those related to cell growth and survival, S1P appears to have opposing effects to ceramide. Both sphingosine kinase 1 and 2 serve as important enzymes in this process. While SphK1 is associated with antiapoptotic and mitogenic activities, SphK2 has a pro-apoptotic role[50]. The actions of S1P and C1P are alike, while ceramide and sphingosine appear to work similarly[51]. It was found that S1P and C1P were both involved in cell migration[36,52]. According to the study, ceramide and sphingosine have also been linked to inflammation[53]. In contrast, there are signs that S1P has an anti-inflammatory function according to a study by Fettel *et al.*[54]. The antiapoptotic characteristics of C1P suggest that sphingosine kinase 1 and ceramide kinase are both essential to maintaining a delicate balance between cell death and life. This suggests that the balance between survival and death may depend on the maintenance of an equilibrium between the intracellular levels of each of these interconvertible SLs. GSLs are widely expressed in membrane domains and support a variety of functions, including cell-cell signaling[55]. The function of gangliosides in cell differentiation and proliferation has been well studied. They also oversee and regulate several of growth factor receptors[56]. Substantial evidence indicates that gangliosides have additional roles beyond their known role

as toxin receptors, such as antigens, mediators of cell adhesion, and modulators of signal transduction[57,58]. Sphingolipid profiles are known to alter dramatically during development of the human central nervous system, indicating a role of these lipids in the construction and functioning of the nervous system[59].

## The role of sphingolipids in pathophysiology

### Metabolic diseases

The comorbidities of obesity, steatosis, type 2 diabetes (T2D), non-alcoholic steatohepatitis (NASH), and major adverse cardiac events have been linked to serum and tissue levels of sphingolipids (ceramides and/or dihydroceramides), according to unbiased analyses of large metabolomics and lipidomics datasets from patients[60-63]. Recent findings show that abnormal sphingolipid synthesis and composition are encouraged in skeletal muscle, pancreas, and adipocytes when plasma free fatty acid levels are raised. It is likely that additional pathways, including oxidative stress, inflammatory and endocrine signaling, are involved in the mechanisms that lead to disruptions in sphingolipid metabolism. Increased ceramide levels have been shown in cell and *in vivo* experiments to attenuate the action of insulin, most likely through inhibition of Akt. An elevated level of ceramide is thought to have an inhibitory effect on glucose uptake because it affects Akt, which is known to stimulate glucose translocation to the cell membrane, among other things[64]. This process causes insulin resistance to develop, worsen, and eventually result in T2D. Ceramide capacity to inhibit phosphorylation and activation of Akt/protein kinase B, a serine/threonine kinase that is a key modulator of insulin action, is primarily responsible for its inhibitory effect on insulin signaling[65]. There is apparently a relationship between a decrease in ceramide levels and an improvement in insulin sensitivity[66]. By using inhibitors of SPT or dihydroceramide desaturase to reduce ceramide production *in vivo*, insulin signaling, glucose and lipid metabolism, as well as metabolic abnormalities and heart dysfunction linked to obesity are all improved[67,68]. Ceramide build-up in the liver, spleen, muscle, and adipose tissue is linked to numerous metabolic processes that underlie T2D and its adverse effects. Pancreatic ß cells undergo apoptosis and lose some of their activities because of ceramide accumulation. Hepatic steatosis caused by C16:0 ceramide is attributed to decreased insulin sensitivity and glucose metabolism[69].

Its overabundance causes inflammation, decreased thermogenesis capacity, and adipose tissue lipid storage, which results in malfunction and is the cause of lipotoxic cardiomyopathy[70,71]. Insulin resistance linked to obesity is facilitated by the accumulation of C18:0 ceramide in skeletal muscle[72]. Several research works have demonstrated that pharmacological reduction of increased ceramides inhibits or even stops advancement of metabolic disorders in mouse models[73]. Nevertheless, rather than their absolute mass in and of themselves, current evidence suggests that subcellular location and/or particular pools of various species of ceramides have a role in disease processes. There is compelling evidence from several studies that long-chain and very-long-chain ceramides have different roles. The various biological impacts noted, however, might potentially be explained by features of ceramides other than their catalytic function, such as subcellular location, induction under high-fat eating, etc.

Furthermore, it has been demonstrated that the ceramides found in low-density lipoprotein particles are sufficient to cause insulin resistance[74]. Like ceramide, additional sphingolipids have also been

linked to the pathophysiology of diabetes, such as glucosylceramide and sphingomyelin[75,76].

Despite an abundance of evidence connecting ceramide increase to the emergence of metabolic disorders, the underlying mechanisms are still poorly understood. It is now widely acknowledged that ceramide causes insulin resistance in the majority of tissue types by inhibiting insulin-stimulated Akt, a crucial serine/threonine kinase that controls gluconeogenesis in the liver and glucose absorption by muscle and adipose tissue[64,77]. When considered collectively, the research indicates that ceramide formation inhibition provides a considerable level of protection. This offers strong support for the creation of powerful pharmacological inhibitors of important enzymes involved in *de novo* sphingolipid biosynthesis.

Ceramide is degraded by ceramidases to sphingosine, which is then phosphorylated by SphKs to generate S1P, as was previously indicated. In addition, S1P is a strong signaling molecule on its own. S1P metabolic functions have also become evident. Important enzymes called SphKs control the concentrations of many bioactive sphingolipid metabolites. A crucial feature of this phosphorylation is the ability of S1P to undergo irreversible degradation, which lowers the load of ceramides and sphingosine overall. Thus, the elimination of excess ceramide may be one of the SphKs roles in metabolic diseases. Different from SphK1, which is found in the cytosol and moves to the plasma membrane when activated, SphK2 is found in various intracellular compartments, such as the nucleus and mitochondria, based on the kind of cell[78].

A number of ATP-binding cassette transporters and the key facilitator superfamily member SPNS2 can carry intracellularly produced S1P out of cells, where it binds S1PR1-5, which mediates signaling in a variety of cell types, in an autocrine or paracrine manner. While S1PR4 is mostly expressed in the immune system and S1PR5 in the central nervous system, S1PR1-3 are found everywhere. Various Gα subunit profiles are linked to these receptors.

Despite these advantageous functions, SphKs and S1P also have harmful ones, most likely as a result of their established impacts on proinflammatory signaling and immune cell trafficking[78]. An excess of saturated fatty acids causes the livers of mice and NASH-afflicted people to overexpress SphK1. Hepatocyte sphingosine-1-phosphate receptor 1 (S1PR1) signaling is subsequently triggered by S1P, which causes NF-kB activation, increased cytokine/chemokine synthesis, and immune cell infiltration[79].

Blood contains high concentrations of S1P, primarily transported by the liver produced HDL-associated apolipoprotein M (ApoM)[78]. Apart from its widely recognized role in removing excess cholesterol, HDL/ApoM linked S1P signaling *via* S1PRs is accountable for several advantageous impacts of HDL, including reduction of inflammation and apoptosis, as well as vasoprotection[80]. ApoM/S1P has been proposed to slow down the onset of insulin resistance by activating Akt and AMPK, which are the primary insulin signaling pathways in the liver, adipose tissue, and skeletal muscle, *via* S1PR1 and/or S1PR3. It may also enhance mitochondrial processes by upregulating SIRT1 protein levels[81]. T2D and metabolic diseases are associated with S1PR signaling in endothelial cells and macrophages.

Endothelial cell S1PR1 is activated by HDL-ApoM-S1P, which also promotes phosphorylation of endothelial nitric oxide synthase (eNOS) in an Akt-dependent manner. Nitric oxide (NO) is produced, which is a crucial regulator of vasorelaxation[82]. Lower S1P and a diminished capacity to activate eNOS and inhibit NF-kB-mediated immune responses were seen in HDL from T2D patients[83]. Likewise, HDL from individuals with non-diabetic metabolic syndrome exhibited decreased S1P and a diminished capacity to activate Akt and eNOS; however, these outcomes may be restored with S1P enrichment[84].

All of these findings point to a possible role of lower S1P in the reduced HDL functionality and antiatherogenic properties in these individuals.

Conversely, in a diabetes-modeling mouse, elevated tumor necrosis factor-alpha (TNF-α) in vascular smooth muscle resulted in S1P-dependent enhanced myogenic tone, indicating that S1P might possibly be involved in microvascular problems associated with diabetes[85].

Together, these findings show that cell type, S1PR signaling effectors, and S1P production and degradation influence S1P diverse actions. Furthermore, a number of studies have discovered that T2D, obesity, and other metabolic disorders are associated with changed levels of additional sphingolipid species, such as glucosylceramides, sphingomyelins, and ganglioside GM3[86,87].

A great deal of questions remain unanswered. Few direct targets of certain ceramides or dihydroceramide species have been found, and even less is known about their mechanisms of action in metabolic disorders, despite the fact that S1PRs and S1P intracellular targets are well-understood. Understanding the roles of important dihydroceramide/ceramide species requires discovery of new molecular targets and processes. Furthermore, it is still unknown if particular dihydroceramide species solely serve as indicators of elevated *de novo* ceramide biosynthesis or function as the primary regulators of metabolic disorders.

Furthermore, it is yet unclear how certain ceramide species or S1P function in the etiology of certain diseases. Assigning specific activities to various sphingolipid species is a difficult undertaking because these bioactive sphingolipid metabolites are intermediates in the formation of complex sphingolipids and are rapidly interconvertible. This presents a difficulty for the field.

To measure the sphingolipidome in human patients, preclinical research employs pharmacological tools, mouse models, and advanced mass spectrometry methods. These methods support the idea of developing new therapeutic approaches that target specific S1PRs or reduce ceramide biosynthesis by inhibiting sphingolipid desaturase enzyme (DES1) or a specific ceramide synthase (CerS), for example, in order to combat metabolic disease. Determining how these bioactive sphingolipids influence the development of disease will require mechanistic research on the activities of ceramide, sphingosine, and S1P with a focus on specific tissues and organelles. The creation of feasible treatment targets and strategies could greatly benefit from deeper comprehension of the sphingolipid synthesis and degradation, as well as how metabolic changes influence these processes.

Vascular diseases, such as atherosclerosis and ischemic injury, have been linked to sphingolipids, particularly ceramide and sphingosine. A higher acid sphingomyelinase (aSMase) activity and ceramide levels have been associated with atherogenesis. A strong clinical argument is emerging for the usefulness of serum sphingolipid (ceramides) measurements as markers of metabolic disorders and atherosclerotic cardiovascular illnesses.

## Cancer

Metabolic enzymes play an essential function in controlling the amount of sphingolipid molecules in the human body. Changes in their expression or activity can induce either cancer cell death or survival. Therefore, changes in sphingolipid metabolism are associated with various types of cancer. Normal cell activity depends on the balance of bioactive sphingolipids, including pro-apoptotic ceramide and sphingosine, as well as pro-proliferative C1P and S1P. Ceramide accumulation primarily causes antiproliferative signaling and cancer cell death in many tumors[88], but depending on the downstream signaling targets, it may also have proliferative effects. Overexpression of the enzymes that direct ceramide metabolism toward the synthesis of proliferative sphingolipid species is frequently observed in the development of cancer. Thus, it has been observed that many cancer types have increased expression of ceramide kinase, ceramidases, and SphK1 and 2.

Numerous researches indicate that altering the innate S1P:ceramide ratio is essential to regulate the survival and death of cancer cells[89]. Depending on the type of tissue and cell, ceramide synthase regulates ceramide species differently, indicating that ceramide functions variably in various types of cancer. Additionally, ceramide is produced when sphingomyelinase hydrolyzes sphingomyelin. Data are consistent with the hypothesis that ceramide, which is produced when sphingomyelinase hydrolyzes sphingomyelin, mediates tumor suppression, growth arrest, and/or death of cancer cells. Ceramide or its analogs, for instance, have been demonstrated to have an anti-tumor effect and to induce apoptosis in cancer cells and cancer cell lines when administered directly[90,91]. Ceramide is metabolically converted to S1P. Bioactive lipid mediator S1P regulates a number of biological processes, such as cell motility, proliferation, and survival, by acting as a signaling molecule for cells and becomes interesting in terms of involvement in the pathogenesis of carcinoma. According to a prior study, S1P, which is generated by SphK1, plays a critical role in mediating angiogenesis, lymphangiogenesis, and metastasis promotion induced by breast cancer[92]. Additionally, it was discovered to be overexpressed in a number of different tumors, such as colon cancers, and to be a sign of a bad prognosis and decreased chance of patient survival[93].

## Lysosomal storage disorders

A set of inherited metabolic diseases, including various lysosomal storage disorders (LSDs), can manifest in infantile, juvenile, or adult life stages. Mutations leading to the absence of a hydrolytic enzyme that breaks down sphingolipids and consequent cell apoptosis are the cause of LSDs. Despite their ability to arise in a variety of cell types, the central and peripheral nervous systems are most susceptible[94]. Gaucher disease, Niemann-Pick disease, GM1 gangliosidoses, and GM2 gangliosidoses are a few of the identified lysosomal diseases or sphingolipidoses.

## Neurodegenerative diseases

Sphingolipids are thought to be involved in certain neurodegenerative diseases since they are necessary for cell signaling and structure of the neuronal membrane. Genetic mutations resulting in altered sphingolipid metabolism can cause aberrant sphingolipid deposition in neural tissue, which can cause severe cognitive impairment[95]. Parkinson's disease (PD), Alzheimer's disease (AD), and depression are among the neurological conditions that have been linked to sphingolipid disbalance[23,96,97].

Parkinson's disease is characterized by abnormalities in autophagy, endosomal trafficking, and mitochondrial function, all of which are regulated by sphingolipids. Sphingolipids, and ceramide in particular, are essential for a number of cellular functions linked to PD[98,99]. Ceramide changes have been found in both PD patients and PD models in recent research, indicating an important link between sphingolipids and associated cellular functions in PD[100].

There is growing evidence that disruptions in the sphingolipid metabolism are important in the pathogenesis of AD[101]. According to a report, sphingomyelin and S1P levels are lower in the brain tissue of AD patients than in controls, but ceramide levels are higher[102,103]. Furthermore, abnormal expression was seen in the sphingolipid pathway enzymes that regulate the synthesis of ceramides[104]. Changes in the sphingolipid metabolism were also detected in plasma, indicating that AD patients had higher amounts of ceramide and less sphingomyelin than controls[105,106]. Methods for pharmacologically lowering ceramide levels in the brain are discussed, with a focus on ceramide, the primary product of the sphingolipid pathway. The possibility of using sphingolipid metabolism as a

model to create novel AD therapeutic techniques is up for discussion. The evidence supporting the use of sphingolipid metabolism modification as a legitimate therapeutic strategy for AD is increasing[106].

### Inflammatory diseases

Sphingolipids play a crucial role in regulating the inflammatory response, which is an important contributor to diseases such as inflammatory bowel disease (IBD), asthma, and cystic fibrosis (CF). Through a number of ways, sphingolipids may play a role in the pathophysiology of CF. In CF mice, Teichgräber *et al*. found that ceramide was a crucial modulator of infection and inflammation[107]. The development of emphysema and pulmonary cell apoptosis have been linked to upregulated ceramide levels[108,109]. It was found that alveolar cell apoptosis was inhibited by *de novo* ceramide synthesis inhibition. Additionally, it was found that activating S1P signaling prevents lung apoptosis, suggesting that a balance between ceramide and S1P levels influences alveolar cell survival[109]. As ceramide and S1P have been connected to inflammation in asthma, further study is needed in this area[110].

Furthermore, a number of sphingolipids are essential for the proinflammatory response seen in IBD, which could be brought on by mutations in the IL6 gene, which codes for IL-6[111]. In experimental models of Crohn's disease and chronic colitis, it was discovered that SM and ceramide levels were significantly elevated. In IBD, sphingosine, S1P, and C1P levels are also higher, which can be explained by increased neutral ceramidase (nCDase) activity and elevated SphK1 expression, respectively[112,113].

Numerous sphingolipid analogs, modulators, and inhibitors have been developed in order to target the sphingolipid metabolic pathway. Research is being conducted on their therapeutic potential and efficacy in IBD and other diseases.

## Conclusions

Due to the great interest in sphingolipids during the last few decades, in this review we have attempted to provide an insight into the main properties and functions of biologically active sphingolipids. Sphingolipids are important bioactive lipids that are involved in multiple cellular pathways and in the pathogenesis of a number of diseases. Because of this, modifying their metabolic pathways may open up novel possibilities for therapeutic intervention. ■

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**SAŽETAK**

## Sfingolipidi u zdravlju i bolesti

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Sfingolipidi su složena skupina lipida koji postaju sve važniji u mnogim aspektima bolesti i stanične fiziologije. Sastoje se od dugolančane sfingoidne baze kao okosnice, dugolančane masne kiseline povezane amidnom vezom i jedne ili više polarnih skupina strukture kojih karakteriziraju različite podtipove sfingolipida kao što su ceramid, sfingomijelin i glikosfingolipidi. Metabolizam ovih lipida ima važnu ulogu u tjelesnim funkcijama. Uključeni su u membranske domene i signalizaciju, upalu, proliferaciju smrt stanica, migraciju te razvoj središnjega živčanog sustava. Zbog otkrića da se radi o snažnim glasničkim i signalnim molekulama u novije vrijeme postoji sve veće zanimanje za sfingolipide te se smatraju i potencijalnim terapijskim ciljevima za niz bolesti. Ovdje dajemo pregled metabolizma sfingolipida i brojnih bioloških funkcija unutar stanice. Usto ukazujemo na mogućnost uključenosti sfingolipida u nizu bolesti kao što su rak, cistična fibroza, upalne bolesti, Alzheimerova bolest, Parkinsonova bolest i bolesti povezane s lizosomskim skladištenjem.

**KLJUČNE RIJEČI**

*Sfingolipidi; Sfingozin-1-fosfat; Ceramid; Glikosfingolipidi; Bolesti*