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Review

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Sphingolipid Mediators of Myocardial Pathology

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ABSTRACT

Cardiomyopathy is the leading cause of mortality worldwide. While the causes of cardiomyopathy continue to be elucidated, current evidence suggests that aberrant bioactive lipid signaling plays a crucial role as a component of cardiac pathophysiology. Sphingolipids have been implicated in the pathophysiology of cardiovascular disease, as they regulate numerous cellular processes that occur in primary and secondary cardiomyopathies. Experimental evidence gathered over the last few decades from both *in vitro* and *in vivo* model systems indicates that inhibitors of sphingolipid synthesis attenuate a variety of cardiomyopathic symptoms. In this review, we focus on various cardiomyopathies in which sphingolipids have been implicated and the potential therapeutic benefits that could be gained by targeting sphingolipid metabolism.

Keywords: Sphingolipids; Cardiomyopathy; Cardiomyocytes; Ceramides; Sphingosine-1-phosphate receptor

INTRODUCTION

Since their discovery over a century ago, sphingolipids have been increasingly acknowledged as key signaling molecules that regulate essential cell functions, with implications for a wide variety of diseases. In addition to their historically recognized function as essential components of eukaryotic cell membranes, modern research has elucidated their roles as signaling molecules that regulate apoptosis, autophagy, nutrient transport, organ homeostasis, and protein synthesis, as well as modulating classical signaling pathways by regulating kinases and phosphatases.[1] Aberrancies in these processes due to perturbed sphingolipid metabolism have been reported in diseases including obesity, type 2 diabetes mellitus (T2DM), neurodegenerative disorders, liver disease, cancer, and cardiovascular disease.[2,3] Numerous studies have demonstrated that dysregulated sphingolipid metabolism induces alterations in cardiomyocyte structure and function.[4-6] Moreover, sphingolipids are known to regulate crucial cell processes involved in cardiac structure and function, including apoptosis, autophagy, cell differentiation, and mitochondrial metabolism, suggesting that sphingolipids likely contribute to cardiomyopathy through these mechanisms. Therefore, the aims of this review are to summarize current knowledge regarding the contribution of

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sphingolipids to various cardiomyopathies and to discuss the current and future clinical potential of targeting sphingolipid metabolism.

Sphingolipids are defined by their sphingoid base, which is generated by condensation of an amino acid with an acyl-CoA. The sphingoid base serves as a 'backbone' upon which all sphingolipids are built, including ceramides, sphingosine-1-phosphate (S1P), sphingomyelins (SM), and glycosphingolipids. The sphingoid base (**Fig. 1A**, leftmost structure) can vary in structure depending on the amino acid and/or acyl-CoA used as substrate; for example, using serine and palmitoyl-CoA yields an 18-carbon sphingoid base (**Fig. 1A**), while utilization of serine and myristoyl-CoA or stearoyl-CoA yields sphingoid bases with 16- or 20-carbon bases (**Fig. 1A**), respectively. Additionally, recent studies have addressed variations in the amino acid used to form the sphingoid base, finding that replacing serine with alanine or glycine gives rise to structurally aberrant sphingoid bases.[7,10] Serine palmitoyltransferase (SPT) is a multi-subunit enzyme that catalyzes this initial reaction, which is the rate-limiting step in sphingolipid synthesis. The typical SPT enzyme is a heterodimer composed of serine palmitoyltransferase long chain base subunit (SPTLC) 1 and SPTLC2 subunits and condenses the 2-carbon serine with the 16-carbon palmitoyl-CoA to synthesize d18:0-dihydrosphingosine (DHS), an 18-carbon sphingoid base (**Fig. 1A**).[10] Palmitate-derived d18-base-containing sphingolipids are the most abundant, as several complex downstream sphingolipids including ceramide, hexosylceramides, SM, and S1P largely are built upon this 18-carbon backbone. In contrast, a heterodimer composed of SPTLC1 and SPTLC3 can also utilize the 14-carbon myristoyl-CoA, generating a subset of d16-based sphingolipids (**Fig. 1B**).[9] Although these sphingolipids are abundant in the myocardium, they remain understudied.[11] Acyl-CoA utilization can also be influenced by 2 SPT small subunits (ssSPTa and ssSPTb), which enable SPT to utilize stearoyl-CoA as a substrate, resulting in a subset of d20-backboned sphingolipids.[12,13]

Ceramide, which have been implicated in apoptosis, senescence, autophagy, and other cell processes, are generated from N-acylation of the sphingoid base with an additional acyl-CoA. The acyl-CoA molecules utilized vary widely, including medium-chain fatty acids (12–14 carbons), long-chain fatty acids (16–20 carbons), and very-long-chain fatty acids (22–26 carbons) in mammals. Ceramide exist in all of these variations and can even include ultra-long-chain fatty acids (≥26 carbons). In highly specialized organs, such as the skin, ceramide undergo numerous structural modifications, including hydroxylation, O-acylation, branching, methylation, and others. Ceramide can also be catabolized yielding a sphingoid base, which can be either re-acylated to ceramide (sometimes with a change in the N-acyl chain length) or phosphorylated to generate S1P, an important sphingolipid. Most sphingolipid metabolic pathways have enzymes that catalyze the forward and reverse steps, and altering the sphingolipid profile occurs through highly dynamic regulation of these processes. Additionally, once a sphingoid base is synthesized, the only way to catabolize sphingolipids to non-sphingolipid components is reduction of S1P by S1P lyase, yielding phosphoethanolamine and a fatty aldehyde. Depletion of the S1P lyase leads to a dramatic accumulation of sphingolipids, usually with deleterious effects. These pathways are presented in depth in **Fig. 1B**.

The *de novo* pathway is initiated in the endoplasmic/sarcoplasmic reticulum by SPT, a dimer composed of SPTLC1 and either 2 or 3 subunits. Each of these complexes can utilize palmitoyl-CoA, yielding d18:0 DHS. Additionally, the SPTLC1/3 complex can use serine and myristoyl-CoA to synthesize d16:0 DHS. The SPT complex can be regulated by small subunits

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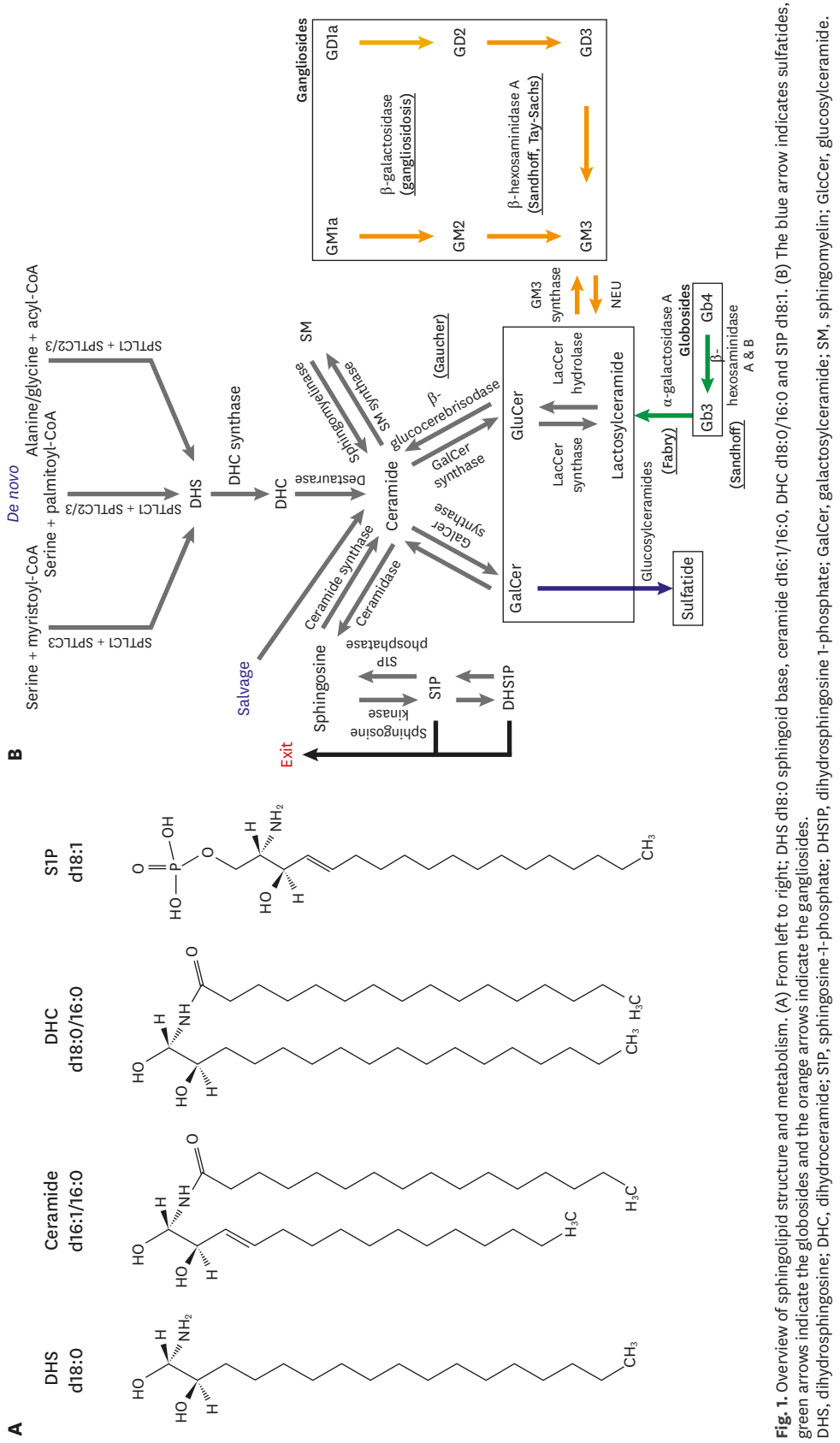

Fig. 1. Overview of sphingolipid structure and metabolism. (A) From left to right; DHS d18:0 sphingoid base, ceramide d16:1/16:0, DHC d18:0/16:0 and S1P d18:1. (B) The blue arrow indicates sulfatides, green arrows indicate the globosides and the orange arrows indicate the gangliosides.
DHS, dihydrosphingosine; DHC, dihydroceramide; S1P, sphingosine-1-phosphate; DHS1P, dihydrosphingosine 1-phosphate; GalCer, galactosylceramide; SM, sphingomyelin; GlcCer, glucosylceramide.

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to alter CoA utilization, including by enabling stearoyl-CoA to be used to generate d20:0 DHS. In terms of amino acid variations, alanine or glycine can be used instead of serine to generate aberrant sphingoid bases. Alterations in amino acid utilization result from mutations of SPT subunits and are largely pathological. DHS is the primary substrate for ceramide synthases, which generate dihydroceramides (DHCs) that are then reduced by DHC desaturase, yielding ceramide, which is used as the substrate for the synthesis of complex sphingolipids, including SM, galactosylceramide (GalCer), glucosylceramide (GlcCer), and ceramide 1-phosphate (not shown) via the enzymes indicated above. *De novo* synthesis of ceramide occurs in the endoplasmic reticulum, and then ceramide is modified in the Golgi apparatus. GlcCer is the predominant precursor of the ganglioside and globoside glycosphingolipids. Lactosylceramide (LacCer) is synthesized from GlcCer to form gangliosidosis and Gaucher disease in the ganglioside and globoside series. Diseases that have been observed in humans due to deficiencies in enzymes in these pathways are shown in parentheses, underlined, and in bold. GalCer is the predominant precursor of the sulfatide glycosphingolipids. Sphingolipid catabolism occurs in lysosomes and at the plasma membrane. SM is hydrolyzed by lysosomal acid sphingomyelinase (aSMase) or plasma membrane neutral sphingomyelinase (nSMase), GalCer by β-galactocerebrosidase, and GlcCer by β-glucocerebrosidase (both lysosomal), and each of these steps yields ceramide. Catabolism of ceramide by ceramidases yields sphingosine, which is phosphorylated by sphingosine kinases 1 and 2 (SphK1-2), yielding S1P. The salvage pathway of ceramide synthesis occurs when ceramide is cleaved by ceramidase and the resulting sphingosine is re-acylated by ceramide synthases.

SPHINGOLIPIDS IN PRIMARY CARDIOMYOPATHIES

In primary (idiopathic) cardiomyopathy, there is no secondary cause such as hypertension or diabetes; however, cardiomegaly, endocardial thickening, mural thrombosis, myocardial scarring, or other lesions may be present. Primary cardiomyopathies are classified as genetic or acquired and historically have been classified according to cardiac morphology. Genetic primary cardiomyopathies can be further subdivided into hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathy. Acquired primary cardiomyopathies are categorized as ischemic cardiomyopathy (ICM), peripartum cardiomyopathy (PPCM), or myocarditis.[14] Dysregulated sphingolipid metabolism has been observed and/or implicated in the following primary cardiomyopathies.

1. DCM

DCM is defined by the presence of left ventricular (LV) dilatation and systolic dysfunction or reduced ejection fraction; it is the end result of many cardiac insults, but a genetic etiology is also associated with DCM. Right ventricular dilation and dysfunction may be present, but are not necessary for the diagnosis of DCM.[15] The excessive accumulation of ceramide and SM within and around the heart has been associated with DCM.[16-18] A DCM hamster model demonstrated elevated levels of ceramide and SM in the LV.[19] Depletion of the antioxidant enzymes manganese superoxide dismutase and glutathione peroxidase-1 resulted in DCM, as well as findings of impaired mitochondrial function, increased ceramide levels, and increased levels of reactive oxygen species.[20,21]

2. ICM

ICM is a disease of the heart muscle induced by narrowing of the coronary arteries, most commonly in patients with a history of myocardial infarction, which is usually a

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manifestation of atherosclerotic coronary artery disease (CAD). Regardless of the cause, ICM ultimately leads to congestive heart failure. Risk factors for ICM include hyperlipidemia, diabetes mellitus, hypertension, obesity, age, sex (with females demonstrating cardioprotective effects), and genetics.

In addition to the ischemic injury itself, some damage occurs upon reperfusion. An ischemia-reperfusion (IR) injury occurs when blood supply returns to the heart tissue after ischemia. Patients with IR injuries and a mouse model of IR injury demonstrated decreased plasma DHS, sphingosine, S1P, and DHS 1-phosphate levels; moreover, the levels of circulating lysosomal aSMase and plasma membrane nSMase decreased, suggesting less ceramide production from catabolic pathways. Of note, the distribution of S1P, which circulates either bound to ApoM on high-density lipoprotein (HDL) or on serum albumin, was altered such that HDL-bound S1P was reduced and non-HDL-bound S1P was elevated in IR injury patients.[22-25] According to current thinking, some beneficial effects attributed to HDL may be mediated by S1P bound to HDL.[26]

Sphingosine is another important sphingolipid player in ICM and IR injury. Studies have shown cardioprotective effects of decreased sphingosine levels, suggesting that it acts as a cardiotoxin in IR injury.[22,27] Other studies have shown benefits of SphK1 in IR models, as it directly elevates S1P.[28]

3. Myocarditis

Inflammation of the myocardium is termed myocarditis, which often causes arrhythmias and contractility issues that gradually weaken the myocardium over time. The most common causes of myocarditis are adenovirus infection (the common cold) or coxsackievirus B3 (CVB3) infection. [29-31] Viral myocarditis caused by dengue, the West Nile virus, or hepatitis C leads to altered host sphingolipid metabolism, which is thought to be advantageous for viral propagation.[32-34] An acute viral myocarditis mouse model showed higher levels of DHS, d18:0/14:0 ceramide, and d18:1/22:0 and d18:0/16:1 SM than observed in the control group, suggesting that the CVB3 virus alters sphingolipid metabolism to enhance its propagation in the host.[35,36] Furthermore, evidence also suggests that autoimmunity plays an important role in myocarditis.[37-39] Previous studies have shown that CD4 T cells, macrophages, and inflammatory cytokines accumulate in cases of myocarditis.[40,41] As S1P is a potent pro-inflammatory lipid, multiple studies have used either S1P receptor (S1PR) agonists or SphK1 inhibitors to treat myocarditis, as further discussed below.

SPHINGOLIPIDS IN SECONDARY CARDIOMYOPATHIES

Secondary cardiomyopathies are diagnosed as a comorbidity of many primary diseases that affect the endocrine system, lysosomal storage, endomyocardial function, or neuromuscular function. Hypertension and tachycardia can also cause secondary cardiomyopathies.

1. Endocrine and metabolic disorders

Diabetic cardiomyopathy (DbCM)

DbCM, which develops in many patients with T2DM, manifests as cardiac hypertrophy in the absence of traditional heart disease risk factors such as hypertension, valve disease, and tachycardia and can lead to heart failure.[42-46] T2DM has a characteristic pattern of dyslipidemia including increased low-density-lipoprotein cholesterol levels,

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hypertriglyceridemia, and reduced HDL cholesterol concentrations.[47] It is thought that these changes promote the accumulation of lipid intermediates in the heart, a phenomenon known as cardiac lipotoxicity. Several animal models of myocardial lipotoxicity have demonstrated protective effects of inhibited sphingolipid synthesis, suggesting that sphingolipids play a major role in DbCM. For example, in a lipotoxic cardiomyopathic mouse model with cardiac-specific overexpression of glycosylphosphatidylinositol-anchored human lipoprotein lipase, it was observed that ceramide levels increased by 45% compared to control mice.[17] Importantly, correcting sphingolipid profiles using an SPT inhibitor or SPTLC1 heterozygous mice improved cardiac function and prolonged survival through reduced ceramide and SM levels.[17,48,49] Moreover, our laboratory demonstrated that high saturated-fat feeding induced a DbCM-like condition in mice, which was completely ameliorated by pharmacological inhibition of sphingolipid synthesis. In primary cardiomyocytes, cell hypertrophy in response to saturated fatty acids was shown to require ceramide synthase 5 (CerS5), which generates medium- and long-chain (e.g., C14–C16) ceramides.[50-54] This was the first identification of a specific ceramide synthase and ceramide species involved in cardiac hypertrophy, which in this case occurred through autophagy-dependent mechanisms. In additional support of a role for specific fatty acids in cardiac hypertrophy, an intriguing study in a Burmese python model demonstrated that adaptive post-prandial cardiac hypertrophy was mediated by a combination of myristate (C14:0), palmitate, (C16:0), and palmitoleate (C16:1).[55] Importantly, the myocardium contains detectable levels of sphingolipids with a C16:1 base, derived from the utilization of myristate by the SPTLC1/3 complex; however, we demonstrated that, in contrast to canonical d18-based sphingolipids, this class of sphingolipids with a shorter sphingoid base caused apoptosis, suggesting a critical need for precise regulation of these lipids, of which the constitutive roles remain unknown.[11]

Studies have demonstrated additional roles for myocardial ceramides in diabetes, including mitochondrial dysfunction and AKT inhibition, presumably via increased oxidative stress and inhibition of insulin signaling, respectively. The glycosphingolipid GlcCer acts independently from ceramide in impairing insulin signaling, which leads to insulin resistance, although the mechanisms have not been fully elucidated.[56-62] In models of DbCM, ceramide has been shown to activate classic protein kinase C (PKC) isoforms to attenuate insulin-stimulated AKT translocation; in addition, we and others have shown that aberrant ceramide production induces reactive oxygen species and impairs mitochondrial function. Additionally, ceramide was shown to activate p38, thereby inhibiting AKT and c-Jun N-terminal kinase (JNK), and resulting in activation of pro-apoptotic B-cell lymphoma 2 associated X protein (BAX) signaling and hypertrophy.[56-62]

Hyperthyroidism

The diagnosis of hyperthyroidism is confirmed by elevated secretion of the thyroid hormone, triiodothyronine (T_3) and/or thyroxine (T_4), in the blood. T_4 is converted into the more active form T_3 in multiple organs including the thyroid, liver, gut, and skeletal muscles. Cardiomyopathy associated with hyperthyroidism is not unique, and mostly mimics cardiac hypertrophy or in rare cases, DCM.[63-65] T_3 is a key regulator of cardiac physiology that also modulates sphingolipid metabolism. Prolonged treatment with T_3 led to a prominent increase of DHS, sphingosine, ceramide and SM levels, but decreased S1P levels, in cardiomyocytes taken from the LV of male mice.[66] Consistent with this, data demonstrated that T_3 treatment reduced the activity of nSMase, but caused no change in ceramidase activity, which would be required to generate sphingosine as a substrate for SphKs.[66]

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2. Lysosomal storage

Many lysosomal storage diseases arise from impaired catabolism of complex sphingolipids including SM and glycosphingolipids; these conditions are also termed 'sphingolipidoses.' Many of these diseases demonstrate a cardiac phenotype; however, there is currently little to no mechanistic information linking specific sphingolipids to these observed disease phenotypes.

Gaucher disease

Gaucher disease, the most common sphingolipidosis, is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme acid-β-glucosidase or glucocerebrosidase. This leads to accumulation of GlcCer, a metabolic intermediate derived from the turnover of ganglioside and globosides, in the lysosomes of macrophages of many organs. In the most extreme cases, GlcCer accumulation occurs in the heart. Gaucher disease is divided into 3 types (GD1-3), depending on the severity and onset of neurological symptoms. Gaucher disease can cause severe congestive cardiomyopathy (Gaucher disease cardiomyopathy, GDC), which has only been observed in adults with GD3.[67-69] GDC is associated with cardiac hypertrophy and mitral and aortic valve calcification.[70-75] In a macrophage model of Gaucher disease, it was shown that although the lysosome is the primary site of GlcCer accumulation, at very high levels of GlcCer, it is distributed among various subcellular locations. This cellular saturation of GlcCer leads to increased levels of ceramides and other glycosphingolipids,[76] which interfere with other biochemical pathways and lead to cell dysfunction and the pathologies observed in Gaucher disease. Generally, enzyme replacement therapy has been successful in Gaucher disease, as further discussed in the section of this review focusing on the therapeutic modulation of sphingolipids.

Anderson-Fabry disease

Anderson-Fabry disease is an X-linked recessive genetic disorder caused by deficiency of lysosomal enzyme α-galactosidase A, which catabolizes globotriaosylceramide, GalCer, LacCer, and other neutral glycosphingolipids. This causes progressive intracellular lysosomal accumulation of these lipids, primarily in the skin, kidneys, and heart.[77] Fabry disease cardiomyopathy (FC) has been reported in up to 6% of men and 12% of women with Fabry disease, and in some individuals FC may be the sole manifestation of the disease.[68,78,79] FC is characterized by progressive symmetrical or concentric left ventricular hypertrophy (LVH), with progressive evolution towards heart failure.[80-83] Most patients with FC are previously misdiagnosed with primary HCM, specifically LVH.[84] A 2006 study found that endomyocardial glycosphingolipid deposition caused enlarged myocytes. Furthermore, ventricular walls became progressively more rigid, impeding ventricular filling. Ultimately, FC patients suffer from heart failure with preserved ejection fraction.[45,85-87] Fabry disease has also been associated with RCM, though this link has not been thoroughly studied.[15] Many therapeutics are available to treat Fabry disease, as discussed in a later section.

Gangliosidosis

The terminal β-galactosyl residues of GM1 gangliosides are hydrolyzed by β-galactosidase. In GM1 gangliosidosis, which is heritable, a lack of β-galactosidase leads to massive accumulations of the GM1 ganglioside, mainly in the central nervous system, but also in the heart. Cardiomyopathy has been reported to be present in 34% of patients with infantile (type I) GM1 gangliosidosis and in 38% of patients with juvenile (type II) or adult (type III) GM1 gangliosidosis. [90-96]

There are 2 types of GM_2 gangliosidosis. Type I, Tay-Sachs disease, results from deficiency of hexosaminidase A, and type II, Sandhoff disease, from a deficiency of hexosaminidase

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A and β-N-acetyl hexosaminidase. Patients with Tay-Sachs disease have accumulations of GM3/GD3 gangliosides, mainly in the brain and rarely in the heart.[97,98] In Sandhoff disease, also called GM2 gangliosidosis, the β-galactosidase A and B enzymes are deficient, leading to accumulation of GM3/GD3 gangliosides. The GM2-ganglioside storage disorders are heritable diseases, which are essentially neurodegenerative diseases of early infancy.[95,99] If cardiomyopathy is present, the cardiological symptoms are very similar to those described above for GM1-gangliosidoses.[100,101]

As stated above, little is known about the mechanisms linking sphingolipidoses to the cardiac pathophysiology observed in these disorders. However, several other storage disorders—Krabbe disease; Niemann-Pick disease types A, B, and C; Farber disease, and hemochromatosis—cause cardiomyopathy very infrequently, if at all. This suggests that the mechanisms of sphingolipidosis-associated cardiomyopathies are linked to specific metabolic pathways and do not result from non-specific mechanisms, such as overall alterations in cell ultrastructure.

3. Neuromuscular disorders

Muscular dystrophy

There are 9 types of muscular dystrophy, of which only 5 cause secondary cardiomyopathy. Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), Emery-Dreifuss muscular dystrophy, Limb-Girdle muscular dystrophy (LGMD), and trinucleotide/tetranucleotide-repeat muscular dystrophy (DM1 and DM2) all exhibit DCM as a cardiac complication. Additionally, DMD, BMD, and LGMD may also cause ARVC, whereas DM1 and DM2 may also result in cardiac hypertrophy.[102] Upregulation of S1P and/or the SPT enzyme, genetically or through a pharmaceutical agent, reduced muscle degeneration or prevented muscle wasting in a dystrophin mutant (DMD or BMD) Drosophila model; however, it was not tested whether these interventions could reverse the pathology of DCM. Reducing the expression of the S1P transporter, spinster 2 (Spns2), which transports intracellular S1P to the extracellular compartment, thereby reducing intracellular S1P, also suppressed dystrophic muscle degeneration, suggesting that intracellular S1P suppresses muscle degeneration.

Mutations in caveolin-3 (CAV3) underlie LGMD, which can cause secondary cardiac arrhythmias or ARVC. CAV3 is a muscle-specific caveolin, unlike CAV1 and CAV2, found in the skeletal and cardiac muscles; it also organizes and concentrate glycosphingolipids within the caveolar membrane.[103,104] Therefore, in LGMD it is likely that sphingolipids are highly dysregulated due to CAV3 mutations, which could open new avenues for therapeutic interventions aimed at modulating membrane sphingolipids.

OTHER DISORDERS

Hypertension

Hypertensive cardiomyopathy (HTNCM) is characterized by concentric LVH and is prevalent in 20%–100% of cases, proportional to the severity of hypertension.[105] Persistent HTNCM can lead to congestive heart failure. Interestingly, both the severity of hypertension and the severity of LVH in a patient have been shown to be proportional to the plasma ceramide level.[106-108] HTNCM is difficult to distinguish from primary HCM, FC, and cardiomyopathy induced by acromegaly.[108] The renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure, is the central regulator of LVH induced by hypertensive cardiomyopathy,

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and sphingolipids are a central regulator of the RAAS system.[109-111] Moreover, numerous links have been established between sphingolipids and regulation of vascular tone. Therefore, it is unsurprising that hypertension may arise from aberrant sphingolipid synthesis, ultimately precipitating cardiac outcomes. This is further discussed below.

Tachycardia

Tachycardia-induced cardiomyopathy (TIC) is caused by prolonged tachycardia or arrhythmia, termed tachyarrhythmias, and eventually leads to heart failure. Upon treatment of the causative tachyarrhythmia, TIC is generally a reversible disease.[112,113] TIC is characterized by LV dysfunction leading to DCM, and is usually only diagnosed after the recovery of LV function with normalization of the heart rate. Atrial fibrillation is the most common cause of TIC, although other tachyarrhythmias associated with TIC include atrial flutter, incessant supraventricular tachycardia, ventricular tachycardia, and premature ventricular depolarizations.[114-119] In a study of a TIC model, plasma and ventricle sphingolipid levels were altered. The LV showed reduced ceramide and S1P levels, stable levels of DHS, and increased levels of sphingosine, whereas the right ventricle (RV) showed increased DHS and sphingosine levels, but reduced ceramide and S1P levels. This suggests that ceramide catabolism was increased and the conversion of sphingosine to S1P was inhibited in the LV, while *de novo* synthesis was unaffected. In the RV, the former pattern was also found, but the data suggest an increase in *de novo* synthesis.[120,121] Long QT syndrome is a condition that affects repolarization of the heart after a heartbeat, resulting in an increased risk of irregular heartbeats. LQT9 is a genetic subtype of long QT syndrome involving mutations in the membrane structural protein, CAV3. LQT9 has been shown to lead to ventricular tachycardia. Ceramide regulates the hERG current (I_{HERG}), which in turn regulates contractions and electrical activity of the heart via K^+ ion channels.[122-124] Ceramide and S1P also seem to play opposite roles in TIC, as in other pathologies (e.g., IR injury) as discussed above.

SIGNALING MECHANISMS AND NOVEL POTENTIAL ROLES FOR SPHINGOLIPIDS IN CARDIOMYOPATHIES

In addition to experimentally supported roles for sphingolipids in cardiomyopathies, the multitude of signaling pathways that sphingolipids regulate suggests that they may play additional roles in cardiac pathologies and also provides hints as to mechanism(s) for these roles. Sphingolipids are involved in regulating or are regulated by hypoxia, tumor necrosis factor (TNF)-α, Ca^{2+} signaling, K^+ signaling, reactive oxygen species, endothelial nitric oxide synthase (eNOS), apoptosis, autophagy, necrosis, and many other cell processes implicated in cardiac pathophysiology.[125-130]

Among signaling sphingolipids, S1P is perhaps the best mechanistically characterized. S1P has known intracellular signaling functions, and its most solidly established activities arise from its autocrine, endocrine, and paracrine activities that are mediated by binding to its receptors (S1P1-5). Cumulative data point towards S1P being involved in cardioprotective signaling pathways such as eNOS production, which is pro-angiogenic, as well as inhibition of class II histone deacetylase (HDAC) complexes, involved in repressing gene expression. It has in fact been proposed that S1P represses HDAC1 and HDAC2 to activate the transcription factor KLF4, thereby inhibiting hypertrophy in HCM.[131-137] AKT activates Bcl2 to induce cell survival and increases eNOS activity to support vasodilation. The phosphoinositide 3-kinase (PI3K)-Rac pathway also induced by S1P promotes cell migration. S1P production may also

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be activated by the hypoxic transcription factors HIF1α and HIF2α and/or shuttled by TNF-α into the cell to activate pro-survival signaling pathways such as AKT, PI3K, Pak1, and Rac in HCM, DCM, Takotsubo cardiomyopathy, and ICM with IR injury.[123,138-144] These activated pathways in *in vitro* and *in vivo* IR models reduced infarct size, endothelial cell migration, and angiogenesis, while increasing the viability of isolated cardiomyocytes.[123,140-143] In addition, S1P can activate Pak1 and protein phosphatase 2 (PP2A) in cardiomyocytes through its interactions with its receptors. This signaling pathway is an important mechanism involved in cardioprotection in ICM and IR injury, and could also potentially be involved in Takotsubo cardiomyopathy.[141,144] In HTNCM, S1P mediates renin release and stimulates aldosterone hormone secretion in the RAAS to maintain electrolyte and fluid balance, thereby maintaining blood pressure in HTNCM.[145,146] Additionally, S1P stimulates aldosterone secretion in a manner dependent on PKC and phospholipase D to maintain electrolyte and fluid balance, thereby maintaining cardiovascular homeostasis.[145] S1P binds the S1PR1 present on cardiac mast cells and mediates the inhibition of cell degradation and renin release.[146] Contrary to these findings, other studies have shown that elevated levels of S1P and SphK1 are associated with negative effects in hypertension.[147,148]

The recent literature has shown that vascular endothelial growth factor (VEGF) induces expression of the S1PR1 receptor in the myocardial vascular endothelium, an instance of crosstalk that is required for proper angiogenic balance.[149] In later stages of gestation, the placenta secretes VEGF inhibitors, often inducing angiogenic imbalance in PPCM.[150] Upon treatment with pro-angiogenic therapies, such as VEGF, PPCM has been entirely reversed in PPCM mouse models.[149] S1P has not been used to counteract the VEGF inhibitors secreted in the late gestational stages, but it seems likely that it would be just as efficacious as VEGF treatment. It seems likely that HTNCM could be reversed by treatment with S1P agonists that directly affect the RAAS. Spns2 transports intracellular S1P out of the cell, but in DM1 and DM2, there is a significant reduction of Spns2 that results in increased levels of intracellular S1P, which suppresses dystrophic muscle degeneration. In hyperthyroidism, T_3 inhibits S1P while activating ceramide to induce cardiomyopathy. Cardiomyopathy caused by acromegaly results from increased intracellular Ca^{2+} and involves roughly 500 times more apoptosis. Because S1P has been demonstrated to serve these signaling functions in other contexts, it seems plausible that S1P signaling should be further elucidated in the context of cardiomyopathies involving perturbations of these signaling pathways.

In the context of cardiomyopathy, increased ceramide production and/or alterations in the ceramide profile (e.g., changes in the ratios between medium/long-chain and very-long-chain ceramides) are generally considered toxic. Ceramide has been shown to increase cytosolic Ca^{2+} levels, but not intramitochondrial Ca^{2+} levels, promoting hypertrophy or contractile function in IR by activating p38 MAPK and PKC. This inhibits AKT and JNK and activates pro-apoptotic BAX signaling. Reactive oxygen species are then increased, affecting the ryanodine receptor in the sarcoplasmic reticulum to stimulate Ca^{2+} release into the cytoplasm.[151-156]

The role of ceramide in apoptosis has been established, and consistent with this, it induces the pro-apoptotic p38 MAPK signaling pathway, which is activated in Takotsubo/stress cardiomyopathy and other cardiomyopathies.[157-159] This pro-apoptotic pathway is also induced in the RAAS by ceramide.[160,161] Ceramide is also a possible vasodilator via the RAAS through the PKC, cAMP, and PP2A signaling pathways.[162-165] Angiotensin II in the RAAS induces SM and intracellular ceramide synthesis via angiotensin II type 2 (AT2) receptors to inhibit cell growth and induce apoptosis in vascular and cardiac tissue.[160,161] Ceramide is also a possible

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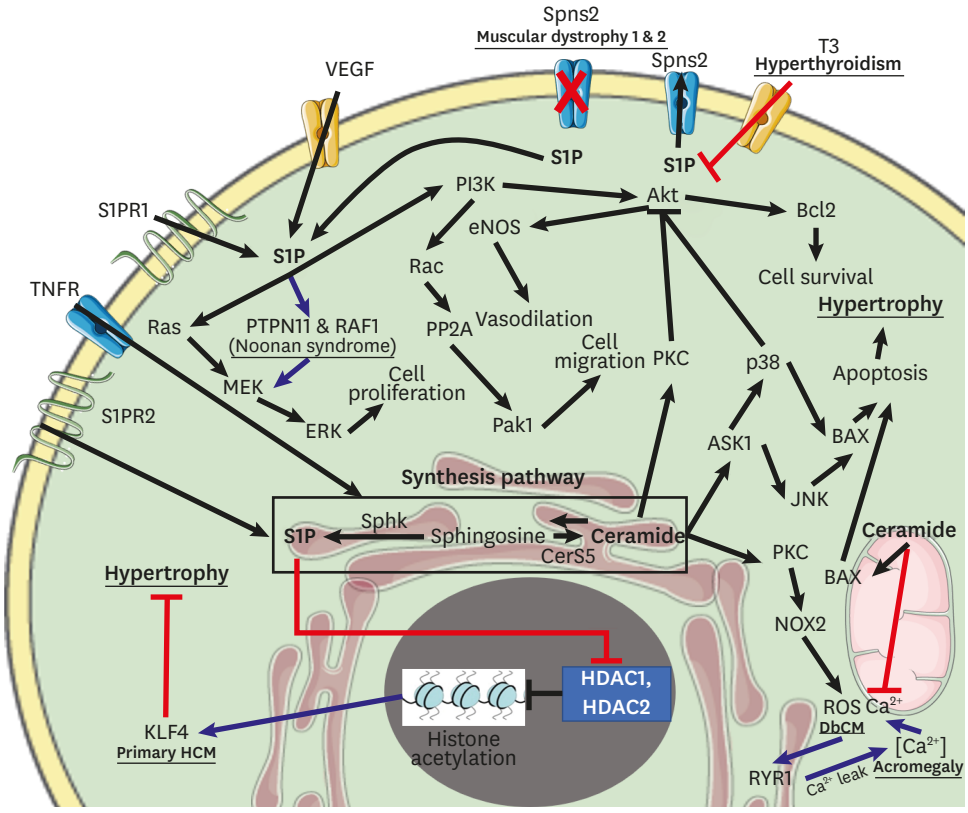

Fig. 2. Summary of the signaling pathways of S1P and ceramide in the various types of cardiac hypertrophy. Activation is indicated with arrows, inhibition by perpendicular lines, black indicates known pathways, blue or red indicate potential pathways.
S1P, sphingosine-1-phosphate; VEGF, vascular endothelial growth factor; Spns2, spinster 2; T3, triiodothyronine; S1PR1, sphingosine-1-phosphate receptor 1; TNFR, tumor necrosis factor receptor; eNOS, endothelial nitric oxide synthase; PP2A, protein phosphatase 2; Pak1, p21-Activated kinase 1; PKC, protein kinase C; HDAC, histone deacetylases; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; BAX, B-cell lymphoma 2 associated X protein; KLF4, Kruppel-like factor 4; HCM, hypertrophic cardiomyopathy; SphK, sphingosine kinase; NOX2, NADPH oxidase 2; ROS, reactive oxygen species; DbCM, diabetic cardiomyopathy; RYR1, ryanodine receptor 1.

vasodilator through the PKC, cAMP, and PP2A signaling pathways via AT2 and inhibiting AT1 action.[162-165] Many of these potentially relevant signaling pathways are depicted in **Fig. 2**.

THERAPEUTIC MODULATION OF SPHINGOLIPIDS

Cardiomyopathy and heart failure remain the leading cause of morbidity and mortality worldwide despite the vast strides made in therapeutic interventions in recent years. Since enzymes, mediators, and inhibitors of the *de novo* sphingolipid pathway are directly involved in some primary and secondary cardiomyopathies, many have emerged as potential therapeutic targets.[62,166,167] Therapeutics that directly or indirectly affect sphingolipid levels in cardiomyopathies are summarized in **Table 1**. The inhibition or ablation of the enzymes involved in ceramide biosynthesis has generally been shown to be cardioprotective.[17,49,168] Studies assessing sphingolipid levels following the treatment of primary cardiomyopathies are rare. The S1P antagonist FTY-720 has been used to prevent the initiation of cardiac hypertrophy. Most intriguing was the profound reversal of existing hypertrophy and/or fibrosis in neonatal rat cardiomyocytes.[169,170] The proposed mechanism for the reversal of hypertrophy and/or fibrosis by FTY-720 is thought to be a dual-mechanism system whereby

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Table 1. List of sphingolipid drug or therapeutic agent in the various cardiomyopathies

Cardiomyopathy	Drug/therapeutic agent	Sphingolipids targeted
Hypertrophic cardiomyopathy	- FTY720 (S1P antagonist)	↓ S1P to reverse fibrotic hypertrophy[169-171]
Dilated cardiomyopathy	- LVAD	↑ Ceramide, DHS[213,214]
Arrhythmogenic right ventricular cardiomyopathy	- Carvedilol	↓ Ceramide, ↓ S1P, ↑ CPT to reduce intracellular Ca^{2+} and prevent arrhythmias[173-175]
Acute viral myocarditis	- Shenfu	↓ SPTLC2, ↓ DHS, ↓ aSMase, ↓ d18:0/14:0 ceramide, ↓ d18:1/22:0 and d18:0/16:1 SM to inhibit viral replication[35,176]
Autoimmune myocarditis	- KRP-203 (S1PR agonist) - FTY720 (S1P antagonist)	↓ S1P to reduce inflammatory cells and cytokines[177,178]
Ischemic cardiomyopathy and ischemic reperfusion	- FTY720 (S1P antagonist) - LVAD - Preconditioning mimetic TNF-α	- ↓ S1P to reduce Ca^{2+} release from sarcoplasmic reticulum and prevent arrhythmias - ↑ Ceramide, DHS - Mediated by cell-permeable (C2) ceramide, SphK1 and S1P to ↓ ceramide[144,213-215]
Gaucher disease cardiomyopathy	- Recombinant β-lucocerebrosidase - Eliglustat tartrate - Zavesca® imiglucerase - Ambroxol	- ↑ Functional β-glucocerebrosidase enzyme - Ceramide glucosyltransferase inhibitor - GlcCer synthase enzyme inhibitor[182-184,188-190,198]
Anderson-Fabry disease cardiomyopathy	- α-galactosidase A - Migalastat	- ↑ Functional α-galactosidase A enzyme to reduce LV thickness - Binds and stabilizes α-galactosidase A, ceramide glucosyltransferase inhibitor[191-197]
Sandhoff/Tay-Sachs disease cardiomyopathy	- Ambroxol - Pyrimethamine - Migalastat + ketogenic diet	- Chaperone of β-hexosaminidase A and improves autophagy by restoring lysosomal calcium release - Improves cardiac function[201-203]
Diabetic cardiomyopathy	- Fumonisin B1 - Fenofibrate - Restricted caloric intake	- ↓ DHC and ceramide to reduce apoptosis - ↓ Deoxysphingolipids - ↓ DHC and ceramide to reduce apoptosis[11,62,204]
Hypertensive cardiomyopathy	- Myriocin - Losartan - Hydralazine	↓ Ceramide levels to reduce blood pressure[62,106]

S1P, sphingosine-1-phosphate; LVAD, left ventricular assist device; DHS, dihydrosphingosine; CPT, carnitine palmitoyltransferase; aSMase, acid sphingomyelinase; SM, sphingomyelin; TNF-α, tumor necrosis factor-α; SphK1, sphingosine kinase 1; GlcCer, glucosylceramide; LV, left ventricular; DHC, dihydroceramide.

Pak1 and NFAT cells are negatively regulated to diminish periostin expression in the extracellular matrix of cardiomyocytes.[171] In 2013, the FDA approved FTY-720 (fingolimod; Novartis, Basel, Switzerland) for treating relapsing multiple sclerosis.[172] Carvedilol, an anti-arrhythmic drug used by ARVC patients, affects the expression of genes encoding enzymes involved in sphingolipid synthesis and increasing levels of carnitine palmitoyltransferase.[173-175] A pharmaceutical agent, Shenfu infection, which is widely used in China for treatment of patients with acquired primary cardiomyopathy and acute viral myocarditis, was recently shown to target and significantly reduce SPTLC2, aSMase, DHS, d18:0/14:0 ceramide, and d18:1/22:0 and d18:0/16:1 SM to prevent viral replication in viral myocarditis.[35,176] A study showed that treatment with a S1PR receptor agonist (KRP-203) before or even after the onset of autoimmune myocarditis in a rat model markedly reduced inflammation by reducing the amounts of CD4 T cells, macrophages, inflammatory cytokines, while also improving lifespan and decreasing the ratio of heart weight to body weight.[177] Another similar study was conducted using FTY-720 and showed similar results.[178] While it is known that both KRP-203 and FTY-720 act at S1P receptors, their downstream mechanistic actions have not been completely elucidated. However, it is known that they are highly effective in attenuating the progression of myocarditis by reducing T cell infiltration and subsequent inflammatory cytokine activation in the inflamed myocardium. Additionally, in another study, FTY-720 prevented arrhythmias induced by IR, in which ischemia suppressed Ca^{2+} release from the sarcoplasmic reticulum and myofilaments, thereby activating the pro-arrhythmic Pak1 and AKT pathways.[144] FTY-720 has also been shown to decrease the infiltration of pro-inflammatory eosinophils and T cells into the airway mucosa and bone marrow in hypereosinophilic syndrome.[179-181]

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Enzyme replacement or enhancement therapy has emerged as an effective treatment for the secondary cardiomyopathies observed as a result of lysosomal storage disorders, and is therefore a likely strategy for treating the resulting cardiomyopathies. Gaucher disease is treated by infusion of recombinant acid β-glucosidase or a ceramide glucosyltransferase inhibitor (eliglustat tartrate). Both treatments reversed the disease-related accumulation of complex sphingolipids in clinical trials.[182-184] More recent technology has allowed for high-throughput screening to identify small-molecule therapeutics, such as chaperones to restore defective enzyme activity and compounds to clear accumulating substrates for many lysosomal storage diseases including Gaucher disease, Fabry disease, and gangliosidoses.[185-187] As additional pharmaceutical agents, Zavesca® (miglustat), Cerezyme™ (imiglucerase), and VPRIV™ (velaglucerase) have been approved to treat all 3 types of Gaucher disease by reducing the accumulation of GlcCer through inhibition of GlcCer synthase.[188-190] Anderson-Fabry disease has also been treated by replacement with recombinant α-galactosidase, which reduced LV wall thickness, improved regional myocardial function, and cleared microvascular endothelial deposits of globotriaosylceramide from the heart.[191-196] Another clinical trial evaluated the long-term effects of a small-molecule pharmacological chaperone, migalastat, that binds and stabilizes α-galactosidase A. Patients showed reduced cardiac mass and stable levels of globotriaosylceramides.[197] Ambroxol is an FDA approved drug used to treat Gaucher and Tay-Sachs diseases, though whether it reduces cardiac symptoms has not yet been addressed.[198-200] Pyrimethamine is another chaperone of β-hexosaminidase A in Tay-Sachs disease which mechanistically improves autophagy by restoring lysosomal calcium release.[201,202] Migalastat in combination with a ketogenic caloric restriction diet led to improved cardiac function and improved seizure control in a patient with Sandhoff disease, although the mechanism of action remains to be determined.[203]

Myriocin, a fungal toxin and specific inhibitor of SPT, has been shown to prevent cancer cell migration, insulin resistance, and cardiomyopathies in mouse models including SPT2 heterozygous mice, T2DM, hypertension, and atherosclerosis by reducing ceramide levels. However, myriocin has not yet been and is unlikely to be approved through clinical trials, as there are numerous toxic and off-target effects in humans and mice.[17,48,62,204-207] The ceramide synthase inhibitor fumonisin B1 (FB1), which inhibits ceramide synthases and thereby prevents synthesis of DHCs from DHS, has been shown to improve insulin sensitivity in rodents and isolated muscles that are lipid-infused; the effects of FB1 are mediated by decreased ceramide levels, which increase activation of PP2A and the PI3K/AKT signaling pathway. This inhibition attenuates apoptosis and other cellular signaling pathways observed in DbCM.[62,204] Fumonisin B1 has not been tested in a primary or secondary cardiomyopathic model, but it was shown that a specific ceramide synthase, CerS5, induced cardiomyocyte hypertrophy; therefore, targeting this enzyme could potentially have therapeutic benefits.[51] To date, however, few inhibitors of specific ceramide synthases have been identified, and this is an area under intense investigation due to its potential benefits in these and other pathologies. In contrast to these largely deleterious roles of ceramide, it also exhibits antiproliferative effects that may be beneficial. In fact, stents have been developed that are coated with a cell-permeable Cer analogue, leading to reduced restenosis.[208-210]

Exogenously administered S1P accelerates neovascularization and blood flow recovery in ischemic limbs, suggesting its usefulness for angiogenic therapy. Baseline concentrations of S1P measured in peripheral blood samples in ischemic patients were more than 4-fold higher in patients with documented CAD undergoing a percutaneous coronary intervention than in healthy controls. By 5 minutes, coronary sinus and peripheral levels of S1P levels increased by 720% and 792%, respectively. Where troponin T was detectable at 12 hours, a strong

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correlation was found with peak S1P levels in ischemia.[211] A recently patented approach assesses the total amount of SMs and SMase as a parameter to diagnose heart failure due to ICM or non-ischemic DCM.[212] Left ventricular assist devices (LVADs), which provide mechanical support for advanced heart failure in patients with end-stage heart failure as a result of ICM or DCM, decreased the levels of numerous myocardial ceramide in patients after implantation compared to patients that did not receive an LVAD.[213,214]

Since ceramide has been implicated in hERG and reactive oxygen species overproduction, as previously mentioned, ceramide may contribute to long QT syndrome and therefore could be targeted as a therapeutic strategy in this context.[122,123] Ischemic preconditioning (IPC) is an experimental technique used to produce resistance against acute IR injury, and may be regulated by ceramide, SphK1, and S1P.[215] S1P is a mediator of IPC, as S1P binds S1PR2 and S1PR3 in myocardial ischemia, causing cardiomyopathy. These results provide evidence for S1P receptor subtype-specific pharmacological interventions as a novel therapeutic approach to myocardial diseases.[216] In patients with ICM, S1P and sphingosine have been shown to be reliable predictors of CAD when a patient is undergoing coronary angiography.[211,217] Another potential therapeutic intervention is targeting aSMase, which hydrolyzes SM to generate ceramide, to reduce the cardiac production of ceramide in ischemic reperfusion after ICM.[218] DbCM model animals fed with low amounts of unsaturated fatty acids and high amounts of saturated fatty acids, especially myristate (C14:0), had more severe phenotypes. This may contribute to the associations between saturated fatty acid consumption and cardiovascular disease, and furthermore suggests that changes in diet to reduce the conception of foods containing myristate and/or other medium-chain fatty acids would benefit patients.

The treatment of hypertension with losartan and/or hydralazine in spontaneously hypertensive rats significantly decreased blood pressure. This was associated with a concomitant lowering of vascular ceramide levels, although this most likely occurred due to decreased blood pressure and not the mechanisms of the drugs themselves.[106]

CONCLUSIONS

In this review, we highlighted the involvement of multiple sphingolipid species in various cardiomyopathies, including direct roles for sphingolipids in DCM, acute right ventricular cardiomyopathy, ICM with IR, AVMC, DbCM, GDC, FC, GM1 gangliosidosis GM1, both forms of GM2 gangliosidosis, DMD, BMD, DM1 and DM2, and cardiomyopathy in hyperthyroidism. In addition to these direct roles, the potential for identification of other direct roles is suggested by the numerous overlaps between signaling pathways known both to regulate cardiac pathophysiology and to be sphingolipid-regulated. This possibility may be relevant for conditions including HCM, Takotsubo disease with LQTS, TIC with LQTS syndrome, HTNCM, and cardiomyopathies in acute MC, PPCM, and Friedreich ataxia. To date, no sphingolipids have been associated with primary RCM, unclassified primary left ventricle non-compaction cardiomyopathy, and ICM without IR. Also discussed are the interventional studies of sphingolipids in various animal models, which show remarkable potential for various drugs, as well as the sphingolipid therapeutics currently in clinical trials or already approved for use in humans.

A major advance in understanding sphingolipid biology in general is the recent appreciation that chemically distinct sphingolipid species often have specific functions. While many

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studies have used genetic or pharmacological strategies to prevent or reduce sphingolipid synthesis in general, mass spectrometry-based strategies have enabled the discovery that different sphingoid bases (e.g., d16:0 vs. d18:0), distinct N-acyl chain lengths and degrees of saturation (e.g., C14:0 vs. C20:0, C18:1, C24:1, etc.), and other structural differences among sphingolipid species lead to distinct biological effects. Therefore, approaches taking these variations into account are leading to a better understanding of mechanisms underlying the pathology of cardiomyopathy, as well as providing more specificity in the identification of novel therapeutic targets.[219]

In summary, targeting enzymes involved in sphingolipid synthesis could have enormous—and thus far, untapped—therapeutic potential. Furthermore, the delivery of beneficial sphingolipids may also be feasible. For example, recently developed nano-liposomal lipid delivery systems are currently being used in a multitude of disease contexts.[220-222] Further studies of sphingolipids in cardiac pathophysiology will undoubtedly continue to provide opportunities for novel therapeutic strategies.

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REFERENCES

1. Hannun YA, Obeid LM. Sphingolipids and their metabolism in physiology and disease. Nat Rev Mol Cell Biol 2018;19:175-191.
PUBMED | CROSSREF
2. Chun J, Hla T, Lynch KR, Spiegel S, Moolenaar WH. International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. Pharmacol Rev 2010;62:579-587.
PUBMED | CROSSREF
3. Cremesti A, Paris F, Grassmé H, Holler N, Tschopp J, Fuks Z, et al. Ceramide enables fas to cap and kill. J Biol Chem 2001;276:23954-23961.
PUBMED | CROSSREF
4. Guo W, Wong S, Xie W, Lei T, Luo Z. Palmitate modulates intracellular signaling, induces endoplasmic reticulum stress, and causes apoptosis in mouse 3T3-L1 and rat primary preadipocytes. Am J Physiol Endocrinol Metab 2007;293:E576-E586.
PUBMED | CROSSREF
5. Park TS, Yamashita H, Blaner WS, Goldberg IJ. Lipids in the heart: a source of fuel and a source of toxins. Curr Opin Lipidol 2007;18:277-282.
PUBMED | CROSSREF
6. Sasset L, Zhang Y, Dunn TM, Di Lorenzo A. Sphingolipid *de novo* biosynthesis: a rheostat of cardiovascular homeostasis. Trends Endocrinol Metab 2016;27:807-819.
PUBMED | CROSSREF
7. Hanada K, Hara T, Nishijima M. D-Serine inhibits serine palmitoyltransferase, the enzyme catalyzing the initial step of sphingolipid biosynthesis. FEBS Lett 2000;474:63-65.
PUBMED | CROSSREF
8. Hannun YA, Linardic CM. Sphingolipid breakdown products: anti-proliferative and tumor-suppressor lipids. Biochim Biophys Acta 1993;1154:223-236.
PUBMED | CROSSREF
9. Hornemann T, Richard S, Rütti MF, Wei Y, von Eckardstein A. Cloning and initial characterization of a new subunit for mammalian serine-palmitoyltransferase. J Biol Chem 2006;281:37275-37281.
PUBMED | CROSSREF

10. Nagiec MM, Baltisberger JA, Wells GB, Lester RL, Dickson RC. The LCB2 gene of Saccharomyces and the related LCB1 gene encode subunits of serine palmitoyltransferase, the initial enzyme in sphingolipid synthesis. Proc Natl Acad Sci U S A 1994;91:7899-7902.
PUBMED | CROSSREF
11. Russo SB, Tidhar R, Futerman AH, Cowart LA. Myristate-derived d16:0 sphingolipids constitute a cardiac sphingolipid pool with distinct synthetic routes and functional properties. J Biol Chem 2013;288:13397-13409.
PUBMED | CROSSREF
12. Han G, Gupta SD, Gable K, Niranjanakumari S, Moitra P, Eichler F, et al. Identification of small subunits of mammalian serine palmitoyltransferase that confer distinct acyl-CoA substrate specificities. Proc Natl Acad Sci U S A 2009;106:8186-8191.
PUBMED | CROSSREF
13. Harmon JM, Bacikova D, Gable K, Gupta SD, Han G, Sengupta N, et al. Topological and functional characterization of the ssSPTs, small activating subunits of serine palmitoyltransferase. J Biol Chem 2013;288:10144-10153.
PUBMED | CROSSREF
14. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. Circulation 2006;113:1807-1816.
PUBMED | CROSSREF
15. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-276.
PUBMED | CROSSREF
16. Ma RC, So WY, Tong PC, Chan JC, Cockram CS, Chow CC. Adiposity of the heart revisited: reversal of dilated cardiomyopathy in a patient with Cushing's syndrome. Int J Cardiol 2011;151:e22-e23.
PUBMED | CROSSREF
17. Park TS, Hu Y, Noh HL, Drosatos K, Okajima K, Buchanan J, et al. Ceramide is a cardiotoxin in lipotoxic cardiomyopathy. J Lipid Res 2008;49:2101-2112.
PUBMED | CROSSREF
18. Chiu HC, Kovacs A, Ford DA, Hsu FF, Garcia R, Herrero P, et al. A novel mouse model of lipotoxic cardiomyopathy. J Clin Invest 2001;107:813-822.
PUBMED | CROSSREF
19. Maekawa K, Hirayama A, Iwata Y, Tajima Y, Nishimaki-Mogami T, Sugawara S, et al. Global metabolomic analysis of heart tissue in a hamster model for dilated cardiomyopathy. J Mol Cell Cardiol 2013;59:76-85.
PUBMED | CROSSREF
20. Li Y, Huang TT, Carlson EJ, Melov S, Ursell PC, Olson JL, et al. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. Nat Genet 1995;11:376-381.
PUBMED | CROSSREF
21. Zhang Y, Ikeno Y, Qi W, Chaudhuri A, Li Y, Bokov A, et al. Mice deficient in both Mn superoxide dismutase and glutathione peroxidase-1 have increased oxidative damage and a greater incidence of pathology but no reduction in longevity. J Gerontol A Biol Sci Med Sci 2009;64:1212-1220.
PUBMED | CROSSREF
22. Cordis GA, Yoshida T, Das DK. HPTLC analysis of sphingomylein, ceramide and sphingosine in ischemic/reperfused rat heart. J Pharm Biomed Anal 1998;16:1189-1193.
PUBMED | CROSSREF
23. Zhang DX, Fryer RM, Hsu AK, Zou AP, Gross GJ, Campbell WB, et al. Production and metabolism of ceramide in normal and ischemic-reperfused myocardium of rats. Basic Res Cardiol 2001;96:267-274.
PUBMED | CROSSREF
24. Borodzicz S, Czarzasta K, Kuch M, Cudnoch-Jedrzejewska A. Sphingolipids in cardiovascular diseases and metabolic disorders. Lipids Health Dis 2015;14:55.
PUBMED | CROSSREF
25. Knapp M, Żendzian-Piotrowska M, Błachnio-Zabielska A, Zabielski P, Kurek K, Górski J. Myocardial infarction differentially alters sphingolipid levels in plasma, erythrocytes and platelets of the rat. Basic Res Cardiol 2012;107:294.
PUBMED | CROSSREF
26. Nofer JR, van der Giet M, Tölle M, Wolinska I, von Wnuck Lipinski K, Baba HA, et al. HDL induces NO-dependent vasorelaxation via the lysophospholipid receptor S1P3. J Clin Invest 2004;113:569-581.
PUBMED | CROSSREF

27. Cavalli AL, Ligutti JA, Gellings NM, Castro E, Page M, Klepper R, et al. The role of TNFα and sphingolipid signaling in cardiac hypoxia: evidence that cardiomyocytes release TNFα and sphingosine. Basic Appl Myol 2002;12:167-175.
28. Duan HF, Wang H, Yi J, Liu HJ, Zhang QW, Li LB, et al. Adenoviral gene transfer of sphingosine kinase 1 protects heart against ischemia/reperfusion-induced injury and attenuates its postischemic failure. Hum Gene Ther 2007;18:1119-1128.
PUBMED | CROSSREF
29. Caforio AL, Malipiero G, Marcolongo R, Iliceto S. Myocarditis: a clinical overview. Curr Cardiol Rep 2017;19:63.
PUBMED | CROSSREF
30. Rose NR. Viral myocarditis. Curr Opin Rheumatol 2016;28:383-389.
PUBMED | CROSSREF
31. Huber SA. Viral myocarditis and dilated cardiomyopathy: etiology and pathogenesis. Curr Pharm Des 2016;22:408-426.
PUBMED | CROSSREF
32. Martín-Acebes MA, Merino-Ramos T, Blázquez AB, Casas J, Escribano-Romero E, Sobrino F, et al. The composition of West Nile virus lipid envelope unveils a role of sphingolipid metabolism in flavivirus biogenesis. J Virol 2014;88:12041-12054.
PUBMED | CROSSREF
33. Perera R, Riley C, Isaac G, Hopf-Jannasch AS, Moore RJ, Weitz KW, et al. Dengue virus infection perturbs lipid homeostasis in infected mosquito cells. PLoS Pathog 2012;8:e1002584.
PUBMED | CROSSREF
34. Hirata Y, Ikeda K, Sudoh M, Tokunaga Y, Suzuki A, Weng L, et al. Self-enhancement of hepatitis C virus replication by promotion of specific sphingolipid biosynthesis. PLoS Pathog 2012;8:e1002860.
PUBMED | CROSSREF
35. Tan G, Zhou Q, Liu K, Dong X, Li L, Liao W, et al. Cross-platform metabolic profiling deciphering the potential targets of Shenfu injection against acute viral myocarditis in mice. J Pharm Biomed Anal 2018;160:1-11.
PUBMED | CROSSREF
36. Vijayan M, Hahm B. Influenza viral manipulation of sphingolipid metabolism and signaling to modulate host defense system. Scientifica (Cairo) 2014;2014:793815.
PUBMED | CROSSREF
37. Huber SA. Autoimmunity in myocarditis: relevance of animal models. Clin Immunol Immunopathol 1997;83:93-102.
PUBMED | CROSSREF
38. Huber SA, Lodge PA. Coxsackievirus B-3 myocarditis in Balb/c mice. Evidence for autoimmunity to myocyte antigens. Am J Pathol 1984;116:21-29.
PUBMED
39. Lawson CM. Evidence for mimicry by viral antigens in animal models of autoimmune disease including myocarditis. Cell Mol Life Sci 2000;57:552-560.
PUBMED | CROSSREF
40. Kodama M, Okura Y, Aizawa Y, Izumi T. Animal models of autoimmune myocarditis. In: Cooper LT, editor. Myocarditis. Totowa (NJ): Humana Press; 2003. p.197-214.
41. Kamiyoshi Y, Takahashi M, Yokoseki O, Yazaki Y, Hirose S, Morimoto H, et al. Mycophenolate mofetil prevents the development of experimental autoimmune myocarditis. J Mol Cell Cardiol 2005;39:467-477.
PUBMED | CROSSREF
42. Velez M, Kohli S, Sabbah HN. Animal models of insulin resistance and heart failure. Heart Fail Rev 2014;19:1-13.
PUBMED | CROSSREF
43. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, et al. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol 2008;52:1793-1799.
PUBMED | CROSSREF
44. Guha A, Harmancey R, Taegtmeyer H. Nonischemic heart failure in diabetes mellitus. Curr Opin Cardiol 2008;23:241-248.
PUBMED | CROSSREF
45. Alonso N, Moliner P, Mauricio D. Pathogenesis, clinical features and treatment of diabetic cardiomyopathy. Adv Exp Med Biol 2008;1067:197-217.
PUBMED | CROSSREF

46. Russo SB, Ross JS, Cowart LA. Sphingolipids in obesity, type 2 diabetes, and metabolic disease. Handb Exp Pharmacol 2013:373-401.
PUBMED | CROSSREF

47. Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism 2014;63:1469-1479.
PUBMED | CROSSREF

48. Park TS, Panek RL, Mueller SB, Hanselman JC, Rosebury WS, Robertson AW, et al. Inhibition of sphingomyelin synthesis reduces atherogenesis in apolipoprotein E-knockout mice. Circulation 2004;110:3465-3471.
PUBMED | CROSSREF

49. Jiang XC, Goldberg IJ, Park TS. Sphingolipids and cardiovascular diseases: lipoprotein metabolism, atherosclerosis and cardiomyopathy. Adv Exp Med Biol 2011;721:19-39.
PUBMED | CROSSREF

50. Lorenzo O, Ramírez E, Picatoste B, Egido J, Tuñón J. Alteration of energy substrates and ROS production in diabetic cardiomyopathy. Mediators Inflamm 2013;2013:461967.
PUBMED | CROSSREF

51. Russo SB, Baicu CF, Van Laer A, Geng T, Kasiganesan H, Zile MR, et al. Ceramide synthase 5 mediates lipid-induced autophagy and hypertrophy in cardiomyocytes. J Clin Invest 2012;122:3919-3930.
PUBMED | CROSSREF

52. Hu W, Ross J, Geng T, Brice SE, Cowart LA. Differential regulation of dihydroceramide desaturase by palmitate versus monounsaturated fatty acids: implications for insulin resistance. J Biol Chem 2011;286:16596-16605.
PUBMED | CROSSREF

53. Rhee EP, Cheng S, Larson MG, Walford GA, Lewis GD, McCabe E, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. J Clin Invest 2011;121:1402-1411.
PUBMED | CROSSREF

54. Bugger H, Abel ED. Rodent models of diabetic cardiomyopathy. Dis Model Mech 2009;2:454-466.
PUBMED | CROSSREF

55. Riquelme CA, Magida JA, Harrison BC, Wall CE, Marr TG, Secor SM, et al. Fatty acids identified in the Burmese python promote beneficial cardiac growth. Science 2011;334:528-531.
PUBMED | CROSSREF

56. Chavez JA, Siddique MM, Wang ST, Ching J, Shayman JA, Summers SA. Ceramides and glucosylceramides are independent antagonists of insulin signaling. J Biol Chem 2014;289:723-734.
PUBMED | CROSSREF

57. Raichur S, Wang ST, Chan PW, Li Y, Ching J, Chaurasia B, et al. CerS2 haploinsufficiency inhibits β-oxidation and confers susceptibility to diet-induced steatohepatitis and insulin resistance. Cell Metab 2014;20:687-695.
PUBMED | CROSSREF

58. Ussher JR, Koves TR, Cadete VJ, Zhang L, Jaswal JS, Swyrd SJ, et al. Inhibition of *de novo* ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. Diabetes 2010;59:2453-2464.
PUBMED | CROSSREF

59. de Mello VD, Lankinen M, Schwab U, Kolehmainen M, Lehto S, Seppänen-Laakso T, et al. Link between plasma ceramides, inflammation and insulin resistance: association with serum IL-6 concentration in patients with coronary heart disease. Diabetologia 2009;52:2612-2615.
PUBMED | CROSSREF

60. Murphy MP. Mitochondrial dysfunction indirectly elevates ROS production by the endoplasmic reticulum. Cell Metab 2013;18:145-146.
PUBMED | CROSSREF

61. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: integrating signaling pathways and substrate flux. J Clin Invest 2016;126:12-22.
PUBMED | CROSSREF

62. Meikle PJ, Summers SA. Sphingolipids and phospholipids in insulin resistance and related metabolic disorders. Nat Rev Endocrinol 2017;13:79-91.
PUBMED | CROSSREF

63. Chariyawong P, Rao A, Panikkath D, Panikkath R. Hyperthyroidism-induced dilated cardiomyopathy. Southwest Respir Crit Care Chron 2019;7:64-66.
CROSSREF

64. Klimaite R, Kinderyte M, Dauksaite N, Barsiene L, Zilaitiene B. Pancytopenia and reversible cardiomyopathy-complications of thyrotoxicosis: case report. 21st European Congress of Endocrinology; 18-21 May 2019; Lyon, France. Bristol: European Society of Endocrinology; 2019.

65. Lino CA, Demasi M, Barreto-Chaves ML. Ubiquitin proteasome system (UPS) activation in the cardiac hypertrophy of hyperthyroidism. Mol Cell Endocrinol 2019;493:110451.
PUBMED | CROSSREF

66. Mikłosz A, Łukaszuk B, Chabowski A, Rogowski F, Kurek K, Żendzian-Piotrowska M. Hyperthyroidism evokes myocardial ceramide accumulation. Cell Physiol Biochem 2015;35:755-766.
PUBMED | CROSSREF

67. Pastores GM, Hughes DA. Gaucher disease. GeneReviews® [Internet]. Seattle (WA): University of Washington; 2018 [accessed on date]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1269/.

68. Riera AR, Schapachnik E, Dubner S. The genetic causes of heart failure a focus on sudden death: from the molecular mechanisms to clinical approach. Lodz: International Society for Holter and Noninvasive Electrocardiology; 2006.

69. Laks Y, Passwell J. The varied clinical and laboratory manifestations of type II Gaucher's disease. Acta Paediatr Scand 1987;76:378-380.
PUBMED | CROSSREF

70. Casta A, Hayden K, Wolf WJ. Calcification of the ascending aorta and aortic and mitral valves in Gaucher's disease. Am J Cardiol 1984;54:1390-1391.
PUBMED | CROSSREF

71. Bohlega S, Kambouris M, Shahid M, Al Homsi M, Al Sous W. Gaucher disease with oculomotor apraxia and cardiovascular calcification (Gaucher type IIIC). Neurology 2000;54:261-263.
PUBMED | CROSSREF

72. Saraçlar M, Atalay S, Koçak N, Özkutlu S. Gaucher's disease with mitral and aortic involvement: echocardiographic findings. Pediatr Cardiol 1992;13:56-58.
PUBMED

73. Sharratt GP, Price D, Curtis JA, Cornel G. Gaucher's disease with mitral valve calcification. Pediatr Cardiol 1992;13:127-128.
PUBMED | CROSSREF

74. Karakoyun M, Canda E, Kiran Tasci E, Dogan E, Coker M, Aydogdu S. Two siblings with Gaucher type 3c: different clinical presentations. J Pediatr Endocrinol Metab 2019;32:533-536.
PUBMED | CROSSREF

75. Chabás A, Cormand B, Grinberg D, Burguera JM, Balcells S, Merino JL, et al. Unusual expression of Gaucher's disease: cardiovascular calcifications in three sibs homozygous for the D409H mutation. J Med Genet 1995;32:740-742.
PUBMED | CROSSREF

76. Hein LK, Meikle PJ, Hopwood JJ, Fuller M. Secondary sphingolipid accumulation in a macrophage model of Gaucher disease. Mol Genet Metab 2007;92:336-345.
PUBMED | CROSSREF

77. Goldman ME, Cantor R, Schwartz MF, Baker M, Desnick RJ. Echocardiographic abnormalities and disease severity in Fabry's disease. J Am Coll Cardiol 1986;7:1157-1161.
PUBMED | CROSSREF

78. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002;105:1407-1411.
PUBMED | CROSSREF

79. Chimenti C, Pieroni M, Morgante E, Antuzzi D, Russo A, Russo MA, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. Circulation 2004;110:1047-1053.
PUBMED | CROSSREF

80. Conway R. The sphingolipidoses. In: Rubin IL, Merrick J, Greydanus DE, Patel DR, editors. Health care for people with intellectual and developmental disabilities across the lifespan. Zurich: Springer International; 2016. p.659-682.

81. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 1995;333:288-293.
PUBMED | CROSSREF

82. Elleder M, Bradová V, Smíd F, Buděsínský M, Harzer K, Kustermann-Kuhn B, et al. Cardiocyte storage and hypertrophy as a sole manifestation of Fabry's disease. Report on a case simulating hypertrophic non-obstructive cardiomyopathy. Virchows Arch A Pathol Anat Histopathol 1990;417:449-455.
PUBMED | CROSSREF

83. Pieruzzi F, Pieroni M, Zachara E, Marziliano N, Morrone A, Cecchi F. Heart involvement in Anderson-Fabry disease: Italian recommendations for diagnostic, follow-up and therapeutic management. G Ital Cardiol (Rome) 2015;16:630-638.
PUBMED

84. Kampmann C, Linhart A, Baehner F, Palecek T, Wiethoff CM, Miebach E, et al. Onset and progression of the Anderson-Fabry disease related cardiomyopathy. Int J Cardiol 2008;130:367-373.
PUBMED | CROSSREF

85. Pieroni M, Chimenti C, De Cobelli F, Morgante E, Del Maschio A, Gaudio C, et al. Fabry's disease cardiomyopathy: echocardiographic detection of endomyocardial glycosphingolipid compartmentalization. J Am Coll Cardiol 2006;47:1663-1671.
PUBMED | CROSSREF

86. Kounas S, Demetrescu C, Pantazis AA, Keren A, Lee PJ, Hughes D, et al. The binary endocardial appearance is a poor discriminator of Anderson-Fabry disease from familial hypertrophic cardiomyopathy. J Am Coll Cardiol 2008;51:2058-2061.
PUBMED | CROSSREF

87. Yogasundaram H, Nikhanj A, Putko BN, Boutin M, Jain-Ghai S, Khan A, et al. Elevated inflammatory plasma biomarkers in patients with fabry disease: a critical link to heart failure with preserved ejection fraction. J Am Heart Assoc 2018;7:e009098.
PUBMED | CROSSREF

88. Ommen SR, Nishimura RA, Edwards WD. Fabry disease: a mimic for obstructive hypertrophic cardiomyopathy? Heart 2003;89:929-930.
PUBMED | CROSSREF

89. Seward JB, Casaclang-Verzosa G. Infiltrative cardiovascular diseases: cardiomyopathies that look alike. J Am Coll Cardiol 2010;55:1769-1779.
PUBMED | CROSSREF

90. Vitner EB, Platt FM, Futerman AH. Common and uncommon pathogenic cascades in lysosomal storage diseases. J Biol Chem 2010;285:20423-20427.
PUBMED | CROSSREF

91. Brunetti-Pierri N, Scaglia F. GM1 gangliosidosis: review of clinical, molecular, and therapeutic aspects. Mol Genet Metab 2008;94:391-396.
PUBMED | CROSSREF

92. Lin HC, Tsai FJ, Shen WC, Tsai CH, Peng CT. Infantile form GM1 gangliosidosis with dilated cardiomyopathy: a case report. Acta Paediatr 2000;89:880-883.
PUBMED | CROSSREF

93. Rosenberg H, Frewen TC, Li MD, Gordon BL, Jung JH, Finlay JP, et al. Cardiac involvement in diseases characterized by β-galactosidase deficiency. J Pediatr 1985;106:78-80.
PUBMED | CROSSREF

94. Hadley RN, Hagstrom JW. Cardiac lesions in a patient with familial neurovisceral lipidosis (generalized gangliosidosis). Am J Clin Pathol 1971;55:237-240.
PUBMED | CROSSREF

95. McMinn TR Jr, Ross J Jr. Hereditary dilated cardiomyopathy. Clin Cardiol 1995;18:7-15.
PUBMED | CROSSREF

96. Benson PF, Barbarik A, Brown SP, Mann TP. GM1-generalized gangliosidosis variant with cardiomegaly. Postgrad Med J 1976;52:159-165.
PUBMED | CROSSREF

97. Rodriguez-Torres R, Schneck L, Kleinberg W. Electrocardiographic and biochemical abnormalities in Tay-Sachs disease. Bull N Y Acad Med 1971;47:717-730.
PUBMED

98. Gilbert-Barness E. Metabolic cardiomyopathy and conduction system defects in children. Ann Clin Lab Sci 2004;34:15-34.
PUBMED

99. Brown M, Goldstein J, Fredrickson D. Familial type 3 hyperlipoproteinemia (dysbetalipoproteinemia). In: Stanbury JB, Wyngaarden JB, Fredrickson DS, editors. Metabolic basis of inherited disease. New York (NY): McGraw-Hill; 1983.

100. Blieden LC, Desnick RJ, Carter JB, Krivit W, Moller JH, Sharp HL. Cardiac involvement in Sandhoff's disease. Inborn error of glycosphingolipid metabolism. Am J Cardiol 1974;34:83-88.
PUBMED | CROSSREF

101. Kohlschütter A, Hausdorf G. Primary (genetic) cardiomyopathies in infancy. A survey of possible disorders and guidelines for diagnosis. Eur J Pediatr 1986;145:454-459.
PUBMED | CROSSREF

102. Verhaert D, Richards K, Rafael-Fortney JA, Raman SV. Cardiac involvement in patients with muscular dystrophies: magnetic resonance imaging phenotype and genotypic considerations. Circ Cardiovasc Imaging 2011;4:67-76.
PUBMED | CROSSREF

103. Fra AM, Williamson E, Simons K, Parton RG. *De novo* formation of caveolae in lymphocytes by expression of VIP21-caveolin. Proc Natl Acad Sci U S A 1995;92:8655-8659.
PUBMED | CROSSREF

104. Li S, Song KS, Lisanti MP. Expression and characterization of recombinant caveolin. Purification by polyhistidine tagging and cholesterol-dependent incorporation into defined lipid membranes. J Biol Chem 1996;271:568-573.
PUBMED | CROSSREF

105. Gardin JM, Lauer MS. Left ventricular hypertrophy: the next treatable, silent killer? JAMA 2004;292:2396-2398.
PUBMED | CROSSREF

106. Spijkers LJ, Janssen BJ, Nelissen J, Meens MJ, Wijesinghe D, Chalfant CE, et al. Antihypertensive treatment differentially affects vascular sphingolipid biology in spontaneously hypertensive rats. PLoS One 2011;6:e29222.
PUBMED | CROSSREF

107. Spijkers LJ, van den Akker RF, Janssen BJ, Debets JJ, De Mey JG, Stroes ES, et al. Hypertension is associated with marked alterations in sphingolipid biology: a potential role for ceramide. PLoS One 2011;6:e21817.
PUBMED | CROSSREF

108. Kuroda K, Kato TS, Amano A. Hypertensive cardiomyopathy: a clinical approach and literature review. World J Hypertens 2015;5:41-52.
CROSSREF

109. Fenger M, Linneberg A, Jørgensen T, Madsbad S, Søbye K, Eugen-Olsen J, et al. Genetics of the ceramide/sphingosine-1-phosphate rheostat in blood pressure regulation and hypertension. BMC Genet 2011;12:44.
PUBMED | CROSSREF

110. Li H, Junk P, Huwiler A, Burkhardt C, Wallerath T, Pfeilschifter J, et al. Dual effect of ceramide on human endothelial cells: induction of oxidative stress and transcriptional upregulation of endothelial nitric oxide synthase. Circulation 2002;106:2250-2256.
PUBMED | CROSSREF

111. Hemmings DG. Signal transduction underlying the vascular effects of sphingosine 1-phosphate and sphingosylphosphorylcholine. Naunyn Schmiedebergs Arch Pharmacol 2006;373:18-29.
PUBMED | CROSSREF

112. Ellis ER, Josephson ME. Heart failure and tachycardia-induced cardiomyopathy. Curr Heart Fail Rep 2013;10:296-306.
PUBMED | CROSSREF

113. Ellis ER, Josephson ME. What about tachycardia-induced cardiomyopathy? Arrhythm Electrophysiol Rev 2013;2:82-90.
PUBMED | CROSSREF

114. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-induced cardiomyopathies: mechanisms, recognition, and management. J Am Coll Cardiol 2015;66:1714-1728.
PUBMED | CROSSREF

115. Chugh SS, Shen WK, Luria DM, Smith HC. First evidence of premature ventricular complex-induced cardiomyopathy: a potentially reversible cause of heart failure. J Cardiovasc Electrophysiol 2000;11:328-329.
PUBMED | CROSSREF

116. Grogan M, Smith HC, Gersh BJ, Wood DL. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol 1992;69:1570-1573.
PUBMED | CROSSREF

117. Luchsinger JA, Steinberg JS. Resolution of cardiomyopathy after ablation of atrial flutter. J Am Coll Cardiol 1998;32:205-210.
PUBMED | CROSSREF

118. Cruz FE, Cheriex EC, Smeets JL, Atié J, Peres AK, Penn OC, et al. Reversibility of tachycardia-induced cardiomyopathy after cure of incessant supraventricular tachycardia. J Am Coll Cardiol 1990;16:739-744.
PUBMED | CROSSREF

119. Jaggarao NS, Nanda AS, Daubert JP. Ventricular tachycardia induced cardiomyopathy: improvement with radiofrequency ablation. Pacing Clin Electrophysiol 1996;19:505-508.
PUBMED | CROSSREF

120. Wojcik B, Baranowski M, Chabowski A, Gorski J. Effect of atrial pacing on the level of bioactive sphingolipids in the heart ventricles of the rat. J Physiol Pharmacol 2015;66:385-389.
PUBMED

121. Wojcik B, Miklosz A, Zabielski P, Chabowski A, Gorski J. Effect of tachycardia on mRNA and protein expression of the principal components of the lipolytic system in the rat's heart ventricles. J Physiol Pharmacol 2017;68:731-736.
PUBMED

122. Hedley PL, Jørgensen P, Schlamowitz S, Wangari R, Moolman-Smook J, Brink PA, et al. The genetic basis of long QT and short QT syndromes: a mutation update. Hum Mutat 2009;30:1486-1511.
PUBMED | CROSSREF

123. Bai Y, Wang J, Shan H, Lu Y, Zhang Y, Luo X, et al. Sphingolipid metabolite ceramide causes metabolic perturbation contributing to HERG K+ channel dysfunction. Cell Physiol Biochem 2007;20:429-440.
PUBMED | CROSSREF

124. Marbán E. Cardiac channelopathies. Nature 2002;415:213-218.
PUBMED | CROSSREF

125. Itoh G, Tamura J, Suzuki M, Suzuki Y, Ikeda H, Koike M, et al. DNA fragmentation of human infarcted myocardial cells demonstrated by the nick end labeling method and DNA agarose gel electrophoresis. Am J Pathol 1995;146:1325-1331.
PUBMED

126. Krown KA, Page MT, Nguyen C, Zechner D, Gutierrez V, Comstock KL, et al. Tumor necrosis factor alpha-induced apoptosis in cardiac myocytes. Involvement of the sphingolipid signaling cascade in cardiac cell death. J Clin Invest 1996;98:2854-2865.
PUBMED | CROSSREF

127. Laderoute KR, Webster KA. Hypoxia/reoxygenation stimulates Jun kinase activity through redox signaling in cardiac myocytes. Circ Res 1997;80:336-344.
PUBMED | CROSSREF

128. Mallat Z, Tedgui A, Fontaliran F, Frank R, Durigon M, Fontaine G. Evidence of apoptosis in arrhythmogenic right ventricular dysplasia. N Engl J Med 1996;335:1190-1196.
PUBMED | CROSSREF

129. Tanaka M, Ito H, Adachi S, Akimoto H, Nishikawa T, Kasajima T, et al. Hypoxia induces apoptosis with enhanced expression of Fas antigen messenger RNA in cultured neonatal rat cardiomyocytes. Circ Res 1994;75:426-433.
PUBMED | CROSSREF

130. Hiroe M, Toyozaki T. Pathogenesis of myocardial injury and cell death in myocarditis: its relation to the fas/fas ligand pathway. In: Kitabatake A, Sasayama S, Francis GS, Okamoto H, editors. Heart failure. Tokyo: Springer; 2000. p.57-69.

131. Robert P, Tsui P, Laville MP, Livi GP, Sarau HM, Bril A, et al. EDG1 receptor stimulation leads to cardiac hypertrophy in rat neonatal myocytes. J Mol Cell Cardiol 2001;33:1589-1606.
PUBMED | CROSSREF

132. Landeen LK, Aroonsakool N, Haga JH, Hu BS, Giles WR. Sphingosine-1-phosphate receptor expression in cardiac fibroblasts is modulated by *in vitro* culture conditions. Am J Physiol Heart Circ Physiol 2007;292:H2698-H2711.
PUBMED | CROSSREF

133. Peters SL, Alewijnse AE. Sphingosine-1-phosphate signaling in the cardiovascular system. Curr Opin Pharmacol 2007;7:186-192.
PUBMED | CROSSREF

134. Kurdi M, Booz GW. Three 4-letter words of hypertension-related cardiac hypertrophy: TRPC, mTOR, and HDAC. J Mol Cell Cardiol 2011;50:964-971.
PUBMED | CROSSREF

135. Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, Singh SK, et al. Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. Science 2009;325:1254-1257.
PUBMED | CROSSREF

136. Yan H, Yi S, Zhuang H, Wu L, Wang DW, Jiang J. Sphingosine-1-phosphate ameliorates the cardiac hypertrophic response through inhibiting the activity of histone deacetylase-2. Int J Mol Med 2018;41:1704-1714.
PUBMED

137. Alonso-Montes C, Naves-Diaz M, Fernandez-Martin JL, Rodriguez-Reguero J, Moris C, Coto E, et al. New polymorphisms in human MEF2C gene as potential modifier of hypertrophic cardiomyopathy. Mol Biol Rep 2012;39:8777-8785.
PUBMED | CROSSREF

138. Kolesnick RN, Haimovitz-Friedman A, Fuks Z. The sphingomyelin signal transduction pathway mediates apoptosis for tumor necrosis factor, Fas, and ionizing radiation. Biochem Cell Biol 1994;72:471-474.
PUBMED | CROSSREF

139. Papathanasiou S, Rickelt S, Soriano M, Schips T, Maier HJ, Davos CH, et al. A novel mechanism of cardioprotection through TNF-α-induced ectopic expression of keratins K8 and K18. Nat Med 2015;21:1076.
PUBMED | CROSSREF

140. Jin ZQ, Zhou HZ, Zhu P, Honbo N, Mochly-Rosen D, Messing RO, et al. Cardioprotection mediated by sphingosine-1-phosphate and ganglioside GM-1 in wild-type and PKC ε knockout mouse hearts. Am J Physiol Heart Circ Physiol 2002;282:H1970-H1977.
PUBMED | CROSSREF

141. Bielawska AE, Shapiro JP, Jiang L, Melkonyan HS, Piot C, Wolfe CL, et al. Ceramide is involved in triggering of cardiomyocyte apoptosis induced by ischemia and reperfusion. Am J Pathol 1997;151:1257-1263.
PUBMED

142. Tao R, Hoover HE, Honbo N, Kalinowski M, Alano CC, Karliner JS, et al. High-density lipoprotein determines adult mouse cardiomyocyte fate after hypoxia-reoxygenation through lipoprotein-associated sphingosine 1-phosphate. Am J Physiol Heart Circ Physiol 2010;298:H1022-H1028.
PUBMED | CROSSREF

143. Zhang J, Honbo N, Goetzl EJ, Chatterjee K, Karliner JS, Gray MO. Signals from type 1 sphingosine 1-phosphate receptors enhance adult mouse cardiac myocyte survival during hypoxia. Am J Physiol Heart Circ Physiol 2007;293:H3150-H3158.
PUBMED | CROSSREF

144. Solaro RJ, Sheehan KA, Lei M, Ke Y. The curious role of sarcomeric proteins in control of diverse processes in cardiac myocytes. J Gen Physiol 2010;136:13-19.
PUBMED | CROSSREF

145. Brizuela L, Rábano M, Peña A, Gangoiti P, Macarulla JM, Trueba M, et al. Sphingosine 1-phosphate: a novel stimulator of aldosterone secretion. J Lipid Res 2006;47:1238-1249.
PUBMED | CROSSREF

146. Marino A, Sakamoto T, Robador PA, Tomita K, Levi R. S1P receptor 1-mediated anti–renin-angiotensin system cardioprotection: pivotal role of mast cell aldehyde dehydrogenase type 2. J Pharmacol Exp Ther 2017;362:230-242.
PUBMED | CROSSREF

147. Haass NK, Nassif N, McGowan EM. Switching the sphingolipid rheostat in the treatment of diabetes and cancer comorbidity from a problem to an advantage. BioMed Res Int 2015;2015:165105.
PUBMED | CROSSREF

148. Yin Z, Fan L, Wei L, Gao H, Zhang R, Tao L, et al. FTY720 protects cardiac microvessels of diabetes: a critical role of S1P1/3 in diabetic heart disease. PLoS One 2012;7:e42900.
PUBMED | CROSSREF

149. Igarashi J, Erwin PA, Dantas AP, Chen H, Michel T. VEGF induces S1P1 receptors in endothelial cells: Implications for cross-talk between sphingolipid and growth factor receptors. Proc Natl Acad Sci U S A 2003;100:10664-10669.
PUBMED | CROSSREF

150. Patten IS, Rana S, Shahul S, Rowe GC, Jang C, Liu L, et al. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature 2012;485:333-338.
PUBMED | CROSSREF

151. Alewijnse AE, Peters SL, Michel MC. Cardiovascular effects of sphingosine-1-phosphate and other sphingomyelin metabolites. Br J Pharmacol 2004;143:666-684.
PUBMED | CROSSREF

152. de Faria Poloni J, Chapola H, Feltes BC, Bonatto D. The importance of sphingolipids and reactive oxygen species in cardiovascular development. Biol Cell 2014;106:167-181.
PUBMED | CROSSREF

153. Hussein AA, El-Dken ZH, Barakat N, Abol-Enein H. Renal ischaemia/reperfusion injury: possible role of aquaporins. Acta Physiol (Oxf) 2012;204:308-316.
PUBMED | CROSSREF

154. Xu L, Meissner G. Regulation of cardiac muscle Ca2+ release channel by sarcoplasmic reticulum lumenal Ca2+. Biophys J 1998;75:2302-2312.
PUBMED | CROSSREF

155. Bers DM. Calcium cycling and signaling in cardiac myocytes. Annu Rev Physiol 2008;70:23-49.
PUBMED | CROSSREF

156. Fearnley CJ, Roderick HL, Bootman MD. Calcium signaling in cardiac myocytes. Cold Spring Harb Perspect Biol 2011;3:a004242.
PUBMED | CROSSREF

157. Paur HE. Adrenaline-mediated biased agonism at the B2 adrenoceptor in an *in vivo* model of takutsubo cardiomyopathy. London: Imperial College London; 2012.

158. Kitatani K, Idkowiak-Baldys J, Bielawski J, Taha TA, Jenkins RW, Senkal CE, et al. Protein kinase C-induced activation of a ceramide/protein phosphatase 1 pathway leading to dephosphorylation of p38 MAPK. J Biol Chem 2006;281:36793-36802.
PUBMED | CROSSREF

159. Kitatani K, Idkowiak-Baldys J, Hannun YA. The sphingolipid salvage pathway in ceramide metabolism and signaling. Cell Signal 2008;20:1010-1018.
PUBMED | CROSSREF

160. Berry C, Touyz R, Dominiczak AF, Webb RC, Johns DG. Angiotensin receptors: signaling, vascular pathophysiology, and interactions with ceramide. Am J Physiol Heart Circ Physiol 2001;281:H2337-H2365.
PUBMED | CROSSREF

161. Gallinat S, Busche S, Schütze S, Krönke M, Unger T. AT2 receptor stimulation induces generation of ceramides in PC12W cells. FEBS Lett 1999;443:75-79.
PUBMED | CROSSREF

162. Johns DG, Osborn H, Webb RC. Ceramide: a novel cell signaling mechanism for vasodilation. Biochem Biophys Res Commun 1997;237:95-97.
PUBMED | CROSSREF

163. Jones MJ, Murray AW. Evidence that ceramide selectively inhibits protein kinase C-α translocation and modulates bradykinin activation of phospholipase D. J Biol Chem 1995;270:5007-5013.
PUBMED | CROSSREF

164. Lee JY, Hannun YA, Obeid LM. Ceramide inactivates cellular protein kinase Cα. J Biol Chem 1996;271:13169-13174.
PUBMED | CROSSREF

165. Zhang DX, Zou AP, Li PL. Ceramide reduces endothelium-dependent vasodilation by increasing superoxide production in small bovine coronary arteries. Circ Res 2001;88:824-831.
PUBMED | CROSSREF

166. Kennedy S, Kane KA, Pyne NJ, Pyne S. Targeting sphingosine-1-phosphate signalling for cardioprotection. Curr Opin Pharmacol 2009;9:194-201.
PUBMED | CROSSREF

167. Sun M, Miao Y, Wang P, Miao L, Liu L, Liu J. Urinary metabonomics study of heart failure patients with HILIC and RPLC separation coupled to TOF–MS. Chromatographia 2014;77:249-255.
CROSSREF

168. Glaros EN, Kim WS, Wu BJ, Suarna C, Quinn CM, Rye KA, et al. Inhibition of atherosclerosis by the serine palmitoyl transferase inhibitor myriocin is associated with reduced plasma glycosphingolipid concentration. Biochem Pharmacol 2007;73:1340-1346.
PUBMED | CROSSREF

169. Liu W, Min Z, Naumann R, Ke Y, Ulm S, Jin J, et al. PAK1 is a novel signal transducer attenuating cardiac hypertrophy. Circulation 2011;124:2702-2715.
PUBMED | CROSSREF

170. Wang Y, Tsui H, Ke Y, Shi Y, Li Y, Davies L, et al. Pak1 is required to maintain ventricular Ca^{2+} homeostasis and electrophysiological stability through SERCA2a regulation in mice. Circ Arrhythm Electrophysiol 2014;7:938-948.
PUBMED | CROSSREF

171. Liu W, Zi M, Tsui H, Chowdhury SK, Zeef L, Meng QJ, et al. A novel immunomodulator, FTY-720 reverses existing cardiac hypertrophy and fibrosis from pressure overload by targeting NFAT (nuclear factor of activated T-cells) signaling and periostin. Circ Heart Fail 2013;6:833-844.
PUBMED | CROSSREF

172. Chun J, Brinkmann V. A mechanistically novel, first oral therapy for multiple sclerosis: the development of fingolimod (FTY720, Gilenya). Discov Med 2011;12:213-228.
PUBMED

173. He L, Kim T, Long Q, Liu J, Wang P, Zhou Y, et al. Carnitine palmitoyltransferase-1b deficiency aggravates pressure overload-induced cardiac hypertrophy caused by lipotoxicity. Circulation 2012;126:1705-1716.
PUBMED | CROSSREF

174. Drake JI, Gomez-Arroyo J, Dumur CI, Kraskauskas D, Natarajan R, Bogaard HJ, et al. Chronic carvedilol treatment partially reverses the right ventricular failure transcriptional profile in experimental pulmonary hypertension. Physiol Genomics 2013;45:449-461.
PUBMED | CROSSREF

175. Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol 2009;54:609-615.
PUBMED | CROSSREF

176. Wen-Ting S, Fa-Feng C, Li X, Cheng-Ren L, Jian-Xun L. Chinese medicine shenfu injection for heart failure: a systematic review and meta-analysis. Evid Based Complement Alternat Med 2012;2012:713149.
PUBMED | CROSSREF

177. Ogawa R, Takahashi M, Hirose S, Morimoto H, Ise H, Murakami T, et al. A novel sphingosine-1-phosphate receptor agonist KRP-203 attenuates rat autoimmune myocarditis. Biochem Biophys Res Commun 2007;361:621-628.
PUBMED | CROSSREF

178. Kitabayashi H, Isobe M, Watanabe N, Suzuki J, Yazaki Y, Sekiguchi M. FTY720 prevents development of experimental autoimmune myocarditis through reduction of circulating lymphocytes. J Cardiovasc Pharmacol 2000;35:410-416.
PUBMED | CROSSREF

179. Sugita K, Kabashima K, Sakabe J, Yoshiki R, Tanizaki H, Tokura Y. FTY720 regulates bone marrow egress of eosinophils and modulates late-phase skin reaction in mice. Am J Pathol 2010;177:1881-1887.
PUBMED | CROSSREF

180. Sawicka E, Zuany-Amorim C, Manlius C, Trifilieff A, Brinkmann V, Kemeny DM, et al. Inhibition of Th1- and Th2-mediated airway inflammation by the sphingosine 1-phosphate receptor agonist FTY720. J Immunol 2003;171:6206-6214.
PUBMED | CROSSREF

181. Nixon GF. Sphingolipids in inflammation: pathological implications and potential therapeutic targets. Br J Pharmacol 2009;158:982-993.
PUBMED | CROSSREF

182. Bennett LL, Turcotte K. Eliglustat tartrate for the treatment of adults with type 1 Gaucher disease. Drug Des Devel Ther 2015;9:4639-4647.
PUBMED | CROSSREF

183. Shayman JA. The design and clinical development of inhibitors of glycosphingolipid synthesis: will invention be the mother of necessity? Trans Am Clin Climatol Assoc 2013;124:46-60.
PUBMED

184. Shayman JA. Developing novel chemical entities for the treatment of lysosomal storage disorders: an academic perspective. Am J Physiol Renal Physiol 2015;309:F996-F999.
PUBMED | CROSSREF

185. Shayman JA, Larsen SD. The development and use of small molecule inhibitors of glycosphingolipid metabolism for lysosomal storage diseases. J Lipid Res 2014;55:1215-1225.
PUBMED | CROSSREF

186. Colussi DJ, Jacobson MA. Patient-derived phenotypic high-throughput assay to identify small molecules restoring lysosomal function in Tay-Sachs disease. SLAS Discov 2019;24:295-303.
PUBMED | CROSSREF

187. Yue WW, Mackinnon S, Bezerra GA. Substrate reduction therapy for inborn errors of metabolism. Emerg Top Life Sci 2019;3:63-73.
CROSSREF

188. Brady RO. Enzyme replacement for lysosomal diseases. Annu Rev Med 2006;57:283-296.
PUBMED | CROSSREF

189. Futerman AH, Sussman JL, Horowitz M, Silman I, Zimran A. New directions in the treatment of Gaucher disease. Trends Pharmacol Sci 2004;25:147-151.
PUBMED | CROSSREF

190. Cox TM, Cachón-González MB. The cellular pathology of lysosomal diseases. J Pathol 2012;226:241-254.
PUBMED | CROSSREF

191. Schiffmann R, Kopp JB, Austin HA 3rd, Sabnis S, Moore DF, Weibel T, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA 2001;285:2743-2749.
PUBMED | CROSSREF

192. Zarate YA, Hopkin RJ. Fabry's disease. Lancet 2008;372:1427-1435.
PUBMED | CROSSREF

193. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart 2007;93:528-535.
PUBMED | CROSSREF

194. Frustaci A, Chimenti C, Ricci R, Natale L, Russo MA, Pieroni M, et al. Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. N Engl J Med 2001;345:25-32.
PUBMED | CROSSREF

195. Young E, Mills K, Morris P, Vellodi A, Lee P, Waldek S, et al. Is globotriaosylceramide a useful biomarker in Fabry disease? Acta Paediatr Suppl 2005;94:51-54.
PUBMED | CROSSREF

196. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, et al. Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. N Engl J Med 2001;345:9-16.
PUBMED | CROSSREF

197. Nicholls K, Olivotto I, Ohashi T, Williams H, Jain V, Skuban N. The effects of long-term migalastat treatment in Fabry disease patients previously treated with enzyme replacement therapy who have migalastat-amenable variants with low alpha-galactosidase A response in the in vitro migalastat amenability assay. Mol Genet Metab 2019;126:S108.
CROSSREF

198. Narita A, Shirai K, Itamura S, Matsuda A, Ishihara A, Matsushita K, et al. Ambroxol chaperone therapy for neuronopathic Gaucher disease: a pilot study. Ann Clin Transl Neurol 2016;3:200-215.
PUBMED | CROSSREF

199. Maegawa GH, Tropak MB, Buttner JD, Rigat BA, Fuller M, Pandit D, et al. Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. J Biol Chem 2009;284:23502-23516.
PUBMED | CROSSREF

200. Clarke JT, Mahuran DJ, Sathe S, Kolodny EH, Rigat BA, Raiman JA, et al. An open-label Phase I/II clinical trial of pyrimethamine for the treatment of patients affected with chronic GM2 gangliosidosis (Tay-Sachs or Sandhoff variants). Mol Genet Metab 2011;102:6-12.
PUBMED | CROSSREF

201. Lieberman AP, Puertollano R, Raben N, Slaugenhaupt S, Walkley SU, Ballabio A. Autophagy in lysosomal storage disorders. Autophagy 2012;8:719-730.
PUBMED | CROSSREF

202. Seranova E, Connolly KJ, Zatyka M, Rosenstock TR, Barrett T, Tuxworth RI, et al. Dysregulation of autophagy as a common mechanism in lysosomal storage diseases. Essays Biochem 2017;61:733-749.
PUBMED | CROSSREF

203. Villamizar-Schiller IT, Pabón LA, Hufnagel SB, Serrano NC, Karl G, Jefferies JL, et al. Neurological and cardiac responses after treatment with miglustat and a ketogenic diet in a patient with Sandhoff disease. Eur J Med Genet 2015;58:180-183.
PUBMED | CROSSREF

204. Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, Liu Y, et al. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. Cell Metab 2007;5:167-179.
PUBMED | CROSSREF

205. Chavez JA, Summers SA. A ceramide-centric view of insulin resistance. Cell Metab 2012;15:585-594.
PUBMED | CROSSREF

206. Hojjati MR, Li Z, Zhou H, Tang S, Huan C, Ooi E, et al. Effect of myriocin on plasma sphingolipid metabolism and atherosclerosis in apoE-deficient mice. J Biol Chem 2005;280:10284-10289.
PUBMED | CROSSREF

207. Holland WL, Summers SA. Sphingolipids, insulin resistance, and metabolic disease: new insights from *in vivo* manipulation of sphingolipid metabolism. Endocr Rev 2008;29:381-402.
PUBMED | CROSSREF

208. Goodwin AJ, Leadley SR, O'neill L, Duffield PJ, McKechnie MT, Pugh S. Process and apparatus for plasma coating, substrates coated by this metod or apparatus. Patent No. WO 2005110626A2. 2008.

209. Kotronen A, Seppänen-Laakso T, Westerbacka J, Kiviluoto T, Arola J, Ruskeepää AL, et al. Comparison of lipid and fatty acid composition of the liver, subcutaneous and intra-abdominal adipose tissue, and serum. Obesity (Silver Spring) 2010;18:937-944.
PUBMED | CROSSREF

210. Kolter T. A view on sphingolipids and disease. Chem Phys Lipids 2011;164:590-606.
PUBMED | CROSSREF

211. Egom EE, Mamas MA, Chacko S, Stringer SE, Charlton-Menys V, El-Omar M, et al. Serum sphingolipids level as a novel potential marker for early detection of human myocardial ischaemic injury. Front Physiol 2013;4:130.
PUBMED | CROSSREF

212. Schatz P, Witt H, Peter E, Ternes P, Mappes P, Katus HA, et al. Means and methods for diagnosing heart failure on the basis of cholesterol parameters, sphingomyelins and/or triacylglycerols. Patent No. WO2016016258A1. 2017.

213. Fine B, Marx A, Topkara V, Gomez E, Vunjak-Novakovic G, Colombo P. An integrated analysis of metabolomics after left ventricular assist device implantation. J Heart Lung Transplant 2017;36:S93.
CROSSREF

214. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, et al. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. Circ Heart Fail 2011;4:266-275.
PUBMED | CROSSREF

215. Lecour S, Smith RM, Woodward B, Opie LH, Rochette L, Sack MN. Identification of a novel role for sphingolipid signaling in TNF α and ischemic preconditioning mediated cardioprotection. J Mol Cell Cardiol 2002;34:509-518.
PUBMED | CROSSREF

216. Vessey DA, Li L, Honbo N, Karliner JS. Sphingosine 1-phosphate is an important endogenous cardioprotectant released by ischemic pre- and postconditioning. Am J Physiol Heart Circ Physiol 2009;297:H1429-H1435.
PUBMED | CROSSREF

217. Deutschman DH, Carstens JS, Klepper RL, Smith WS, Page MT, Young TR, et al. Predicting obstructive coronary artery disease with serum sphingosine-1-phosphate. Am Heart J 2003;146:62-68.
PUBMED | CROSSREF

218. Klevstig M, Ståhlman M, Lundqvist A, Scharin Täng M, Fogelstrand P, Adiels M, et al. Targeting acid sphingomyelinase reduces cardiac ceramide accumulation in the post-ischemic heart. J Mol Cell Cardiol 2016;93:69-72.
PUBMED | CROSSREF

219. Grösch S, Schiffmann S, Geisslinger G. Chain length-specific properties of ceramides. Prog Lipid Res 2012;51:50-62.
PUBMED | CROSSREF

220. Jiang Y, DiVittore NA, Kaiser JM, Shanmugavelandy SS, Fritz JL, Heakal Y, et al. Combinatorial therapies improve the therapeutic efficacy of nanoliposomal ceramide for pancreatic cancer. Cancer Biol Ther 2011;12:574-585.
PUBMED | CROSSREF

221. Kester M, Bassler J, Fox TE, Carter CJ, Davidson JA, Parette MR. Preclinical development of a C6-ceramide NanoLiposome, a novel sphingolipid therapeutic. Biol Chem 2015;396:737-747.
PUBMED | CROSSREF

222. Hankins JL, Doshi UA, Haakenson JK, Young MM, Barth BM, Kester M. The therapeutic potential of nanoscale sphingolipid technologies. Handb Exp Pharmacol 2013:197-210.
PUBMED | CROSSREF