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REVIEW

Emerging roles of the acid sphingomyelinase/ceramide pathway in metabolic and cardiovascular diseases: Mechanistic insights and therapeutic implications

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Abstract

Metabolic diseases have emerged as a leading cause of mortality from non-communicable diseases, posing a significant global public health challenge. Although the association between ceramides (Cers) and metabolic diseases is well-established, the role of the acid sphingomyelinase (ASMase)/Cer pathway in these diseases remains underexplored. This review synthesizes recent research on the biological functions, regulatory mechanisms, and targeted therapies related to the ASMase/Cer pathway in metabolic conditions, including obesity, diabetes, non-alcoholic fatty liver disease, and cardiovascular disease. The effects of the ASMase/Cer pathway on metabolic disease-related indicators, such as glycolipid metabolism, insulin resistance, inflammation, and mitochondrial homeostasis are elucidated. Moreover, this article discusses the therapeutic strategies using ASMase/Cer inhibitors for inverse prevention and treatment of these metabolic diseases in light of the possible efficacy of blockade of the ASMase/Cer pathway in arresting the progression of metabolic diseases. These insights offered herein should provide insight into the contribution of the ASMase/Cer pathway to metabolic diseases and offer tools to develop therapeutic interventions for such pathologies and their severe complications.

Key Words: Acid sphingomyelinase; Ceramide; Metabolic and cardiovascular diseases; Glycolipid metabolism; Inflammation; Mitochondrial homeostasis

Core Tip: Metabolic diseases represent a major global public health challenge, and the mechanisms of the acid sphingomyelinase/ceramide (ASMase/Cer) pathway in these diseases remain under-explored. This review synthesizes recent studies on the biological functions, regulatory mechanisms, and targeted therapies associated with the ASMase/Cer pathway in metabolic conditions including obesity, diabetes mellitus, non-alcoholic fatty liver disease, and cardiovascular disease. The effects of the ASMase/Cer pathway on glucose-lipid metabolism, insulin resistance, inflammation and mitochondrial homeostasis are elucidated. The insights provided in this review could aid in the development of therapeutic interventions for metabolic diseases and their severe complications.

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INTRODUCTION

Since the year 2000, the prevalence of metabolic diseases has consistently increased, particularly in countries with a high sociodemographic index[1]. Regions characterized by poor lifestyles, economic conditions, and health education, as well as urban industrialization, and insufficient medical security, are more susceptible to the development of metabolic diseases[1,2]. Metabolic diseases encompass a range of conditions caused by metabolic disorders, such as obesity, diabetes mellitus (DM), and cardiovascular disease (CVD)[3]. Specific metabolic disturbances include carbohydrate metabolism disorders [insulin resistance (IR), insufficient insulin secretion, and hyperglycemia], lipid metabolism disorders (hypercholesterolemia and hypertriglyceridemia), protein metabolism disorders (amino acid metabolism abnormalities and urea cycle defects), energy metabolism abnormalities (mitochondrial dysfunction), endocrine imbalances (thyroid and adrenal dysfunction), antioxidant system disorders, and vitamin and mineral metabolism disorders (vitamin D and iron metabolism issues)[4]. When metabolic disorders occur, the body's cells respond poorly to insulin, leading to IR, which makes it harder for cells to take up glucose and raises blood sugar levels[5]. Metabolic disorders also cause dysregulation of the cellular antioxidant system, causing an increase in reactive oxygen species (ROS) and leading to oxidative stress[6]. Furthermore, intricate bidirectional relationships exist among these conditions.

Metabolic diseases are often metabolic disorders causing excessive accumulation of triglycerides. Recent research indicates that the progression of metabolic diseases involves more than just triglyceride accumulation in adipose tissue; it also encompasses the production and extracellular accumulation of specific lipids, such as sphingolipids[7]. Ceramide (Cer) is central to sphingolipid metabolism, with the acid sphingomyelinase (ASMase) pathway for the synthesis of Cer being the fastest one. These deleterious lipid metabolites intricately regulate insulin action, inflammation, and cellular metabolic pathways[8]. The ASMase/Cer pathway plays a pivotal role in numerous physiological and pathological processes. The importance of studying this pathway is underscored by several key points: (1) Cer, as a crucial cellular signaling molecule, profoundly influences cell survival, death, and other physiological functions by regulating various signaling pathways [such as phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase, and nuclear factor-κB (NF-κB)]; and (2) Cer accumulation is closely associated with metabolic diseases, neurodegenerative diseases, cancer, and immune regulation. Investigating this pathway aids in elucidating the molecular mechanisms underlying these diseases and may provide novel therapeutic targets. This review aims to summarize recent findings on the role of the ASMase/Cer pathway in cell signaling and the mechanisms of metabolic diseases, enhancing our understanding of the potential mechanisms behind these conditions and providing a theoretical foundation for potential therapeutic strategies[8-10]. The review first explores the fundamental aspects of the ASMase/Cer pathway, outlining its key components and how they interact within the cell. It then delves into the various ways in which this pathway is involved in cell signaling processes, highlighting the complex networks of communication it facilitates.

THE ASMASE/CER PATHWAY

SMase encompasses acidic (ASMase or SMPD1), neutral (NSMase or SMPD2, 3, 4), and alkaline SMase (Alk-SMase or ENPP7), which differ from each other by their optimal pH and sub-cellular localization[8]. ASMase is ubiquitously expressed across various cell types, with particularly high expression in endothelial cells, surpassing that in hepatocytes or renal cells by up to 20-fold. This facilitates Cer production within specific cellular compartments, such as the plasma membrane and lysosomes[9]. NSMase is located in the cell membrane and cytoplasm and is involved in sphingomyelin metabolism on the cell surface[9,11]. Alk-SMase is a hydrolase enzyme that aids in the digestion of sphingomyelin in the intestine, catalyzing the production of Cer and phosphocholine from sphingomyelin, with important biological functions in phospholipid metabolism[12,13]. While the location, conditions for activation, and function of these different SMases (ASMase, NSMase, and Alk-SMase) differ, they nevertheless participate combinatively in cellular reactions, immune responses, apoptosis, metabolic regulation, and, in general, cell health and disease states.

ASMase plays a crucial role in regulating diverse cellular processes. These processes include metabolism, membrane structural dynamics, signal transduction, immune modulation, inflammation, response to bacterial infections, and apoptosis[9,10,14]. A vital bioactive lipid and primary sphingolipid metabolite, exerts multiple cellular effects, such as IR, oxidative stress, endoplasmic reticulum (ER) stress, inflammation, energy metabolism, and apoptosis[15,16]. Cer synthesis can occur by *de novo* synthesis, conversion from sphingomyelin (SM), and from the salvage pathway, and conversion from SM is the most direct and fastest pathway[17,18]. The regulation of the ASMase/Cer pathway is complex, involving multiple intracellular and extracellular signaling pathways, enzyme activity modulation, and external stimuli. The main regulatory factors and mechanisms are as follows: (1) Cellular stress and environmental stimuli: Oxidative stress can activate ASMase by generating free radicals[19]. Ultraviolet radiation induces ASMase activation in skin cells[20]. Cytokines and extreme temperature changes can activate ASMase[21,22]; (2) Signaling pathway regulation: MAPK and NF-κB pathways can activate ASMase or induce its expression. The PI3K/AKT pathway inhibits ASMase activity, reducing Cer production[23,24]; (3) Lipid metabolism regulation: Sphingomyelin is the substrate for ASMase, and the intracellular levels of sphingomyelin directly influence ASMase activity[25]; (4) Post-translational modifications: ASMase activity is regulated by phosphorylation, with certain kinases [such as protein kinase C (PKC) and AMP-activated protein kinase (AMPK)] enhancing its activity through phosphorylation[26]. ASMase stability and activity can also be regulated *via* the ubiquitin-proteasome pathway. Acetylation of ASMase affects its function, with deacetylation enhancing its activity[27,28]; and (5) Gene expression regulation: Transcription factors such as Sp1 and sterol regulatory element binding protein 1 (SREBP-1) increase the transcription of the *ASMase* gene[29].

The ASMase/Cer pathway is implicated in many cellular functions, including cellular metabolism, immune responses, and apoptosis. Furthermore, the impact of this pathway is critical to glycolipid metabolism, IR, inflammation, and mitochondrial homeostasis, with implications for the pathogenesis of obesity, DM, non-alcoholic fatty liver disease (NAFLD), and CVD[9,30,31].

THE ASMASE/CER PATHWAY IN METABOLIC AND CVDS

Disruption of glucose homeostasis and IR

Transport and subsequent oxidation of glucose into pyruvate or conversion of glucose into carbon dioxide and water is referred to as glucose metabolism[32]. Glucose uptake is facilitated mainly in muscle and adipose tissues by insulin, and the normal blood glucose levels are maintained[33]. However, this process is impaired by IR, a precursor to type 2 DM (T2DM), hepatic steatosis, and CVD through decreased glucose uptake in muscle, adipose, and liver cells[5,25,33,34]. Therefore, there is a close relationship between IR and glucose metabolism abnormalities in metabolic illnesses.

In metabolic diseases, disorders of glucose metabolism and ASMase/Cer are closely related. ASMase activity and Cer buildup in liver, muscle, and adipose tissue is markedly elevated by a high-fat diet (HFD), according to animal studies[14,35,36]. According to clinical research, people with T2DM and obesity had higher levels of Cer in their plasma and adipose tissue[9,14,37,38]. Patients with IR and T2DM had higher levels of C16-Cer and C18-Cer[39]. By inhibiting the PI3K/AKT signaling pathway and lowering the expression of glucose transporters type 4 transporter proteins, which impact glucose absorption and metabolism, C16-Cer accumulation results in IR[40]. By controlling fatty acid release and changing adipocyte differentiation in adipose tissue, C18-Cer encourages fat formation and raises IR[41]. C16-Cer and C18-Cer levels can be used to gauge the degree of metabolic abnormalities in the condition. By activating inflammatory pathways (*e.g.*, NF-κB) and NADPH oxidative enzymes, the accumulation of C16-Cer and C18-Cer in arterial endothelial cells raises oxidative stress, resulting in endothelial dysfunction and vascular endothelial cell injury[30]. Increased SMase and C6-Cer levels impact vasoconstriction and endothelial cell function[42]. Atherosclerosis, coronary heart disease, and heart failure are among the cardiovascular disorders that can be predicted by looking for changes in C16, C18, SMase, and C6 Cer.

This elevated ASMase activity is also evident in patients with NAFLD and heart failure. High glucose levels and ER stress stimulate ASMase activation, leading to Cer accumulation and glucose intolerance in diabetic cells[43]. Hypertensive patients also exhibit increased plasma ASMase activity and elevated levels of NADPH oxidase 2 (NOX2)-derived peptides[43]. Various stimuli associated with metabolic diseases, such as chemo-therapeutics, high glucose, lipopolysaccharides (LPS), and palmitic acid, activate ASMase *via* PKC delta, significantly increasing Cer levels through SM metabolism[30,44-46] (Figure 1). The activation of the ASMase/Cer pathway by high glucose and coagulation factors further promotes Cer synthesis, inhibits insulin signaling, induces IR, and increases the risk of CVD in patients with T2DM and NAFLD[9,37,38].

When hyperlipidemia are present, IR progresses due to a variety of causes. Adipose tissue plays a key role in the development of IR by releasing lipids, including Cer. This inhibits insulin signaling components such as the insulin receptor, insulin receptor substrate, or AKT[33,47]. Additionally, Cer enhances skeletal muscle IR and triggers inflammation in macrophages through its interaction with low-density lipoprotein (LDL), increasing the expression of pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α)[48].

In skeletal muscle, Cer diminishes AKT activity through mechanisms involving PKC zeta and protein phosphatase 2A [36,49] (Figure 1). The decrease in AKT activity increases the expression of SREBP1c, which increases lipid synthesis and declines lipid degradation, finally causing IR in skeletal muscle[49] (Figure 1). Elevated IR in skeletal muscle and adipose tissues leads to the elevation of blood glucose and lipid levels and insufficient renal filtration, followed by osmotic diuresis[50]. This accelerates the utilization of fat and protein, thereby advancing the progression of diabetes. Hyperglycemia triggers immune defenses and inflammation, with TNF-α disrupting insulin receptor tyrosine phosphorylation. This impedes insulin signaling, increases IR, and raises blood glucose levels, thus perpetuating a vicious cycle[51].

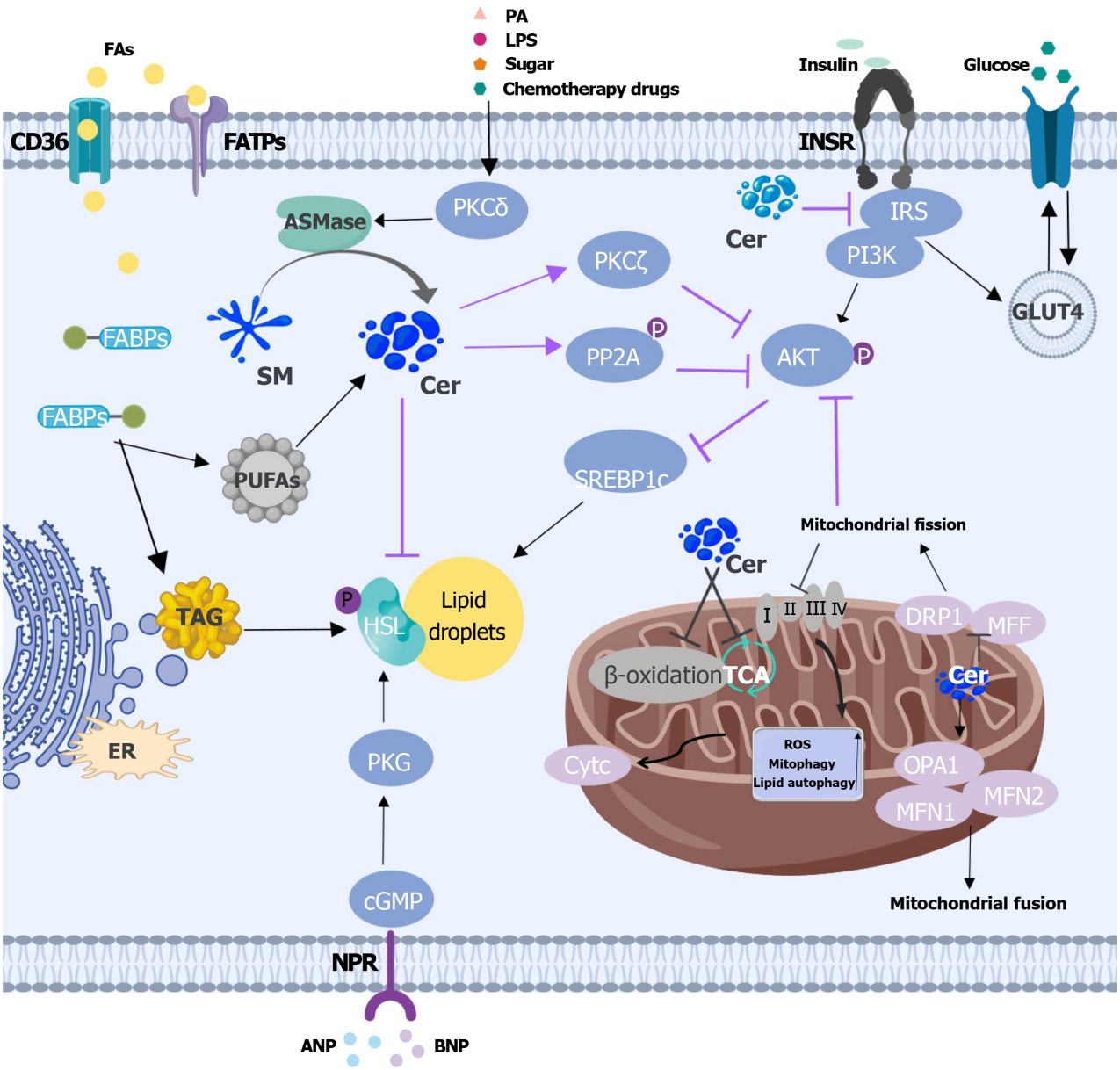

Figure 1 The acid sphingomyelinase/ceramide pathway regulates glycolipid metabolism and mitochondrial homeostasis in liver, fat, and skeletal muscle cells. Palmitic acid, lipopolysaccharides, sugar, chemicals can activate acid sphingomyelinase *via* protein kinase C delta, causing an increase in ceramide (Cer). Oxidative stress/mitochondrial stress (endoplasmic reticulum) and polyunsaturated fatty acids also cause Cer accumulation. Cer reduces AKT activity through the mechanism of protein kinase C delta zeta and protein phosphatase 2A, increases SREBP1c expression, and affects glucose and Cer can also affect insulin receptor substrate signalling, thereby affecting PI3K/AKT and glucose transporters type 4 and reducing glucose uptake. Cer can increase the permeability of CD36 and fatty acid transport proteins to fatty acids, increasing TAG synthesis, and also inhibit hormone-sensitive triglyceride lipase enzyme activity, decreasing TAG catabolism. And atrial natriuretic peptide and brain natriuretic peptide can activate HSLase through cyclic guanosine mono-phosphate/protein kinase G. In mitochondria, Cer affects the mitochondrial respiratory chain, β-oxidation, and the tricarboxylic acid cycle causing decreased ATP synthesis decreased ATP production, elevated reactive oxygen species, lipid autophagy, and mitochondrial autophagy. Cer can affect the respiratory chain protein complex II affecting membrane permeability, and pro-apoptotic substances (*e.g.*, cytochrome c) are released from mitochondria. Cer is released from mitochondria through an increase in the dynamin-related protein 1 expression, decreasing mitochondrial fusion protein 1 and optic atrophy protein 1 expression, increasing mitochondrial fission and decreasing fusion. FAs: Fatty acids; PA: Palmitic acid; LPS: Lipopolysaccharides; FATPs: Fatty acid transport proteins; ASMase: Acid sphingomyelinase; PKC: Protein kinase C; INSR: Insulin receptor; Cer: Ceramide; IRS: Insulin receptor substrate; PI3K: Phosphatidylinositol 3-kinase; FABPs: Fatty acid-binding proteins; SM: Sphingomyelin; PP2A: Protein phosphatase 2A; AKT: Protein kinase B; GLUT4: Glucose transporters type 4; PUFAs: Polyunsaturated fatty acids; SREBP1c: Sterol regulatory element binding protein 1c; TAG: Triacylglycerol; HSL: Hormone-sensitive triglyceride lipase; DRP1: Dynamin-related protein 1; MFF: Mitochondrial fission factor; ER: Endoplasmic reticulum; PKG: Protein kinase G; cGMP: Cyclic guanosine mono-phosphate; ROS: Reactive oxygen species; OPA1: Optic atrophy protein 1; MFN1: Mitochondrial fusion protein 1; MFN2: Mitochondrial fusion protein 2; NPR: Natriuretic peptide receptors; ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide.

Enhanced glucose metabolism and IR *via* inhibition of the ASMase/Cer pathway improves conditions including DM, NAFLD, and CVD. Study have shown that the inhibition of the ASMase/Cer pathway ameliorates hyperglycemia and β-cell damage in diabetic mice and improves IR in diabetic patients[37]. Additionally, the knockdown of ASMase using small interfering RNA has been shown to prevent endothelial dysfunction and enhance insulin sensitivity by inhibiting the overproduction of ROS derived from NOX. In rodent models of CVD, the pharmacological inhibition of Cer has been effective in preventing heart failure and addressing CVD-related and IR-related issues such as hypertension and atherosclerosis[52]. Drugs that promote muscle contraction have been found to reduce overall Cer content, thereby improving IR and associated metabolic diseases. Furthermore, adiponectin, which possesses Cer hydrolase activity, degrades Cer and exerts anti-diabetic, cardio-protective, and insulin-sensitizing effect[53].

Triacylglycerol accumulation and steatosis

ASMase-Cer is also closely linked to lipid metabolism disorders. Lipids play a crucial role in energy storage and cellular membrane composition. Insufficient glucose availability or disrupted glucose metabolism can inhibit proper lipid metabolism, to which cellular signaling may become disrupted and cause ketoacidosis, IR, and hyperlipidemia[54]. These metabolic disruptions contribute to the development of NAFLD, diabetes, obesity, and atherosclerosis. In obesity and NAFLD, the synthesis of saturated fatty acids increases *de novo* Cer synthesis and activates SM pathway[55].

Lipid droplet and Cer accumulation are closely linked to NAFLD and frequently co-occur with T2DM and immune dysfunction[56]. Elevated SM levels in non-alcoholic steatohepatitis (NASH) mice may be associated with increased ASMase activity[57]. NASH-induced inflammation and oxidative stress activate ASMase, raising blood Cer levels and impacting multiple signaling pathways. Cer can promote the expression and activity of fatty acid transporter CD36 and accelerate the trans-membrane transport of free fatty acids. Cer reduces AKT phosphorylation through the insulin receptor tyrosine kinase/PI3K pathway, activates the expression of SREBP, which promotes the presence of free fatty acids in response to various enzymes, increasing triacylglycerol (TAG) synthesis and reducing its breakdown[36,58] (Figure 1). Additionally, Cer inhibits hormone-sensitive triglyceride lipase (HSL) in reducing TAG breakdown[59] (Figure 1). Alternatively, the natriuretic peptides (atrial natriuretic peptide and brain natriuretic peptide) stimulate the cyclic guanosine mono-phosphate-protein kinase G pathway that causes HSL activation and breakdown of TAG[60] (Figure 1).

Atherosclerosis, a significant underlying pathology for CVD, is the process of lipid and inflammatory cell accumulation into artery walls. In a porcine familial hypercholesterolemia model mimicking human atherosclerosis, the necrotic core co-localized with ether-linked phosphatidylcholine, Cer, or lysophosphatidylcholine[61]. The ASMase/Cer pathway promotes LDL transport to endothelial cells, leading to LDL aggregation, macrophage foam cell formation, and accelerated atherosclerosis and plaque rupture[62]. Thus, the activation of the ASMase/Cer pathway or decreased natriuretic peptides inhibits cyclic guanosine mono-phosphate and cyclic adenosine monophosphate signaling, reducing HSL activity and TAG breakdown, promoting obesity, T2DM, NAFLD, and CVD progression.

Inflammation and immune dysregulation

In metabolic diseases, inflammation and ASMase/Cer work together to promote disease progression. Inflammation, a pathological defensive response to factors such as trauma or infection, is commonly associated with metabolic diseases [63]. Obesity induces the release of pro-inflammatory and anti-inflammatory cytokines from adipose tissue, which results in persistent systemic inflammation[64,65]. This mild inflammation is exacerbated by the presence of macrophages in fatty tissue, leading to the onset of T2DM and CVD[65].

The activation of the ASMase/Cer pathway and the accumulation of Cer and other lipotoxic substances inevitably lead to ER stress in conditions such as obesity, diabetes, and NAFLD[9,37,38]. This process is accompanied by varying degrees of inflammation, which promote the progression of these metabolic diseases. Research by Alarcón-Vila *et al*[10] has demonstrated that a HFD or genetic mutations in methionine adenosyltransferase 1A reduce S-adenosyl-L-methionine/S-adenosylhomocysteine levels, activating the ASMase/Cer pathway and promoting inflammation in conditions resembling steatohepatitis[10]. IR, either directly or through the ASMase/Cer pathway, triggers the formation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes, leading to the activation of caspase-1 and the secretion of pro-inflammatory cytokines such as IL-1β and IL-18, thereby inducing inflammation[35,51].

Obesity is frequently accompanied by an imbalance in gastric microbiota. The alteration of gut microbiota may influence the ASMase/Cer pathway through various mechanisms, including the release of LPS, disruption of bile acid metabolism, and the generation of inflammatory factors. This, in turn, can exacerbate both local and systemic inflammatory responses. Through positive feedback processes, this process may further accelerate the course of metabolic disorders, such as DM and NAFLD. Because of the reorganization of the cell membrane composition and permeability induced by excess Cer, pathogens stick to the outer part of the Toll-like receptor on macrophages. The association of this attachment with bridging proteins such as MyD88 that go on to recruit proinflammatory signaling molecules, including IL-1R associated kinase, TNF receptor associated factor 6 (TRAF6), transforming growth factor β-activated kinase 1, and transforming growth factor β-activated kinase 1 binding proteins 1 and 2 (TAB1 and TAB2). The recruitment of these proteins activates the NF-κB and MAPK pathways, as well as NLRP3 inflammasome. The activation of the NLRP3 inflammasome, in turn, activates caspase-1 and triggers the release of inflammatory cytokines, including TNF-α and ILs[35,51,66-69] (Figure 2).

Furthermore, Cer is involved in the recruitment of enzymes that promote ROS production, such as NOX. The increased generation of ROS leads to damage to endothelial cells, activating the ASMase/Cer pathway, which SM on lipoprotein particles, resulting in a continuous increase in Cer levels[45]. Moreover, ASMase mediates the impairment of endothelial function triggered by TNF-α through the suppression of endothelial nitric oxide synthase phosphorylation and the stimulation of the MAPK pathway. This process leads to elevated Cer levels and accumulation in vascular endothelial

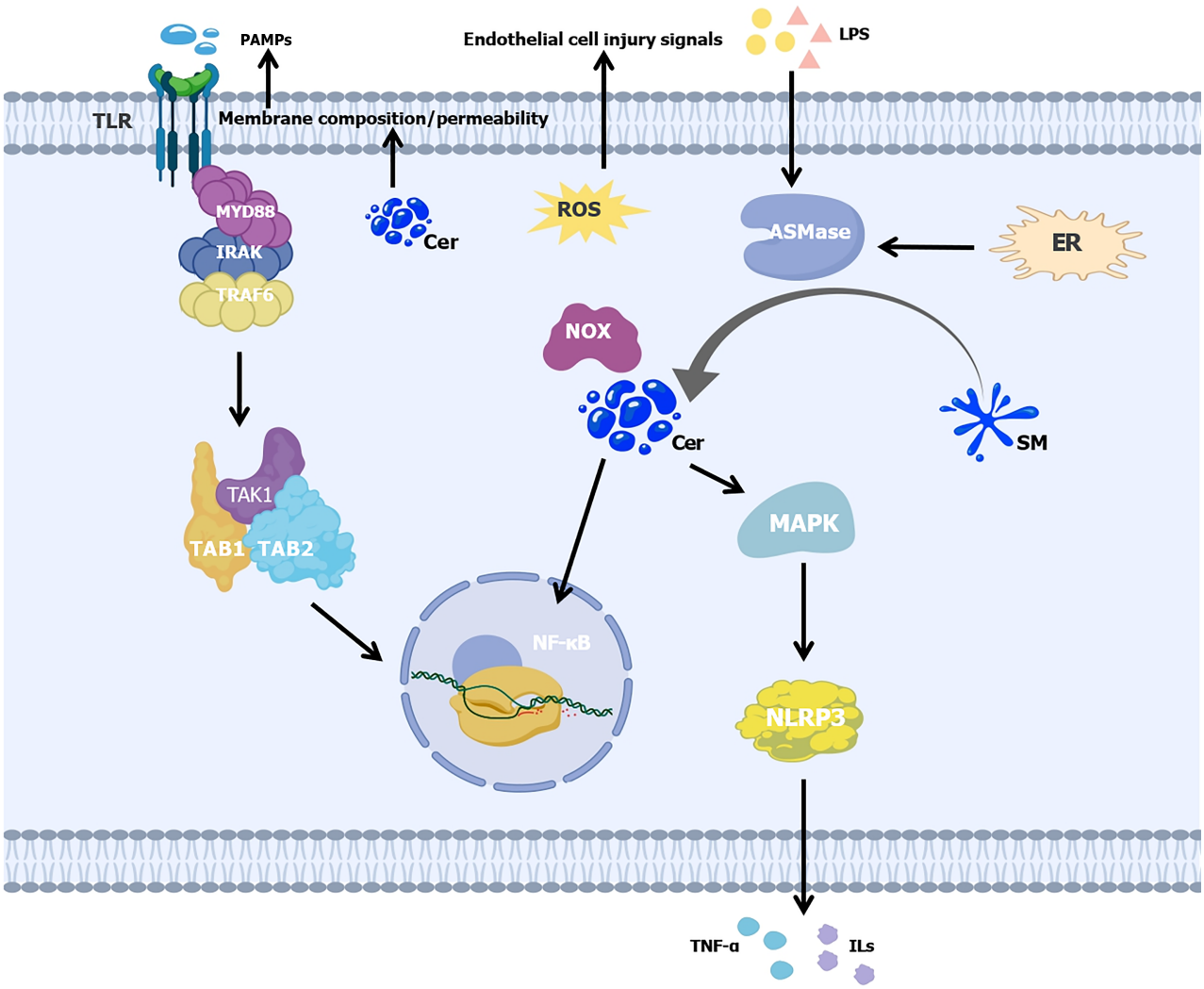

Figure 2 The acid sphingomyelinase/ceramide pathway induces chronic inflammation in macrophages. Activation of acid sphingomyelinase by bacterial product lipopolysaccharides, cell damage signalling and endoplasmic reticulum signalling causes increased ceramide. Pathogens attach to the extracellular segment of the Toll-like receptor on macrophages due to altered cell membrane composition and permeability caused by excess ceramide. This attracts bridging proteins like MyD88, activates the nuclear factor-κB and mitogen-activated protein kinase pathways, and activates the NOD-like receptor protein 3 inflammasome, which in turn activates caspase-1 and releases inflammatory cytokines (tumor necrosis factor-alpha and interleukins). Caspases 1 are activated and inflammatory cytokines (tumor necrosis factor-alpha and interleukins) are released when the NOD-like receptor protein 3 inflammasome is activated. PAMPs: Pathogen-associated molecular patterns; LPS: Lipopolysaccharides; TLR: Toll-like receptor; IRAK: Interleukin-1R associated kinase; TRAF6: Tumor necrosis factor receptor associated factor 6; Cer: Ceramide; ROS: Reactive oxygen species; ASMase: Acid sphingomyelinase; ER: Endoplasmic reticulum; NOX: NADPH oxidase; TAK1: Transforming growth factor β-activated kinase 1; TAB1: Transforming growth factor β-activated kinase 1 binding protein 1; TAB2: Transforming growth factor β-activated kinase 1 binding protein 2; MAPK: Mitogen-activated protein kinase; SM: Sphingomyelin; NF-κB: Nuclear factor-κB; NLRP3: NLR family pyrin domain containing 3; TNF-α: Tumor necrosis factor-alpha; ILs: Interleukins.

cells, stimulating cell death and inflammatory responses. This induces endothelial cell damage and potentially contributing to the development of atherosclerosis[19].

Therefore, reducing the accumulation of Cer is essential to slow down inflammation in metabolic diseases. According to a clinical study, astragalus and nicotinamide riboside decreased harmful lipid Cer levels and indicators of hepatic inflammation in NAFLD[70]. An additional clinical study demonstrated that fenofibrate and omega-3 fatty acids can lower plasma Cer levels and lessen the inflammatory response linked to CVD in NAFLD patients, improving heart and liver health[71].

Mitochondrial dysfunction and oxidative stress

Dysregulated energy metabolism and ASMase/Cer interactions influence in metabolic diseases. Mitochondria are an energy metabolism factory and play an important role here. Mitochondria are the main site of cellular energy production, where energy is generated through the tricarboxylic acid (TCA) cycle and fatty acid β oxidation in eukaryotic cells[72]. Homeostasis of mitochondria, so important for metabolic health, is composed of maintaining a stable population of mitochondria through appropriate fission and fusion, proper respiratory chain activity, effective oxidative stress, and adequate ATP production[73]. Recent research has shown that obesity due to excess nutrient supply depresses the activity of the mitochondrial electron transport chain and oxidative phosphorylation. This impact leads to increased

production of ROS and fragmentation of mitochondria[74,75]. Conditions such as obesity, IR, and T2DM are associated with a decrease in mitochondrial oxidative capacity and ATP generation, heightened oxidative stress, disturbed mitochondrial dynamics due to interrupted fission and fusion processes, impaired removal of damaged mitochondria (mitophagy), reduced mitochondrial DNA replication, and modifications in mitochondrial structure and quantity[74].

LOW MITOCHONDRIAL PERSPIRATION AND OXIDATIVE CAPACITY

The activation of ASMase and the subsequent accumulation of Cer act as mitochondrial metabolic antagonists. In rodent models of diet-induced obesity, Cer accumulates and results in hepatic mitochondrial dysfunction and precedes the IR and NAFLD that follow[76]. In the presence of obesity and T2DM, Cer accumulation adversely affects aspects of mitochondrial respiration-related metabolism, including the TCA cycle, membrane potential, and oxidative phosphorylation[77]. Cer accumulates within the outer membrane of the mitochondria, producing channels that enhance the outer membrane permeability and then cause the release of pro-apoptotic factors, such as Bcl-2, Bcl-xL, and cytochrome c, in the inner membrane space of the mitochondria (Figure 1). In the end, this process results in mitochondrial dysfunction and cell death[78,79]. Furthermore, mitochondrial Cer (C16:0) participates in the phosphorylation-mediated activation of the p38 AMPK protein kinase, disrupting mitochondrial membrane potential and promoting apoptosis[73]. Mitochondria exhibit close inter-connectivity with the ER through shared mitochondrial-associated membranes[67,80]. ER stress in NAFLD precipitates mitochondrial impairment, heightened enzymatic reactions involving ASMase and Cer synthases, increased mitochondrial Cer (C16:0) levels, and the activation of the AMPK/p38 MAPK pathway[76].

For example, in NASH, the activation of ASMase and ensuing accumulation of mitochondrial Cer may inhibit function of the mitochondrial ETC, enhance the production of ROS, and mobilize events such as mitophagy, lipophagy (lipid turnover), and β-oxidation disorders[81]. In states of nutrient excess (obesity), Cer decreases lipid β-oxidation and TCA cycle activities that result in suppression of ATP synthesis[82] (Figure 1). Moreover, Cer has also been shown to reduce the binding of tubulin to voltage-dependent anion channel 1 (VDAC1) and to interfere with ADP/ATP transport throughout mitochondria, thereby impairing ATP production[83]. Cer affects mitochondrial metabolism and also participates in cardiomyocyte function since Cer accumulation negatively affects the processes of energy metabolism and ultimately induces cardiomyocyte apoptosis[84]. In particular, Cer concentration in the inner mitochondrial membrane reduces ETC activity and respiratory capacity, whereas accumulation in the mitochondrial outer membrane increases membrane permeability, resulting in triggering apoptotic pathways[82,85]. On the outer mitochondrial membrane, Cer directly interacts with VDAC2, resulting in full opening of the VDAC2 channel to facilitate cytochrome c release and to decrease mitochondrial membrane potential by blocking ETC[85] (Figure 1). In a cardiomyocyte model, Bekhite *et al*[86] reported that an accumulation of long chain Cer leads to mitochondrial oxidative stress, which causes mitochondrial damage and dysfunction. Activation of the ASMase/Cer pathway activates membrane-bound NOX to generate ROS, leading to mitochondrial injury and contributing to the pathogenesis of diabetic cardiomyopathy[37].

Mitochondrial network dynamics disorderation

In obesity, T2DM, NAFLD, and CVD, where ASMase is activated and Cer accumulates, mitochondrial morphology is altered. They have smaller mitochondria, more fragmented mitochondria, and decreased fusion of mitochondria. To assess mitochondrial morphology in skeletal muscle cells, Elhage *et al*[87] used electron microscopy to show that skeletal muscle cells of obese and T2DM individuals were smaller than those isolated from lean individuals. Likewise, Guarini *et al*[88] showed that skeletal muscle cell mitochondria in Zucker obese rats are severely fragmented, leading to a 25% reduction in mitochondrial volume relative to control animals. Cers also prevent mitochondrial autophagy by changing the activity of autophagy-related proteins like mechanistic target of rapamycin and Unc-51-like kinase 1. This results in the intracellular buildup of damaged mitochondria, which worsens IR and dysfunctional lipid metabolism and raises the risk of type 2 diabetes and obesity[89-91].

Mitochondrial dysfunction is caused by an imbalance of mitochondrial dynamics, dominated by abnormal fission relative to fusion. However, Cer plays an important part in inducing mitochondrial fission by increasing the expression of dynamin-related protein 1 (DRP1)[86,92]. Cer treatment promotes mitochondrial fission, and inhibition of DRP1 using mitochondrial division inhibitor (mdivi-1) treatment robustly prevents Cer proponents of mitochondrial fission[86,92] (Figure 1). Cer-mediated mitochondrial fission in this process leads to diminished mitochondrial respiration, indicated by compromised complex II levels, excess ROS generation, and decreased AKT signaling[86] (Figure 1). Moreover, some studies demonstrated that the downregulation of ASMase transcription levels in the melanoma cell line B16-F1 resulted in decreased Cer levels[92,93]. This reduction in Cer promoted mitochondrial fusion by modulating the expression of key fusion proteins such as mitochondrial fusion protein 1 and optic atrophy protein 1, while concurrently inhibiting mitochondrial fission through the suppression of DRP1 expression[92,93] (Figure 1). Consequently, in the context of metabolic diseases, the activation of ASMase and the subsequent accumulation of Cer lead to aberrant mitochondrial dynamics characterized by reduced mitochondrial size, increased fragmentation, and enhanced mitophagy. Conversely, the down-regulation of ASMase expression promotes mitochondrial fusion, thereby ameliorating cellular energy metabolism disorders.

Therapeutic strategies targeting the ASMase/Cer pathway

The ASMase/Cer pathway serves as a pivotal regulator of glycolipid metabolism, inflammation, and mitochondrial homeostasis in the context of metabolic and CVDs. Inhibition of ASMase/Cer emerges as a crucial strategy for

ameliorating IR, obesity, T2DM, NAFLD, and CVD. However, it's noteworthy that, presently, only functional inhibitors of ASMase have been developed, with structural inhibitors remaining largely unexplored.

Functional inhibitors of ASMase

Related study has found that TCAs can functionally inhibit ASMase. The widely used drugs in clinical management of depression are TCAs, including imipramine, desipramine, amitriptyline, and doxepin[94]. These experiments have shown that imipramine prevents ethanol-induced ASMase/Cer and protein phosphatase 2A activation and reverses hepatic steatosis in ethanol-fed mice. This suggests a candidate as a therapeutic target for alcoholic hepatitis[95]. Imipramine triggers the lysosomal degradation of ASMase, leading to a decrease in NOX4 expression[25,30]. This results in reduced generation of ROS and programmed cell death, ultimately improving diabetic cardiomyopathy[30]. It is noteworthy that imipramine achieves this effect by inhibiting ASMase activity without affecting Cer levels. In contrast, amitriptyline possesses dual capabilities, inhibiting both ASMase activity and reducing Cer levels[45] (Table 1).

Desipramine is an active metabolite of imipramine. It is employed in the management of emotional distress, depression, and anxiety[96]. Desipramine, by inhibiting ASMase activity and modulating Cer concentrations, also reduces transforming growth factor-beta, TNF-α, and malondialdehyde levels and prevents IR and diabetes (Table 1).

The mitochondrial protein FAM3A plays a crucial role in inhibiting hepatic gluconeogenesis and lipogenesis[97]. Doxepin, another TCA, activates the FAM3A signaling pathway within the liver and brown adipose tissue, thereby improving hyperglycemia and steatosis in obese diabetic mice. Notably, the corrective effects of doxepin on glucose and lipid metabolism disorders are absent in FAM3A-deficient mice subjected to a HFD. Furthermore, in the liver of FAM3A-deficient mice, the impact of doxepin on ATP production, AKT activation, and inhibition of gluconeogenesis and lipogenesis is significantly attenuated (Table 1).

Natural compounds

Natural compounds can also inhibit the ASMase/Cer pathway. Alpha-mangostin (α-MG), a naturally occurring xanthone derived from mangosteen pericarp, has garnered attention for its promising therapeutic properties, including anticancer, antibacterial, anti-inflammatory, and antioxidant activities[98]. Known pathways of α-MG include induction of poly(ADP-ribose) polymerase cleavage and initiation of apoptosis *via* the retinoid X receptor alpha-AKT signaling pathway, as well as the attenuation of inflammatory response by inhibition of sirtuin 1 and Toll-like receptor 4/NF-κB signaling pathways[99-101]. Through these effects, α-MG may have therapeutic potential for inflammatory responses in metabolic diseases. Investigations into α-MG have revealed its ability to inhibit the ASMase/Cer pathway in mouse aorta, consequently reducing ROS production while enhancing signaling of endothelial nitric oxide synthase/nitric oxide. Moreover, α-MG has been observed to reverse impaired endothelium-dependent vasodilation in diabetic mice[37]. These findings position α-MG as a potential candidate for the treatment of vascular endothelial injury and other CVDs (Table 1).

Emerging therapeutics

Some of the drugs used to treat hypertension-related conditions also have the potential to inhibit ASMase. Empagliflozin, an inhibitor of the sodium-glucose cotransporter 2, has shown effectiveness in decreasing levels of soluble methane in the plasma, kidneys, and liver of hypertensive rats[38,56]. It also reduces concentrations of sphingosine-1-phosphate in the blood and kidneys and in cardiac tissue ASMase. These results support the hypothesis that empagliflozin may be used in the treatment of metabolic-related disorders (Table 1).

Current pharmacological intervention targets functional inhibitors; however, the therapeutic landscape for targeting the ASMase/Cer pathway appears promising. Future endeavors should focus on structural inhibitors as well as natural compounds and new therapeutics. These efforts have substantial potential as a means to selectively modulate the ASMase/Cer pathway for a range of metabolic and CVDs.

CONCLUSION

The cleavage of sphingomyelin into Cer by an enzyme called ASMase is of major importance in sphingolipid biology. Activation of the ASMase/Cer pathway is involved in several cellular activities, including apoptosis, inflammation, and autophagy. These activities are closely related to the occurrence and development of various metabolic diseases. Metabolic diseases, such as DM and CVD, are a series of diseases caused by metabolic disorders, and their prevalence is on the rise. Metabolic diseases like obesity and IR are often accompanied by elevated concentrations of Cer, which mediates the effects of inflammatory molecules on insulin sensitivity by inhibiting AKT and decreasing insulin function. The ASMase/Cer pathway has a wide range of important functions in the physiological and pathological regulation of the vascular system and can promote the development of atherosclerosis and diabetic cardiomyopathy by affecting lipid metabolism and mitochondrial function. Aberrant activation of the ASMase/Cer pathway has been implicated in the development of various metabolic and CVDs. Therefore, the ASMase/Cer pathway can be considered a potential therapeutic target for the treatment of vascular dysfunction induced by metabolic disorders. Studies have shown that therapeutics that reduce Cer levels in plasma, blood vessels, and heart tissue show potential in managing a range of cardiometabolic diseases.

Although significant progress has been made in understanding the role and mechanisms of the ASMase/Cer pathway in metabolic-related diseases, most of the research is still at the cellular and animal model level, with few clinical trials and a particular lack of longitudinal clinical studies. Moreover, most ASMase inhibitors are drugs used for treating psychiatric disorders, and no specific structural inhibitors have been developed yet. While it is difficult to study the

Table 1 Acid sphingomyelinase/ceramide functional inhibitors

Serial number	FIASMAs	Current functional or therapeutic disease	Potential therapeutic metabolic disease
1	Amitriptyline	Depression	Diabetic cardiomyopathy
2	Desipramine	Depression	Insulin resistance. Diabetes
3	Doxepin	Depression	Diabetes
4	Imipramine	Depression	Diabetic cardiomyopathy
5	Alpha-mangostin	Anti-cancer, antibacterial, anti-inflammation, antioxidant	Vascular endothelial injury. Cardiovascular disease
6	Empagliflozin	Diabetes	Cardiovascular disease

FIASMAs: Functional inhibitors of acid sphingomyelinase.

ASMase/Cer pathway in the context of metabolic diseases and CVD, further exploration and study is hopeful in the development of new drugs targeting the ASMase/Cer pathway, offering new paths for treatment.

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FOOTNOTES

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