Sphingosine 1-phosphate in metabolic syndrome (Review)

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Abstract. Metabolic syndrome (MetS), a clustering of components, is closely associated with the development and prognosis of cardiovascular disease and diabetes. Sphingosine 1-phosphate (S1P) is a lysophospholipid with paracrine and autocrine effects, which is associated with obesity, insulin resistance, hyperglycemia, dyslipidemia and hypertension through extracellular and intracellular signals to achieve a variety of biological functions. However, there is controversy regarding the role of S1P in MetS; the specific role played by S1P remains unclear. It ameliorates abnormal energy metabolism and deviant adipogenesis and mediates inflammation in obesity. Despite the fact that sphingosine kinase (SphK)2/S1P increases the glucose-stimulated insulin secretion of β-cells, more evidence showed that activation of the SphK1/S1P/S1P2R pathway inhibited the feedback loop of insulin secretion and sensitivity. The majority of S1P1R activation improves diabetes whereas S1P2R activation worsens the condition. In hyperlipidemia, S1P binds to high-density lipoprotein, low-density lipoprotein and very low-density lipoprotein exerting different effects. Moreover, low concentrations of S1P lead to vasodilation whereas high concentrations of S1P result in vasocontraction of isolated arterioles. This review discusses the means by which different SphKs, S1P concentrations or S1P receptor subtypes results to diverse result in MetS, and then examines the role of S1P in MetS.

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1. Introduction

Over the past decade, various diagnostic criteria for metabolic syndrome (MetS) have been proposed by different organizations (1-6). However, generally speaking, MetS is defined by a cluster of factors including obesity/central obesity, insulin resistance (IR), dyslipidemia and hypertension. As a worldwide problem, the prevalence of age-adjusted MetS estimated by the National Health and Nutrition Examination Survey (NHANES) is 22.9% in the US adult population (age ≥20) in the last decade (7). According to a representative sample of elderly people aged 60-95 in Beijing in two cross-sectional surveys, the prevalence of MetS in elderly Chinese individuals was 50.4% in 2001 and increased to 58.1% in 2010 (8). Besides high morbidity, MetS is associated with the development of cardiovascular disease (9), type 2 diabetes and cancer (10). Mottillo *et al* (11) found that MetS is associated with a 2-fold increase in cardiovascular outcomes. In addition, MetS is also involved in the development of cancer, as colorectal cancer is one of the most common types of cancer in patients with MetS (12).

Thus, it is important to identify a biomarker significantly associated with MetS. As a biological molecule involved in carbohydrate and lipid metabolism, sphingosine 1-phosphate (S1P) is a potent sphingolipid mediator that regulates an array of cellular responses, including cell migration, differentiation, apoptosis, lymphocyte trafficking and inflammation, by acting as both an extracellular signal and an intracellular second messenger (13). Herein, we reviewed the association between S1P and MetS, with emphasis upon the ways in which researchers have gained knowledge of this correlation.

2. S1P metabolism and signaling

Sphingosine, the substrate for S1P synthesis which is produced by the degradation of ceramide, may be phosphorylated by sphingosine kinases (SphKs) to form S1P. In subcellular organelles, S1P synthesis is initiated in the endoplasmic reticulum (ER), whereas later steps of the complex metabolism mainly occur in the Golgi apparatus, together with the involvement of lysosomes, nuclei and mitochondria (14). SphK1 is

mainly localized in the cytoplasm and translocates to the cell membrane for activation, whereas SphK2 is primarily but not exclusively localized in the nucleus (15). S1P is either dephosphorylated by two S1P-specific phosphatases (SPP1 and SPP2), or irreversibly degraded by S1P lyase (SPL) to phosphoethanolamine (PE) and hexadecenal which are incorporated into glycerolipids. Extracellular S1P may also be degraded by lysophospholipid phosphatase (LPP)1 and LPP3 into sphingosine, which is taken up by cells for further metabolism (16).

In healthy subjects, the concentration of plasma S1P is 100-300 nM and approximately 100 nM in lymph (17-21). Plasma S1P is principally derived from erythrocytes (22) and vascular endothelial cells (23), whereas the majority of lymph S1P originates from lymphatic endothelial cells (24). S1P in vascular and lymphatic endothelial cells is exported by the specific transporter Spns2 (25,26). However, in erythrocytes, S1P is exported by an ATP-dependent, vanadate- and glyburide-sensitive transporter. Requiring an extracellular stimulus such as thrombin, S1P is exported from platelets through two independent transporters, a Ca^{2+}-dependent transporter and an ATP-dependent glyburide-sensitive transporter (27). The majority of plasma S1P is combined with apolipoprotein M (apoM) which preferentially associates with high-density lipoprotein (HDL) (28,29). The remaining part binds to albumin, low density lipoproteins (LDLs) and very low density lipoproteins (VLDLs) (29).

S1P signals through 5 specific G-coupled S1P receptors designated as S1P1R-5 (30,31) and each subtype exhibits differential coupling efficacy to G protein α subunits. Windh *et al* (32) revealed that S1P1R coupled exclusively to G_i, whereas both S1P2R and S1P4R coupled to G_i and to $G_{12/13}$ as well as to the G_q family using the heterologous expression system of insect Sf9 cells. S1P4R (33) and S1P5R (34) were shown to couple to G_i and G_{12}, by determining ^{35}S-GTPγS binding to G proteins in CHO cells. This coupling resulted in the activation of small GTPases such as Rho, Rac and Ras (35-37). Further downstream effectors of S1P receptors include adenylate cyclase, phosphatidylinositol 3-kinase (PI3K), phospholipase C, protein kinase C and intracellular calcium (38). Although widely expressed, S1P1R, S1P2R and S1P3R were principally expressed in vascular tissues, whereas S1P5R and S1P4R were largely expressed in the hematopoietic and nervous systems, respectively (39).

On the other hand, S1P has been suggested to function as an intracellular messenger. Parham *et al* found that S1P activated a luciferase-tagged peroxisome proliferator-activated receptor γ (PPARγ)-specific gene reporter by ~12-fold in human endothelial cells, independently of its known effects on canonical signaling through S1P receptors (40). S1P in the nucleus, produced by SphK2 bound to the histone deacetylases HDAC1 and HDAC2 specifically, inhibited their enzymatic activity, which then affects the dynamic balance of histone acetylation and thus, the epigenetic regulation of specific target genes (41). Similar to nuclear S1P, the majority of mitochondrial S1P produced by mitochondrial SphK2 specifically binds to homomeric PHB2, which regulates mitochondrial assembly and function. Furthermore, mitochondrial respiration through cytochrome oxidase was reduced by depleting SphK2 or PHB2, suggesting that the interaction between S1P and PHB2 is important for mitochondrial assembly and respiration (42). On the other hand, independently of S1P extracellular signals, SphK1 as well as the production of intracellular S1P are necessary for nuclear factor-κB (NF-κB) activation by tumor necrosis factor-α (TNF-α) (43) (Fig. 1).

3. S1P in obesity

S1P is positively associated with obesity. Plasma levels of S1P were higher in obese patients than those in non-obese and lean individuals (44). In addition, it was demonstrated that plasma S1P positively correlates with body mass index (BMI), total body fat percentage and waist circumference (45). The pathophysiology of obesity is complex; it is known to involve abnormal energy metabolism, deviant adipogenesis and inflammation. Recent studies have suggested that S1P is involved in these pathophysiological processes and in fact, reduces obesity.

S1P ameliorates obesity through the regulation of energy homeostasis. Silva *et al* (46) found that S1P1R protein is highly expressed in the hypothalamic pro-opiomelanocortin neurons of rats. Additionally, food consumption was decreased and energy expenditure was increased by intra-cerebroventricular injections of S1P through the activation of signal transducer and activator of transcription 3 (STAT3) and the melanocortin system, and vice versa. Moreover, the expression of S1P1R in neurons was controlled by STAT3 in neurons through a positive feedback mechanism. As several models of obesity display an imbalance of the hypothalamic S1P/S1P1R/STAT3 axis, whereas pharmacological intervention improves these phenotypes, this indicates that the S1P/S1P1R/STAT3 signaling pathway in neurons plays a vital role in controlling energy homeostasis in rats.

S1P reduces fat mass by affecting adipogenesis and lipolysis through several pathways. In maturing 3T3-L1 preadipocytes, S1P significantly decreased lipid accumulation in a dose-dependent manner with the downregulation of the transcriptional levels of the CCAAT/enhancer binding proteins α (C/EBPα), PPARγ and adiponectin, which are markers of adipogenic differentiation. Moreover, the activation of Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (p38 MAPK) were also downregulated by S1P treatment in human preadipocytes. These results suggest that S1P mediates the downregulation of adipogenic transcription factors and by inactivating the JNK and p38 MAPK signaling pathways subsequently affects adipogenesis (47). FTY720, an analogue of S1P, phosphorylated by SphK2 to form FTY720(S)-phosphate (FTY720-P), which binds to S1P1R, S1P3R, S1P4R and S1P5R, significantly downregulated the markers of adipogenic differentiation (PPARγ, C/EBPα and adiponectin) and upregulated the regulators of lipolysis, [hormone-sensitive lipase (HSL), adipose triglyceride lipase (ATGL) and perilipin], indicating that FTY720 prevented obesity by modulating adipogenesis and lipolysis (48). This evidence suggests that S1P affects several pathways to adjust the balance between adipogenesis and lipolysis, subsequently altering the fat mass which reduces obesity, indicating that S1P may be used in the treatment of obesity. However, the internal mechanisms responsible for these effects remain to be elucidated. Further investigation is warranted into whether extracellular and intracellular S1P signals are involved in this process as well as into the mechanisms responsible for achieving these effects.

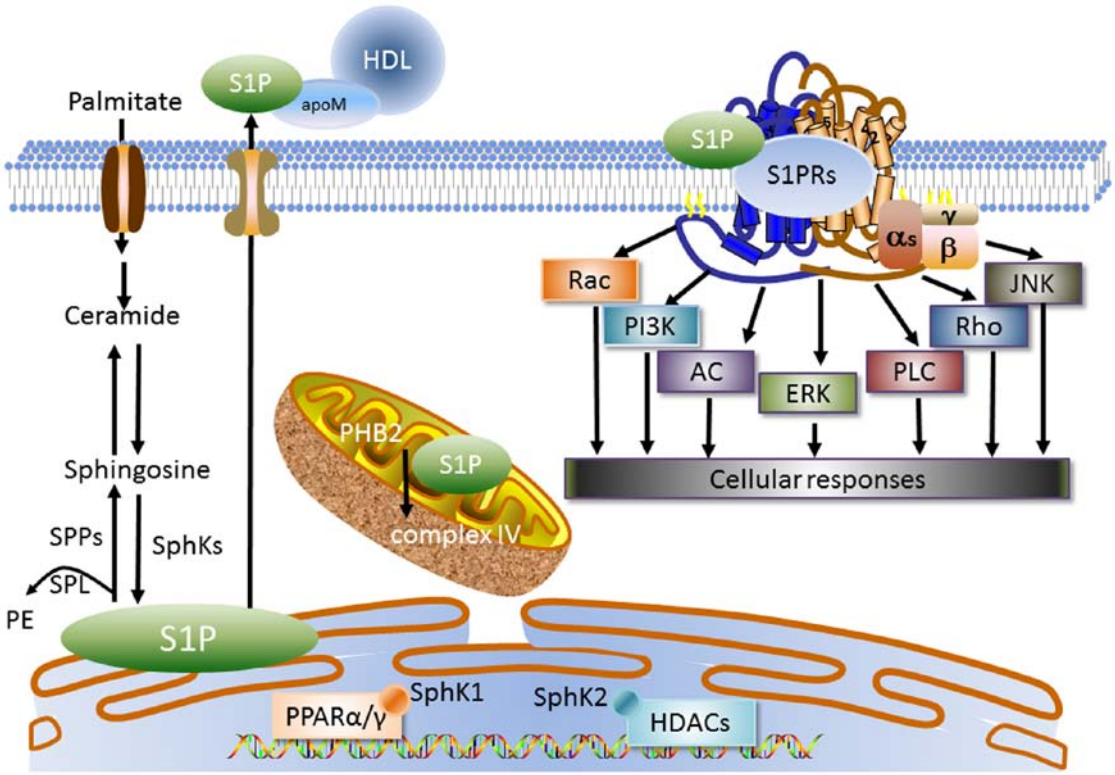

Figure 1. Sphingosine 1-phosphate (S1P) metabolism and signaling. Sphingosine, the substrate for S1P synthesis, which is produced by the degradation of ceramide, may be phosphorylated by sphingosine kinases (SphK1 and SphK2) to form S1P. SphK1 is generally localized in the cytoplasm, whereas SphK2 is primarily but not exclusively localized in nucleus. In subcellular organelles, S1P synthesis initiates in the endoplasmic reticulum (ER), where S1P is irreversibly degraded by S1P lyase (SPL) to phosphoethanolamine (PE) or dephosphorylated by S1P phosphatases (SPPs) to sphingosine. In vascular and lymphatic endothelial cells, S1P is transported out by specific Spns2 transporters. S1P is exported out of vascular and lymphatic endothelial cells by the specific transporter Spns2. However, in erythrocytes, S1P is exported by an ATP-dependent, vanadate- and glyburide-sensitive transporter. The majority of plasma S1P is bound to apolipoprotein M (apoM) which preferentially associates with high densiy lipoprotein (HDL). The extracellular S1P signals through specific G-coupled S1P receptors designated as S1P1R-5, activating Rac, phosphatidylinositol 3-kinase (PI3K), adenylate cyclase (AC), extracellular-regulated protein kinase (ERK), phospholipase C (PLC), Rho and Jun N-terminal kinase (JNK) to contribute to cellular responses. Intracellular S1P also directly activates prohibitin 2 (PHB2) in the mitochondria, which stabilizes cytochrome *c* oxidase. In the nucleus, S1P is also involved in the activation of nuclear transcription factors PPARα and PPARγ, and histone deacetylases (HDACs).

As chronic low-grade inflammation and activation of the immune system participate in the pathogenesis of MetS (49) inflammation is also involved in the interaction between S1P and obesity. A cross-sectional study recruited 30 healthy overweight and 15 lean adolescents, and found that there was a significant association between S1P and TNF-α (50). In animal studies, Samad *et al* found that S1P was elevated in obese (*ob*/*ob*) mice, and S1P induced the gene expression of interleukin (IL)-6, TNF-α, monocyte chemoattractant protein-1 and keratinocyte-derived chemokine in cultured adipocytes (51). On the other hand, Wang *et al* found that genetic disruption of the SphK1/S1P signaling pathway in mice with diet-induced obesity (DIO) increased adipose gene expression of the anti-inflammatory molecules IL-10 and adiponectin whereas it reduced adipose tissue macrophage recruitment and the expression of the proinflammatory molecules TNF-α and IL-6 (52). These findings suggest that the SK1/S1P signaling pathway contributed to the proinflammatory phenotype of the obese adipose tissue, and played a critical role in the pathogenesis of obesity-mediated metabolic disease.

As S1P ameliorates abnormal energy metabolism and deviant adipogenesis, while mediating inflammation, it plays an alternative role in the development of obesity. There is a possibility that, in the early stages of obesity, S1P increases the expression of proinflammatory factors, which activate the protective mechanisms of the body, thereby attenuating further development of obesity. Thus, S1P effectively adjusted the balance between adipogenesis and lipolysis in order to decrease the fat mass, which is the most prominent feature of obesity. On the other hand, S1P is a lipid with multiple biological activities mediated through intracellular and extracelluar pathways, and the activation of different pathways leads to different results. Thus, it is necessary to explore more specific mechanisms, and additional animal models and clinical trials are required in order to confirm the effects of S1P.

4. S1P in IR

S1P is synthesized by SphKs. SphK1 and SphK2 mediate opposite effects in insulin sensitivity. Qi *et* (53) found that all high fat diet (HFD)-fed SphK1(-/-) mice manifested evident diabetes, accompanied by a nearly 3-fold reduction in insulin levels compared with the WT mice which developed glucose intolerance and compensatory hyperinsulinemia. Pancreatic β-cell mass was increased by 140% in HFD-fed WT mice and decreased to 50% in HFD-fed SphK1(-/-) mice, in comparison with the chow diet control groups, respectively. The SphK1 level was also elevated in obese, type 2 diabetic humans. Enhanced insulin signaling in adipose and muscle as well as improved systemic insulin sensitivity and glucose

tolerance were demonstrated in SphK1(-/-) mice, suggesting that the SphK1-S1P axis improves IR associated with obesity and type 2 diabetes (52). In addition, primary islets isolated from SphK1(-/-) mice exhibited higher susceptibility to lipotoxicity than WT controls. Of note, S1P profoundly abrogated lipotoxicity in β cells or the cells lacking SphK1 activity and SphK1(-/-) islets, highlighting a pivotal role of S1P in β-cell survival under lipotoxic conditions (53). Recognizing that S1P is metabolized by SphK2, the change of SphK2 is also involved in the process of IR. Cantrell Stanford *et al* (54) demonstrated that glucose elevates intracellular S1P by activating SphK2 in MIN6 cells and mouse pancreatic islets. Notably, the elevation of S1P correlates with the increase in glucose-stimulated insulin secretion (GSIS). On the other hand, downregulated levels of S1P and the knockdown of SphK2 in MIN6 cells or primary islets results in decreased GSIS, whereas the knockdown of the S1P phosphatase, SPP1, leads to a rise in GSIS. These data suggest that glucose-activated SphK2/S1P is important for GSIS in pancreatic β cells.

Apart from pancreatic islets, SphK1/S1P/S1P receptors also acted as an insulin-mimetic cue in insulin sensitive tissues. SphK1 transgenic mice fed an HFD showed increased SphK1 activity in skeletal muscle, accompanied by ameliorated muscle insulin resistance, which may be associated with a concomitant reduction in the phosphorylation of c-JNK, a serine threonine kinase associated with IR, thus indicting that skeletal muscle and whole-body insulin sensitivity were improved in SphK1 transgenic mice on an HFD (55). In addition, the inhibition of SphK1 decreased the effect of palmitate on insulin-stimulated glucose uptake by attenuating the activity of the AKT/glycogen synthase kinase 3β (GSK3β) signaling pathway and insulin signaling proteins in L6 myotubes (56) Furthermore, SphK1 gene delivery significantly enhanced the phosphorylation of insulin-signaling kinases such as Akt and GSK3β in the livers of diabetic animals (57). S1P, through engagement with S1P2R, has been found to produce a transient burst of reactive oxygen species (ROS) through calcium-dependent activation of the small GTPase Rac1 in skeletal muscle cells, accompanied by a redox modulation of protein tyrosine phosphatase-1B (TPT-1B) activity, the main negative regulator of insulin receptor phosphorylation. It is indicative of critical crosstalk occurring between S1P, insulin pathways and ROS (58). The extra- and intracellular S1P from the liver, another important organ involved in IR, was markedly increased by palmitate. Once generated, S1P bound to S1P2R via reduced insulin-mediated glycogen synthesis and PI3K/Akt-GSK3β activation to impair insulin signaling (59).

The malignant crosstalk of pancreatic islet β-cell dysfunction and insulin sensitivity leads to insulin resistance. In spite of the fact that SphK2/S1P increases the GSIS of β-cells, more evidence showed that SphK1/S1P/S1P2R pathway activation inhibits the feedback loop of insulin secretion and sensitivity.

5. S1P in hyperglycemia

Plasma levels of S1P in patients with type 2 diabetes were significantly higher (~50%) than those in healthy individuals (60). Additionally, plasma S1P positively correlated with HbA1c (%) levels in humans (45). It is well known that β-cell dysfunction and insulin resistance are the most important pathophysiological mechanisms associated with the development of diabetes. Zhao *et al* found that oral administration of FTY720 to diabetic (*db/db*) mice increased β-cell mass and blood insulin levels to normalize fasting blood glucose levels. Further investigation confirmed that S1P controls β-cell regeneration in the islets isolated from the treated mice by decreasing cyclin-dependent kinase inhibitor p57 (KIP2) levels and increasing cyclin D3 expression via the PI3K pathway (61).

More importantly, S1P ameliorates the complications of diabetes. Diabetic nephropathy (DN) is the leading cause of end-stage renal failure, which may be attenuated by S1P. FTY720 or SEW2871, a selective S1P1R agonist, significantly reduced urinary albumin excretion which led to tubule injury and increased urinary TNF-α in rats with streptozotocin (STZ)-induced diabeties (62). A dorsal skin wound was made in the healthy and diabetic mice; S1P injection alone promoted wound healing in the diabetic mice compared with the control, and the combination of S1P and JTE-013 (S1P2R antagonist) administration induced maximal wound healing in diabetic mice (63). These findings indicate that S1P possesses unique potential in the therapy of DN and diabetic wounds.

However, controversy still exists. As the connective tissue growth factor (CTGF) is a marker in mesangial cells for the progression of DN, El-Shewy *et al* found that SphK1/S1P1/3R activation is upstream of extracellular regulated protein kinases (ERK)1/2 and JNK, which are essential for LDL-regulated expression of CTGF in renal mesangial cells (64). The SphK1/S1P pathway also plays a critical role in fibronectin accumulation, which is a glomerular extracellular matrix protein associated with DN, in both kidneys from STZ-induced diabetic rats and high glucose-treated glomerular mesangial cells (65). Lan *et al* (66) identified that fibronectin expression was upregulated via S1P-S1P2R-MAPK (ERK1/2 and p38 MAPK) axis activation in mesangial cells under high glucose conditions, suggesting that SphK1-S1P-S1P2R-MAPK may be a potential therapeutic target for the treatment of DN.

In diabetes, elevated S1P levels are evident. While the downstream receptors have the opposite effect under hyperglycemic conditions, S1P1R activation ameliorates diabetes whereas S1P2R activation worsens the condition (Table I). Finding an equilibrium point between S1P1R and S1P2R, and then balancing the activation of S1P1R and S1P2R, may provide a novel target for the treatment of diabetes.

6. S1P in hyperlipidemia

S1P contributes to the protective role of HDL. Tong *et al* (67) found that HDL in diabetic patients with elevated S1P levels exhibited more powerful protective effects, inducing COX-2 expression and PGI2 release from human umbilical vein endothelial cells, than control HDL through the activation of S1P1R/3R. Additionally, S1P compensated for the reduction in COX-2 expression through glycated HDL by phosphorylating the ERK/MAPK-CREB pathway (68). These findings confirmed the protective role of HDL-binding S1P in patients with type 2 diabetes mellitus, suggesting a possible novel therapeutic target. There is no S1P in HDL in apoM$^{(-/-)}$ mice, whereas HDL in transgenic mice overexpressing human apoM has an increased S1P content, indicating that the bridge between HDL and S1P in plasma is apoM. The 1.7-Å structure

Table I. Role of S1P and downstream signaling in insulin resistance and hyperglycemia.

Subjects	Intervening substance/ target molecules	Downstream signal	Biological outcome	Refs.
SphK1 transgenic mice	Fed an HFD	A concomitant reduction in the phosphorylation of c-JNK	Ameliorate muscle insulin resistance	(55)
MIN6 cells, pancreatic islets	Glucose	Activate SphK2/S1P	Increased GSIS	(54)
db/db mice	FTY720 (10 mg/kg, intraperitoneal injection daily for 6 weeks)	Increase cyclin D3 and decline KIP2 via PI3K	Increase β-cell mass and blood insulin levels	(61)
STZ-exposed diabetic rats	FTY720 (0.3 mg/kg, oral gavage, 9 weeks)	Upregulate S1P1R	Reduce the urinary albumin excretion	(62)
db/db mice	S1P (10 or 100 mM injected into the wound bed daily) and JTE-013	Downregulate S1P2R	Promote the healing of wound	(63)
DIO mice	SphK1 deficiency	Increase IL-10 and adiponectin levels; reduce ATM recruitment, TNF and IL-6	Enhanced insulin signaling in adipose and muscle and improved systemic insulin sensitivity and glucose tolerance	(52)
C2C12 cells	S1P (0.01-5 μM, 15-90 min)	Calcium-dependent activation of the small GTPase Rac1	Produce a transient burst of ROS	(58)
Primary rat hepatocytes	S1P (1 Mm, 5 h)	S1PR2, reduces PI3K/ Akt-GSK-3β activation	Reduce insulin mediated glycogen synthesis and impair insulin signaling	(59)
Renal mesangial cells	SphKs inhibitor, VPC23019	Inhibit activation of ERK1/2 and JNK via S1PR1 and S1P3R	Essential for expression of CTGF induced by LDL	(64)
	SphK1, S1P (1 μm, 12 h)	S1P2R-MAPK (ERK1/2 and p38 MAPK)	Mediate high glucose-induced fibronectin expression	(66)

HFD, high fat diet; c-JNK, c-Jun N-terminal kinase; GSIS, glucose-stimulated insulin secretion; KIP2, cyclin-dependent kinase inhibitor p57; PI3K, phosphatidylinositol 3-kinase; JTE-013, S1P2R antagonist; ATM, adipose tissue macrophage; ROS, reactive oxygen species; VPC23019, S1P3R antagonist; AKT, protein kinase B; ERK, extracellular regulated protein kinases; GSK3α/β, glycogen synthase kinase 3α/β; CTGF, connective tissue growth factor; p38 MAPK, p38 mitogen-activated protein kinase.

of the S1P-apoM complex suggests that S1P specifically interacts with an amphiphilic pocket in the lipocalin fold of apoM. Human apoM(+) HDL induced S1P1R internalization, downstream MAPK and Akt activation, endothelial cell migration, and formation of endothelial adherence junctions, whereas apoM(-) HDL did not. Moreover, the HDL fraction of apoM(-/-) mice which lacked S1P showed dampened basal endothelial barrier function in lung tissue. This demonstrated that apoM is an essential vascular protective constituent of HDL by delivering S1P to the S1P1R on endothelial cells (28).

Plasma S1P not only positively correlated with LDL cholesterol in a human study (45), but also in experimental animal studies, showing the important role of S1P in the context of hyperlipidemia. High fructose-fed rats induced hyperlipidemia and activated the SphK1/S1P signaling pathway, which in turn led to the activation of NF-κB signaling and inflammation in rat livers. Importantly, lipid metabolic disorder as well as hepatic insulin and leptin signaling impairment were observed in this animal model, which resulted in lipid accumulation in the liver (69). Additionally, SphK1 gene delivery significantly attenuated elevated levels of plasma non-esterified fatty acid (NEFA), triacylglycerol, LDL and cholesterol, which markedly ameliorated liver, heart and kidney injuries induced by hyperglycaemia in KK/Ay diabetic mice (57). As in other animal models of hyperlipidemia, the capability to generate and release S1P were significantly higher in the hypersensitized platelets and blood plasma obtained from rabbits with hypercholesterolemia. Moreover, co-treatment with S1P (0.125-0.5 mM) potentiated the ox-LDL-induced proliferation of vascular smooth

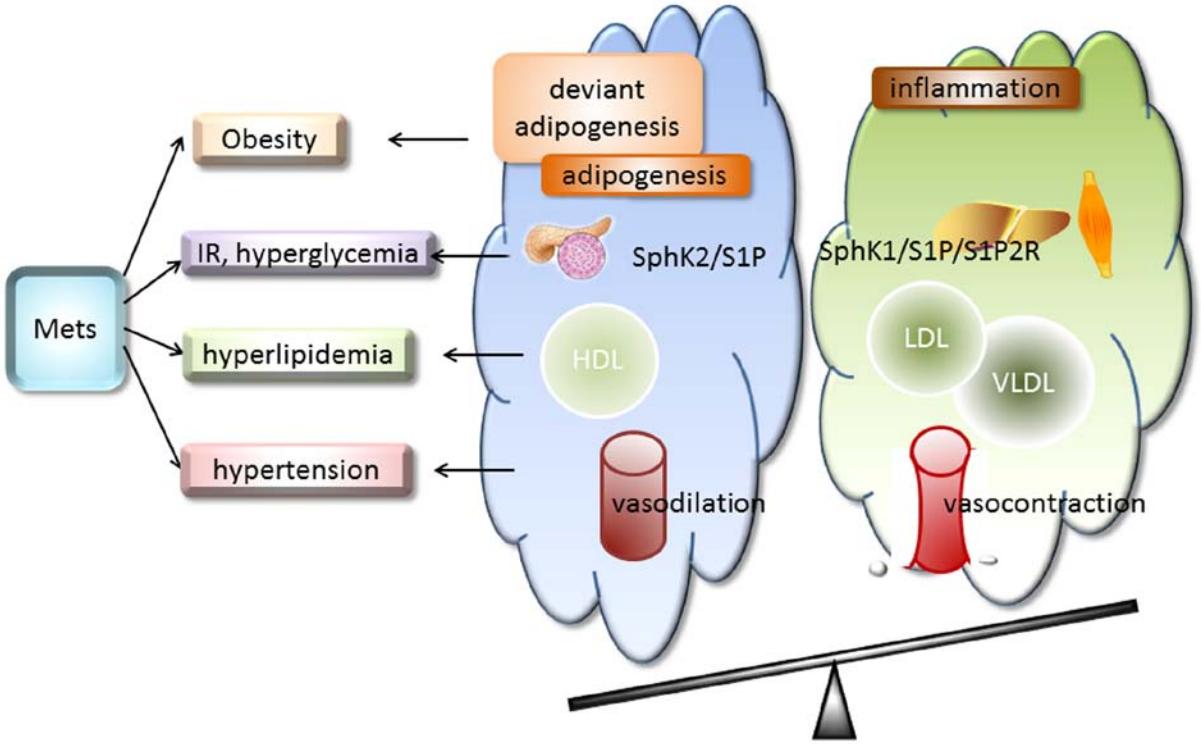

Figure 2. Sphingosine 1-phosphate (S1P) in metabolic syndrome (MetS). MetS is defined by a cluster of factors including obesity/central obesity, hyperglycemia, dyslipidemia, hypertension and insulin resistance (IR). S1P plays multiple roles in the occurrence and development of this disease. However, the specific role played by S1P remains unclear. It ameliorates abnormal energy metabolism and deviant adipogenesis and mediates inflammation in obesity. The majority of S1P1R activation improves diabetes, whereas S1P2R activation worsens the condition. In hyperlipidemia, S1P binds to high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-denity lipoprotein (VLDL) to exert direct different effects. Moreover, low concentrations of S1P (10-100 nM) lead to vasodilation whereas high concentrations (100-10,000 nM) result in the vasocontraction of isolated arterioles. SphK2/S1P increases the glucose-stimulated insulin secretion (GSIS) of β-cells. More evidence showed that activation of the sphingosine kinase 1 (SphK1)/S1P/S1P2R pathway deteriorates the feedback loop of insulin secretion and sensitivity. Different SphKs, S1P concentrations or S1P receptor subtypes result in diverse results; alterations to the balance between these factors may provide novel treatments for MetS.

muscle cells in a dose-dependent manner through the S1P1R dependent pathway (70). Thus, the SphK1/S1P/S1P receptor signaling pathway may be a novel mechanism which is important in hyperlipidemia.

It is well known that hyperlipidemia is always accompanied by a low HDL level, and the majority of plasma S1P is bound to HDL. It has been hypothesized that amount of S1P which binds to HDL is less, whereas more S1P may bind to LDL and VLDL under conditions of hyperlipidemia. From the above studies, we can deduce that S1P exhibits a protective function by binding HDL, wheras the combination with LDL shows the opposite effects.

7. S1P in hypertension

Plasma S1P levels are significantly higher in patients with hypertension in comparison with normotensive patients. In fact, the S1P1R gene is a candidate for the control of salt sensitivity and hypertension in the stroke-prone spontaneously hypertensive rat (SHRSP) (71). In SHR, application of dimethylsphingosine, a sphingosine kinase inhibitor, led to a marked upregulation in mean arterial pressure (MAP) with a further rise in carotid artery resistance. However, in Wistar-Kyoto (WKY) rats, dimethylsphingosine had little effect on MAP (72). S1P induced transient relaxation of isolated pressurized mesenteric arterioles with low concentrations (10-100 nM) in a dose dependent manner. Maximal vasodilation (55±8%) was demonstrated at 2 min after S1P addition and returned to baseline levels by 5 min via G protein-dependent, calcium-sensitive, and PI3K signaling pathways (73).

However, controversy continues to exist. FTY720 produced modest hypertension (2-3 mmHg) in patients in a 1 year trial. Furthermore, FTY720 elicited dose-dependent hypertension after multiple days of oral administration through the activation of S1P3R in rats (74). Furthermore, S1P induced vasocontraction through the activation of the Rho/Rho-kinase signaling pathway in the canine basilar artery at high concentrations ranging between 100 and 10 mM (75). The S1P extracellular signals induced hypertension. S1P/S1P3R selectively constricted isolated cerebral arteries mainly by Rho and partly through $G_{(i/o)}$ protein (76). On the other hand, Yogi *et al* (77) identified that S1P/S1P1R is associated with specific pathways through epidermal growth factor receptor and platelet-derived growth factor transactivation, a process upregulated in the vascular smooth muscle cells of SHRSP rats which contributes to vascular inflammation in hypertension.

The complex cardiovascular effects of S1P are likely to be due to differential concentrations of S1P. Low concentrations (10-100 nM) lead to vasodilation whereas high concentrations (100-10,000 nM) result in the vasocontraction of isolated arterioles. The activation of different S1P receptor subtypes may also contribute to different results. Thus, the investigation of more mechanisms is necessary in order to identify the multiple roles of S1P in hypertension.

8. Conclusion

Due to the high prevalence of MetS worldwide, a condition which is closely assicated with the development and prognosis of diabetes and cardiovascular disease, studies were taken to find a biomarker or effective way to diminish the development and progress of MetS. S1P has been demonstrated to play multiple roles in the occurrence and development of this disease, mainly through S1P1R-S1P3R. There is controversy regarding the role of S1P in MetS, such as anti-inflammation versus pro-inflammation, and anti-hypertension versus pro-hypertension. Different SphKs, S1P concentration or S1P receptor subtypes result in diverse results (Fig. 2). Thus, the possible implications of S1P-directed mechanisms on the occurrence and development of MetS remains to be elucidated. Further investigations may provide novel candidates for the treatment of MetS.

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