Histol Histopathol (2022) 37: 213-226

http://www.hh.um.es

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW **Open Access**

Sphingosine 1-phosphate and its regulatory role in vascular endothelial cells

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Summary. Sphingosine 1-phosphate (S1P) is a bioactive metabolite of sphingomyelin. S1P activates a series of signaling cascades by acting on its receptors S1PR1-3 on endothelial cells (ECs), which plays an important role in endothelial barrier maintenance, anti-inflammation, antioxidant and angiogenesis, and thus is considered as a potential therapeutic biomarker for ischemic stroke, sepsis, idiopathic pulmonary fibrosis, cancers, type 2 diabetes and cardiovascular diseases. We presently review the levels of S1P in those vascular and vascular-related diseases. Plasma S1P levels were reduced in various inflammation-related diseases such as atherosclerosis and sepsis, but were increased in other diseases including type 2 diabetes, neurodegeneration, cerebrovascular damages such as acute ischemic stroke, Alzheimer's disease, vascular dementia, angina, heart failure, idiopathic pulmonary fibrosis, community-acquired pneumonia, and hepatocellular carcinoma. Then, we highlighted the molecular mechanism by which S1P regulated EC biology including vascular development and angiogenesis, inflammation, permeability, and production of reactive oxygen species (ROS), nitric oxide (NO) and hydrogen sulfide (H_2S), which might provide new ways for exploring the pathogenesis and implementing individualized therapy strategies for those diseases.

Key words: Sphingosine 1-phosphate, Endothelial cells, Permeability, Angiogenesis, Inflammation, ROS, NO, H2S

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DOI: 10.14670/HH-18-428

Introduction

Vascular endothelial cells (ECs) constitute the endothelium that is located in the lumen of blood vessels and play a key role in cardiovascular homeostasis. Normal vascular endothelium is considered as the gatekeeper of cardiovascular health, and the dysfunction of vascular ECs is closely related to hypertension, diabetes, hyperlipidemia, hypoxia, aging and so on, which are of wide concern from basic to clinical medicine. As the largest functionally heterogeneous "organ" of the human body (Aird, 2003), the endothelium also has functions of secretion, metabolism and immunity, which can regulate the immune response, hemodynamics and reactions of surrounding organs. The vascular tone and EC function is regulated by bioactive factors such as sphingosine 1-phosphate (S1P).

In recent years, more and more attention has been paid to the change in S1P concentrations in body fluid, such as blood and synovial fluid in various diseases. In a prospective observational study, Winkler et al. (2015) found that serum S1P concentration was significantly reduced in sepsis patients, which was negatively correlated with the severity of sepsis. Bekpinar et al. (2015) found that S1P levels were significantly reduced in patients with diabetic nephropathy and proteinuria overdosage. Conversely, the level of S1P and its receptor S1PR1 in synovial fluid of patients with rheumatoid arthritis is considerably increased compared with healthy subjects (Lai et al., 2008). Thus, the concentration of S1P is dependent on the disease conditions. We therefore desired to review the association between changes in S1P concentration and endothelium-related diseases.

S1P in blood is produced by a variety of cells, such as red blood cells, platelets and ECs (Pappu et al., 2007; Hla et al., 2008). ECs can synthesize and secrete a large amount of S1P, which to a large extent leads to the high level of S1P in the blood (Venkataraman et al., 2006; Olivera et al., 2013). S1P is presented with different carbon long-chain base lengths, the major S1P species including 16-carbon monounsaturated S1P d16:1, d17:1, d18:0 and d18:1 in mammals. Among them, as the most abundant form, d18:1 accounts for about 80% of the

total S1P in plasma (Narayanaswamy et al., 2014). As a blood-derived lipid, S1P is transported by high-density lipoprotein cholesterol (HDL) in about 60% of plasma (Tran-Dinh et al., 2013). S1P carried by red blood cells and platelets is transported mainly through promoter superfamily transporter 2b (Mfsd2b) (Vu et al., 2017; Kobayashi et al., 2018), while S1P is translocated across the ECs by sphingomipin transporter 2(Spns2) (Fukuhara et al., 2012). However, it has also been proposed that the intracellular transport of S1P is mediated by specific ABC transporters (Nagahashi et al., 2013).

S1P controls a variety of endothelial activities, including proliferation (Lee et al., 2000), survival (Kwon et al., 2001), migration of ECs (Wang et al., 1999) and their pro-inflammatory responses (Zhang et al., 2013a). Also, S1P regulates angiogenesis (Camaré et al., 2015) and endothelial barrier integrity (McVerry and Garcia, 2004; Rosen et al., 2007; Xiong and Hla, 2014; Radeva and Waschke, 2018). Among the five S1PRs, S1PR1, S1PR2 and S1PR3 are expressed by ECs (Zhang et al., 2013b), which are the initial signal transduction elements responding to S1P. S1PR1 is closely related to the gastrointestinal tract in a pertussis toxin sensitive way and is the main barrier enhancing receptor (Sammani et al., 2010). In embryos with S1PR1 receptor deficiency, blood vessels are incompletely covered by vascular smooth muscle cells, indicating that S1PR1 also regulates vascular maturation (Allende et al., 2003). In contrast, S1PR2 and S1PR3 couple with corresponding G proteins to mediate barrier destruction (Lee et al., 2009). Indeed, the interaction of S1P and its receptors in EC-related physiological and pathophysiological processes such as atherosclerosis and angiogenesis are complex. For instance, when atherosclerosis occurs, S1P can promote the expression of endothelial nitric oxide synthase (eNOS) by activating S1PR1 and S1PR3, increase the secretion of NO and protect the vascular endothelium, thus playing an anti-atherosclerosis role (Kurano and Yatomi, 2018). However, S1P can also promote the development of atherosclerosis by activating S1PR2 under abnormal conditions such as inflammation (Skoura et al., 2011). S1PR2 is upregulated under inflammatory conditions (such as in atherosclerosis) and participates in the endothelial inflammatory response (Zhang et al., 2013a; Zhao et al., 2015). Moreover, S1PR1 inhibits angiogenesis (Ben Shoham et al., 2012), while S1PR3 can activate the receptor vascular endothelial growth factor (VEGF) and fetal liver kinase-1 (Flk-1) to promote angiogenesis (Jin et al., 2018). Thus, S1P plays a critical role in angiogenesis, inflammation, and atherosclerosis, which is mediated by its receptor S1PR1-3.

The present work reviews the levels of S1P in diseases including atherosclerosis, coronary artery calcification, septic shock, cardiopulmonary bypass, acute lung injury associated with malaria, sepsis, ischemic stroke, pre-infarction angina, idiopathic pulmonary hypertension, chronic heart failure, type 2 diabetes, hepatocellular carcinoma, idiopathic pulmonary fibrosis, end-stage liver disease, acquired pneumonia, vasculitis, Alzheimer's disease and vascular cognitive impairment, and highlights the molecular mechanism by which S1P regulates EC biology, including vascular development and angiogenesis, inflammation, permeability, and production of reactive oxygen species (ROS), nitric oxide (NO) and hydrogen sulfide (H_2S), which might provide new ways for exploring the pathogenesis and therapy strategy for those diseases.

Plasma S1P levels and diseases

In healthy human subjects, the plasma concentration of S1P ranges mostly from 0.1-1.2 μmol/L (Venkataraman et al., 2008; Hammad et al., 2010), while smaller concentrations of S1P (0.5-0.75 pmol/mg) have been observed in other tissues such as lymph (Xiong and Hla, 2014).

Atherosclerosis, coronary artery calcification, and atherosclerosis in type 2 diabetes (dropped S1P levels)

In atherosclerosis, the concentration of S1P is 0.687±0.266 mmol/mL. It was demonstrated that S1P level is a more accurate indicator of atherosclerosis than HDL-C level (51.5±19.8 mmol/mL) (Soltau et al., 2016). Coronary artery calcification is closely related to coronary atherosclerosis (Yao et al., 2020a). In coronary artery calcification, the concentration of S1P is 0.69-0.93 μmol/L with a median value of 0.81 μmol/L, suggesting that the level of S1P in plasma and the level of ApoM in plasma and HDL were not associated with coronary artery calcification, but the plasma S1P and ApoM levels were associated negatively and independently with mortality in patients with type 2 diabetes (Liu et al., 2019). Paradoxically, the S1P level is elevated in type 2 diabetes. In type 2 diabetes with atherosclerosis, the S1P levels in isolated HDL were significantly increased compared with those type 2 diabetes patients without (235.6±13.4 vs 195.0±6.4 ng/mg) (Tong et al., 2013). Note that in the type 2 diabetes with significant atherosclerosis, the S1P levels in isolated HDL were reduced compared with those type 2 diabetes without atherosclerosis (212.5±8.8 vs 235.6±13.4 ng/mg). Therefore, the S1P level might be reduced along with the development of atherosclerosis in type 2 diabetes. Diabetic HDL carries a higher level of S1P, which has the potential to protect ECs by inducing COX-2 and PGI-2. These findings provide a new insight of S1P in type 2 diabetes. However, why S1P does not prevent atherosclerosis in type 2 diabetes remains a mystery.

Sepsis, infection and inflammation (dropped S1P levels)

In sepsis, serum S1P concentrations were lower in

patients (580±24 nmol/L) than that in healthy controls (1156±17 nmol/L), which were inversely associated with the severity of inflammation (such as IL-6) and organ failures (Winkler et al., 2015). Plasma syndecan-1 and S1P were decreased in patients with organ failure in septic shock patients, compared with healthy controls [86.5 (IQR 63.7-120.0) ng/mL vs. 302 (IQR 253.3-404.0) ng/mL] (Piotti et al., 2021).

In malaria-infected mice with acute lung injury/acute respiratory distress syndrome (ALI/ARDS), the S1P concentrations in plasma and lung tissue were approximately twofold lower than that of control mice or malaria-infected mice without ALI/ARDS (Punsawad and Viriyavejakul, 2019).

Plasma S1P concentrations were reduced in patients with chronic hepatitis C regardless of gender, compared with healthy subjects with the same hemoglobin concentration (280.3±29.6 nmol/L vs 386.8±55.5 nmol/L) (Ikeda et al., 2010).

S1P levels were decreased to 0.37 (IQR 0.31-0.47) μmol/L after cardiopulmonary bypass and to 0.46 (IQR 0.36-0.51) μmol/L after off-pump procedures, while the baseline S1P levels were 0.77 (IQR 0.61-0.99) (Greiwe et al., 2021). There is a contrary trend of S1P with inflammatory markers such as IL-6, suggesting that S1P may be inversely associated with sterile inflammation induced by cardiac surgery. Thus, Maintenance of S1P concentration is a promising way to prevent cytokine storm in sepsis.

Neurodegeneration and cerebrovascular damage (elevated S1P levels)

In contrast to atherosclerosis, in humans who had suffered from acute ischemic stroke, the concentration of S1P was increased in patients (6.53±5.0 ng/mg), compared with controls (4.55±2.1 ng/mg), which suggests that if the S1P-S1PR-axis orchestrates neuronal positioning this may offer new therapeutic perspectives after ischemic stroke (Lucaciu et al., 2020). The plasma levels of S1P were increased to about 2149.7 nmol/L in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which is much higher than those in healthy volunteers (274.6±94.2 nmol/L) (Wu et al., 2020). Although there was no considerable change in plasma S1P levels between the AAV patients with or without coagulation-related complications, the S1P levels in AAV patients with coagulation-related complications including thrombo-embolism, cerebral ischemia, and cerebral hemorrhage were all higher than the heathy controls (Wu et al., 2020). Plasma S1P levels were highest in the AAV patients with thromboembolism, and lowest in the AAV patients with cerebral hemorrhage, and AAV patients with cerebral ischemia (Wu et al., 2020), suggesting that S1P level might predict coagulation-related complications in AAV.

Interestingly, plasma d16:1 S1P was reduced in vascular dementia and Alzheimer's disease, whereas the other S1P species including d17:1 and d18:1 were not changed. d18:1 was competitive with d16:1 for expression of inflammation cytokines interleukin (IL)-8 and tumor necrosis factor (TNF) (Chua et al., 2020). Thus, dysregulation of S1P-mediated immuno-modulation was speculated in chronic inflammation-associated neurodegeneration and cerebrovascular damage. Investigation on the precise role of S1P species in various neurodegeneration and cerebrovascular damage might reveal novel mechanisms of S1P in those diseases.

Angina and heart failure (elevated S1P levels)

In pre-infarction angina, the median level of serum S1P in patients was significantly higher than that in patients without pre-infarction angina, both at admission and discharge [0.54 (IQR 0.14-1.35) vs. 0.26 (IQR 0.12-0.62) /0.51 (IQR 0.20-1.81) vs. 0.30 (IQR 0.13-0.68) μmol/L] (Kiziltunc et al., 2014). Serum S1P levels both at admission and discharge tended to be higher in patients with more angina episodes, but the differences between these subgroups were not statistically significant. This study suggested that the cardio-protective effects of pre-infarction angina may be partially mediated by S1P. In chronic heart failure patients, compared with the control group, the plasma S1P demonstrated a higher level (1.27±0.44 vs 1.12±0.32 μmol/L) (Xue et al., 2020). It was demonstrated that plasma S1P levels in systolic heart failure patients are related to the long-term all-cause mortality with a U-shaped correlation.

Idiopathic pulmonary fibrosis, and community-acquired pneumonia (elevated S1P levels)

The serum S1P level was increased in patients with idiopathic pulmonary fibrosis (IPF), compared with healthy controls (1.40(IQR 0.4) vs. 1.00(IQR 0.26) μmol/L) (Milara et al., 2012). The bronchoalveolar lavage level of S1P was also increased in those patients, compared with healthy controls (1.12(IQR 0.53) vs. 0.20(IQR 0.50) μmol/L) (Milara et al., 2012). S1P induced transformation of alveolar type II into mesenchymal cells in the range of 1 nmol/L to 10 μmol/L (Milara et al., 2012), showing an important role in aberrant epithelial to mesenchymal transition (EMT) and myofibroblast accumulation.

Patients with community-acquired pneumonia (CAP) had higher plasma S1P levels than healthy individuals (27.54 (IQR 4.78-18.91) vs. 10.58 (IQR 14.37-49.99) ng/ml) (Hsu et al., 2019). S1P levels were inversely correlated with hospital mortality, intensive care unit admission and long hospital stay of CAP patients, while corticosteroid/methylprednisolone treatment during hospitalization further elevated the S1P levels to 42.23 (IQR 30.29-62.93) ng/mL, suggesting that S1P may be responsible for the pathogenesis of CAP (Hsu et al., 2019).

Hepatocellular carcinoma and end-stage liver disease (elevated S1P levels)

In hepatocellular carcinoma (HCC), serum levels of sphingolipid metabolites, S1P and SA1P show a significant upregulation in patients as compared to patients with cirrhosis (Grammatikos et al., 2016). In HCC, the serum S1P was significantly higher than healthy controls (1.69±0.52 vs. 0.34±0.13 μmol/L) (Zeng et al., 2016). S1R1 levels were elevated in HCC tumor tissues by 1.603±0.792 folds, compared to surrounding non-tumorous tissues (Zeng et al., 2016). S1P is associated with HCC progression but is also associated with the anti-cancer immune response (Satyananda et al., 2021). Identifying the biomarkers for HCC diagnosis is rapidly progressed in recent years (Yao et al., 2021). In patients with end-stage liver disease, S1P and SA1P concentrations were significantly higher in patients who survived 3 months or 1 year compared with patients who died, suggesting that low plasma S1P concentration is highly associated with the prognosis of end-stage liver disease (Becker et al., 2017).

Therefore, plasma S1P levels were reduced in various inflammation-related diseases such as atherosclerosis and sepsis, but were increased in other diseases, type 2 diabetes, neurodegeneration and cerebrovascular damage such as acute ischemic stroke, Alzheimer's disease, vascular dementia, angina, heart failure, idiopathic pulmonary fibrosis, community-acquired pneumonia and cancer such as HCC. Therapeutic loading of HDL with S1P suppressed inflammation in coronary artery disease, and S1P suppressed inflammation in vascular smooth muscle cells even hours after initial TNF-α stimulation via the S1PR2 pathway (Keul et al., 2019). Whether increased HDL/S1P level in coronary artery disease will lead to risks in other diseases cannot be disregarded. In fact, our current knowledge is based solely on S1P d18:1. Recently, it was reported that S1P d20:1 slightly induces COX-2 expression and can block the S1P d18:1-induced COX-2 expression mediated via S1P2 activation in glioblastoma cells (Vutukuri et al., 2020). The role of the S1P specie in human diseases and their interactions are other important issues. The S1P levels in the diseases summarized in the present study are shown in Table 1.

Mechanism of S1P regulated EC biology

S1P level is closely associated with endothelial function in hemostasis and the mentioned diseases above. Endothelial barrier disruption is a marker of acute inflammatory diseases such as sepsis and acute lung injury (ALI) (Opal and van der Poll, 2015), and an important factor in promoting the invasion and metastasis of cancer cells (Reymond et al., 2013) and the development of atherosclerosis (Kurano and Yatomi, 2018). S1P activates a series of signaling cascades by acting on S1PRs (Fig. 1). An understanding of the molecular mechanism by which S1P and its related signaling pathway regulate ECs in vascular and vascular-related diseases should aid the diagnosis of those diseases.

S1P signaling in vascular development and angiogenesis

Angiogenesis is considered to be one of the key pathophysiological events in a variety of diseases. Excessive angiogenesis can lead to atherosclerotic plaque rupture (Perrotta et al., 2020) and progression of cancer (Hosein et al., 2020), while insufficient angiogenesis can lead to myocardial infarction, stroke, ischemia in neurodegenerative diseases and obesity-related diseases, as well as ischemic eye diseases (Zeng et al., 2019; Yao et al., 2020b; Zeng and Fu, 2020). S1P binds to different subtypes of S1PRs to play a regulatory role in angiogenesis. S1P stimulates the proliferation, survival, migration and capillary lumen formation of ECs mainly through S1PR1 and, to a lesser extent, S1PR3, thus promoting angiogenesis (Fu et al., 2016). S1P promoted angiogenesis through S1PR1 and S1PR3, which was firstly reported using a mice Matrigel implant model (Lee et al., 1999). Further studies have shown that S1PR1 and S1PR3 mediate activation of the Rho family guanosine triphosphatase (GTPase) Rac1 pathway, which plays an important role in S1P-induced angiogenesis (Mendelson et al., 2014). In contrast to S1PR1/3, S1PR2 inhibited angiogenesis. With human umbilical vein ECs (HUVECs) as the research model, S1PR2 inhibits angiogenesis primary through the RhoC pathway (Del Galdo et al., 2013). Besides the S1PRs, recent studies have shown that S1P regulates angiogenesis by acting on transcription factor peroxidase proliferator activated receptor γ (PPARγ) and forming S1P/PPARγ/PGC1β complex in EC (Parham et al., 2015).

During the development of the vascular system in vivo, S1PR1 signaling can prevent excessive sprouting angiogenesis and help stabilize blood vessels (Gaengel et al., 2012; Jung et al., 2012). In the mature vascular system, S1PR1 signal stabilizes endothelial adhesion and promotes development of blood flow, while S1PR2 and S1PR3 promote contraction of vascular smooth muscle cells, thereby regulating vascular tension (Garcia et al., 2001; Oo et al., 2011). Although S1PR2 inhibits angiogenesis, S1PR2 is required for vascular maturation. Studies have shown that S1PR2 or S1PR3 deletion will aggravate embryonic defects in S1PR1-deficient mice, including vascular maturation defects and bleeding, leading to early intrauterine death (Ben Shoham et al., 2012).

VEGF has been identified as the most critical driver of angiogenesis. S1PR1 (Chemical lead 2) selective antagonist can inhibit VEGF-induced angiogenesis, indicating that endogenous S1P is involved in VEGF-induced angiogenesis (Yonesu et al., 2009). The microRNA (miR)-9 can induce angiogenesis by inducing VEGF and activating autophagy pathways in HUVECs

(Zeng et al., 2019). MiR-9 can induce angiogenesis by downregulating S1PR1, but not S1PR3 (Yao et al., 2020). HDL promotes angiogenesis by promoting S1P/S1PR3-dependent VEGFR2 expression and activation of VEGFR2. Inhibition of S1PR3 blocks the upregulation and activation of VEGFR2 by HDL or S1P, thereby

Table 1. The S1P levels in various diseases.

Diseases	S1P level		Assay Method	Effect and mechanism	Reference
	Diseases	Control			
Atherosclerosis (AS)	AS 0.687±0.266 nmol/mL	0.879±0.212 nmol/mL	MS	Serum S1P has more power to indicate AS than HDL-C	Soltau et al., 2016
Coronary artery calcification (CAC)	0.74 (IQR 0.63, 0.87) μmol/L, Deceased	0.83 (IQR 0.70, 0.94) μmol/L, Living	LC-MS/MS	Plasma S1P and apoM were inversely and independently associated with mortality of patients with type 2 diabetes, but not CAC	Liu et al., 2019
Ischemic stroke	6.53±5.0 ng/mg	4.55±2.1 ng/mg	HPLC-MS/MS	The S1P-S1PR axis promotes the outlet of splenic T cells and is associated with cerebral recruitment of S1PR+ Th and Treg cells	Lucaciu et al., 2020
Cardiopulmonary bypass	0.46 (IQR 0.36-0.51) μmol/L	0.77 (IQR 0.61-0.99) μmol/L	LC-MS/MS	Low postoperative S1P may be a new marker of the severity of inflammation caused by cardiac surgery	Greiwe et al., 2021
Pre-infarction angina	0.54 (IQR 0.14-1.35) μmol/L	0.26 (IQR 0.12-0.62) μmol/L	ELISA	S1P activates ischemic preconditioning pathways, which may play a role in cardiac protection	Kiziltunc et al., 2014
Chronic heart failure (CHF)	1.269±0.441 μmol/L	1.122±0.316 μmol/L	LC-MS/MS	Plasma S1P at 1.06 μmol/L had the lowest risk of all-cause death	Xue et al., 2020
Septic shock	86.5 (IQR 63.7-120.0) ng/mL	302 (IQR 253.3-404.0) ng/mL	HPLC-MS/MS	S1P is associated with rupture of endothelial glycocalyx and endothelial damage	Piotti et al., 2021
Sepsis	580±24 nmol/L	1156±17 nmol/L	MS	Serum S1P levels are dramatically decreased and are inversely with sepsis severity	Winkler et al., 2015
Chronic hepatitis C virus	280.3±29.6 nmol/L	386.8±55.5	HPLC	Plasma S1P concentration was inversely correlated with serum hyaluronic acid	Ikeda et al., 2010
Acquired pneumonia (CAP)	27.54 (IQR 14.37-49.99) ng/mL	10.58 (IQR 4.781-18.91) ng/mL	ELISA	The level of S1P in CAP patients was negatively correlated with the severity of disease	Hsu et al., 2019
Acute lung injury associated with malaria (ALI)	0.2 μmol/L	0.4 μmol/L	ELISA	S1P may activate the Sphk-1 signaling pathway to promote ALI/ARDS by binding to S1PR3	Punsawad and Viriyavejakul, 2019
Idiopathic pulmonary fibrosis (IPF)	1.4 (IQR 0.4) μmol/L	1 (IQR 0.26) μmol/L	ELISA	S1P promoted the epithelial-to-mesenchymal transformation (EMT) through S1PR2 and S1PR3 and the activation of p-Smad3, RhoA-GTPases, oxidative stress, and TGF-1 release	Milara et al., 2012
Type 2 diabetes (T2DM)	235.6±13.4 ng/mg	195.0±6.4 ng/mg	UPLC-MS/MS	Diabetic HDL carries higher level of S1P than normal HDL, might induce COX-2 and PGI-2 in ECs	Tong et al., 2013
Hepatocellular carcinoma (HCC)	500 ng/mL	100 ng/mL (Cirrhosis)	MS	S1P and C16-ceramide may serve as novel diagnostic markers for HCC	Grammatikos et al., 2016
	1.69±0.52 μmol/L	0.34±0.13 μmol/L	ELISA	S1P induces advanced tumor phenotypes of HCC by establishing the MMP-7/Syndecan-1/TGF-β1 autocrine loop and suggests that the targeted S1P signaling pathway plays a role in HCC metastasis	Zeng et al., 2016
End-stage liver disease	82.43 (Range 38.82-139.00) ng/mL, Death within 3 months	141.50 (Range 78.22-252.22) ng/mL, Survival after 3 months	LC-MS/MS	S1P is associated with prognosis in end-stage liver disease	Becker et al., 2017
	91.19 (Range 38.82-201.33) ng/mL, Death within a year	150.14 (Range 87.18-245.31) ng/mL, Survival after a year			
ANCA - associated vasculitis (AAV)	2149.7 (Range 1855.9-2334.5) nmol/L	274.6 (Range 149.2-452.9) nmol/L	ELISA	Plasma S1P level can be used as a biomarker to predict coagulation-related complications in AAV	Wu et al., 2020
Alzheimer's disease (AD) and vascular cognitive impairment	Ratio of d18:1 to d16:1 is 9.8 (IQR 5.3), AD with dementia; 9.6 (IQR 5.0), cognitive impairment without dementia 11.5 (IQR 5.2), vascular dementia	Ratio of d18:1 to d16:1 is 8.5 (IQR 3.9), non-cognitive impairment	LC-MS/MS	plasma d16:1 S1P was reduced in vascular dementia and Alzheimer's disease. d18:1 was competitive with d16:1 for inflammation cytokines expression	Chua et al., 2020

ALI/ARDS, acute lung injury/acute respiratory distress syndrome; ANCA, anti-neutrophil cytoplasmic antibody; IQR, median with interquartile range; MS, mass spectrometry; LC-MS/MS, liquid chromatography tandem MS; HPLC-MS/MS, high-performance liquid chromatography coupled with MS; UPLC-MS/MS, ultra-high performance liquid chromatography coupled with MS; ELISA, enzyme-linked immunosorbent assay.

preventing HDL from promoting angiogenesis (Jin et al., 2018). Thus, S1P-S1PR3-VEGFR2 signaling cascade may be a target for HDL-based angiogenesis promotion strategies in the prevention and treatment of atherosclerotic ischemic diseases. The combination inhibition of S1P and VEGF destroyed tumor vascular bed and showed a better suppression of tumor development than S1P/VEGF alone in renal cell carcinoma (Fischl et al., 2019). The complex interaction between S1P/S1PRs and VEGF/VEGFR2 during angiogenesis needs to be further clarified.

S1P signaling in inflammation

In ECs, pro-inflammatory cytokines promote tissue inflammation by stimulating the expression and the presentation of cell-adhesion molecules (CAM) such as E-selectin, intercellular adhesion molecule-1 (ICAM-1), and p-selectin (Gotsch et al., 1994; Bradley, 2008). In investigating the role of endothelial S1PR1 in adult mice, the endothelial S1PR1 signal was enhanced in regions of the arterial vasculature experiencing inflammation. The abundance of proinflammatory adhesion proteins, such as ICAM-1, was enhanced in mice with EC-specific deletion of S1PR1 and suppressed in mice with EC-specific overexpression of S1PR1, suggesting an anti-inflammatory and protective function of S1PR1 in vascular disease (Galvani et al., 2015).

In ECs, S1P/S1PR2 also aggravates inflammatory responses by activating NF-κB, increasing the release of vascular cell adhesion molecule-1 (VCAM-1) and intercellular ICAM-1 (Zhang et al., 2013a). After challenging with LPS, S1PR2-knockout mice exhibit reduced expression of E-selectin, VCAM-1, and ICAM-1 in multiple organs. Data also elucidate the mechanism by which S1PR2 promotes endothelial inflammation by binding G12/13 to activate the stress activated protein kinase (SAPK) and ROCK/NF-κB pathways (Zhang et al., 2013b). Recent studies have shown that S1P in combination with S1PR2 also exerts an anti-inflammatory effect. ApoM-S1P also inhibited oxidized low-density lipoprotein (ox-LDL)-induced HUVECs inflammation through the S1PR2-mediated PI3K/Akt signaling pathway (Zheng et al., 2019). The S1PR2 antagonist JTE-013 can reverse the improvement of apoptosis and inflammation of HUVECs by ApoM-S1P,

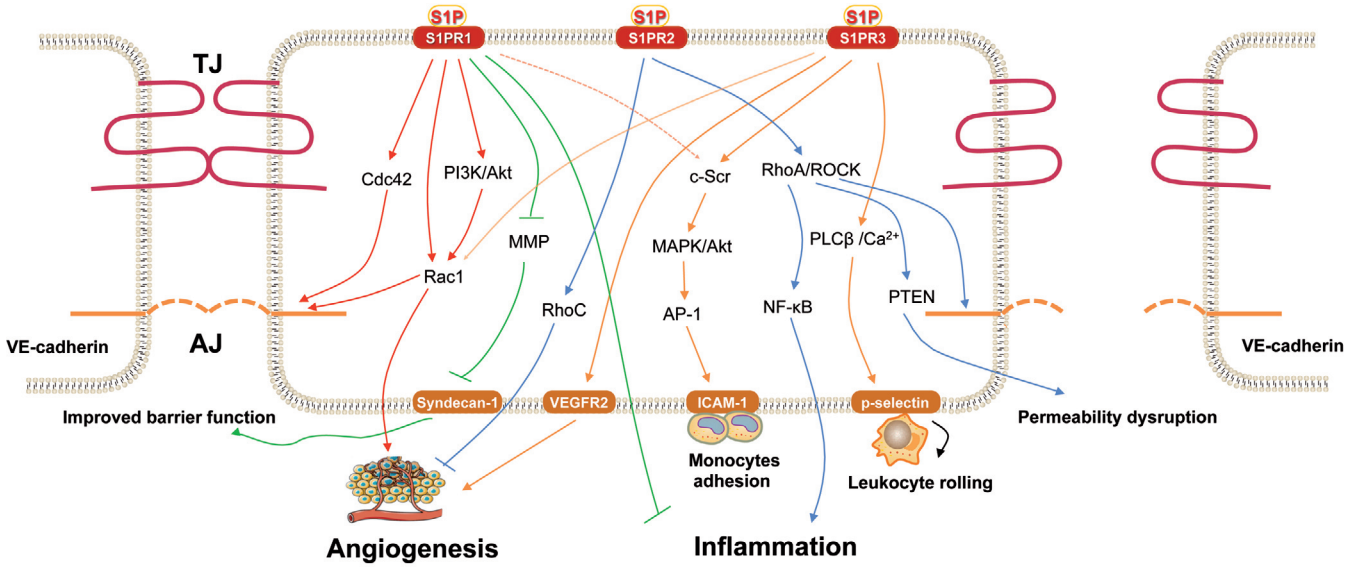

Fig. 1. Main regulatory effect of S1P on EC biology. S1P regulates EC mainly through its receptors S1PR1-3. S1PR1 and S1PR3 mediate the activation of Rac1 that is a member of the Rho family of small guanosine triphosphatases (GTPases), which play an important role in S1P-induced angiogenesis. S1P activates PI3K dependent signals to inhibit vascular permeability, and promotes vascular barrier integrity through S1PR1/Rac1 and S1PR1/Cdc42 pathways. S1P/S1PR1 singal maintains EC barrier integrity through protecting endothelial glycocalyx against syndecan-1 shedding which is caused by MMPs activation. Yet S1PR2 mainly increases endothelial permeability by inducing cell contraction and disrupting the adherens junction (AJ) through Rho-ROCK and PTEN pathway, and inhibits angiogenesis through the RhoC pathway. In addition, S1PR3 also promotes angiogenesis through VEGFR2. In terms of inflammatory response, S1PR1 mainly plays an anti-inflammatory role. Conversely, activation of S1PR2 or S1PR3 has an opposite effect on inflammation. S1PR2 promotes endothelial inflammation by activating the ROCK/NF-κB pathway. S1P induces ICAM-1 expression in ECs and monocyte adhesion to ECs through inducing activation of S1PR3 and formation of c-Src/EGFR/PDGFR complex and its downstream MAPK/Akt/AP-1 signaling activation. S1P promotes p-selectin dependent leukocyte rolling through S1PR3 and PLC β /Ca2+. However, S1PR1 is also involved in the S1P-induced ICAM-1 expression and monocyte adhesion to ECs. AJ, adheren junction; ICAM-1, intercellular adhesion molecule; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; ROCK, Rho-associated protein kinase; PI3K, phosphatidylinositol-3-hydroxykinase; PLC, phospholipase C; S1P, sphingosine-1-phosphate; TJ, tight junction.

suggesting that ApoM-S1P can protect HUVECs from injury and inflammation via S1PR2-mediated activation of the PI3K/Akt pathway (Liu and Tie, 2019). Furthermore, S1PR3 mediated the p-selectin dependent leukocyte rolling (Nussbaum et al., 2015). S1PR1 agonism also reduced cytokine release in lungs following ischemia-reperfusion injury (Stone et al., 2015). S1P induces ICAM-1 expression in ECs and monocyte adhesion to ECs through inducing activation of S1PR1, S1PR3, and formation of c-Src/EGFR/PDGFR complex and its downstream MAPK/Akt/AP-1 signaling activation (Lin et al., 2015).

Exocytosis of the Weibel-Palade body is a key early step in vascular inflammation and thrombosis. S1P has two opposite effects on Weibel-Palade somatic exocytosis. S1P partially triggers weibel-Palade extracellular secretion by activating the PLC-γ pathway. However, S1P also regulates weibel-Palade extracellular secretion by activating the PI3K pathway (Matsushita et al., 2004). S1PR3 also promotes platelet aggregation by stimulating exocytosis of Weibel Palade bodies from EC (van Hooren et al., 2014).

Until recently, S1P has been a key mediator directly linking the clotting factor system to vascular inflammation. Platelets release large amounts of S1P when activated directly by clotting or PKC signaling agonists such as thrombin (English et al., 2000). Thromboxane is a key factor regulating S1P release of human platelets (Ulrych et al., 2011). Thrombin may limit its role in inducing vascular leakage through PAR-1 mediated S1P/S1PR1 interaction (Mahajan-Thakur et al., 2015).

Therefore, S1P may inhibit the inflammation, but promote thrombin production under pro-inflammatory conditions such as atherosclerosis. In fact, serum S1P was decreased in atherosclerosis. However, an elevated S1P level in local lesion might be induced by the activation of the coagulation cascade and platelets during atherosclerosis. The details in local S1P concentration with EC dysregulation during atherosclerosis should be analyzed.

S1P signaling in endothelial permeability

The integrity of the EC junction and glycocalyx is important for maintenance of the EC barrier. Cell junction is closely associated with cytoskeleton. The remodeling of cytoskeleton is mediated by Rho GTPase such as RhoA and Rac1 (Citi et al., 2014). The disruption of the EC junction or glycocalyx will lead to the increase of endothelial permeability, which further leads to vascular leakage, even serious consequences such as bleeding, edema and inflammation (Xiong and Hla, 2014). An in vivo study conducted by Camerer et al. (2009) showed that mice lacking S1P in plasma had increased vascular leakage and then increased mortality after receiving an allergic response, platelet activating factor (PAF) or histamine injection. In vitro studies have shown that S1P can decrease the permeability of albumin by protecting the endothelial monolayer (McVerry and Garcia, 2004). S1P antagonizes the increase of acute microvascular permeability caused by inflammatory mediators such as PAF (Adamson et al., 2010) and bradykinin (Adamson et al., 2012) through S1PR1 receptor (Adamson et al., 2014). Studies in pulmonary perfusion with S1P have also shown that S1P reduces vascular permeability by binding to endothelial S1PR1 (Zhang et al., 2010). Glycocalyx plays a critical role in vascular and vascular-related diseases (Zeng et al., 2022a). S1P protects ECs by inhibiting the activity of matrix metalloproteinases (MMPs), stabilizes endothelial glycocalyx by reducing GAG degradation and shedding (Tarbell et al., 2014; Zeng et al., 2014), and regulates barrier function by regulating the expression of vascular endothelial cadherin and β-catenin in the endothelium cell-cell contact area (Xiong and Hla, 2014). The depletion of plasma albumin that stabilizes the endothelial glycocalyx structure results in the shedding of glycocalyx from the endothelial surface and the destruction of barrier integrity (Zhang et al., 2016). S1P protects endothelial glycocalyx by inhibiting the shedding of the extracellular domains of syndecan-1 by a S1PR1/MMP activity dependent pathway (Zeng et al., 2014). S1P further induced synthesis of endothelial glycocalyx via PI3K pathways (Zeng et al., 2015).

The effect of S1P on vascular permeability is strongly dependent on its concentration. Studies have shown that physiological concentrations of S1P (0.5~1 μM) stimulated cells to produce RhoA-dependent barrier protection, while exposure to extremely high concentrations of S1P (5 μM) mediated RhoA-dependent barrier destruction (Shikata et al., 2003). S1PR1 is closely associated with the gastrointestinal tract in a pertussis toxin-sensitive manner and is the primary barrier enhancing receptor (Garcia et al., 2001). Instead, S1PR2 and S1PR3 couple with additional G proteins, primarily disrupting the EC barrier (Sammani et al., 2010). S1PR1 activates Gi- and PI3K- (Igarashi et al., 2001) dependent signals to inhibit vascular permeability, while S1PR2 inhibits the PI3K pathway by coupling to the Rho-ROCK and PTEN to disrupt adherens junction and thus increase paracellular permeability (Sanchez et al., 2007). Reinhard and colleagues found that S1PR1/GαI/ Rac1 and S1PR1/GαI/Cdc42 signals promote EC diffusion and vascular barrier integrity, while S1PR2/Gα12/13/RhoA signals increase endothelial permeability by inducing cell contraction (Reinhard et al., 2017).

For the cellular signal cascades, it was demonstrated that S1P enhanced the self-recovery of the disrupted EC barrier induced by LPS, TNF-α, IL-1β, IFN-γ, and IL-6 via its transporter Spns2 and rapid phosphorylation of AMP-activated protein kinase (AMPK) in human microvascular ECs (Dennhardt et al., 2019). However, AMPK was found to be rapidly and strongly phosphorylated in response to VEGFA or bradykinin and to increased vascular permeability (Dragoni et al., 2021). In an earlier study, it was reported that S1P activated

AMPK and activated the downstream Rac1, promoting the eNOS activation in ECs (Levine et al., 2007). How the S1PRs and cellular signals such as AMPK coordinate the cytoskeleton remodeling and NO production to regulate the vascular permeability remains unknown, which limits the development of therapy strategy for microcirculation improvement.

S1P and ROS, NO, H_2S production in ECs

The excessive production of reactive oxygen species (ROS) by NADPH oxidase (NOX) (referred to as "oxidative stress") is commonly thought to be responsible for tissue damage associated with inflammatory diseases (Lee and Yang, 2012). Oxidative stress enhances the accumulation of misfolded proteins in the endoplasmic reticulum, leading to ER stress and disruption of cell homeostasis (Ozcan et al., 2004). Exogenous S1P stimulates intracellular ROS production in human lung microvascular ECs (Harijith et al., 2013). ROS induced by hyperoxia was mediated by increasing of SphK1 and its metabolized product S1P in human lung microvascular ECs (Harijith et al., 2016). S1PR1 and S1PR2, but not S1PR3 were responsible for the hyperoxia-induced ROS (Harijith et al., 2016). The poor control of EC redox environment in cardiovascular disease and type 2 diabetes, especially the overproduction of ROS by NOX can cause uncoupling of eNOS and endothelial dysfunction (Meza et al., 2019). Hydrogen sulfide (H_2S) suppressed ROS generation and suppressed NLPR3 inflammasome activation in paraquat-induced acute liver injury (Liu et al., 2020). H_2S inhibition by PAG suppressed ROS increase in cardiomyocytes in mouse hearts with myocardial infarction or apex resection (Pei et al., 2020). Homocysteine induced ECs apoptosis, which might be reversed by shear stress (Zeng et al., 2022b). Sodium hydrosulfide (NaHS, an H_2S donor) inhibited homocysteine-induced EC injured and cellular ROS production (Zhao et al., 2018). High glucose-induced ROS production and EC injury can be inhibited by H2S via activating the PI3K/Akt/eNOS signaling pathway (Lin et al., 2020).

Nitric oxide (NO) and H_2S are two gas transmitters produced by vascular cells such as ECs. S1P can increase eNOS activity and NO production in cultured vascular ECs (Igarashi et al., 2001). eNOS acts as a downstream target of S1P-induced vasodilation (di Villa Bianca et al., 2006; Roviezzo et al., 2006). Alganga et al. (Alganga et al., 2019) found that S1P had endothelium-dependent vasodilation on rat aorta in hypoxia, which partly depended on sphingosine kinase SK1 activity and NO release mediated by S1PR3 in ECs. These data have important implications for tissue perfusion during ischemia-attack. Kerage et al. (Kerage et al., 2021) found that S1P directly interacts with the endothelium to regulate the vascular tone of the pressurized arteries in mice by producing NO that prevents endothelial permeability and dilation simultaneously. Also, Sphk1/S1P signaling stimulated eNOS and NO production in brain microvascular ECs, and promoted angiogenesis following cerebral ischemia-reperfusion injury (Lv et al., 2020).

Plasma H_2S level and aortic H_2S production in ApoE-/- mice is lower than that in control mice (Wang et al., 2009). Mitidieri et al. (2020) demonstrated that L-cysteine is converted into L-serine and H_2S, and both L-cysteine and L-serine relaxed the mouse aorta rings in an endothelium-dependent manner via NO and S1P/S1PR1. The inhibitor of H_2S PAG could not reverse the L-

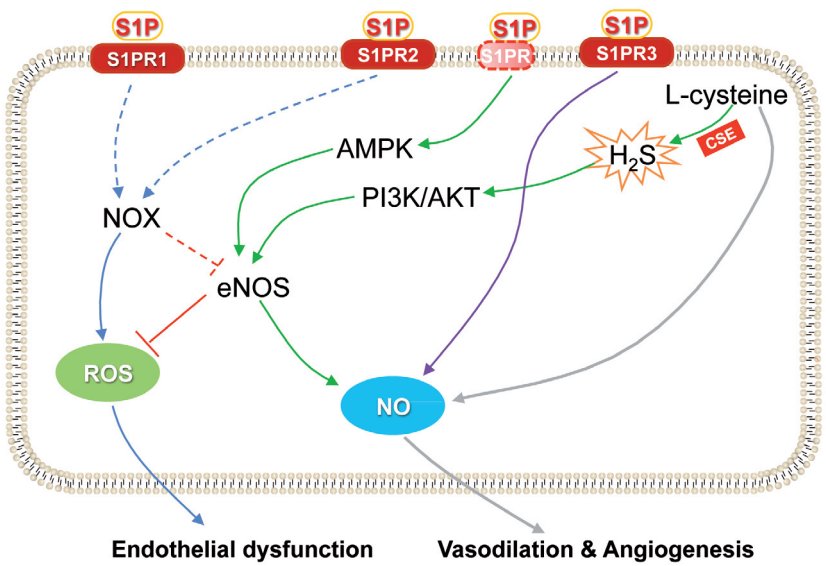

Fig. 2. Production of ROS, NO and H2S in ECs and their modulation by S1P. L-cysteine is the substrate for H2S generation, which is catalyzed by cystathionine γ-lyase (CSE). H_2S can increase eNOS activity through the PI3K/Akt signaling pathway. S1P also promotes endothelial vasodilation and angiogenesis by activating the AMPK/eNOS pathway to produce NO via an unknown S1PR. Yet L-cysteine can directly promote NO production and vasodilation via an H_2S indepdnent pathway. S1PR1/2 promotes endothelial ROS production by activating NOX, leading to endothelial dysfunction. Overproduction of ROS by NOX can cause uncoupling of eNOS and endothelial dysfunciton. H_2S can suppress ROS genereation. AMPK, phosphate (AMP)-activated protein kinase; eNOS, endothelial NO synthase; CSE, Cythionine γ-lyase; H_2S, Hydrogen sulfide; NO, nitric oxide; ROS, reactive oxygen species.

cysteine (1 mM)-induced NO production and L-serine-induced relaxant effect (Mitidieri et al., 2020).

Therefore, S1P prevents inflammation against ROS and increases vasodilation via NO. H_2S inhibited ROS production, but may not affect vascular tone (Fig. 2). Both S1P and H_2S play an important role in atherosclerosis, but whether S1P and H_2S play a synergistic role in regulating endothelial function and treating atherosclerosis remains unclear. Further investigation on intrainteraction among S1P, S1PRs and H_2S in EC inflammation and permeability will greatly improve our understanding of the mechanisms of vascular tone and remodeling.

Concluding remarks

In conclusion, S1P level varies in diseases and regulates a variety of endothelial functions to control vascular morphology, angiogenesis, permeability, coagulation and inflammation, yet its complex role remains to be further studied:

1) S1P concentration varies in diseases. Plasma S1P levels were decreased in atherosclerosis, sepsis and acute lung injury. Conversely, in ischemic stroke, angina pectoris before infarction and diabetes, the S1P levels in blood were increased. Although S1P level was indicated as an independent indicator in the diagnosis and prevention of those diseases, other organs might be challenged by altered S1P during replenishment or removal of S1P for targeting special organs for therapeutic purposes. In addition, the details in local S1P concentration with EC dysregulation during atherosclerosis should be analyzed.

2) The role of S1P is closely associated with its receptors S1PR1-3. The order or strength of activation of S1PRs will lead to distinct results in atherosclerosis and angiogenesis regulation. In general, S1P promotes angiogenesis through S1PR1/3, while it inhibits via S1PR2. Yet the complex interaction between S1P/S1PRs and VEGF/VEGFR2 in angiogenesis needs to be further clarified.

3) S1P can induce intracellular ROS production. Also, S1P can activate the Rac1 to promote eNOS activation in ECs. Rac1 is also involved in ROS production and VE-cadherin-mediated reduction of intercellular adhesion, which may lead to increased permeability in some cases (Guilluy et al., 2011; Zhang et al., 2021). The precise role and the mechanism by which S1P controls cytoskeleton remodeling and permeability remains to be determined.

4) More and more evidence indicate that the reduction of H_2S is involved in the pathogenesis of various vascular diseases such as hypertension, atherosclerosis and pulmonary hypertension. Thus, H_2S supplementation may greatly prevent the progression of vascular diseases by inhibiting vascular inflammation and inhibiting oxidative stress. H_2S is expected to be an effective target for drug development against atherosclerosis. However, intrainteraction among S1P, S1PRs and H_2S in EC inflammation and permeability remains unknown.

Acknowledgements. Supported by the Key Research and Development Projects in Sichuan Province in China No.2021YFS0188, the National Natural Science Foundation of China No.11932014, and Science and Technology Support Project of Xinjiang Uygur Autonomous Region No.2020E0285.

Conflict of interest. The authors declare no conflict of interest.

Author contributions. YZ came up with this idea. YQ and YZ drew the mechanism diagrams, sorted out table data, wrote and edited the manuscript. All the authors consulted the literature, revised the manuscript, and approved the final version of the manuscript.

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Accepted February 4, 2022