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REVIEW ARTICLE

Dual roles of sphingosine-1-phosphate receptor 3 in inflammation, ischemia-reperfusion injury, and vascular homeostasis

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Abstract

Sphingosine-1-phosphate receptor 3 (S1PR3) is a member of the G protein-coupled receptor (GPCR) family, structurally characterized by seven transmembrane domains. It exhibits diverse biological functions by binding to three major Gα protein subtypes (Gi/o, Gq, and G12/13), thereby activating downstream signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), phospholipase C/calcium (PLC/Ca^{2+}), and Ras homolog family member A/Rho-associated coiled-coil containing protein kinase (RhoA/ROCK). S1PR3 displays tissue- and cell-specific expression patterns, with high levels observed in the cardiovascular system (endothelial cells, vascular smooth muscle cells, cardiac fibroblasts), immune system (macrophages, dendritic cells), nervous system (astrocytes, microglia), and liver (hepatocytes, hepatic stellate cells). This expression profile enables S1PR3 to play pivotal roles in regulating inflammation, maintaining vascular homeostasis, repairing liver damage, protecting neural function, and preserving immune balance. Under pathological conditions, S1PR3 exhibits dual functionality. At physiological concentrations or under mild pathological conditions, it exerts protective effects—for instance, preventing cardiomyocyte and hepatocyte apoptosis and maintaining blood-brain barrier (BBB) integrity. Conversely, overactivation leads to tissue damage, including exacerbated inflammatory infiltration (e.g., in acute respiratory distress syndrome, ARDS), promotion of fibrosis (e.g., hepatic fibrosis), and vascular injury (e.g., atherosclerosis). S1PR3 has emerged as a promising therapeutic target for cardiovascular diseases, neurological injuries, and liver disorders. However, clinical application of S1PR3 modulators is hindered by off-target effects (e.g., bradycardia due to insufficient subtype selectivity) and risks of immunosuppression, underscoring the need for more selective ligands and personalized therapeutic regimens.

Keywords: Sphingosine-1-phosphate receptor 3, Sepsis, Liver injury, Inflammation

Highlights

- Clarifies S1PR3's dual functionality, which shifts depending on S1P concentration, injury stage, and cell type—resolving long-standing controversies in the field.
- Bridges basic research and clinical translation by defining S1PR3's roles in diseases like sepsis, ARDS, and liver fibrosis, laying a solid foundation for its development as a potential therapeutic target.
- Deciphers the complex regulatory network involving S1PR3, CXCR1, PAR1, and the NF-κB pathway; identifies the key role of S1PR3/CXCR1 heterodimers in neutrophils of pneumonia patients as a major breakthrough; and addresses current limitations while proposing targeted future research strategies.

1 BASIC CHARACTERISTICS AND DISTRIBUTION OF SPHINGOSINE-1-PHOSPHATE RECEPTOR 3 (S1PR3)

Sepsis is a life-threatening systemic inflammatory response syndrome triggered by infection, characterized by a dysregulated host immune response that often leads to progressive immune dysfunction, organ damage, and even death [1]. Sphingosine-1-phosphate receptors (S1PRs) are an important type of non-Toll-like receptors (non-TLRs) belonging to the G protein-coupled receptor (GPCR) family. They bind to ligands like sphingosine-1-phosphate (S1P), initiating intracellular transmembrane signal transduction, promoting activation of G protein downstream signaling pathways, and enabling diverse biological functions, including regulation of cell proliferation, inflammatory responses, and angiogenesis [2].

Five S1PR subtypes (S1PR1 to S1PR5) have been identified, among which S1PR1, S1PR2, and S1PR3 are ubiquitously expressed. In recent years, S1PR3 has garnered increasing research attention. It is highly expressed in macrophages and can couple with three types of G proteins (Gi, Gq, and G12/13), participating in various pathophysiological processes by regulating oxidative stress responses [3, 4]. Specifically, S1PR3 activates downstream signaling pathways, including PI3K/Akt, phospholipase C (PLC), Rho family GTPases (Rac and Rho), adenylyl cyclase, Jun N-terminal kinase (JNK), and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), thereby exerting its biological effects [5].

2 S1PR3 AND INFLAMMATORY RESPONSE

S1P is a bioactive signaling molecule derived from mammalian membrane sphingolipids, functioning in immune and inflammatory responses as well as the cardiovascular system [2]. Most of S1P's biological functions are mediated by S1PR1 to S1PR5. Among these, S1PR3 participates in numerous biological activities, including inflammation and vascular barrier function [6-8]. S1PR3 promotes myeloid differentiation at the expense of other cell lineages (especially erythropoiesis) and enhances the survival of long-term hematopoietic stem cells (LT-HSCs), closely resembling tumor necrosis factor alpha (TNF-α)-induced emergency hematopoiesis [9]. Thus, S1PR3 acts as an enhancer of TNF-α, utilizing the NF-κB inflammatory signaling pathway to promote HSC survival and myeloid differentiation.

Although TNF-α levels increase with aging and in myeloid malignancies, the mechanisms by which this inflammatory environment induces leukemia and the specific cell subtypes prone to transformation remain unknown [10-12]. Recent studies have revealed that acute TNF-α treatment upregulates S1PR3 membrane levels in primary acute myeloid leukemia (AML) cell lines, while S1PR3 antagonism counteracts TNF-α-induced myeloid differentiation [13]. Previous research demonstrated that S1PR3 overexpression (S1PR3OE) driven by the lysosomal M promoter—rather than the F4/80 promoter—induced leukemic transformation in mice, suggesting that the initiating cell originates from primitive subsets rather than the mature myeloid lineage [13]. However, S1PR3OE in human HSCs did not cause de novo AML in xenografts, indicating that other factors such as the microenvironment and species differences must be considered [14].

S1PR3 expression is elevated in circulating neutrophils of patients with sepsis and pneumonia, forming heterodimers with chemokine (C-X-C motif) receptor 1 (CXCR1), a biomarker of inflammation also known as interleukin-8 (IL-8) receptor alpha (IL-8RA) [15, 16]. This positions S1PR3 as a molecular target for sepsis-associated lung injury.

Furthermore, in vivo studies on S1PR3-mutant mice revealed that protease-activated receptor 1 (PAR1) amplifies inflammation through sphingosine kinase 1 (SphK1)-S1PR3 signaling crosstalk, promoting disseminated intravascular coagulation and death [3]. Endothelial microparticles—complex vesicular structures shed by activated or apoptotic endothelial cells (ECs)—contain enzymes, transcription factors, and mRNA, and are released in response to inflammatory stimuli such as TNF-α, other cytokines, lipopolysaccharide (LPS), and thrombin [17-19]. Studies have shown that EC-damaging substances may induce nitration and shedding of EC S1PR3 into microparticles [20]. Our experiments further demonstrated that S1PR3-containing microparticles enhance EC barrier disruption in vitro, consistent with their role in sickle cell disease, suggesting that microparticles serve as both biomarkers of EC damage and cellular sources of inducers for vascular dysfunction [20].

Table 1. S1PR3-related core signaling pathways and their biological functions

Category	Key information	Related references
S1P basic characteristics & functions	Sphingosine-1-phosphate (S1P) (from membrane sphingolipids): acts in immunity, inflammation, cardiovascular system; functions mediated by S1PR1-S1PR5.	[2]
S1PR3 core biological functions	(1) Inflammation, vascular barrier, myeloid differentiation, long-term hematopoietic stem cells (LT-HSCs) survival; (2) Myeloid differentiation (erythropoiesis impaired); (3) Enhances tumor necrosis factor-α (TNF-α) via nuclear factor-κB (NF-κB): supports hematopoietic stem cells (HSCs) survival/differentiation; (4) Heterodimerizes with C-X-C chemokine receptor type 1 (CXCR1) in neutrophils.	[6-9, 15]
S1PR3 in hematopoiesis & leukemia	(1) Human HSCs S1PR3 mimics murine TNF-α-NF-κB; (2) TNF-α upregulates S1PR3 in AML; antagonism reverses differentiation; (3) Murine S1PR3OE (lysosomal M promoter) induces leukemia; (4) Human S1PR3OE no de novo acute myeloid leukemia (AML) in xenografts (species/microenvironment).	[9, 13, 14]
S1PR3 in inflammatory signaling crosstalk	(1) Protease-activated receptor 1 (PAR1) amplifies inflammation via sphingosine kinase 1–sphingosine-1-phosphate receptor 3 (SphK1–S1PR3) (murine): promotes coagulation/death; (2) TNF-α/thrombin: EC S1PR3 nitration, shedding into microparticles.	[17, 18, 21]
S1PR3-containing endothelial microparticles	(1) EC microparticles (activated/apoptotic ECs) carry S1PR3; released by TNF-α/lipopolysaccharide (LPS)/thrombin; (2) S1PR3-microparticles disrupt EC barrier (consistent with sickle cell disease); (3) LPS+cytokines boost EC microparticles; high levels link to thrombosis/dysfunction.	[17-22]
S1PR3 in disease-related expression & target value	(1) S1PR3 high in sepsis/pneumonia neutrophils; (2) CXCR1 (interleukin-8 receptor α (IL-8RA), inflammation marker) binds S1PR3; S1PR3 is a target for sepsis lung injury.	[15, 16]
Unclear research directions	(1) TNF-α-enriched inflammation: leukemia induction mechanism/cell subtypes; (2) S1PR3-microparticles: EC barrier disruption mechanism; (3) Functional differences: nitrated vs non-nitrated S1PR3.	[10-12, 20]

Note: S1PR3, Sphingosine-1-phosphate receptor 3; GPCR, G protein-coupled receptor; PKC, Protein kinase C; CXCR1, C-X-C chemokine receptor type 1; CXCL8, C-X-C motif chemokine ligand 8; IRI, Ischaemia–reperfusion injury; CXCL12, C-X-C motif chemokine ligand 12; DARC, Duffy antigen receptor for chemokines; ELR+, Glutamic acid-leucine-arginine positive; TNF-α, Tumour necrosis factor-α; β2AR, Beta-2 adrenergic receptor.

Combined LPS and cytokine treatment increases EC microparticles production [21]. Microparticles are detectable in plasma of healthy individuals, and higher concentrations under pathological conditions are linked to increased thrombotic risk and endothelial dysfunction (ED) [22]. Related signaling pathways are summarized in **Table 1**.

3 S1PR3 AND HEPATOCELLULAR INJURY

3.1 Hepatic fibros

Hepatic fibros is a common consequence of various liver injuries, including viral infection, drug abuse, and alcohol intoxication. After liver injury, levels of SphK1 and S1P increase substantially. In vitro studies have shown that S1PR1/3 mediate S1P-triggered migration of human HSCs and activation of fibrosis [23]. Blockade of S1PR1/3 significantly reduces pathological angiogenesis and hepatic fibrosis in mice with bile duct ligation (BDL) [24]. As hepatic fibrosis progresses, S1P promotes bone marrow mesenchymal stem cell (BMSC) migration via S1PR3. Suramin markedly reduces the number of bone marrow-derived cells during cholestasis, suggesting that the S1P/S1PR3 signaling pathway significantly affects cholestatic hepatic fibrosis by facilitating bone marrow cell homing [25]. Additionally, S1PR1 and S1PR3 are essential for transforming growth factor-β1 (TGF-β1)-induced transdifferentiation of BMSCs into hepatic myofibroblasts [26].

The RNA-binding protein HuR regulates tumor cell migration. HuR mRNA levels are elevated in hepatic fibrotic tissues from humans and mice. In vitro experiments confirmed that the S1PR3/p38 signaling pathway promotes BMSC migration by inducing HuR phosphorylation and cytoplasmic translocation [27]. Furthermore, the S1PR2/3/Gi/PI3K/Rac1 signaling pathway participates in the migration and recruitment of bone marrow mesenchymal monocytes. Administration of the S1PR2 antagonist JTE-013 or the S1PR3 antagonist CAY-10444 significantly reduces recruitment of these monocytes to fibrotic livers, alleviating inflammation and fibrosis in BDL mice [28]. Palmitic acid induces S1P formation in hepatocellular carcinoma cells and promotes its extracellular release. S1P participates in HSC fibrosis via S1PR3. Conditioned medium from hepatocellular carcinoma cells upregulates α-smooth muscle actin (α-SMA) expression in HSCs in an S1P-dependent manner, initiating hepatic fibrosis [29]. Recent studies have shown elevated S1PR3 levels in patients with endometriosis, and S1PR3 participates in TGF-β1-induced fibrosis of endometrial adenocarcinoma cells [29, 30].

Our study provides spatial (zonal) characterization of liver sinusoidal endothelial cells (LSECs; zones 1–3), identification

of transcriptomic changes associated with liver cirrhosis, and demonstration of relationships between these transcriptomic changes and phenotypic alterations. Zone 3 LSECs are most susceptible to cirrhosis-associated damage, exhibiting increased capillarization and decreased endocytic capacity. Identification of the most dysfunctional LSEC populations will be valuable for developing effective therapeutic strategies. Furthermore, CD34 is a more useful marker of LSEC capillarization in liver cirrhosis than CD31 [31].

With recent advances in molecular and cell biology technologies, understanding of the pathogenesis of portal vein thrombosis (PVT) associated with liver cirrhosis has deepened. PVT occurrence involves multiple factors, including local and systemic inflammatory responses, disturbances in coagulation-fibrinolysis balance, endothelial dysfunction, and alterations in gut flora [32-34]. The crosstalk among these molecular and cellular mechanisms renders PVT pathogenesis a complex process.

Under cirrhotic conditions, changes in the hepatic microenvironment form an intricate network with systemic immune disorders and coagulation system imbalances. Elucidating the functional network underlying PVT occurrence not only clarifies its pathogenesis but also informs early diagnosis and personalized treatment. This article reviews literature from the past five years, discussing relationships between key factors (inflammatory response, coagulation-fibrinolysis balance, endothelial dysfunction, gut flora) and PVT formation in cirrhotic patients, aiming to provide theoretical support for improving patient management and prognosis [35].

3.2 Regulatory role of S1P and its receptors in sepsis-induced liver injury

S1P and its receptors play key roles in immune and metabolic processes, closely associated with various inflammatory responses, oxidative stress, and lipid deposition diseases. As an integral organ for immunity and metabolism, the liver not only defends against bacterial toxins during sepsis but also regulates metabolism of deposited substances post-injury. S1P and S1PR1 to S1PR3 are highly expressed in the liver and act through multiple signaling pathways. For instance, the spinster homolog 2 (Spns2)/S1P signaling pathway exerts inhibitory effects during early inflammatory responses to prevent cytokine storms and promotes later-stage effects to reduce immunosuppression-induced damage [36]. Additionally, S1P likely plays an essential role in bile acid metabolism regulation, particularly relevant in liver injury. Further research on mutual regulation among liver injury, immunity, and metabolism may facilitate discovery of novel therapeutic targets [37]. S1PR-targeted drugs have shown efficacy in regulating immunity, and future studies should explore new metabolic targets to advance treatment strategies for inflammatory and metabolic disturbances associated with sepsis-induced liver injury [38].

3.3 Expression of markers and functional specificity of LSECs versus portal vein endothelial cells

Endothelial cell cultures are valuable tools for investigating liver physiology and pathophysiology in vitro. However, the marked heterogeneity of endothelial cells within and between organs, combined with the tendency for cultured cells to lose tissue-specific markers, complicates such studies. Although all endothelial cells share certain characteristic features, specific markers or marker combinations are needed to define distinct endothelial populations. To date, the study of human sinusoidal endothelial cells (HSECs) in vitro has been hampered by the lack of specific markers that conclusively identify these cells and discriminate them from vascular or lymphatic endothelial cells. This remains partially true, as many classic endothelial markers are widely expressed, and considerable variability exists in phenotypic marker detection between animal and human systems (e.g., CD31 and von Willebrand factor). Currently, no single molecule is known to be expressed exclusively on hepatic sinusoidal endothelium. However, increasing knowledge of endothelial receptors is providing a larger, better-defined set of phenotypic markers. In addition to their utility in phenotyping or sorting specific endothelial cells for culture, tissue-specific receptors offer clues to the functions of the cells under study, exemplified by the numerous scavenger receptors expressed on HSECs.

Very low-passage cells retain fenestrations in vitro for a short time, but these rapidly disappear within one or two passages, as does expression of vascular adhesion protein-1 (VAP-1) [39-41]. Apart from these changes, the cells remain relatively phenotypically stable for 7–8 passages and can be identified by expression of CD31, lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin-related (L-SIGN), Stabilin-1, and lack of CD34 and prospero homeobox 1 (PROX-1) [39, 42]. These markers confirm endothelial identity while excluding vascular and lymphatic endothelial contamination and, together with markers excluding leukocyte origin, can confirm the sinusoidal nature of the cells [38].

4 EFFECTS OF S1PR3 ON VASCULAR FUNCTION

Cardiovascular diseases are leading causes of death worldwide. Endothelial cells, vascular smooth muscle cells, cardiomyocytes, and cardiac fibroblasts all express S1PR1–S1PR3, but expression patterns differ significantly. Endothelial cells primarily express S1PR1 and S1PR3, with S1PR1 being most abundant. Vascular smooth muscle cells highly express S1PR2 and S1PR3. Cardiomyocytes predominantly express S1PR1, followed by S1PR3 at approximately half the level. Cardiac fibroblasts express S1PR3 at much higher levels than S1PR1 and S1PR2 [43].

4.1 Regulation of angiogenesis

Walter et al. discovered that S1PR3 knockout mice exhibit impaired angiogenesis. Conversely, S1P or fingolimod (FTY720) activates Src kinase and C-X-C chemokine receptor type 4 (CXCR4)-dependent Janus kinase 2 (JAK2) signaling via S1PR3, promoting angiogenesis in endothelial progenitor cells [44].

In vitro experiments demonstrated that S1P triggers activation of the S1PR3/PI3K/Akt signaling pathway. Under low-concentration S1P stimulation (100 nM), S1PR3 in endothelial progenitor cells primarily mediates Gi protein-dependent PI3K/Akt pathway activation, thereby promoting cell proliferation and inhibiting apoptosis [45].

High-density lipoprotein (HDL)/S1P activates vascular endothelial growth factor receptor 2 (VEGFR2) through S1PR3, promoting proliferation of human umbilical vein endothelial cells and angiogenesis [46]. Li et al. found that S1P/S1PR3 facilitates transdifferentiation of epicardial progenitor cells into smooth muscle-like cells [47]. Recently, Yasuda et al. demonstrated that S1P/S1PR3 promotes corneal angiogenesis by increasing vascular endothelial growth factor A (VEGF-A) production in mice [48].

4.2 Regulation of vascular barrier function

S1PR3 is highly expressed in patients with acute lung injury and severe falciparum malaria complicated by pulmonary edema, primarily in pulmonary endothelial cells and plasma, serving as a potential biomarker for acute lung injury [49]. In LPS-induced acute inflammatory lung injury mouse models, Sammani et al. found that intratracheal administration of high-dose S1P (final plasma concentration ~1 mM) significantly disrupted the alveolar-capillary barrier, an effect prevented by S1PR3 silencing [50]. Different S1P concentrations exert opposing effects on the endothelial barrier: physiological concentrations (10 nM–2 μM) protect the endothelial barrier via the Gi/Rac signaling pathway, whereas higher concentrations activate the S1PR3/RhoA/ROCK pathway, increasing vascular permeability—an effect that may completely counteract the barrier-protective Gi/Rac pathway [51, 52]. Therefore, reducing S1PR3 expression and activation may be an effective strategy for preventing inflammation, acute lung injury, and other diseases linked to endothelial barrier dysfunction [53].

4.3 Regulation of vascular tone

Activating S1PR3 in endothelial cells promotes nitric oxide (NO) production and induces vasorelaxation. In contrast, S1PR3 in vascular smooth muscle cells induces vasoconstriction by increasing intracellular calcium concentration and activating Rho [54]. HDL/S1P promotes calcium mobilization and Gi/PI3K/Akt signaling activation in endothelial cells through S1PR3, facilitating endothelial nitric oxide synthase (eNOS) phosphorylation and ultimately leading to vasodilation [55, 56]. However, other studies have shown that S1P causes vasoconstriction in rat coronary arteries and mouse mesenteric arteries, an effect significantly reduced by pretreatment with the S1PR3-specific antagonist TY52156 [57, 58]. Thus, the effect of S1PR3 activation on vascular tone is complex and requires further detailed investigation.

4.4 Ischemia-reperfusion injury

Accumulating evidence indicates that S1PR3 signaling plays a key role in protecting the heart from ischemia-reperfusion injury (IRI). Administration of HDL/S1P or pretreatment with a specific S1PR3 agonist reduces myocardial infarct size following IRI. Both in vitro and in vivo experiments demonstrate that S1PR3-mediated Akt- and NO-dependent pathways protect cardiomyocytes from apoptosis [52-54]. RhoA has also been implicated in cardioprotection. The G12/13/RhoA/ROCK signaling pathway triggers MRTF-A activation and increases stromal cell protein CCN1 expression, thereby protecting cardiomyocytes from ischemic injury [59-63]. Connexin 43 (Cx43) is a major component of ventricular gap junctions, which transmit action potentials and bioactive substances. Recent studies have shown that S1P regulates Cx43 phosphorylation, expression, and distribution via S1PR2/3, ultimately reducing myocardial cell death and sudden cardiac death caused by IRI [64]. Cx43 uncouplers (e.g., heptanol and Gap26) lower IRI-induced mortality mediated by S1PR2/3 [65]. Interestingly, Wafa et al. found that in the early stage of acute coronary syndrome, S1P/S1PR3 induces coronary artery constriction and impairs myocardial contractile function, although S1PR3-induced vasoconstriction may be counteracted by S1PR2-mediated vasorelaxation [53-66]. Thus, S1PR3 activation may represent an important strategy for preventing myocardial IRI.

Studies have demonstrated that S1PR3 participates in inflammation, proliferation, migration, tumor invasion, IRI, tissue fibrosis, and vascular activity [67]. In a mouse model of myocardial IRI, HDL and its component S1P protect the heart via an S1PR3-mediated signaling pathway [68]. S1PR3(–/–) mice are protected from renal IRI through mechanisms involving bone marrow-derived dendritic cells (BMDCs) and their immunomodulatory functions [69]. Adoptive transfer of S1PR3(–/–) BMDCs prevents renal IRI through splenic interactions and expansion of splenic CD4+Foxp3+ regulatory T cells. In contrast to its protective role in cardiac IRI, S1PR3 exerts opposite effects in renal IRI, likely due to differences in disease stage and cell/tissue contexts.

S1PR1 and S1PR2 have been implicated in microglial activation during cerebral IRI [70-72]. A recent study showed that S1PR3 contributes to microglial activation and M1 macrophage polarization in a mouse brain IRI model [73]. Our study

demonstrated that S1PR3 inhibition reduces IRI, confirmed by reduced infarct volume. H&E, Nissl, and Fluoro-Jade C staining confirmed that S1PR3 mediates brain damage during cerebral IRI [74].

Neuronal nitric oxide synthase (nNOS) mediates early neurological damage, with nNOS overexpression playing a key role in early ischemia and excitotoxic injury [75]. Inducible NOS (iNOS) subsequently increases, and both adversely affect cerebral ischemia. NO production, catalyzed by NOS from L-arginine and oxygen, can react with superoxide to form peroxynitrite, a potent oxidant [76]. During ischemia, NO produced by nNOS and iNOS may be neurotoxic, partly due to peroxynitrite free radical formation causing direct damage to mitochondrial enzymes and DNA [77]. Additionally, increased NO production from nNOS or iNOS promotes ischemic damage through free radical injury, tissue inflammation, and microcirculatory failure [78]. nNOS knockout mice exhibit smaller infarct sizes and fewer neurological deficits after middle cerebral artery occlusion [79]. iNOS knockout mice also show fewer neurological deficits and reduced infarct volumes [80]. In our experiment, nNOS and iNOS expressions were elevated following cerebral ischemia compared with sham-operated controls, consistent with previous studies. S1PR3 inhibition reduced nNOS expression and NO content. Heo and Im found that S1PR3 inhibition reduces LPS-induced inflammatory gene expression, including iNOS and cyclooxygenase-2 [74]. However, our study found that S1PR3 inhibition did not reduce iNOS expression, suggesting that S1PR3 reduces NO primarily by decreasing nNOS rather than iNOS.

4.5 Atherosclerosis

Atherosclerosis is a chronic inflammatory disease, with ED being a key driver of its development. HDL is considered atheroprotective. Kimura et al. found that HDL activates PI3K/Akt, p38, and Rho/ROCK pathways via S1P/S1PR3, promoting endothelial cell migration and exerting anti-atherosclerotic effects [81]. Additionally, S1P prevents macrophage apoptosis by activating the S1PR3/STAT3/surviving signaling pathway, reducing the risk of plaque rupture in advanced atherosclerotic lesions [82].

Macrophages with S1PR3 knockout are resistant to 22(R)-hydroxycholesterol-stimulated cholesterol efflux. Conversely, the S1P/S1PR3/Gq/PLC/protein kinase C (PKC) signaling pathway may promote cholesterol efflux by phosphorylating and stabilizing the ATP-binding cassette transporter A1 (ABCA1) protein [83]. A recent study emphasized the core role of ED as a major precursor of inflammation, not only accelerating atherosclerosis progression but also causing plaque instability. Hallmarks of ED include reduced NO production/availability and endothelial cells exhibiting an inflammatory phenotype. The endothelial glycocalyx, a gel-like structure composed of glycoproteins and extracellular matrix components, participates in transendothelial transport. Endothelial glycocalyx damage impairs eNOS expression, leading to reduced NO availability and production [84].

Various inflammatory signals activate endothelial cells, triggering upregulation of cell adhesion molecules, including pro-inflammatory E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). Leukocyte diapedesis occurs, accompanied by increased endothelial permeability [85]. Activated endothelial cells secrete cytokines and function similarly to macrophages. Dysfunctional, inflamed endothelium facilitates lipoprotein penetration and trapping beneath the endothelial cell layer, where these lipoproteins are subsequently oxidized [66]. Deposited lipoproteins are taken up by macrophages and smooth muscle cells, leading to foam cell formation and fatty streak accumulation. Abnormalities in cell clearance—specifically, failure to properly remove apoptotic endothelial cells—result in vascular sclerosis [86]. Some endothelial cells may undergo endothelial-mesenchymal transition, promoting extracellular matrix deposition and further exacerbating vascular stiffness [87]. Arterial constriction caused by lipid accumulation, combined with impaired vasodilation, expands regions of turbulent or oscillatory blood flow, further intensifying endothelial cell activation and denudation. These regions carry a high risk of rupture for lipid-rich plaques with thin fibrous caps, potentially leading to thrombotic occlusion. Expression of procoagulant factors—tissue factor, plasminogen activator inhibitor-1 (PAI-1), and von Willebrand factor (vWF)—further heightens this risk [84-88]. Thus, ED serves as a precursor to both atherosclerosis and thrombosis.

Patients with coronary artery disease often experience sleep disturbances, reduced melatonin levels, and circadian rhythm misalignment [89]. Sleep disturbances are linked to higher levels of inflammatory markers, ED, and reduced cardiac vagal modulation—all contributing to coronary artery disease development and progression [90]. Relatively few studies have established a clear connection between lifestyle behaviors (e.g., physical activity level, a modifiable cardiovascular risk factor) and endothelial function in patients with cardiovascular disease [91]. In the present study, multiple regression analysis revealed a significant association between low physical activity levels and ED (**Table 1**). Analysis of the control group found that physically active patients had better endothelial function than sedentary ones. Consistent with this, a study involving 2,363 patients with prediabetes and type 2 diabetes showed that sedentary behavior is linked to higher levels of low-grade inflammatory biomarkers (C-reactive protein, soluble ICAM-1, IL-6, and TNF-α) as well as biomarkers of ED, which are key components of the atherosclerotic process illustrated in **Figure 1** [92].

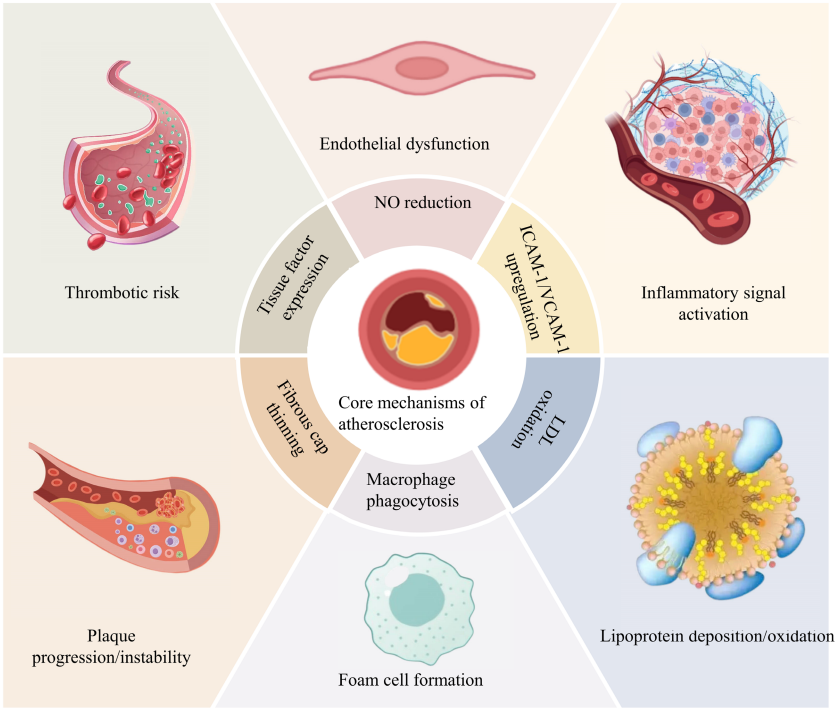

Figure 1. Core mechanisms of atherosclerosis. Binding of sphingosine-1-phosphate (S1P) to S1P receptor 3 (S1PR3) exerts pleiotropic effects in vascular biology, regulating angiogenesis, vascular tone, atherosclerosis, and ischemia-reperfusion injury protection via distinct signaling pathways. This figure depicts the core mechanisms of atherosclerosis, including endothelial dysfunction (manifested as reduced nitric oxide (NO) bioavailability and upregulated intercellular adhesion molecule 1 (ICAM-1)/vascular cell adhesion molecule 1 (VCAM-1)), inflammatory signaling activation, lipoprotein deposition and oxidation (involving low-density lipoprotein (LDL) oxidation), macrophage phagocytosis and subsequent foam cell formation, plaque progression and instability (characterized by fibrous cap thinning and tissue factor expression), as well as heightened thrombotic risk. Created with Microsoft PowerPoint.

5 S1PR3 AND IMMUNE RESPONSE

Growing evidence suggests that S1PR3 regulates the biological functions of certain immune cells, including dendritic cells (DCs), macrophages, and natural killer cells. In vitro studies have shown that S1PR3 is essential for S1P-induced maturation, migration, and endocytosis of DCs [69]. Additionally, S1PR3 in DCs plays a key role in recruiting NKT cells and neutrophils to damaged kidneys following IRI. Notably, DCs lacking S1PR3 induce a Th2-like response in NKT cells—specifically prompting them to produce higher levels of IL-4—which protects the kidneys against IRI [69, 93].

S1PR3 is a pro-inflammatory receptor. Hyperglycemia inhibits M2 macrophage polarization and promotes M1 polarization via the S1P/S1PR3 signaling pathway, worsening hepatic IRI. However, pretreatment of diabetic mice with CAY10444 (an S1PR3 antagonist) significantly reduces hepatic IRI [94].

S1PR2 and S1PR3 promote migration of bone marrow-derived monocytes/macrophages by activating the Gi/o/PI3K/Rac1 signaling pathway. Administration of JTE-013 (S1PR2 antagonist) or CAY-10444 (S1PR3 antagonist) to BDL-treated mice significantly reduces recruitment of these cells to fibrotic livers [4, 26]. Yang et al. found that S1PR2/3 activates the Gi/PI3K/JNK signaling pathway, mediating S1P-induced M1 polarization of bone marrow-derived monocytes/macrophages [95]. However, Bryan et al. showed that FTY720 reduces macrophage phagocytic capacity and reactive oxygen species production via S1PR3, thereby reactivating Cryptococcus infection in granulomas [96]. Therefore, S1PR3 exerts dual roles in macrophages: promoting M1 polarization to trigger inflammation while also enhancing phagocytic and killing activities to inhibit bacterial diseases. **Figure 2** provides a schematic overview of these roles.

6 S1PR3 SIGNALING IN NEURAL FUNCTION

Astrocytes are one of the most common cell types in the brain and are critical for maintaining the brain's microenvironment [97]. In vitro studies have demonstrated abundant S1PR3 expression in astrocytes, which increases further during inflammation. S1PR3-G12/13 activates RhoA, leading to increased production of inflammation-related genes [98]. CAY10444, a specific S1PR3 antagonist, has shown protective effects in models of cerebral infarction, spinal cord injury, and intracerebral hemorrhage [99-101].

In vitro experiments show that S1P/S1PR3/Ras/pERK signaling promotes pericyte proliferation, contributing to scar formation after spinal cord injury [99]. Dong et al. found that FTY720P protects astrocytes from oxygen-glucose deprivation-induced injury and inflammation by inhibiting S1PR3-dependent TLR2/4-PI3K-NFκB signaling [101]. Additionally, S1PR3 inhibition exerts neuroprotective effects via the S1P/CCL2/p-p38 MAPK pathway [100]. S1PR3 antagonists may represent a potential therapeutic approach for nervous system injuries.

ED is a hallmark of ARDS [99]. The endothelium is a monolayer of cells that controls the permeability of fluids, proteins and blood cells [86]. In ARDS, endothelial barrier permeability increases as monolayer integrity is disrupted, allowing fluid to enter interstitial tissue, further decreasing gas exchange and inducing hypoxia [102, 103]. Endothelial cell-cell adhesions, including adherens junctions (AJs), tight junctions, and gap junctions, regulate barrier permeability [104]. Among these, AJs have more significant microvascular effects, and expres-

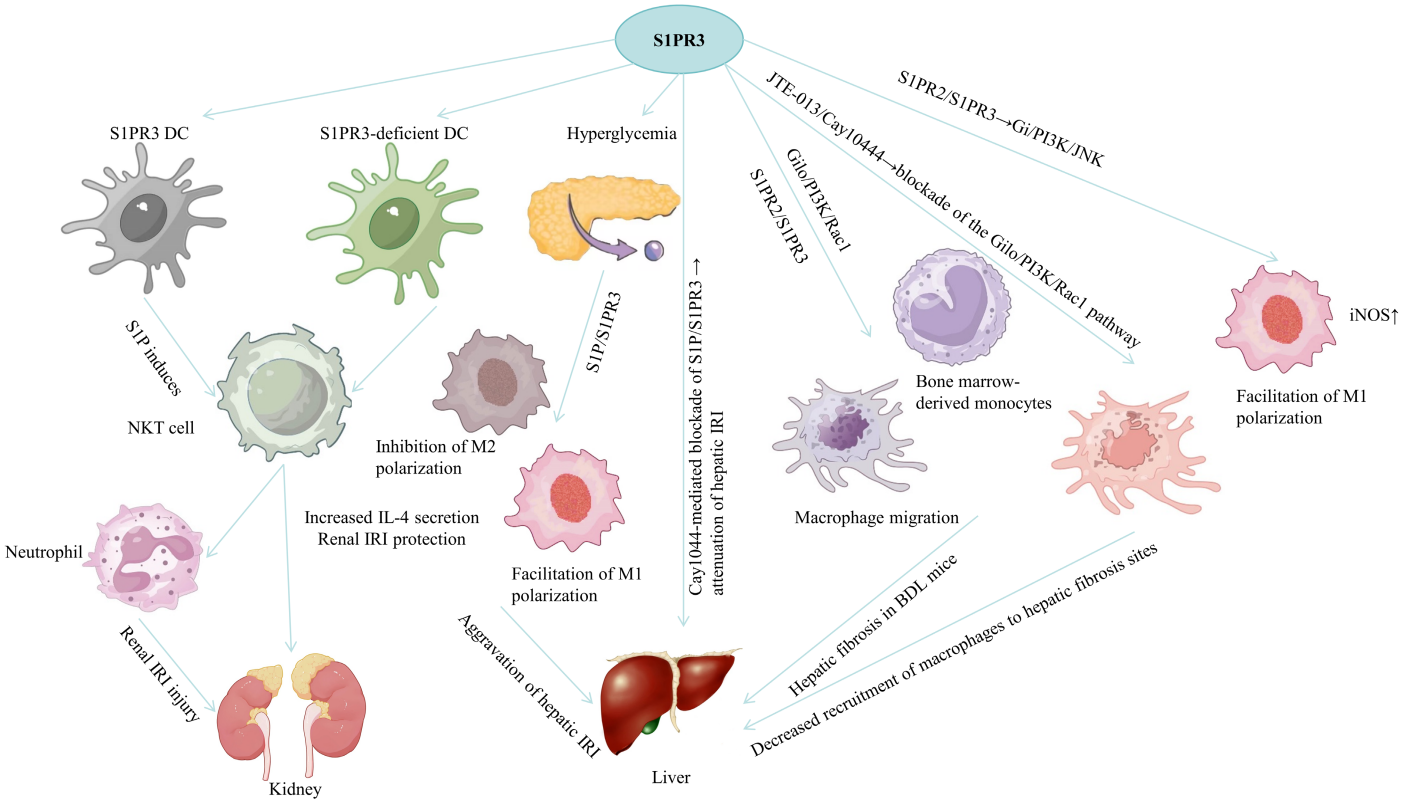

Figure 2. Multifaceted roles of S1PR3 in immune cell regulation and tissue injury responses. S1PR3 orchestrates immune cell functions, including those of dendritic cells (DCs) and macrophages, to mediate renal ischemia-reperfusion injury (IRI), hepatic injury/fibrosis, and anti-infection responses. This figure outlines the multifaceted roles of S1PR3. In renal IRI, S1PR3-expressing DCs (S1PR3 DCs) trigger natural killer T (NKT) cell activation and interleukin-4 (IL-4) secretion, whereas S1PR3-deficient DCs inhibit M2 macrophage polarization, together shaping renal injury outcomes; in hepatic IRI and fibrosis, S1PR3 signals through Gi/o/PI3K/Rac1 or Gi/PI3K/JNK pathways to drive M1 macrophage polarization (marked by elevated inducible nitric oxide synthase (iNOS) expression) and macrophage migration, while S1PR3 blockade with CAY10444 alleviates hepatic IRI and reduces macrophage recruitment to fibrotic lesions; furthermore, hyperglycemia and S1P/S1PR3 signaling amplify M1 polarization to worsen hepatic IRI, and S1PR3 promotes the migration of bone marrow-derived monocytes. Created with Microsoft PowerPoint.

sion of vascular endothelial cadherin (VE-cadherin) at endothelial AJs is essential for endothelial barrier function [48]. AJ structure involves interactions among VE-cadherin, β-catenin, and the actin cytoskeleton [105]. In this study, we found that in LPS-induced ARDS mouse models and LPS-stimulated cell models, S1PR3 inhibition significantly restored expression of VE-cadherin and β-catenin, as shown by Western blotting and immunofluorescence [106]. Additionally, rhodamine phalloidin staining of the cytoskeleton revealed that S1PR3 inhibition significantly reduced LPS-induced cytoskeletal disruption. S1PR3 mediates VE-cadherin mRNA levels in two types of endothelial cells. In a murine ventilator-induced lung injury model, S1PR3 induced endothelial barrier loss through ADAM10-mediated VE-cadherin cleavage [107].

To date, more than 600 clinical trials have targeted Rho signaling [108-110]. In contrast, no clinical trial targeting S1PR3 has ever been conducted. Targeting S1PR3 in clinical trials may be beneficial, as S1PR3 is not only an upstream regulator of Rho but also a mediator of other pathways, such as VE-cadherin cleavage and NFκB-mediated inflammation. Moreover, most existing S1P-modulated drugs targeting S1PR1 agonistically induce downregulation of S1PR1, leading to suboptimal clinical effects and long-term pulmonary function decompensation due to immunosuppression [111]. In contrast, inhibiting S1PR3—a negative regulator of vascular barrier function upregulated during mechanical stress—does not affect S1PR1 expression, ensuring specific therapeutic effects during ventilator-induced lung injury with few side effects under normal lung conditions. However, S1PR3 is also expressed in the cardiovascular system, kidney, and spleen [112, 113]. S1PR3 inhibition could also lead to hypertension, bradycardia, macular edema, reduced pulmonary function, hepatic adverse effects, and neoplasms [114]. Inhalation delivery of S1PR3 inhibitors via aerosol or nanoparticles, which facilitates direct delivery of drugs deep into the airways, may mitigate these effects. Notably, TY-52156, although a selective S1PR3 inhibitor, may carry significant off-target effects, including inhibiting other S1P receptors with relatively lower affinity [115].

S1P, a metabolic mediator of sphingolipid catabolism predominantly formed through SphK1 catalysis, mediates inflammation in sepsis by binding to S1PR3 expressed in macrophages. We demonstrated that the SphK1/S1PR3 axis is upregulated in LPS-induced macrophages and septic mouse lungs, cascading activation of pro-glycolytic signaling molecules such as HIF-1α, HK2, and PFKFB3. Targeted inhibition of SphK1 by PF-543 effectively abrogated the upregulated SphK1/S1PR3 axis in vitro and in vivo. Additionally, PF-543 significantly suppressed sepsis-related inflammation and multi-organ injury in vivo. Furthermore, PF-543 not only blunted key glycolytic enzymes (HIF-1α, HK2, and PFKFB3) in LPS-treated macrophages but also inhibited HK2 and PFKFB3 in septic mice. Silencing or inhibiting SphK1 tempered pro-inflammatory M1 macrophages while boosting anti-inflammatory M2 macrophages. Intriguingly, S1PR3 knockdown efficiently dampened glycolysis-associated markers, reversed LPS-modulated M1/M2 polarization, and attenuated NF-κB p65 activation. In conclusion, this study provides the first evidence that PF-543 orchestrates proportional imbalance of macrophage polarization and the Warburg effect in a SphK1/S1PR3-dependent manner during sepsis, mitigating both hyperinflammation and multi-organ failure, adding a novel puzzle piece to pharmacologically exploitable therapy for sepsis [116].

7 S1PR3-MEDIATED SIGNAL CROSSTALK

Sphingosine-1-phosphate receptors are members of the GPCR family, also known as seven-transmembrane receptors. The peptide chains that traverse the membrane seven times form extracellular and intracellular loops, receiving extracellular signals and initiating intracellular signaling. The intracellular domain interacts with heterotrimeric G proteins, composed of α, β, and γ subunits. Upon ligand activation, the receptor binds G proteins, causing dissociation of the α subunit from the βγ subunits, which then activate downstream effector molecules and regulate biological effects [117].

S1PRs are ubiquitously expressed but exhibit tissue-specific patterns. S1PR1 and S1PR2 are expressed in most tissues: S1PR1 localizes to the plasma membrane, vesicles, cytoplasm, nucleus, and perinuclear regions, while S1PR2 is found in the plasma membrane and cytoplasm. S1PR3 is highly expressed in heart, lung, kidney, and spleen, and is located in the plasma membrane; S1PR4 is mainly expressed in blood cells and lymphoid tissues; S1PR5 is expressed in brain, skin, and natural killer cells [118].

S1PR1 is the most widely expressed S1P receptor in the brain and couples only with Gi/o [83-85]. S1PR2 can couple with Gi/o, G12/13, and Gs, exhibiting highest binding affinity for G12/13 [103, 104, 117-120]. S1PR3 is known to couple with Gi/o, Gq, and G12/13; however, due to its higher affinity for Gq, it can induce intracellular calcium accumulation and PKC activation [88-90]. S1PR4 and S1PR5 can couple with Gs, Gq, and G12/13 [121-127].

S1PR3 has relatively high affinity for Gq proteins. When it forms a heterodimer with CXCR1, ligand binding still prioritizes Gq pathway activation, driving extracellular calcium influx and simultaneously switching on PKC. Once the calcium signal is activated, it further triggers activation of Rho family small GTPases, which then activate downstream Rho-associated protein kinases, regulating cytoskeletal assembly and disassembly by phosphorylating substrates such as myosin light chains. This process adjusts neutrophil morphology and motility, facilitating their migration across the vascular wall to infection sites. Interestingly, this regulatory effect is only significantly evident in neutrophils from pneumonia patients and is induced by S1P. CXCR1/2 G-protein signaling is tightly regulated and quickly desensitized to prevent constitutive signaling through mechanisms including phosphorylation, β-arrestin1/2 recruitment, AP-2 adaptor protein association, and receptor cross-desensitization.Inflammation is a defense mechanism triggered by infection and tissue damage [128]. The CXCL8-CXCR1/2 axis recruits neutrophils to infection sites and induces neutrophil oxidative burst and granule release to eliminate inflammatory stimuli and increase bacterial clearance, thereby protecting the host from further infection and tissue damage [129-131]. Disruption of this axis severely affects host immune mechanisms against infection and may even be fatal. Impaired neutrophil recruitment often leads to decreased bacterial clearance and reduced survival rates in experimental infectious disease models [128].

Given the multiplicity of CXCR1 and CXCR2 ligands and the more selective inhibition of the CXCR1-related pathway via reparixin, the impact of reparixin could be counterbalanced by redundant mechanisms of neutrophil chemotaxis, resulting in perpetuation of inflammation independently of the initial signal. For example, the Duffy antigen receptor for chemokines (DARC), considered a “silent” chemokine receptor, has recently been shown to regulate bioavailability of several chemokines, including CXCL1, CXCL2, CXCL5, and CXCL8, resulting in DARC-enhanced neutrophil trafficking into tissues [132, 133]. The CXCR2 ligand CXCL5 regulates binding site availability for other ELR+ CXC chemokines released during inflammation through its interaction with erythrocyte DARC. CXCL5 inhibits chemokine scavenging, at least in part, through its homeostatic, high-affinity binding with erythrocyte DARC. Thus, in the absence of CXCL5, DARC scavenges proinflammatory chemokines, contributing to reshaping chemokine gradients for neutrophil influx into, for example, the lung [134]. During severe inflammatory responses, such as in a model of Escherichia coli-induced pneumonia, further expression of CXCL5 by alveolar type 2 cells inhibits DARC chemokine scavenging when production of CXCL1 and CXCL2 dramatically increases, resulting in marked increases in circulating plasma concentrations of these chemokines and adverse conse-

quences for efficient neutrophil accumulation [134, 135]. This example illustrates the complexity and alternative pathways of neutrophil recruitment and regulation independent of overwhelming CXCR1 pathway blockade [134].

Cardiac dysfunction has been associated with elevated circulating chemokine levels in both animals and humans. CXCL8 was among the first chemokines detected in the myocardium in response to IRI, and it has been hypothesized to participate in neutrophil-induced myocardial injury. However, several other chemokines, including CCL2 and CXCL10, have been detected early in animal models of myocardial injury. Cardiac myocytes also express other receptors such as CXCR2, CCR2, and CXCR4 (the receptor for SDF-1/CXCL12). These receptors are constitutively expressed and upregulated following oxidative stress both in vivo and in vitro [136]. In an animal model of IRI, Tarzami et al. found a direct myocardial protective action of CXCR2 during IRI, but the magnitude of this protective effect was smaller than the damaging effect of CXCR2-mediated inflammatory cell recruitment [137]. The authors attributed this to different CXCR2-induced signaling between two different cell types—cardiac myocytes and neutrophils [136]. Additionally, new data highlight the relevance of the CXCL12/CXCR4 axis in myocardial IRI. CXCR4 overexpression in vivo worsened cardiac function in an animal model of IRI, enhancing inflammatory cell recruitment, TNF-α production, and cell death, possibly due to increased CXCL12 production [137, 138]. Furthermore, under stress conditions, paracrine and/or autocrine activation of CXCR4 by its ligand may trigger intracellular signaling pathways that exacerbate contractile dysfunction. CXCR4 activation also modulates β2-adrenergic receptor structure and downstream signaling in ventricular cardiac myocytes and has been shown to be a key mediator of calcium handling in adult rat cardiac myocytes [139]. Thus, independently of reparixin action, myocardial IRI may be triggered and maintained by different chemokine/chemokine-receptor inter-relationships (e.g., the CXCL12/CXCR4 axis), which could explain the lack of significant differences in primary endpoints for myocardial IRI in our study [134]. The biological characteristics and functions of S1P and S1PR3 related to these processes are summarized in **Table 2**.

8 CLINICAL APPLICATIONS OF S1PR3

S1PR3 plays a critical role in regulating inflammatory responses and endothelial barrier function in ARDS. It is highly expressed in lung tissue and endothelial cells and has been widely described as a mediator of various biological responses, but its exact role varies across different cells, tissues, and diseases under distinct conditions [140]. Wang et al. reported that S1PR3 inhibition suppressed NLRP3 inflammasome activation in LPS-stimulated macrophages and in the lungs of septic mice [141]. Bajwa et al. reported that S1PR3-deficient dendritic cells exerted protective effects against IRI-induced acute kidney injury [7]. However, the relationship between S1PR3 and ARDS remains unclear. Our results demonstrated that S1PR3 expression was increased in the lungs of LPS-induced ARDS mice, and S1PR3 inhibition alleviated inflammation and endothelial injury both in vivo and in vitro, thereby reducing LPS-induced ARDS [142].

Mechanistically, S1PR3 modulates key inflammatory signaling cascades, including the NF-κB pathway, to orchestrate the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [142, 143]. The NF-κB pathway is considered the central regulator of inflammation and endothelial function in various diseases, and our previous study revealed the importance of the NF-κB pathway in ARDS [143, 144].

NF-κB has five subunits, with p65 being the key transcriptionally active component. IκBα is a crucial controller of NF-κB p65 activation and is phosphorylated by IKKβ to release active NF-κB p65 into the nucleus, thereby promoting transcription of proinflammatory cytokines and chemokines [145]. In endothelial cells, activated NF-κB contributes to VCAM-1 expression, mediating endothelial inflammation and damage [146]. Previous research has indicated an association between S1PR3 and the NF-κB pathway. Yan et al. reported that the NF-κB pathway participates in S1PR3-mediated human renal cell carcinoma progression [147]. Moreover, previous studies have revealed the NF-κB-dependent proinflammatory role of the S1P/S1PR3 axis in lung adenocarcinoma cells, with S1PR3 activation facilitating tumor cell proliferation [136, 148]. Mitochondria, the main powerhouses of cells, are crucial for regulating inflammatory responses and barrier function in endothelial cells [135]. Mitochondrial oxidative phosphorylation is the primary pathway for ATP production, dependent on mitochondrial membrane potential and respiratory chain complex activity [149]. Consistent with previous studies, we found that LPS suppressed mitochondrial oxidative phosphorylation [150]. S1PR3 inhibition decreased reactive oxygen species levels in lung tissues and mitochondrial ROS levels in endothelial cells while increasing the aggregate-to-monomer ratio. Additionally, ATP production and mitochondrial respiratory chain complex activity were restored after S1PR3 inhibition. The complex V inhibitor oligomycin abolished the protective effect of S1PR3 inhibition on ARDS. Therefore, mitochondrial oxidative phosphorylation may mediate the S1PR3 protective effect in ARDS [142].

9 POTENTIAL SIDE EFFECTS OF S1PR3 MODULATION

Preclinical studies have shown that S1PR1 and S1PR3 may be primary contributors to S1P receptor modulator (S1PRM)-induced cardiovascular adverse events [151]. Due to initial S1PR1 agonism, S1PRM administration triggers a decrease in heart rate and blood pressure, activating G protein-coupled inwardly rectifying potassium channels, followed by myocyte hyperpolarization and transient reduction in excitability.

Table 2. Biological characteristics, functions and disease associations of S1P and S1PR3

Core category	Simplified	Related references
S1PRs basic attributes	(1) S1PRs (Sphingosine-1-phosphate receptors, GPCR family) are seven-transmembrane receptors; (2) Extracellular/intracellular loops: receive and initiate signals; (3) Intracellular part interacts with G proteins (α, β, γ); (4) Ligand activation: α-βγ separation→activate downstream effectors.	[117]
S1PRs tissue distribution & localization	(1) S1PRs: ubiquitous, tissue-specific expression; (2) S1PR1: most tissues, abundant in brain; (3) S1PR2: most tissues; (4) S1PR3: high in heart/lung/kidney/spleen; (5) S1PR4: blood cells/lymphoid tissues; (6) S1PR5: brain/skin/NK cells (natural killer cells).	[118]
S1PRs-G protein coupling specificity	(1) S1PR1: only couples with Gi/o; (2) S1PR2: couples with Gi/o/G12/13/Gs (high G12/13 affinity); (3) S1PR3: couples with Gi/o/Gq/G12/13 (Gq→Ca^{2+}/PKC (protein kinase C) activation); (4) S1PR4/5: couple with Gs/Gq/G12/13.	[86-88, 101-103, 119-127]
S1PR3-CXCR1 heterodimer signaling	(1) S1PR3-CXCR1 (C-X-C motif chemokine receptor 1) heterodimer: ligand→prioritize Gq activation; (2) Gq→Ca^{2+} influx+PKC (protein kinase C) activation; (3) Ca^{2+}→Rho GTPases (Rho guanosine triphosphatases)→Rho-associated kinases (Rho-associated kinases); (4) Kinases→regulate cytoskeleton→adjust neutrophil (neutrophil) function; (5) Promote neutrophil migration to infection sites (pneumonia patients: obvious S1P (sphingosine-1-phosphate) effect).	[128]
CXCR1/2 signaling regulation	(1) CXCR1/2 (C-X-C motif chemokine receptor 1/2) signaling: tightly regulated, quick desensitization; (2) Desensitization mechanisms: phosphorylation, β-arrestin1/2 (β-arrestin1/2), AP-2 (adaptor protein 2), cross-desensitization.	[128]
CXCL8-CXCR1/2 axis in inflammation	(1) Inflammation: defense response to infection/damage; (2) CXCL8 (C-X-C motif chemokine ligand 8)-CXCR1/2: recruit neutrophils, induce oxidative burst/granule release; (3) Effects: eliminate inflammation, clear bacteria, protect host; (4) Disruption: impair immunity, reduce clearance/survival.	[128-132]
Redundant mechanisms of neutrophil chemotaxis	(1) Reparixin (Reparixin) effect counterbalanced by redundant pathways; (2) DARC (Duffy antigen/receptor for chemokines): regulates CXCL1/2/5/8 bioavailability; (3) CXCL5 (C-X-C motif chemokine ligand 5) binds DARC and inhibits chemokine scavenging; (4) No CXCL5: DARC scavenges chemokines and reshapes gradients; (5) E. coli (Escherichia coli) pneumonia: CXCL5 upregulation leads to increased CXCL1/2 and affects neutrophils.	[133-136]
Chemokine receptors in myocardial IRI	(1) Myocardial IRI (myocardial ischemia-reperfusion injury): CXCL8 early detected; CXCR2/CCR2 (C-C motif chemokine receptor 2)/CXCR4 (C-X-C motif chemokine receptor 4) upregulated by oxidative stress; (2) CXCR2: mild protection, but severe inflammatory damage.	[135-138]

Note: S1P, Sphingosine-1-phosphate; S1PR3, Sphingosine-1-phosphate receptor 3; LT-HSCs, Long-term hematopoietic stem cells; TNF-α, Tumour necrosis factor-α; NF-κB, Nuclear factor kappa-B; CXCR1, C-X-C chemokine receptor type 1; AML, Acute myeloid leukemia; S1PR3OE, S1PR3 overexpression; PAR1, Protease-activated receptor 1; SphK1, Sphingosine kinase 1; EC, Endothelial cell; LPS, Lipopolysaccharide; IL-8RA, Interleukin-8 receptor alpha.

Continuous administration leads to S1PR1 downregulation, subsequent shifts in the S1P receptor profile, and increased blood pressure [152].

Furthermore, S1PR3 agonism may play a role in heart rate effects: fingolimod induces bradycardia in wild-type mice, but not in S1PR3 knockout mice [153, 154]. However, the potential involvement of S1PR3 in humans remains unclear. Although extensive efforts have been made to develop new modulators with lower affinity for S1PR3 (e.g., siponimod and ozanimod), minimizing S1PR3 binding does not prevent the cardiac effects observed upon first-dose administration [155-159].

A recent study employed gene clustering functional analysis to identify signaling pathways affected by CAY10444 treatment and S1PR3 knockdown, aiming to explore molecular pathways through which targeting S1PR3 influences WEE1 expression [160]. Although CAY10444 treatment affected the PI3K/Akt, PI3K/Akt/mTOR, and MAPK signaling pathways, the PI3K/Akt pathway was the only common pathway affected by both treatments. Studies have reported that S1PR3 can bind to various Gα proteins, including Gi, Gq, and G12/13, thereby regulating signaling pathways such as adenylyl cyclase/cAMP, Ras/ERK/AC, PI3K/Akt, PLC/Ca^{2+}, and Rho/ROCK [161].

Thus, targeting S1PR3 in oral squamous cell carcinoma (OSCC) may inhibit PI3K/Akt signaling pathway activation. The PI3K/Akt pathway exerts crucial biological functions in tumors [162]. Results confirmed that S1PR3 inhibition decreased Akt phosphorylation levels. Conversely, the Akt ago-

nist SC79 restored S1PR3 inhibition-induced suppression of OSCC cell growth both in vitro and in vivo. Additionally, SC79 partially reversed the downregulation of WEE1 and phosphorylated CDC2 induced by S1PR3 targeting. These findings indicate that S1PR3 knockdown inhibits OSCC cell growth by regulating the Akt/WEE1 signaling pathway.

10 CONCLUSION

S1PR3 is a GPCR and seven-transmembrane receptor that binds to extracellular S1P, activating downstream signaling pathways. S1PR3 plays important roles in controlling normal physiological functions and disease processes across multiple systems, including the cardiovascular, immune, nervous, and hepatic systems. S1PR3 exhibits cell- and tissue-specific effects, contributing to both maintenance of normal tissue homeostasis and pathogenesis of diseases such as inflammation, IRI, and atherosclerosis.

This article systematically summarizes the core biological characteristics of S1PR3, its mechanisms of action in various systems, and its prospects for clinical application. It also clarifies the dual roles and regulatory rules of S1PR3 in inflammation, IRI, and atherosclerosis. Notably, conflicting conclusions exist in current research, with the most typical being the controversy over S1PR3's role in myocardial IRI. Some studies have confirmed that activating S1PR3 inhibits cardiomyocyte apoptosis and reduces infarct size via the Gi-Akt-NO pathway; however, others have found that it exacerbates cell damage via the G12/13-RhoA pathway. The core of this contradiction lies in the failure to fully consider the context-dependent activation characteristics of the S1PR3 signaling pathway.

Based on the mechanistic analysis in this article, this controversy can be explained from three aspects. First, differences in injury stage: in the early stage of ischemia (0~2 h after reperfusion), cardiomyocytes secrete low-concentration S1P (approximately 500 nM) in response to stress. At this time, S1PR3 preferentially couples with highly expressed Gi proteins to initiate the PI3K/Akt protective pathway. In the late stage of reperfusion (>6 h), inflammatory factors induce S1P concentrations to rise above 2 μM and simultaneously upregulate G12/13 protein expression, shifting the pathway toward a pro-injury direction. Differences in intervention timing among different studies directly lead to divergent results. Second, cellular heterogeneity: basal Gi protein expression levels in cardiomyocytes are significantly higher than those in vascular smooth muscle cells, and they retain partial Gi coupling activity even in pathological high-concentration S1P environments. However, some studies have failed to distinguish signal differences between cardiomyocytes and interstitial cells, potentially confounding overall injury effects with cell-specific roles. Third, differences in regulatory methods: non-specific agonists (such as S1P itself) are likely to trigger pathway switching due to concentration fluctuations, whereas specific agonists targeting the S1PR3-Gi coupling domain can stably exert protective effects. This also explains why different intervention strategies yield opposite conclusions.

Currently, several deficiencies remain in S1PR3-related research. Besides the PI3K/Akt, PLC/Ca^{2+}, and RhoA/ROCK pathways, crosstalk mechanisms between S1PR3 and other signaling pathways have not been fully elucidated. The specific molecular switches (e.g., specific phosphorylation sites and regulatory proteins) governing S1PR3 signaling pathway conversion under different disease states still need to be identified. Targeted delivery systems and side effect control strategies for S1PR3-specific modulators require optimization. In the future, combining technologies such as single-cell sequencing and proteomics to analyze context-dependent activation mechanisms of the S1PR3 signaling pathway and developing cell-specific S1PR3-modulating drugs will provide new directions for precision treatment of related diseases.

DECLARATIONS

Author contributions

Yichen He, Xiangyi Zhang, and Qin Zhang contributed to the study design and manuscript drafting; Weiqi Lin, Yan Zhang, Haiyi Qian, and Wen Ke were responsible for data acquisition and statistical analysis; Cuifeng Zhang and Qun Chen provided critical insights during data interpretation, participated in constructive discussions, and revised the manuscript for intellectual content.

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Data availability

All source data for this work (or generated in this study) are available upon reasonable request.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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