REVIEW

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Role of sphingosine-1-phosphate receptors in vascular injury of inflammatory bowel disease

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Abstract

Sphingosine-1-phosphate receptors (S1PRs) have an impact on the intestinal inflammation of inflammatory bowel disease (IBD) by regulating lymphocyte migration and differentiation. S1PR modulators as an emerging therapeutic approach are being investigated for the treatment of IBD. However, the role of S1PRs in intestinal vessels has not drawn much attention. Intestinal vascular damage is one of the major pathophysiological features of IBD, characterized by increased vascular density and impaired barrier function. S1PRs have pleiotropic effects on vascular endothelial cells, including proliferation, migration, angiogenesis and barrier homeostasis. Mounting evidence shows that S1PRs are abnormally expressed on intestinal vascular endothelial cells in IBD. Unexpectedly, S1PR modulators may damage intestinal vasculature, for example increase intestinal bleeding; therefore, S1PRs are thought to be involved in the regulation of intestinal vascular function in IBD. However, little is understood about how S1PRs regulate intestinal vascular function and participate in the initiation and progression of IBD. In this review, we summarize the pathogenic role of S1PRs in and the underlying mechanisms behind the intestinal vascular injury in IBD in order for improving IBD practice including S1PR-targeted therapies.

KEYWORDS
inflammatory bowel disease, lymphocyte, sphingosine-1-phosphate receptor, vascular injury

1 | INTRODUCTION

IBD is a group of chronic, non-specific and diffuse inflammatory diseases that occur in the gastrointestinal tract.[1] IBD is manifested by recurrent attack, poor drug efficacy, high risk of developing related complications and high disability rate.[2] The conventional treatments for IBD include glucocorticoid, salicylazosulfapyridine/5-aminosalicylic acid and biological agents, which, however, have limited effectiveness because of low specificity, high prevalence of drug resistance and poor long-term efficacy.[3] As new immunomodulators, S1PR modulators could significantly reduce the localization

of CD4 + T cells to the site of inflammation, regulate T-lymphocyte differentiation and resultantly ameliorate inflammatory disorders. A phased series of clinical trials have been carried out to evaluate the efficacy of S1PR modulators in patients with IBD.[4-6] However, because of the undesirable off-target effects of these drugs, some unexpected vascular complications have been observed.

With an in-depth understanding of the pathogenesis of IBD, the importance of blood vessel dysfunction in the intestinal mucosal lesions of IBD has received special attention.[7,8] It has been reported that IBD is frequently accompanied by endothelial injury, and endothelial progenitor cells, a marker for both endothelial repair and

vascular healing, are significantly reduced in patients with IBD.[9] Indeed, chronic inflammation can not only damage the structure of blood vessels but also cause their functional disorder.[10,11] More particularly, IBD-associated functional changes in intestinal vasculature feature a diminished barrier function but increased angiogenesis.[12,13] Moreover, impaired vasodilation and aberrant leucocyte adhesion resulted from inflammation are also involved in the onset of IBD.[14] Clearly, the expression of adhesion molecules, such as ICAM-1, VCAM-1, MAdCAM-1 and E-selectin secreted from vascular endothelial cells, is significantly increased in the intestinal microvessels in active IBD.[7] However, the precise mechanism behind intestinal vascular injury in IBD is still unclear.

Sphingosine-1-phosphate (S1P) is an important signalling molecule produced during the metabolism of sphingomyelin, an abundant cell membrane component. By binding to S1P receptors (S1PRs) on the cell membrane, S1P exerts a multitude of regulatory effects including cell proliferation, migration, apoptosis, senescence, angiogenesis and barrier integrity, among others, and participates in the pathophysiology of various diseases.[15-17] As important regulatory receptors during intestinal inflammation, S1PRs have been extensively examined for their association with lymphocyte migration. In recent years, S1PRs have been found abundantly expressed on vascular endothelial cells and regulate their function. Therefore, it is possible that manipulating the S1P/S1PR signalling may produce off-target effects on intestinal vasculature while protecting against the immune disorder of IBD. We previously reported that increased expression of S1PR2 is closely related to the disruption of vascular endothelial cell barrier and angiogenesis, but inhibition of S1PR2 expression can reverse the vascular endothelial cell injury.[18] In line with this finding, more studies support the involvement of S1PRs in the regulation of vascular endothelial cell barrier function, vascular density and leucocyte migration across vascular endothelium within inflame tissues.[19,20] However, little is known about the special importance of S1PRs in the intestinal vascular changes in IBD. Herein, we review the newly identified role and possible mechanism of S1PRs in intestinal vascular injury in IBD in order to help improve treatment options for patients with IBD.

2 | INTESTINAL VASCULAR INJURY IN IBD

The aetiology of IBD is more complex than previously thought of being closely related to environment, microorganism, heredity and immunity.[21-23] It seems that a combination of more than multifaceted factors mediates abnormal immune and inflammatory response in intestinal mucosa and promotes the occurrence of IBD.[24,25] Conventional drugs in the treatment of immune disorders are mainly anti-inflammatory. However, their long-term curative effects are poor due to low specificity and high prevalence of drug resistance. Therefore, seeking alternative therapeutic targets is gaining appreciation for improving IBD management. It has been found that vascular injury plays an important role in the pathogenesis of IBD. Pulse wave velocity, a measure of the severity of vascular injury, typically shows a significant increase in patients with IBD,[26] suggesting that altered vascular structure and function occur in patients with IBD. In intestinal mucosa, microvessels are the major type of blood vessels, and in the submucosal microcirculation, arterioles and venules are dominant.[27] As vascular endothelial cells line microvessels and small vessels that make them a key component of intestinal circulation, intestinal vascular endothelial cells may be required in the development of IBD.

Vascular endothelial cell injury, indicated by appreciable changes in endothelial cell function and/or structure, is a result of the imbalance of various regulatory substances.[28,29] IBD patients usually have a significantly reduced number of endothelial progenitor cells,[9] suggesting that vascular endothelial cells are damaged in these patients. The functional damage of vascular endothelial cells in an inflammatory state primarily presents with impaired barrier function, vascular dysplasia, increased adhesion molecule expression, enhanced leucocyte permeability and dysregulated nitric oxide (NO) secretion. The major cause for intestinal vascular endothelial injury is the abnormal secretion of inflammatory mediators such as interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-α, NO and vascular endothelial growth factor (VEGF) in intestinal mucosa.[30,31] The increased production of VEGF promotes intestinal vascular endothelial cell proliferation, whereas the increased secretion of other inflammatory mediators such as TNF-α and IL-6 can damage the structural integrity of endothelial cells, leading to vascular abnormality in barrier homeostasis and cell adhesion. Mechanistically, TNF-α induces endothelial cell damage by activating NADPH oxidase (NOX), whose activation results in the increased production of superoxide.[32] NO can dilate blood vessels and inhibit the expression of inflammatory cytokines and adhesion molecules; however, NO has been observed significantly decreased in the intestinal tissues of patients with IBD.[33] TNF-α can impair endothelium-dependent vasodilation by affecting the utilization of NO.[34] In addition, leucocyte adhesion and transmigration are also important steps in the inflammatory response.[35,36] It was found that the expression levels of adhesion molecules such as ICAM-1, VCAM-1, MAdCAM-1 and E-selectin in vascular endothelial cells are significantly up-regulated in intestinal microvessels of IBD.[7,37,38] Collectively, increased angiogenesis and impaired barrier function are the main causes of intestinal vascular injury in IBD.

3 | S1PRs AND INTESTINAL ANGIOGENESIS IN IBD

Chronic inflammation is often associated with increased angiogenesis, which is a key contributor to the maintenance of chronic inflammation in gastrointestinal tract.[39] Blood vessels are mainly composed of endothelial cells and parietal cells (vascular smooth muscle cells and pericytes).[40] Angiogenesis normally originates from the sprouting of endothelial cells, followed by the destruction of blood vessel walls and the proliferation and migration of endothelial cells.[41] The angiogenic process is tightly regulated by a wide array of angiogenic factors. For example, VEGF is a known potent angiogenic factor, which promotes endothelial cell proliferation, migration and angiogenesis.[42]

In inflamed IBD tissues, different types of inflammatory cells (eg macrophages and lymphocytes) can produce angiogenic factors and promote pathological angiogenesis.[13] Compared with patients who are in remission, patients with active IBD have significantly higher levels of serum VEGF, indicative of VEGF as a promoter of abnormal angiogenesis in IBD.[43] Hypoxia at the intestinal inflammatory sites has the ability to stimulate angiogenesis by inducing the production of VEGF, fibroblast growth factor and TNF-α.[44] In addition to VEGF, the expression levels of avβ3, a marker of angiogenesis, are increased in intestinal microvascular endothelial cells of IBD.[45] Patients with IBD also show increased intestinal vascular density caused by vascular dysplasia. This increased intestinal vascular density has been confirmed in DSS-induced experimental enteritis.[46] Consistent with this, anti-angiogenic therapy has been proved to be an effective approach for experimental enteritis. Small molecule inhibitors such as VEGF blocker can effectively reduce the production of inflammatory mediators and accordingly relieve intestinal inflammation induced by DSS.[47]

As a group of cell surface receptors, S1PRs are widely expressed on many types of cells, thus regulating cell proliferation, migration and angiogenesis.[48,49] S1PRs are highly expressed in vascular endothelial cells as well and therefore influence their function. The expression levels of S1PR1 were observed obviously increased in the intestinal mucosa of patients with ulcerative colitis and were related to the increased intestinal mucosal blood vessel density.[50] In the mouse chronic IBD model, the expression of S1PR1 was also increased in intestinal submucosa and muscular microvessels.[51] Further studies have shown that there is a significant change in vascular density in the inflamed tissues of myeloid S1PR1 knockout mice.[52] Additionally, S1PR2 is another important driver of pathological angiogenesis in the process of inflammation, and S1PR2 antagonists can reverse the increase in vascular density caused by inflammation.[53] Therefore, S1PRs are intimately associated with the increase in intestinal vascular density in IBD, but their downstream effectors are unclear.

There are several important mechanisms governing angiogenic disorders, including oxidative stress, endoplasmic reticulum (ER) stress, abnormal glycolysis and activated VEGF signalling. In intestinal mucosa of patients with IBD, significantly increased ROS levels were seen.[54] Under basic conditions, low levels of reactive oxygen species (ROS) act as messenger molecules to promote angiogenesis; however, high levels of ROS inhibit angiogenesis.[55] ER stress levels were also increased significantly in inflammatory state.[56] Like ROS, ER stress is closely related to angiogenesis; low levels of ER stress stimulate angiogenesis, whereas high levels of ER stress inhibit angiogenesis [57] (Figure 1). As it is difficult to quantitatively determine the levels of ROS and ER, the relationship between the ROS and ER levels and intestinal angiogenesis in IBD needs to be further evaluated. Moreover, glycolysis is known to be enhanced inflammation and S1P/S1PR signal pathway impacts glycolysis.[58,59] It has been demonstrated that glycolysis intermediates (eg lactate and succinate) and glycolytic enzymes (eg fructose-6-phosphate-2 kinase and fructose-2,6-diphosphatase 3) are implicated in the regulation of angiogenesis.[60] Besides this, S1PRs have a role in the regulation of VEGF-mediated angiogenesis (co-ordination function).[61] Together, S1PRs may harbour broad effects on the intestinal angiogenesis of IBD by regulating ROS, ER stress, glycolysis, VEGF signal pathway and other processes, and hence, more understanding of their specific mechanisms is of great significance to the prevention and treatment of IBD (Figure 2).

4 | S1PRs AND INTESTINAL VASCULAR BARRIER FUNCTION IN IBD

Vascular endothelium is a highly specialized monolayer epithelium that lines the inner surface of blood vessels and functions in regulating the transport of substances and leucocyte transmigration across
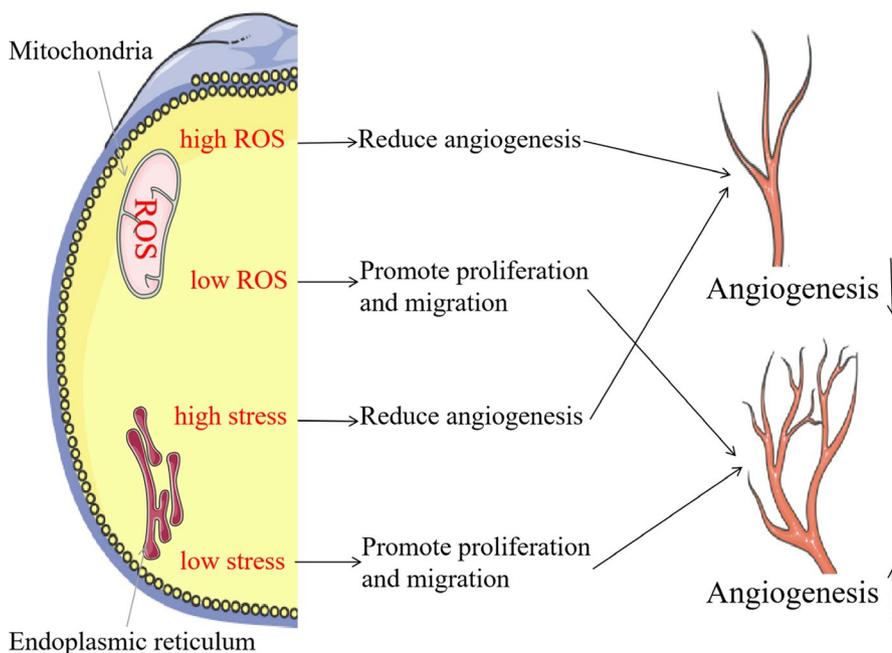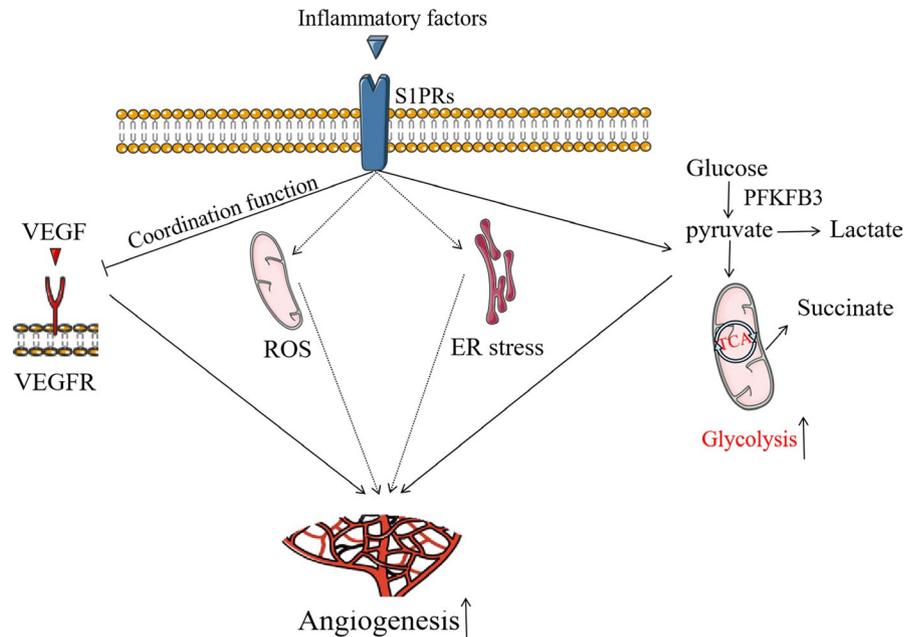

FIGURE 1 Low levels of ER stress/ROS stimulate angiogenesis, whereas high levels of ER stress/ROS inhibit angiogenesis

FIGURE 2 S1PRs may mediate intestinal angiogenesis of IBD by regulating ROS, ER stress, glycolysis and VEGF signal pathway

blood vessels.[62,63] Under physiological conditions, endothelial cells protect against excessive vascular permeability and leucocyte adhesion.[64] During inflammation, vascular endothelial response leads to vasodilation and increased permeability, followed by structural changes such as endothelial cell proliferation and vascular remodelling.[65,66] It has been confirmed that the intestinal vascular barrier function is impaired in the animal model of ulcerative colitis.[7] The disruption of vascular barrier function can be attributed to the elevated levels of endothelial cell oxidative stress and ER stress as well as other subcellular ultrastructural abnormalities. Oxidative stress in intestinal vascular vessels of IBD patients can damage vascular endothelium and increase microvascular permeability.[12] Moreover, inflammation exacerbates such endothelial damage by increasing ROS production and enhancing ER-mitochondria contact.[67,68] ER stress impairs vascular barrier function by disturbing the endothelial cell-to-cell junctions.[69,70] ER stress is increased in endothelial cells under inflammatory conditions, and inhibition of ER stress will reverse the impairment of barrier function.[71,72] Therefore, endothelial cell oxidative stress and ER stress are two key culprits in the dysfunction of intestinal vascular barriers in IBD, but the precise mechanisms that link these aspects need further clarification.

S1PRs may represent an important mechanism in the regulation of vascular barrier function.[73] S1PR1-3 has been proven to be responsible for this complex regulatory mechanism. S1PR1 basically maintains the vascular barrier function. This was demonstrated by deleting S1PR1 gene in IBD that resulted in increased intestinal vascular permeability, indicated by increased bleeding in experimental enteritis.[50] On the contrary, S1PR2 contributes to the impairment of vascular barrier function. An increased expression of S1PR2 has been observed in endothelial cells in the state of inflammation, which resulted in the impairment of endothelial cell barrier function.[74] Similarly, S1PR3 is a player in the regulation of vascular barrier function. Either S1PR2 gene knockout or decreased expression

of S1PR3 can reverse the impairment of vascular barrier function in inflammatory state.[75] The same studies showed that the expression levels of both S1PR1 and S1PR2 in vascular endothelial cells were increased under the condition of IBD or inflammation, indicating that these two S1PRs with opposite effects on vascular barrier function may control each other's regulatory magnitude. Although these studies have highlighted the role of S1PR2 in the impairment of intestinal vascular barrier function in IBD, we have reported that S1PR2 antagonists can reduce the production of ROS in endothelial cells.[76] The increase in ROS is mediated by mitochondrial stress or ER-mitochondrial contact. In addition, ER stress is closely related to abnormal intercellular junctions. Therefore, S1PR2 may affect intestinal vascular barrier function in IBD by increasing oxidative stress, ER stress or ER-mitochondrial contact (Figure 3).

5 | S1PRs AND LEUCOCYTE MIGRATION ACROSS VASCULAR ENDOTHELIUM IN IBD

The extravasation of leucocyte from the bloodstream into inflamed tissues is a hallmark of inflammatory response, which involves the interaction between immune cells and vascular endothelial cells.[77,78] Leucocyte migration across vascular endothelium proceeds in several steps including rolling, activation, adhesion and transport. Adhesion is the key step in determining whether leucocytes migrate to sites of inflammation. Inflammatory mediators signal vascular endothelial cells to express adhesion molecules and chemotactic cytokines to promote the adhesion of leucocytes to vascular endothelial cells. The adhesion ability of leucocytes and the expression of adhesion molecules such as ICAM-1 and VCAM-1 by intestinal microvessels of patients with IBD are enhanced.[13,63] The expression of fractalkine, a CX3C chemokine, is also significantly up-regulated in endothelial cells of patients with IBD.[79] Intriguingly, there is a
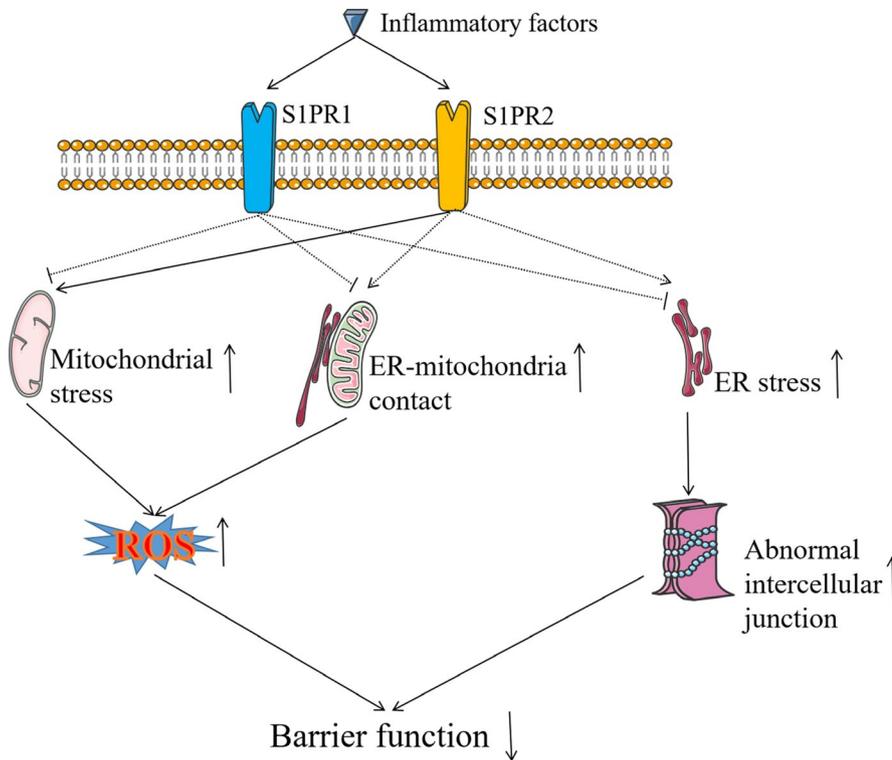
complex interplay of immune cells and angiogenesis in intestinal inflammation. For instance, VEGF-A can induce cAMP production and activate the cAMP signalling in intestinal vascular endothelial cells to promote leucocyte adhesion.[80] On the other hand, the increased leucocyte migration across vascular endothelium results in increased intestinal inflammation, thus creating a positive feedback loop that exacerbates inflammatory response.[4] Therefore, blockade of leucocyte adhesion and migration across vascular endothelium holds the key to alleviating intestinal inflammation in IBD and is becoming important for an effective IBD therapeutic tactic.

As important receptors on leucocytes, S1PRs participate in the regulation of leucocyte transport and differentiation.[4,81] Emerging studies have shown evidence of the active involvement of S1PRs in the occurrence and development of the intestinal inflammation by regulating endothelial function and its interaction with immune cells. It has been found that S1PR1 is expressed in intestinal lymphocytes and vascular endothelial cells of IBD. Because of this, S1PR1 modulators have been used to reduce lymphocytes in intestinal tissue by inhibiting lymphocyte migration, thereby alleviating intestinal inflammation.[51] In addition, S1PR1 modulators inhibit the adhesion of monocytes to endothelial cells by reducing the expression of VCAM-1 in vascular endothelial cells.[82] The expression of S1PR2 in vascular endothelial cells is increased in inflammatory state.[74] It has been found that S1PR1 and S1PR4 differentially regulate T cell migration and adhesion, whereas S1PR2 promotes T cell migration across endothelial cells by increasing endothelial cell permeability and VCAM-1 expression.[83] Therefore, S1PRs take part in intestinal inflammation of IBD by regulating leucocyte migration across vascular endothelial cells, and S1PR modulators have an inhibitory effect on intestinal inflammation.

6 | S1PRs AND ENDOTHELIAL NITRIC OXIDE SYNTHASE IN IBD

Endothelial nitric oxide synthase (eNOS) is one of the main modulators of the vascular function by promoting NO secretion, with the latter causing vasorelaxation and inhibiting the expression of cytokines and adhesion molecules. Therefore, eNOS-mediated NO release from vascular endothelial cells is important in the regulation of vascular inflammation. There is evidence in support of eNOS as a key molecule in colitis by regulating the expression of adhesion molecules (eg AdCAM-1).[84] Considering the protective role of eNOS in experimental colitis, it was not surprised to observe a significant decrease in eNOS expression in the intestinal microvessels of IBD patients.[85] Moreover, decreased eNOS in endothelial cells is considered a possible reason for the thickening of arteries and the increased number of capillaries in IBD intestinal mucosa.[85] It has been observed that NO deficiency in intestinal microvascular endothelial cells aggravates experimental colitis.[86] Also, decreased NO affects the dilation for microvessels, which further decreases arterial perfusion and delays wound healing.[87] Nevertheless, excessive release of NO may have an opposite effect on vascular tone. Previous studies have demonstrated that excessive NO produced by the inducible isoform of NOS contributes to intestinal inflammation in IBD, though eNOS produces NO with a far less amount, which in fact has a physiological role in the gut.[88,89] Therefore, both the source and quantity of NO matter; they decide how intestinal inflammation is controlled in IBD.

S1PRs play a vital important role in eNOS regulation. They regulate eNOS by activating protein kinase B (AKT), which is involved in the regulation of endothelial cell migration and angiogenesis.[90]

However, the overexpression of eNOS may cause an injury under pathological conditions, for example, promote angiogenesis and damage barrier function. It has been proposed that S1PR2 activation in vascular endothelial cells enhances the expression of eNOS, and thus, antagonizing S1PR2 may be a new approach for the treatment of pathological angiogenesis.[53] On the other hand, in anaphylactic shock S1PR2 inhibits excessive eNOS-mediated endothelial barrier dysfunction by decreasing AKT.[91] Therefore, more evidence is needed to understand the regulation of intestinal eNOS by S1PRs in IBD. Considering the significant role of eNOS in the regulation of vascular function and inflammation, it is necessary to determine the regulatory roles of different sources and quantities of eNOS in various disease states (Figure 4). Collectively, It is of great significance to clarify the regulatory effects of S1PRs on intestinal eNOS in IBD.

7 | EFFECTS OF S1PR REGULATORS ON INTESTINAL VESSELS OF IBD

The pathological process of IBD ranges from active stage to remission stage, and an effective therapeutic strategy is to control the active phase of the illness.[92,93] The injury of intestinal vascular endothelial cells during the active stage is chiefly because of the sustained inflammation and oxidative stress. Therefore, anti-inflammatory and antioxidant therapy on IBD is very important. For example, the anti-inflammatory treatment using TNF-α antagonists could largely decrease the levels of plasma biomarkers of endothelial dysfunction in patients with IBD.[14] Targeting the S1P/S1PR axis is an efficacious option for IBD, leading to the development of S1PR modulators in recent years. As a new class of immunomodulators, S1PR modulators can improve intestinal inflammation by reducing the intestinal infiltration of lymphocytes and inhibiting T cell differentiation in patients with IBD.[4,51,94] However, other studies have found that S1PR modulators may have some intestinal vascular effects while suppressing immune responses (Figure 5). Karuppuchamy et al suggest that S1PR modulators may have unwanted effects on intestinal vascular barrier function.[51] Montrose et al found that the genetic deletion of S1PR1 increased intestinal vascular permeability and bleeding in experimental colitis.[50] In addition, FTY720 produces anti-inflammatory effects by inhibiting the interaction between immune cells and vascular endothelial cells.[95] Although S1PR
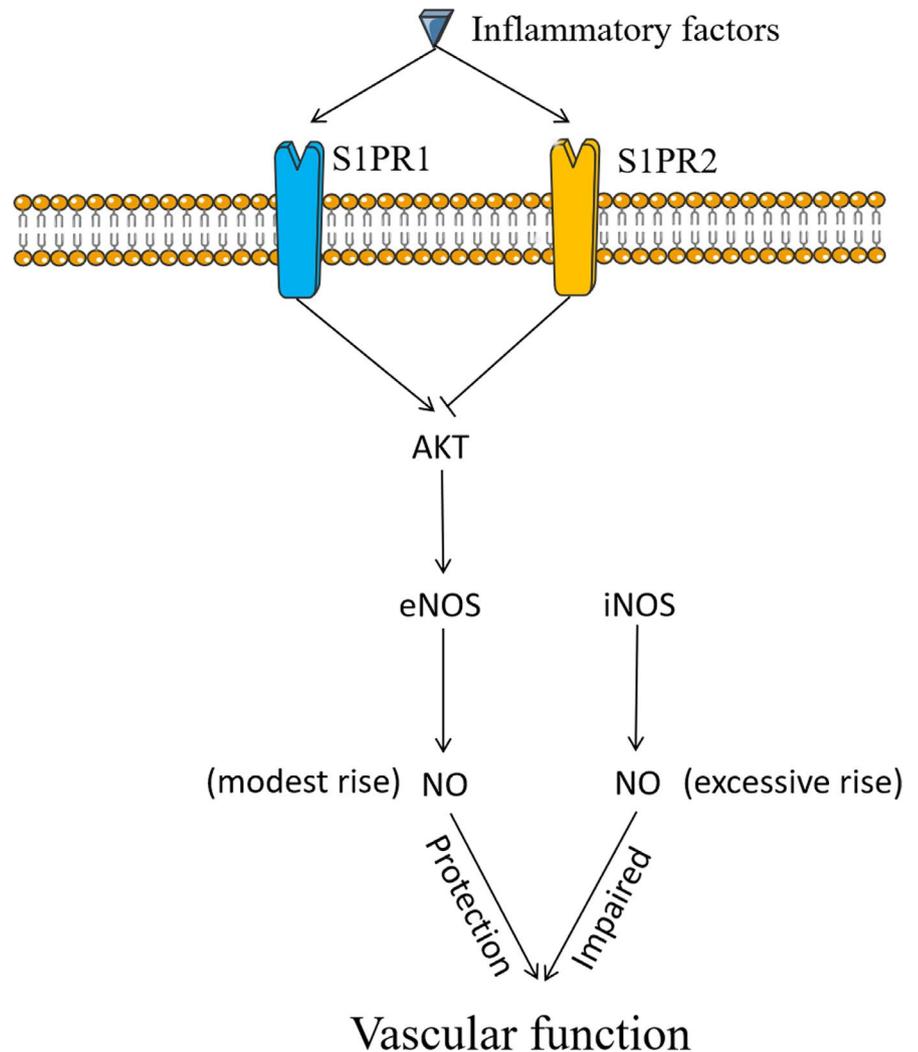

FIGURE 4 S1PRs may regulate vascular function by regulating the source and quantity of eNOS
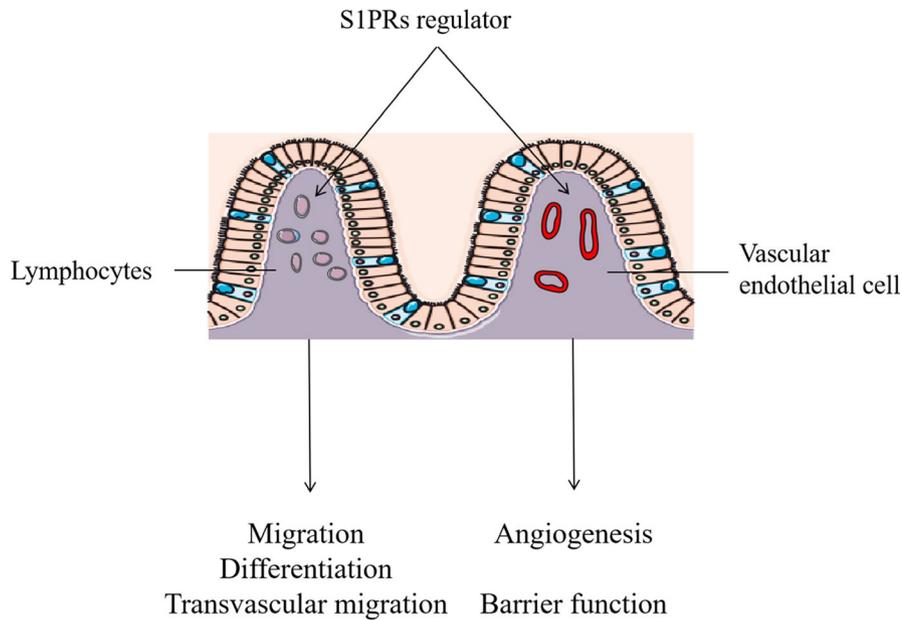
FIGURE 5 S1PR regulators have influences not only on lymphocytes but also on vascular endothelial cells

modulators have unexpected side effects on intestinal vessels and different subtypes of receptor modulators have distinct effects, the underlying mechanisms are not completely clear.

At present, the S1PR modulators used in IBD mainly include non-specific regulators such as FTY720 and specific regulators such as ozanimod (targeting S1PR1 and S1PR5), etrasimod (targeting S1PR1) and amiselimod (targeting S1PR1 and S1PR5), which have entered phase II or III clinical trials or approved for IBD. The expression levels of S1PR1, S1PR2 and S1PR4 are significantly higher in the intestinal mucosa of IBD, and S1PR1 is primarily present on leucocytes and vascular endothelial cells.[51,96,97] As the up-regulated S1PR1 in lymphocytes mediates immune abnormalities at sites of inflammation, these novel regulators mainly exert influence on the immunomodulatory function of S1PR1. For example, the S1PR agonist FTY720 first activates S1PR1 on the cell surface through a high-affinity binding, but then causes the down-regulation of S1PR1, thus preventing lymphocyte infiltration.[98] This regulator, which first activates the surface receptor and then downregulates the receptor, is often called a reverse agonist. Conventional S1PR inhibitors mostly work via a direct inhibition of the expression of cell surface receptors, but the S1PR reverse agonist acts through a process named receptor endocytosis. Under physiological conditions, the endocytosed S1PRs return to the cell surface through S1P lyase–mediated mechanism, but under continuous stimulation by the reverse agonist, endocytosed S1PRs are degraded by the proteasome, resulting in complete inactivation of S1PR1.[99] As mentioned earlier, in the intestinal tract of IBD, S1PR1 is mainly involved in the regulation of angiogenesis and barrier function, whereas S1PR2 is essential for the regulation of barrier function. At present, the most reported intestinal vascular effects of S1PR regulators are substantially attributable to the potential impact of barrier function mediated by the down-regulation of S1PR1. However, whether the altered blood vessel density is related to S1PR1 regulators or the barrier dysfunction related to S1PR2

regulators remains unclear. Therefore, it is necessary to explore the effects of S1PR modulators on intestinal vascular function, which may help improve or develop new S1PR modulators.

8 | CONCLUSION

S1PRs are a group of receptors expressed on the surface of various cell types, and different subtypes have distinct regulatory functions. In this review, we depicted the negative role of S1PRs in intestinal vascular injury in IBD and their possible mechanism. So far, the exact mechanisms behind the biological regulation of S1PRs in the intestinal vascular disease are rather limited. Because of their vital role in lymphocytes, S1PRs have become an important target for immunomodulatory therapy. The application of S1PR modulators in patients with IBD is a focus of this review. A series of clinical trials have, however, disclosed that S1PR modulators may cause intestinal vascular effects. For example, S1PR1 modulators downregulate S1PR1 of vascular endothelial cells while inhibiting S1PR1 of lymphocytes, resulting in a decline in vascular barrier function. So, how to overcome the unwelcome side effects of S1PR modulators is still a challenge. S1PRs seem to have a widespread impact on intestinal vascular biology, such as vascular density, barrier function and ultrastructural changes in vascular endothelial cells (ie ER stress, mitochondrial stress, ER-mitochondria contact). Further studies of the role of S1PRs in intestinal vessels will be of benefit in improving IBD care.

CONFLICT OF INTEREST

AUTHOR CONTRIBUTION

Xuewen Wang: Conceptualization (equal); Investigation (lead); Resources (equal); Writing-review & editing (lead). **Shuhua Chen:** Funding acquisition (lead); Supervision (equal). **Hong Xiang:** Investigation (supporting); Resources (equal). **Ziwei Liang:** Investigation (supporting); Resources (equal). **Hongwei Lu:** Conceptualization (lead); Funding acquisition (lead); Supervision (equal); Writing-review & editing (equal).

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REFERENCES

1. Wanders LK, Cordes M, Voorham Q, et al. IBD-Associated dysplastic lesions show more chromosomal instability than sporadic adenomas. *Inflamm Bowel Dis.* 2020;26(2):167-180.
2. Lo B, Julsgaard M, Vester-Andersen MK, Vind I, Burisch J. Disease activity, steroid use and extraintestinal manifestation are associated with increased disability in patients with inflammatory bowel disease using the inflammatory bowel disease disability index: a cross-sectional multicentre cohort study. *Eur J Gastroenterol Hepatol.* 2018;30:1130-2113.
3. Yang C, Merlin D. Nanoparticle-mediated drug delivery systems for the treatment of IBD: current perspectives. *Int J Nanomedicine.* 2019;14:8875-8889.
4. Nielsen OH, Li Y, Johansson-Lindbom B, Coskun M. Sphingosine-1-phosphate signaling in inflammatory bowel disease. *Trends Mol Med.* 2017;23(4):362-374.
5. Ma C, Battat R, Dulai PS, et al. Innovations in oral therapies for inflammatory bowel disease. *Drugs.* 2019;79:1321-1335.
6. Perez-Jeldres T, Tyler CJ, Boyer JD, et al. Cell trafficking interference in inflammatory bowel disease: therapeutic interventions based on basic pathogenesis concepts. *Inflamm Bowel Dis.* 2019;25:270-282.
7. Cibor D, Domagala-Rodacka R, Rodacki T, Jurczyszyn A, Mach T, Owczarek D. Endothelial dysfunction in inflammatory bowel diseases: Pathogenesis, assessment and implications. *World J Gastroenterol.* 2016;22(3):1067-1077.
8. Langer V, Vivi E, Regensburger D, et al. IFN-γ drives inflammatory bowel disease pathogenesis through VE-cadherin-directed vascular barrier disruption. *J Clin Invest.* 2019;129:4691-4707.
9. Garolla A, D'Incà R, Checchin D, et al. Reduced endothelial progenitor cell number and function in inflammatory bowel disease: a possible link to the pathogenesis. *Am J Gastroenterol.* 2009;104(10):2500-2507.
10. Swart C, Lammertyn L, Welsh PI, Botha-Le RS. Vascular structure and inflammation in a South African population: The SABPA Study. *Pulse (Basel).* 2020;7(1-4):60-68.
11. Ho-Tin-Noe B, Boulaftali Y, Camerer E. Platelets and vascular integrity: how platelets prevent bleeding in inflammation. *Blood.* 2018;131:277-288.
12. Tolstanova G, Deng X, French SW, et al. Early endothelial damage and increased colonic vascular permeability in the development of experimental ulcerative colitis in rats and mice. *Lab Invest.* 2012;92(1):9-21.
13. Neubauer K, Bednarz-Misa I, Walecka-Zacharska E, et al. Oversecretion and overexpression of nicotinamide Phosphoribosyltransferase/Pre-B colony-enhancing factor/visfatin in inflammatory bowel disease reflects the disease activity, severity of inflammatory response and hypoxia. *Int J Mol Sci.* 2019;20:166.
14. Steyers CM 3rd, Miller FJ Jr. Endothelial dysfunction in chronic inflammatory diseases. *Int J Mol Sci.* 2014;15(7):11324-11349.
15. Lu H, Yuan H, Chen S, et al. Senescent endothelial dysfunction is attributed to the up-regulation of sphingosine-1-phosphate receptor-2 in aged rats. *Mol Cell Biochem.* 2012;363(1–2):217-224.
16. Zeng Y, Liu X, Yan Z, Xie L. Sphingosine 1-phosphate regulates proliferation, cell cycle and apoptosis of hepatocellular carcinoma cells via syndecan-1. *Prog Biophys Mol Biol.* 2019;148:32-38.
17. Zhang L, Dong Y, Wang Y, Hu W, Dong S, Chen Y. Sphingosine-1-phosphate (S1P) receptors: promising drug targets for treating bone-related diseases. *J Cell Mol Med.* 2020;24:4389-4401.
18. Chen S, Yang J, Xiang H, et al. Role of sphingosine-1-phosphate receptor 1 and sphingosine-1-phosphate receptor 2 in hyperglycemia-induced endothelial cell dysfunction. *Int J Mol Med.* 2015;35:1103-1108.
19. Burg N, Swendeman S, Worgall S, Hla T, Salmon JE. Sphingosine 1-phosphate receptor 1 signaling maintains endothelial cell barrier function and protects against immune complex-induced vascular injury. *Arthritis Rheumatol.* 2018;70(11):1879-1889.
20. Syed SN, Raue R, Weigert A, Von KA, Brune B. Macrophage S1PR1 signaling alters angiogenesis and lymphangiogenesis during skin inflammation. *Cells.* 2019;8(8):E785.
21. de Souza HSP, Fiocchi C, Iliopoulos D. The IBD interactome: an integrated view of aetiology, pathogenesis and therapy. *Nat Rev Gastroenterol Hepatol.* 2017;14(12):739-749.
22. Xiaowen T, Browning Brian L, Browning SR. Estimating the genome-wide mutation rate with three-way identity by descent. *Am J Hum Genet.* 2019;105:883-893.
23. Evans LM, Tahmasbi R, Jones M, et al. Haplotype Reference Consortium. Narrow-sense heritability estimation of complex traits using identity-by-descent information. *Heredity (Edinb).* 2018;121:616-630.
24. Ma C, Wu W, Lin R, et al. Critical role of CD6highCD4+ T cells in driving Th1/Th17 cell immune responses and mucosal inflammation in IBD. *J Crohns Colitis.* 2019;13(4):510-524.
25. Na YR, Stakenborg M, Seok SH, Matteoli G. Macrophages in intestinal inflammation and resolution: a potential therapeutic target in IBD. *Nat Rev Gastroenterol Hepatol.* 2019;16:531-543.
26. Zivkovic PM, Matetic A, Tadin HI, et al. Serum catestatin levels and arterial stiffness parameters are increased in patients with inflammatory bowel disease. *J Clin Med.* 2020;9:628.
27. Low S, Hirakawa J, Hoshino H, Uchimura K, Kawashima H, Kobayashi M. Role of MAdCAM-1-expressing high endothelial venule-like vessels in colitis induced in mice lacking sulfotransferases catalyzing L-Selectin ligand biosynthesis. *J Histochem Cytochem.* 2018;66:415-425.
28. Wang J, Chen S, Bihl J. Exosome-mediated transfer of ACE2 (Angiotensin-Converting Enzyme 2) from endothelial progenitor cells promotes survival and function of endothelial cell. *Oxid Med Cell Longev.* 2020;2020:4213541.
29. Shah D, Torres C, Bhandari V. Adiponectin deficiency induces mitochondrial dysfunction and promotes endothelial activation and pulmonary vascular injury. *FASEB J.* 2019;33:13617-13631.
30. Yan X, Managlia E, Tan XD, De PIG. Prenatal inflammation impairs intestinal microvascular development through a TNF-dependent mechanism and predisposes newborn mice to necrotizing enterocolitis. *Am J Physiol Gastrointest Liver Physiol.* 2019;317:G57-G66.
31. Liu YH, Ding Y, Gao CC, Li LS, Wang YX, Xu JD. Functional macrophages and gastrointestinal disorders. *World J Gastroenterol.* 2018;24(11):1181-1195.
32. Zhu Z, Li J, Zhang X. Astragaloside IV protects against oxidized low-density lipoprotein (ox-LDL)-induced endothelial cell injury by reducing oxidative stress and inflammation. *Med Sci Monit.* 2019;25:2132-2140.
33. Gravina AG, Dallio M, Masarone M, et al. Vascular endothelial dysfunction in inflammatory bowel diseases: pharmacological and nonpharmacological targets. *Oxid Med Cell Longev.* 2018;12(2018):2568569.

34. Spillmann F, Van LS, Miteva K, et al. LXR agonism improves TNF-α-induced endothelial dysfunction in the absence of its cholesterol-modulating effects. *Atherosclerosis*. 2014;232:1-9.

35. Kong X, Huo G, Liu S, Li F, Chen W, Jiang D. Luteolin suppresses inflammation through inhibiting cAMP-phosphodiesterases activity and expression of adhesion molecules in microvascular endothelial cells. *Inflammopharmacology*. 2019;27:773-780.

36. Clemente-Napimoga JT, Silva Maria ASM, Peres SNC, et al. Dioclea violacea lectin ameliorates inflammation in the temporomandibular joint of rats by suppressing intercellular adhesion molecule-1 expression. *Biochimie*. 2019;158:34-42.

37. Bian Y, Liu P, Zhong J, et al. Kaempferol inhibits multiple pathways involved in the secretion of inflammatory mediators from LPS induced rat intestinal microvascular endothelial cells. *Mol Med Rep*. 2019;19:1958-1964.

38. Li X, Wang Q, Ding L, et al. Intercellular adhesion molecule-1 enhances the therapeutic effects of MSCs in a dextran sulfate sodium-induced colitis models by promoting MSCs homing to murine colons and spleens. *Stem Cell Res Ther*. 2019;10:267.

39. Knod JL, Crawford K, Dusing M, Collins MH, Chernoguz A, Frischer JS. Angiogenesis and vascular endothelial growth factor-A expression associated with inflammation in pediatric crohn's disease. *J Gastrointest Surg*. 2016;20:624-630.

40. Zhang H, Chalothorn D, Faber JE. Collateral vessels have unique endothelial and smooth muscle cell phenotypes. *Int J Mol Sci*. 2019;20:3608.

41. Liu Z, Wang J, Xing W, Peng Y, Quan J, Fan X. LPS binding to HMGB1 promotes angiogenic behavior of endothelial cells through inhibition of p120 and CD31 via ERK/P38/Src signaling. *Eur J Cell Biol*. 2017;96:695-704.

42. Wang J, Yang L, Liang F, Chen Y, Yang G. Integrin alpha x stimulates cancer angiogenesis through PI3K/Akt signaling-mediated VEGFR2/VEGF-A overexpression in blood vessel endothelial cells. *J Cell Biochem*. 2019;120:1807-1818.

43. Algaba A, Linares PM, Fernandez-Contreras ME, et al. Relationship between levels of angiogenic and lymphangiogenic factors and the endoscopic, histological and clinical activity, and acute-phase reactants in patients with inflammatory bowel disease. *J Crohns Colitis*. 2013;7:e569-579.

44. Koutroubakis IE, Tsiolakidou G, Karmiris K, Kouroumalis EA. Role of angiogenesis in inflammatory bowel disease. *Inflamm Bowel Dis*. 2006;12:515-523.

45. Danese S, Sans M, de la Motte C,, et al. Angiogenesis as a novel component of inflammatory bowel disease pathogenesis. *Gastroenterology*. 2060e;130:2060e73.

46. Haep L, Britzen-Laurent N, Weber TG, et al. Interferon gamma counteracts the angiogenic switch and induces vascular permeability in dextran sodium sulfate colitis in mice. *Inflamm Bowel Dis*. 2015;21:2360-2371.

47. Ardelean DS, Yin M, Jerkic M, et al. Anti-VEGF therapy reduces intestinal inflammation in Endoglin heterozygous mice subjected to experimental colitis. *Angiogenesis*. 2014;17:641-659.

48. Hubner K, Cabochette P, Dieguez-Hurtado R, et al. Wnt/β-catenin signaling regulates VE-cadherin-mediated anastomosis of brain capillaries by counteracting S1pr1 signaling. *Nat Commun*. 2018;9:4860.

49. Khattar M, Deng R, Kahan BD, et al. Novel sphingosine-1-phosphate receptor modulator KRP203 combined with locally delivered regulatory T cells induces permanent acceptance of pancreatic islet allografts. *Transplantation*. 2013;95:919-927.

50. Montrose DC, Scherl EJ, Bosworth BP, et al. S1P$_1$ localizes to the colonic vasculature in ulcerative colitis and maintains blood vessel integrity. *J Lipid Res*. 2013;54:843-851.

51. Karuppuchamy T, Behrens EH, Gonzalez-Cabrera P, et al. Sphingosine-1-phosphate receptor-1 (S1P) is expressed by lymphocytes, dendritic cells, and endothelium and modulated during inflammatory bowel disease. *Mucosal Immunol*. 2017;10:162-171.

52. Syed SN, Raue R, An W, Von KA, Brune B. Macrophage S1PR1 signaling alters angiogenesis and lymphangiogenesis during skin inflammation. *Cells*. 2019;8(8):E785.

53. Skoura A, Sanchez T, Claffey K, Mandala SM, Proia RL, Hla T. Essential role of sphingosine 1-phosphate receptor 2 in pathological angiogenesis of the mouse retina. *J Clin Invest*. 2007;117:2506-2516.

54. Simanovich E, Brod V, Rahat MA. Active vaccination with emmprin-derived multiple antigenic peptide (161-MAP) reduces angiogenesis in a dextran sodium sulfate (DSS)-induced colitis model. *Front Immunol*. 2018;9:2919.

55. Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury: part II: animal and human studies. *Circulation*. 2003;108:2034-2040.

56. Jung TW, Park HS, Choi Geum H, et al. Maresin 1 attenuates pro-inflammatory reactions and ER stress in HUVECs via PPARα-mediated pathway. *Mol Cell Biochem*. 2018;448:335-347.

57. Binet F, Sapieha P. ER stress and angiogenesis. *Cell Metab*. 2015;22:560-575.

58. Wang L, Cao Y, Gorshkov B, et al. Ablation of endothelial Pfkfb3 protects mice from acute lung injury in LPS-induced endotoxemia. *Pharmacol Res*. 2019;146:104292.

59. Shen Y, Zhao S, Wang S, et al. S1P/S1PR3 axis promotes aerobic glycolysis by YAP/c-MYC/PGAM1 axis in osteosarcoma. *EBioMedicine*. 2019;40:210-223.

60. Deng F, Zhou R, Lin C, et al. Tumor-secreted dickkopf2 accelerates aerobic glycolysis and promotes angiogenesis in colorectal cancer. *Theranostics*. 2019;9:1001-1014.

61. Yanagida K, Engelbrecht E, Niaudet C, et al. Sphingosine 1-phosphate receptor signaling establishes AP-1 gradients to allow for retinal endothelial cell specialization. *Dev Cell*. 2020;52:779-793.

62. Baszczuk A, Kopczynski Z, Thielemann A. Endothelial dysfunction in patients with primary hypertension and hyperhomocysteinemia. *Postepy Hig Med Dosw (Online)*. 2014;68:91-100.

63. Deban L, Correale C, Vetrano S, Malesci A, Danese S. Multiple pathogenic roles of microvasculature in inflammatory bowel disease: a Jack of all trades. *Am J Pathol*. 2008;172:1457-1466.

64. Jamieson JJ, Linville RM, Ding Yuan Y, Gerecht S, Searson PC. Role of iPSC-derived pericytes on barrier function of iPSC-derived brain microvascular endothelial cells in 2D and 3D. *Fluids Barriers CNS*. 2019;16:15.

65. Guignabert C, Tu L, Girerd B, et al. New molecular targets of pulmonary vascular remodeling in pulmonary arterial hypertension: importance of endothelial communication. *Chest*. 2015;147:529-537.

66. Weckbach LT, Preissner KT, Deindl E. The role of midkine in arteriogenesis, involving mechanosensing, endothelial cell proliferation, and vasodilation. *Int J Mol Sci*. 2018;19:2559.

67. Filadi R, Greotti E, Pizzo P. Highlighting the endoplasmic reticulum-mitochondria connection: focus on Mitofusin 2. *Pharmacol Res*. 2018;128:42-51.

68. Yu S, Zhang L, Liu C, Yang J, Zhang J, Huang L. PACS2 is required for ox-LDL-induced endothelial cell apoptosis by regulating mitochondria-associated ER membrane formation and mitochondrial Ca elevation. *Exp Cell Res*. 2019;379:191-202.

69. Lenin R, Nagy PG, Jha KA, Gangaraju R. GRP78 translocation to the cell surface and O-GlcNAcylation of VE-Cadherin contribute to ER stress-mediated endothelial permeability. *Sci Rep*. 2019;9:10783.

70. Nan D, Jin H, Deng J, et al. Cilostazol ameliorates ischemia/reperfusion-induced tight junction disruption in brain endothelial cells by inhibiting endoplasmic reticulum stress. *FASEB J*. 2019;33:10152-10164.

71. Jung TW, Park HS, Choi GH, et al. Maresin 1 attenuates pro-inflammatory reactions and ER stress in HUVECs via PPARα-mediated pathway. *Mol Cell Biochem*. 2018;448:335-347.

72. Leonard A, Paton AW, El-Quadi M, Paton JC, Fazal F. Preconditioning with endoplasmic reticulum stress ameliorates endothelial cell inflammation. *PLoS One*. 2014;9:e110949.

73. Wan Y, Jin HJ, Zhu YY, et al. MicroRNA-149-5p regulates blood-brain barrier permeability after transient middle cerebral artery occlusion in rats by targeting S1PR2 of pericytes. *FASEB J*. 2018;32:3133-3148.

74. Du J, Zeng C, Li Q, et al. LPS and TNF-α induce expression of sphingosine-1-phosphate receptor-2 in human microvascular endothelial cells. *Pathol Res Pract*. 2012;208:82-88.

75. Sammani S, Moreno-Vinasco L, Mirzapoiazova T, et al. Differential effects of sphingosine 1-phosphate receptors on airway and vascular barrier function in the murine lung. *Am J Respir Cell Mol Biol*. 2010;43:394-402.

76. Chen W, Xiang H, Chen R, et al. S1PR2 antagonist ameliorate high glucose-induced fission and dysfunction of mitochondria in HRGECs via regulating ROCK1. *BMC Nephrol*. 2019;20:135.

77. De LM, Sousa C, Meena M, et al. Increased transendothelial transport of ccl3 is insufficient to drive immune cell transmigration through the blood-brain barrier under inflammatory conditions in vitro. *Mediators Inflamm*. 2017;2017:6752756.

78. Dong C, Greathouse KM, Beacham RL, Palladino SP, Helton ES, Ubogu EE. Fibronectin connecting segment-1 peptide inhibits pathogenic leukocyte trafficking and inflammatory demyelination in experimental models of chronic inflammatory demyelinating polyradiculoneuropathy. *Exp. Neurol*. 2017;292:35-45.

79. Kuboi Y, Nishimura M, Ikeda W, et al. Blockade of the fractalkine-CX3CR1 axis ameliorates experimental colitis by dislodging venous crawling monocytes. *Int Immunol*. 2019;31:287-302.

80. Goebel S, Huang M, Davis WC, et al. VEGF-A stimulation of leukocyte adhesion to colonic microvascular endothelium: implications for inflammatory bowel disease. *Am J Physiol*. 2006;290:G648e54.

81. Li H, Zhou X, Li Y, et al. The selective sphingosine 1-phosphate receptor 1 modulator RP101075 improves microvascular circulation after cerebrovascular thrombosis. *FASEB J*. 2019;33:10935-10941.

82. Whetzel AM, Bolick DT, Srinivasan S, et al. Sphingosine-1 phosphate prevents monocyte/endothelial interactions in type 1 diabetic NOD mice through activation of the S1P1 receptor. *Circ Res*. 2006;99:731-739.

83. Xiong Y, Piao W, Brinkman CC, et al. CD4 T cell sphingosine 1-phosphate receptor (S1PR)1 and S1PR4 and endothelial S1PR2 regulate afferent lymphatic migration. *Sci Immunol*. 2019;4:1263.

84. Okaniwa N, Sasaki M, Mizushima T, et al. eNOS plays an important role in the regulation of colonic inflammation: a novel therapeutic target and a predictive marker for the prognosis of ulcerative colitis. *Free Radic Res*. 2015;49(1):35-44.

85. Palatka K, Serfozo Z, Vereb Z, et al. Changes in the expression and distribution of the inducible and endothelial nitric oxide synthase in mucosal biopsy specimens of inflammatory bowel disease. *Altorjay I Scand J Gastroenterol*. 2005;40(6):670-680.

86. Sasaki M, Bharwani S, Jordan P, et al. Increased disease activity in eNOS-deficient mice in experimental colitis. *Free Radic Biol Med*. 2003;35:1679-1687.

87. Hatoum OA, Binion DG, Otterson MF, Gutterman DD. Acquired microvascular dysfunction in inflammatory bowel disease: Loss of nitric oxide-mediated vasodilation. *Gastroenterology*. 2003;125:58-69.

88. Rumi G, Tsubouchi R, Nishio H, Kato S, Mozsik G, Takeuchi K. Dual role of endogenous nitric oxide in development of dextran sodium sulfate-induced colitis in rats. *J Physiol Pharmacol*. 2004;55:823-836.

89. Almasi N, Torok S, Dvoracsko S, et al. Lessons on the Sigma-1 receptor in TNBS-induced rat colitis: modulation of the UCHL-1, IL-6 pathway. *Int J Mol Sci*. 2020;21(11):4046.

90. Sukocheva O, Wadham C, Gamble J, Xia P. Sphingosine-1-phosphate receptor 1 transmits estrogens' effects in endothelial cells. *Steroids*. 2015;104:237-245.

91. Cui H, Okamoto Y, Yoshioka K, et al. Sphingosine-1-phosphate receptor 2 protects against anaphylactic shock through suppression of endothelial nitric oxide synthase in mice. *J Allergy Clin Immunol*. 2013;132(5):1205-1214.

92. Marinelli C, Savarino E, Inferrera M, et al. Factors influencing disability and quality of life during treatment: a cross-sectional study on IBD patients. *Gastroenterol Res Pract*. 2019;2019:5354320.

93. Pugliese D, Daperno M, Fiorino G, et al. Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: An IG-IBD study. *Dig Liver Dis*. 2019;51(7):972-977.

94. Nielsen OH, Seidelin JB, Ainsworth M, Coskun M. Will novel oral formulations change the management of inflammatory bowel disease? *Expert Opin Investig Drugs*. 2016;25(6):709-918.

95. Imeri F, Blanchard O, Jenni A, et al. FTY720 and two novel butterfly derivatives exert a general anti-inflammatory potential by reducing immune cell adhesion to endothelial cells through activation of S1P(3) and phosphoinositide 3-kinase. *Naunyn Schmiedebergs Arch Pharmacol*. 2015;388:1283-1292.

96. Sukocheva OA, Furuya H, Ng ML, et al. Sphingosine kinase and sphingosine-1-phosphate receptor signaling pathway in inflammatory gastrointestinal disease and cancers: a novel therapeutic target. *Pharmacol Ther*. 2020;207:107464.

97. Suh JH, Degagne E, Gleghorn EE, et al. Sphingosine-1-phosphate signaling and metabolism gene signature in pediatric inflammatory bowel disease: a matched-case control pilot study. *Inflamm Bowel Dis*. 2018;24:1321-1334.

98. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol*. 2010;33:91-101.

99. Currò D, Pugliese D, Armuzzi A. Frontiers in drug research and development for inflammatory bowel disease. *Front Pharmacol*. 2017;8:400.