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REVIEW ARTICLE

# Role of the SphK-S1P-S1PRs pathway in invasion of the nervous system by SARS-CoV-2 infection

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## Abstract

Global spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still ongoing. Before an effective vaccine is available, the development of potential treatments for resultant coronavirus disease 2019 (COVID-19) is crucial. One of the disease hallmarks is hyper-inflammatory responses, which usually leads to a severe lung disease. Patients with COVID-19 also frequently suffer from neurological symptoms such as acute diffuse encephalomyelitis, brain injury and psychiatric complications. The metabolic pathway of sphingosine-1-phosphate (S1P) is a dynamic regulator of various cell types and disease processes, including the nervous system. It has been demonstrated that S1P and its metabolic enzymes, regulating neuroinflammation and neurogenesis, exhibit important functions during viral infection. S1P receptor 1 (S1PR1) analogues including AAL-R and RP-002 inhibit pathophysiological responses at the early stage of H1N1 virus infection and then play a protective role. Fingolimod (FTY720) is an S1P receptor modulator and is being tested for treating COVID-19. Our review provides an overview of SARS-CoV-2 infection and critical role of the SphK-S1P-SIPR pathway in invasion of SARS-CoV-2 infection, particularly in the central nervous system (CNS). This may help design therapeutic strategies based on the S1P-mediated signal transduction, and the adjuvant therapeutic effects of S1P analogues to limit or prevent the interaction between the host and SARS-CoV-2, block the spread of the SARS-CoV-2, and consequently treat related complications in the CNS.

**KEYWORDS**
ACE2, COVID-19, cytokine storm, immuno-modulators, SARS-CoV-2, sphingosine 1-phosphate

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is likely to overtake the Spanish flu as being the most severe pandemic.[1] Common symptoms of COVID-19 include fever, fatigue, cough, conjunctivitis, and dyspnea. In some severe cases, acute respiratory distress syndrome (ARDS) can be noted, which is characterized by acute pulmonary inflammation and increased pulmonary permeability due to alveolar capillaries

**Abbreviations:** ACE2, angiotensin-converting enzyme 2; AKT, protein kinase B; APP, amyloid precursor protein; CNS, central nervous system; ERK, extracellular signal-regulated kinase; FTY720, Fingolimod; HIV, human immunodeficiency virus; MFS, major facilitator superfamily; MODS, multiorgan dysfunction; NF-kB, nuclear factor kappa B; NLRP3, NOD-like receptor protein 3; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLC, phospholipase C; S, spike; S1P, sphingosine 1-phosphate; S1PR1, S1P receptor 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGPL1, S1P lyase type 1; SphK, sphingosine kinase; TMPRSS2, transmembrane protease serine 2.

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oedema.[2] SARS-CoV-2 infection also can damage other organs, such as the liver, kidneys, heart, and intestines, even causing multiple organ dysfunction syndrome (MODS).[3] Thrombotic complications are evident in some severe COVID-19 patients.[4,5] Moreover, patients reported ischaemic stroke, acute disseminated encephalomyelitis, and brain damage.[6] There are also some patients who reported neurological and neuropsychiatric dysfunctions.[7]

Although there are many reports of neurological symptoms in COVID-19 patients, such as headache, nausea and vomiting,[8] stroke,[2] isolated Guillain-Barré syndrome,[9] and demyelination.[10] However, it is not clear whether the neurological symptoms are transported via synapses to the nervous system or are the result of passing through the blood–brain barrier (BBB) endothelial cells and inflammatory cells reaching the nervous system. In response to SARS-CoV-2 infection, immune cells will be recruited from the circulation to the infected tissues, and these cells will release cytokines in large quantities, which will cause a "cytokine release storm".[2] It is also accompanied by an increased production of a variety of inflammatory mediators including lipid factors, chemokines, cytokines, and extracellular matrix proteins. Overcontrolled immune responses can worsen the condition of COVID-19 patients.[3]

Sphingolipids, biologically active signalling molecules, play an important role in both physiological and pathological conditions (viral infections).[11,12] Sphingosine 1-phosphate (S1P) contributes to determining cell fate through the interaction between ceramide and sphingosine.[13] S1P is a kind of lipid mediator produced by the metabolism of sphingomyelin where is extracellular located. Main functions of SIP include regulating cell–cell and cell–matrix adhesion and affecting cellular migration and differentiation.[14,15] S1P also plays a variety of roles in various disease processes, including inflammation and cancer.[16] S1P has five different cell surface G protein (Gi/o, G12/13, and Gq)-coupled receptors, termed S1PR1-5 have been described, which are related to cannabinoid and lysophosphatidic acid receptors.[17] Most cells of vertebrates express S1P receptor subtypes, different types of cells express different subtypes.[14,18] S1P can act as an intracellular mediator or as a receptor-ligand. S1P receptors (S1PRs) bind to S1P with high affinity to induce cellular responses. S1P can be transported across the membrane and released from the intracellular environment to the extracellular environment.[2] S1PRs exhibit unique G protein coupling characteristics with S1PR1 being only coupled to the Gi/o family. S1PR2 can be coupled to the families of Gi/o, G12/13 and Gq, causing the activation of small GTPases such as Rac, Rho, and Ras.[19] Among these five receptors of S1P, S1PR1-3 are mainly expressed in the immune system, central nervous system (CNS) and vascular endothelium. S1PR4 is mainly expressed in lymphatic tissues, while S1PR5 is mainly expressed in the CNS and natural killer cells.[19,20] Emerging studies have suggested that the activation of S1PR1 plays an important role in the process of newborn neuroblasts moving from the neurogenic niches to the olfactory bulb.[2,21] S1PRs are highly expressed in the olfactory epithelium.[22,23] Netland and colleagues[24] have proved that SARS-CoV has the ability to reach the brain through the olfactory bulb and then causes transneuronal spread to the brain.

Sphingosine-1-phosphate binds to the S1PRs on the outer membrane of the cell, activating the Ras/Raf/ERK signal pathway in order to stimulate DNA synthesis, promote cell growth and cell survival.[25] The Ras/Raf/ERK extracellular signal promotes the production of S1P through sphingosine kinase (SphK), which actually forms a positive feedback loop and blocks the pro-apoptotic function of ceramide.[26] Rho GTPase can be coupled to S1PRs to activate the Hippo signalling pathway and also activate the Hippo signalling related transcriptional effectors.[27] S1P has been proved to regulate the release of free calcium ion in the endoplasmic reticulum[28] (Figure 1). Studies have shown that lacking S1P leads to increased vascular leakage, and S1P signalling is essential for angiogenesis and development.[29] S1P has also been reported to perform their functions through other G protein-coupled receptor-independent pathways, such as Histone Deacetylase,[30] TRAF2[31] and Prohibitin 2.[32] SphK and S1P lyase contribute to lymphocyte transport through S1P gradient, playing a role in host inflammatory responses.[33,34] Sphingosine analogue FTY720 used for the treatment of multiple sclerosis has been extensively studied.[35] Olfactory epithelial cells have relatively high expression and activity of S1P lyase.[22] S1PR1 analogues AAL-R[36] and RP-002[36] inhibit pathophysiological responses in the early stage of H1N1 virus infection. Compared with the antiviral drug oseltamivir, RP-002 is more effective in reducing lung injury, while a combination therapy being more effective than single treatment.[36] The combination of S1PR1 agonist CYM-5442 and antiviral drug oseltamivir can provide a maximum protection against acute lung injury.[37] The use of S1PR agonists has been proved to be effective in reducing acute lung injury caused by viral infection. We propose that S1PR agonists may serve as a new therapeutic approach for treating COVID-19.

## 2 | SEARCH METHODOLOGY

The literature review was done through the systematic search for current findings mainly from Google Scholar and the National Centre for Biotechnology Information – PubMed database. The following defined words were used as a search strategy to obtain relevant information: (SARS-CoV-2; sphingosine 1-phosphate), (SARS-CoV-2; Pathogenic mechanisms), (SARS-CoV-2; Nervous system; Clinical features), (COVID-19; vaccine), and (COVID-19; Therapeutic strategy or treatment strategy). Supplementary information on vaccine development was obtained from the World Health Organization (WHO) website.

## 3 | PATHOGENIC MECHANISMS OF SARS-COV-2 AND POTENTIAL ROLE OF THE SPHK-S1P-SIPR PATHWAY

### 3.1 | Non-nervous system

Approximately 85% sequences are similar between SARS-CoV-2 and SARS-CoV.[38] The SARS-CoV-2 sequences are almost the same among different infected persons with the sequence homology exceeding 99.9%.[39] This newly emerged virus has 380 amino acids

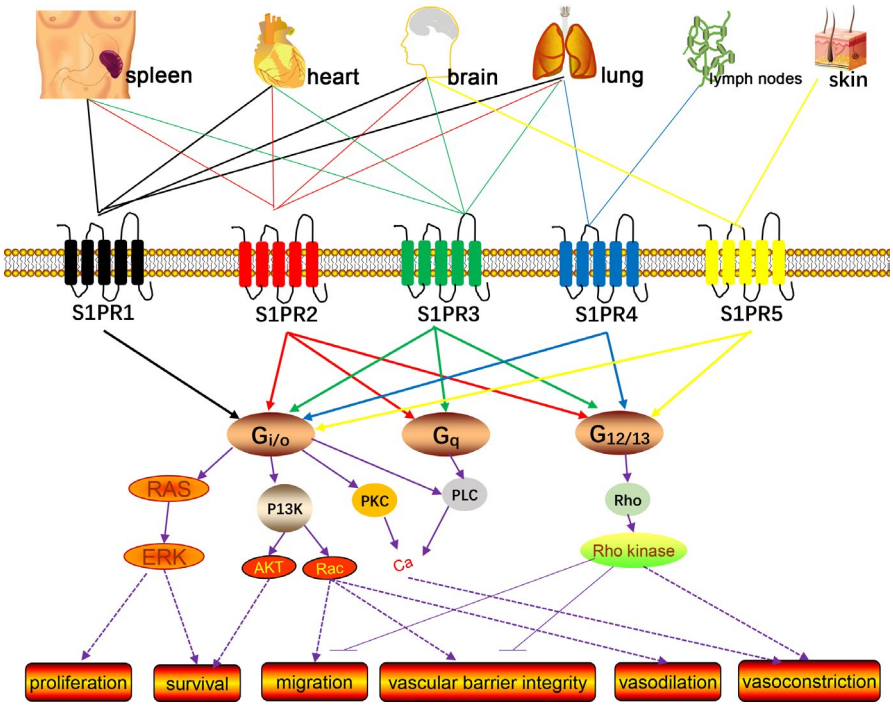


**FIGURE 1** Schematic diagram describing the signalling pathways transduced by S1PRs. S1P activates the S1PRs, S1PR1-5, which transmits various intracellular signals according to the coupled Gα subunit of the heterotrimeric G protein. S1PR1 is coupled with Gi/o, while S1PR2 and S1PR3 are coupled with Gi/o, Gq and G12/13; S1PR4 and S1PR5 are coupled with Gi/o and G12/13. The signalling through Gi/o is related to the activation of Ras/ERK to promote proliferation and survival, improve survival rate through PI3K/Akt; through PI3K/Rac promote migration, enhance vascular barrier integrity and vasodilation; increase intracellular $Ca^{2+}$ through PKC or PLC. Signalling through Gq mainly activates the PLC pathways. Signalling through G12/13 can promote the activation of Rho/Rho kinase, thereby inhibiting migration, reducing the integrity of the vascular barrier and inducing vasoconstriction. ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PKC, protein kinase C; PLC, phospholipase C

substitution differences in the receptor binding domain with the virus spike (S) protein of human ACE2 being expressed on the surface.[40] Similar to SARS-CoV, SARS-CoV-2 also finds ACE2 in order to invade cells, suggesting that SARS-CoV-2 may target and infect similar cell types as SARS-CoV did.[41] The ACE2 gene is widely expressed in our body including heart, brain, kidneys, eyes, upper respiratory tract, lungs, gut, vasculature, and liver[42] (Figure 2). It has been gradually established that SARS-CoV-2 uses human ACE2 proteins as its receptors in order to enter into the ACE2-expressing cells and SARS-CoV-2 does not use other coronavirus targeting receptors such as dipeptidyl peptidase 4 and aminopeptidase N.[43] Growing evidence confirms that ACE2 is closely associated with lung injury in patients with COVID-19[44] and could also mediate SARS-CoV-2 S-mediated entry into cells.[45–47] The change of several key amino acid residues leads to the enhancement of hydrophobic interaction and the formation of a salt bridge, making the affinity between SARS-CoV-2 and ACE2 much stronger than that of SARS-CoV.[42,48] This can be one of the reasons that current global influence of SARS-CoV-2 is far greater than that of SARS-CoV. Emerging data have suggested that sphingosine can competitively bind to the cell receptor ACE2 with SARS-CoV-2 and prevent biological interactions between the viral S protein receptor binding domain and ACE2.[49] This indicates that S1P can interfere with the interaction between the virus and its receptor to prevent viral infection.

The SARS-CoV-2 S protein has been widely recognized as an important determinant of host tropism, representing a key target for vaccine development.[42,45] Both SARS-CoV[50] and SARS-CoV-2[45] S protein can downregulate the expression of ACE2 and induce the shedding of the ACE2 extracellular domain.[51] Subsequently, the function of the renin–angiotensin system can be affected, leading to excessive inflammation and vascular permeability.[45,52] In a study of 12 patients with COVID-19, the level of circulating Ang II levels (linear to viral load) was increased significantly in the COVID-19 group than the healthy control group.[53] This finding indicates a direct relationship between the down-regulated expression of ACE2 and systemic renin–angiotensin system imbalance caused by the SARS-CoV-2 infection. Sphingosine specifically interacts with ACE2. Strikingly, the ability of binding recombinant ACE2 to the SARS-CoV-2 S protein is inhibited significantly after incubating with a low concentration of sphingosine.[49] Amphiphilic sphingosine molecules can bind to the polar and hydrophobic amino acids in the ACE2 pocket, then interacting with the receptor binding domain of the SARS-CoV-2 S protein.[54–56] Sphingosine may also interact with other domains of ACE2.[49] The interaction of sphingosine and ACE2 may cause the conformational change of the ACE2 inner S-binding domain, thereby preventing binding of virus S protein.

During the early stage of infection rapid replication of the SARS-CoV-2 may cause epithelial and endothelial cellular apoptosis,

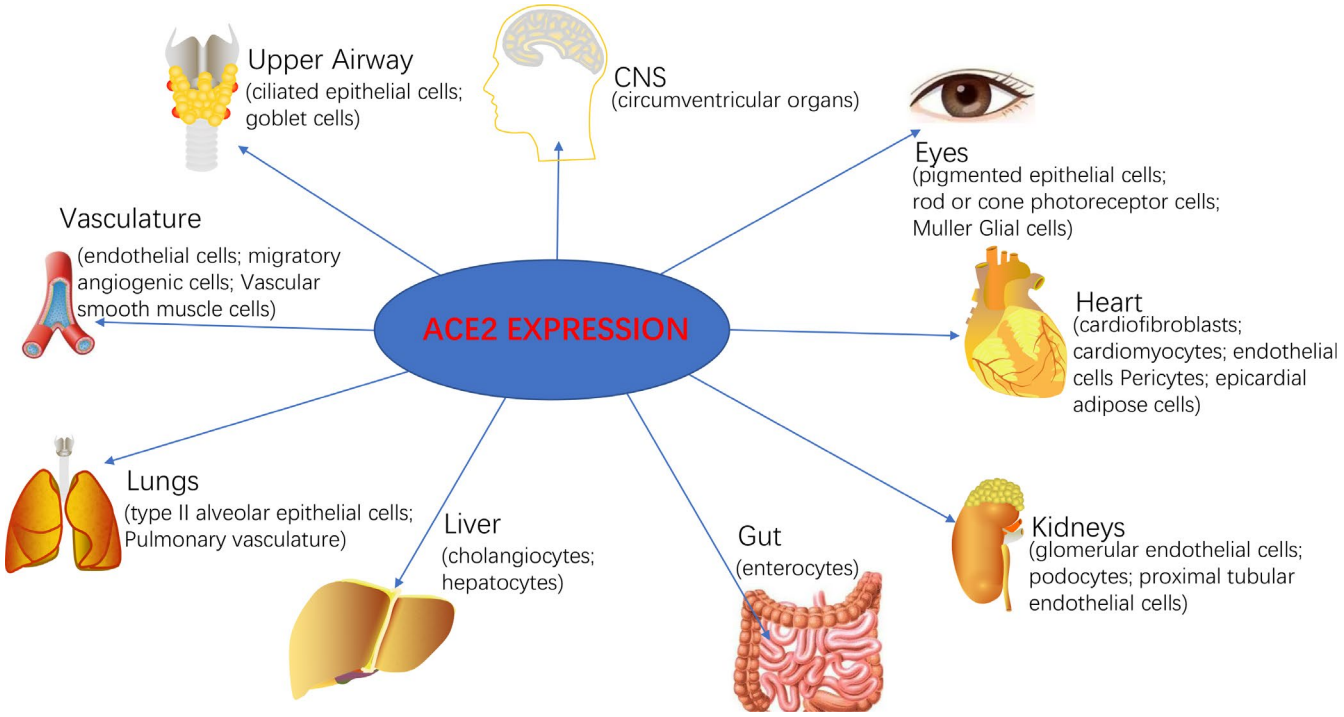


**FIGURE 2** Schematic diagram of the main expression of ACE2 in the whole body. ACE2 is expressed in the circumventricular organs of the CNS, upper respiratory tract (goblet and ciliated epithelial cells), the vascular system (endothelial cells, migratory angiogenic cells, and vascular smooth muscle cells), alveolar Type II epithelial cells of the lungs, and pulmonary vasculature, the liver (cholangiocytes and hepatocytes), enterocytes of the gut, kidneys (glomerular endothelial cells, podocytes, and proximal tubule epithelial cells), heart (cardiofibroblasts, cardiomyocytes, endothelial cells, pericytes, and epicardial adipose cells), eyes (pigmented epithelial cells, rod, and cone photoreceptor cells and Müller glial cells)

vascular leakage,[57] pyroptosis of macrophages and lymphocytes, subsequently triggering the release of pro-inflammatory cytokines and chemokines.[52] Guan et al[58] found that among 1099 COVID-19 patients, 82.1% of patients had peripheral blood lymphopenia, indicating pulmonary infiltration of lymphocytes and cell damage through apoptosis. Studies have shown that SARS-CoV infection leads to increased expression of IFN-α, β, γ, λ at mRNA level in the lungs,[59,60] and SARS-CoV up-regulates the expression of IL-6, TNF-α, and IL-12 at the mRNA level of monocyte-derived macrophages.[61] SARS-CoV-2 shows similar cytokine trends to SARS-CoV.[62] In severe COVID-19 cases, the serum levels of IL-2, IL-1β, IL-6, IFN-γ, MIP1A, MCP-1, and TNF-α are increased.[63,64] After SARS-Cov-2 infection, it can trigger the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and the secretion of IL-1b in bone marrow-derived macrophages,[52,65,66] which can induce apoptosis and cause the release of inflammatory mediators.[65] Endothelial cell activation is an important part of systemic inflammation and immune response, TNFα can induce the activation of SphK1 and S1P in cells, thereby mediating the activation of endothelial cells and the expression of adhesion molecules.[67] The activation of SphK1 is also related to TNF receptor-associated factor 2, and locally produces S1P, which mediates the activation of TNFα-stimulated nuclear factor kappa B (NF-kB) to promote cell survival and the release of pro-inflammatory mediators.[31] SphK1 activation can also lead to an increase in the production of IL-6 induced by lipopolysaccharide and aggravate the inflammatory response.[68] Although SphK2 also has the same ability to phosphorylate sphingosine to S1P as SphK1,[69] SphK2 is considered to be a negative regulator of inflammation.[70] SphK2 has also been confirmed to exert anti-inflammatory function in human macrophages, and human macrophages are the main regulator of inflammation, its overexpression inhibits the transcriptional activity of NF-κB and the release of cytokines.[71] The early degradation of SphK2 can cause the activation of macrophages, and the late up-regulation of SphK2 may be involved in the termination of the production of inflammatory cytokines.[71]

In the process of SARS-CoV-2 invading cells, both S-protein and ACE2 are proteolytically modified by host cell proteases.[42,72] So host cell proteases also play a key role in the process of SARS-CoV-2 invasion. It has been proven that SARS-CoV-2 can use a variety of host proteases,[42] including cathepsin L/B, factor X, trypsin, elastase, transmembrane protease serine 2 (TMPRSS2) and furin to trigger S protein and promote cell entry after receptor binding.[73]

## 3.2 | Nervous system

In most COVID-19 cases, the virus spreads along the upper respiratory tract, resulting in limited clinical manifestations. There are also a small number of COVID-19 cases of SARS-CoV-2 reaching the lungs and preferentially affecting type II alveolar cells, leading to

serious diseases or possibly entering the brain through some way. Mice transgenic to the SARS-CoV receptor expressing human ACE2 are highly susceptible to the virus,[74] lung and brain infections were observed in all mice after intranasal inoculation,[75,76] confirming that SARS-CoV infects the brain through olfactory receptor neurons. Although the expression level of human ACE2 in the brain does not exceed 0.1%–1% of the lungs,[24] the level of virus replication in the lungs of these mice is high, but extensive virus replication has also been detected in the brain, SARS-CoV may use a transneuronal/synaptic pathway that uses axon transport in the brain,[75,77] which is also true for SARS-CoV-2. Studies showed that SARS-CoV-2 enters the endoplasmic cavity in the early and late stages in non-neuronal cells; therefore, it may be directed to the vesicular axon pathway of neurons.[78,79] ACE2 is encoded in neurons, oligodendrocytes and astrocytes, and is also found in the substantia nigra, posterior cingulate cortex, middle temporal gyrus, and ventricles.[80] There are regional differences in the degree of infection in the brain, some areas of the brain (such as the cerebellum) are uninfected, while other areas (such as the thalamus, cerebrum, and brainstem) are severely infected.[24,75] There is about a 60-h delay from nasal infection to the detection of SARS-CoV in the olfactory bulb.[79] Within these 60 h, the virus may replicate and accumulate in different olfactory epithelial cells, because its subsequent transport to other parts of the brain requires a relatively short time.[79] Considering the similarities between SARS-CoV and SARS-CoV-2, the same is true for SARS-CoV-2.

In humans, the cells co-expressing ACE2 and protease (such as TMPRSS2) are not only upper respiratory tract epithelial cells.[81] After querying the previously published large amounts of RNA-seq data from the entire olfactory mucosa of macaques, marmosets, and humans,[82,83] it was found that all olfactory mucosa samples expressed almost all genes related to SARS-CoV-2 entry. Immunostaining of human olfactory neuroepithelial biopsy tissues confirmed the expression of ACE2 protein, revealing the expression of ACE2 in horizontal basal cells and sustentacular cells, while there is no ACE2 protein expressed in olfactory sensory neurons.[82] The olfactory epithelium is a pseudo-layered epithelium composed of basal cells (ie stem cells), sensory neurons, supporting cells.[84] In human olfactory epithelium, sustentacular cells and olfactory stem cells may be the direct targets of SARS-CoV-2. And sustentacular cells have the highest expression frequency of ACE2[85,86] (2.9%), although the frequency is slightly lower than that observed in respiratory cilia (3.6%) and secretory cells (3.9%).[82] Similarly, all horizontal basal cell subtypes express ACE2, but olfactory horizontal basal cells (0.8%) have a lower frequency of expression than respiratory horizontal basal cells (1.7%).[82] Although mature neurons of olfactory receptors do not present or present ACE2 at low levels,[86] SARS-CoV-2 may enter and damage stem cells and the sustentacular cells in the nasal epithelium, which are necessary for normal olfactory function or regeneration of impaired neurons.[2] But SARS-CoV-2 virus must first invade the non-neural olfactory epithelial cells which expressing high ACE2, then be transmitted to mature olfactory receptor neurons which expressing low ACE2, and finally be transported along the olfactory axons to the brain. TMPRSS2 transcript is expressed in the lower layers of the olfactory bulb epithelium and sustentacular cells, including stem cells and immature olfactory receptor neurons, single-cell RNA-Seq data set and database analysis, as well as subsequent in situ hybridization and immunochemistry experiments, showed that most TMPRSS2 is expressed in sustentacular cells, but the expression level in mature olfactory receptor neurons is very low.[82,86,87] Although the expression level of SARS-CoV-2 entry-related genes in the olfactory epithelium is lower than that in the respiratory epithelium isolated from the nasal mucosa, it was found that the co-expression levels of ACE2 and TMPRSS2 in human olfactory epithelial sustentacular cells were similar to those observed in the rest of the non-nasal respiratory tract.[82,88] The co-expression of TMPRSS2 and ACE2 with their higher expression levels make sustentacular cells more susceptible to SARS-CoV-2 infection[86] (Figure 3).

In addition to the olfactory axon pathway, SARS-CoV-2 may also be directly transmitted from non-neuroolfactory epithelial cells to the cerebrospinal fluid surrounding the olfactory nerve bundle, located near the cribriform plate.[79] Once SARS-Cov-2 enters the cerebrospinal fluid, it can reach most areas of the brain, including the medulla oblongata. More severe pneumonia can cause systemic hypoxia, which can cause brain damage. Factors that cause damage include peripheral vasodilation, hypercapnia, accumulation of toxic compounds, anaerobic metabolism and hypoxia. These may lead to neuron swelling and brain oedema, and ultimately to nervous system damage.[89]

Sphingosine-1-phosphate can promote the olfactory ensheathing cells' proliferation in vivo and in vitro through the S1PR1/RhoA/Yes-associated protein pathway, thereby promoting the projection of the olfactory nerve layer and axons, and the growth of olfactory neurons to the olfactory bulb.[23] S1P plays a key role in stem cells proliferation and olfactory sensory neuron function. S1PRs show different tissue expressions, and S1PRs are highly expressed in the olfactory epithelium both in vitro and in vivo.[23] S1P lyase is an essential enzyme for S1P degradation, it generates S1P chemical gradient and promotes lymphocyte trafficking.[90] S1P lyase is also highly expressed in the CNS, including the cerebral cortex, cerebellum, arachnoid lining cells, choroid plexus, specific neurons of the olfactory bulb, the spinal cord, trigeminal nerve ganglion, midbrain, and hindbrain.[90] Olfactory neurons are one of the tissues that express S1P lyase most strongly around the olfactory bulb.[90]

Sphingosine-1-phosphate proved to be a powerful neurogenesis stimulant.[91] S1PRs are expressed in different neural progenitor stem cells and different neural cell types.[92] The ATP-binding cassette transporter has been confirmed as an S1P transporter for various types of normal cells and tumor cells.[16] One of the Major Facilitator Superfamily (MFS) named spinster homologue 2, which hasn't a typical ATP-binding motif, was identified as promoting S1P output in the heart and brain.[93] MFS domain-containing 2b (MFSd2b) is also an S1P transporter, which is essential for exporting bioactive lipids from endothelial cells in the brain.[94] The study found that by deleting the gene encoding S1P lyase type 1 (SGPL1) in mice, S1P could accumulate in the brain and then determined the activation of microglia and IL-6 secretion; this process was related to defective autophagy

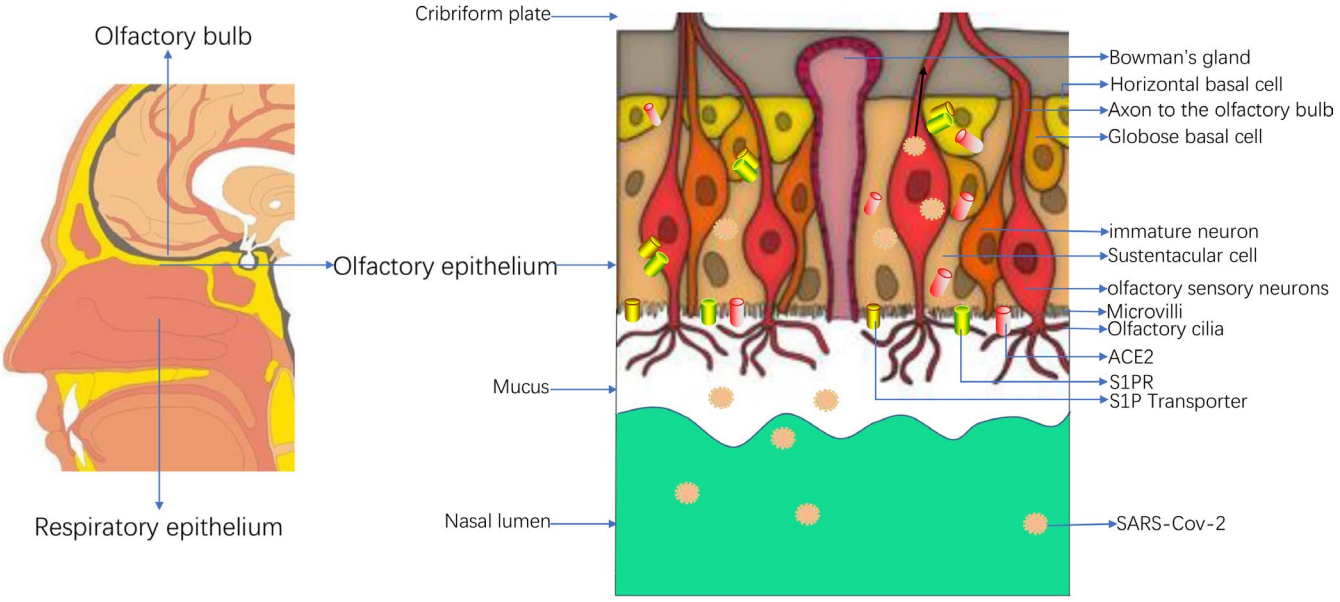


**FIGURE 3** Left: Schematic diagram of the distribution of olfactory bulb, olfactory epithelium, and respiratory epithelium in the nasal cavity: The sagittal view of the human nasal cavity, the arrow points out the position of the olfactory bulb, olfactory epithelium, and respiratory epithelium. Right: Anatomical diagram of the olfactory epithelium and the main known cell types, schematic diagram of SARS-Cov-2 invasion of the olfactory epithelium. The olfactory epithelium is mainly composed of olfactory cilia, microvilli, olfactory sensory neurons, sustentacular cells, immature neurons, globular basal cells, horizontal basal cells, Bowman's glands. The expression of ACE2 receptor, S1PR, and S1P transporter is shown in supporting cells and neuronal cells. Some of these cells are the direct targets of SARS-CoV-2. The reduced nutritional support caused by damaged sustentacular cells infected by SARS-CoV-2 may lead to impaired basal cell renewal

and was caused by S1P/S1PR2 axis mediated.[95] Van Doorn et al[96] demonstrated that reactive astrocytes cultured in MS lesions and under pro-inflammatory conditions strongly enhanced the expression of S1P receptors 1 and 3. S1PRs can regulate the release of pro-inflammatory chemokines in astrocytes and microglia. FTY720 blocked the transcription of chemokines CXCL10, CXCL5/LIX, and monocyte chemotactic protein 1 in astrocytes, and decreased CXCl7 released by microglia.[97]

## 4 | SYMPTOMS AND COMPLICATIONS

Generally, the severity of symptoms depends on the patient's immune system status and age, the mortality rate is higher in individuals with weakened immune function and those older than 70 years.[98] The main risk factors for patients with SARS-Cov-2 infection include pre-existing respiratory diseases, hypertension, cardiovascular disease, diabetes, and chronic obstructive pulmonary disease.[99]

### 4.1 | Non-nervous symptoms and complications

The symptoms of each SARS-Cov-2 infection patient are different, from asymptomatic infection in mild patients to respiratory failure in severe patients.[100] SARS-CoV-2 attacks the lower respiratory tract and upper respiratory tract, the common symptoms of COVID-19 patients are similar to the common cold and flu symptoms,[100] ranging from mild respiratory diseases, ground-glass opacity to pneumonia, RNA anaemia, and ARDS.[98] In the early stages of COVID-19, the increase in the levels of systemic and local blood chemokines and cytokines will trigger the individual's immune response and eventually clear the infection. SARS-CoV-2 causes tissue damage, triggers inflammation, and host cell death.[67]

A cohort study reported that about 50%–75% of people with positive results of throat swab from nucleic acid tests have no clinical symptoms, most of the remaining people have minor flu-like symptoms, there are also a small number of people have difficulty breathing, severe interstitial pneumonia, ARDS, and MODS.[100] The common symptoms of SARS-Cov-2 infection are cough, fever, fatigue, mild breathing difficulties, headache, sore throat, and conjunctivitis.[64,101] A few cases have symptoms of gastrointestinal involvement, including diarrhoea, nausea, and vomiting.[100] Most patients with clinical symptoms and almost all critically ill patients suffer from one or more coexisting underlying diseases, such as diabetes, and cardiovascular diseases, hypertension.[102,103] SARS-CoV-2 also has a high affinity for the cardiovascular system, which can lead to acute cardiovascular-related diseases such as congestive heart failure, cerebral medullary cardiopulmonary dysfunction, and other chronic heart diseases.[104–106] The main cause of death in patients with COVID-19 is respiratory failure, occurring mostly in older people, people with weakened immunity, and patients with other potential health problems.[43,107]

### 4.2 | Nervous system symptoms and complications

Severe acute respiratory syndrome coronavirus 2 infection primarily affects the respiratory system; therefore, the clinical symptoms of COVID-19 are predominantly respiratory. But, it is not uncommon for the nervous system to be affected. If it is not detected and treated early, it can lead to serious complications. Under normal circumstances, neurological complications appear in severely ill patients, and sometimes they may even appear earlier than respiratory symptoms, or many COVID-19 patients only have neurological symptoms.

Varatharaj et al[7] reported COVID-19 related neurological and neuropsychiatric complications in 125 patients. Of the 125 patients, 77 cases (62%) had cerebrovascular events, including 57 cases of ischaemic stroke (74%), 9 (12%) cases of cerebral haemorrhage (12%), and 1 (1%) case of CNS vasculitis. Among 125 patients, 39 (31%) had changes in mental status, including 7 (18%) patients with encephalitis and 9 (23%) undiagnosed patients. According to the clinical case definition of psychiatry, the remaining 23 (59%) patients with changed mental status met the definition. Of the 23 neuropsychiatric patients, 10 (43%) had new-onset psychosis, 6 (26%) had the neurocognitive syndrome, and 4 (17%) had affective disorders. Of the 37 patients with changed mental status, 18 (49%) patients ≤ 60 years old, and 19 (51%) patients > 60 years old, and 13 (18%) of 74 patients with cerebrovascular events ≤ 60 years old, and 61 (82%) patients > 60 years old.

Mao et al[8] reported on two groups of patients with mild and severe conditions. They found that severe patients had less typical coronavirus symptoms, such as dry cough (34.1%) vs. (61.1%) and fever (45.5%) vs. (73%). But, compared with minor cases (45.5%) vs. (30.2%), neurological symptoms in severe cases are significantly more common. The most common neurological symptoms that have been reported are headache and dizziness. There is a prospective case series involving 58 patients that showed a higher incidence of neurological complications, with 49 (84%) patients experiencing neurological symptoms.[108] Agitation was the most common symptom, accounting for 69%, followed by confusion, accounting for 65%. 39 (67%) patients had corticospinal tract signs, and 14 (36%) patients were found to have executive dysfunction syndrome at discharge.

Poyiadji et al[109] reported the first case of acute haemorrhagic necrotizing encephalopathy associated with COVID-19., which may be due to cytokine storm caused damaged the brain parenchyma and the destruction of the BBB. Zhao et al[110] reported a patient with COVID-19-related acute myelitis with fever and body pain, possibly due to cytokine storms and overactive inflammation response. Sharifi et al[111] reported case of intracranial haemorrhage leading to cerebrovascular accidents. Varatharaj,[7] Mao,[8] Helms,[108] and others have also reported similar cases. It is considered that the dysregulation of ACE 2 receptors affects brain self-regulation, cerebral blood flow, and the sympathetic-adrenal system, even cause brain haemorrhage. Divani et al[112] reported that stroke rates did increase in areas with a surge in COVID-19 cases, with a significant increase in the number of strokes presenting with large vessel occlusions in some areas and occurring in younger patients without vascular risk factors.

## 5 | CURRENT METHODS OF TREATING SARS-COV-2 INFECTION AND RESEARCH PROGRESS OF VACCINES

Many drugs that have antiviral properties have been proposed for the treatment of SARS-CoV-2. But so far, no specific antiviral therapy for human COVID-19 has been approved. It is now generally accepted that the rationale for treating people with SARS-Cov-2 infection is to administer antiviral drugs as soon as possible from the onset of symptoms in order to rapidly reduce viral load and suppress the cytokine response. Through reviewing the literature, we have summarized the current treatment methods for COVID-19 that are currently in clinical use and are considered for clinical use. Mainly include the following: 1. Use of antiviral drugs; 2. Use of interleukin receptor antagonists; 3. Use of convalescent plasma neutralizing antibodies; 4. Use of monoclonal antibodies. Antiviral drugs are mainly divided into: 1. RNA-dependent RNA polymerase inhibitors; 2. Viral protease inhibitors; 3. Endosome acidification inhibitors; 4. Late endosome entry inhibitors; 5. Host interferons; 6. Immunomodulator. Antiviral drugs are mainly divided into: 1. RNA-dependent RNA polymerase inhibitors, a. Remdesivir. It is a kind of adenosine triphosphate nucleoside analogue, and its active metabolite can reduce the production of viral RNA by interfering with virus-dependent RNA polymerase.[113] A report of 1059 patients showed that the median recovery time of patients receiving remdesivir was significantly reduced by 4 days compared to the median recovery time of patients in the placebo group.[114] In a randomized controlled trial, in patients with symptoms lasting 10 days or less, compared with placebo, the use of redesivir accelerated the clinical improvement time but showed no statistical difference. There is also no difference in virological inhibition[115]; b. Favipiravir. It can selectively inhibit viral RNA-dependent RNA polymerase.[116] The effect of treating influenza has been confirmed and approved in China and Japan.[117] Compared with lopinavir/ritonavir, virus clearance time is shortened, radiology is improved significantly, and side effects are less.[118] c. Ribavirin. Research on SARS-CoV showed that when lobavirin is used in combination with ritonavir, better clinical efficacy can be obtained.[116] A retrospective study by Tong et al[119] did not prove that ribavirin treatment has any clinical effects on SARS-CoV-2 infection; 2. Viral protease inhibitors, a. Ritonavir/Lopinavir. Ritonavir/Lopinavir has a better effect on patients infected with SARS-CoV and is associated with low anti-SARS-CoV-2 activity.[120] But, Lopinavir/Ritonavir was evaluated in randomized controlled trials in severe cases and late-stage patients (median 13 days after the onset of symptoms), and compared with standard treatment, there was no significant virological or clinical response improvement.[121] b. Nelfinavir. Nelfinavir is currently used to treat HIV infection. It was found in vitro experiments that it is an effective cell fusion inhibitor caused by SARS-CoV-2 S-glycoprotein; 3. Endosome

acidification inhibitors. Azithromycin/Hydroxychloroquine/Chloroquine; Azithromycin and Hydroxychloroquine were first demonstrated to be effective in suppressing viral load in a small, non-randomized clinical trial.[122] But, a larger clinical trial failed to prove the clinical benefit of hydroxychloroquine in the treatment of COVID-19 and did not get the same results as before.[123] 4. Late endosome entry inhibitors, Teicoplanin. Teicoplanin is active against Gram-positive bacteria and can inhibit bacterial cell wall synthesis. It has been shown to inhibit the MERS-CoV virus in vitro, affect the replication of MERS-CoV, and has the potential to treat SARS-Cov-2 infection;[124] 5. IFN-β acts as host interferon, and SARS-CoV-2 can induce low interferon I–III levels.[125] A randomized controlled trial showed that the future clinical research of dual antiviral therapy based on IFN-β-1b is worthy of recognition.[126] Another randomized trial for patients with severe COVID-19 showed that treatment of SARS-Cov-2 infection with IFN-β-1a can reduce mortality and allow early patients to be discharged from the hospital.[127] The results of inhaled IFN-b and IFN-a-2b in the treatment of SARS-Cov-2 infection are encouraging[128]; 6. Immunomodulator, Corticosteroids. Although the use of corticosteroids for the treatment of severe respiratory viral infections and respiratory distress syndrome in adults has been controversial, a randomized controlled trial showed that in patients with critical cases of COVID-19 using ventilators, the use of dexamethasone 6 mg daily for 10 days can reduce the mortality rate by about 12%, while with oxygen support, it can be reduced by 2.9%.[129]

Vaccine development is complicated. This is a highly complex science that requires a lot of labour and time. The vaccines developed for SARS-Cov-2 mainly include five types: (a) inactivated or attenuated live viruses; (b) subunit vaccines made with partial immune responses to viruses; (c) delivery of messenger RNA to cells Gene vaccines that counteract viral RNA; (d) engineering a part of viral protein to trigger an immune response made viral vector vaccines; (e) vaccines that target the virus reproduction machinery.[67,130,131] There are hundreds of vaccines currently in development worldwide, and some vaccines show great potential. Oxford University scientists developed a genetically modified adenovirus vaccine, named ChAdOx1 nCoV-19, which is in the final phase of phase III clinical trials (ClinicalTrials.gov Identifier NCT04324606). The vaccine expresses a S-glycoprotein that allows entry to human cells through the ACE2 receptor.[67] By identifying this S protein on the ChAdOx1 nCoV-19 vaccine, the human body can produce an immune response and can prevent the virus from entering human host cells. Researchers have found that ChAdOx1 nCoV-19 produces similar immune responses in both young and old people, with older people having lower adverse reactions than young people. CanSino Biologics cooperated with Beijing Institute of Biotechnology to develop another vaccine in China.[132] The vaccine was modified to express the SARS-CoV-2's S protein using human adenovirus type 5 as vector.[132] This vector has previously been used in the Ebola vaccine Ad5-EBOV and has shown good safety in clinical trials.[133] It was found in clinical trials that the vaccine can induce neutralizing antibodies and specific T cell responses.[134] The WHO maintains a running list of candidate vaccines in development, and as of December 2nd 2020, there were 51 candidate vaccines in clinical evaluation (Table S1).

## 6 | TARGETING SPHK/S1P/S1PR IN SARS-COV-2 INFECTION AND S1P ANALOGUES AS AN ADJUNCTIVE THERAPY IN COVID-19

Sphingolipid signalling plays an indispensable role in virus replication, immune response activation, and maintenance of vascular system integrity.[67] Edwards et al.[49] proved that exogenous sphingosine can prevent epithelial cells from infecting SARS-Cov-2, and it can also prevent SARS-CoV-2 from infecting freshly isolated nasal epithelial cells. 0.25 μmol/L sphingosine is sufficient to inhibit SARS-Cov-2 infection of human epithelial cells, and 2 μmol/L sphingosine can almost completely inhibit SARS-Cov-2 infection.[49] At present, sphingosine has not been found to have side effects or toxicity on cultured experimental cells or human nasal epithelial cells.

Fingolimod is one of the most unique sphingolipid-based drugs and is currently the main drug candidate for the treatment of COVID-19. Activated FTY720 is a paradox that acts as both an antagonist and an agonist.[67] FTY720 is a non-selective agonist of four out of five G-protein-coupled S1PRs, namely S1PR1, 3, 4, and 5.[67] Different from naturally occurring S1P, activated FTY720 acts as a selective antagonist of S1PR1 by specifically inducing the internalization and down-regulation of S1PR1.[135] FTY720 is a kind of sphingosine analogue and also requires SphK for activation and phosphorylation.[136] FTY720 also can act as a substrate and transforms into active state, compared with SphK1, FTY720 is activated by the action of SphK (SphK1,2) isoenzymes and has a higher affinity for SphK2.[137] The potential positive effect of FTY720-P's antagonism against S1PR1 in the treatment of SARS-Cov-2 infection is to inhibit excessive inflammation or "the cytokine storm".[67] FTY720-P can reduce excessive inflammation causes blood vessel damage. Lymphocytes usually circulate between blood with higher S1P levels and lymphatic tissues with lower S1P levels. Through gradient adjustment, S1P binds to S1PR1, S1PR3, S1PR4, and S1PR5 on lymphocytes.[67] The combination of FTY720-P with S1PR1 on lymphocytes firstly cause its activation, and then down-regulation of S1PR1, preventing lymphocytes from infiltrating into the blood from lymphoid tissues, leading to a decrease in peripheral lymphocytes and limiting inflammation.[136] (Figure 4) FTY720 can also be used as a functional antagonist to desensitize the intracellular S1PRs pathway and inactivate the SIPR pathway in potential inflammatory cells.[138] Unlike most immunosuppressants, FTY720 prevents lymphocytes from penetrating into the blood from lymphoid tissues and does not cause cytotoxicity.[139,140]

As an FDA approved drug, FTY720 has the potential to help intervene and treat the more serious neurological side effects of SARS-Cov-2 infection. The FTY720 prodrug (FTY720-P) can cross the BBB and play a variety of direct roles in the CNS, from neuroprotection to reducing neuroinflammation.[67] FTY720-P inhibits

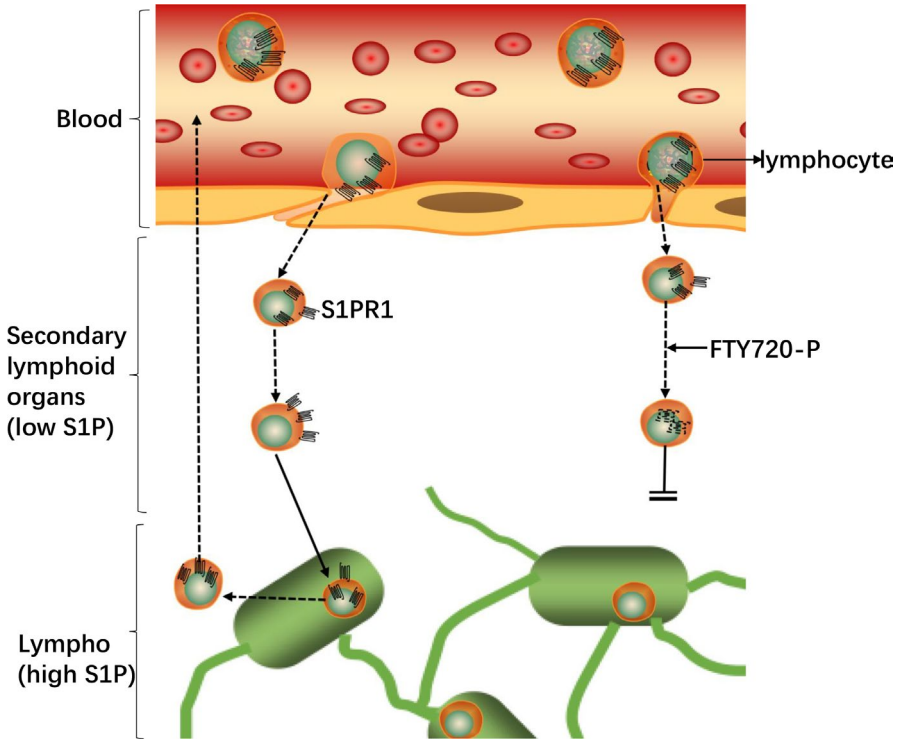


**FIGURE 4** A schematic diagram of the relationship between S1P and lymphocyte transport. Due to the high S1P concentration in circulation, S1PR1 of lymphocytes in circulation mostly internalized. After entering the secondary lymphoid organs with low S1P concentration, they gradually restore the surface expression of S1PR1 and regain the ability to egress from the lymphoid organs toward S1P in circulation. SphK 2 phosphorylates FTY720 and induces the internalization and subsequent degradation of S1PR1, thereby inhibiting the outflow of lymphocytes

the invasion of lymphocytes into the CNS by limiting the invasion of lymphocytes in the lymphatic tissue, thereby limiting neuroinflammation.[135] The maintenance of the S1P/S1PR signal can protect vascular endothelial function.[67] FTY720 blocks the inflammatory response mediated by S1P/S1PR1 and has a positive effect on against heart disease.[141] It has been observed to have a protective effect on acute and chronic myocardial damage in mice experiments with ischaemia and hypoxia.[142]

Ozanimod is a S1PR agonist that targets S1PR1 and S1PR5, its function is similar to FTY720. When bound to S1PR1 and/or 5, it can lead to the internalization and degradation of S1PRs and the decrease of circulating lymphocytes.[143] Ozanimod does not show side effects like FTY720, such as abnormal cardiac conduction, hypertension, fibrosis, etc., and Ozanimod's half-life and lymphocyte recovery period are much shorter than FTY720.[143] Ozanimod can competitively bind to SphK2 and prevent the phosphorylation of sphingosine into the active form S1P.[144] SphK2 is a key factor in virus replication and plays an important role in the single-stranded RNA viruses' replication-transcription complex. Opaganib's blocking of SphK2 caused a decline in the virus's ability to reproduce and minimizes the possible risk of drug resistance due to virus mutation.[144] In a small group of severely symptomatic COVID-19 patients treated by Opaganib, Opaganib showed good safety and tolerability, and all the patients' clinical and laboratory examinations were improved.[67]

As a selective S1PR1 agonist, AUY954 has been shown in animal experiments to reduce microvascular permeability and inflammation.[29] In contrast, the two S1PR1 antagonists W146[67] and NIBR-0213[145] showed a loss of capillary integrity in animal experiments.

## 7 | PERSPECTIVES

As SARS-CoV-2 infection brings a cytokine storm, another serious complication, namely ARDS, is more likely to occur in elderly and severe cases of COVID-19 patients.[63,146,147] Recent studies have pointed out that compared with healthy controls, patients with ARDS have lower serum S1P levels, which is further related to non-pulmonary organ failure.[148] Lipid species have been shown to be involved in different stages of the virus life cycle and different stages of cell host infection.[2] At present, several drugs that affect lipid metabolism can be used for antiviral treatment, and statins can be used to treat hepatitis C virus infection[149] and the treatment of SARS-Cov-2 infection.[150] FTY720 can enter the CNS, where its active metabolite FTY720 phosphate (FTY720-P) has a pleiotropic neuroprotective effect in the inflammatory microenvironment.[151] FTY720-P can be used to treat human immunodeficiency virus (HIV) remission that affects virus persistence and T cell function, in neurons exposed to HIV, FTY720-P reduces the expression of the amyloid precursor protein (APP) gene, thereby reducing APP protein.[151] At present, FTY720 has been reported in the treatment of patients with MS and SARS-Cov-2 infection, indicating that the immunomodulatory effect of S1P analogues might be beneficial to reduce mortality.[152] Another patient who has relapsing–remitting MS showed activation of SARS-Cov-2 and signs of the hyperinflammatory syndrome after FTY720 was discontinued,[153] indicating that the time of administration may be critical. New S1PRs agonist and S1PRs antagonist drugs have been developed/under development, some of them are undergoing or preparing for clinical trials. S1PR1 and S1PR1 agonists Mayzent and Ozanimod have been approved by the FDA in the past 2 years.[67]

## 8 | LIMITATIONS

As an immunomodulator, the effects of S1P analogues on host cells are diverse. We must clarify the potential risks of S1P analogues to the host. First of all, among the existing S1P analogues, only FTY720 is approved for the clinical treatment of multiple sclerosis.[154] FTY720 has broad specificity for S1PR1 and 3–5, and more precise S1P analogues, for instance, CYM5542 or RP-002, need to be studied to reduce off-target effects. Second, S1P analogues have shown good therapeutic potential in animal models of pulmonary infections, and their effects on humans have not been studied. Regarding the clinical treatment effect of FTY720 on COVID-19, clinical trials are currently underway. Third, the effect of S1P analogues on lymphocyte outflow does not involve agonism but is directed at the functional antagonistic activity of S1PR1.[155] It has been reported that both S1P and fingolimod phosphate induced lymphopaenia through agonistic activation of S1PR1 and subsequent internalization of S1P1 in lymphocytes.[154,156,157] Fourth, due to the lack of S1PR1 on the cell surface, the recirculation of lymphocytes from secondary lymphoid organs to the blood is blocked,[154] because lymphocytes flow out through S1PR1 by a chemotactic response to the S1P concentration gradient.[156,158] For S1P, the internalized S1PR1 circulated back to the cell surface within a few hours.[139] But for S1PR1 modulators such as fingolimod phosphate, internalized S1PR1 underwent proteasomal degradation, resulting in a long-term lack of S1PR1 until it was synthesized de novo.[159] It has a long action time and sometimes may be detrimental to the body.[160] Considering the above factors, we must also consider all potential risks while exploring the huge therapeutic potential of S1P analogues.

## 9 | SUMMARY AND CONCLUSIONS

Overall, S1P analogues may enhance the integrity of lung endothelial cells, and help to prevent and treat the nervous system damage caused by SARS-Cov-2 infection in the early stage. The cytokine storm induced by SARS-CoV-2 is a very serious immunopathology, which may cause the death of COVID-19 patients. S1P analogues protect against pulmonary infection earlier by suppressing cytokine storms. And the regulation of sphingolipid signalling has shown many beneficial effects, including selective vascular barrier protection, neuroprotection, limiting inflammation, regulation of coagulation, and cardioprotection. The regulation of S1P release or S1P content by S1P transporter, SphK or S1P lyase activity, and S1PRs-mediated signal transduction may prevent SARS-CoV-2 infection or virus transmission. Currently, three S1P-based drugs FTY720, Opaganib and Ozanimod, which have been approved by the FDA, have been considered for the treatment of COVID-19 patients, and clinical trials are currently underway, highlighting the potential of targeting SphK-S1P-S1PRs to alleviate symptoms in COVID-19 patients. S1P analogues have great potential in the treatment of COVID-19, and further research is needed to explore the therapeutic effects and risks of S1P analogues in SARS-Cov-2 infected patients.

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None.

### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Methodology, software, formal analysis: Yuehai Pan, Shuai Zhao, Jinming Han; writing—original draft preparation: Fan Chen, Fei Gao; writing—review and editing: Fan Chen; all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at https://www.doi.org//10.1016/S2215-0366(20)30287-X, reference number [reference number] and supplementary materials.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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