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Basic implications on three pathways associated with SARS-CoV-2

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interacts between the host and virus and govern induction, resulting in multiorgan impacts. Its pathophysiology involves the followings: 1) the angiotensin-converting enzyme (ACE2) and Toll-like receptor (TLR) pathways: 2) the neuropilin (NRP) pathway: 3) the spike protein pathway. Therefore, it is necessary to block the pathological course with modulating innate lymphoid cells against diverse corona variants in the future.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has structural S, M, H, and E proteins and non-structural accessory and replicase proteins in the genome. They play an important role in its infectivity and in the pathogenesis of chronic diseases, including hypercoagulability, hyperinflammation, stroke via microvascular circulation abnormalities, microthrombus formation, and multifocal lesions [1]. This pathological combination contributes to the breakdown of the endothelial–epithelial barrier [2].

The life cycle of SARS-CoV-2 begins after binding to the angiotensin-converting enzyme (ACE2) in the epithelium of the oral mucosa, lung, heart, and kidney, and the expression of ACE2 increases with age [3]. SARS-CoV-2 differently dictates viral replication and inflammatory responses via ACE2-dependent in epithelial cells and -independent entries in myeloid cells. During the early ACE2-dependent infection stage, it replicates strongly with scarce inflammatory response, and in the late ACE2-independent infection stage, low with potent inflammatory response by Toll-like receptor 1 (TLR1) [4]. ACE2 and Toll-like receptor 4 (TLR4, CD284) on the cell surface belong to the pattern recognition receptor (PRR) family. ACE2 and TLR4 are highly expressed in hematopoietic stem and progenitor cells. These cells are highly susceptible to the SARS-CoV-2 spike protein (SP). ACE2 and TLR4 produce inflammatory cytokines and activate innate immune responses [5].

Neuropilin-1 (NRP1) is a pleiotropic single-transmembrane coreceptor for class 3 semaphorins and vascular endothelial growth factors. Along with ACE2, NRP1 facilitates the entry of SARS-CoV-2 into host cells. NRP1 is a highly conserved transmembrane receptor lacking a cytosolic protein kinase domain [6,7]. In combination with host transmembrane protease serine 2 (TMPRSS2), SARS-CoV-2 uses the ACE2 receptor for cell entry, which cleaves the viral spike glycoprotein (SP) [8,9]. Glycoproteins are required for viral entry and fusion. The SP is a trimeric glycoprotein encoded by ORF2 in the viral genome. The membrane-distal S1 subunit and proximal S2 subunit in the virus envelope form homotrimers [10]. Our study describes the important molecular pathways associated with SARS-CoV-2 infection and provides

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detailed descriptions of pathological pathways based on three tracks.

2. Results

2.1. ACE2 and TLR pathways

Smoking affects ACE2 expression and induces mineral dust-induced gene (MDIG) expression, which alters the transcription of several essential proteins implicated in exacerbating Corona Virus Disease 2019 (COVID-19) [11,12]. This type of epigenetic gene expression alters gene locus function without changing the underlying DNA sequence. Instead, it relies on posttranslational chemical changes in chromatin, RNA, and DNA. These changes include acetylation, methylation, phosphorylation, ubiquitination and SUMOylation. These changes are linked to genotype and phenotype [13]. The interaction of ACE2 with the SARS-CoV-2 spike protein (SP) in tiny numbers of embryonic-like stem cells (VSELs) and

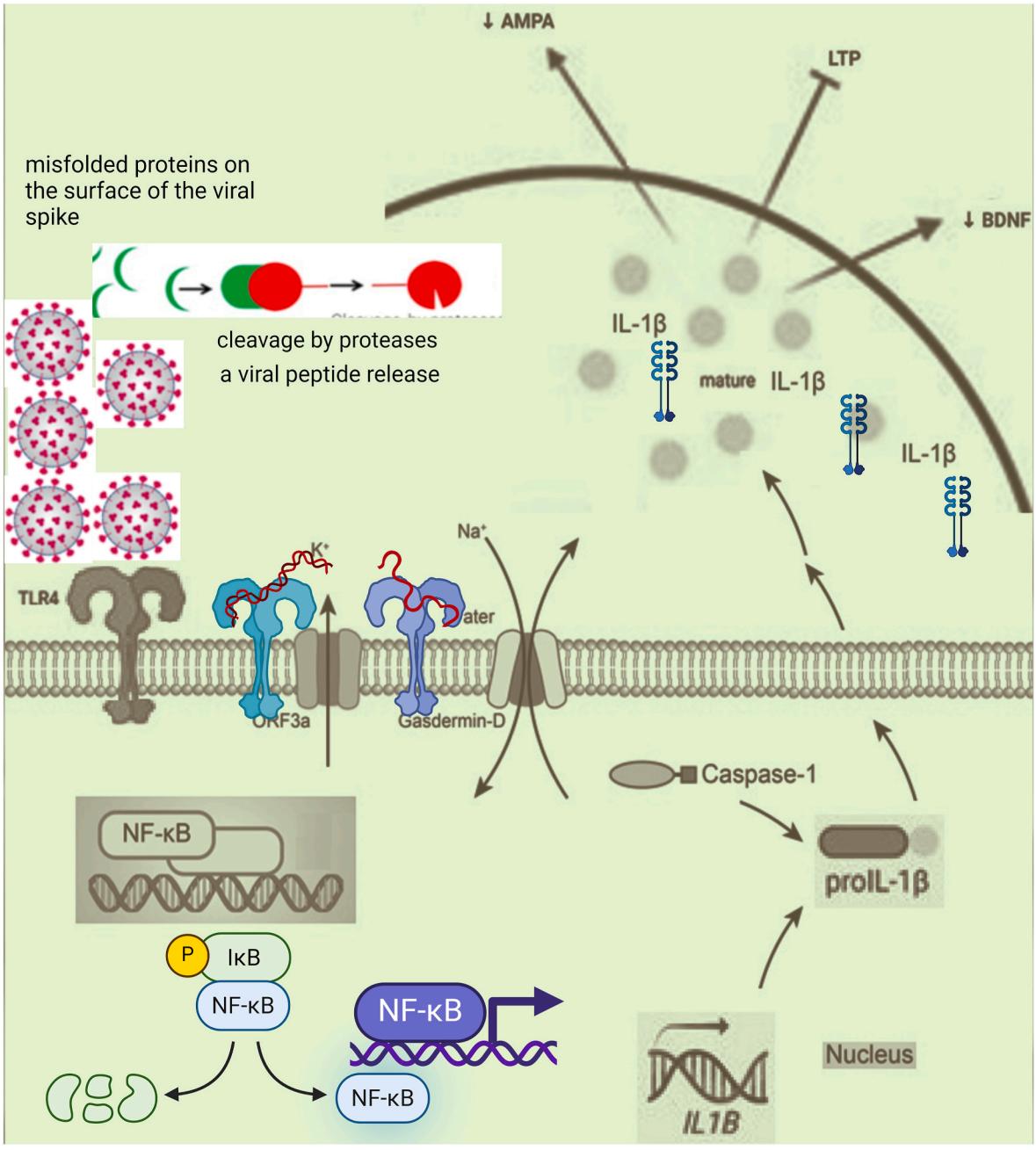

Fig. 1. Mechanism of activation of TLR4.
Peripheral immune insults are known to activate the pattern recognition receptor TLR4. TLR4 leads to the activation of nuclear factor-κB (NF-κB). Ultimately, TLR4 produces immature IL-1β, which is cleaved by caspase-1 and inflammasome components into mature IL-1β. As a result, IL-1β is released into the extracellular fluid. IL-1β elicits multiple effects on synaptic plasticity-related processes, including suppression of BDNF (brain-derived neurotrophic factor) production, reduction of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor membrane expression, and inhibition of LTP (long-term potentiation). IL-1β elicits multiple effects on synaptic plasticity-related processes, including suppression of BDNF production, reduction of AMPA receptor membrane expression, and inhibition of LTP. SARS-CoV-2 also activates TLR4, leading to the activation of NF-κB and ultimately the production of immature IL-1β. The transcriptional activation of NF-κB induces and releases proinflammatory cytokines. The final sequence of NF-κB activation is joined with cytokine receptor- and TLR-mediated signaling cascades. SARS-CoV-2 induces TLR4-mediated and endoplasmic reticulum (ER)-induced NF-κB activation. They play a pivotal role in the neurodegenerative process of misfolded protein disorders.

hematopoietic stem cells (HSCs) activates the NLR family PYRIN domain containing-3 (NLRP3) inflammasome. The exposure of human umbilical cord blood (UCB)-purified VSELs to recombinant SP can lead to the upregulation of NLRP3 mRNA expression [14]. Human VSELs in adult tissues can be damaged by SARS-CoV-2, which has downstream and subsequent effects on tissue/organ regeneration [14]. SARS-CoV-2 activates mitochondrial reactive oxygen species (ROS) production and glycolytic shift. SP alone can damage vascular endothelial cells by downregulating ACE2 and inhibiting mitochondrial function [15]. Compared with other brain regions, SARS-CoV-2 may exhibit tropism to the brainstem, which has relatively high expression of the ACE2 receptor [16].

SARS-CoV-2 increased total cardiac macrophage counts after the intratracheal instillation of TLR ligands and an ACE2, which means viral ARDS promotes cardiac inflammation [17]. Erythroid precursor cells (from CD 34^{+}) differentiate into red blood cell (RBC) precursors and subsequently express ACE2. The SP interacts with RBC precursors, leading to dysregulation of hemoglobin and degradation of Fe-heme [5, 18]. TLR4 is the most abundantly upregulated TLR in human lung tissue irrespective of the underlying pathology. TLR4 blockage prevents exaggerated inflammatory responses in human macrophages infected with different SARS-CoV-2 variants including omicron [19].

The SP has been proposed to have the most substantial protein–protein interaction with TLR4. TLR2 and TLR4 are expressed intracellularly in dendritic, epithelial, and endothelial cells [20,21]. The molecular influence of TLR4 is understood as a prime regulatory factor associated with immunity [22]. TLR4 mediates anti-gram-negative bacterial immune responses by recognizing lipopolysaccharide (LPS) from bacteria [23]. *Staphylococcus aureus* triggers an inflammatory response in innate immune cells via TLR4 and the inflammasome [24]. SARS-CoV-2 infection results in viral sepsis and provokes an antibacterial-like response at the very early stage of infection via TLR4 [25] [Fig. 1].

TLRs are a class of membrane pattern recognition receptors that detect microbes on the cell surface and in the cytoplasm, and a cytokine surge is induced by TLRs, mainly through the activation of TLR3, TLR4, TLR7, and TLR8 [26]. Subunit 1 of the SARS-CoV-2 spike protein (S1) induces sickness behavior and a subacute neuroinflammatory response for approximately 24 h and a chronic neuroinflammatory response for approximately 7 days. Moreover, S1 directly induces a proinflammatory response in primary microglia and activates TLR4 signaling [27]. Neuroinflammation induced by microglia is mediated through the activation of nuclear factor kappa B (NF-κB) and p38 mitogen-activated protein kinase (MAPK) due to TLR2 and TLR4 activation [26–28]. TLR4 has been shown to play a role in mediating the neurotoxicity induced by α-synuclein (α-Syn) oligomers. Misfolded α-Syn induces inflammatory responses; however, α-Syn uptake is independent of TLR4. Furthermore, extracellular α-Syn can activate the proinflammatory TLR4 pathway in astrocytes [29]. The interaction between the SP and TLR4 can trigger an intracellular TLR4 signaling cascade. The NF-κB-mediated transcriptional activation of specific genes induces the release of proinflammatory cytokines, which can damage neurons and pathologically modify α-Syn [30]. The final sequence of NF-κB activation involves a range of cytokine receptor- and TLR-mediated signaling cascades. SARS-CoV-2 induces TLR4-mediated NF-κB activation, and erythroreticulum (ER) stress induces NF-κB activation and the production of immature IL-1β (pro-IL-1β) [31]. SARS-CoV-2 might have direct infectivity beyond ACE2 in the kidney. TLR-4, kidney injury molecule-1/T cell immunoglobulin mucin domain 1 (KIM-1/TIM-1), CD147 are associated with renal damage [32].

Long-COVID, referred to as post-acute sequelae of SARS-CoV-2 infection, may cause direct renal damage by infiltrating inflammatory cells or through the overactivation of the renin-angiotensin-aldosterone (RAAS) system, and the formation of blood clots, which in turn leads to ischemia in the kidneys with subsequent tissue damage [33], and postural orthostatic tachycardia such as palpitations, lightheadedness, fainting, brain fog, and tachycardia without orthostatic hypotension [34]. These damages have relations to the heart macrophage and autonomic nervous system in vascular endothelial cells, RBC precursors, human lung tissue, neuroinflammation, and the RAAS system in the ACE2 or TLR pathway [5,15,17–19,29,30,35].

2.2. The neuropilin-1 pathway

NRP1 is expressed in all vertebrates. NRP1 is the primary coreceptor for ACE2. NRP1 contributes to the primary tissue or organ tropism of SARS-CoV-2. NRP1 and 2 are involved in angiogenesis, axon control, cell proliferation, immune function, neuronal development, and vascular permeability because NRP1 is a coreceptor for vascular endothelial growth factors [36]. NRP1 plays a complex role in the secondary $CD8^{+}$ T-cell response to control VRDs and tumors [37]. A complete understanding of NRP1 or NRP2 and its associated mechanical pathways will facilitate understanding of SARS-CoV-2 infectivity and improve patient treatments. Phenothiazines inhibit binding SP to NRP1, not to ACE2, and potently inhibit SARS-CoV-2 cell entry [38]. Cysteine residues located in the vestigial plasminogen-apple-nematode (PAN) domain of NRP1 directly impact SARS-CoV-2 binding. The mutated PAN domain of NRP1 reduces SP abundance in cells [39]. The cell surface entry of 1) NRP1/Furin-mediated 2) ACE2/TMPRSS2-mediated 3) endodermal entry hijacked by cathepsin L has been observed in various human tissues and organs, thus facilitating viral activation [40]. These viruses contribute to the tropism of SARS-CoV-2 in diverse tissues and organs and its related symptoms and representing the essential host factors for SARS-CoV-2 pathogenicity.

NRP1 is a tissue-specific marker of lung group 2 ILCs (ILC2s) and is induced postnatally and sustained by lung-derived transforming growth factor-β1 (TGFβ1). TGFβ1–NRP1 signaling enhances ILC2s functions and type 2 immunity, suggesting that NRP1 is a tissue-specific regulator of lung-resident ILC2s and that the NRP1 regulator is a potential therapeutic agent for pulmonary fibrosis [41]. ILC2s are involved in virus-induced exacerbation of airway inflammation and are critical in pulmonary fibrosis and autoimmune disease [42,43]. ILC2s and eosinophils play vital roles in pulmonary arterial hypertrophy [44] [Fig. 2].

The genetic susceptibility locus in respiratory failure patients with COVID-19 is located on chromosomes 3p21.31 and 9q34.2 and is related to severity; the 3p21.31 gene cluster can be found on chromosome 3 [45]. According to the protein docking crystal structures, the receptor binding domain (RBD) of the SARS-CoV-2 spike protein has a potentially high affinity for dipeptidyl peptidase-4 (DPP4). The present genetic variants from a Neanderthal heritage plant were located in six genes on chromosome 3p21.31, which is in the proximal promoter region of DPP4 [46]. MDIGs are mainly responsible for the expression of inflammatory cytokines, the critical component of the inflammasome, and most of the genes involved in glycan metabolism for hyaluronan generation and glycosylation. MIDGs are crucial determinants of viral infection and cytokine storms. MDIG is an essential regulator of NRP1 and NRP2. MDIG plays a critical role in preventing SARS-CoV-2 infection and reducing the severity of COVID-19. The MDIG-dependent expression of NRP1 or NRP2 enhances SARS-CoV-2 infection in cells with lower ACE2 expression [47].

Clinically, COVID-19-related acute respiratory distress syndrome (ARDS) is characterized by relatively preserved aeration on chest computed tomography (CT) despite severe respiratory hypoxemia. However, this early, high-compliance phenotype can develop into a low-compliance phenotype with poor aeration as L-type, characterized by low elastance, high compliance, and preserved aeration; and H-type, characterized by high elastance, low compliance, and poor aeration [48]. Patients with cryptococcus-associated immune reconstitution inflammatory syndrome can suffer from pulmonary dysfunction caused by T-cell-driven neurodegeneration in the vital medullary nucleus responsible for respiratory control [49,50]. SARS-CoV-2 targets ciliated cells in the respiratory mucosa, but in the olfactory mucosa, the primary target

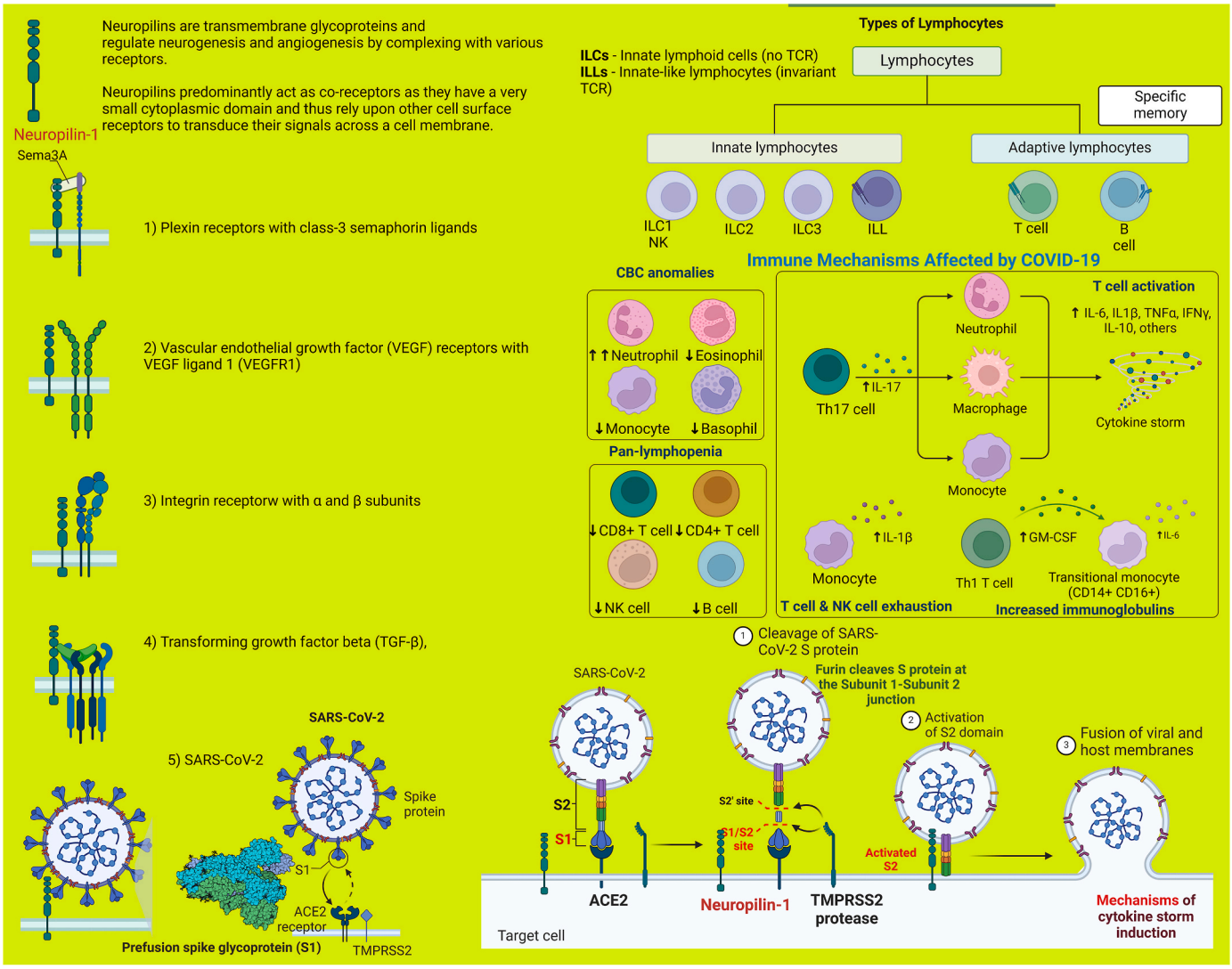

Fig. 2. Association of Neuropilin with SARS-CoV-2.
Neuropilins are transmembrane glycoproteins that regulate neurogenesis and angiogenesis by complexing with various receptors and predominantly act as coreceptors because they have a microscopic cytoplasmic domain. Neuropilins thus rely upon other cell surface receptors, such as ACE2, to transduce signals across the cell membrane, mitochondria and nucleus. Neuropilin 1,2 can be found in soluble forms produced by alternative splicing or ectodomain shedding from the cell surface. The neuropilin complex comprises 1) plexin receptors with class 3 semaphorin ligands, 2) vascular endothelial growth factor (VEGF) receptors with VEGF ligand 1 (VEGFR1), and 3) integrin, a receptor with α and β subunits 4, and transforming growth factor beta (TGF-β). SARS-CoV-2 spike glycoprotein subunit 1 binds to ACE2. In contrast, subunit 2 mediates the fusion of the spike protein with cell membranes via transmembrane protease serine 2 (TMPRSS2). Furin cleaves the spike protein at two subunit 1-subunit junctions, which consist of a sequence of essential amino acids. Subunit 1-Subunit two junction cleavage exposes a carboxyl-terminal motif conforming to the C-end rule motif. This C-end rule motif of subunit 1 can bind to neuropilin-1 via its b1 domain [6]. Innate lymphoid cells (ILCs) include non-T and non-B lymphoid cells in humans. ILCs are divided into three groups based on their distinct cytokine profiles and transcription factor profiles. Neuropilin-1 is a tissue-specific marker of lung group 2 innate lymphoid cells (ILC2s). TGFβ1–neuropilin-1 signaling enhances ILC2 function and type 2 immunity, which identifies neuropilin-1 as a tissue-specific regulator of lung-resident ILC2s and features a neuropilin-1 regulator as a potential therapeutic for pulmonary fibrosis.

is nonneuronal sustentacular cells. NRP1 is expressed in olfactory-related neuronal regions [51,52]. The recognized pathways involve transsynaptic transfer via peripheral, olfactory, or cranial nerves and blood–brain barrier (BBB) penetration from the systemic circulation to invade the brainstem [16,53,54]. The recognized pathways invade the brainstem and involve transsynaptic transfer via peripheral, olfactory, or cranial nerves. The paralysis of the pre-Bötzinger complex on the medullar oblongata in the brainstem might affect L-type ARDS and COVID-19-associated fatality [55]. NRP-1 might induce the tropism of SARS-CoV-2 in the brainstem [16,55,56] [Fig. 3].

NRP1 is highly expressed in pancreatic tissue and its overexpression is linked with developing acute pancreatitis by activating release of proinflammatory cytokines [57,58]. ACE2 and NRP1 is highly expressed in brain parenchymal cells include microglia, astrocytes, neurons and oligodendrocytes as well as cerebral lymphocytes [16,51,52,59]. Viral affinity for DPP4 and ILC2s-based effects affect to COVID-19-related central nervous system (CNS). Their changes are mediated by MDIG as a regulator of NRP1 or NRP2 in brain parenchymal cells, including microglia, astrocytes, neurons and oligodendrocytes as well as cerebral lymphocytes [47]. Neuro-cognitive-post-acute sequelae of COVID-19 are brain fog, dizziness, loss of attention, and confusion. Pulmonary symptoms are general fatigue, dyspnea, cough, throat pain and cardiovascular symptoms are chest pain, tachycardia, palpitations [59]. Viral affinity for DPP4, MDIG, and ILC2s explain to neuro-cognitive-pulmonary-cardiovascular post-acute sequelae.

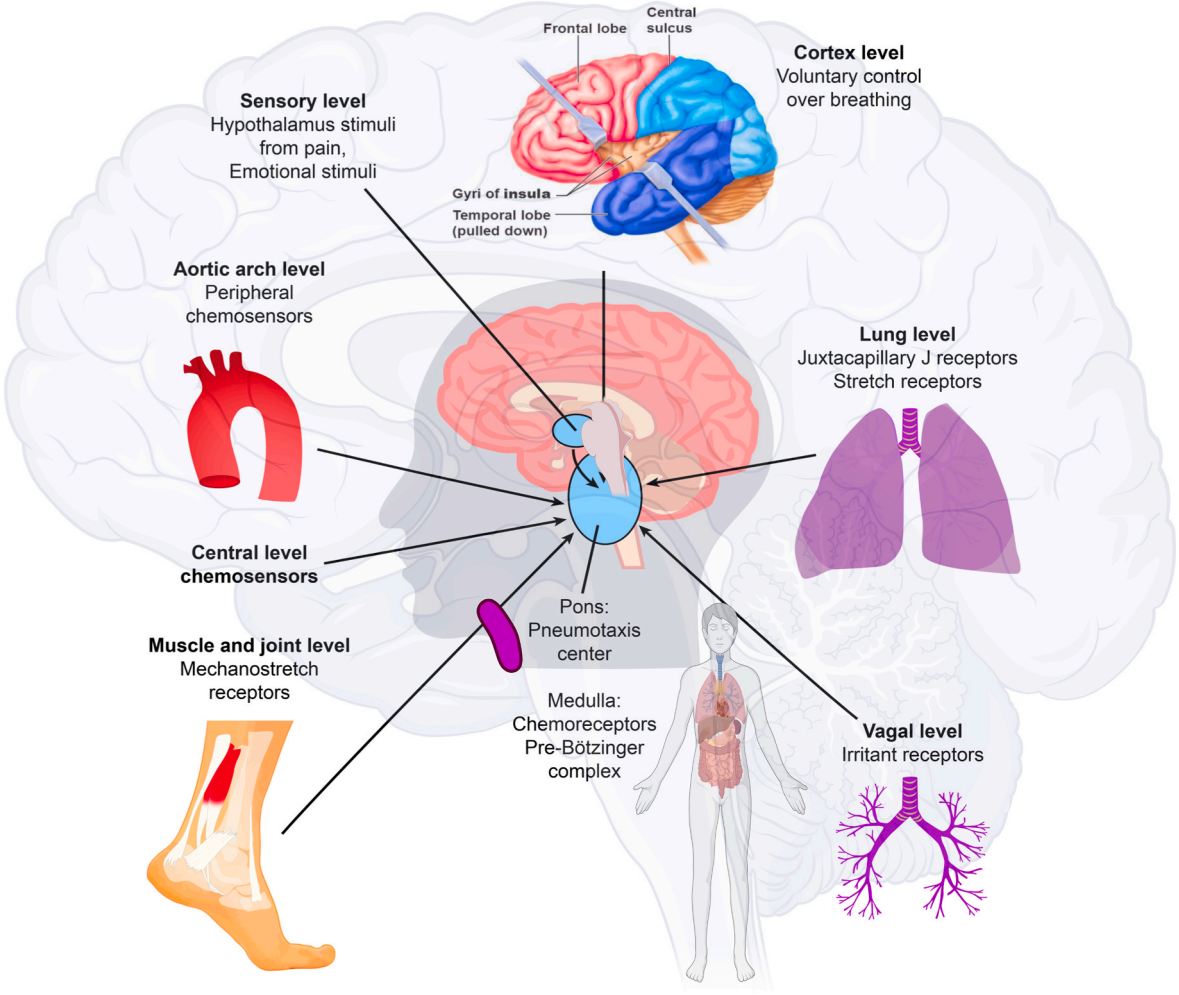

Fig. 3. Respiratory muscles during healthy breathing.
Respiratory muscles cannot be intentionally activated during healthy breathing. Human sensory stimuli and abnormal muscular sensations affect breathing via the cerebral cortex and hypothalamus. ACE2 is localized to the cytoplasm, and its expression can be highly regulated by other RAAS components in the nucleus tractus solitarius/dorsal motor nucleus on the vagus and ventrolateral medulla. SARS-CoV-2 may exhibit tropism because the brainstem has relatively high expression levels of the ACE2 receptor compared with other brain regions. Neuropilin-1 is a coreceptor that facilitates SARS-CoV-2 infection in ACE2 and is expressed in the brainstem. The recognized pathways involve transsynaptic transfer via peripheral, olfactory, or cranial nerves and BBB penetration from the systemic circulation to affect the brainstem. SARS-CoV-2 may exhibit tropism to the brainstem, which has relatively high expression of the ACE2 receptor.

2.3. Spike protein pathway

Glycoproteins derived from SARS-CoV-1, SACR-Co-V-2, human cytomegalovirus, and hepatitis C virus potentially trigger NLRP3 activation and pyroptosis in a spontaneously immortalized monocyte-like cell line (THP-1) macrophages [60,61]. The SP binding to ACE2 induces NF-κB activation and inflammation via ACE2 in endothelial cells [62]. The furin cleavage product of SP uses the vascular endothelial growth factor A (VEGF-A) binding site on NRP-1 as an entry point [63]. Moreover, the RBD of SP induced up-regulated expression of inflammatory indicators and activated the release of induced cytokines, like IL-6 and IL-8, in human bronchial epithelia [64]. The S1 activated the NF-κB and c-JNK signaling pathways [65].

The SP is a PAMP that requires macrophage preactivation for NLRP3 formation, and vigorous SP-driven inflammasome activity releases IL-1β in the convalescent macrophages of COVID-19 patients [66]. Furthermore, SP interacts with and activates TLR4 [25]. After SARS-CoV-2 infection, the augmented immunogenicity of the SP results from macrophage reprogramming. The SP-driven IL-1β secretion in macrophages requires nonspecific monocyte preactivation in vivo. Then, macrophages trigger NLRP3 signaling [66]. Moreover, the SP signals through TLR2 and activates NLRP3 in human macrophages from convalescent patients with COVID-19 but not from healthy SARS-CoV-2–naïve individuals [66]. The SP drives inflammasome activation in macrophages from convalescent COVID-19 patients, correlating with distinct epigenetic and gene expression signatures. SARS-CoV-2 infection causes profound and long-lived reprogramming of macrophages. This results in augmented immunogenicity of the SP, an effective vaccine antigen [66].

Lipid nanoparticles of the formulated nucleoside-modified mRNAs of SPs are stabilized in their prefusion conformation. They induce an immune reaction involving IL-2^{+} CD8^{+} and CD4^{+} T helper type 1 cells or IFNγ+ cells [67]. Lipid nanoparticles encode the prefusion conformation of SP. General adverse reactions include pain, swelling, redness, muscle pain, headache, fever, and chills after vaccination. Adverse events of special interest (AESI) included anaphylaxis, life-threatening disease, permanent disability/sequelae, and death. The overall seroprevalence of Korean anti-SARS-CoV-2 was very low on September 6, 2021, but the incidence of AESI was very high, as was the case in England during the pandemic. We compared AESI after vaccination in England and South Korea. These findings suggested that AESI might originate from immune reactions induced by lipid nanoparticles, including the SARS-CoV-2 SP,

in mRNA vaccines [66–69]. Various side effects caused by the vaccine's SP appear in a real-time setting. The SP has a unique pathological mechanism: there are strange similarities with amyloid disease-associated blood coagulation and fibrinolytic disturbances together with neurologic and cardiac problems [70]. As a result, rare hypersensitivity reactions to mRNA-based SARS-CoV-2 vaccines develop, such as anaphylaxis, chest pain, chills, flushing, hypertension, and tachycardia [68,71]. Specifically, myocarditis develops rapidly in younger patients. It occurred mainly after the second vaccination. However, pericarditis, which occurs after receiving mRNA vaccines, affects older people after the first or second vaccination [72] [Fig. 4].

SARS-CoV-2 infection can lead to syncytium formation within cells. The syncytia express ACE2 and SP, which produce approximately four micronuclei per syncytium. Remarkably, these micronuclei are highly expressed during the DNA damage response or during cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) (cGAS–STING) signaling, which is associated with cellular devastation and poor immune reactions [73,74]. The SP upregulates senescence-associated inflammatory factors and the expression of senescence-associated cytokines in zebrafish retina in vivo likely by activating ER stress, ROS, and NF-κb [75]. SP induces lung cancer migration invasion via TLR2-dependent activation of NF-κB [76].

Like other RNA viruses, SARS-CoV-2 undergoes genetic evolution and develops mutations over time, resulting in the emergence of multiple variants that may have different characteristics than their ancestral strains [77,78]. SARS-CoV-2 variants of interest (VOI) undergoes genetic evolution and shows differential proinflammatory effects [79]. The wild-type/Wuhan variant S1 is highly proinflammatory in zebrafish, but the SP of the VOI shows differential proinflammatory effects [79]. RBDs in VOI showed lower thermodynamic stability with higher kinetic fluctuations. The exposure of low/moderate E-field reduced the binding of the SP to the ACE2 [80].

The SP can prime the NLRP3 and enhance caspase-1 activity through NF-κB signaling. S1 interacts with amyloid-β, prion protein, α-Syn, and tau. SP contains several prionogenic domains and triggers a neurodegenerative condition known as prion-disease-like pathology, such as the worsening of demyelinating diseases, Guillain–Barré syndrome, immune thrombotic thrombocytopenia, amyotrophic lateral sclerosis (ALS), Parkinson's disease, AD and stroke [69,81–85].

The hyperinflammatory state by SP and diverse VOI triggers CNS neuroinflammation.

3. Discussion for management

Among the COVID-19-positive veterans who were in the Armed Forces, a previous aspirin prescription was clinically significantly associated with a decrease in overall mortality at 14 days (OR, 0.38) and 30 days (OR, 0.38). Dexamethasone administered at a cumulative dose between 60 and 150 mg was associated with reduced mortality only in patients requiring respiratory support. In COVID-19 and other ARDS cases, a high neutrophil-to-lymphocyte ratio (NLR) is associated with increased myeloid-derived suppressor cells (MDSCs). Dapsone treatment was associated with a lower NLR in the ICU. At least 20% of individuals with an HLA-B*15:01 status are asymptomatic. The weak binding affinity of HLA polymorphisms might contribute to SARS-CoV-2 Omicron's immune evasion. Dapsone hypersensitivity is susceptible to the expression of HLA-B*13:01. It relates the treatment asymptomatic with an HLA-B*15:01 status. Anticatalysis might be used as an asymptomatic

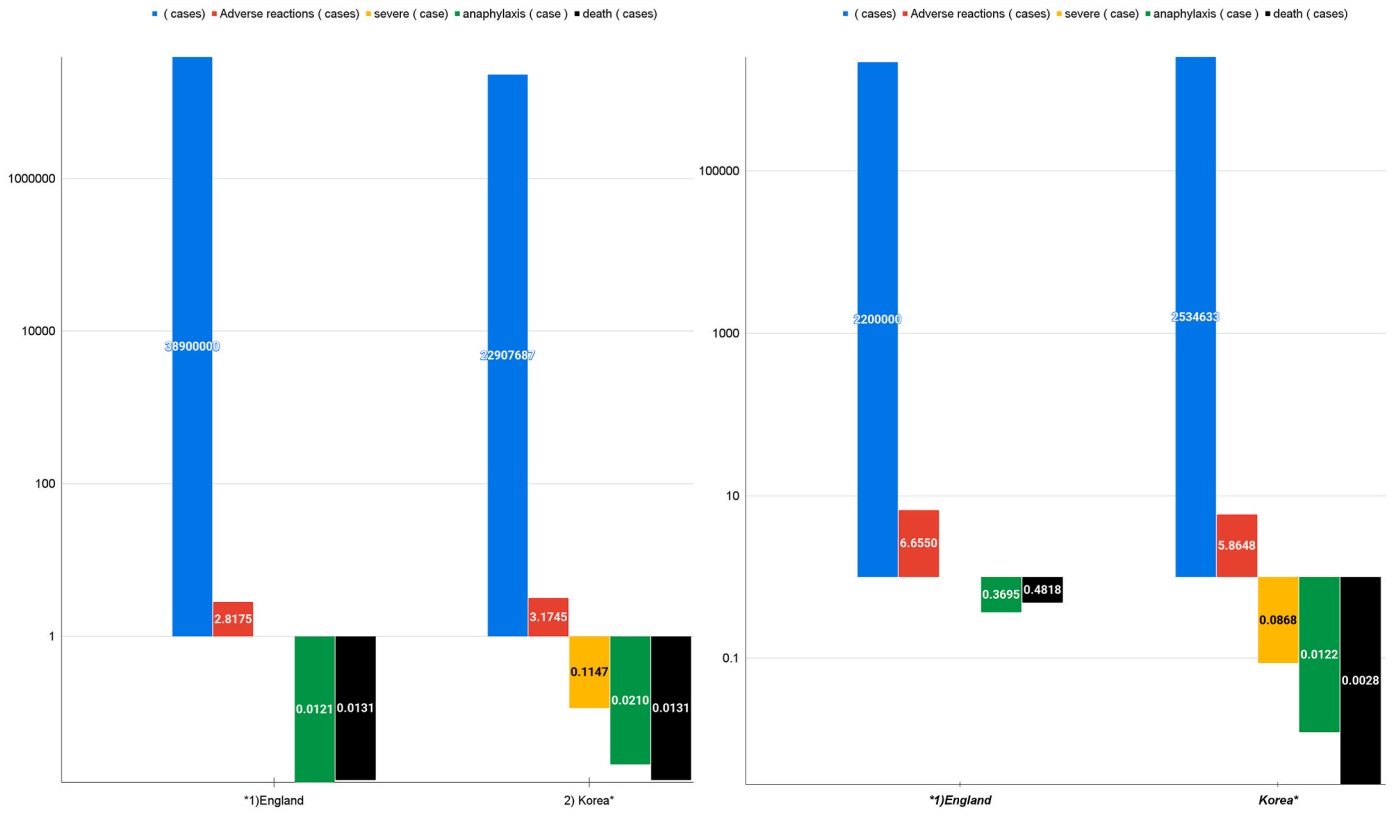

Fig. 4. Comparison of adverse events of special interest (AESI) after vaccination in England and South Korea.
In the graph, the X-axis represents England and South Korea, and the Y-axis represents adverse reaction cases, severe cases, anaphylaxis cases, and deaths as crude rates. The overall seroprevalence of anti-SARS-CoV-2 was very low on September 6, 2021, in South Korea. Nevertheless, the incidence of adverse events of special interest (AESI) was very high in England according to the summary of yellow card reporting by the Medicines & Healthcare Products Regulatory Agency (MHRA) at approximately the same time [68]. The spike protein of SARS-CoV-2 can induce AESI [62].*1) In the case of the UK, both anaphylaxis and anaphylaxis-like reactions are included. * It is not intended to suggest a causal relationship between an adverse reaction. Vaccination Response Promotion Team of Korea CDC, '21.9.6.

treatment for COVID-19, as in asymptomatic individuals carrying HLA-B*15:01. We explored immune strategies for preventing long COVID-related exacerbation of pathophysiology [68] [Table 1].

4. Conclusion

SARS-CoV-2 start to exacerbate COVID-19 via three pathways: ACE2-TLRs, NRPs, and SP. The first-line anti-catalytic triad needs to prevent and block pathological processes, mutations, and deterioration.

Method

Two years ago, we reviewed 500 SCI journals and analyzed the SARS-CoV-2 penetration route. And now, two years later, we have found they were three pathways. Inclusion criteria. Through information search, key words were connected based on the research results. The order is as follows: 1) the ACE2 and TLR, 2) the NRP, and 3) the spike protein. Exclusion criteria: If experimental data was not repeated at SCI journals, those were excluded [100].

CRediT author statement

Jong hoon Lee: Conceptualisation, Methodology, Software, Data curation, Visualization, Investigation, Writing- Original draft preparation. Consolato Sergi: Data curation, Writing- Reviewing and Editing. Richard E. Kast: Investigation, Writing- Reviewing and Editing. Badar A. Kanwar: Investigation,Writing- Reviewing and Editing. Jean Bourbeau: Writing- Reviewing and Editing. Sangsuk Oh: Investigation, Writing-Reviewing and Editing. Mun-Gi Sohn: Investigation, Chul Joong Lee: Writing- Reviewing and Editing, Michael D. Coleman: Supervision, Writing- Reviewing and Editing.

Ethical approval

The National Agency approved this study for the Management of Life-sustaining Treatment, which certified that life-sustaining treatments were managed properly (Korea National Institute for Bioethics Policy (KoNIBP) approval number P01-202007-22-006).

Consent to publish

The authors affirm that the human research participants provided informed consent for the publication of the manuscript results.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations:

A549 cell	A549 cells are adenocarcinomic human alveolar basal epithelial cells, and constitute a cell line.
ACE	Angiotensin-converting enzyme
AD	Alzheimer's disease
AESI	Adverse events of special interest
AIDS	Acquired Immune Deficiency Syndrome
AGS	Aicardi–Goutières syndrome
AIM2	Absent in melanoma 2
ALI	Air–liquid interface
ALP	Alkaline phosphatase
α-Syn	α-synuclein
AMI	Acute myocardial infarction
AMI I/R injury	AMI ischemia–reperfusion injury
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid

(*continued on next page*)

Table 1
The exacerbations of COVID-19 and their treatment modes of immune triad [68].

	Acetylation, cGAS-STING axis	Neutrophil, IFN pathways	NETs[a]	Inflammasome	ILCs[d] Cytokine	Results	Ref.
COVID-19	IFN^{active} (↑)	IFN^{active} (↑)	cell-free DNA, MPO[b]-DNA complexes (↑)	NLRP3 (↑)	$CD8^+$ T cells (↑)		[86,87]
Aspirin	IFN^{active} ([e]↓)				ILC2s (nasal mucosa↑, blood↓)	Mortality (↓)	[88,89]
Dapsone	IFN^{active} (↓)	IFN^{active} (↓)	MPO-DNA NETs (↓)	NLRP3[c] (↓)	ILCs (↓)	Mortality (↓) NLR ratio (↓) Exacerbation (↓)	[68,88, 90–96]
Dexamethasone		IFN^{active} (↓)	immature neutrophils ([f]↑)		blood ILC2s (↓)	Mortality (↓) NLR ratio (↓)	[97–99]

[a] Neutrophil extracellular traps.
[b] Myeloperoxidase.
[c] NLR family pyrin domain-containing 3 (previously known as NACHT, LRR, and PYD domain-containing protein 3 [NALP3] and cryopyrin).
[d] Innate lymphoid cells.
[e] Decreased.
[f] Increased.

(*continued*)

APC	Antigen-presenting cells
ARDS	Acute respiratory distress syndrome
ASC	Apoptosis-associated speck-like protein containing a CARD
ATF4	Activated parkin via protein kinase RNA-like endoplasmic reticulum kinase-activating transcription factor 4
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
BiPAP	Bilevel positive airway pressure
BV-2	A type of microglial cell derived from C57/BL6 mice
CAPS	Cryopyrin-associated periodic syndromes
CARD	Caspase activation and recruitment domain
CCNE2	Essential for the control of the cell cycle at the late G1 and early S phases; belongs to the cyclin family
CCR5	C–C motif chemokine receptor 5
CH	Clonal hematopoiesis, hematopoietic stem and progenitor cells
CDK1	Cyclin-dependent kinase 1
CI	Confidence interval
CK-MB	Creatine kinase-MB fraction
COPD	Chronic obstructive pulmonary disease
COX-1	Cyclooxygenase 1
CRP	C-reactive protein
CRS	Cytokine release syndrome
CtIP	C-terminal binding protein 1 (CtBP1) interacting protein
Cyclin-A2	A protein that in humans is encoded by the CCNA2 gene. It is one of the two types of cyclin A: cyclin A1 is expressed during meiosis and embryogenesis while cyclin A2 is expressed in the mitotic division of somatic cells.
Cyclin D1	A protein required for progression through the G1 phase of the cell cycle
Cyclin D3	A cofactor of retinoic acid receptors, modulating their activity in the presence of cellular retinoic acid-binding protein II
Cyclin E2	Cyclin E2 is a protein that in humans is encoded by the CCNE2 gene
Cyclin-G1	A protein that in humans is encoded by the CCNG1 gene
CXCR-4	C-X-C chemokine receptor type 4
DDS	4,4′-Diaminodiphenyl sulfone (dapsone)
DPP4	Dipeptidyl peptidase-4
DIC	Disseminated intravascular coagulation
ECG	Electrocardiogram
ER	Endoplasmic reticulum
cGAMP	2′,3′-cyclic GMP-AMT
cGAS–STING	cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING)
G6PDH	Glucose-6-phosphate dehydrogenase
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1
HSPC	hematopoietic stem/progenitor cell
ICU	Intensive care unit
IFN	Interferon
IFNAR2	Interferon-alpha and beta receptor subunit 2
IL	Interleukin
IL-1β	Interleukin-1 beta
IMV	intensive mechanical ventilation
IRF3	Interferon regulatory factor 3
JNK	Jun N-terminal kinases
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LL	Lepromatous leprosy
LPS	Lipopolysaccharide
LTP	Long-term potentiation
M receptor	Muscarinic receptor
MADDS	Monoacetyldapsone
MAPK	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
MDIG	Mineral dust-induced gene
MHC	Major histocompatibility complex
MIS-C/A	Multisystem inflammation syndrome in children and adults
MPO	Myeloperoxidase
N receptor	Nicotinic receptor
NAIP	A family of NLRs with seven paralogs in mice (NAIP1–7)
NOD2	Nucleotide-binding oligomerization domain containing 2
N protein	Nucleocapsid protein
MDA5	melanoma differentiation-associated gene 5
mRNA	Messenger RNA
mtDNA	Mitochondrial DNA
NACHT	Domain conserved in NAIP, CIITA, HET-E, and TP1
NFL	Neurofilament light chain
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLRC4	NLR Family CARD Domain Containing 4
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3 NLR family pyrin domain-containing 3
NRP	Neuropilin
PAI-1	Plasminogen activator inhibitor-1

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PAMPs	Pathogen-associated molecular patterns
PBMCs	Human peripheral blood mononuclear cells
PD	Parkinson's disease
PEDF	Pigment epithelium-derived factor
PEDFR/iPLA2	PEDF/calcium-independent phospholipase A2
Phosphomimetics	Amino acid substitutions that mimic a phosphorylated protein.
Phospho-p65	Anti-phospho-NFkB p65 (Ser536) monoclonal antibody (T.849.2)
Phospho-IκBα	Phospho-IκBα (Ser32/36) (5A5) mouse mAb #9246
PRMT5	Protein arginine methyltransferase 5
PTGS2	Prostaglandin synthase 2
PTM	Multiple posttranslational modification
RIG-I	Retinoic acid-inducible gene I
ROS	Reactive oxygen species
SP	Spike glycoprotein of SARS-CoV-2
S1	SARS-CoV-2 spike protein subunit 1
SAMHD1	Sterile alpha motif (SAM) and histidine-aspartate domain (HD)-containing protein
SCLS	Systemic capillary leak syndrome
RCT	Randomized controlled trial
SOD	Superoxide dismutase
TBK1	Tank-binding kinase 1
TGFβ	Transforming growth factor-β
Th	T helper type
THP-1	A spontaneously immortalized monocyte-like cell line
TNF	Tumor necrosis factor
TLR	Toll-like receptor
TMPRSS2	Transmembrane protease serine subtype 2
TRIF	TLR3-TIR-domain-containing adapter-inducing interferon-β
TTS	Thrombosis with thrombocytopenia syndrome
TREX1	Tthree-prime repair exonuclease 1
TYK2	Tyrosine kinase 2
UCB	Umbilical cord blood
VRD	Viral respiratory disease
VSEL	Very small embryonic-like stem cell

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bj.2024.100766.

References

[1] Hautecloque G, Kempf C, Stan C, Arentz-Dugay MH, Vuillemet F, Ahle G, et al. Multifocal and microvascular involvement in ischemic stroke during COVID-19: a cohort study with comparison with non-COVID-19 stroke. Front Neurol 2021;12:732194.

[2] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med 2021;27(4):601–15.

[3] Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect 2020;53(3):425–35.

[4] Duan T, Xing C, Chu J, Deng X, Du Y, Liu X, et al. ACE2-dependent and -independent SARS-CoV-2 entries dictate viral replication and inflammatory response during infection. Nat Cell Biol 2024;26(4):628–44.

[5] Kucia M, Ratajczak J, Bujko K, Adamiak M, Ciechanowicz A, Chumak V. et al.An evidence that SARS-Cov-2/COVID-19 spike protein (SP) damages hematopoietic stem/progenitor cells in the mechanism of pyroptosis in Nlrp3 inflammasome-dependent manner. Leukemia 2021;35(10):3026–9.

[6] Daly JL, Simonetti B, Klein K, Chen KE, Williamson MK, Antón-Plágaro C, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science 2020;370(6518):861–5.

[7] Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science 2020;370(6518):856–60.

[8] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–80. e278.

[9] Mollica V, Rizzo A, Massari F. The pivotal role of TMPRSS2 in coronavirus disease 2019 and prostate cancer. Future Oncol 2020;16(27):2029–33.

[10] Örd M, Faustova I, Loog M. The sequence at Spike S1/S2 site enables cleavage by furin and phospho-regulation in SARS-CoV2 but not in SARS-CoV1 or MERS-CoV. Sci Rep 2020;10(1):16944.

[11] Kumar S, Kumar P, Kodidela S, Duhart B, Cernasev A. Nookala A,et al. Racial health disparity and COVID-19. J Neuroimmune Pharmacol 2021;16(4):729–42.

[12] Shirvaliloo M. The unfavorable clinical outcome of COVID-19 in smokers is mediated by H3K4me3, H3K9me3 and H3K27me3 histone marks. Epigenomics 2022;14(3):153–62.

[13] Chlamydas S, Papavassiliou AG, Piperi C. Epigenetic mechanisms regulating COVID-19 infection. Epigenetics 2021;16(3):263–70.

[14] Ratajczak MZ, Bujko K, Ciechanowicz A, Sielatycka K, Cymer M, Marlicz W, et al. SARS-CoV-2 entry receptor ACE2 is expressed on very small CD45− precursors of hematopoietic and endothelial cells and in response to virus spike protein activates the Nlrp3 inflammasome. Stem Cell Reviews and Reports 2021;17(1):266–77.

[15] Lei Y, Zhang J, Schiavon CR, He M, Chen L, Shen H, et al. SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. Circ Res 2021;128(9):1323–6.

[16] Yong SJ. Persistent brainstem dysfunction in long-COVID: a hypothesis. ACS Chem Neurosci 2021;12(4):573–80.

[17] Grune J, Bajpai G, Ocak PT, Kaufmann E, Mentkowksi K, Pabel S, et al. Virus-induced acute respiratory distress syndrome causes cardiomyopathy through eliciting inflammatory responses in the heart. Circulation 2024;150(1):49–61.

[18] Kronstein-Wiedemann R, Stadtmüller M, Traikov S, Georgi M, Teichert M, Yosef H, et al. SARS-CoV-2 infects red blood cell progenitors and dysregulates hemoglobin and iron metabolism. Stem Cell Reviews and Reports 2022;18(5):1809–21.

[19] Sahanic S, Hilbe R, Dünser C, Tymoszuk P, Löffler-Ragg J. Rieder D,et al. SARS-CoV-2 activates the TLR4/MyD88 pathway in human macrophages: a possible correlation with strong pro-inflammatory responses in severe COVID-19. Heliyon 2023;9(11):e21893.

[20] Choudhury A, Mukherjee S. In silico studies on the comparative characterization of the interactions of SARS-CoV-2 spike glycoprotein with ACE-2 receptor homologs and human TLRs. J Med Virol 2020;92(10):2105–13.

[21] Choudhury A, Das NC, Patra R, Mukherjee S. In silico analyses on the comparative sensing of SARS-CoV-2 mRNA by the intracellular TLRs of humans. J Med Virol 2021;93(4):2476–86.

[22] Patra R, Chandra Das N, Mukherjee S. Targeting human TLRs to combat COVID-19: a solution? J Med Virol 2021;93(2):615–7.

[23] Poltorak A, He X, Smirnova I, Liu MY, Huffel CV, Du X, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 1998;282(5396):2085–8.

[24] Gonzalez JJI, Hossain MF, Neef J, Zwack EE, Tsai CM, Raafat D, et al. TLR4 sensing of IsdB of *Staphylococcus aureus* induces a proinflammatory cytokine response via the NLRP3-caspase-1 inflammasome cascade. mBio 2023;15(1):e0022523.

[25] Zhao Y, Kuang M, Li J, Zhu L, Jia Z, Guo X, et al. SARS-CoV-2 spike protein interacts with and activates TLR41. Cell Res 2021;31(7):818–20.
[26] Manik M, Singh RK. Role of toll-like receptors in modulation of cytokine storm signaling in SARS-CoV-2-induced COVID-19. J Med Virol 2022;94(3):869–77.
[27] Frank MG, Nguyen KH, Ball JB, Hopkins S, Kelley T. Baratta MV,et al.SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: evidence of PAMP-like properties. Brain Behav Immun 2022;100: 267–77.
[28] Olajide OA, Iwuanyanwu VU, Adegbola OD, Al-Hindawi AA. SARS-CoV-2 spike glycoprotein S1 induces neuroinflammation in BV-2 microglia. Mol Neurobiol 2022;59(1)::445–58.
[29] Rannikko EH, Weber SS, Kahle PJ. Exogenous α-synuclein induces toll-like receptor 4 dependent inflammatory responses in astrocytes. BMC Neurosci 2015; 16:57.
[30] Conte C. Possible link between SARS-CoV-2 infection and Parkinson's disease: the role of toll-like receptor 4. Int J Mol Sci 2021;22(13):7135.
[31] Zeberg H, Pääbo S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature 2020;587(7835):610–2.
[32] Habeichi NJ, Amin G, Lakkis B, Kataya R, Mericskay M, Booz GW, et al. Potential alternative receptors for SARS-CoV-2-induced kidney damage: TLR-4, KIM-1/ TIM-1, and CD147. FBL 2024;29(1):8.
[33] Yende S, Parikh CR. Long COVID and kidney disease. Nat Rev Nephrol 2021;17 (12):792–3.
[34] Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol 2009;20(3):352–8.
[35] Chadda KR, Blakey EE, Huang CL, Jeevaratnam K. Long COVID-19 and postural orthostatic tachycardia syndrome- is dysautonomia to Be blamed? Front Cardiovasc Med 2022;9:860198.
[36] Kyrou I, Randeva HS, Spandidos DA, Karteris E. Not only ACE2—the quest for additional host cell mediators of SARS-CoV-2 infection: neuropilin-1 (NRP1) as a novel SARS-CoV-2 host cell entry mediator implicated in COVID-19. Signal Transduct Targeted Ther 2021;6(1):21.
[37] Hwang JY, Sun Y, Carroll CR, Usherwood EJ. Neuropilin-1 regulates the secondary CD8 T cell response to virus infection. mSphere 2019;4(3):e00221-19.
[38] Hashizume M, Takashima A, Ono C, Okamoto T, Iwasaki M. Phenothiazines inhibit SARS-CoV-2 cell entry via a blockade of spike protein binding to neuropilin-1. Antivir Res 2023;209:105481.
[39] Pal D, De K, Yates TB, Kolape J, Muchero W. Mutating novel interaction sites in NRP1 reduces SARS-CoV-2 spike protein internalization. iScience 2023;26(4): 106274.
[40] Naidu AS, Wang CK, Rao P, Mancini F, Clemens RA, Wirakartakusumah A, et al. Precision nutrition to reset virus-induced human metabolic reprogramming and dysregulation (HMRD) in long-COVID. npj Science of Food 2024;8(1):19.
[41] Zhang J, Qiu J, Zhou W, Cao J, Hu X, Mi W, et al. Neuropilin-1 mediates lung tissue-specific control of ILC2 function in type 2 immunity. Nat Immunol 2022;23 (2):237–50.
[42] Clottu AS, Humbel M, Fluder N, Karampetsou MP, Comte D. Innate lymphoid cells in autoimmune diseases. Front Immunol 2021;12:789788.
[43] Spits H, Mjösberg J. Heterogeneity of type 2 innate lymphoid cells. Nat Rev Immunol 2022;22(11):701–12.
[44] Ikutani M, Tsuneyama K, Kawaguchi M, Fukuoka J, Kudo F, Nakae S, et al. Prolonged activation of IL-5–producing ILC2 causes pulmonary arterial hypertrophy. JCI Insight 2017;2(7):e90721.
[45] Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Severe Covid-19 GWAS Group. et al.Genomewide association study of severe Covid-19 with respiratory failure. N Engl J Med 2020;383(16):1522–34.
[46] Li Y, Zhang Z, Yang L, Lian X, Xie Y, Li S, et al. The MERS-CoV receptor DPP4 as a candidate binding target of the SARS-CoV-2 spike. iScience 2020;23(6):101160.
[47] Zhang Q, Wadgaonkar P, Xu L, Thakur C, Fu Y. Bi Z,et al. Environmentally-induced *mdig* contributes to the severity of COVID-19 through fostering expression of SARS-CoV-2 receptor NRPs and glycan metabolism. Theranostics 2021;11(16):7970–83.
[48] Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323(22):2329–30.
[49] Kawano T, Zhou J, Anwar S, Salah H, Dayal AH, Ishikawa Y, et al. T cell infiltration into the brain triggers pulmonary dysfunction in murine Cryptococcus-associated IRIS. Nat Commun 2023;14(1):3831.
[50] Dangarembizi R, Drummond R. Immune-related neurodegeneration in the midbrain causes pulmonary dysfunction in murine cryptococcal IRIS. Trends Neurosci 2023;46(12):1003–4.
[51] Davies J, Randeva H, Chatha K, Hall M, Spandidos D, Karteris E, et al. Neuropilin1 as a new potential SARSCoV2 infection mediator implicated in the neurologic features and central nervous system involvement of COVID19. Mol Med Rep 2020;22(5):4221–6.
[52] Khan M, Yoo SJ, Clijsters M, Backaert W, Vanstapel A, Speleman K, et al. Visualizing in deceased COVID-19 patients how SARS-CoV-2 attacks the respiratory and olfactory mucosae but spares the olfactory bulb. Cell 2021;184 (24):5932–49. e15.
[53] Lucchese G, Vogelgesang A, Boesl F, Raafat D, Holtfreter S, Bröker BM, et al. Anti-neuronal antibodies against brainstem antigens are associated with COVID-19. EBioMedicine 2022;83:104211.
[54] Lee JH, Kanwar B, Khattak A, Balentine J, Nguyen NH, Kast RE, et al. COVID-19 molecular pathophysiology: acetylation of repurposing drugs. Int J Mol Sci 2022; 23(21):13260.
[55] Kanwar B, Lee CJ, Lee JH. Specific treatment exists for SARS-CoV-2 ARDS. Vaccines 2021;9(6):635.
[56] Ferren M, Favède V, Decimo D, Iampietro M, Lieberman NAP, Weickert JL, et al. Hamster organotypic modeling of SARS-CoV-2 lung and brainstem infection. Nat Commun 2021;12(1):5809.
[57] Wen E, Xin G, Li S, Dong Y, Zhu Y, Wan C, et al. Tuftsin ameliorates splenic inflammatory injury by promoting neuropilin-1 in severe acute pancreatitis. Biochem Pharmacol 2022;199:115030.
[58] Deng W, Bao L, Song Z, Zhang L, Yu P, Xu Y, et al. Infection with SARS-CoV-2 can cause pancreatic impairment. Signal Transduct Targeted Ther 2024;9(1):98.
[59] Meinhardt J, Streit S, Dittmayer C, Manitius Rv, Radbruch H, Heppner FL. The neurobiology of SARS-CoV-2 infection. Nat Rev Neurosci 2024;25(1):30–42.
[60] Eisfeld HS, Simonis A, Winter S, Chhen J, Ströh LJ, Krey T, et al. Viral glycoproteins induce NLRP3 inflammasome activation and pyroptosis in macrophages. Viruses 2021;13(10):2076.
[61] Sergi CM, Chiu B. Targeting NLRP3 inflammasome in an animal model for coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). J Med Virol 2021;93(2):669–70.
[62] Montezano AC, Camargo LL, Mary S, Neves KB, Rios FJ, Stein R, et al. SARS-CoV-2 spike protein induces endothelial inflammation via ACE2 independently of viral replication. Sci Rep 2023;13(1):14086.
[63] Perez-Miller S, Patek M, Moutal A, Duran P, Cabel CR, Thorne CA, et al. Novel compounds targeting neuropilin receptor 1 with potential to interfere with SARS-CoV-2 virus entry. ACS Chem Neurosci 2021;12(8):1299–312.
[64] Zhang RG, Liu XJ, Guo YL, Chen CL. SARS-CoV-2 spike protein receptor binding domain promotes IL-6 and IL-8 release via ATP/P2Y2 and ERK1/2 signaling pathways in human bronchial epithelia. Mol Immunol 2024;167:53–61.
[65] Shirato K, Kizaki T. SARS-CoV-2 spike protein S1 subunit induces pro-inflammatory responses via toll-like receptor 4 signaling in murine and human macrophages. Heliyon 2021;7(2):e06187.
[66] Theobald SJ, Simonis A, Georgomanolis T, Kreer C, Zehner M, Eisfeld HS, et al. Long-lived macrophage reprogramming drives spike protein-mediated inflammasome activation in COVID-19. EMBO Mol Med 2021;13(8):e14150.
[67] Sahin U, Muik A, Vogler I, Derhovanessian E, Kranz LM, Vormehr M, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 2021;595(7868):572–7.
[68] Lee JH. Treatment mechanism of immune triad from the repurposing drug against COVID-19. Translational Medicine of Aging 2023;7:33–45.
[69] Prabhakaran M, Matassoli F, Leggat D, Hoover A, Srikanth A, Wu W, et al. Adjuvanted SARS-CoV-2 spike protein vaccination elicits long-lived plasma cells in nonhuman primates. Sci Transl Med 2024;16(728):eadd5960.
[70] Cai Y, Zhang J, Xiao T, Peng H, Sterling SM, Walsh RM, et al. Distinct conformational states of SARS-CoV-2 spike protein. Science 2020;369(6511): 1586–92.
[71] Szebeni J, Storm G, Ljubimova JY, Castells M, Phillips EJ, Turjeman K, et al. Applying lessons learned from nanomedicines to understand rare hypersensitivity reactions to mRNA-based SARS-CoV-2 vaccines. Nat Nanotechnol 2022;17(4): 337–46.
[72] Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA 2021;326 (12):1210–2.
[73] Liu X, Wei L, Xu F, Zhao F, Huang Y, Fan Z, et al. SARS-CoV-2 spike protein–induced cell fusion activates the cGAS-STING pathway and the interferon response. Sci Signal 2022;15(729):eabg8744.
[74] Ren H, Ma C, Peng H, Zhang B, Zhou L, Su Y, et al. Micronucleus production, activation of DNA damage response and cGAS-STING signaling in syncytia induced by SARS-CoV-2 infection. Biol Direct 2021;16(1):20.
[75] Zhang Y, Peng X, Xue M, Liu J, Shang G, Jiang M, et al. SARS-COV-2 spike protein promotes RPE cell senescence via the ROS/P53/P21 pathway. Biogerontology 2023;24(5):813–27.
[76] Kim MJ, Kim JY, Shin JH, Son J, Kang Y, Jeong SK, et al. The SARS-CoV-2 spike protein induces lung cancer migration and invasion in a TLR2-dependent manner. Cancer Commun 2024;44(2):273–7.
[77] Tao K, Tzou PL, Nouhin J, Gupta RK, de Oliveira T, Kosakovsky Pond SL, et al. The biological and clinical significance of emerging SARS-CoV-2 variants. Nat Rev Genet 2021;22(12):757–73.
[78] Yao L, Zhu KL, Jiang XL, Wang XJ, Zhan BD, Gao HX, et al. Omicron subvariants escape antibodies elicited by vaccination and BA. 2.2 infection. Lancet Infect Dis 2022;22(8):1116–7.
[79] Tyrkalska SD, Martínez-López A, Arroyo AB, Martínez-Morcillo FJ, Candel S, García-Moreno D, et al. Differential proinflammatory activities of Spike proteins of SARS-CoV-2 variants of concern. Sci Adv 2022;8(37):eabo0732.
[80] Nguyen TH, Wang H, Chen LY, Echtermeyer D, Pliquett U. Modulating SARS-CoV-2 spike protein reactivity through moderate electric fields: a pathway to innovative therapies. ACS Omega 2023;8(48):45952–60.
[81] Chakrabarti SS, Tiwari A, Jaiswal S, Kaur U, Kumar I, Mittal A, et al. Rapidly progressive dementia with asymmetric rigidity following ChAdOx1 nCoV-19 vaccination. Aging and disease 2022;13(3):633–6.
[82] Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384(22):2124–30.
[83] Albornoz EA, Amarilla AA, Modhiran N, Parker S, Li XX, Wijesundara DK, et al. SARS-CoV-2 drives NLRP3 inflammasome activation in human microglia through spike protein. Mol Psychiatr 2023;28(7):2878–93.
[84] Idrees D, Kumar V. SARS-CoV-2 spike protein interactions with amyloidogenic proteins: potential clues to neurodegeneration. Biochem Biophys Res Commun 2021;554:94–8.

[85] Wang J, Dai L, Deng M, Xiao T, Zhang Z, Zhang Z. SARS-CoV-2 spike protein S1 domain accelerates α-synuclein phosphorylation and aggregation in cellular models of synucleinopathy. Mol Neurobiol 2024;61(4):2446–58.
[86] Moon C. Fighting COVID-19 exhausts T cells. Nat Rev Immunol 2020;20(5):277.
[87] Heidel F, Hochhaus A. Holding CoVID in check through JAK? The MPN-approved compound ruxolitinib as a potential strategy to treat SARS-CoV-2 induced systemic hyperinflammation. Leukemia 2020;34(7):1723–5.
[88] Dai J, Huang YJ, He X, Zhao M, Wang X, Liu ZS, et al. Acetylation blocks cGAS activity and inhibits self-DNA-induced autoimmunity. Cell 2019;176(6):1447–60. e14.
[89] Eastman JJ, Cavagnero KJ, Deconde AS, Kim AS, Karta MR, Broide DH, et al. Group 2 innate lymphoid cells are recruited to the nasal mucosa in patients with aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 2017;140(1): 101–8. e3.
[90] Lee JH, An HK, Sohn MG, Kivela P, Oh S. 4,4′-Diaminodiphenyl sulfone (DDS) as an inflammasome competitor. Int J Mol Sci 2020;21(17):5953.
[91] Chakraborty A, Panda AK, Ghosh R, Biswas A. DNA minor groove binding of a well known anti-mycobacterial drug dapsone: a spectroscopic, viscometric and molecular docking study. Arch Biochem Biophys 2019;665:107–13.
[92] Rashidian A, Rashki A, Abdollahi A, Haddadi NS, Chamanara M, Mumtaz F, et al. Dapsone reduced acetic acid-induced inflammatory response in rat colon tissue through inhibition of NF-kB signaling pathway. Immunopharmacol Immunotoxicol 2019;41(6):607–13.
[93] Mohammad Jafari R, Shayesteh S, Ala M, Yousefi-Manesh H, Rashidian A, Hashemian SM, et al. Dapsone ameliorates colitis through TLR4/NF-kB pathway in TNBS induced colitis model in rat. Arch Med Res 2021;52(6):595–602.
[94] Yousefi-Manesh H, Noori T, Asgardoon MH, Derakhshan MH, Tavangar SM, Sheibani M, et al. Protective effect of dapsone against bleomycin-induced lung fibrosis in rat. Exp Mol Pathol 2022;124:104737.
[95] Cho SC, Rhim JH, Choi HR, Son YH, Lee SJ, Song KY, et al. Protective effect of 4,4'-diaminodiphenylsulfone against paraquat-induced mouse lung injury. Exp Mol Med 2011;43(9):525–37.
[96] Mahale A, Kumar R, Sarode LP, Gakare S, Prakash A, Ugale RR. Dapsone prolong delayed excitotoxic neuronal cell death by interacting with proapoptotic/survival signaling proteins. J Stroke Cerebrovasc Dis 2020;29(8):104848.
[97] Claman HN. Corticosteroids and lymphoid cells. N Engl J Med 1972;287(8): 388–97.
[98] Nagakumar P, Puttur F, Gregory LG, Denney L, Fleming L, Bush A, et al. Pulmonary type-2 innate lymphoid cells in paediatric severe asthma: phenotype and response to steroids. Eur Respir J 2019;54(2):1801809.
[99] Liu S, Verma M, Michalec L, Liu W, Sripada A, Rollins D, et al. Steroid resistance of airway type 2 innate lymphoid cells from patients with severe asthma: the role of thymic stromal lymphopoietin. J Allergy Clin Immunol 2018;141(1):257–68. e6.
[100] Lee JH, Sergi C, Kast R, Kanwar B, Altschuler E, Bourbeau J, et al. The picture theory of seven pathways associated with COVID-19 in the real world. Research Square 2024.