Inflammopharmacology

REVIEW

Neuropathophysiology of coronavirus disease 2019: neuroinflammation and blood brain barrier disruption are critical pathophysiological processes that contribute to the clinical symptoms of SARS-CoV-2 infection

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) first discovered in Wuhan, Hubei province, China in December 2019. SARS-CoV-2 has infected several millions of people, resulting in a huge socioeconomic cost and over 2.5 million deaths worldwide. Though the pathogenesis of COVID-19 is not fully understood, data have consistently shown that SARS-CoV-2 mainly affects the respiratory and gastrointestinal tracts. Nevertheless, accumulating evidence has implicated the central nervous system in the pathogenesis of SARS-CoV-2 infection. Unfortunately, however, the mechanisms of SARS-CoV-2 induced impairment of the central nervous system are not completely known. Here, we review the literature on possible neuropathogenic mechanisms of SARS-CoV-2 induced cerebral damage. The results suggest that downregulation of angiotensin converting enzyme 2 (ACE2) with increased activity of the transmembrane protease serine 2 (TMPRSS2) and cathepsin L in SARS-CoV-2 neuroinvasion may result in upregulation of proinflammatory mediators and reactive species that trigger neuroinflammatory response and blood brain barrier disruption. Furthermore, dysregulation of hormone and neurotransmitter signalling may constitute a fundamental mechanism involved in the neuropathogenic sequelae of SARS-CoV-2 infection. The viral RNA or antigenic peptides also activate or interact with molecular signalling pathways mediated by pattern recognition receptors (e.g., toll-like receptors), nuclear factor kappa B, Janus kinase/signal transducer and activator of transcription, complement cascades, and cell suicide molecules. Potential molecular targets and therapeutics of SARS-CoV-2 induced neurologic damage are also discussed.

Keywords COVID-19 · SARS-CoV-2 · Neuroinflammation · Blood brain barrier disruption · Neuroinfection · Neuropathogenesis

Introduction

Coronavirus (CoV) (from "*corona*"—Latin for "crown") is a family of enveloped, single-stranded, positive-sense RNA viruses with protruding spike-like appearance on the membrane that gives rise to a crown-like shape (McBride et al. 2014; Li 2015; Chen et al. 2020a). CoV is one of the two virus genera within the family *Coronaviridae* of the order *Nidovirale*s that is widely distributed in humans and animals, including bats, dogs, mice, cats etc. (Ksiazek et al. 2003; Zaki et al. 2012; McBride et al. 2014). To date, 7 species belonging to the α- and β-CoV genera of the *Coronaviridae* family have been identified to infect humans (Lefkowitz et al. 2018). The species of α-CoV genus are 229E and NL63, while those of β-CoV genus include OC43, HKU1, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) (Esper et al. 2006; Li 2015; Wu et al. 2020a; Yeo et al. 2020) and SARS-CoV-2 (novel CoV 2019) (Chen et al. 2020a).

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This review is focused on the recently discovered SARS-CoV-2 that causes CoV disease 2019 (COVID-19), first identified in Wuhan, the capital of Hubei province, China in December 2019 (Wu et al. 2020a; Yeo et al. 2020). CoV is a frequent cause of upper and lower respiratory tract infections, affecting all age groups. Symptoms of COVID-19 include fever, cough, fatigue (Yeo et al. 2020; Zhu et al. 2020), sore throat, breathlessness, malaise (Singhal 2020), diarrhea (Yeo et al. 2020), and vomiting (Yeo et al. 2020). Notably, data have shown that a subset of patients with positive SARS-CoV-2 RNA test initially experience gastrointestinal symptoms such as diarrhea and nausea about 24–48 h prior to development of fever and respiratory symptoms (Yeo et al. 2020). Evidence also indicates that intestinal epithelial inflammation and degeneration precede pulmonary infection in CoV disease, suggesting that respiratory impairment, at least in part, may be due to dysfunction of the gut-lung axis (Yeo et al. 2020). Though the majority of reported CoV infections are mild (Conti et al. 2020), CoV-19 may cause potentially serious damage to the respiratory system (Ksiazek et al. 2003; Zaki et al. 2012) and other organs of the body (Zhu et al. 2020). As of March 4, 2021, more than 115 million people have been infected with several disabilities and over 2.5 million deaths worldwide (John Hopkins University and Medicine 2020). Alas, SARS-CoV-2 infection has also resulted to huge global economic losses (Baldwin and Mauro 2020; Fernandes 2020).

Though the respiratory and gastrointestinal tracts have been frequently implicated in the pathogenesis of SARS-CoV-2 infection, available evidence also indicates a critical role of central nervous system (CNS) dysfunction in COVID-19 pathogenesis (Yeo et al. 2020). Unfortunately, however, the mechanisms of SARS-CoV-2 induced cerebral damage are not completely known. Here, we review the literature on possible neuropathogenic mechanisms of SARS-CoV-2 induced cerebral damage. Potential molecular targets and emerging therapeutics for SARS-CoV-2 induced neurologic damage are also discussed.

Neurological manifestations of SARS-COV-2 neuroinvasion

The SARS-CoV-2 exhibits neurotropic properties (Wu et al. 2020b) and has been found to cause a range of neurological diseases including Guillain–Barré syndrome, Miller Fisher syndrome, polyneuritis cranialis and epilepsy (Gutiérrez-Ortiz et al. 2020; Zhao et al. 2020b) as well as cerebral stroke (Al Saiegh et al. 2020; Helms et al. 2020; Mao et al. 2020a). Similarly, neurologic injury was reported in previous CoV outbreak involving the MERS-CoV (Arabi et al. 2015; Kim et al. 2017), human CoV-OC43 (Salmi et al.

1982; Morfopoulou et al. 2016), and human CoV-229E (Salmi et al. 1982) among others (Li et al. 2017).

Interestingly, biomolecular analysis by polymerase-chain-reaction (PCR) reportedly revealed the presence of CoV RNA in the cerebrospinal fluid (CSF) or cerebral tissues of CoV infected patients. So, Gutiérrez-Ortiz et al. (2020) reported the presence of SARS-CoV-2 RNA in the CSF of SARS-CoV-2 infected patients (Gutiérrez-Ortiz et al. 2020). Previous studies have reported the identification of human CoV-229E (Fazzini et al. 1992; Dessau et al. 2001, 2009), human CoV-OC43 (Fazzini et al. 1992; Yeh et al. 2004; Morfopoulou et al. 2016), SARS-CoV (Hung et al. 2003; Yeh et al. 2004) in human CSF or postmortem brain tissues. In contrast, Al Saiegh et al. (2020) reported the absence of SARS-CoV-2 RNA in CSF despite the presence of neurological problems such as headache, loss of consciousness and ischaemic/haemorrhagic cerebral injury in SARS-CoV-2 infected patients (Al Saiegh et al. 2020). Consistent with these findings, Helms et al. (2020) also demonstrated the absence of SARS-CoV-2 RNA in CSF of patients admitted for SARS-CoV-2 infection, confirmed by reverse-transcriptase PCR assay of the nasopharyngeal tissue (Helms et al. 2020). Though these inconsistencies remain to be clarified, neurological symptoms of possible SARS-CoV-2 neuroinvasion reported across studies (Gutiérrez-Ortiz et al. 2020; Mao et al. 2020b; Al Saiegh et al. 2020; Helms et al. 2020) should not be ignored.

The SARS-CoV-2 invasion of the brain may cause cerebral vascular/endothelial dysfunctions, which may result in cerebral circulatory impairments that characterise the acute cerebrovascular problems of SARS-CoV-2 infection as reported by Mao et al. (2020b), Al Saiegh et al. (2020), and Helms et al. (2020). Indeed, Helms et al. (2020), using perfusion imaging, demonstrated in COVID-19 patients that SARS-CoV-2 neuroinvasion causes bilateral frontotemporal hypoperfusion, indicating cerebral circulatory impairment (Helms et al. 2020).

The neurological problems of COVID-19 may be due to the ensuing inflammatory or immune system responses to SARS-CoV-2 neuroinvasion. Gutiérrez-Ortiz et al. (2020) reported a range of neurological damages, concomitantly with inflammatory/immune dysfunction in two patients diagnosed with COVID-19 in Madrid, Spain. The patients had ageusia, anosmia, bilateral abducens palsy (or right internuclear ophthalmoparesis, right fascicular oculomotor palsy), ataxia and areflexia (Gutiérrez-Ortiz et al. 2020). Furthermore, a CSF positive test was demonstrated for albuminocytologic dissociation, indicating a hallmark of inflammatory demyelinating polyneuropathies, while immunoglobulin (Ig)G antibodies to GD1b ganglioside was also positive, which suggests acute immune-mediated ataxic neuropathies (Gutiérrez-Ortiz et al. 2020). Interestingly, for both patients, these neurological damages occurred 3–5 days before onset

of cough, malaise, diarrhea, fever, headache, and low back pain, after which COVID-19 was confirmed by PCR using oropharyngeal tissue (Gutiérrez-Ortiz et al. 2020). These findings suggest that neurological manifestations may be the initial symptoms of SARS-CoV-2 infection or neuroinvasion and may be responsible for peripheral organ dysfunctions in some COVID-19 patients.

Consistent with the data of Gutiérrez-Ortiz et al. (2020), other clinicians have shown that SARS-CoV-2 infection adversely affects the neuromuscular system (Guidon and Amato 2020). In addition to ataxia and areflexia reported by Gutiérrez-Ortiz et al. (2020), Zhao et al. (2020b), Guidon and Amato (2020), and Mao et al. (2020b) described associated muscle weakness in COVID-19 patients. At the same time, Zhao et al. (2020b) showed reduced tendon reflexes in both legs and feet in COVID-19 patients. In contrast, Helms et al. (2020) reported enhanced tendon reflexes among 67% of the 58 patients admitted for SARS-CoV-2 infection with positive reverse-transcriptase PCR test using nasopharyngeal samples. These patients also had disorganized movement in response to command and ankle clonus (Helms et al. 2020).

In a retrospective study, conducted among 214 patients with laboratory confirmed diagnosis of COVID-19 in Wuhan, China, Mao et al. (2020b) reported central and peripheral dysfunctions such as headache, impaired consciousness, ataxia, generalized tonic–clonic seizures, hyposmia and hypogeusia in 36% patients. Indeed, headache was one of the most frequently reported symptoms of SARS-CoV-2 neuroinvasion (Gutiérrez-Ortiz et al. 2020; Zhu et al. 2020). In addition, neurological manifestations of COVID-19 included fatigue (Wang et al. 2020a), nausea, vomiting (Guan et al. 2020; Wang et al. 2020a), disorientation, inattention (Helms et al. 2020), delirium tremens, and coma (Gutiérrez-Ortiz et al. 2020; Helms et al. 2020), which are similar to data reported by other authors (Mao et al. 2020b). Neuropathic pain as a neurological symptom was frequently reported by the majority of studies (Guidon and Amato 2020; Gutiérrez-Ortiz et al. 2020; Mao et al. 2020b; Wang et al. 2020a). For instance, Guidon and Amato (2020) and Wang et al. (2020a) described an association between SARS-CoV-2 infection and myalgia or low back pain (Gutiérrez-Ortiz et al. 2020). Wang et al. (2020a) reported abdominal pain in COVID-19. However, pain arising from the gastrointestinal tract may be due to local injury caused by the virus or SARS-CoV-2 induced neurogenic injury that generates pain sensation.

Though the precise mechanisms of neurological manifestations of SARS-CoV-2 infection are not clearly known, neuroinflammation and blood brain barrier disruption appear to be critical pathophysiological processes responsible for the central and peripheral nervous system damages, and thus provide important information for the prevention and management of patients with initial symptoms of the disease.

The next section will be concerned with the receptors and enzymes required for SARS-CoV-2 entry into the host cells. In subsequent sections, the key pathways involved in SARS-CoV-2 neuroinvasion, neuroimmune dysregulation by SARS-COV-2 neuroinvasion, including inflammatory and oxidative stress, and cytokine storm as well as the molecular signalling cascades implicated in these processes will be discussed.

Receptors and enzymes required for SARS-CoV-2 entry into the host cells

SARS-CoV-2 infection occurs via the fecal–oral route of transmission (Yeo et al. 2020). The virus can be transmitted via direct droplet transmission, excrements, contact, fomites, and environmental contamination (Yeo et al. 2020). SARS-CoV-2 enters the host cells by binding to the angiotensin converting enzyme 2 (ACE2) with its spike (S) protein, followed by priming of the S protein through the activities of the transmembrane protease, serine 2 (TMPRSS2) (Fig. 1) (Sungnak et al. 2020) and cathepsin L (Ou et al. 2020).

The serine protease, TMPRSS2, is a transmembrane enzyme required for SARS-CoV-2 invasion of the host cells. TMPRSS2 is responsible for cleaving and activating the S protein of SARS-CoV-2, thereby enhancing the fusion of the virus with the host cell membrane (Hoffmann et al. 2020). TMPRSS2 is primarily expressed in nasal epithelial cells and alveolar epithelial type II cells of subsegmental bronchial branches (Chen et al. 2020c; Sungnak et al. 2020), pancreatic and renal tissues (Glowacka et al. 2011). TMPRSS2 is highly expressed in the fetal brain (Ubuka et al. 2018), but available data suggest that expression of the protease is low in the adult brain (Glowacka et al. 2011; Ubuka et al. 2018). It is, therefore, important for future investigation to identify key aspects of TMPRSS2 ontogenesis, and the implication of age-dependent expression of this protease in neuroinvasiveness of CoV.

It is widely acknowledged that ACE2 receptor binding affinity constitutes a key determinant of viral infectivity (Yeo et al. 2020). ACE2 is a zinc-dependent carboxy-peptidase, comprising an integral component of the central renin–angiotensin system that has been consistently implicated in the regulation of cardiovascular/cerebrovascular functions (Doobay et al. 2007; Xia and Lazartigues 2008). Interestingly, ACE2 downregulation has been associated with neuroinflammation and cerebral endothelial disruption (vide infra). ACE2 is expressed on vascular endothelial cells, nasal epithelial and type II alveolar cells of the lungs (Oudit et al. 2009; Chen et al. 2020c; Sungnak et al. 2020), cardiac cells (Oudit et al. 2009), corneal epithelial cells (Sungnak et al. 2020), intestinal epithelial cells, vascular endothelial cells and smooth muscle cells of lungs, kidney and heart
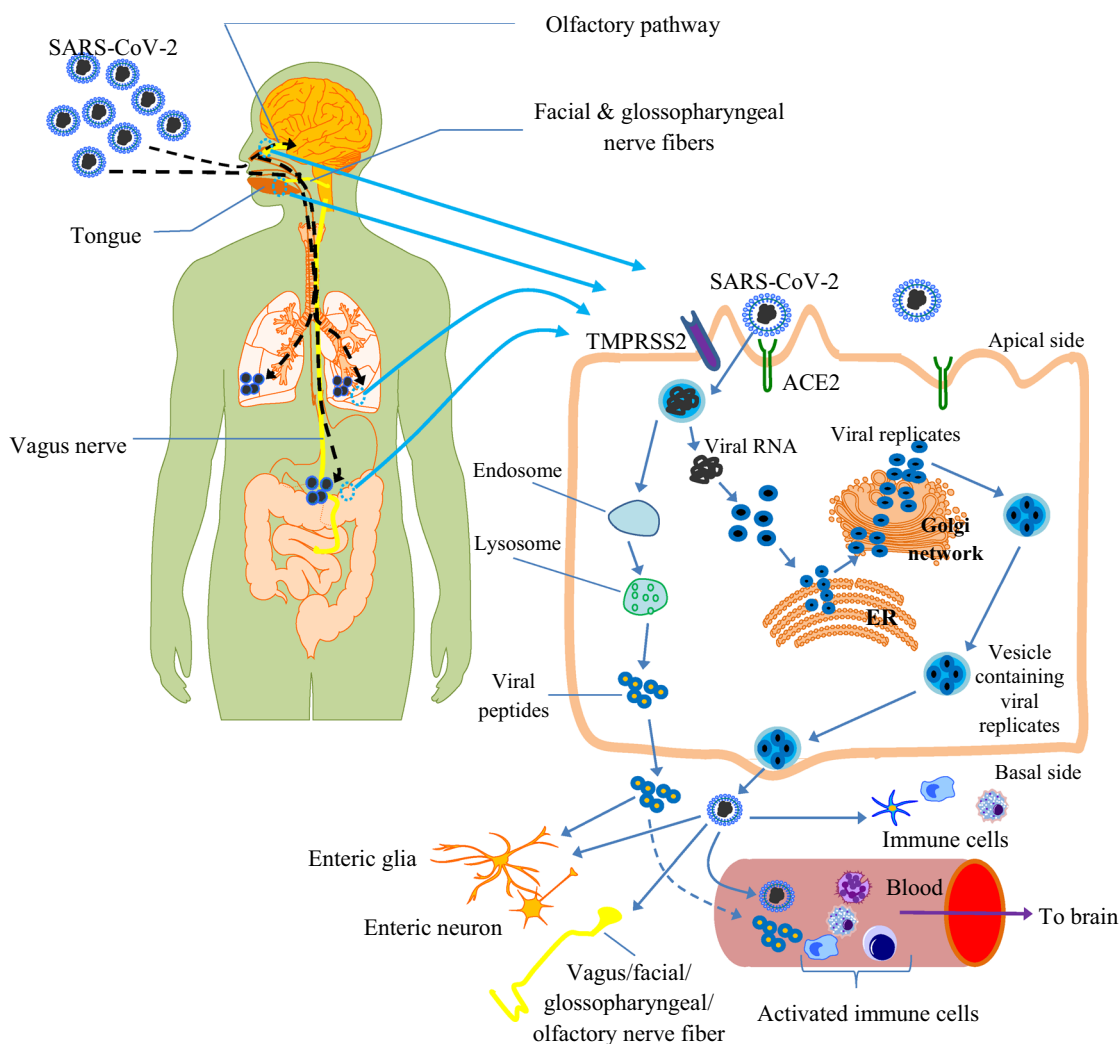
Fig. 1 Schematic representation of SARS-CoV-2 invasion of olfactory/nasopharyngeal, pulmonary, intestinal and tongue or oropharyngeal epithelial cells. *ACE2* angiotensin converting enzyme 2, *ER* endoplasmic reticulum, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TMPRSS2* transmembrane protease, serine 2 (see explanation in text)

(Hamming et al. 2004; Sungnak et al. 2020). The widespread expression of ACE2 points to the severe complications that arise from SARS-CoV-2 infection: acute respiratory distress syndrome, acute kidney injury, acute cardiac injury, shock, and disseminated intravascular coagulopathy (Deng et al. 2020).

ACE2 is highly expressed in the brain of animals (Doobay et al. 2007; Xia and Lazartigues 2008; Chen et al. 2020c) and humans with comparative distribution in these organisms (Chen et al. 2020c). ACE2 is richly expressed in the cerebral ventricles, substantia nigra, middle temporal gyrus, posterior cingulate cortex, olfactory bulb (Chen et al. 2020c), subfornical organ, dorsal motor nucleus of the vagus nerve and the ventrolateral medulla (Doobay et al. 2007). ACE2 expression has been documented in multiple cerebral neurons (Doobay et al. 2007; Chen et al.

2020c), and oligodendrocytes (Chen et al. 2020c). The high expression of ACE2 in cellular components of the blood brain barrier [vascular endothelial cells, pericytes, and astrocytes (Chen et al. 2020c)] suggests that SARS-CoV-2 invasion of the brain may cause blood brain barrier disruption. Scientific evidence (Welcome 2020a, b) indicates that these components of the blood brain barrier also represent principal mediators of neuroinflammatory processes in several CNS diseases. Consequently, inflammatory responses to SARS-CoV-2 invasion of the brain can potentially cause serious CNS dysfunctions in COVID-19 (Chen et al. 2020c). So, Al Saiegh et al. (2020) reported ischaemic and haemorrhagic cerebral injury [(which is often associated with neuroinflammation and blood brain barrier disruption (Welcome 2020a, b)] accompanied by headache and loss of consciousness in COVID-19 patients,

suggesting a role of SARS-CoV-2 infection in blood brain barrier impairment.

Cathepsin L is a cysteine protease that is primarily expressed in endolysosomal vesicles. This protease mediates proteolytic cleavage of multiple proteins, including receptors, enzymes, and transcription factors to regulate several aspects of cell physiology (Rawlings and Salvesen 2013). Ou et al. (2020) showed that treatment of 293/hACE2 cells with the cathepsin L inhibitor, SID 26681509, resulted in over 76% decrease in the entry of SARS-CoV-2 S virions into the cells (Ou et al. 2020). Interestingly, cathepsin L (Hook et al. 2012) is expressed in the brain, suggesting a potential role of this protease as a target for the treatment of SARS-CoV-2 infection. Zhang and co-researchers reported that teicoplanin, a glycopeptide antibiotic, suppressed the activation of the SARS-CoV-2 S protein inside endosomes by inhibiting cathepsin L (Zhang et al. 2020a). Indeed, Zhou et al. (2016) previously showed that teicoplanin, which is recommended for use in the clinic, effectively blocked both CoVs and Ebola virus from invading the host cells (Zhou et al. 2016).

Though the mechanisms are not well understood, phosphatidylinositol 3-phosphate 5-kinase (PIKfyve)/FAB1 (formation of aploid and binucleate cells) and two pore channel subtype 2 (TPC2) may also play a role in SARS-CoV-2 invasion of the host cells (Ou et al. 2020). PIKfyve is a lipid kinase involved in the regulation of endosome biogenesis and vesicle transport. It is the main enzyme responsible for the synthesis of phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) (a lipid molecule regulating intracellular trafficking of vesicles and membrane recycling to the Golgi network) in early endosome (Nelson et al. 2017; Qiu et al. 2018). TPC2 is an intracellular voltage- and ligand-gated ion channel and a key downstream effector of PI(3,5)P2 signalling in lysosomes (Patel 2015). Interestingly, PIKfyve (Martin et al. 2013) and TPC2 (Kelu et al. 2018) are expressed in the brain, suggesting a possible role of these molecules in SARS-CoV-2 neuroinfection. Ou et al. (2020) demonstrated that the PIKfyve inhibitor, YM201636 or apilimod, and the TPC2 inhibitor, tetrandrine, effectively inhibited the entry of CoV virion into 293/hACE2 cells (Ou et al. 2020). Notably, previous studies have shown that both CoVs and Ebola virus require the PIKfyve for effective entry into the host cells (Nelson et al. 2017; Qiu et al. 2018). These data suggest that PIKfyve and TPC2 may serve as critical targets for the treatment of SARS-CoV-2 infection.

The molecular architecture that regulates SARS-CoV-2 entry into the host cells are not limited to ACE2, TMPRSS2, cathepsin L, PIKfyve, and TPC2, but also, T cell cluster of differentiation (CD) 32/CD64, CD147/besigin, and bradykinin B2 receptor. CD147 is expressed on the surface of T lymphocytes (Wang et al. 2020b). Bradykinin B2 receptor (van de Veerdonk et al. 2020) and CD32/CD64 (Yip et al. 2016; Quinlan et al. 2020) are expressed in neurons, glia and endothelial cells (Curtin et al. 2007; Zhu et al. 2014; Sharma et al. 2019). These receptors have been reportedly shown to play a role in SARS-CoV-2 invasion of the host cells (Wang et al. 2020b; van de Veerdonk et al. 2020; Quinlan et al. 2020). Interestingly, these receptors, especially CD147 and bradykinin B2 receptor, are involved in neuroinflammatory response and blood brain barrier breakdown (Li et al. 2013a; Zhu et al. 2014; Sharma et al. 2019). Further research is required to ascertain the contribution of each of these receptors and proteases to SARS-CoV-2 invasion of the host cells.

Pathways mediating SARS-COV-2 induced cerebral infection

Literature data indicate that the humoral and neural pathways are the main routes through which the neurotropic SARS-COV-2 infects the CNS (vide infra). However, due to the paucity of information on SARS-CoV-2 neuroinvasiveness, data on similar viruses will be used at strategic point of the discussion to ultimately achieve the main goals of this review.

Humoral pathway

The humoral pathway mediates the transport of viral components (including viral RNA), cytokines, toxic metabolites, certain hormones, and peptide molecules produced as a result of SARS-CoV-2 activities (Fig. 1) (Zhu et al. 2020). These molecules may be produced in the respiratory, gastrointestinal tract or other regions of the body, and are then transported via the circulatory system to the brain (Zhu et al. 2020). In the brain, the molecules first interact with the cerebral vascular endothelium to mediate a range of pathological processes that promote neuroinflammation and blood–brain barrier disruption (Fig. 2) (Peña-Silva et al. 2012).

Neural pathway

In the neural pathway, viral components or molecules released during SARS-CoV-2 invasion interact with enteric neurons and glia, vagus, facial, glossopharyngeal and olfactory nerve fibers to initiate neural signalling or modulate neurotransmission that may lead to cerebral dysfunctions. Indeed, activation of nerve fibers, enteric neurons or glia can stimulate or inhibit the activities of their control centers (enteric ganglia, brainstem nuclei or olfactory nuclei) (Fig. 1) (Mengeling et al. 1972; Andries and Pensaert 1980; Butowt and Bilinska 2020).

CoV can transmigrate via peripheral nerve fibers into the brain (Fig. 1) (Andries and Pensaert 1980; Butowt and Bilinska 2020; Li et al. 2020d). Niu et al. (2020), using
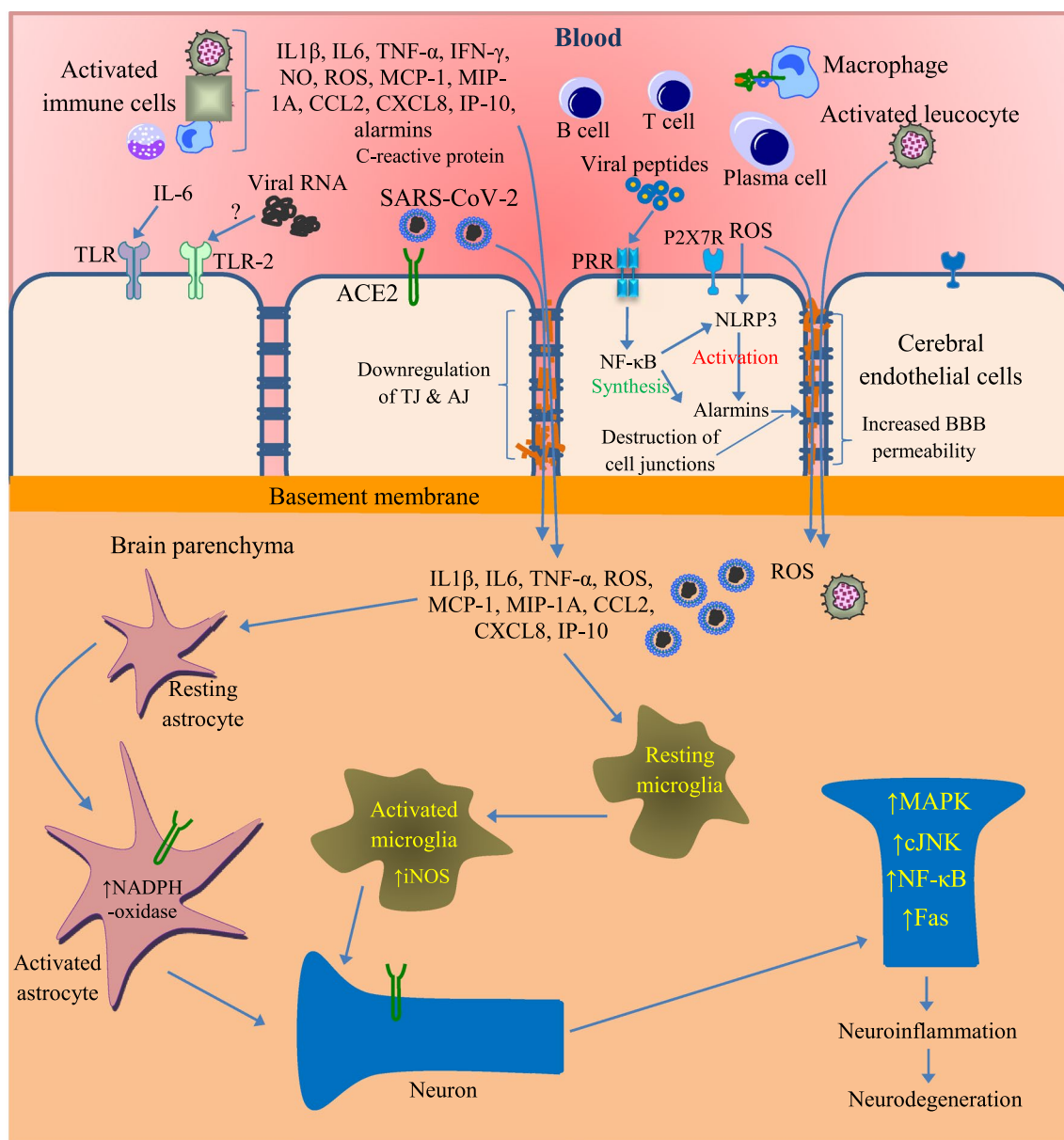
Fig. 2 Mechanisms involved in SARS-CoV-2 induced neuroinfection, neuroinflammation and neurodegeneration. *ACE2* angiotensin converting enzyme 2, *AJ* adherens junction, *BBB* blood brain barrier, *CCL-2* C–C motif chemokine ligand, *cJNK* c-Jun N-terminal kinase, *CXCL-8* C-X-C motif chemokine ligand, *Fas* FS-7-associated surface antigen, *IFN-γ* interferon gamma, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *IP-10* IFNγ-induced protein 10, *MAPK* mitogen-activated protein kinase, *MCP-1* monocyte chemoattractant protein-1, *MIP-1A* macrophage inflammatory protein-1A, *NADPH* nicotinamide adenine dinucleotide phosphate, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *NLRP3* nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3, *NO* nitric oxide, *P2X7R* P2X purinergic receptor 7, *PRR* pattern recognition receptor, *ROS* reactive oxygen species, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TGF-β* transforming growth factor, *TJ* tight junction, *TLR* toll-like receptor, *TMPRSS2* transmembrane protease, serine 2, *TNF-α* tumor necrosis factor alpha (see explanation in text)

non-invasive bioluminescence imaging, investigated the spatio-temporal progression of human CoV-OC43 in the CNS of mice after intranasal or intracerebral inoculation and showed substantial expression of the viral RNA in the brain before the infection spread to the spinal cord of the laboratory animals (Niu et al. 2020). Niu et al. (2020)

also demonstrated that the viral replication was effectively inhibited with chloroquine/hydroxychloroquine in live mice (Niu et al. 2020) or humans (Liu et al. 2020a) due to its ability to inhibit toll-like receptors and high mobility group box 1 (HMBG1), thereby attenuating the proinflammatory responses (Liu et al. 2020a). In addition,

the inhibitory action of chloroquine and hydroxychloroquine on CoV is also due to their ability to cause impairment in glycosylation of ACE2 receptor and thus binding of the S protein. Again, these quinolones can increase the intraorganellar pH of endosomes and lysosomes—organelles critical to SARS-CoV-2 replication and accumulation in the host cells (Liu et al. 2020b).

Previous studies conducted by independent groups of researchers also reported the transmigration of CoV via peripheral nerve fibers into the brain. So, experimental data have shown that HEV 67 N, the CoV that causes hemagglutinating encephalomyelitis, infects the respiratory and intestinal epithelial cells, transmigrating in a retrograde direction through peripheral nerves to the brainstem neurons (Mengeling et al. 1972; Andries and Pensaert 1980). Though the mechanism of transmigration of CoV from the peripheral nerves into the central neurons are not completely understood, Li et al. (2013a, b) showed that trans-synaptic communication of HEV 67 N occurs via a special membranous-coating that facilitates migration of the virus in nerve fibers or neurons (Li et al. 2013b). Importantly, HEV 67 N shares over 90% amino acid sequence homology with human CoV-OC43 (González et al. 2003) and also shares about 90% homology with SARS-CoV (Li et al. 2020d). The SARS-CoV in turn shares about 75% homology with SARS-CoV-2 (Xie et al. 2020). Indeed these CoVs also have other properties in common. For example, SARS-CoV and SARS-CoV-2 use the same receptor to gain access into the host cells (Xie et al. 2020). Interestingly, interneuronal and synaptic transfer of similar viruses and subsequent neuroinfection has been reported (Matsuda et al. 2004). Identification of infectivity of the SARS-CoV-2 in different regions of the brain confirms the neuroinvasiveness of CoV. Previous data have demonstrated the presence of viral antigens in regions of the brain, where SARS-CoV receptors are widely expressed (Kalia and Mesulam 1980; Hadziefendic and Haxhiu 1999; Raux et al. 2000). Data also indicate that the olfactory epithelium, where ACE2 and TMPRSS2 are highly expressed, can facilitate SARS-CoV-2 binding, replication, and accumulation, suggesting that the nasal cavity may be a better site from collecting samples for SARS-CoV-2 detection at the early stages of invasion (Butowt and Bilinska 2020). Again, the olfactory pathway represents a relatively fast pathway through which the virus can cause neuroinfection/neuroinflammation, in addition to smell impairment in COVID-19 patients (Butowt and Bilinska 2020). Previous studies have consistently shown the involvement of CoVs in cerebral neuroinfection: 229E (Dessau et al. 2009), SARS-CoV (Lau et al. 2004) and human CoV-HKU1 (Esper et al. 2006).

Neuroimmune dysregulation by SARS-CoV-2 neuroinvasion

SARS-CoV-2 invasion of host cells, replication and accumulation

SARS-CoV-2 invades the brain cells by binding to the ACE2 with its S protein S1 subunit, triggering conformational change of the S2 subunit, which enables membrane fusion with the host cell (Fig. 2). SARS-CoV-2 initially interacts with the cerebral vascular endothelial cells through the humoral pathway to initiate endothelial dysfunction, thereby allowing direct access of the virus and its components to the elements of the blood brain barrier such as pericytes, perivascular astrocytes, neurons and microglia (Fig. 2) (Xia et al. 2020). Some proteases (vide supra) also facilitate the entry of the virions into the host cells. In addition to membrane fusion, SARS-CoV-2 may enter the host cell through clathrin-dependent mechanism, which has been previously reported for SARS-CoV (Wang et al. 2008; Kuba et al. 2010). Experimental investigation by Li and coworkers revealed that HEV 67 N infects cerebral neurons by clathrin-mediated endocytosis and exocytosis (Li et al. 2020d). Furthermore, viruses may enter the cell via cell adhesion molecules (Li 2015; Mateo et al. 2015). Research findings reported by Kubo and colleagues showed that the murine CoV, mouse hepatitis virus, invades the host cells via the cell–cell adhesion molecule, CEACAM1 (carcinoembryonic antigen related cell adhesion molecule 1) (Kubo et al. 1994). Frankly, upregulation of CEACAM8 by activated monocytes and granulocytes has been reported in SARS-CoV infection (Reghunathan et al. 2005).

The virus enters the host cell through an endocytic pathway, hijacking the endosomes for delivery of its RNA molecule into the cytosol. The viral RNA is then translated into several structural proteins required for viral assembly, non-structural proteins (produced from the cleavage of two large polyproteins) required for viral RNA synthesis, and accessory proteins required to overcome the immunity of the host (Fig. 1) (Bartlam et al. 2005; Perlman and Netland 2009; Liu et al. 2014; Valencia 2020). Thereafter, the virus starts to replicate, and subsequently assembled to form similar viruses, which may be slightly different from the original viral RNA genome. However, the viral RNA genome may be transcribed to the corresponding mRNA, which is then translated in the cytoplasm to form envelope glycoproteins (Fig. 1) (Bartlam et al. 2005; Perlman and Netland 2009; Liu et al. 2014; Valencia 2020). These glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi network, and together with the nucleocapsid protein, germinate in the endoplasmic

reticulum-Golgi intermediate compartment. The products are assembled; bud off to form new viral replicates (Fig. 1) (Bartlam et al. 2005; Perlman and Netland 2009; McBride et al. 2014; De Wit et al. 2016; Valencia 2020). The viral vesicles then fuse with the plasma membrane, releasing the virus to infect other cells (Fig. 1) (De Wit et al. 2016).

Some pharmacological agents acting as viral RNA polymerase inhibitors [(Clevudine, NCT04347915; Favipiravir, NCT04336904 & NCT04359615; Lopinavir/ritonavir, NCT04321993; and Remdesivir, NCT04292899 (https://www.clinicaltrials.gov)] that specifically target the SARS-CoV-2 replication machinery have shown promise for potential application in the treatment of COVID-19.

Immune responses from SARS-CoV-2 invasion

Some viruses in the endosomal compartment are channeled into the lysosomal degradation pathway, which produces viral components (i.e., CoV antigenic peptides) that are subsequently loaded into major histocompatibility complex (MHC I & II molecules) or human leukocyte antigen (HLA) and presented on the surface of the brain perivascular macrophages, their tissue specific subtype—microglia, dendritic cells and other antigen presenting cells (APC) (Figs. 1, 2) (Jensen et al. 2018). Flanked CoV antigenic molecules by

the APC are recognized by naïve T cells through viral specific T-cell receptor, thereby triggering their proliferation and differentiation with the formation of different isotypes of T cells (Fig. 3). Homing of activated T cells to the site of invasion occurs with the aid of environmental cues (Jensen et al. 2018).

At the point of invasion, virus-specific effector T cells produce cytokines and chemokines directed against viral replication, facilitation of antigen presentation, and recruitment of immune cells (Channappanavar et al. 2014; Chen et al. 2020b). CoV antigenic peptides-APC-T cell complex also activates CD4+ and CD8+ T cells that participate in blocking APC-CoV antigenic peptide complex. However, the T cell responses may not be effective enough to resolve SARS-CoV-2 in the majority of infected patients (Li et al. 2020a). The ability of CD4+ and CD8+ T cells to secrete cytokines such as interleukin-2 (IL-2), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α has been demonstrated to be higher in severe cases of infection compared to mild cases (Peng et al. 2006; Li et al. 2008a; Fan et al. 2009). However, previous data about the effects of SARS-CoV infection showed marked decrease in CD4+ and CD8+ T cells in approximately 80–100% of patients compared to similar indices in healthy controls, which was demonstrated to be due to impaired activation of these T cells in SARS-CoV
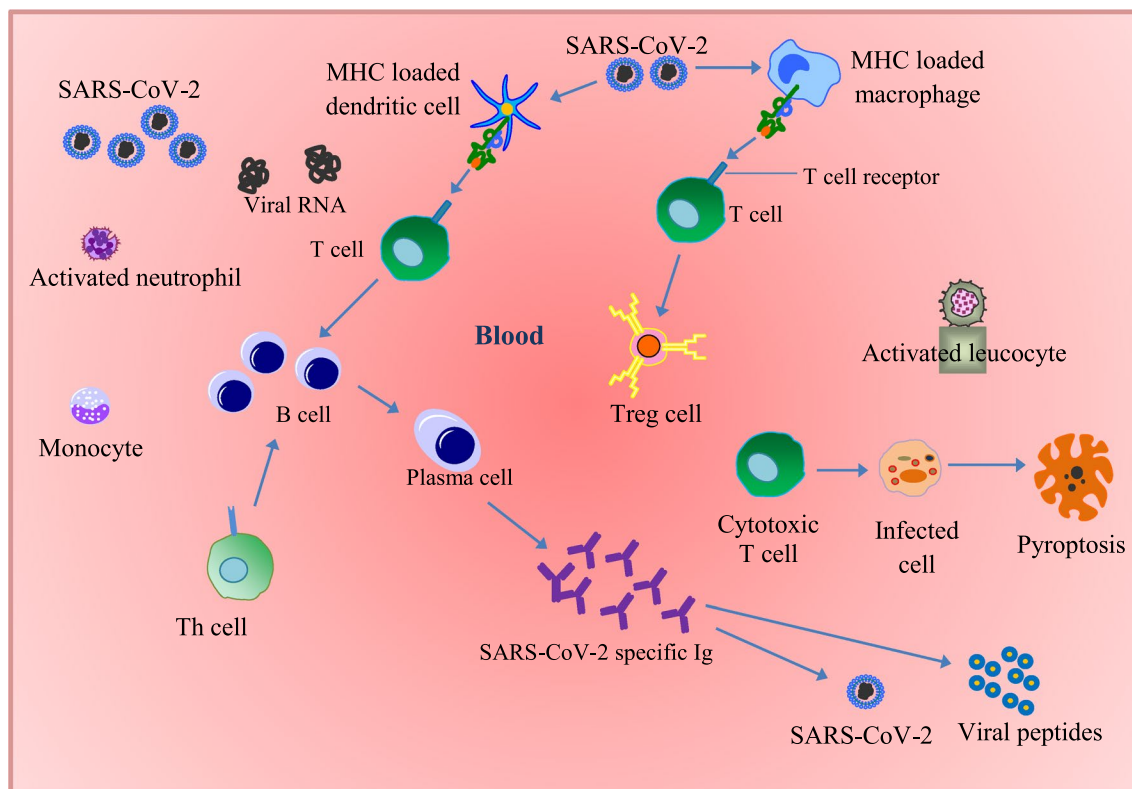

Fig. 3 Simplified schematic representation of SARS-CoV-2 infection of blood. *MHC* major histocompatibility complex, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *Th* T helper, *Treg* T regulatory (see explanation in text)

infected patients (Channappanavar et al. 2014). Similarly, data about SARS-CoV-2 infection also showed substantial decrease in CD4+ and CD8+ T cells in the peripheral blood (Diao et al. 2020; Qin et al. 2020; Wang et al. 2020c; Xu et al. 2020; Zhou et al. 2020b), indicating impaired activation of T cells (Zhou et al. 2020b). The cytotoxic T cells can directly kill the CoV, but may not efficiently execute their functions, in part, due to impaired immune responses. These data strongly suggest that T-cell responses to SARS-CoV-2 invasion may not be adequate enough to prevent or resolve the activities of the pathogen.

The generated helper T cells (Th1, Th2, and Th17) present the viral antigens to the B cells (differentiated plasma cells), which produce CoV-specific antibodies or Ig required to neutralise the virus (Fig. 3) (Li et al. 2017, 2020a; Ahmed et al. 2020; Huang et al. 2020). Several studies have shown association between higher antibody production with stronger helper T cell cytokine secretion in SARS-CoV infection (Peng et al. 2006; Li et al. 2008a; Fan et al. 2009). However, Qin et al. (2020) reported a substantial reduction in the number of serum helper T cells and regulatory T (Treg)/suppressor T cells in patients with COVID-19 of different severities (Qin et al. 2020). Again, Qin and coworker reportedly established substantial reduction in the number of B- and natural killer (NK) cells in severe cases of COVID-19 (Qin et al. 2020). Furthermore, generated memory cells may not effectively protect from reinfection (Peng et al. 2006; Chen et al. 2010; Channappanavar et al. 2014). Importantly, Qin et al. (2020) reported considerable reduction of memory cells in severe COVID-19 (Qin et al. 2020). Indeed cases of reinfection have been reported in patients who were previously diagnosed and treated of COVID-19 (Lan et al. 2020). Notwithstanding, convalescent serum has demonstrated effectiveness in treating COVID-19 patients, suggesting that viral-specific antibodies may play a critical role in preventing reinfection (Shen et al. 2020). On the contrary, however, decreased immunity of previously treated COVID-19 patients, especially in severe cases, may increase the likelihood of reinfection during a repeat exposure.

The CoV antigenic peptides and single-stranded RNA trigger cellular signalling pathways that mediate the production of inflammatory mediators/molecules in the immune cells (Li et al. 2020a). Experimental investigation by Iwata-Yoshikawa et al. (2019) showed that replication and accumulation of SARS-CoV were integral causes of elevated inflammatory chemokines observed in wild type mice (Iwata-Yoshikawa et al. 2019). The authors also suggested a likely involvement of TMPRSS2 and related proteases in development of inflammatory reactions in SARS-CoV infection (Iwata-Yoshikawa et al. 2019). Accumulation of SARS-CoV peptides and RNA due to viral replication also triggers the activation of neutrophils (Figs. 2, 3) (Li et al. 2020a). Consistent with these findings, Qin et al. (2020)

demonstrated increased neutrophil count in the blood of COVID-19 patients (Qin et al. 2020). Upon activation by CoV, neutrophils release C3a, granzyme B, defensin and other alarmins that inhibit the viral activities by killing infected cells (Reghunathan et al. 2005; Chen et al. 2020b; Li et al. 2020a). However, reports by Guan et al. (2020), Liu et al. (2020c), and Deng et al. (2020) showed leukopenia in COVID-19 patients, which are comparable with previous data reported by Channappanavar et al. (2014) about the marked leukopenia in the acute phase of SARS-CoV infection in humans (Channappanavar et al. 2014). These inconsistencies in data regarding the effects of SARS-CoV-2 on blood cell indices may be due to the different stages of progression of the disease as well as sequestering of both lymphocytes and granulocytes into the sites of inflammation.

The serum monocyte and basophil (Diao et al. 2020; Qin et al. 2020; Wang et al. 2020c; Xu et al. 2020; Zhou et al. 2020b), eosinophil and lymphocyte (Deng et al. 2020; Guan et al. 2020; Liu et al. 2020c; Qin et al. 2020) and thrombocyte (Deng et al. 2020; Guan et al. 2020; Liu et al. 2020c) counts have been consistently shown to decrease in COVID-19 patients. In COVID-19, abnormal blood cell counts suggest atypical immune responses that prime the blood brain barrier for subsequent disruptive processes, resulting to neuroimmune dysregulation and neuroinflammation that worsen the course of progression of SARS-CoV-2 infection (Fig. 2).

Therefore, modulators of the immune system such as cyclosporine A (Liu et al. 2020a), intravenous IgG (Ye et al. 2020), fingolimod (NCT04280588, https://www.clinicaltrials.gov), and anti-CoV-19 antibody from recovered COVID-19 patients (ChiCTR2000030012, http://www.chictr.org) may provide benefits in SARS-CoV-2 infection. Though the effects of several immunomodulators are yet to be reported, preliminary evidence indicates that intravenous IgG, for instance, improves COVID-19 symptoms (Fu et al. 2020), at least in part, by downregulating proinflammatory cytokines, complement proteins and promoting T suppressor cell functions (vide infra) (Katz et al. 2000; Aschermann et al. 2010; Kaufman et al. 2015). In addition, Fu et al. (2020) demonstrated that the anti-inflammatory effects of intravenous IgG against SARS-CoV-2 occur via inhibition of Fc receptor activation.

Immuno-inflammatory stress, oxidative stress, and cytokine storm in SARS-CoV-2 infection

The immune dysregulation in COVID-19 (Ye et al. 2020) favors upregulation of multiple genes that enhance proinflammatory and oxidative stress responses, resulting to inflammatory stress (Reghunathan et al. 2005), oxidative stress (Horowitz et al. 2020; Zhao et al. 2020a), hormonal and neuro-peptide/-transmitter signaling disorder (Zhang

et al. 2020a, b), as well as cytokine storm (Huang et al. 2020; Li et al. 2020b; Liu et al. 2020a) in severe cases of infection.

Oxidative stress

Though there is a scarcity of data, available information indicates the involvement of oxidative stress in the pathogenetic mechanisms of the SARS-CoV-2 infection (Horowitz et al. 2020; Zhao et al. 2020a). Increased expression of oxidative stress genes due to SARS-CoV invasion was reportedly demonstrated to promote downregulation of antioxidant enzymes with elevated expression of prooxidants (Reghunathan et al. 2005). An abnormal level of lactate dehydrogenase was observed in SARS-CoV-2 infected patients (Zhao et al. 2020a). A recent report by Horowitz et al. (2020) also revealed that COVID-19 may cause substantial decrease in antioxidant enzymes such as glutathione, and promote pro-oxidative stress enzymes (Horowitz et al. 2020). Interestingly, high dose (2000 mg) glutathione (per os or intravenous) showed improvement in symptoms one hour after treatment, indicating that antioxidants may provide substantial benefits for use in the treatment of SARS-CoV-2 infection (Horowitz et al. 2020). Importantly, several antioxidants (including vitamin A, C, D, and E) have shown promise for potential use as adjuncts in the treatment of COVID-19 (NCT04323228, NCT04323514, NCT04351490, NCT04363840, NCT04334005, and NCT04344041, https://www.clinicaltrials.gov).

Immuno-inflammatory stress predisposes to hormonal, neuropeptide and neurotransmitter dysregulation in SARS-CoV-2 infection

Up-regulation of alarmins (including the 55–60 kDa microbicidal permeability increasing protein) by SARS-CoV activated monocytes and granulocytes along with increased immune cell chemotaxis (Reghunathan et al. 2005) not only primes the cerebral microenvironment for inflammatory processes, but also, favors disruptive processes in the blood brain barrier by downregulating the expression of junctional proteins that seal the cerebral endothelium (Welcome 2020a, b). Indeed increased leucocyte chemotaxis has been consistently demonstrated in blood brain barrier disruption or neuroinflammation (Takeshita 2012; Welcome 2020c).

Though the mechanisms are not clearly understood, immune dysregulation and inflammatory stress can potentially cause disordered signaling of hormones, neuro-peptide and -transmitters such as VEGF and melatonin (Zhang et al. 2020a, b). VEGF dysregulation due to inflammatory stress has been recently associated with SARS-CoV-2 infection and may underlie the development of neuroinflammation and blood brain barrier disruption in COVID-19 (Zhang et al. 2020a, b). Experimental data indicate that VEGF

can trigger cerebral inflammation (Argaw et al. 2009) and blood brain barrier leakage (Zhang et al. 2000) in several brain pathologies. Argaw et al. (2009) showed that upregulation of VEGF-A in brain disorders downregulates the endothelial tight junction proteins, occludin and claudin-5, in animal model of autoimmune encephalomyelitis (Argaw et al. 2009). Furthermore, intracerebral injection of VEGF-A in mice resulted to corresponding loss of occludin and claudin-5 with concomitant breakdown of the blood brain barrier (Argaw et al. 2009). Thus, VEGF dysregulation in SARS-CoV-2 infection (Zhang et al. 2020a, b) can predispose to blood brain barrier breakdown. The neurotransmitter, melatonin, was demonstrated to effectively attenuate the proinflammatory and oxidative responses in animal models of COVID-19, suggesting that neurotransmitter dysregulation may play a critical role in the pathogenesis of the disease (Zhang et al. 2020a, b). There is also a possible role of glucocorticoid signalling disorder caused by immuno-inflammatory stress in SARS-CoV-2 infection. Indeed, impaired glucocorticoid signalling has been consistently implicated in viral infection (Ng et al. 2013; Biron 2018). A recent analysis showed that impaired glucocorticoid signalling can result from inflammatory/immune dysregulation (Welcome 2020c). Though the mechanisms are not exactly clear, data indicate that impaired glucocorticoid signalling can also prime neuroinflammatory responses especially in stress responsive brain regions (Welcome 2020c). Though glucocorticoids exert pleiotropic effects on the cell, short term treatment in severe cases of COVID-19 was reportedly associated with some benefits (Ye et al. 2020). Clinical trials on short term use of corticosteroids or glucocorticoids (e.g., NCT04329650, NCT04244591, https://www.clinicaltrials.gov) as adjunct therapy in severe cases of SARS-CoV-2 infection also demonstrated evidence of health benefits.

Excessive inflammatory and oxidative stress due to immune dysregulation is responsible for triggering the cytokine storm in SARS-CoV-2 infection

Excessive activation of the immune effector cells by SARS-CoV-2 causes continued release of proinflammatory cytokines such as IL-1β, IL-6, IL-8, IL-12, IL-18, IL-33, granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), TNF-α, transforming growth factor (TGF)-β, IFN-α, IFN-β, IFN-γ, etc. (Li et al. 2017, 2020b; Conti et al. 2020; Ye et al. 2020; Zhang et al. 2020a, b) and chemokines such as C–C motif chemokine ligand (CCL)-2, CCL3, CCL5, CCL7, CCL12, C-X-C motif chemokine ligand (CXCL)-8, CXCL9, CXCL10, IFNγ-induced protein 10 (IP-10), etc. (Li et al. 2020b; Ye et al. 2020). These proinflammatory cytokines and chemokines along with elevated reactive oxygen species (Figs. 2, 3)

(Conti et al. 2020; Zhang et al. 2020a, b) trigger cytokine release syndrome, also known as cytokine storm, a fatal irrepressible systemic inflammatory response (Huang et al. 2020; Li et al. 2020b; Liu et al. 2020a) that progresses to acute respiratory distress syndrome/acute respiratory injury, acute kidney injury, acute cardiac injury, multiple organ failure, coma and death in severe cases of SARS-CoV-2 infection (Xu et al. 2020).

The expression of the pro-inflammatory cytokines/chemokines largely depends on the severity of the illness. Multiple lines of evidence indicate that mild to moderate cases of COVID-19 may be associated with such plasma pro-inflammatory cytokines/chemokines as IL-1β, IFN-γ, MCP-1 and IP-10. In a severe form of the disease, significantly higher levels of TNF-α, IL-8, IL-10, G-CSF, MCP-1, MIP-1A and IP-10 have been reported (Huang et al. 2020; Qin et al. 2020). Furthermore, several studies (Deng et al. 2020; Guan et al. 2020; Liu et al. 2020c) have identified elevation of C-reactive protein (CRP) in COVID-19. Notably, sustained increase of inflammatory molecules in circulation has been associated with blood brain barrier inflammation and leakage (Haruwaka et al. 2019), as well as neuroinflammation in the affected brain regions (Fig. 2) (Biesmans et al. 2013; Zhang et al. 2018). Li et al. (2017) investigated 183 and 236 paediatric patients with acute encephalitis-like syndrome and respiratory tract infection, respectively. The researchers documented increased level of cytokines not only in the serum, but also, significantly higher IL-6, IL-8, MCP-1, and granulocyte macrophage colony-stimulating factor (GM-CSF) levels in CSF of patients with CoV-induced CNS infection than in matched serum samples, indicating a greater vulnerability of the brain to SARS-CoV infection than other organs (Li et al. 2017).

Other inflammatory molecules that may be associated with SARS-CoV infection include lipocalin-2, oligoclonal bands and IgG. Lipocalin 2 is a glycoprotein that is secreted by activated neutrophils, cerebral endothelial cells, and perivascular astrocytes in response to pathological (e.g., inflammatory) stimuli (Ni et al. 2013; Jin et al. 2014; Ferreira et al. 2015). Serum lipocalin-2 is thought to be a crucial biomarker of peripheral inflammation (Ni et al. 2013; Moschen et al. 2017). More importantly, due to its high expression in the CNS and involvement in innate immunity, cerebrospinal lipocalin-2 (Llorens et al. 2020) is currently considered as a potential biomarker of cerebral inflammation or damage (Llorens et al. 2020). Increased expression of lipocalin-2 is associated with cerebral inflammation and blood brain barrier hyperpermeability (Jin et al. 2014; Du et al. 2019). Indeed deficiency of lipocalin 2 expression in the brain reportedly attenuates neuroinflammatory responses and blood brain barrier disruption in animal models of cerebral stroke (Jin et al. 2014). Reghunathan et al. (2005) previously established up-regulation of genes coding for lipocalin 2 in SARS-CoV-infected patients (Reghunathan et al. 2005). These data strongly suggest that SARS-CoV-2 induced upregulation of lipocalin genes can predispose to blood brain barrier damage or neuroinflammation. In recent study, Helms et al. (2020) reported identification of oligoclonal bands and elevated IgG level in the serum of SARS-CoV-2 infected patients (Helms et al. 2020). These oligoclonal bands and IgG indicate B-cell responses resulting from CNS inflammation (Link and Huang 2006; Franciotta et al. 2008). Thus, CNS dysfunctions in SARS-COV-2 infection may be triggered by neuroinflammation and blood brain barrier disruption.

The majority of clinical studies investigating inflammatory biomarkers in COVID-19 frequently showed elevated expression of IL-6 (Huang et al. 2020; Sun et al. 2020; Wang et al. 2020e; Zhou et al. 2020a). For instance, Chen et al. (2020b) and Qin et al. (2020) demonstrated a positive correlation between serum IL-6 levels and severity of illness in COVID-19 patients, suggesting that approved monoclonal antibodies can be explored for potential treatment of COVID-19. Indeed, clinical trials have shown that some monoclonal antibodies such as siltuximab (anti-IL-6 antibody) (NCT04329650, https://www.clinicaltrials.gov) may be beneficial in attenuating the proinflammatory responses in SARS-CoV-2 infection (Table 1). However, due to the relatively long period required in getting approval for these drugs (Table 1), already approved monoclonal antibodies, especially those that inhibit IL-6 and TNF, as well as Bevacizumab (Food and Drug Administration, FDA, 2018), Ruxolitinib (FDA, 2019), Baricitinib (FDA, 2018), and Emapalumab (FDA, 2019) may be considered for possible use in the treatment of SARS-CoV-2 infection with associated inflammatory stress or cytokine storm. Even though the effects of these antibodies on neuroinflammation are not known, previous studies have demonstrated a beneficial role of monoclonal antibodies in psychopathological illnesses (Essali et al. 2019) and multiple sclerosis (Sirbu and Budisteanu 2020), which are characterized by neuroinflammatory response and blood brain barrier disruption (Welcome 2020a, b).

Molecular signalling in SARS-CoV-2 induced immuno-inflammatory stress, oxidative stress, and cytokine storm

Research data suggest the involvement of critical molecular signalling pathways (vide infra) in SARS-CoV-2 infection along with immuno-inflammatory stress, oxidative stress, and cytokine storm. Identification of key molecular mechanisms mediating SARS-CoV-2 invasion of the host cells may provide useful information for COVID-19 therapeutics.

Table 1 List of ongoing clinical trials on the effects of monoclonal antibodies in SARS-CoV-2 infection

Category	Agents	Trial identification number	Country of trial	Current status
Anti-C5aR antibody	Avdoralimab	NCT04371367	France	Phase II
Anti-CCR5 humanized mAb	Leronlimab	NCT04343651	United States	Phase II
Anti-C5 recombinant humanized mAb	Eculizumab	NCT04346797	France	Phase II
Anti-GM-CSF humanized mAb	Gimsilumab	NCT04351243	United States	Phase II
	TJ003234 (TJM2)	NCT04341116	United States	Phase II
Anti-IFNγ mAb	Emapalumab	NCT04324021	Italy	Phase III
Anti-IL-1β humanized mAb	Canakinumab	NCT04365153	United States	Phase II
Anti-IL-6 humanized mAb	Clazakizumab	NCT04343989	United States	Phase II
Anti-IL-6R humanized mAb	Tocilizumab	NCT04317092	Italy	Phase II
	Sarilumab	NCT04315298	United States	Phase III
Anti-PD-1 humanized mAb	Nivolumab	NCT04333914	France	Phase II
	Pembrolizumab	EUCTR2020-001160-28-ES	Spain	Phase II
Anti-VEGF recombinant humanized mAb	Bevacizumab	NCT04305106	China	–
IL-1 receptor antagonist	Anakinra	NCT04324021	Italy	Phase III
JAK 1/2 inhibitor	Ruxolitinib	NCT04334044	Mexico	Phase II
	Baricitinib	NCT04321993	Canada	Phase II

This table is based on data retrieved from "The US National Library of Medicine, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/results?cond=COVID-19&Search=Apply&recrs=a&recrs=f&recrs=e&age_v=&gndr=&type=&rslt= and World Health Organization Database, International Clinical Trials Registry Platform (ICTRP), https://www.who.int/ictrp/search/en/, https://clinicaltrials.gov/ct2/who_table"

mAb monoclonal antibody, *PD-1* programmed cell death receptor 1, *C5aR* complement protein 5a receptor, *CCR5* C–C Motif Chemokine Receptor 5, *C5* complement protein 5, *GM-CSF* granulocyte–macrophage colony stimulating factor, *IFNγ* interferon gamma, *IL-1β* interleukin 1 beta, *IL-6* interleukin 6, *IL-6R* interleukin 6 receptor, *VEGF* vascular endothelial growth factor, *JAK* Janus kinase

JAK/STAT signalling

JAK/STAT (Janus kinase/signal transducer and activator of transcription) signalling is an immune signalling pathway that regulates the processes of proliferation, differentiation, migration, cell survival, and antiviral immunity depending on the cell/tissue type and the physiological/pathophysiological state of the host (Harrison 2012; Jupatanakul et al. 2017). The JAK/STAT pathway also interacts with mitogen-activated protein (MAP) kinase and PI-3-kinase signalling pathways to mediate a range of physiological processes (Fig. 4) (Harrison 2012). The JAK/STAT pathway is activated by cytokines (IFN-α/β/γ, IL1-7, GM-CSF etc.) and growth factors (platelet derived growth factor, growth hormone, epidermal growth factor etc.) (Fig. 4) (Li et al. 2020a; Xin et al. 2020). IFN mediated activation of the JAK/STAT pathway is used by the host cells as a defense mechanism against viral infection by enhancing the expression of IFN-regulated genes (Ma and Suthar 2015; Nelemans and Kikkert 2019). Unfortunately, however, some viruses have acquired properties that are able to overpower the IFN-antiviral effects (Fig. 4). For instance, Lin et al. (2004) reported inhibition of IFN-α-activation of Stat-1, -2, and -3 by the Japanese encephalitis virus (Lin et al. 2004). This virus inhibits the tyrosine phosphorylation of Tyk2 (tyrosine kinase 2), which is associated with IFN-induced JAK activation (Lin et al. 2004). Similarly, SARS-CoV and other

CoVs can block IFN-α/β-induced JAK/STAT signalling using their N protein to antagonise the responses initiated by IFN (Spiegel et al. 2005; Kopecky-Bromberg et al. 2007; Lu et al. 2011).

Evidence indicates that impaired JAK/STAT signalling affects the infectivity of viruses, suggesting that this pathway may serve as a critical target for potential treatment of SARS-CoV infection (Schneider et al. 2014). Interestingly, the JAK/STAT signalling has been implicated in neuroinflammatory and neurodegenerative disorders (Copf et al. 2011). JAK/STAT signalling disorder primes T and myeloid cells to pathogenic phenotypes that cause neuroinflammation (Yang et al. 2010; Qin et al. 2016), in part, by activation of microglia (Qin et al. 2016). In an in vivo study, Qin et al. (2016) demonstrated that AZD1480, a JAK1/2 inhibitor, effectively inhibited the α-synuclein-induced MCH II molecule and inflammatory gene expression in both macrophages and microglia by blocking the activation of Stat-1 and -3 (Qin et al. 2016). Baricitinib, a selective JAK inhibitor with potentially powerful anti-inflammatory action, effectively reduced the levels of the proinflammatory cytokines reported in COVID-19 patients (Richardson et al. 2020; Stebbing et al. 2020). This agent also inhibited clathrin-mediated endocytosis to suppress SARS-CoV-2 invasion of the host cells (Stebbing et al. 2020). The results of a completed clinical trial (NCT04358614, https://www.clinicaltrials.gov) conducted in Italy showed considerable effectiveness of
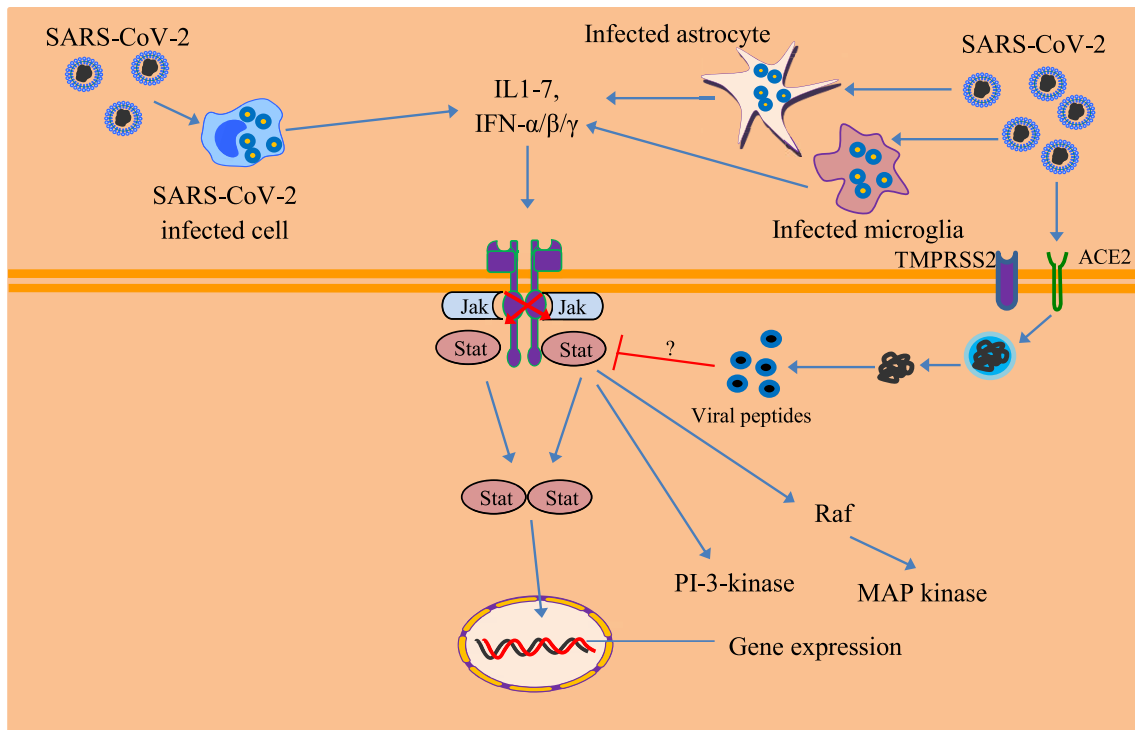
Fig. 4 JAK-STAT signalling in SARS-CoV-2 infection. *IFN* interferon, *IL* interleukin, *JAK* Janus kinase, *MAP kinase* mitogen activated protein kinase, *PI-3-kinase* phosphoinositide 3-kinase, *Raf* Rapidly Accelerated Fibrosarcoma (protein that interacts with small GTPases), *STAT* signal transducers and activators of transcription (see explanation in text)

baricitinib against proinflammatory cytokines (Richardson et al. 2020). Another clinical trial in Germany is evaluating the immunomodulatory and inflammatory role of the JAK 1/2 inhibitor, ruxolitinib (NCT04338958) in SARS-CoV-2 infected patients.

TLR signalling

TLR (toll like receptor) is a type of pattern recognition receptors (PRRs) involved in translating pathogenic signals into cellular responses that are initially aimed at counteracting the invasion but may also lead to collateral tissue damage. There are three main groups of PRRs, which include the membrane type (TLR2, TLR4, mannose receptor, scavenger receptor), the cytoplasmic type (melanoma differentiation-associated gene 5, MDA5; retinoid/inducible gene 1, RIG-1; TLR3, TLR7, TLR8, TLR9, and NLRs—nucleotide-binding oligomerization domain-like receptors) and the secretory type (CRP and mannose/binding lectin, MBL) (Gordon 2002; Kato et al. 2006; Phadwal et al. 2012; De Wit et al. 2016). Interestingly, different PRR types have been implicated in SARS-CoV infection. However, emphasis is made on TLR due to its widespread implication in viral infection (Fig. 5) (De Wit et al. 2016), neuroinflammation and blood brain barrier disruption (Fig. 2) (Welcome , 2019,2020a; b).

The singled stranded RNA and viral proteins constitute the viral pathogen-associated molecular patterns (PAMPs), which are recognized by the innate immune system (Hopcraft and Damania 2017). Following endocytosis of the virus in dendritic, macrophages and vascular endothelial cells, SARS-CoV-2 PAMPs (single stranded RNA) are recognized by the endosomal receptors, TLR7/8/9, and the cytosolic sensors, MDA5 and RIG-1 to trigger the synthesis of cytokines/chemokines and type I IFN such as IFN-α/β (Fig. 5) (Phadwal et al. 2012; De Wit et al. 2016; Li et al. 2016, 2020a; Channappanavar and Perlman 2017). Activation of membrane TLRs (e.g., TLR-2) (Law et al. 2009) by viral components or molecules resulting from the activities of the virus (e.g., HMGB1) can also trigger such reactions (Chen et al. 2004; Wang et al. 2006). Type I IFN synthesis is triggered by interferon response factor (IRF)-3/7 (Fig. 5) (Yang et al. 2015; Deng et al. 2019). The initiation of cytokine/chemokine synthesis is triggered by downstream stimulation of the nuclear factor κB (NF-κB), a transcription factor that is currently known as a master regulator of inflammation (Fig. 5) (Yang et al. 2015; Deng et al. 2019; Conti et al. 2020). The stimulation of NF-κB causes its nuclear translocation, activating gene expression with subsequent release of pro-IL-1β and other inflammatory mediators. The pro-IL-1β for instance, undergoes cleavage by caspase-1, then inflammasome activation, accompanied
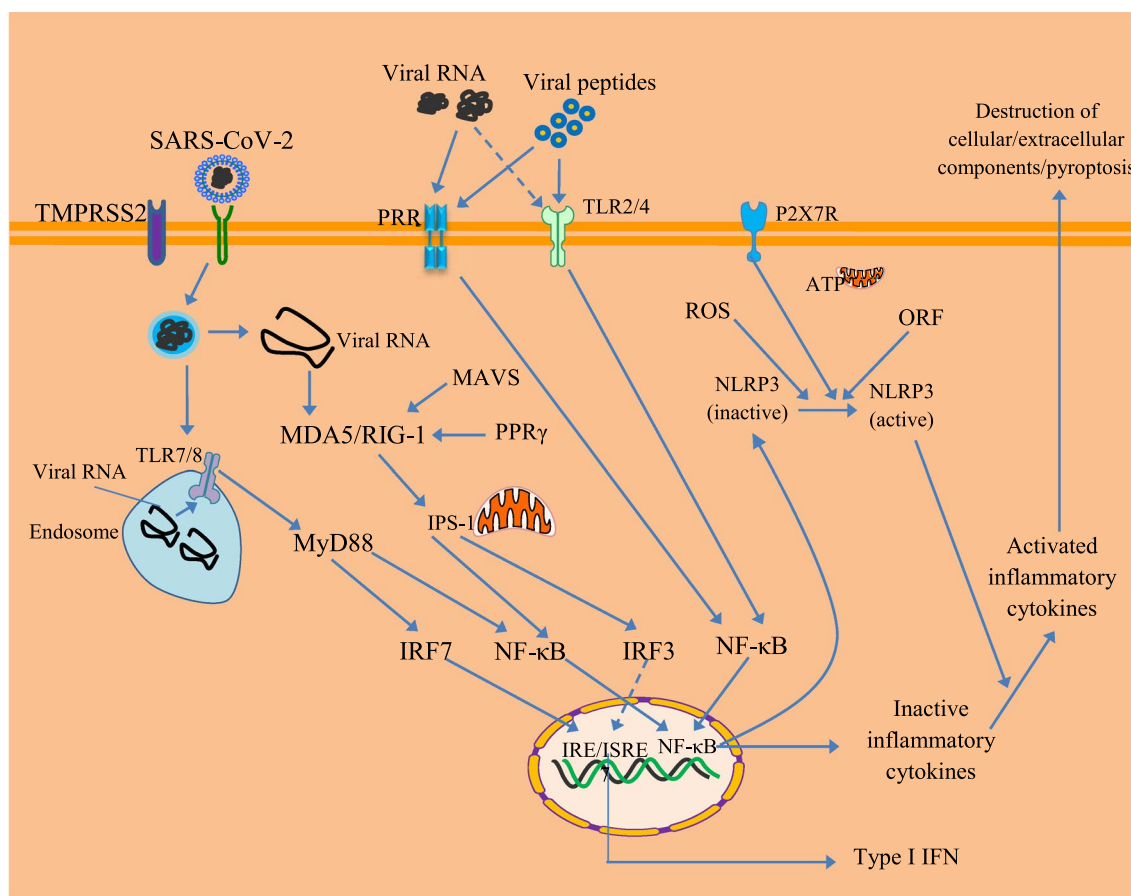
Fig. 5 TLR signalling in SARS-CoV-2 infection. *ACE2* angiotensin converting enzyme 2, *IFN* interferon gamma, *IPS-1* interferon-β promotor stimulator-1, *IRE* interferon regulatory element, *IRF* interferon regulatory factor, *ISRE* Interferon-sensitive response element, *MAVS* mitochondrial antiviral signalling protein, *MDA5* melanoma differentiation-association gene 5, *MyD88* myeloid differentiation primary response 88, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *NLRP3* nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3, *ORF* open reading frame, *P2X7R* P2X purinergic receptor 7, *PPRγ* peroxisome proliferator-activated receptor gamma, *PRR* pattern recognition receptor, *RIG-1* retinoic acid inducible gene-I, *ROS* reactive oxygen species, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TLR* toll-like receptor, *TMPRSS2* transmembrane protease, serine 2 (see explanation in text)

by generation and secretion of active mature IL-1β along with other alarmins that mediate destructive processes in the brain microenvironment (Fig. 5) (Conti et al. 2020). Data indicate that MAVS (mitochondrial antiviral signalling), an adapter protein localized at the outer membrane of the mitochondria, physically interacts with the cytoplasmic viral RNA sensors, RIG-I and MDA5 receptors, to trigger antiviral response through the induction of IFN type I and NF-κB inflammatory signalling (Fig. 5) (Belgnaoui et al. 2011; Sun et al. 2016).

Recent experimental results have implicated the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome in CoV induced immune response (Fig. 5). So, Shi et al. (2019a) showed that SARS-CoV open reading frame (ORF) 8b, which is a type of accessory proteins, activates the NLRP3 inflammasome through the Leucine Rich Repeat domain of

NLRP3 and ASC (apoptosis-associated speck-like protein) to mediate endoplasmic stress and dysfunctional innate immune response in macrophages. Consistently with the functions of NLRP3 inflammasome activation (Welcome 2020c), ORF8b reportedly induced pyroptosis (a form of cell death) in the macrophages (Shi et al. 2019a).

Data also indicate that SARS-CoV moderately upregulates NF-κB and B-cell lymphoma 3-encoded protein (bcl-3) (Reghunathan et al. 2005), a proto-oncogene involved in regulation of cell cycle and granulopoiesis (Kreisel et al. 2011). Interestingly, bcl-3 also interacts with NF-κB (Mansour et al. 2015), Stat3 (Zhao et al. 2016) and peroxisome proliferator-activated receptor gamma (Yang et al. 2009), which are implicated in the regulation of neuroinflammatory responses (Mrak and Landreth 2004; Borlongan et al. 2012; Bai et al. 2016) or blood brain barrier disruption (Borlongan et al. 2012; Bai et al. 2016; Nishikawa et al. 2018). Recent

investigation indicates that SARS-CoV may share similar inflammatory mechanisms with SARS-CoV-2, suggesting that these inflammatory and apoptotic signalling pathways may serve as critical treatment targets in COVID-19 (Fu et al. 2020). Thus, anti-inflammatory agents that inhibit the activation of NF-κB or other key inflammatory signalling pathways may be harnessed for potential treatment of SARS-CoV-2 infection. These anti-inflammatory agents include, but are not limited to, doxycycline (NCT04371952, NCT04407130, https://www.clinicaltrials.gov), minocycline (IRCT20081019001369N4, https://www.irct.ir) (Sun et al. 2015), azithromycin (NCT04332107, NCT04359316) (Stellari et al. 2014; Haydar et al. 2019), fluoxetine (NCT04377308), vinpocetine (NCT02878772), ezetimibe (NCT01370603), atorvastatin (NCT04380402), simvastatin (NCT01424891, NCT04348695), statin (NCT04407273), lenalidomide (NCT04361643), zinc and vitamin D3 (NCT03005496), N-acetylcysteine (NCT04374461), and dexamethasone (NCT04347980, NCT04327401, NCT04395105) (https://www.clinicaltrials.gov).

Complement protein hyperactivation may drive the pathological sequelae of SARS-CoV-2 induced CNS damage

The complement system is a critical part of the host defense system that functions in concert with PRRs to neutralize microbial (including viral) invasion through the activation of adaptive immune response (Gralinski et al. 2018). In a study conducted by Gralinski et al. (2018), it was demonstrated that intranasal SARS-CoV infection of C57BL/6J mice resulted in considerable activation of the complement system beginning from day 1 of inoculation along with inflammatory cytokines/chemokines and immune system dysregulation in the lung (Gralinski et al. 2018). In contrast, C3 deficient mice infected with SARS-CoV had substantially reduced pulmonary impairment with decreased expression of proinflammatory cytokines/chemokines, infiltration of the lungs by neutrophils and monocytes despite similar pulmonary viral load compared with the wild type mice (Gralinski et al. 2018). Previous investigation has also implicated this central component of the complement cascade in SARS-CoV induced innate immune dysregulation (Reghunathan et al. 2005). Accumulating evidence indicates that disordered activation of the complement proteins can trigger neuroinflammation and prime the blood brain barrier for destructive processes (Orsini et al. 2014; Magdalon et al. 2020). Some pathogens can induce the stimulation of the G-protein coupled receptor, C5a receptor 1 (C5aR1), to initiate inflammatory processes in brain (Herrmann et al. 2018). Indeed, the complement protein C5a activates its cognate receptor (C5aR1) to cause hyperpermeability of the blood brain barrier in neuroinflammatory disorders, in part, by

interacting with the NF-κB and microRNA (Jacob and Alexander 2014). Interestingly, inhibition of C5aR1 was reportedly shown to confer a considerable level of protection in brain disorders involving neuroinflammatory responses and blood brain barrier disruption (Jacob and Alexander 2014). Jiang et al. (2019) reported complement overactivation in macrophages, which resulted in immunopathology with overexpression of caspase-1 and IL-1β levels in the serum, and subsequently, pyroptosis of these cells in a mouse model of MERS-CoV infection (Jiang et al. 2019). Notwithstanding, treatment with anti-C5aR1 antibody effectively suppressed the expression of caspase-1 and IL-1β, to abrogate the immunopathology and pyroptosis of the macrophages, suggesting that C5a/C5aR1 signalling pathway constitutes a potential target for the treatment of SARS-CoV-2 infection (Jiang et al. 2019). Comparable findings were reported by Jiang et al. (2018). Inhibition of the complement proteins or their receptors is currently considered as a novel treatment option in many neuropathological diseases (Brennan et al. 2016; Carpanini et al. 2019). Importantly, some clinical trials on SARS-CoV-2 also target the complement proteins (Table 1).

Fas and other apoptotic signalling pathways

Fas (CD95) signalling is a pathway that involves interaction between the type II transmembrane Fas ligand (FasL) and the membrane spanning Fas receptor (FasR) that leads to apoptosis in activated cells (Fig. 6) (Marfè et al. 2011). Upon activation of FasL/FasR, the adaptor Fas-associated death domain (FADD) is recruited to activate caspases-8/10, forming the 'death-receptor complex', which contains procaspases (Fig. 6). The procaspases pass through a series of cleavage reactions that generate active caspases, which in turn mediate the generation of caspases-3/6/7, ultimately culminating in apoptosis (Fig. 6) (Ye et al. 2020). Apart from the FasL/FasR, the TNF/TNFR (tumor necrosis factor receptor)/TNFR-associated death domain (TRADD) signalling has also been implicated in apoptosis (Fig. 6) (Ye et al. 2020). Again, IFN-α/β/γ can induce inflammatory reactions that mobilize the Fas/FasL or TNF-related apoptosis-inducing ligand (TRAIL)/DR5 (death receptor 5) to cause apoptotic cell death (Fig. 6) (Ye et al. 2020). Furthermore, Xiong et al. (2020) reported upregulation of p53 pathway with resultant apoptotic events in monocytes and lymphocytes of COVID-19 patients, suggesting the involvement of multiple pathways in SARS-CoV-2 induced cell-death signalling (Xiong et al. 2020). Experimental results suggest that the mouse hepatitis virus (also known as murine CoV, and closely related to the human CoV-OC43) that causes hepatitis and CNS pathology in mice activates the Fas signalling pathway through the recruitment of Fas, FADD and procaspase-8 to form the 'death-receptor complex' (Liu and
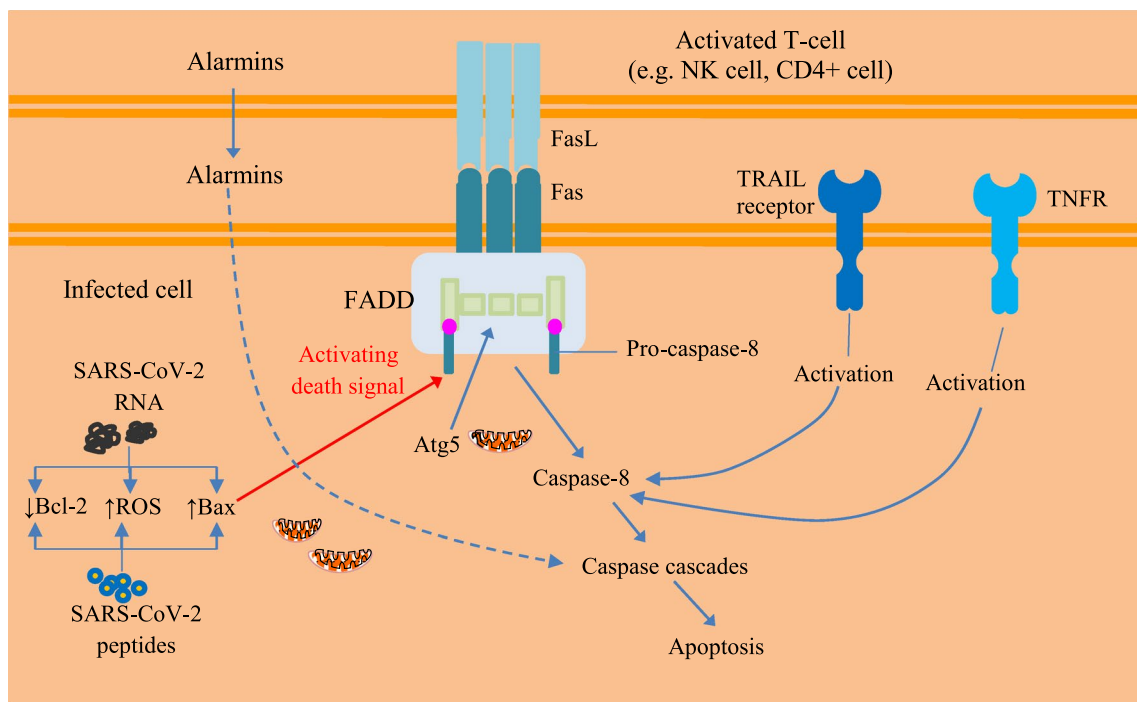
Fig. 6 Fas signalling in SARS-CoV-2 infection. *Atg5* autophagy 5 protein, *bax* Bcl-2-associated X protein, *bcl-2* B-cell lymphoma 2-encoded protein, *CD* cluster of differentiation, *FADD* Fas-associated death domain, *Fas* FS-7-associated surface antigen, *FasL* Fas ligand, *FasR* Fas receptor, *NK* natural killer, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *TNFR* tumor necrosis factor receptor, *TRAIL* TNF(tumor necrosis factor)-related apoptosis-inducing ligand (see explanation in text)

Zhang 2007). Through a series of cleavage reactions, this complex activates apoptotic cell death in rat oligodendrocytes (Liu and Zhang 2007). However, treatment with the Fas/FasL blocker, Fas/Fc chimera, effectively suppressed apoptosis by inhibiting the formation of the 'death-receptor complex', at least in part, via repression of caspase-8 activation in murine CoV-infected oligodendrocytes (Liu and Zhang 2007). Marfè et al. (2011) also studied the effects of canine CoV type II in A-72 canine cell line and showed that CoV induces substantial increase in TRAIL expression along with up-regulation of Fas/FasL (Marfè et al. 2011). Concomitantly, there was an increase in bax (Bcl-2-associated X) and a decrease in bcl-2 protein expression, indicating a proapoptotic response (Marfè et al. 2011). Though the mechanisms are yet to be completely understood, further research revealed that the effects of canine CoV type II infection on cell death signalling was associated with modulation of sirtuin and forkhead box O (Marfè et al. 2011). Evidence also suggests that mitochondrial metabolic dysregulation resulting to elevated ROS can trigger the cytochrome c activities to activate caspase-3/9, which in turn initiates the proapoptotic response in SARS-CoV (Wong et al. 2005; Zhang et al. 2007). In an in vitro model using SARS-CoV-infected Vero cell line, Ren et al. (2005) showed caspase 3 activation, bcl-2 downregulation, and bax upregulation, which ultimately resulted to apoptosis of the cells (Ren et al.

2005). Though the exact mechanisms are not completely known, MAVS is speculated to play a role in regulation of apoptotic events and metabolic activities by engaging multiple signalling pathways that link the mitochondria with endoplasmic reticulum, peroxisomes and autophagosomes (Belgnaoui et al. 2011). Further investigation is required to unravel specific molecular mechanisms involved in translating pathogenic signals from CoV to cytosolic metabolic and stress sensors such as the sirtuins and forkhead box O that modulate cellular responses to inflammation, immune and metabolic dysregulation.

Autophagy signalling

Autophagy refers to a process of self-degradation of cellular constituents, characterized by sequestration of cell organelles or cytosolic components into autophagosomes that merge with lysosomes for degradation (He and Klionsky 2009). The process is usually triggered by inflammatory, oxidative, and endoplasmic reticulum stress, as well as pathogenic invasion (Kolattukudy and Niu 2012; Trachsel-Moncho et al. 2018). Research data have implicated multiple signalling pathways in the initiation of autophagy (Vergne et al. 2009; Li et al. 2015; Zeng and Ju 2018; Rahman et al. 2020). Though autophagy is a survival mechanism essential in clearing worn out components of the cell (Glick et al.

2010), defective autophagy signalling plays an important role in the pathogenesis of several diseases including infectious and inflammatory diseases of the CNS (He and Klionsky 2009). While the mechanisms are not clearly understood, data (Maier and Britton 2012; Shi et al. 2019a) indicate that the cytotoxic effects exerted by SARS-CoV on the host cells not only cause dysfunctional activation of the innate immune system, but also, aberrant activation of the autophagy signalling pathway. Indeed Shi et al. (2019a, b) demonstrated that aggregation of SARS-CoV ORF8b activates endoplasmic reticulum stress response, lysosomal dysfunction and the transcription factor EB, a master regulator of autophagy and lysosomal biogenesis (Shi et al. 2019a). Similarly, Liu et al. (2014) showed that SARS-CoV ORF-9b interacts with the MAVS through a series of signalling reactions that trigger the degradation of MAVS and TNF receptor associated factor 3/6 by ubiquitination with the involvement of proteasomes, thereby reducing the host cell IFN responses. Importantly, the authors also demonstrated that increase in ORF-9b expression resulted in autophagy induction, which was dependent on expression of Atg5 (autophagy 5 protein) (Shi et al. 2014), a protein that plays a central role in cell death by interacting with FADD (Fig. 6) (Pyo et al. 2005). MAVS activation has been consistently known to play an integral role in autophagy (Belgnaoui et al. 2011; Sun et al. 2016; Shi et al. 2019b). Available evidence also suggests that CoV infected cells, especially during viral replication, generate autophagosomes with increased expression of the microtubule associated protein 1A/1B light chain 3 (LC3)—a central autophagy protein involved in the biogenesis of autophagosomes (Klionsky et al. 2012; Maier and Britton 2012). Importantly, Sun et al. (2016) demonstrated that MAVS directly interacts with LC3 to trigger autophagy, suggesting that MAVS may serve as a major receptor during autophagy induction (Sun et al. 2016). Interestingly, Xiong et al. (2020) found upregulation of autophagy in monocytes, T-, NK- and B cells of SARS-CoV-2 infected patients (Xiong et al. 2020). These data suggest that defective autophagy signalling due to SARS-CoV-2 infection may promote uncontrolled immune cell death, and provide information for further research that may unravel possible mechanisms involved in SARS-CoV-2 induced leukopenia and thrombocytopenia, and identification of effective treatment options for SARS-CoV-2 infection.

Effects of ACE2 downregulation by SARS-CoV-2 neuroinvasion

Downregulation of ACE2 by CoV facilitates cellular and tissue injury (Li 2015), which further worsens the neuroinflammatory responses, oxidative stress and cerebrovascular endothelial impairment (Peña-Silva et al. 2012; Zhang et al. 2020a, b). The neuroinflammatory responses are characterized by increased macrophage infiltration with continued production of proinflammatory cytokines and chemokines (Oudit et al. 2009). However, the proinflammatory cytokines and chemokines may be transported into the brain via the circulatory system (from other sites of viral invasion—lungs, gut etc.), which further worsen blood brain barrier dysfunction or inflammatory processes in the cerebral microenvironment (Welcome 2020b). SARS-CoV invasion with downregulation of ACE2 has been reportedly associated with inflammation in postmortem tissues (Oudit et al. 2009). ACE2 downregulation due to SARS-CoV infection reportedly reversed the protective role of ACE2 overexpression not only in peripheral tissues, but also, CNS (Xia and Lazartigues 2008). Cerebral ACE2 overexpression was demonstrated to substantially reduce cyclooxygenase (COX)-1 or COX-2-mediated neuroinflammation and oxidative stress, thereby resulting in an improvement in the antioxidant status and nitric oxide homeostasis (Sriramula et al. 2015). Thus, pharmacological activation of ACE2 may confer substantial protection against the neuropathological sequelae of SARS-CoV-2 infection. Pharmacological ACE2 activators, which include diminazene aceturate (Hernández Prada et al. 2008; Shenoy et al. 2013; Haber et al. 2014), resorcinolnaphthalein and xanthenone (Hernández Prada et al. 2008; Haber et al. 2014) have been demonstrated to confer anti-inflammatory and vasoprotective effects, and restoration of endothelial dysfunction in animal models. However, their roles in attenuating inflammatory responses and endothelial dysfunction have not been established in humans. Two clinical trials in Europe are assessing potential use of recombinant human ACE2 (EUCTR2020-001172-15-AT & EUCTR2020-001172-15-DK, https://www.clinicaltrialsregister.eu) as a treatment option in COVID-19 patients.

Factors determining the severity of SARS-CoV-2 infection

The infectivity of SARS-CoV-2 depends on a range of factors including genetic polymorphisms of molecules implicated in immune response (Conti et al. 2020), viral load (Liu et al. 2020d; Zheng et al. 2020), presence of chronic illnesses (Li et al. 2020c), ageing, development, and lifestyle such as smoking and diet (Li et al. 2020c).

Research has shown that certain polymorphisms of the *HLA* gene either promote or reduce susceptibility to SARS-CoV infection (Yuan et al. 2014). In particular, *MBL* gene polymorphisms have been reportedly demonstrated to be associated with risk of SARS-CoV infection (MBL is a component of the innate immune system, whose activation can lead to complement protein C3 and C4 cleavage, required for opsonization and phagocytosis) (Zhang et al. 2005). Similar data were reported by Tu et al. (2015), who revealed an

association between the *MBL* B allele and increased risk of SARS-CoV infection in a Chinese population of 932 patients with SARS-CoV. Notably, Tu et al. (2015) also showed that the G-2518A polymorphism at the *CCL2* gene can potentially increase the susceptibility to SARS-CoV infection (Tu et al. 2015). Furthermore, *MBL* B allele and *CCL2* G-2518A polymorphisms had a cumulative effect on SARS-CoV infection (Tu et al. 2015) that may, at least in part, explain why some individuals with multiple susceptible polymorphisms may develop serious complications associated with SARS-CoV-2 infection. More so, polymorphism of CLEC4M (type II transmembrane C-type lectin domain family 4 member M), a putative receptor for CoV is also associated with risk of SARS-CoV infection (Li et al. 2008b).

Importantly, ACE2 polymorphisms have been associated with susceptibility to SARS-CoV-2 infection, multi-organ dysfunctions, and COVID-19 outcome (Devaux et al. 2020). In contrast to the results of previous research (Chiu et al. 2004), recent experimental findings indicate that certain variants of the human ACE2 can increase the susceptibility to SARS-CoV-2 infection, whereas other ACE2 variants confer protection against SARS-CoV-2 invasion (Stawiski et al. 2020). Indeed, the ACE2 receptors on the surface of endothelial cells of blood vessels (Hamming et al. 2004) provide crucial pathway for SARS-CoV-2 entry, and may be responsible for the 'endotheliopathic' effects of SARS-CoV-2 on organ damage at a very early stage of infection. SARS-CoV-2 invasion of endothelial cells can cause inflammation of the endothelium (endotheliitis) and may also be responsible for CoV-associated disorders such as disseminated intravascular coagulopathy, and the recently identified pediatric multisystem inflammatory syndrome (Varga et al. 2020). Interestingly, in vitro experiment using engineered human blood vessel organoids and in vivo data from COVID-19 patients have confirmed the involvement of endothelial cells in the pathogenesis of COVID-19 (Varga et al. 2020). These data suggest that COVID-19 associated cerebrovascular diseases such as cerebral thrombosis, ischaemic and haemorrhagic stroke, at least in part, may be due to endotheliitis triggered by SARS-CoV-2 invasion of the endothelial cells. Though the mechanism of dysregulation of vascular endothelial cell ACE2 that resultsin organ dysfunctions is not clearly understood, ACE2 dysregulation can potentially cause calcium dyshomeostasis and metabolic derangement, activating platelet aggregation, concomitantly with increased cell permeability and inflammatory responses as well as oxidative stress that trigger a series of pathophysiological processes, culminating in blood brain barrier disruption, neuroinflammation, and neurodegeneration (Pierce et al. 2017). Thus, endothelial cells are critical to several aspects of organ and system malfunctions, including dysregulation of immune cell trafficking across the endothelium in SARS-CoV-2 infection.

In a relatively recent report, Wang and colleagues revealed that elevated glycosylated hemoglobin (HbA1c) level is associated with higher mortality in COVID-19 patients (Wang et al. 2020d). Indeed, HbA1c is associated with systemic inflammation, hypercoagulability, and low arterial oxygen saturation in COVID-19 (Wang et al. 2020d). Furthermore, Wang et al. (2020d) reported a positive correlation between HbA1c and CRP levels (Wang et al. 2020d). Guo et al. (2020) also found that COVID-19 patients with diabetes, without evidence of comorbidity, were at higher risk of excessive inflammation (due to uncontrolled secretion of IL-6 and CRP) and hypercoagulable states. Surprisingly, the inflammatory responses in diabetes itself have been shown to also predispose to blood brain barrier impairment and neuroinflammation. Evidence from animal experimental indicates that diabetes causes blood–brain barrier dysfunction, neuroinflammation and neurodegeneration (Srodulski et al. 2014; Takechi et al. 2017). Similar findings are reported elsewhere (Brook et al. 2019). These data may explain why the severity of COVID-19 is higher in diabetic patients compared to those without diabetes. Therefore, HbA1c level on admission may be essential is determining the severity of COVID-19. Consequently, reduction in HbA1c level with pharmacological agents such as sevelamer (NCT01493050, https://www.clinicaltrials.gov) (Vlassara et al. 2012) and vitamin C (Kotb and Azzam 2015) may provide health benefits to diabetic patients with COVID-19.

The neuroimmnue dysregulation in SARS-CoV-2 infection is also dependent on the viral load and the severity of COVID-19 (Liu et al. 2020d; Zheng et al. 2020). The effect of chronic diseases, ageing, development, and lifestyle pattern (smoking and diet) on the severity of SARS-CoV-2 infection has been discussed (Li et al. 2020c).

Conclusion

In addition to the pathological impact on the respiratory and gastrointestinal tract, SARS-CoV-2 infection considerably affects CNS functions through the humoral and neural pathways due to the widespread cerebral expression of ACE2 and proteases essential for the viral invasion. SARS-CoV-2 induced cerebral damage is mainly characterized by neuroinflammation and blood brain barrier disruption due to replication and accumulation of viral RNA, its antigenic peptides, downregulation of ACE2, increased activity of the transmembrane protease serine 2, and cathepsin L. These changes favor upregulation of proinflammatory cytokines/chemokines, generation of reactive oxygen species, downregulation of antioxidant defense system, and hormonal/neurotransmitter dysregulation, which collectively underlie the neuropathologic sequelae of SARS-CoV-2 neuroinvasion. The viral RNA or antigenic peptides activate or interact with

molecular signalling pathways mediated by pattern recognition receptors (e.g., toll-like receptors), nuclear factor kappa B, Janus kinase/signal transducer and activator of transcription, and complement cascades, as well as cell suicide molecules, which constitute key molecular targets for potential treatment of COVID-19. The spate of emerging therapeutics for SARS-CoV-2 infection (including associated CNS impairment) provides hope in the fight against COVID-19.

Declarations

Conflict of interest None declared.

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