SARS-CoV-2 may trigger inflammasome and pyroptosis in the central nervous system: a mechanistic view of neurotropism

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Received: 11 June 2021 / Accepted: 21 June 2021 / Published online: 9 July 2021
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Abstract
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can enter the central nervous system and cause several neurological manifestations. Data from cerebrospinal fluid analyses and postmortem samples have been shown that SARS-CoV-2 has neuroinvasive properties. Therefore, ongoing studies have focused on mechanisms involved in neurotropism and neural injuries of SARS-CoV-2. The inflammasome is a part of the innate immune system that is responsible for the secretion and activation of several pro-inflammatory cytokines, such as interleukin-1β, interleukin-6, and interleukin-18. Since cytokine storm has been known as a major mechanism followed by SARS-CoV-2, inflammasome may trigger an inflammatory form of lytic programmed cell death (pyroptosis) following SARS-CoV-2 infection and contribute to associated neurological complications. We reviewed and discussed the possible role of inflammasome and its consequence pyroptosis following coronavirus infections as potential mechanisms of neurotropism by SARS-CoV-2. Further studies, particularly postmortem analysis of brain samples obtained from COVID-19 patients, can shed light on the possible role of the inflammasome in neurotropism of SARS-CoV-2.

Keywords SARS-CoV-2 · Inflammasome · Pyroptosis · Neurotropism · Pro-inflammatory cytokines

Abbreviations

ACE2 Angiotensin-converting enzyme 2
ALR AIM-2-like receptor
ARDS Acute respiratory distress syndrome
ASC Adaptor protein apoptosis-associated speck-like protein containing a caspase-recruitment domain
BBB Blood–brain barrier
CCL2 Chemokine (C–C motif) ligand 2
CD147 Cluster of differentiation 147
CNS Central nervous system
CoVs Coronaviruses
COVID-19 Coronavirus disease 2019
CXCL10 CXC motif chemokine ligand 10
DAMP Damage-associated molecular pattern
DPP4 Dipeptidyl-peptidase 4
E protein Envelope protein
GFAP Glial fibrillary acidic protein
IFNβ Interferon beta
IL-1β Interleukin 1beta
IL-6 Interleukin 6
IL-18 Interleukin 18
MERS-CoV Middle East respiratory syndrome coronavirus

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Introduction

Neurological manifestations have been reported in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The neuroinvasive susceptibility of coronaviruses has been depicted in humans in previous epidemics (Hung et al., 2003; Sepehrinezhad et al., 2020). Recently, the brain autopsy findings in a patient with SARS-CoV-2 have suggested that this virus may gain access to the CNS by infecting endothelial cells via transcytosis to neural tissue (Paniz-Mondolfi et al., 2020). Furthermore, the post-mortem findings in patients who died from COVID-19 have revealed the presence of SARS-CoV-2 in the cortical neurons associated with minimal immune cell infiltrates in brain tissues (Song et al., 2020a). Recently, we demonstrated the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) of patients with COVID-19 infection, who suffering from severe neurological manifestations. Despite several reports of neurological manifestations and neuroinvasiveness of SARS-CoV-2 during infection (Guan et al., 2020; Sepehrinezhad et al., 2020; Mao et al., 2020; Paniz-Mondolfi et al., 2020; Song et al., 2020b), the determination of mechanisms underlying SARS-CoV-2-mediated neurological manifestation and brain injury are warranted. Among different mechanisms described for SARS-CoV-2, cytokine storm (i.e., releasing of the pro-inflammatory cytokines) has been suggested as the major life-threatening complication (Zhao et al., 2021). Growing evidence has revealed that the inflammasome is activated by CoVs infections. Increasing levels of inflammasome-induced pro-inflammatory cytokines, such as interleukin-1beta (IL-1β) and interleukin 6 (IL-6), have been reported in MERS-CoV and SARS-CoV cases (He et al., 2006; Lau et al., 2013). In SARS-CoV-2, alveolar macrophages have been speculated as the main source of inflammation (Channappanavar et al., 2016). Immunofluorescence observations of samples from patients who died from SARS-CoV-2 infection indicated that the inflammasome pathway plays an important role in the pathogenesis of SARS-CoV-2 (Toldo et al., 2021). Recently, it has been shown that cell death of monocytes derived from COVID-19 patients was caused by the production of IL-1B, expression of caspase-1, and cleavage of gasdermin D as the main components of the inflammasome (Ferreira et al., 2021). Furthermore, interleukin 18 (IL-18) as other inflammasome-induced cytokines was increased in COVID-19 patients (Satış et al., 2021). In the same way, inhibition of IL-1B displayed efficient effects on oxygenation in patients with COVID-19 pneumonia (Landi et al., 2020). These findings suggest the involvement of inflammasomes in the pathophysiology of CoVs infections. Therefore, the aim of the present study was to review neurotropism mechanisms of SARS-CoV-2 and discuss the probable mechanisms of the inflammasome in COVID-19 patients with neurological manifestations.

A brief overview of inflammasome and pyroptosis

The three genetically described cell death pathways that have been extensively explored during the last decades are apoptosis, necroptosis, and pyroptosis. The first programmed cell death is apoptosis known as immunologically silent, which usually causes cell death through caspase-3/7-dependent manner. On the other hand, lytic cell death is caused by necroptosis and pyroptosis via the release of immunostimulatory substances. Pyroptosis in the canonical model is induced by activation of intracellular multiprotein signalling complexes known as the inflammasomes. Inflammasomes are cytosolic molecular complexes of the innate immune system that are activated in response to cellular infections and other stressors. Activation of caspase-1 and maturation of pro-inflammatory cytokines, such as IL-1β, IL-6, and IL-18 as consequences of inflammasome assembly, can restrict the intracellular pathogen replication through induction of programmed cell death (Bergsbaken et al., 2009). Inflammasome activity usually is triggered by various sensor proteins, such as nucleotide-binding oligomerization domain-like receptor (NOD-like receptor; NLR) or AIM-2-like receptor (ALR). Inflammasomes are named according to their sensor proteins, such as NLRP1, NLRP2, NLRP3, NLRP6, NLRP12, NLRC4, and AIM2 (Ting et al., 2008; Lugrin and Martinon, 2018). The adaptor protein apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) is associated with pro-inflammatory
SARS-CoV-2 may trigger inflammasome and pyroptosis in the central nervous system: a mechanistic…

Among different types of sensor proteins, NLRP3 is an important inflammasome, because it can restrict intracellular pathogen replication. The NLRP3 inflammasome is expressed by several myeloid cells, especially macrophages. The NLRP3 is activated by several stimuli including pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and viral pathogens (He et al., 2010; Toma et al., 2010; Thomas et al., 2009; Mariathasan et al., 2006). The NLRP3 inflammasome response can be classified into activation and maintenance processes. The activation of the NLRP3 inflammasome is usually induced by ligands (i.e., PAMPs or DAMPs). These ligands bind to a pattern recognition receptor (PRR), mainly toll-like receptor-4 (TLR-4), and activate the nuclear factor kappa B (NF-κB) pathway. NF-κB increases the expression of NLRP3 protein and its proinflammatory cytokines (e.g., Pro-IL-1β and Pro-IL-18) (Bauernfeind et al., 2009). On one hand, the release of the lysosomal components, potassium efflux, and mitochondrial dysfunctions play important roles in the maintenance phase of NLRP3 inflammasome. In this step, the generation of reactive oxygen species (ROS), the increase of calcium concentration, and the release of mitochondrial DNA into the cytosol maintain the inflammasome complex (Guo et al., 2015). Followed by the activated inflammasome, caspase-1 is activated and cleavages the N-terminal domain of gasdermin-D. These changes lead to a pore in the plasma membrane called pyroptosis (Chen et al., 2016). Furthermore, activated inflammasome converts the Pro-IL-1β and Pro-IL-18 to mature forms and releases them into the extracellular space (Fig. 2).

**Fig. 1** Schematic representation of NLRP3 inflammasome components. Three components of inflammasome are NLRP3 proteins, ASC, and caspase-1.

### Activation of inflammasome and coronavirus infections

The inflammasome is activated by CoVs infections and releases pro-inflammatory cytokines. Raising the production of pro-inflammatory cytokines is the main reason for the progression of acute respiratory distress syndrome (ARDS) and death followed by CoVs infections (Badraoui et al., 2020; Petrosillo et al., 2020). Increasing levels of inflammasome-induced pro-inflammatory cytokines, such as IL-1β and IL-6, have been reported in MERS-CoV and SARS-CoV cases (He et al., 2006; Lau et al., 2013). In the case of SARS-CoV-2, the source of inflammation is macrophages that are activated by PAMPs/DAMPs-derived infected pneumocytes (Channappanavar et al., 2016). The expression of NLRP3 inflammasome and caspase-1 were significantly increased in COVID-19 patients (Toldo et al., 2021). Viroporins are hydrophobic multifunctional proteins that play vital roles in inflammasome activation. Viroporins are encoded by viral RNA and contribute to both virus entry to the host cells and virus release from infected cells (Nieva et al., 2012). These viroporins can form oligomeric ion channels or pores across the cell membrane. The SARS-CoV can encode several viroporins, such as the envelope (E) protein and open reading frame 3a (e.g., ORF3a, ORF8a, and ORF8b) (Nieto-Torres et al., 2014). The E protein activates the NF-kB pathway (DeDiego et al., 2014) and increases the release of calcium from the Golgi apparatus (Nieto-Torres et al., 2015). On the other hand, ORF3a modifies ASC through a tumor necrosis factor receptor-associated factor 3 (TRAF3)-dependent
mechanism (Siu et al., 2019), while ORF8b interacts with the NLRP3 protein (Shi et al., 2019). Finally, by combining these interactions, NLRP3 inflammasome is activated and pyroptosis is formed by cleavage of the gasdermin-D at the linker section between the amino-terminal and carboxyl tail (Fig. 3). During pyroptosis, sodium and water can enter the infected cells and cause cell swelling. The ORF3a accelerates the inflammasome assembly by increasing the potassium efflux and releasing ROS generation (Xu et al., 2020). Most important, as it has been shown in recent studies, SARS-CoV-2 has several similarities in terms of phylogenetically, structurally, and pathogenicity with SARS-CoV. For instance, genomic sequence analysis tools indicated that SARS-CoV, SARS-CoV-2, and MERS belong to the cluster of beta coronaviruses (Chen et al., 2020; Cui et al., 2019). SARS-CoV and SARS-CoV-2 use ACE2 receptors to enter the host cells (Wan et al., 2020). Furthermore, both of them present very similar symptoms and clinical manifestations in infected people (Gerges Harb et al., 2020; Hu et al., 2020). Therefore, inflammasome-dependent pathogenicity may be seen in SARS-CoV-2.

**Inflammasome may mediate SARS-CoV-2-induced neurotropism**

The activation of NLRP3 and its role in the pathophysiology of several neurological disorders, such as Alzheimer’s disease (Halle et al., 2008; Scott et al., 2020), Parkinson’s disease (Wang et al., 2016; Zhou et al., 2016), multiple sclerosis (Jahanbazi Jahan-Abad et al., 2019; Malhotra et al., 2020), and traumatic brain injury (O’Brien, 2020) have been described. Neuroinflammation is a distinguished inflammatory process in response to virus infections (i.e., neuroinvasion). It seems that SARS-CoV-2 can target and infect the BBB endothelial cells, neurons, microglia, and astrocytes (Ribeiro et al., 2021) via ACE2 and cluster of
SARS-CoV-2 may trigger inflammasome and pyroptosis in the central nervous system: a mechanistic approach.

Differentiation 147 (CD147) receptors (Ribeiro et al., 2021; Chen et al., 2021). Microglia and astrocytes are two major sources of proinflammatory cytokines and consequently neuroinflammation (Kwon and Koh, 2020). Microglia have phagocytosis activity against infiltrating pathogens and remove neurotoxic agents. SARS-CoV-2 can directly infect brain astrocytes neurons in COVID-19 patients (Crunfli et al., 2020). Another postmortem analysis indicated reactive astrogliosis and microglial activation in the medulla oblongata and cerebellum as well as lymphocyte infiltration in the perivascular and parenchymal area in patients who died from COVID-19 (Matschke et al., 2020).

Therefore, following SARS-CoV-2 infections, microglia and astrocytes are two main targeted cells by the virus. As studies revealed, SARS-CoV-2 can activate NLRP3 inflammasome (Xu et al., 2020; Ferreira et al., 2021; Sepehrinezhad et al., 2020; Rezaeitalab et al., 2021). Exposure of BV-2 microglia to SARS-CoV-2 spike glycoprotein S1 increased the production of NLRP3 protein, IL-1β, IL-6, tumor necrosis factor-alpha (TNFα), and nitric oxide.

**Fig. 3** Proposed mechanisms of neuronal injury by SARS-CoV-2. In the CNS, SARS-CoV-2 enters into the glial cells, in particular microglia, through an endocytosis-dependent manner via interaction of spike proteins with ACE2 receptor. After internalization, viral RNA replicates and viral structural proteins, as well as viroporins, such as E protein, ORF3a, and ORF8b, are translated. The E proteins cause the release of calcium from the Golgi apparatus. The ORF8b interacts with NLRP3 protein. The ORF3a interacts with TRAF3 ubiquitinates ASC protein as well as increases the efflux of potassium from the cell membrane. These events along with mitochondrial dysfunctions, potassium efflux, and activated P2X7 receptors lead to activation of NLRP3 inflammasome and consequently activated caspase-1-induced pyroptosis in the glial cells. Activated proinflammatory cytokines, such as IL-1β and IL-18, trigger the production of other proinflammatory cytokines, such as TNFα, IFNβ, IL-6, and CCL2 into the CNS.
Interestingly, SARS-CoV-2 spike glycoprotein S1 increased the activity of NF-κB and caspase-1 in BV-2 microglial cell line (Olajide et al., 2020). Furthermore, SARS-CoV-2 spike protein triggered the production of interferon-beta (IFN-β), NF-κB, and TNFα in human microglia (Mishra and Banerjea, 2021). Infected of both microglia and astrocyte cultures with murine coronavirus MHV-A59 increased expression of pro-inflammatory cytokines in supernatants (Lavi and Cong, 2020). In addition, infecting mouse microglia and astrocytes with murine coronavirus MHV increased the expression of TNFα and IL-6 (Yu and Zhang, 2006). Moreover, SARS-CoV-2 can infect human astrocytes through ACE2 and activates caspase-1 in the structure of NLRP3 inflammasome and consequently induces pyroptosis and releases of IL-1β and IL-18 into the extracellular space. Caspase-1 causes BBB disruption and initiates neuroinflammation (Israelov et al., 2020; Venere et al., 2013; Mamik et al., 2017). In this context, IL-1β and IL-18 progress neuroinflammation and produce other proinflammatory cytokines by neuronal cells, microglia, and astrocytes (Hauptmann et al., 2020; Hewett et al., 2012; Davis et al., 2018; Arend et al., 2008). IL-1β has also a major role in permeabilization of BBB and activation of astrocytes and microglia and consequently infiltration of peripheral immune cells into the CNS (Wang et al., 2014). Activation of microglia and astrocytes can induce further production of cytokines and chemokines, such as TNFα, IL-6, chemokine (C–C motif) ligand 2 (CCL2), and C–X–C motif chemokine ligand 10 (CXCL10) (Thelin et al., 2018; Riazi et al., 2008; Ferrari et al., 2004). IL-18 can also activate microglia and increase the activity of caspase-1 and the production of proinflammatory cytokines into the CNS (Felderhoff-Mueser et al., 2005; Gong et al., 2020). On the other hand, SARS-CoV-2 viroporins and the P2X7 receptors (P2X7R) can trigger inflammasome assembly and induce pyroptosis in the infected glial cells (Campagnolo and Mitchell, 2021; Ribeiro et al., 2021). As a result, inflammasome

| Table 1 Some suggested drugs with targeting inflammasome may be used for the treatment of SARS-CoV-2-induced neurological manifestations |
| --------------------------------- | --------------------------------- | --------------------------------- |
| Mechanism                        | Drug or agents                   | Mentioned in COVID-19 studies    |
| Anti-IL-1β therapy               | Anakinra                         | (Mariette et al., 2021; Kooistra et al., 2020; Pasin et al., 2021; Franzetti et al., 2021) |
|                                 | Canakinumab                      | (Landi et al., 2020; Katia et al., 2021; Generali et al., 2021) |
| NLRP3 inhibitors                 | Glibenclamide                     | (Rodrigues et al., 2021) |
|                                 | MCC950                            | (Rodrigues et al., 2021) |
|                                 | CY-09                             | (Rodrigues et al., 2021) |
|                                 | OLT117                            | (Rodrigues et al., 2021) |
|                                 | benzoxathiie derivative BOT-4-one | (Rodrigues et al., 2021) |
|                                 | β-hydroxybutyrate                  | (Rodrigues et al., 2021) |
|                                 | INF4E                             | (Rodrigues et al., 2021) |
|                                 | 3,4-methylenedioxy-β-nitrostyrene | (Rodrigues et al., 2021) |
|                                 | Artemisinin                       | (Li et al., 2021a; Uckun et al., 2021; Gendrot et al., 2020) |
|                                 | Probenecid                         | (Swayne et al., 2020) |
|                                 | Mefenamic acid                    | (Pareek 2020; Shah et al., 2021) |
|                                 | Parthenolide                       | (Bahrami et al., 2020; Nemati and Rami, 2020) |
|                                 | Oridonin                          | (Pareek 2020; Shah et al., 2021) |
|                                 | Bay 11–7082                       | (Olajide et al., 2021) |
|                                 | microRNA-7: inhibited microglial    | (Pareek 2020; Shah et al., 2021) |
| Anti-inflammatory drugs          | Tocilizumab and other IL-6         | (Li et al., 2021b) |
|                                 | antibodies                       | (Ulhaq and Soraya, 2020; Aziz et al., 2021; Salama et al., 2021; Horby et al., 2021) |
|                                 | Emalumab: anti-IFN-γ antibody     | (Magro, 2020) |
|                                 | Polaprezinc                       | (Sepehrinezhad et al., 2021) |
|                                 | Colchicine                        | (Madrid-Garcia et al., 2021; Reyes et al., 2021) |
|                                 | Glucocorticoids                   | (Mishra and Mulani, 2021; Annane, 2021; Robinson and Morand, 2021) |
| P2X7R antagonist                 | Brilliant blue G                  | – |
| Anti-IL-18 therapy               | Anti-IL-1R7 antibody: block the    | (Li et al., 2021b) |
|                                 | activity of IL-18                 | (Li et al., 2021b) |
| Anti-caspase-1 therapy           | Pralnacasan                       | – |
|                                 | Belnacasan                        | – |
assembly forms pores in the cell membrane that causes sudden depletion of proinflammatory cytokines from infected glia into the extracellular matrix. Finally, all these pathological processes exacerbate neuroinflammation-induced neuronal injury (Kempuraj et al., 2016) and present neurological manifestations following SARS-CoV-2 infection (Fig. 3).

Final Remarks

In this review, we suggested that inflammasome with its downstream signals can be targeted as a main pathology of SARS-CoV-2 in neurological cases. Knowledge of early signs of possible mechanisms after neurological manifestations in the course of SARS-CoV-2 is needed to be able to timely intervene with a suitable treatment. Some possible drugs are available that are previously investigated in clinical practice (Table 1). Considerably more work will need to be done to determine the effects of these drugs on inflammasome in COVID-19 patients with neurological manifestations. In the same way, post mortem analysis is needed to clarify the exact mechanisms of inflammasome and pyroptosis in the CNS with COVID-19 infections.

Acknowledgements Not applicable.

Author’s contributions Ali Sepehrinezhad and Sajad Sahab Negah designed the study, performed the literature review and drafted the manuscript. In addition, Ali Gorji and Sajad Sahab Negah critically edited the manuscript. All authors read and approved the final manuscript.

Funding Funding information is not applicable.

Availability of data and materials Not applicable.

Declarations

Conflicts of interest The authors declare that there is no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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