Neuroinflammation and Its Involvement in the COVID-19 Associated Neurological Symptoms

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Abstract: SARS-CoV-2 is the novel coronavirus that has caused the global coronavirus disease 2019 (COVID-19) pandemic for more than two years, primarily invading the respiratory symptom and inducing pneumonia. However, emerging evidence suggested a neurological manifestation of COVID-19, resulting in long-term sequelae. Numerous previous papers highlighted the involvement of neuroinflammation in these sequelae, indicating that neuroinflammation might be the central mechanism at the cellular level. Thus, this paper aimed to discuss the various neurological disorders associated with COVID-19 infections, mainly focusing on the involvement of neuroinflammation in each disorder and reveal some underlying key factors, including glial cells, innate immune cells, mitochondria, blood-brain-barrier (BBB) and cytokine storm. Neuroinflammation is initiated both indirectly via the global effect of COVID-19 infection and directly via neuronal infections. The initial immune response of innate immune cells within CNS induces a cytokine storm with various pro-inflammatory immune mediators, which promote neuroinflammation and alter the glial cells to their pro-inflammatory reactive form, resulting in more cytokine release as a vicious cycle. This paper discussed such a process in various disorders and brought out several therapeutical advances, and highlighted their relative advantages and disadvantages were briefly discussed.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused the ongoing global pandemic, which led to massive death and lifestyle change, posing a major public health crisis[1]. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that belongs to the same subgenus as the severe acute respiratory syndrome (SARS) virus that caused the SARS-CoV epidemic in 2003[2]. SARS-CoV-2 shares the same receptor as SARS for cell entry, the angiotensin-1-converting enzyme 2 (ACE2), making the pulmonary system the primary entry site[3]. Thus, in severe cases, patients suffer from acute symptoms including respiratory failure, septic shock, multi-organ failure, and death, taking up about 5% of the total cases[4].

Moreover, neurological manifestations have also been reported, especially in these severe cases[5]. Emerging data indicated that 85% of long-haulers of COVID-19 also suffer multiple neurological symptoms such as acute ischemic stroke, meningitis/encephalitis, anosmia, neuromuscular diseases, epileptic seizures, focal neurological deficits, suggesting its impact on the brain[6,7]. Neuro-COVID is a term referring to the syndrome caused by chronic neuroinflammation and neuronal damage in COVID-19 and has become a new focus of the research[6]. Indeed, in one study examining the biomarkers of central nervous system (CNS) injury, elevated level of neurofilament light chain (NfL) protein, glial fibrillary acidic protein (GFAp), and total tau was found in the cerebrospinal fluid (CSF) of COVID-19 patients with neurological symptoms[7]. Other evidence includes identification of various vascular events, intracerebral hemorrhage, encephalitis, and hypoxia or anoxia injury in the postmortem brain of COVID-19 patients, which indirectly revealed SARS-CoV-2 presence in the brain[8]; and also, the direct localization of the viral RNA in the cerebellum, cornea, conjunctiva, oral mucosa, and gyrus rectus in postmortem samples[9]. Furthermore, the ACE2 receptor has been found in the brain, including cerebrum, cerebellum, brainstem, retina, and olfactory mucosa, expressed by neurons, vascular pericytes and smooth muscle, and glia, providing entrances for viral invasion[10].

Currently, there is limited knowledge about the mechanism of neuro-COVID, but new findings are quickly accumulating. One proposed mechanism is autoimmune attack, as anti-neuronal autoantibodies have been detected in CSF and serum of the patients, indicating potential therapeutical intervention of immunotherapies[11]. Another study highlighted the importance of microglia in the process of SARS-CoV-2 infection demonstrated elevated pro-inflammatory cytokines and reactive oxygen species (ROS) production, along with increased oxygen consumption rate and altered phospholipid composition, suggesting a microglial mitochondrial dysfunction that ultimately leads to apoptosis[6]. However, both proposed mechanisms involve immune response and neuroinflammation, pinpointing an essential role of neuroinflammation in such processes. In addition, profound neuroinflammation has also been identified in postmortem samples, opening another pathway to neurological damage[12]. Studies suggested that SARS-CoV-2 infection is associated with systemic inflammation, which might involve cytokine storm and neuroinflammation in severe cases[13]. In another study integrating clinical features, neuroimaging and CSF findings, researchers confirmed a series of CNS inflammatory disorders associated with COVID-19[14]. Thus, neuroinflammation might be the core mechanism for neuro-COVID, which serves as an underlying link behind multiple pathways. This paper will discuss the role of neuroinflammation in different neurological disorders in the neuropathogenesis of COVID-19 and highlight some potential therapeutical approaches.

2. Disorders Associated with COVID-19 and Related Neuroinflammation

2.1 Cough and the Vagal Sensory Neurons

As one of the representing symptoms of COVID-19, cough sometimes persists for weeks or months after SARS-CoV-2 infection[15]. One view hypothesized that chronic cough might result from the hypersensitized cough pathway via the amplification of afferent cough signaling to the brainstem[1]. Results from several studies provide some experimental evidence for this view. A study localized ACE2 receptors in odor-sensing cilia containing-neuroepithelium of supporting cells around neuronal dendritic projections, which might also explain the observed anosmia on SARS-CoV-2 infected patients[16]. Moreover, other studies discovered that some cough-inducing vagal sensory neurons share some developmental lineage and molecular subtype with a subset of nociceptive dorsal root ganglion neurons, which express ACE2 receptors, indicating possible ACE2 expressing capability of these neurons[17]. In a study examining the postmortem sample of COVID-19 patients, SARS-CoV-2 RNA and protein were localized in both the olfactory mucosa and the trigeminal sensory ganglia, further suggesting a possible route for the virus to retrogradely invade the CNS via sensory neurons[18].

Although the above studies suggested that SARS-CoV-2 might infect the sensory neurons, whether the cough pathway is altered remains unknown. Indeed, multiple pathways were highlighted for the SARS-CoV-2 to affect neuronal functions (Fig. 1). First, direct infection activates the neuronal antiviral signaling, together with the response from neuronal support cells, release a variety of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6, resulting in a local inflammatory environment[15]. Second, the virus might directly interact with Toll-like receptors (TLRs) expressed on the outside of sensory neurons such as dorsal root ganglion neurons, and this TLR activation leads to alteration of gating states in transient receptor potential (TRP) channels, a mechanism independent of viral infection[19]. Third, initial direct infection-induced cough might change to a prolonged cough caused by dysregulated inflammation[15]. Many cytokines are released in the inflammation caused by SARS-CoV-2 induced innate immune response, such as interleukin (IL)-1β, TNF, and interferons whose receptors are commonly expressed on immune cells and peripheral neurons[20]. The downstream effects include depolarization of vagal sensory neurons and following cough hyper-responsiveness induced by interferons[21], as well as the recruitment and activation of more immune cells and inflammatory cells, increased vascular permeability, and aggravated inflammation induced by neuropeptides[20]. Many of these downstream ligand-receptor interactions indeed produce and promote neurogenic inflammation, adding on the contribution from various glia cells, together making a pro-inflammatory micro-environment and altering sensory neuron activity[15].

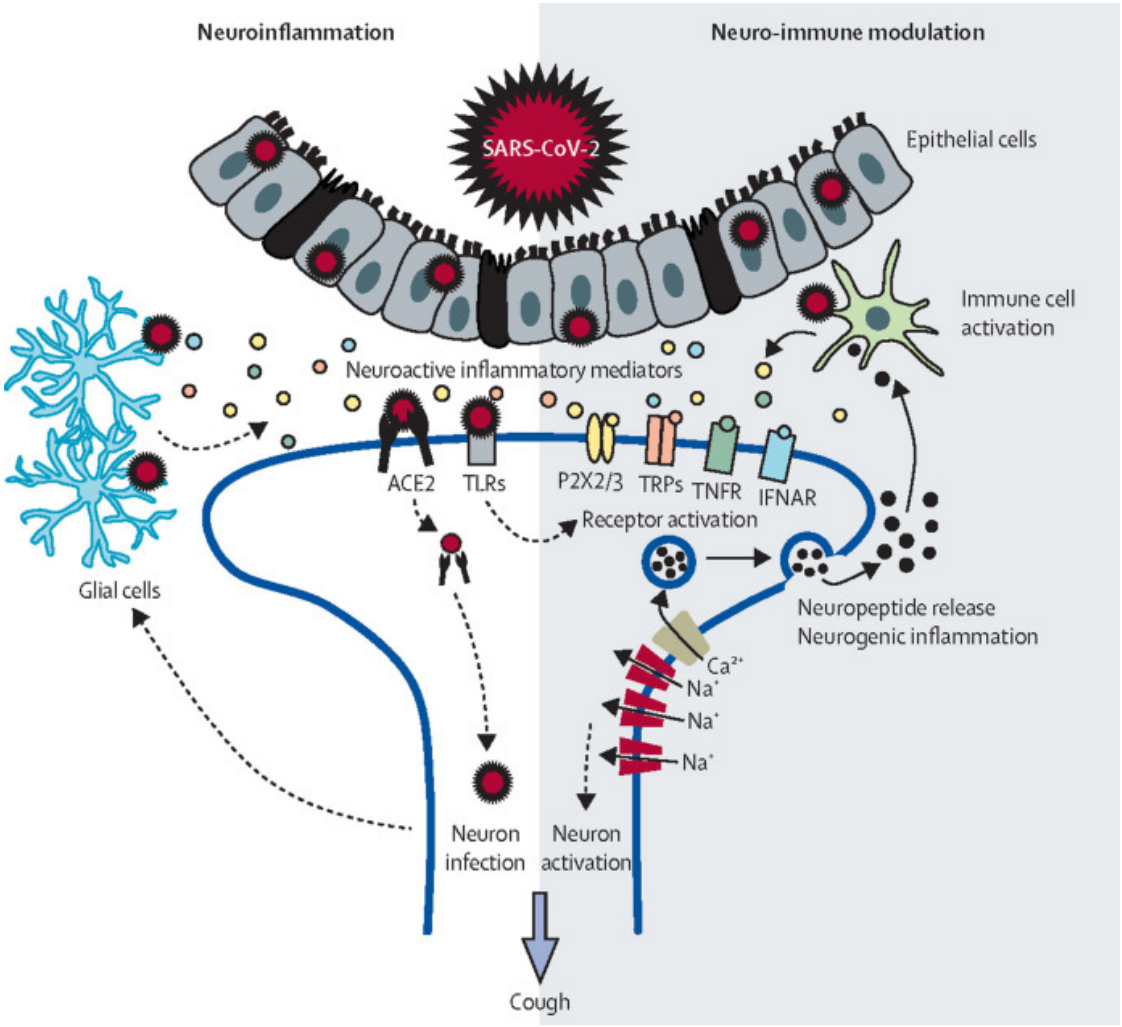

Figure 1. SARS-CoV-2 infection-induced cough mechanism. (Left) Neuroinflammation is promoted via direct viral infection virus recognition by vagal sensory neurons and associated glial cells. Various neuroactive inflammatory mediators are released, including interferons and glial-derived ATP. (Right) Traditional immune cells release more inflammatory mediators, including many that can activate the vagal sensory neuron via cognate receptors or gating ion channels. Such activation will promote the release of neuropeptides, which recruit immune cells and start neurogenic inflammation. Both mechanisms synergistically alter the cough signaling pathway and induce cough[15].

2.2 Neurodevelopmental Disease and the Role of Microglia Although children are considered less susceptible to COVID-19, recent research suggested that the long-term effect of SARS-CoV-2 infection might compromise brain development, especially in synaptic pruning and formation of functional neural circuitry[22]. Indeed, clinical evidence suggested possible fetal infection. ACE2 receptors are expressed on the placenta, and utero infection of SARS-CoV-2 has been identified with placental viremia, inflammatory cells presence in the cerebrospinal fluid, and neurological manifestations[23]. Moreover, viruses, or the cytokines and maternal leukocytes released upon viral infection, can both activate the fetal microglia[22]. The activation of microglia might be potentially detrimental to normal brain development. The identification of ACE2 receptors on microglia raises the possibility of microglia activation directly via viral infection, suggesting a higher risk for late-onset neurodevelopmental diseases[24]. Previous research on other viruses suggested that neuroinflammation induced by a viral infection can disrupt the physiological role of microglia during brain development, an effect more detrimental than the direct cytopathic effect of the virus on infected cells[22].

Microglia plays a vital role in synaptic pruning and neural network formation in developing brains, especially during the late gestational and early postnatal period[22]. Any disruption of microglia physiological function during such period might result in the formation of an inappropriate neural

network, demonstrating a higher risk for neurodevelopmental and psychiatric disorders such as schizophrenia, autistic spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD)[24].

On the other hand, during viral infections, phagocytic microglia eliminate pathogens and cellular debris[22]. Microglia might also release oxidants, which then activate the release of the inflammasome to mediate a neurotoxic process[25]. In such a way, the normal neuroprotective function of microglia on synaptic pruning is disrupted upon coronavirus invasion, resulting in disrupted brain development. This process relies on the microglia-related triggering receptor expressed on myeloid cells 2 and DAP12, which are found to be highly expressed in a model of murine coronavirus[26]. In addition, the cytokine storm observed in SARS-CoV-2 pathogenesis involves the release of interferon (IFN) -Ɣ and IL-6, which mediate a pro-inflammatory response and damage the normal cytokine-mediated crosstalk in the choroid plexus, resulting in impaired peripheral immune cells recruitment, microglia maturation, and functional neuroplasticity[27].

2.3 Neuroinflammation in the Immune-Mediated Demyelinating Disease

Coronavirus RNA and antigen were found in active demyelinating plaques of multiple sclerosis patients, suggesting potential involvements of coronavirus in the pathogenesis of immune-mediated demyelinating disease[28]. Indeed, infection of human coronavirus strain OC43 on human astrocytic cell lines and human microglial cell lines resulted in the increased transcription of IL-6, TNF-α, and MCP-1, altered matrix metalloproteinases (MMP)-2 and 9 activity, and upregulation of nitric oxide production[29]. This increase in the release of pro-inflammatory cytokines suggested a possible glial cell-mediated inflammation, potentially induced by coronavirus infection. The result might be the immune-mediated demyelination of neurons observed in multiple sclerosis[28].

In rats, coronavirus infection initially downregulates the production of myelin protein proteolipid protein, which then proceeds to infected oligodendrocytes, leading to necrosis of the demyelinating lesions. At the same time, oligodendrocytes that cannot detect coronavirus antigen also undergo apoptosis, a process not rescued by virus clearance[30]. In another study analysing coronavirus-induced encephalomyelitis in Lewis rats, similar results were observed, with increased expression of a series of inflammatory cytokines detected at the demyelination site, including IFN-γ, IL-2, TNF-α, iNOS[31]. Other researchers inoculated human coronavirus OC43 in mice and demonstrated CNS global infection and devastating results mainly mediated by microglial activation and inflammatory reactions[32]. Another study using murine coronavirus revealed upregulation of Class I major histocompatibility complex antigens in oligodendrocytes and astrocytes and highlighted that H-2 antigen induction triggers glial-immune reactions[33]. Taking together, the above pieces of evidence suggest a coronavirus-induced, glial-mediated neuroinflammatory response with devastating tissue loss in myelinated neurons and might explain multiple sclerosis observed in some COVID-19 patients.

2.4 The link Between Mast Cells, Psychological Stress, and Neuroinflammation

Mast cells are innate immune cells that also communicate with the adaptive immune system. They are very heterogeneous, different in their structure, morphology, receptor expression, and responding stimuli, and they exist in a great variety of physiological environments, including lung, respiratory tract, gastrointestinal tract, skin, nasal passage, and meninges[34]. Mast cells are one of the first responders to invading pathogens, and together with monocytes/macrophages, neutrophils, T cells, natural killer (NK) cells, resident tissue epithelial and endothelial cells, they serve as the initial defense against SARS-CoV-2 infection and trigger cytokine storm[35]. Mast cells contain cytoplasmic granules, which store TNF-α, histamine, and various proteases that can be immediately released upon activation, and also synthesize and release other cytokines and chemokines in later stages[36]. They express TLRs that recognize damage-associated molecular patterns (DAMPs) from many viruses, including SARS-CoV-2[37].

Since ACE2 receptors are expressed in endothelial cells, glial cells, neurons, and mast cells, SARS-CoV-2 can damage the neurovascular unit and breakthrough BBB via inflammatory mediators, therefore invading the brain[34] (Fig. 2). Thus, neurological functions altered by COVID-19, adding on

psychological stress caused by the environmental factor during the COVID-19 pandemic, inducing multiple neuroinflammatory and psychiatric disorders or even neurodegenerative disorders, including Alzheimer's disease (AD)[38]. Such psychological stress could initiate physiological change by inducing the release of corticotropin-releasing hormone (CRH) and activates the hypothalamic-pituitary-adrenal (HPA) axis, and results in stress-induced depression, anxiety, psychiatric disorders, and posttraumatic stress disorder (PTSD)[39]. CRH is indeed also produced and reacted by mast cells, together with other neuropeptides, triggering detrimental neuroinflammation that in turn further damage the brain, leading to neuroinflammatory and autoimmune diseases. In addition, mast cells activation triggers the cytokine storm, which damages the BBB, allowing more inflammatory mediators, SARS-CoV-2 viruses, and immune infiltrations to enter the brain[34]. Such entries further activate inflammatory responses from neurons, glial cells and endothelial cells, exacerbate the chronic inflammatory response, and contribute to the pathogenesis of multiple neurodegenerative diseases, including AD, Parkinson's disease (PD), multiple sclerosis (MS)[40]. Moreover, mast cell-derived inflammatory mediators are known to participate in itch sensation in atopic dermatitis and urticaria, a phenomenon observed in COVID-19 patients under increasing psychological stress[41]. This finding indicates mast cells involvement in COVID-19 pathogenesis.

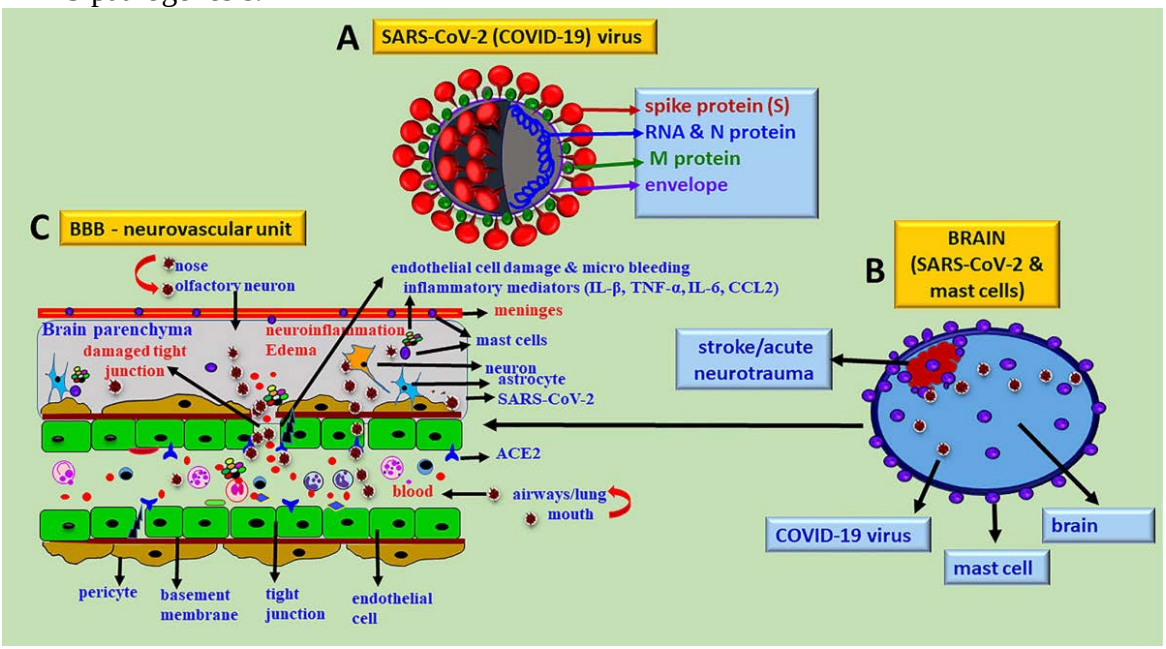

Figure 2. SARS-CoV-2 induces and exacerbates inflammation in the brain. SARS-CoV-2 can enter the brain through the nose, olfactory nerve, impaired BBB, and lymphatic drainage. SARS-CoV-2 attaches to the ACE2 receptors expressed on capillary endothelial cells, activating immune response and damaging BBB. Mast cells, glial cells, endothelial cells, and neurons can be activated by SARS-CoV-2 and trigger immune responses. Mast cells and glial cells will release inflammatory mediators upon activation. Inflammatory mediators released from brain cells and periphery could cause BBB breach, tight junction damage, edema, micro bleeding, cognitive decline, stroke, and neuroinflammation[34].

3. Some Novel Therapeutical Approaches to Neuro-COVID

Since mast cells degranulation is involved in initial immune activation that proceeds to chronic inflammation in neurological disorders of COVID-19, Sodium cromoglicate and palmitoylethanolamide (PEA) were found to be effective mast cell stabilizers[34]. Both drugs prevent activation and degranulation of mast cells, therefore decreasing the release of pro-inflammatory mediators from cast cells and inhibiting inflammation in the lungs. However, its role in the brain remains to be investigated[42].

Baricitinib is an experimental drug that inhibits the pro-inflammatory JAK-STAT signaling pathway, therefore relieving neuroinflammation[43]. SARS-CoV-2 infection in the liver and overall

morbidity and mortality in COVID-19 patients were decreased by JAK inhibition in a pilot clinical trial. Moreover, inhibition of neuroinflammation by baricitinib is also under research, with several clinical trials going on (NCT04320277 and NCT04321993)[43].

The anti PD1/PD-L1 immune checkpoint is another potential treatment for the pro-inflammatory immune response in the brain. High expression of PD-1 was observed on CD8 T cells and in microglial nodules, with the closely interacting microglial nodule clusters expressing PD-L1, indicating a fine modulation of T cells activity via PD1/PD-L1[12]. Furthermore, in some COVID-19 patients with neurological disorders, T cell exhaustion has been identified via transcriptomic biomarkers in the CSF[44]. Therefore, the immune checkpoint blockade of PD-1/PD-L1 is predicted to boost T cell activation and adaptive immunity, but whether it is beneficial needs to be carefully considered since PD-1-positive T cells were also observed at the vasculature and contributed to impaired BBB[12].

Semi-synthetic second-generation tetracyclines are another group of drugs with anti-inflammatory and antiviral functions[45]. They can inhibit microglial reactivity and neuroinflammation by inhibiting nuclear factor kappa B (NF-kB) signaling, cyclooxygenase 2, and MMPs. In addition, they also perform well against bacteria associated with community-based pneumonia, which are often observed as secondary bacterial infections in COVID-19 patients. Thus, they might serve as a promising multi-modal drug for treating the neurological disorders of COVID-19, and over ten clinical trials are investigating this[45].

4. Future Steps and Conclusion

Although the involvement of neuroinflammation in COVID-19 associated neurological disorders has been well accepted, the exact cellular mechanisms and key molecules remain unknown. This paper discussed several typical symptoms and disorders linked to SARS-CoV-2 induced inflammatory response, highlighted the importance of neuroinflammation in such processes, and related them to glial cells activation, mitochondrial functionality, BBB integrity, mast cell degranulation, phycological stress and cytokine storm. The neurological symptoms of COVID-19 include a spectrum of disorders, including neuropsychiatric disorders, neurodegenerative disorders, neurodevelopmental disorders and even cough, which does not seem to have a neurological root at first glance. Furthermore, this paper briefly listed several therapeutical approaches with promising results. Thus, neuroinflammation is such a complicated and multifaceted process involving various pathways, mediators, and cells, and there is still a far way to go until the complete understanding of this process.

The future steps should be focused on two aspects. First, more large-scale experiments should be designed to establish a systematic view of neuroinflammation caused by COVID-19. Such experiments should implicate bioinformatic methods, applying genetic, transcriptomic, and protein interactome data, together achieve a better understanding of neuro-COVID mechanisms. Next, the research on novel therapeutics should be continued simultaneously. Although it is important to achieve theoretical advances on COVID-19 induced neuroinflammation, novel treatments are more urgent and significant. Many of the therapeutics mentioned in this paper lack studies on their safety, effectiveness, and mechanisms. Advancing both aspects synergistically is crucial for preventing potential long-term neurological sequelae of COVID-19 from occurring globally, as current mutants of SARS-CoV-2 become increasingly contagious and infect massive populations.

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