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Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host–Virus Interaction, and Proposed Neurotropic Mechanisms

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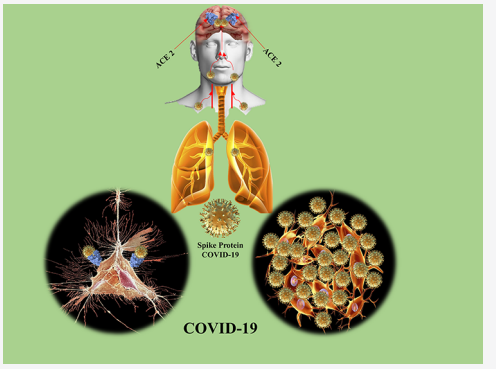
ABSTRACT: The recent outbreak of coronavirus infectious disease 2019 (COVID-19) has gripped the world with apprehension and led to a scare of epic proportions related to its potential to spread and infect humans worldwide. As we are in the midst of an ongoing near pandemic outbreak of COVID-19, scientists are struggling to understand how it resembles and varies with the severe acute respiratory syndrome coronavirus (SARS-CoV) at the genomic and transcriptomic level. In a short time following the outbreak, it has been shown that, similar to SARS-CoV, COVID-19 exploits the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry inside the cells. This finding raises the curiosity of investigating the expression of ACE2 in neurological tissue and the possible contribution of neurological tissues damage to the morbidity and mortality of COIVD-19. Here, we investigate the density of the expression levels of ACE2 in the CNS and the host–virus interaction and relate it to the pathogenesis and complications seen in recent cases of the COVID-19 outbreak. Also, we debate the need for a model of staging COVID-19 based on neurological tissue involvement.



KEYWORDS: *Coronavirus, COVID-19, tissue distribution, host–virus interaction, proposed mechanisms*

1. THE NOVEL COVID-19 VIRUS

The first reports of a viral infection attracted attention in late December 2019 in Wuhan, the capital of Hubei, China. Later, it was revealed that the virus responsible for causing the infections was contagious between humans. In early January, the terms like "the new coronavirus" and "Wuhan coronavirus" were in common use. On February 11, 2020, a taxonomic designation "severe acute respiratory syndrome coronavirus 2″ (SARS-CoV-2) became official in order to refer to the virus strain, that was previously termed as 2019-nCoV and Wuhan coronavirus. Within a few hours on the same day, the WHO officially renamed the disease as COVID-19.

2. THE GENOME OF THE COVID-19 VIRUS

The complete genome of COVID-19 virus from Wuhan, China was submitted on January 17, 2020 in the National Center for Biotechnology[1] (NCBI) database, with ID NC_045512. It is a 29,903 bp single-stranded RNA (ss-RNA) coronavirus. It has now been shown that COVID-19 is a SARS-like coronavirus that had previously been reported in bats in China.

3. THE TISSUE DISTRIBUTION OF ACE2 IN HUMAN ORGANS AND TISSUES

In order to discover the neurological pathogenic potential of COVID-19 and relate it to neurological tissue expression of ACE2, data retrieval was done from human protein databases. Most of the evidence of ACE2 expression in the brain (Figure 1) comes from literature and mammalian tissue expression databases,[2] which prompted us to investigate neurotropic effects of COIVD-19 and its contribution toward the morbidity and mortality of patients with COVID-19.

3.1. Evidence of the Distribution of ACE2 in the Human Brain. The brain has been reported to express ACE2 receptors (Figure 1A, C) that have been detected over glial cells and neurons, which makes them a potential target of COVID-19. Previous studies have shown the ability of SARS-CoV to cause neuronal death in mice by invading the brain via the nose close to the olfactory epithelium.[3] The contribution of

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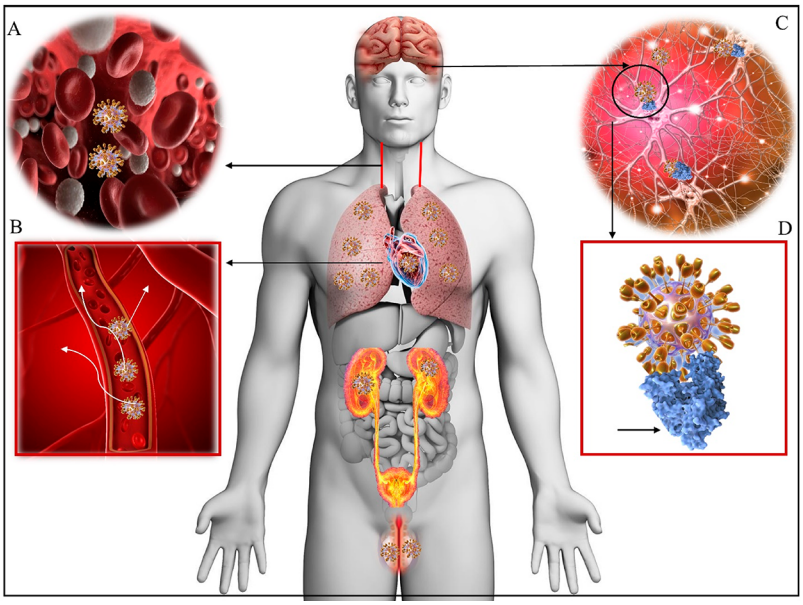

Figure 1. Tissue distribution of ACE2 receptors in humans. Viremia (A) disseminates the COVID-19 virus throughout the body via the bloodstream (B). Neurotropism may occur via circulation that enables the COVID-19 to reach the brain (C) and bind and engage with the ACE2 receptors (D, blue). COVID-19 docks on the ACE2 via spike protein (D, golden spikes). Shown are lungs, heart, kidneys, intestines, brain, and testicles that are well-known to express ACE2 receptors and are possible targets of COVID-19.

neural targeting of COVID-19 in patients reported in the recent outbreak remains to be established. In the SARS-CoV infections reported in the past, autopsy findings of the patients have shown the evidence-based presence of SARS-CoV via electron microscopy, immunohistochemistry, and real-time reverse transcription-PCR [3]. Patients with acute SARS-CoV illness have also shown the presence of the virus in cerebrospinal fluid. The role of the blood-brain barrier in containing the virus and preventing it from gaining access to the neural tissues needs to be further explored in COVID-19. Recently, a study posted in medRxiv[4] has reported neurological manifestations in COVID-19 in the current outbreak that involved 214 patients, of which 78 (36.4%) patients had neurologic manifestations, which affirms our rationale of the neurotropic potential in the COVID-19 virus. Also, a finding published on a patient who had loss of involuntary control over breathing[5] during the recent outbreak implores healthcare professionals and clinicians to segregate COVID-19 patients into neurologically affected cases and those who are devoid of neurological deficits.

4. HOST−VIRUS INTERACTION: HOW THE ACE2 RECEPTOR IS EXPLOITED BY THE COVID-19 VIRUS TO GAIN ENTRY INSIDE THE HOST CELLS

With the mRNA encoding 12 proteins,[1] the COVID-19 virus, like SARS-CoV, uses a spike protein S1 that enables the attachment of the virion to the cell membrane by interacting with host ACE2 receptor[3,6] (Figure 1C, D). In the later study,[6] it was shown that the ACE2 binding affinity of the 2019-nCoV spike protein ectodomain was 10−20-fold higher than ACE2 binding to SARS-CoV spike protein. A BLASTp search of the COVID-19 RBD subdomain-1 (319th to 591st aa) fetched a spike glycoprotein [bat coronavirus RaTG13] and S1 protein and partial [SARS coronavirus GD322] as a homologue. Pairwise sequence alignments of the three sequences show that though the spike proteins of all three CoV are highly similar, they are not identical (Figure 2A, horizontal arrows), which may be the reason for the higher binding affinity of the COVID-19 spike protein to the human ACE2 receptor. Homology modeling of COVID-19 RBD subdomain-1 (319th to 591st aa) in the SWISS-MODEL automated server developed a template-based model of the 2019-nCoV (COVID-19) spike glycoprotein with a single receptor-binding domain up configuration (Figure 2A1) with 100% sequence identity. Of the other template-based models developed, it expectedly showed a model of the structure of the SARS-CoV spike glycoprotein, conformation 2 with about 74% sequence identity (Figure 2B, B1), which shows them to be structurally and evolutionarily related.

5. A PROPOSED CASCADE OF CEREBRAL INVOLVEMENT IN THE COVID-19 INFECTIONS

The dissemination of COVID-19 in the systemic circulation or across the cribriform plate of the ethmoid bone (Figure 1) during an early or later phase of the infection can lead to cerebral involvement as has been reported in the past for SARS-CoV affected patients.[3] The presence of COVID-19 in general circulation understandably enables them to pass into the cerebral circulation (Figure 1A−C) where the sluggish movement of the blood within the microcirculation could be one of the factors that could facilitate the interaction of the COVID-19 virus with ACE2 expressed in the capillary endothelium. Subsequent budding of the viral particles from the capillary endothelium and damage to the endothelial lining can favor viral access to the brain (Figure 1B). Other possible mechanisms like the transendothelial migration of the virus can also enable virus entry into the brain. Once with the milieu of the neuronal tissues, its interaction with ACE2 receptors (Figure 1C, D) expressed in neurons[2] can initiate a cycle of viral budding accompanied by neuronal damage without substantial inflammation as has been seen with cases of SARS-CoV[3] in the past. It is important to mention here that, long before the proposed anticipated neuronal damages occur, the endothelial ruptures in capillaries accompanied by bleeding

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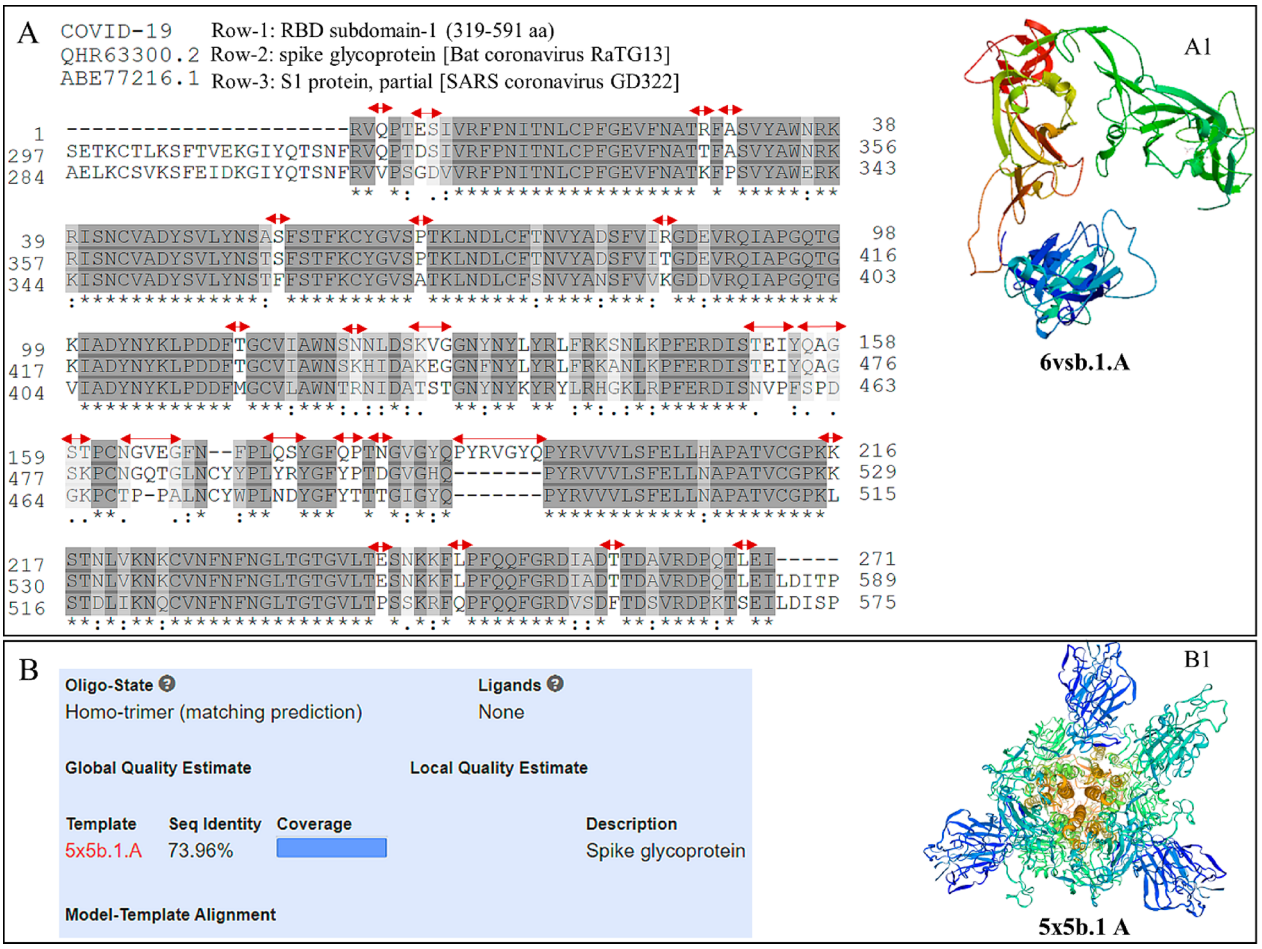

Figure 2. (A) Sequence alignment of COVID-19 RBD subdomain-1 (319th to 591st) amino acid (top row) with the bat and SARS-CoV spike protein (middle and bottom row) that were fetched by BLASTp results of COVID-19 RBD subdomain-1 (319th to 591st) amino acids. Note horizontal arrows that show areas of contrast. (A1) The homology modeling of COVID-19 RBD subdomain-1 (319th to 591st) amino acid developed a template (6vsb.1. A)-based model of the 2019-nCoV (COVID-19) spike glycoprotein with a single receptor-binding domain up configuration. (B). Homology modeling of COVID-19 RBD subdomain-1 (319th to 591st) amino acid developed a template-(5x5b.1.A) based model of the prefusion structure of SARS-CoV spike glycoprotein in conformation 2 (B1) with 73.96% sequence identity. [Uniprot and SWISS-MODEL automated server were used for sequence alignments and development of the templates and models, respectively.]

within the cerebral tissue can have fatal consequences in patients with COIVD-19 infections. The movement of the COVID-19 virus to the brain via the cribriform plate close to the olfactory bulb can be an additional pathway of the virus to affect the brain, and finding of an altered sense of smell or hyposmia in an uncomplicated early stage COVID-19 patient should be investigated thoroughly for CNS involvement.

6. CONCLUSIONS AND FUTURE DIRECTIONS

Autopsies of the COVID-19 patients, detailed investigation, and attempts to isolate COVID-19 from the endothelium of cerebral microcirculation, cerebrospinal fluid, glial cells, and neuronal tissue can clarify the role played by this novel COVID-19 coronavirus in the mortalities observed in the recent outbreak. It is important to mention here that though the cerebral damage may complicate a COVID-19 infection, it appears that it is the widespread dysregulation of the homeostasis caused by pulmonary, renal, cardiac, and circulatory damage that proves fatal in COIVD-19 patients. With that being said, a dominant cerebral involvement alone with the potential of causing cerebral edema in COVID-19 can take a lead in causing death long before systemic homeostatic dysregulation sets in. Access of COVID-19 to the brain via the transcribrial route, as described previously for other CNS targeting pathogens,[7] appears to be the case in a recently reported patient with hyposmia,[5] which needs to be further investigated by attempting to isolate the COVID-19 virus from zones in proximity to the olfactory bulb. The differences in the spike proteins of COVID-19 and SARS-CoV (Figure 2A) may enable scientists to exploit the contrast in sequences in order to identify epitopes in COVID-19 for the development of monoclonal antibodies against this virus. With the recent COVID-19 outbreak, there is an urgent need to understand the neurotropic potential of the COVID-19 virus in order to prioritize and individualize the treatment protocols based on the predominant organ involvement. Also, a staging system based on the severity and organ involvement is needed for COVID-19 in order to rank the patients for aggressive or conventional treatment modalities.

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The authors declare no competing financial interest.

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