Reassessment of the blood-brain barrier: a potential target for viral entry into the immune-privileged brain

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Significant alteration of cognitive and affective behaviors mediated by neural pathways in the central nervous system (CNS), currently referred to as "brain fog", is a major long-term complication following recovery from an acute infectious event.[1-3] Persistent cognitive deficits have been identified in patients who have recovered from acute infection with severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the etiologic agent of coronavirus disease-2019 (COVID-19). Post-infectious cognitive dysfunction has been observed in previous pandemics, including those associated with the widespread transmission of Asiatic (Russian) influenza, myalgic encephalomyelitis, Spanish influenza, diphtheria, encephalitis lethargica, and chronic fatigue syndrome (also known as post-viral fatigue syndrome).[3] Furthermore, chronic cognitive behavioral deficits have been listed as significant complications of Ebola, Zika, influenza A, and human immunodeficiency virus (HIV) infections.[4] Collectively, these data strongly suggest that secondary targeting of brain neural structures by viruses that have previously-established primary sites of infection outside the CNS may contribute to both acute and chronic neuropsychiatric symptoms.[4] We also speculate that multiple convergent mechanisms including direct viral neuroinvasion as well as the indirect effects of debilitating proinflammatory conditions that develop both systemically and within key CNS structures promote global virus survival and may drive additional cycles of infection at later times.

Historically, the mammalian brain has long been considered to be an immune-privileged organ. This is largely due to the actions of the blood-brain barrier (BBB) which inhibits the free passage of immune cells and humoral factors such as cytokines and immunoglobulins between peripheral circulation and the CNS.[5-8] Recent critical thinking and empirical studies have significantly modified the concept of an immune-privileged CNS. Several new hypotheses and findings suggest that the BBB may be more mechanistically flexible and may function not only to separate but to unite the CNS and peripheral immune signaling in response to current physiological demand.[5-8] Interestingly, the ganglionic nervous systems of many invertebrate species, i.e., mollusks, do not include a BBB. In these species, immune cells, i.e., microglia, are directly associated with neurons in ganglionic-type nervous systems.[9] There is a long evolutionary history of direct associations between and interactions among neurons and immune cells. Given the obvious benefits toward promoting survival, it is not surprising to find that there are similar interactions between neurons and immune cells in the mammalian CNS.

Our group has recently reviewed the literature on differential regulation of gene expression in cells of the BBB and the choroid plexus that develops in response to COVID-19.[4] Plasticity with respect to their immune-privileged

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status coupled with disease-related changes in bi-directional transport of activated T-cells, dendritic cells, microglia, and/or astrocyte subpopulations via these structures may be functionally associated with the progression of COVID-19. Accordingly, a "leaky" BBB may facilitate direct viral access to cortical neurons involved in the processing and integration of cognitive behaviors.

Taken together, we hypothesize that altered CNS processing leading to a state of cognitive confusion/dysfunction may be a sentinel signal provided by immune cells to neurons to indicate excessive and inappropriate activation.[10,11]

CNS dysfunction may result from one of several virus-mediated mechanisms. Viruses may elicit CNS dysfunction via direct penetration of the BBB or they may enter the brain by hijacking the immune cell trafficking network (e.g., via circulating macrophages).[11] Alternatively, active molecular agents generated by virus infection at a distant site (e.g., the lung) may have the capacity to modify the cognitive function of the host.[12] CNS tissues may also serve as virus reservoirs, thereby promoting viral persistence and leading to chronic and/or recurrent cognitive dysfunction.[12] Interestingly, the capacity to target the brain may be the result of virus-directed natural selection, as this process may ultimately promote the longevity and persistence of these pathogens. Viruses may also be capable of "masking" themselves; this will increase their capacity for survival and secondary infections. It is also worth noting that the aforementioned relationships between neurons and neuroimmune cells observed in invertebrate organisms may serve to promote evolutionary fine-tuning of the vertebrate immune system.

Bidirectional immune cell trafficking together with the development of virus-induced inflammation at the vascular endothelium may enhance normal immune cell trafficking to the brain, similar to a phenomenon that has been already reported in cases of Alzheimer's disease.[13] Likewise, the virus-induced cytokine storm and enhanced immune cell trafficking may result in inflammation-associated psychiatric manifestations similar to those reported in cases of dementia, HIV infection, and post-cardiotomy delirium.[11] Insights into the molecular basis of bidirectional trafficking and the limited protection provided by the selectively-penetrable BBB offer the opportunity for the development of efficacious novel therapeutics.

In light of these findings, we hypothesize that hypoxic regions in the brain areas resulting from the acute infection may promote virus reproduction. As one example, neuronal cell energy metabolism and/or glial components may be compromised in response to SARS-CoV-2-induced mitochondrial dysfunction.[14-16] Selective neuronal/microglial mitochondrial targeting by SARS-CoV-2 and other viral pathogens may result in cognitive dysfunction and additional physiologic changes that favor viral propagation. Thus, a full characterization of cognitive changes associated with SARS-CoV-2 and other severe virus infections will be critical for the diagnosis, prognosis, and plans for long-term care of these patients.

Results reported in several recent publications have led us to conclude that viral infections may initiate dysfunctional processing in the CNS, leading to a diversity of cognitive and affective behaviors. Chronic manifestations of these adverse neurological events may also lead to the exacerbation of pre-existing neurological/neuropsychiatric concerns, including depression, anxiety, and sleep disorders.[17] Recent studies reveal that many pathogenic viruses can directly or indirectly influence CNS function and may have a significant influence on the progression of pre-existing neurodegenerative disease (e.g., Alzheimer's disease). Given these findings, it may be worthwhile to focus on the functional plasticity of the BBB and the possibility of substantial bidirectional communication via immune cell trafficking. Furthermore, numerous pathogenic viruses may have developed mechanisms that permit them to enter and remain protected within the CNS for extended periods. Similar to what has been observed for HIV, changes in the patient's immune status might lead to a second round of infection; in this case, the virus can then undergo replication without the need for transmission to a secondary host.

In summary, viruses are extremely successful products of 3.5 billion years of evolution taking place simultaneously within both prokaryotic and eukaryotic cells.[18,19] Recent developments, including sophisticated new knowledge and technologies, may ultimately provide us with the insights needed to avert the negative neuropsychiatric sequelae associated with acute infection in a human host.

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