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Starting signal: Aberrant kinase activation as a trigger for SARS-CoV-2 induced axonal damage

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Introduction

Coronaviruses have been responsible for severe outbreaks worldwide over the past 20 years. Most recently, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus was responsible for a global pandemic leading to over 500 million documented cases and over 6 million deaths as of May 2022 (1). Although the primary symptoms of SARS-CoV-2 infection are associated with the respiratory system, there is increasing evidence that severe infection is also associated with neurological complications. Over one third of patients diagnosed with SAR-CoV-2 experience neurological symptoms including stroke, headache, fatigue, impairment of consciousness, myalgia, seizures, smell impairment and taste impairment (2–4). The cause of the neurological symptoms remains unknown.

Damage to neuronal axons in the central nervous system (CNS) can cause headaches, fatigue, nausea, and disorientation (5, 6). In addition, axonal damage is associated with the development of several neurodegenerative diseases including multiple sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), and Alzheimer's disease (7–9). The overlap in the symptoms of axonal damage and the neurological symptoms associated with severe SARS-CoV-2 infection led to the hypothesis that SARS-CoV-2 infection may result in axonal damage (10, 11). In support of this hypothesis serum levels of neurofilament light chain (NfL), a highly specific biomarker of axonal damage, are elevated in in SARS-CoV-2 infected patients.

Coronaviruses, including Middle Eastern Respiratory (MERS), SARS-CoV and SARS-CoV-2, activate the cellular kinases p38-MAPK and Casein kinase 2 (CK2) (12–20). Inhibition of these kinases during infection reduces viral replication suggesting that these kinases are specifically targeted by the virus to promote infection (16, 19). Aberrant activation of both p38-MAPK and CK2 can induce axonal damage through the disruption of axonal transport (21–25). In this opinion piece we discuss a possible role

for SARS-CoV-2 mediated activation of CK2 and p38-MAPK in inducing the axonal damage associated with infection. We also discuss how the release of pro-inflammatory cytokines by neighboring cells may trigger the initial phosphorylation events that ultimately result in axonal damage. Finally, we discuss how pharmaceutical interventions targeting aberrant kinase activation during SARS-CoV-2 infection could be used to reduce the axonal damage associated with infection.

CNS infection by SARS-CoV-2

Although they are not typically thought of as neuroinvasive viruses, there is ample evidence demonstrating that coronaviruses can infect neurons if given the opportunity. SARS-CoV can infect neurons within the central nervous system and cause neurological symptoms similar to what has been observed for SARS-CoV-2 (26). Another closely related coronavirus, HCoV-OC43, uses axonal transport to spread between neurons (27). The neurotropism of SARS-CoV-2 has been an area of intense research since the beginning of the pandemic. The majority of the early data on this topic came from autopsies on patients who succumbed to the infection. In support of direct neuronal infection by SARS-CoV-2, neurons stained positive for the SARS-CoV-2 spike protein in sections of fixed brain tissue (28). However, it should be noted that viral RNA levels in the brain appear significantly lower than in other organs such as the lung or kidneys (29). In addition, some studies have failed to find viral infection in neurons of patients that succumbed to infection (30). These data suggest that the CNS is likely not a primary target of SARS-CoV-2, however, even a low level of infection may be sufficient to cause significant damage.

While primary brain samples have provided valuable insights into the neurological pathology of SARS-CoV-2 infection, the interpretation of results is complicated by interpatient variability and the heterogenous nature of the clinical course of infection. Recent advances in the derivation of 3-D cerebral organoids from human pluripotent stem cells have facilitated the study of viral CNS pathology in a highly controlled system. Cerebral organoids contain the cell types, multi-cellular structures, and epigenomic signatures typically found in the developing human brain (31, 32). Immunofluorescence imaging of SARS-CoV-2 infected cerebral organoids showed co-localization of the SARS-CoV-2 nucleocapsid protein with both neurons and neuronal progenitor cells further demonstrating the capacity of SARS-CoV-2 to infect neural cells (28, 33). Additional data generated using single cell sequencing of infected brain organoids showed SARS-CoV-2 transcripts present in multiple CNS cell types including neurons, glia, and neural stem cells (28). Areas of the brain organoid with high levels of infection also had increased levels of TUNEL-positive cells suggesting that infection may lead to local toxicity within the brain (33). This result is consistent with reports on SARS-CoV which showed extensive neuronal loss at the sites of high levels of infection (34).

Axonal damage as a result of SARS-CoV-2 infection

Axons are long projections in nerve cells that are responsible for transmitting information both within the CNS and from the CNS to peripheral organs. The severe neurological manifestations of SARS-CoV-2 infection prompted researchers to investigate if infection could cause damage to axons within the CNS. To determine if axonal damage occurred as a result of SARS-CoV-2 infection researchers measured the levels of neurofilament light chain (NfL) in the serum of patients hospitalized for SARS-CoV-2 infection. Neurofilaments (NFs) are highly abundant cytoskeletal proteins found primarily in axons. Damage to the axonal membrane leads to release of NFs into the cerebrospinal fluid (CSF) and blood. Serum and CSF levels of neurofilament light change (NfL), which has the highest solubility of the subunits, are used as a biomarker to detect axonal damage (35, 36). During the acute stage of infection serum NfL levels were significantly higher than in healthy controls (37–39). Higher serum NfL levels correlated with worse clinical outcomes including admittance to intensive care unit and the need for mechanical ventilation (39). Follow up examination on patients with elevated NfL levels showed that NfL levels decline rapidly after the acute stage of infection (37). These data suggest that the axonal damage caused be SARS-CoV-2 infection may be more temporary than what is observed in neurodegenerative diseases.

As research continues into the neurological manifestations of SARS-CoV-2 infection it will be important to quantify the extent of axonal damage using proton magnetic resonance spectroscopy to noninvasively measure axonal damage. This method has been successfully used to measure axonal damage in patients with MS (5). Analysis of magnetic resonance imaging (MRI) images from SARS-CoV-2 patients with neurological complications showed significant changes due to infection however a more targeted examination is needed to determine if these changes included axonal injury (40).

Disruption of axonal transport leads to axonal damage

Healthy neurons require the translocation of a wide variety of cellular cargo to spatially discrete neuronal regions including the neuronal soma, axonal initial segment, pre-synaptic terminals, and nodes of Ranvier (24, 41). Within the axon cellular cargo is primarily transported by the molecular motor

proteins conventional kinesin (kinesin-1) and cytoplasmic dynein (CDyn) which move along microtubules in a process referred to as fast axonal transport (FAT) (42). Conventional kinesin powers anterograde FAT which moves cargo away from their place of synthesis in the neuronal soma to distal regions of the axon. Conversely, retrograde FAT is driven by CDyn and involves the movement of degraded materials, defective organelles, or neurotrophic signals from axonal subdomains back to the neuronal soma. Inhibition or misregulation of FAT can directly lead to axonal damage and eventual neuronal death [reviewed in (43–45)]. More specifically, mutations that disrupt the activity of molecular motor proteins result in progressive axonal degeneration in a distal to proximal manner (22, 46).

The activity of both CDyn and conventional kinesin can be modulated through cellular kinases. These effects can either be direct, through the phosphorylation of specific subunits of the motor proteins [reviewed (47, 48)], or indirect by phosphorylation of the adaptor proteins that link cellular cargoes to the motor proteins. Activation of the cellular kinases casein kinase 2 (CK2) and p38-MAPK can inhibit retrograde FAT, however, it is not known whether this inhibitory effect involves direct phosphorylation of specific CDyn subunits (23–25). CK2 and p38-MAPK activation also has the potential to impact anterograde FAT. p38-MAPK directly phosphorylates the motor domain of kinesin-1, which reduces the interaction of kinesin-1 with axonal microtubules (Figure 1) (24). Aberrant CK2 activation leads to increased phosphorylation of both kinesin-1 heavy and light chains, the later resulting in the release of kinesin from its cargo (Figure 1) (25).

SARS-CoV-2 infection activates p38 and CK2

Multiple respiratory viruses including respiratory syncytial virus, and influenza virus, have been shown to active p38 signaling (49, 50). Coronavirus infection can result in activation of both p38-MAPK and CK2 (12–14, 16–19). The spike protein of SARS-CoV was sufficient to activate CK2 whereas the 3a protein has been shown to activate p38-MAPK (12, 14). Bouhaddou et al. investigated overall changes in phosphorylation of cellular and viral proteins following SARS-CoV-2 infection (16). Their results showed that infection of Vero E6 cells, which are highly susceptible to SARS-CoV-2, resulted in dramatic increases in the activity of multiple cellular kinases including p38-MAPK and CK2. Expression of the SARS-CoV-2 N protein alone was sufficient to activate CK2, suggesting that this protein may be responsible for kinase activation during infection (16). Inhibitors of p38-MAPK reduce viral replication of both MERS and SARS-CoV-2 demonstrating that this kinase is likely specifically targeted by these viruses and increasing that likelihood of activation being conserved across multiple cell types (16, 19). In addition to activation of p38-MAPK through the expression of SARS-CoV-2 proteins, it is also possible that the generation of double stranded RNA (dsRNA), which occurs during viral genome replication, could result in p38-MAPK activation (51, 52).

Neurons express both p38 and CK2 (53, 54). Therefore, if neurons were to be infected with SARS-CoV-2 it is possible that these kinases could become activated. Consideration of the activation of p38-MAPK and CK2 during SARS-CoV-2 infection – both pathways with known connections to axonal dysfunction, and the observed axonal damage in SARS-CoV-2 infected patients results in a hypothesis that SARS-CoV-2 infects cortical neurons resulting in increased activity of p38-MAPK and CK2 which in turn causes deficits in FAT. This misregulation of axonal transport damages the axon which leads to the observed increase in serum NfL (Figure 1).

As noted in the previous section, SARS-CoV-2 infection of CNS neurons remains a rare outcome of infection (30). In addition, olfactory sensory neurons appear to be resistant to infection, with the virus instead infecting sustentacular cells in the olfactory epithelium (55). In mice ACE2 is primarily expressed in astrocytes around the microvasculature, radial glial cells, epithelial cells, as well as cerebral pericytes (56). A very recent publication showed that in the developing human cortex SARS-CoV-2 infection was limited to cortical astrocytes with minimal infection of other cortical populations (57). For this reason, one essential question to ask is if the virus could induce axonal damage through kinase activation in the absence of direct neuronal infection. SARS-CoV-2 infection induces a massive inflammatory cytokine response which includes IL-6 and IL-1β (58–60). Exposure to the SARS-CoV-2 spike protein alone is sufficient to induce secretion of IL-6 by epithelial cells (61). In addition, viral activation of IL-1β can promote the secretion of IL-6 demonstrating the feedback loops that promote the production of these cytokines from infected cells (62). Both IL-6 and IL-1β can activate CK2 and p38 respectively (63–66). p38 activation following viral infection has been shown to promote IL-1β expression which may in turn promote further kinase activation (50). For this reason, direct infection of neurons by SARS-CoV-2 may not be required for the induction of axonal damage. If the virus infects non-neuronal supporting cells, such as astrocytes, which are adjacent to neurons these cells may secret IL-1β and IL-6 which could activate p38-MAPK and CK2 within nearby neurons leading to misregulated axonal transport and subsequent axonal damage (Figure 1).

Critical to testing both of these hypotheses will be an examination of axonal FAT following SARS-CoV-2 infection. To determine if any observed defects in axonal transport are due to kinase activation, *in vitro* experiments should be performed with and without inhibitors of p38-MAPK and CK2.

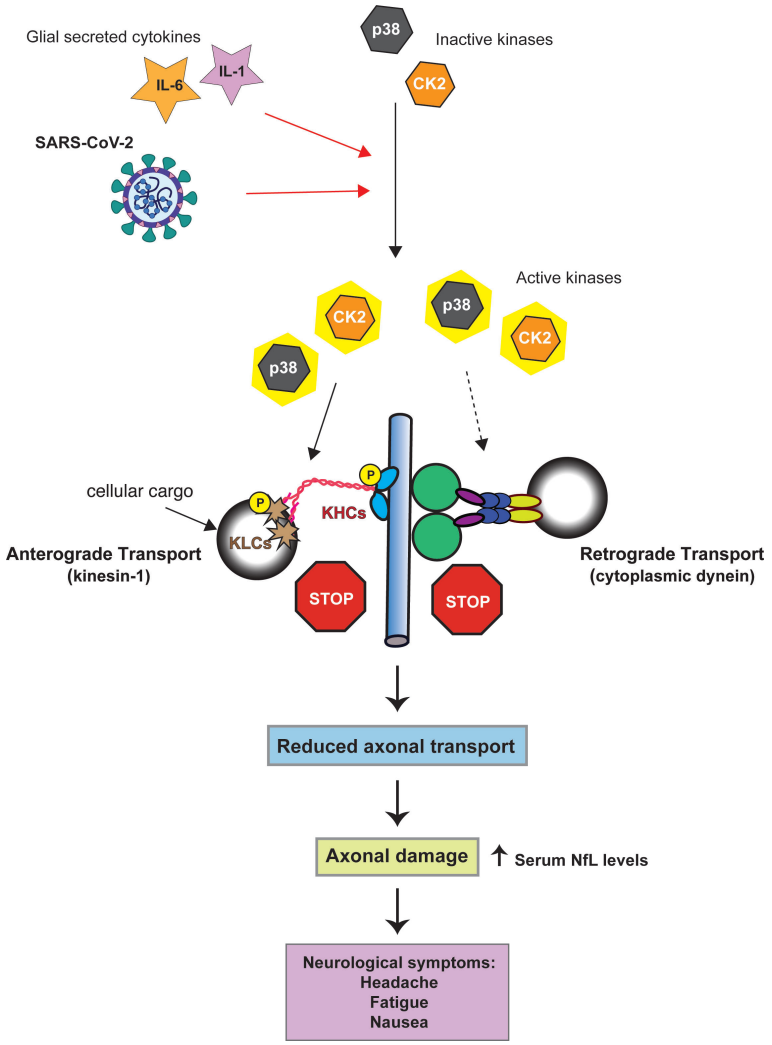

FIGURE 1
Model linking SARS-CoV-2 kinase activation to axonal damage. Both SARS-CoV-2 and the cytokines IL-1 and IL-6 can activate p38-MAPK and CK2 (red arrows). Activation of p38-MAPK and CK2 can impair the axonal transport of the molecular motor proteins cytoplasmic dynein and kinesin-1(conventional kinesin). Solid black arrows indicate phosphorylation of kinesin-1 subunits (KHC = kinesin heave chain, KLC = kinesin light chain). Whether p38-MAPK and CK2 inhibit retrograde axonal transport through dynein phosphorylation has not yet been established (dashed arrow). By altering the activity of kinases involved in the regulation of FAT SARS-CoV-2 may promote FAT abnormalities eventually triggering neuronal dysfunction and pathology.

Discussion

SARS-CoV-2 activates cellular kinases as it proceeds through the viral life cycle. Activation of these kinases has the potential to impact a number of cellular processes. It has begun to be appreciated that one of the processes directly impacted by cellular kinases is axonal transport. Misregulation of axonal transport can cause axonal damage. Therefore, activation of cellular kinases may be one of the mechanisms by which SARS-CoV-2 induces the axonal damage that leads to impaired nerve function. The association between the acute and chronic neurological symptoms associated with SARS-CoV-2 infection is only beginning to be understood but it is possible that axonal damage contributes to both of these pathological conditions. It's worth noting that related coronaviruses have been found in the brains of patients with MS and a link has been suggested between viral infection and development of the disease (67). The symptoms of MS differ widely from those associated with SARS-CoV-2 infection, however, this finding suggests the potential for long term neurological complications following viral neuroinvasion.

Viral activation of neuronal kinases may represent an essential event in the development of axonal damage, and could be a promising target of therapeutic intervention. Highly

specific, brain-permeable kinase inhibitors have recently been developed (68). Inhibitors of p38 and CK2 activation show great potential as antivirals against SARS-CoV-2 (69–71). Treatment with these drugs may have a multifaceted effect on the development of neurological symptoms first by reducing the overall viral load, second by rescuing axonal transport and improving the neurological symptoms associated with SARS-CoV-2 infection.

Author contributions

AR and RJ contributed equally to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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