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RESEARCH HIGHLIGHT

Mild Respiratory COVID-Induced Neuroinflammation Causes Neurological Deficits

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To date, more than 580 million people worldwide have been diagnosed with infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 (coronavirus disease 2019) not only affects lung function but also unexpectedly causes brain dysfunction as about a quarter of the survivors of this pandemic to have persistent cognitive impairment. While this sequela is more common in severely ill patients with COVID, those with mild symptoms also frequently experience cognitive impairment [1], and the pathogenic mechanism has not yet been elucidated.

Neuroinflammation is a defense mechanism that initially protects the brain by eliminating pathogens and removing cellular debris. However, persistent inflammatory responses generate neurotoxicity mediated by pro-inflammatory cytokines and microglia [2]. In the case of chronic inflammation caused by neurodegenerative diseases, activated microglia exert further detrimental effects by secreting interleukin-1β (IL-1β), tumor necrosis factor α (TNF-α), IL-6, and proteases [3]. In addition to endogenous factors (e.g., gene mutation and protein aggregation), environmental factors (e.g., infections and drugs) can also induce persistent inflammatory stimulation. A persistent inflammatory response has been reported in the brains of mice treated with chemotherapeutic drugs, and histological studies have shown that these drugs disrupt oligodendroglial lineage dynamics and myelin microstructure by activating microglia, leading to impaired performance in cognitive behavioral tests [4], similar to the cancer-chemotherapy-related cognitive impairment found in cancer survivors [5]. It was recently further demonstrated that inflammatory microglia in mouse models of chemotherapy induce neurotoxic A1 astrocytes by secreting IL-1α, TNF, and complement component 1q [6], which in turn secrete saturated lipids to mediate neurotoxicity [7]. Infection-induced neuroinflammation has been reported in both neurotropic [8] and non-neurotropic [9] virus-infected mice. The non-neurotropic H1N1 strain of influenza induces elevation of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and interferon-α) in cerebrospinal fluid (CSF) and hippocampal microglial reactivity, altering the morphology of hippocampal neurons and impairing cognitive function [9].

Recently, Fernández-Castañeda and colleagues found that mild respiratory COVID induces dysregulations associated with cognitive impairment such as impaired hippocampal neurogenesis, decreased subcortical oligodendrocytes, and loss of myelin due to CCL11 (C-C motif chemokine 11) elevation and microglial activation [10]. The authors first verified that mild respiratory COVID can indeed cause prominent neuroinflammation. Although no overt disease symptoms were observed in post-COVID mice, the cytokine profiles in serum and CSF were significantly elevated for at least 7 weeks (Fig. 1). In particular, the levels of CCL11, a chemokine associated with cognitive dysfunction in aging [11], were substantially increased. At the same time, white-matter-specific microglial reactivity was detected ($IBA1^+CD68^+$). This regionally-restricted microglial activation was also validated in humans with mild respiratory SARS-CoV-2 infection.

Next, the researchers further analyzed the state of white matter microglia following mild respiratory COVID using single-cell RNA sequencing. Consistent with inflammation, the abundance of chemokine-enriched microglia, a subset of cells expressing chemokines and cytokines, was

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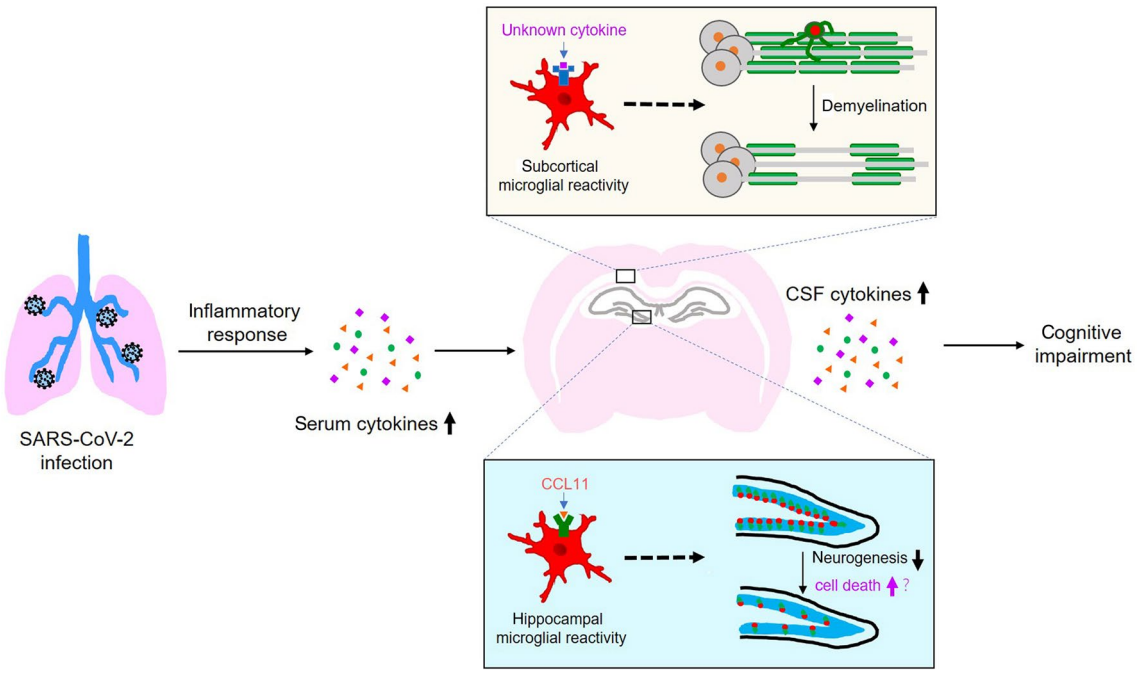

Fig. 1 Schematic of inflammation-elicited dysregulation of myelinogenesis and neurogenesis in brain tissue during mild COVID infection. Mild respiratory SARS-CoV-2 infection triggers the immune response, resulting in increased levels of serum inflammatory cytokines, which, in turn, stimulate the elevation of CSF cytokines levels by increasing the abundance of chemokine-enriched microglia in the central nervous system. Mild respiratory COVID-induced CCL11 elevates white-matter-specific microglial reactivity which impedes hippocampal neurogenesis. Microglia in the subcortical white matter are activated by an unknown factor and induce the persistent loss of oligodendrocytes leading to demyelination.

significantly increased in post-COVID mice. Even in the homeostatic microglia cluster, genes related to antigen processing and presentation, such as B2m, H2-D1, and H2-K1, were also up-regulated following mild respiratory COVID. More importantly, the microglial transcriptome profiling of post-COVID mice displayed high similarity to that of Alzheimer-associated microglia and aging-associated white-matter microglia. These data suggest that mild respiratory COVID indeed induces typical neuroinflammation.

Considering the previous reports that reactive microglia and cytokines/chemokines (e.g. IL6 and CCL11) induced by systemic illness or aging inhibit the generation of new neurons in the hippocampus [11, 12], the authors examined hippocampal neurogenesis following mild respiratory COVID. They found that microglial reactivity in the hippocampal white matter of post-COVID mice robustly increased, coinciding with the marked reduction of doublecortin-positive (DCX^+) new neurons in the same period (Fig. 1).

To investigate whether CCL11 is responsible for cognitive impairment in post-COVID patients, the authors measured the CCL11 levels in the plasma of people suffering from COVID with and without cognitive symptoms. Unsurprisingly, the plasma levels of CCL11 were significantly higher in COVID patients exhibiting cognitive deficits than in COVID patients without cognitive symptoms. The CCL11 levels in the plasma were significantly elevated in both mild respiratory COVID mice and COVID patients with cognitive symptoms, which is reminiscent of the finding that CCL11 mediates cognitive impairment by inhibiting hippocampal neurogenesis, an ongoing mechanism of neural plasticity thought to support healthy memory function. Indeed, when CCL11 was administered intraperitoneally, a systemic microglial activation was induced specifically in hippocampal white matter, and impaired hippocampal neurogenesis was confirmed.

To investigate whether mild respiratory SARS-CoV-2 infection damages myelinating oligodendrocytes like chemotherapy [4], the researchers examined oligodendroglial lineage cells in subcortical white matter. The number of oligodendrocyte precursor cells did not change significantly at first, but a mild decrease (~10%) was detected later. Mature oligodendrocytes were significantly reduced initially and this continued for a long time. In keeping with the loss of oligodendrocytes, the density of myelinated axons in subcortical white matter was significantly reduced (Fig. 1) for at least 6 months following mild respiratory SARS-CoV-2 infection.

In the end, the comparison of cytokine profiles between H1N1 influenza and SARS-CoV-2 infection revealed overlapping but not identical neuroinflammatory profiles, with the notable shared feature of persistently elevated CCL11.

In mild respiratory infection with H1N1 influenza, the same pattern of white matter-selective microglial reactivity was observed initially in the subcortical and hippocampal white matter. However, subcortical microglial reactivity became normal soon after. Concordant with the pattern of microglial reactivity in mice with H1N1 influenza, oligodendrocytes were initially decreased in the subcortical white matter but recovered rapidly as microglial reactivity resolved. However, hippocampal neurogenesis was deficient for a long time. These data further demonstrate the neurotoxicity of microglial reactivity.

In summary, this study provides strong evidence that mild respiratory COVID can induce CSF cytokine elevation and white matter-specific microglial reactivity in mice and humans, and the sustained inflammatory responses further impair hippocampal neurogenesis, reduce mature oligodendrocytes, and increase demyelination (Fig. 1). More importantly, the authors identified the key cytokine CCL11 that induced hippocampal microglial reactivity and impaired neurogenesis, suggesting CCL11 as a potential therapeutic target for mild respiratory COVID.

The findings of this study provide a scientific explanation for the impairment of cognition by mild respiratory COVID, but several important issues remain to be resolved. First of all, the authors attribute the reduction of hippocampal DCX^+ neuroblasts caused by SARS-CoV-2 infection and CCL11 administration to impaired neurogenesis, but they cannot rule out the possibility that neuroblast apoptosis may also contribute to this defect. Therefore, detecting the apoptosis of hippocampal neurons is necessary. In addition, intraperitoneal injection of CCL11 only caused microglial reactivity in the hippocampus, but not in subcortical white matter, indicating that the subcortical microglia are not sensitive to CCL11. A similar phenomenon was reported in mice with respiratory H1N1 influenza, that is, the CSF CCL11 levels were consistently higher at least 7 weeks post-infection, but microglial reactivity in the subcortical white matter was only detected at 7 days post-infection. The finding that mild respiratory COVID can continue to activate microglia in the subcortical white matter for at least 7 weeks implies that other inflammatory factors may be responsible for the pro-inflammatory effects during this period. Identification of the related cytokines/chemokines will help to further understand the mechanism of respiratory COVID-induced myelin dysregulation (Fig. 1). It is also noted that reactive microglia contribute to a decrease in myelinated axons and adult hippocampal neurogenesis, but the exact underlying mechanism remains unclear. Liddelow *et al*. demonstrated that reactive microglia activate neurotoxic A1 astrocytes by secreting cytokines [6], which in turn secrete saturated lipids to kill oligodendrocytes and neurons [7]. Are the impaired hippocampal neurogenesis, decreased oligodendrocytes, and myelin loss caused by mild respiratory COVID mediated through the same mechanism? Hopefully, future discoveries will help to unravel these mysteries.

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Conflict of interest The authors declare no competing financial interests.

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