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How the Interaction of SARS-Cov-2 with the Interleukin-17A Receptor May Contribute to Neuropathology

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Abstract

The inflammatory response in the context of SARS-CoV-2 infection has been implicated in corresponding neurological and neuropsychiatric manifestations. Severe coronavirus disease coincides with substantial serum concentrations of interleukin-17. Previous clinical studies and reports have indicated that inteleukin-17 may contribute to various neurological and neuropsychiatric conditions, as well as to severe disease in the course of SARS-CoV-2 infection. Interestingly, the viral ORF-8 protein, that is unique to SARS-CoV-2 and contributes to severity of COVID-19, interacts with the interleukin-17A receptor. This review will elucidate the possible role of interleukin-17 in brain conditions and how, together with SARS-CoV-2, it may interfere and enhance coronavirus disease of the brain.

Keywords: COVID-19; SARS-CoV-2; Interleukin-17; IL-17RA; Neuropathology; Stroke; Thrombosis; Neuron; Glia; Endothelial cell

Abbreviations: COVID-19: Coronavirus Disease of 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus 2; IL-17: Interleukin-17; IL-17RA: Interleukin-17 Receptor A; ACE2: Angiotensin-Converting Enzyme 2; TMPRSS2: Transmembrane Protease Serin Subtype 2; ORF8: Open Reading Frame 8

Introduction

Clinical manifestation of the brain has been well documented in the context of severe COVID-19 (coronavirus disease of 2019) that is caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection (for review [1-3]). All brain regions can be affected by COVID-19 [4-12], resulting in complex acute symptoms and syndromes [13-19], as well as chronic complications and residual damage [20-23]. Besides various neurological and neuropsychiatric manifestations related to neuronal and glial infection with SARS-CoV-2, COVID-19 related cerebrovascular thrombosis [24,25] and stroke [26,27] have also been reported as COVID-19 is associated with endothelial cell infection, endotheliopathy and coagulopathy [13,28]. To date, various neuropathological mechanisms have been considered [29]. There is published evidence that brain cells [30], including neurons [31-33]), astrocytes [34, 35], microglia [34], cells of the choroid plexus [36] and endothelial cells [37-40] can be infected by SARS-CoV-2 [41]. Susceptible cells need to express the ACE2 (angiotensin-converting enzyme 2) membrane protein [42] for binding of SARS-CoV-2 through its spike proteins [33,43,44], as well as one of the two membrane proteins, either TMPRSS2 (transmembrane protease serin sub type 2) [45]) or neuropilin-1 [46] as co-receptors for entry into the cell. Infected cells may die through cytopathic effects of the virus [47]) or they may be eliminated by the cytotoxic immune response against the virus [48,49]. Either way, cell death of neurons and glia cells results in disruption of cellular function in neuronal networks, whereas damage to endothelial cells leads to local coagulopathy with thrombosis and stroke [50]. Interestingly, endothelial von Willebrand factor may play a crucial role in infected and activated endothelial cells [51], whereby its expression pattern in endothelial cells varies substantially between different brain regions [52], providing a possible explanation for focal lesions and consequently for enhanced thrombosis and stroke in certain brain regions. In summary, SARS-CoV-2 infects neurons, glia cells and endothelial cells resulting in COVID-19 manifestations of the brain.

Interleukin-17 Effects on the Nervous System

The inflammatory cytokine interleukin-17 (IL-17) contributes substantially to severe COVID-19 [53,54]. IL-17 is produced by activated gamma-delta T lymphocytes [55], T helper 17 lym-

phocytes (TH17) [56], astrocytes [57] and microglia [58,59]. In addition to exhibiting neuropathological effects that are explained in this paragraph, IL-17 is a versatile cytokine supporting diverse physiological functions, including efficient immune defence against certain bacteria and fungi, as well as tissue repair and regeneration [60]. IL-17 binds to and signals through its unique interleukin-17 receptor 17A (IL-17RA) (for review of IL-17 and its receptor see [61]). In the central nervous system, the IL-17RA is expressed by astrocytes [60,62], microglia [62,63] and neurons [64-66]. Interestingly, infection with neurotropic viruses and corresponding encephalitis increases expression of IL-17RA in the brain [67,68]. Locally produced IL-17 may physiologically contribute to brain development, regeneration, and remodelling [61]. IL-17 certainly contributes to anti-viral immune defence in the brain. However, out of balance production of IL-17 causes encephalitis [67,69], as well as neurocognitive disorders [70]. However, IL-17 actions on the brain are best known for its corresponding chronic inflammatory effects (for review see [71]), many of them reminding chronic COVID-19 complications. Il-17 contributes to various neurological and neuropsychiatric conditions, including depression [72], cognitive impairment [73], multiple sclerosis [74], schizophrenia [75,76] and Parkinson's disease [77]. Most important, however, is the contribution of IL-17 in the context of cerebrovascular events (for review see [78]), especially in post-stroke neurodegeneration [79,80], relevant acute manifestation of severe COVID-19. IL-17 acts on endothelial cells affecting the blood-brain barrier [70,81,82], infiltration of immune cells into the brain tissue [83] and thrombosis [80,84], also by releasing von Willebrand factor [52,84,85]. Cerebrovascular thrombosis may then also be enhanced by IL17 acting on platelets [86], as they express IL-17RA [87], as well as ACE2 allowing binding of SARS-CoV-2 and subsequent thrombotic activation [88]. Summarizing, IL-17 and its receptor are key players in COVID-19 and they contribute substantially to complications of the brain. The question now is, whether it is possible to interfere with IL-17 effects. Various IL-17 and IL-17RA antagonist or inhibitors have been developed and explored in recent years in the context of severe autoimmune-related diseases where IL-17 play a major role [89, 90]. Consequently, IL-17 inhibitors have been proposed to treat patients with severe COVID-19 [91, 92]. However, clinical trials would be needed to explore the benefit of IL-17 inhibitors in patients with neurological manifestations due to COVID-19.

The role of SARS-CoV-2 ORF8 Protein in IL-17 Neuropathology

ORF8 (open reading frame 8) protein of SARS-CoV-2 is unique to this virus and not present in the other coronaviruses [93-95]. ORF8 somehow influences the immune response [96,97]. ORF8 modifications or deletion, which happen naturally along the evolution of the virus, as well as experimentally in research laboratories, indicate that variations of ORF8 correlate with severity of COVID-19 [98]. Interestingly, it has recently been shown that ORF8 protein forms a complex with IL-17RA [99], which may modify or influence the IL-17 cellular response. The interaction of ORF8 protein with IL-17RA enhances SARS-Cov-2 production in the infected cell. However, IL-17 binding to the receptor does not influence viral reproduction, but the wild-type version of ORF8 associated with severe COVID-19 increases substantially IL-17 serum concentration [100]. In the context of brain cells infected with SARS-CoV-2 and expression of IL-17RA, the interaction of ORF8 protein with IL17-RA may enhance virus production and thus spread the virus locally which may increase local immune response and tissue damage. In addition, in brain cells that also produce IL-17, the interaction between the ORF8 protein and IL-17RA may dysregulate IL-17 feedback and cellular response, resulting in uncontrolled continuous secretion of IL-17 and subsequent local neuropathological and cardiovascular effects, described in the previous paragraph. The most reasonable way to interfere with SARS-CoV2 and IL-17 effects on the brain might be to develop new small molecules that disrupt specifically the interaction between ORF8 and the IL-17RA for prevention of major neuropathologies early in SARS-CoV-2 infection.

Conclusion

The inflammatory cytokine IL-17 plays a major role in severe COVID-19 and may have a substantial contribution to corresponding neurological and neuropsychiatric acute and chronic manifestations. IL-17 related neuropathological effects may be enhanced by the interaction of SARS-CoV-2 ORF8 protein with the IL-17RA in brain cells. COVID-19 patients may benefit from treatment with already available IL-17 inhibitors in the early stage of the infection. In addition, new inhibitory small molecules ought to be developed that interfere with the complex formation of the ORF8 protein and the IL-17RA for decreasing or blocking viral reproduction and for preventing COVID-19 related neuropathologies.

Conflict of Interest

There is no economic interest and no conflict of interest with any of the co-authors.

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