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Latest Evidence of Neuropathological Consequences of SARS-Cov-2 Infection in the K18-hACE2 Transgenic Mouse Model

Simona Dedoni[1*], Chiara Camoglio[1], Carlotta Siddi[1], Walter Fratta[1], Maria Scherma[1], Valeria Avdoshina[2], Paola Fadda[3]

[1]Department of Biomedical Sciences, University of Cagliari, Sardinia, Italy
[2]Department of Neuroscience, Georgetown University Medical Center, Washington, USA
[3]Department of Neuroscience, Institute of Neuroscience-Cagliari, National Research Council, Italy

INTRODUCTION

Severe Acute Respiratory Syndrome caused by SARS-CoV-2 virus represents a large global outbreak. Currently there are no specific therapies against SARS-CoV-2 infection for potential human use. Preventive measures are the current strategy to limit the spread of the cases. From the beginning of the pandemic to date, animal models have played crucial roles in the understanding of the pathogenesis of COVID-19 and the development of vaccines. Many animal models have been proposed for the study of SARS-CoV-2 infection. However, current animal models have some limitations and there is an urgent need for new models to assess the virulence of variants, antibody-dependent enhancement, and various COVID-19 comorbidities. Current studies on COVID-19 pathogenesis are mainly focused on the role of ACE2 protein in SARS-CoV-2 infection, as allows the virus to enter the host cells. Clinical reports underlined the link between SARS-CoV-2 infection and different neurological complications experienced by COVID-19 patients. Starting from this evidence, several researchers focused on investigating the mechanisms behind these neurological symptoms using transgenic animals. In particular, K18 and CAG-hACE2 transgenic mice models are the most widely used. These animals express hACE2 in various tissues, including brain that makes them suitable for the study of SARS-CoV-2 neuroinvasion and consequent neuropathology. With this short comment we want to discuss the latest research investigating the neuropathological effects of SARS-CoV-2 infection in the widely used K18-hACE2 transgenic mouse model.

DESCRIPTION

As previously discussed in our review [1], transgenic mice have been extensively used to study the neurological consequences of SARS-CoV-2 infection. Several research confirmed that these transgenic animals are highly susceptible to SARS-CoV-2 infection and develop severe and often fatal neurological complications. Various mechanisms have been hypothesized for SARS-CoV-2-related neurological dysfunction: the neuronal damage could be caused by direct virus neuroinvasion and/or be a consequence of the cytokine storm evoked following systemic infection, giving rise to a wide range of neurological symptoms and manifestations that have not been fully characterized yet. To try to shed some light on this unclear scenario, it was recently carried out a study that aimed at characterizing the lesions induced by SARS-CoV-2 in K18-hACE2 transgenic mice at different time points, in order to analyse the virus-induced neuropathology from a chronological point of view [2]. The animals were infected intranasally with different doses of SARS-CoV-2 (10^3 and 10^4 $TCID_{50}$/mouse SARS-CoV-2) and then sacrificed at 2, 4, 6 and 7 days post infection (dpi) to perform histological and molecular analyses on the brain and olfactory mucosa. From 3 dpi the animals started to lose weight, and from 5 to 7 dpi they showed clinical symptoms like hunched posture, trembling and seizures when touched. Molecular analyses detected significant amounts of viral genomic and sub genomic RNA (gRNA and sgRNA) starting from 4 dpi until the end of the study, with the highest detection at 6 and 7 dpi. Consistent with the viral RNA

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Corresponding author Simona Dedoni, Department of Biomedical Sciences, University of Cagliari, Sardinia, Italy, E-mail: dedoni@unica.it

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detection, brain lesions, including non suppurative meningitis, encephalitis or meningoencephalitis, started to become evident in some of the animals at 4 dpi (thalamus, piriform cortex, and mesencephalon) and at 7 dpi all the animals from the higher dose group presented lesions in all the analysed areas. In line with results from previous research, cerebellum was spared. The lesions were characterized by inflammatory infiltrates, vascular damage, thrombosis, gliosis and spongiosis, diffuse neuronal degeneration was also evident. Immunohistochemistry also showed strong microglial and astroglia responses at 4 and 7 dpi. SARS-CoV-2 nucleocapsid protein (NP) was detectable at 2, 4 and 6 dpi in the olfactory mucosa and at 4, 6 and 7 dpi in neurons, suggesting a rapid spreading of the virus from the olfactory mucosa throughout the brain and giving further confirmation of the important role of the olfactory mucosa for the entry and diffusion of the virus into the CNS. Considering this ability of SARS-CoV-2 to activate microglia, that is the most representative immune cell type of the human brain, some researchers focused their attention on the effects of the virus in this cell type [3] and evidenced the possibility that SARS-CoV-2 could infect directly microglial human cells using primary microglia derived from the immortalised human embryonic brain (HMC3), microglia derived from human induced pluripotent stem cells (ipsc-Microglia) and human brain microglial cells (PHM). In addition, in this work they also used K18-transgenic mice and defined that SARS-CoV-2 can infect microglia leading to microgliosis and cell death. The analysis of cerebral homogenates showed the presence of three separate immune cells populations represented by lymphocytes, macrophages, and microglia. Microglia represented the majority of the leukocytes in the CNS of non-infected mice, but it was significantly depopulated after SARS-CoV-2 infection. On the other hand, the number of lymphocytes and infiltrating macrophages increased by about 7 times in infected mice. Moreover, most of the microglia was activated, with high expression of TNF-α and IL-6 indicating that SARS-CoV-2 induces neuroinflammation. Researchers from all over the world are putting a huge effort in trying to unravel the mechanisms behind the virus-related neuronal complications and their long-term consequences, in order to evaluate possible interventions or preventive treatments. In this research area, one of the most recently published studies is a work that draws attention to the possibility that SARS-CoV-2 infection may in some way predispose to post-encephalic parkinsonism syndrome [4]. To evaluate this hypothesis transgenic K18-hACE2 mice previously infected and cured by SARS-CoV-2 were injected with a sub-toxic dose (10 mg/kg[4] at 2-hour intervals, intraperitoneally) of the parkinsonian toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Seven days after MPTP injection, the brains were examined to detect signs of death of the dopaminergic neurons (DA) of the substantia nigra pars compacta (SNpc) and microglial activation. SARS-CoV-2 or MPTP alone were unable to determine the death of DA neurons in the SNpc, however, in mice infected with SARS-CoV-2 (4×10^3 $TCID_{50}$) and left to heal for 38 days, MPTP induced a significant loss of DA neurons. Moreover, from the analyses of total microglia it emerged that a previous infection with SARS-CoV-2 is able to increase neuroinflammation; in particular, there is a significant increase in microglial activation the SARS-CoV-2+MPTP group compared to SARS-cov-2 or MPTP group.

CONCLUSION

Despite the limitations of transgenic animal models for studying SARS-CoV-2, this short communication examines the latest research on hACE2 transgenic mice focusing on the neurological consequences of SARS-CoV-2 infection. The main objective is to clarify the unclear scenario of neurological symptoms of the COVID-19 pandemic in order to push and improve research in this field to identify possible molecular targets and to lay the foundations for the development of new drugs.

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CONFLICT OF INTEREST

The authors have declared no war of interest

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