Brain, Behavior, and Immunity 87 (2020) 93–94

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion?

Dear editor,

We read with interest the article by Wu et al. (2020). This letter aims at offering an alternative viewpoint on the pathophysiological mechanisms underlying SARS-CoV2 neuroinvasion. As elegantly reported by the Authors, direct neuroinvasion via hematogenous spread or migration through the olfactory tract are possible infection routes to the Central Nervous System (CNS). However, the virus could also gain access to the CNS from the periphery and, notably, the brainstem invasion via the vagal afferents from the lung and upper airways has been postulated in COVID-19 patients (Li et al., 2020).

In this context, the gastrointestinal (GI) tract emerges as a largely underestimated niche for viral replication, given 1) the higher relative expression of ACE-2 receptor along the GI epithelium than in the lungs 2) the evidence that SARS-CoV-2 is able to directly infect and replicate in intestinal cells 3) the worse clinical outcome of COVID-19 patients with concomitant GI symptoms with increased acute respiratory distress and need of mechanical ventilation (Jin et al., 2019).

Zhou et al. (2017) showed that in Middle East Respiratory Syndrome coronavirus (MERS-CoV) the enteric involvement could precede the respiratory infection and observed brain infection in intranasally injected mice with MERS-CoV. More surprisingly, they also described increased viral load in brains from infected mice by intragastric inoculation. In these mice, indeed, direct intragastric gavage spread infectious virions in both lung and brain homogenates 5 days after the inoculation.

The digestive tract is largely exposed to a variety of immunogenic noxae from the external world in the form of ingested particles, including viruses. Increasing evidence supports the hypothesis that the gut may be the “entrance door” by which prions or viruses may: (1) directly neuroinvade or indirectly immunologically prime the enteric nervous system (ENS) and (2) ascend to the CNS through intestinal vagal afferents.

The ENS is strictly interconnected with the enteric glial cells (EGCs) and the gut epithelium cooperating in a neuro-epithelial unit that is key to gut homeostasis. EGCs express the major histocompatibility complex II and respond to harmful stimuli mainly through the Toll-like receptors-2 and -4, regulating the neuro-immune axis and defending the host against gut pathogens.

EGCs are antigen presenting cells to innate and adaptive immune cells housed in the so-called gut-associated lymphoid tissue (GALT), representing de facto the central repository of these lymphocytes in the body and coordinate the transition from naïve CD4+ lymphocytes to different subtypes.

In keeping with this, EGCs activation by viruses or their antigens, is a key step for the peripheral neuroglial immune priming by viruses and is responsible for late onset of neurological impairment, through a gut-brain axis for neuroinvasion (Esposito et al., 2017). Finally, EGCs activation is accompanied by a massive release of IL-6 and other inflammatory mediators that could contribute to acute respiratory distress as observed in the COVID19-induced cytokine storm (Fig. 1).

A growing number of scientists are now considering the SARS-CoV-2 related-diarrhea, not a merely accessory symptom. The GI dysfunction is a possible marker of involvement of ENS/EGC, offering an alternative pathophysiological mechanism underlying SARS-CoV2 neuroinvasion.

https://doi.org/10.1016/j.bbi.2020.04.060
Received 21 April 2020; Accepted 22 April 2020
Available online 23 April 2020

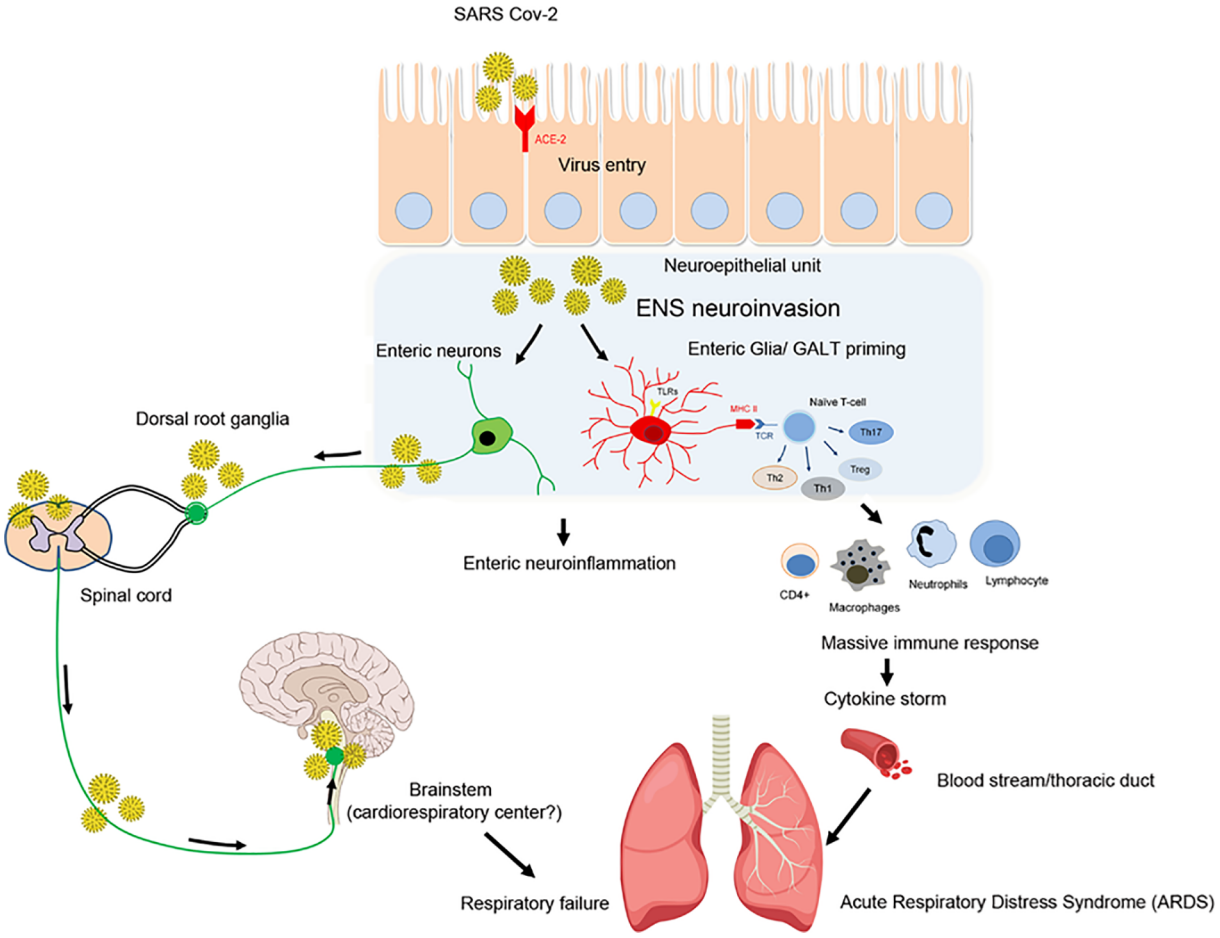

Fig. 1. The Enteric nervous system and its potential involvement in SARS-CoV2 neuroinvasion.

References

Wu, Yeshun, et al., 2020. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav. Immunity. https://doi.org/10.1016/j.bbi.2020.03.031.

Li, Y., Bai, W., Hashikawa, T., 2020. The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients. J. Med. Virol. https://doi.org/10.1002/jmv.25728.

Jin, X., Lian, J., Hu, J., et al., 2020. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus- infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut epub ahead of print: doi: 10.1136/gutjnl-2020-320926.

Zhou, J., Li, C., Zhao, G., et al., 2017. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. Sci. Adv. 3, eaao4966.

Esposito, G., Capoccia, E., Gigli, S., et al., 2017. HIV-1 Tat-induced diarrhea evokes an enteric glia-dependent neuroinflammatory response in the central nervous system. Sci. Rep. 7 (1), 7735. https://doi.org/10.1038/s41598-017-05245-9. Published 2017 Aug 10.

Giuseppe Esposito[a], Marcella Pesce[b], Luisa Seguella[a], Walter Sanseverino[c], Jie Lu[d], Giovanni Sarnelli[b,*]

[a] *Department of Physiology and Pharmacology, Sapienza University of Rome, Italy*

[b] *Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy*

[c] *Sequentia Biotech SL, Carrer Comte D'Urgell 240 3D, Barcelona, Spain*

[d] *Department of Human Anatomy, College of Basic Medical Sciences, China Medical University, Shenyang City, Liaoning, China*

E-mail address: sarnelli@unina.it (G. Sarnelli).

* Corresponding author.