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SARS-CoV-2 and type I interferon signaling in brain endothelial cells: Blurring the lines between friend or foe

George D. Vavougios,[1,2,*] Sotirios G. Zarogiannis,[3] Georgios Hadjigeorgiou,[1] Karen A. Krogfelt,[4] and Konstantinos I. Gourgoulianis[2]

[1]Department of Neurology, Faculty of Medicine, University of Cyprus, 75 Kallipoleos Street, 1678, Lefkosia, Cyprus
[2]Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Biopolis, 41500, Larissa, Greece
[3]Department of Physiology, Faculty of Medicine, School of Health Sciences, University of Thessaly, Biopolis, 41500, Larissa, Greece
[4]Department of Molecular and Medical Biology, Centre for Mathematical Modeling – Human Health and Disease, PandemiX Center, Universitetsvej 1, 28A.1, 4000 Roskilde, Denmark
*Correspondence: gvavougyios@uth.gr
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A recent paper published in *Stem Cell Reports* (Krasemann et al., 2022) described gene-, pathway-, and tissue-resolution evidence on the mechanisms involved in SARS-CoV-2 CNS entry via the blood-brain-barrier (BBB). The work provided further evidence on how the virus may interact with the neurovascular unit, resulting in enhanced inflammatory signaling in affected cells.

The authors used a unique experimental model to study this process. However, they failed to mention much of the previous *in vivo*, *in vitro*, and *in silico* data on the very biological phenomenon they model. Furthermore, their specific findings on type I interferon signatures (IFN-I) have already been reported in studies on interactions between SARS-CoV-2 and brain endothelial cells. These prior studies, which were not cited in the Krasemann paper, both provide support for and indicate caveats in their study, effectively constituting its context (Constant et al., 2021). In its current form, with these prior studies remaining insufficiently discussed by Krasemann et al., their model appears somewhat preliminary. Considering that their model aims to surpass existing models, in our opinion a comparison with preceding work should be accurately represented in order to obtain the full framework of the authors' findings, their importance, and its limitations. Historically, the first specific description of detection of SARS-CoV-2 in brain capillary endothelial cells is a case report by Paniz-Mondolfi and colleagues (Paniz-Mondolfi et al., 2020). Notably, neuroinvasion was noted, providing an early indication of SARS-CoV-2's neuroinvasive potential. Subsequent neuropathological studies have corroborated brain microvascular involvement (Lee et al., 2021). A subsequent study by Iadecola and colleagues (Iadecola et al., 2020) indicated that SARS-CoV-2-neurovascular unit interactors may be modulated by interferon stimulated gene (ISG) expression including interferon-induced transmembrane proteins (IFITMs). SARS-CoV-2-neurovascular unit interactions were directly implicated and corroborate Krasseman and colleagues' findings—on both a gene and a pathway level. Another earlier study demonstrated SARS-CoV-2 tropism for brain microvascular endothelial cells and the induction of microglial inflammation (Zhang et al., 2021), indicated that the virus can cross the BBB via inducing disruption of the cellular basal membrane, a finding compatible with preceding research on SARS-CoV-2-BBB interactions (Kim et al., 2021a). Yang and colleagues have indicated that brain endothelial cells as infected by SARS-CoV-2 upregulate IFN-I signaling with interferon-induced transmembrane protein 2 (IFITM2) among specific ISGs included (Yang et al., 2021), once more predicting Krasseman et al.'s findings. Notably, Yang et al. indicate that interferon stimulation in the setting of hyperinflammation and several overlapping or identical ISGs, specifically IFITMs, may result in a non-productive replication of SARS-CoV-2 within the CNS, a finding corroborated by Zhang et al. (2021).

In contrast to Krasemann et al.'s findings, Wenzel and colleagues report that during SARS-CoV-2 infection of brain endothelial cells, interactions between its main protease (M^{pro}) and the NF-kappa-B essential modulator (NEMO) result in apoptosis and subsequent BBB disruption (Wenzel et al., 2021). Furthermore, unless a consistent inflammatory signal is present, SARS-CoV-2 may not productively replicate within brain endothelial cells and subsequently cross the BBB (Constant et al., 2021). This complex relationship is reflected in *ex vivo* findings linking endothelial and brain injury with inflammation in COVID-19 (Savarraj et al., 2021). Another study exploring the brain microvascular transcriptomes in response to SARS-CoV-2 that is not cited by Krasemann et al. (2022) is the work by Zhou and colleagues(Zhou et al., 2021), where IFITM2 is shown to be constitutionally upregulated in brain endothelial cells compared to other cell types comprising the neurovascular unit.

The authors' (Krasemann et al., 2022) work provides tremendous context and impetus for a recently emerging concept of innate immunity at the neurovascular unit. We feel that the recognition of these omitted and preceding

works will provide greater context to the authors (Krasemann et al., 2022) and provide realistic context for the concept's further development. The inclusion of the works presented herein (Constant et al., 2021; Kim et al., 2021a, 2021b; Lee et al., 2021 Paniz-Mondolfi et al., 2020; Wenzel et al., 2021; Yang et al., 2021; Zhang et al., 2021; Zhou et al., 2021) already indicates that while the authors provide a novel model of SARS-CoV-2-neurovascular unit interaction, the majority of their findings had already been predicted by preceding models, and additional strengths and caveats on its utilization apply—as indicated by clinical and *in vitro* studies.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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