

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

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As pointed out by Vavougiou et al., correct citation is the backbone to scientific publishing. We prepared our Krasemann et al. manuscript (Krasemann et al., 2022) with utmost precision and scientific rigor, taking into account all literature published to date. Some of the references mentioned by Vavougiou et al. had not been published when we submitted to *Stem Cell Reports* (Constant et al., 2021; Kim et al., 2021; Savarraj et al., 2021; Wenzel et al., 2021; Zhang et al., 2021) and were therefore not cited. Some published studies were not included because of space constraints, in part resulting from specific requests during the revision, and were deprioritized; others because they did not fit the focus of our paper. Nevertheless, we believe that we discussed all relevant topic-related aspects in the Krasemann et al. manuscript sufficiently.

It is reassuring to see that the majority of studies mentioned by Vavougiou et al. came to similar conclusions as we did. Based on *in vitro* and *in vivo* models, Zhang et al. postulated a similar mechanism-of-action of SARS-CoV-2 at the blood-brain barrier (BBB) and we would have cited this work if it had been published earlier (Zhang et al., 2021). The studies by Lee et al. (2021) and Paniz-Mondolfi et al. (2020) are case studies and were as such not cited by us. Several authors of the Krasemann et al. paper have conducted and published a thorough neuropathological assessment of postmortem COVID-19 brains already prior to the Lee et al. study in November 2020 (Matschke et al., 2020), which was cited in the Krasemann et al. manuscript.

Zhou et al. (2021) bring up an interesting aspect of mechanistic overlap between AD and COVID-19, but this is contextually too far from the focus of our paper.

The review by Iadecola et al. was referenced by us in the introduction section (Iadecola et al., 2020).

The findings by Savarraj et al. nicely complement our data, since here, plasma was analyzed in rather acute COVID-19 cases (Savarraj et al., 2021). However, this is in contrast to the patient CNS material that was used in our study, which was investigated postmortem after sometimes

long disease durations. Thus, these datasets are not directly comparable. While every novel study provides another snapshot of the entire SARS-CoV-2-mediated pathomechanism, to date, it is impossible to assess what is actually happening in the human brain directly after infection with SARS-CoV-2. However, as discussed in our manuscript, cell culture models only allow for the investigation of certain aspects of SARS-CoV-2 biology, while animal models lack several disease features and the complexity of symptoms of human patients suffering from COVID-19. Further investigations of SARS-CoV-2 infection and consequences on the brain's neuro-vascular niche in a temporal and spatial manner are thus warranted.

We addressed *in vitro* and *in vivo* studies conducted with spike protein at the BBB in the discussion section of the Krasemann et al. paper (Buzhdygan et al., 2020; Rhea et al., 2021). Both Buzhdygan et al. (2020) and Rhea et al. (2021) were published prior to the Kim et al. paper (Kim et al., 2021).

The study by Yang et al. from the Wyss-Coray lab is a key study in the field, yet is focused on the choroid plexus in COVID-19, a topic that was not touched in our study; therefore this paper was not cited (Yang et al., 2021).

We decided to not cite the study by Constant et al. (2021). During the revision of our manuscript, we infected an alternative and widely accepted *in vitro* model based on hCMEC/D3 cells with SARS-CoV-2 and saw very different rates of infection compared to the hiPSC-BCEC model. The latter strongly correlated with data from COVID-19 postmortem tissue.

The study by Wenzel et al. (2021), which shares authors with the Krasemann et al. study, provides interesting mechanistic insight on BBB deregulation. Nevertheless, we did not cite this study due to space constraints.

All in all, we thank Vavougiou et al. for pointing out the importance of correct citation in scientific publishing, but we do think that we cited all relevant references that existed at that given time accordingly. We are especially pleased to see that a number of papers mentioned by



Vavougiou et al. that were published during the course of our revisions came to similar conclusions as we did.

## CONFLICTS OF INTERESTS

The authors declare no competing interests.

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