Rapid Reviews COVID-19 •

Review 1: "SARS-CoV-2 Infection Impacts Carbon Metabolism and Depends on Glutamine for Replication in Syrian Hamster Astrocytes"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Review:

Acute respiratory syndrome is the hallmark feature of severe COVID-19, and therefore a main focus of research is understanding the impact of SARS-CoV-2 infection on the respiratory system. However, there is compelling evidence that SARS-CoV-2 infection can also significantly impact the normal function of other organs and systems, which has raised great interest in understanding the long-term consequences of COVID-19 beyond its effects on the respiratory system. In this regard, neurological complications of COVID-19 are frequently reported. SARS-CoV-2 RNA has been detected in autopsy brain samples and in the CSF of some patients—though different studies have reported conflicting findings. How SARS-CoV-2 enters the brain, which cell types it targets in the brain, and the mechanisms whereby SARS-CoV-2 infection can impact normal brain function are all issues that have not been solved and remain controversial. Hence the significance of the present work by Gomes de Oliveira and colleagues examining the effects of SARS-CoV-2 infection on the metabolism of hamster's astrocytes.

The authors have provided convincing evidence that SARS-CoV-2 productively infects hamsters' astrocytes, which is associated with very significant changes in protein expression and metabolic pathways involved in carbon metabolism, glycolysis, mitochondrial respiration, and synaptic transmission. Notably, results presented by the authors strongly support that SARS-CoV-2 multiplication in hamsters' astrocytes does not depend on glycolysis, but rather on glutamine. Accordingly, treatment with the glutaminolysis inhibitor 6-Diazo-5-oxo-L-norleucine resulted in reduced levels of SARS-CoV-2 multiplication.

Based on their findings, the authors proposed that in COVID-19 cases, glutamine consumption due to the viral hijacking of cellular metabolism may affect glutamate/glutamine balance, and thus lead to the neurological symptoms reported in a significant number of COVID-19 cases.

The paper is well written. The experimental section of the paper was well executed and the results—which are clearly presented and nicely illustrated—support the authors' key conclusion that SARS-CoV-2 can productively infect hamsters' astrocytes, which is associated with disturbances in the normal astrocyte metabolism.

The main weakness of this very elegant study is the limited discussion of the authors' findings in the context of SARS-CoV-2 infection of human brain cells. Published studies have documented that exposure of a variety of cerebral organoids (CO) to SARS-CoV-2 results in infection of different brain cell populations, but their numbers and identity have not been unequivocally established—underscoring the need for additional studies aimed at resolving these questions. Particularly relevant to the present work are studies using primary organotypic slice cultures and cortical organoids at late gliogenic stages showing that a significant number of cortical astrocytes (GFAP⁺) can be infected by SARS-CoV-2. Despite their susceptibility to SARS-CoV-2, cortical astrocytes expressed undetectable levels of ACE-2 but readily detectable levels of the alternative SARS-CoV-2 receptors DPP4 and CD147. It would be interesting if the authors could provide information about results using blocking antibodies to determine the receptor used by SARS-CoV-2 to enter hamsters' astrocytes. Another issue that needs clarification is a clear presentation of the absolute numbers (total %) of SARS-CoV-2 infected astrocytes detected in either tissue culture or in brain sections from infected hamsters. It would be important to discuss these results in the context of the apparently very low numbers of human brain cells, including astrocytes and neurons, that are detected in the different experimental systems using human cells and organoids.