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Supplementary information

Dysregulation of brain and choroid plexus cell types in severe COVID-19

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Dysregulation of brain and choroid plexus cell types in severe COVID-19
Supplementary information document

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Supplementary Discussion

Based on gene expression patterns uncovered here, we propose a model where brain-barrier cells relay peripheral inflammatory signals into the brain parenchyma. In this increasingly neuroinflammatory milieu, a COVID-19 associated microglia and astrocyte cell subpopulation emerges that shares features with pathological cell states reported in human neurodegenerative disease[4,5]. The over-representation of overlapping DEGs in glia suggests that existing CNS disease knowledge may be relevant to understand COVID-19 neuropathology. Together, these perturbations converge on impaired neuronal function, with upper-layer projection neurons in particular exhibiting a transcriptomic signature of compromised neurotransmission and information processing[7,40,89].

While our study size is on par with prior brain snRNA-seq studies, limitations on high-quality sample availability have precluded even larger and more representative cohorts. It also remains possible that direct neuroinvasion is involved in cases with severe neurological symptoms not studied here. Nevertheless, the appearance of disease-associated brain cell subtypes with their own specific transcriptional profiles in the absence of detectable neuroinvasion suggests a remarkably potent and persistent mechanism of pathological blood-brain inflammatory or autoimmune[90] signaling in severe COVID-19. Indeed, the COVID-19-associated glial populations were not found in our terminal influenza patient, though more work is needed to distinguish which effects are truly specific to COVID-19.

The combination of a strong neuroinflammatory milieu and deficits in upper cortical-layer neurons in COVID-19 brains provides a consistent molecular hypothesis for long COVID complaints, from “brain fog” to memory loss to difficulty concentrating[13].

Supplementary References

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