CD4+ T cells isolated from brain tissue had a unique gene-expression profile, including increased expression of markers of tissue residency such as CD69. Overall, the relative frequency of CD4+ T cells in the mouse brain was highest at birth and then declined with age. Notably, similar observations were made in studies using resected human brain tissue, indicating a conserved ‘brain-resident’ CD4+ T cell phenotype. Parabiosis studies in mice indicated that CD4+ T cells acquired this resident phenotype in the brain following entry from the blood. Most CD4+ T cells entered the brain transiently, but activated CD4+ T cells entered at higher rates than naive CD4+ T cells, and a small fraction of these activated T cells acquired the brain-resident phenotype. Further experiments with T cell receptor transgenic CD4+ T cells suggested that Th1 cells in the brain are specific for brain-expressed antigens, whereas the activated CD4+ T cells in brain do not necessarily recognize brain-expressed antigens, but instead depend on peripheral activation for brain entry. Microbiota depletion studies supported this idea.

The authors proceeded to show that microglia in MHC class II-deficient mice (which lack CD4+ T cells) maintain an immature fetal-type transcriptional profile and fail to turn on key microglial transcription factors. Experiments in other systems also indicated that CD4+ T cells are necessary for microglial maturation, with imaging studies suggesting that CD4+ T cells support the acquisition of microglial synaptic pruning functions. Strikingly, in the absence of CD4+ T cells, cortical pyramidal neurons showed increased spine density at synapses, similar to what is seen in human neurological conditions such as Down syndrome and Rett syndrome. Accordingly, MHC class II-deficient mice showed many behavioural abnormalities, including reduced mobility, increased anxiety, depressed-like behaviour and impaired contextual and spatial learning.

Kirsty Minton

**COVID-19**

**No cross-protective immunity in children?**

Lower infection rates and milder clinical course of COVID-19 have been reported in children. In this preprint, the authors hypothesize that this protection could originate from cross-protective immunity following prior infections by seasonal human coronaviruses (HCoVs). The authors measured antibody responses to SARS-CoV-2 in 739 pauci- or asymptomatic children as well as 36 children with suspected multisystem inflammatory syndrome in children (MIS); in a subset of 187 patients, they also tested the presence of antibodies to the four HCoVs: HKU1, OC43, 229E and NL63. Their data did not show significant differences in antibody levels to HCoV antigens between SARS-CoV-2 seropositive and seronegative patients, regardless of MIS. Together, this study suggests that antibody responses raised against seasonal HCoVs do not confer protection from SARS-CoV-2 and associated MIS in children.

**Antibody responses to SARS-CoV-2 short-lived**

In the absence of confirmed cases of reinfection by SARS-CoV-2, the duration of immune protection elicited after initial infection is still unknown. This preprint describes a longitudinal analysis of antibody responses in 65 SARS-CoV-2-infected individuals. Although the magnitude of neutralizing antibody (nAb) responses correlated with disease severity, there was a rapid decline in nAb titers in most patients within 3 months after onset of symptoms. The authors argue that the transient nAb responses elicited by SARS-CoV-2 resemble those observed following seasonal coronavirus infections. However, the consequences on secondary immune responses and their ability to prevent reinfection remain to be determined.

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**COVID-19**

**Virus dissociated from inflammation in fatal COVID-19**

SARS-CoV-2 infection is often associated with a hyperinflammation that is thought to drive disease severity and death. However, it is unclear whether tissue inflammation is induced by a direct response to the virus or by an independent immunopathological process. By analysing SARS-CoV-2 organotropism and organ inflammation in post-mortem tissues from 11 patients who died of COVID-19, Dorward et al. report that, despite a wide distribution of viral products in pulmonary and extra-pulmonary tissues, severe inflammation was limited to the lung and reticuloendothelial system and was not consistently associated with presence of virus. Overall, this preprint suggests that immune mechanisms of SARS-CoV-2 tissue-specific tolerance function independently of viral clearance and that fatal COVID-19 is a consequence of immunopathology that may be dissociated from virus presence.

**ORIGINAL ARTICLE** Dorward, D. A. et al. Tissue-specific tolerance in fatal Covid-19. Preprint at medRxiv https://doi.org/10.1101/2020.07.02.20145003 (2020)

**COVID-19**

**ReseaRch highlights**