
Credit: Bruce Rolff/UIG/Getty

(such as *Ifngr1*) had high levels of chromatin accessibility in almost all samples. On the basis of predicted transcription factor binding sites in open chromatin and H3K4me2 regions, they identified some transcription factors that were active in all structural cells and others with cell type-specific or organ-specific activity. So, structural cells have both a core set of immune functions and additional functions determined by cell type or tissue.

Comparing the chromatin accessibility of a gene with its expression level identifies genes that are primed for activation. In this way, the authors identified 355 primed immune genes in structural cells. This epigenetic potential, which presumably enables a rapid response to challenge, was most pronounced in liver, lymph node, spleen and thymus.

To test the functional relevance of the epigenetic potential, mice were challenged with lymphocytic choriomeningitis virus (LCMV) 8 days before the structural cells were analysed. Genes that were upregulated in response to LCMV were enriched for both immune function and epigenetic potential under homeostatic conditions. Similar results were reported for spleen endothelial cells after the administration of recombinant cytokines, including interferons, to the mice. By contrast, there was little overlap in the transcriptional response to LCMV and cytokine administration for liver fibroblasts, although the latter response did involve primed genes. In summary, structural cells have an epigenetically primed immune potential, with both organ-specific and cell type-specific features.

Kirsty Minton

ORIGINAL ARTICLE Krausgruber, T. et al. Structural cells are key regulators of organ-specific immune responses. *Nature* **583**, 296–302 (2020)

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 T_{reg} 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, depressive-like behaviour and impaired contextual and spatial learning.

Yvonne Bordon

ORIGINAL ARTICLE Pasciuto, E. et al. Microglia require CD4 T cells to complete the fetal-to-adult transition. *Cell* https://doi.org/10.1016/j.cell.2020.06.026 (2020)

IN BRIEF

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

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 (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.

ORIGINAL ARTICLE Sermet-Gaudelus, I. et al. Prior infection by seasonal coronaviruses does not prevent SARS-CoV-2 infection and associated multisystem inflammatory syndrome in children. Preprint at *medRxiv* https://doi.org/10.1101/2020.06.29.20142596 (2020)

COVID-19

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 titres 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.

ORIGINAL ARTICLE Seow, J. et al. Longitudinal evaluation and decline of antibody responses in SARS-CoV-2 infection. Preprint at *medRxiv* https://doi.org/10.1101/2020.07.09.20148429 (2020)

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