IN BRIEF

COVID-19

SARS-CoV-2 on the neural battleground

This preprint explores the ability of SARS-CoV-2 to infect and replicate in neural tissues of mouse and human origin. Induced pluripotent stem cell lines derived from healthy donors were used to generate human brain organoids for modelling SARS-CoV-2 infection. Extensive cell death and metabolic changes occurred in both infected and neighbouring neurons, inducing locally hypoxic regions with no evidence of a type I interferon response. Organoids incubated with antibodies to ACE2 or to viral spike protein from the cerebrospinal fluid of patients with COVID-19 had decreased SARS-CoV-2 infection. Transgenic mice overexpressing human ACE2 (hACE2) in the brain had decreased survival after SARS-CoV-2 infection compared with those expressing hACE2 in lungs. This study provides insight into the neuroinvasive potential of SARS-CoV-2, which could explain neurological symptoms experienced by some patients.

ORIGINAL ARTICLE Song, E. et al. Neuroinvasive potential of SARS-CoV-2 revealed in a human brain organoid model. Preprint at *bioRxiv* https://doi.org/10.1101/2020.06.25.169946 (2020)

COVID-19

CRISPRing for host genes regulating SARS-CoV-2

In this preprint, Wei et al. screened the African green monkey genome using CRISPR–Cas9 for genes involved in SARS-CoV-2 infection and cell death. Surprisingly, SARS-CoV-2, which replicates in the cytosol, depends on a large number of host genes that function in the nucleus. Amongst the crucial genes, the SWI/SNF chromatin remodelling complex, several TGFβ signalling components and the alarmin HMGB1 were proviral, whereas the histone H3.3 complex was antiviral, highlighting the importance of epigenetic regulation in antiviral responses. Treatment of cells with small-molecule inhibitors of the SWI/SNF complex and of the TGFβ signalling pathway protected against SARS-CoV-2 infection. Further studies will need to investigate how these host genes regulate infection and whether these inhibitors could be used therapeutically.

ORIGINAL ARTICLE Wei, J. et al. Genome-wide CRISPR screen reveals host genes that regulate SARS-CoV-2 infection. Preprint at *bioRxiv* https://doi.org/10.1101/2020.06.16.155101 (2020)

COVID-19

T cell renaissance in COVID-19

This preprint identifies 1,739 and 1,591 SARS-CoV-2-derived peptides that bind to HLA-A/B/C or HLA-DR, respectively, from 180 SARS-CoV-2 convalescent donors and 185 healthy controls. Nelde et al. show that convalescent donors have T cell responses to multiple SARS-CoV-2 epitopes, with a predominant IFNγ$^+$CD8$^+$ T cell response to HLA-A/B/C-binding peptides but a multifunctional (IFNγ$^+$TNF$^+$CD107a$^+$) CD4$^+$ T cell response to HLA-DR-binding peptides. Some donors had T cell responses but not antibodies, which highlights the potential importance of T cells in COVID-19 vaccine development. IgG responses were associated with severe cases, whereas those with diverse T cell responses had milder disease. Cross-reactive T cell responses to 31% of HLA-A/B/C-binding epitopes and to 70% of HLA-DR-binding epitopes were detected in unexposed individuals, supporting the potential existence of heterologous immunity.

ORIGINAL ARTICLE Nelde, A. et al. SARS-CoV-2 T-cell epitopes define heterologous and COVID-19-induced T-cell recognition. Preprint at *Research Square* https://doi.org/10.21203/rs.3.rs-35331/v1 (2020)

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IMMUNOGENETICS

A gene atlas of 'structural immunity'

The haematopoietic cells of the immune system carry out their functions within tissue frameworks created by structural cells of the epithelium, endothelium and stroma (mainly fibroblasts). Interactions of these structural cells with immune cells have been difficult to study owing to their essential roles in organ function. Krausgruber et al. used multi-omics profiling of structural cells from 12 mouse organs to create a high-resolution atlas of immune gene activity. They hope that this will aid further study of immune functions in non-haematopoietic cells — a field they refer to as 'structural immunity'.

Structural cells purified from mouse organs were sorted on the basis of expression of CD31 (endothelial cells), EPCAM (epithelial cells) and GP38 (fibroblasts). Gene expression profiling by RNA sequencing (RNA-seq) showed that different structural cells within the same organ were more similar to each other than the same structural cells across organs, which indicates that there is a major effect of the tissue environment. As well as predicting crosstalk between structural cells and haematopoietic cells on the basis of known receptor–ligand pairs, the RNA-seq dataset showed high levels of activity of 'immune gene' modules in structural cells in cell type-specific and organ-specific patterns.

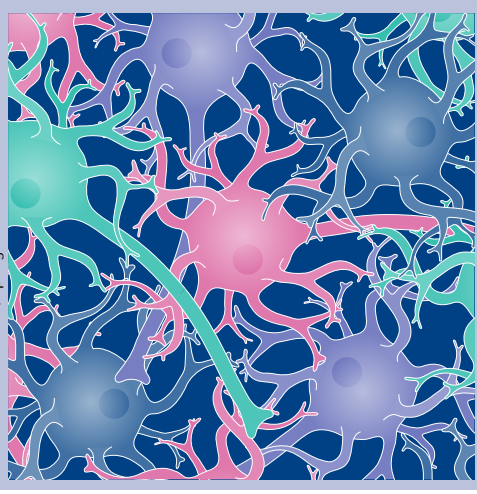
Next, the authors looked at gene regulation by profiling chromatin accessibility and active H3K4me2 marks. Similar to the RNA-seq data, chromatin and histone profiles were generally more similar within an organ than within a structural cell type, although a subset of immune genes

NEUROIMMUNOLOGY

T cells shape behaviour by helping microglia to mature

There is mounting evidence that the immune system influences behavioural responses, but limited understanding of the processes involved. Adrian Liston and colleagues now report that CD4$^+$ T cells are resident in the healthy brain and are necessary for the proper maturation of microglia. The absence of brain-resident CD4$^+$ T cells leads to defective microglial cell function and behavioural abnormalities.

The presence of CD4$^+$ T cells in the brain is typically associated with disease. Here, Pasciuto et al. asked whether CD4$^+$ T cells also have physiological roles in the healthy brain. By a combination of confocal microscopy and high dimensional flow cytometry, they were able to detect rare CD4$^+$ T cells scattered throughout the healthy mouse brain. They estimated there are ~2,000 CD4$^+$ T cells, of which ~150 are regulatory T (T_{reg}) cells, in the healthy adult mouse brain. The vast majority were not detected in blood vessels or in the meninges, but in the underlying brain tissue. Single-cell sequencing showed that, compared with peripheral blood counterparts,



Credit: Simon Bradbrook/Springer Nature Limited