IN BRIEF

COVID-19

Type I and type III interferon in opposition?

In this preprint, Boudewijns et al. examined the interferon (IFN) response in Syrian hamsters, which develop significant lung pathology after SARS-CoV-2 infection, and in C57BL/6 mice, which do not. However, SARS-CoV-2-infected *Ifnar1*$^{-/-}$ mice had an increased infiltration of inflammatory cells in the lung, suggesting that an active, functional and immediate type I IFN response restricts pathogenesis in mice. The analysis of hamsters with a deletion of *Stat2* (which causes a loss of type I and type III IFN signalling) or of *Il28r* (resulting in loss of type III IFN signalling alone) suggested that type III IFNs help to restrict viral dissemination, whereas type I IFNs exacerbate bronchopneumonia in hamsters. These opposing roles warrant further study, and the histological findings suggest that the Syrian hamster is a better model for COVID-19 than the mouse.

ORIGINAL ARTICLE Boudewijns, R. et al. STAT2 signaling as double-edged sword restricting viral dissemination but driving severe pneumonia in SARS-CoV-2 infected hamsters. Preprint at *bioRxiv* https://doi.org/10.1101/2020.04.23.056838 (2020)

COVID-19

SARS-CoV-2 likes it cool

In this preprint, V'kovski et al. investigated the impact of respiratory tract temperature on SARS-CoV and SARS-CoV-2 replication. Primary human airway epithelial cells (hAECs) were infected and maintained at 33 °C or 37 °C to mimic the human upper and lower respiratory tracts, respectively. SARS-CoV-2 replicated more efficiently at 33 °C than at 37 °C but this was not observed for SARS-CoV. Transcriptional analysis of SARS-CoV-2-infected hAECs suggested that stronger and earlier induction of an innate immune programme at 37 °C could explain the enhanced SARS-CoV-2 replication at 33 °C. The evaluation of how temperature impacts interferon responses in a larger number of donors will be essential to understand its effect on SARS-CoV-2 transmissibility and may open new avenues for therapy.

ORIGINAL ARTICLE V'kovski, P. et al. Disparate temperature-dependent virus – host dynamics for SARS-CoV-2 and SARS-CoV in the human respiratory epithelium. Preprint at *bioRxiv* https://doi.org/10.1101/2020.04.27.062315 (2020)

COVID-19

Modulation of immune crosstalk in COVID-19

In this preprint, Wilk et al. used single-cell RNA sequencing to compare immune profiles in 7 patients hospitalized with COVID-19 to 6 healthy controls. In CD14$^+$ monocytes from patients, HLA class II expression as well as a pathway associated with DC–NK cell immune crosstalk were reduced, whereas a pathway associated with PD1–PDL1 interactions was increased. A cluster of highly proliferative T cells and NK cells was enriched, with immune checkpoint as well as interferon-stimulated genes uniquely upregulated in NK cells. Collectively, these results indicate that dysregulation of immune crosstalk is associated with severity of COVID-19. Further studies will need to investigate the contribution of these mechanisms to the reduced numbers and impaired functions of NK cells and T cells observed in patients with COVID-19.

ORIGINAL ARTICLE Wilk, A. J. et al. A single-cell atlas of the peripheral immune response to severe COVID-19. Preprint at *medRxiv* https://doi.org/10.1101/2020.04.17.20069930 (2020)

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NEUROIMMUNOLOGY

Brain–spleen link tunes immunity

Many of the mechanisms through which the brain and the immune system interact have not been defined. Zhang et al. now uncover the key components of a direct brain–spleen pathway in mice, through which behaviour can modulate adaptive immune responses.

The spleen is a key site for T cell activation and B cell differentiation into antibody-producing splenic plasma cells (SPPCs). These activities are modulated by noradrenergic signalling via the autonomic nervous system and are thought to be under top-down control from the brain.

To further investigate these pathways, the authors surgically ablated the nerve that innervates the spleen (the splenic nerve) in mice and examined the responses of spleen cell populations to immunization with an antigen (NP-KLH) that triggers a T cell-dependent adaptive immune response. In animals with an intact splenic nerve, immunization increased the abundance of SPPCs; however, this response was severely impaired in the denervated mice.

Spleen denervation did not affect SPPC formation after immunization with a T cell-independent antigen, suggesting that the effects of splenic

IMMUNOMETABOLISM

Faulty engines in T cells accelerate ageing and disease

A new report in *Science* has found that mice with T cell-specific mitochondrial defects show premature ageing and multi-system morbidity. The authors link this to an aberrant T helper 1 (T_H1)-type response, which accelerates inflammageing.

Previous studies have detailed age-related declines in mitochondrial function. To examine the impact of a T cell-specific loss of mitochondrial function, Desdín-Micó et al. generated *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice. In these mice, both CD4$^+$ T cells and CD8$^+$ T cells lack mitochondrial transcription factor A (TFAM), which is important for the stabilization and replication of mitochondrial DNA. *Tfam* deficiency in T cells led to a reduction in their overall numbers and biased their cellular metabolism towards glycolysis. Of note, T cells from young (2-month-old) *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice showed metabolic dysfunction resembling that normally seen in aged (22-month-old) wild-type mice, and this was associated with increased expression of T-bet, IFNγ and tumour necrosis factor (TNF). Young *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice were also immunocompromised; both old wild-type mice and young *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice universally succumbed to acute infection with a highly virulent poxvirus, whereas young wild-type mice all survived this infection.

From the age of 7 months, *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice had a prematurely aged appearance and progressively developed anaemia and curving of the spine and lost body weight. Metabolic cage experiments showed that *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice were less active and slower than age-matched wild-type mice, despite expending more energy. The *Tfam*$^{fl/fl}$*Cd4*^{Cre} mice also showed premature loss of muscular, cardiovascular and cognitive function and, on average, only lived for half as long as controls. Importantly, the authors generated a distinct mouse