Finally, the authors measured the levels of ADAMTS4 in respiratory tract samples from cohorts of paediatric or adult patients with moderate or severe influenza virus infection. They found that, across all age groups, levels of ADAMTS4 in the lower respiratory tract strongly correlated with increased risk for respiratory failure and death following severe influenza virus infection.

These findings indicate a crucial role for damage-responsive fibroblasts in regulating the magnitude of the immune response and the propensity to develop lung failure in response to severe respiratory infections. The authors propose that targeting ADAMTS4 or other ECM proteases could improve clinical outcomes in patients who have developed ARDS in response to influenza viruses, SARS-CoV-2 or other respiratory infections.

Yvonne Bordon

ORIGlNAL Article Boyd, D. F. et al. Exuberant fibroblastl activity compromising lung function via ADAMTS4. Nature https://doi.org/10.1038/s41586-020-2877-5 (2020)

COVID-19

Intestinal attenuation of COVID-19 inflammation

Gastrointestinal (GI) symptoms are observed in patients with COVID-19, but the link between GI immune responses and disease outcomes is unclear. This preprint shows that COVID-19 severity and mortality, and levels of circulating inflammatory cytokines, are reduced in patients with GI symptoms. The SARS-CoV-2 receptor ACE2 was highly expressed in small intestinal enterocytes and viral particles were detected in these cells in patients with COVID-19. GI inflammation was absent in patients with COVID-19, as shown by a reduction of cellular inflammatory subsets and downregulation of inflammatory pathways. This study provides a basis for exploring the mechanisms involved in attenuation of SARS-CoV-2-associated GI inflammation to aid a comprehensive understanding of organ-specific immune responses in COVID-19.

ORIGlNAL ARTICLE Livano, A. E. et al. Gastrointestinal involvement attenuates COVID-19 severity and mortality. Preprint at bioRxiv https://doi.org/10.1101/2020.09.07.20187666 (2020)

IL-18-dependent MAIT cell activation in COVID-19

Flament et al. report a marked reduction of circulating mucosal-associated invariant T (MAIT) cells in patients with severe COVID-19, compared with controls sharing co-morbidities. These MAIT cells had very high levels of activation that correlated with disease severity. Among T cells, alterations in MAIT cells preferentially associated with mortality, and high CD69 expression correlated with poor outcome. Severe inflammation, particularly high levels of IL-18, was associated with increased cytotoxicity of circulating MAIT cells. Co-culture studies of in vitro SARS-CoV-2-infected macrophages with MAIT cells suggest a two-step process of MAIT cell activation, through type I IFN and later IL-18. Together with other reports, this preprint supports a pivotal role for MAIT cells, through an IL-18-dependent mechanism, in the pathology of COVID-19.

ORIGlNAL ARTICLE Flament, H. et al. Outcome of SARS-CoV-2 infection linked to MAIT cell activation and cytotoxicity: evidence for an IL-18-dependent mechanism. Preprint at bioRxiv https://doi.org/10.1101/2020.08.31.20185082 (2020)

At the heart of COVID-19

Cardiac damage, even after recovery, has been reported in COVID-19, with nearly 50% of mildly ill patients having echocardiogram abnormalities. This preprint investigated the cellular alterations that occur after SARS-CoV-2 infection in vitro of cardiomyocytes derived from human induced pluripotent stem cells. The authors show that cardiomyocytes can be infected by SARS-CoV-2 and that this results in marked cytoskeletal, inflammatory and proteasomal alterations at the transcriptional level. Infected cardiomyocytes increase cytokine production and have pronounced myofibrillar fragmentation. Fragmentation was also observed in uninfected cardiomyocytes in vitro and in post-mortem cardiac tissue. Cytoskeletal fragmentation in the absence of infection might indicate putative effects of pro-inflammatory cytokines and stress responses on long-term cardiac changes in COVID-19.

ORIGlNAL ARTICLE Pérez-Bermejo, J. A. et al. SARS-CoV-2 infection of human iPSC-derived cardiac cells predicts novel cytopathic features in hearts of COVID-19 patients. Preprint at bioRxiv https://doi.org/10.1101/2020.08.25.265656 (2020)

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RESEARCH HIGHLIGHTS

IN BRIEF