



Credit: Science Photo Library/Alamy Stock Photo

in inflammatory lung diseases compared with in healthy lungs.

Compared with controls, *Adams4^{-/-}* mice showed improved survival following a lethal dose of influenza virus, and this was associated with reduced inflammation and improved lung function. The lungs of infected *Adams4^{-/-}* mice also showed higher levels of intact versican, and a series of additional experiments suggested that degradation of versican by ADAMTS4-expressing DRFibs permits the recruitment of CD8⁺ T cells, which are one of the main drivers of immunopathology during influenza virus infection.

immunity. For example, MPPs had regions of higher chromatin accessibility near the promoters of genes that regulate key cytokines such as TNF and IL-6, and transcriptomic and pathway analysis demonstrated an upregulation of genes associated with innate immune function and with metabolic rewiring in both HSCs and MPPs.

MTP₁₀-HDL-treated mice had enhanced myelopoiesis and increased numbers of granulocyte–monocyte progenitor cells, and bone marrow cells harvested from these mice showed enhanced cytokine responses after re-stimulation with lipopolysaccharide.

To study potential contributions of adaptive immune cells to the anticancer activity of the nanobiologic, *Rag1^{-/-}* mice, which lack T and B cells, were injected with B16F10 melanoma cells and then treated with MTP₁₀-HDL. The treatment did not appear to affect tumour growth rates, leading the authors to conclude that optimal therapeutic activity of MTP₁₀-HDL requires both ‘trained’ myeloid cells and an adaptive immune response.

The interplay of innate and adaptive immunity in anticancer responses

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

ORIGINAL ARTICLE Boyd, D. F. et al. Exuberant fibroblast activity compromises lung function via ADAMTS4. *Nature* <https://doi.org/10.1038/s41586-020-2877-5> (2020)

was further explored by combining MTP₁₀-HDL treatment with checkpoint inhibitors, which enhance T cell responses. A combination of CTLA4- and PD1-targeted checkpoint inhibitors had no anti-tumour effects in the B16F10 melanoma model; however, when MTP₁₀-HDL was added to anti-CTLA4/anti-PD1 combination therapy, a dramatic suppression of tumour growth was observed, with complete responses in 4 of 10 animals. Further analysis revealed that MTP₁₀-HDL not only enhances myelopoiesis and sensitizes myeloid cells for activation but also appears to affect the tumour microenvironment by shrinking the population of immunosuppressive tumour-associated macrophages.

MTP₁₀-HDL was well tolerated in non-human primates. The authors suggest that peptidoglycan-functionalized nanobiologics may be particularly useful for sensitizing tumours to checkpoint therapy.

Alexandra Flemming

ORIGINAL ARTICLE Priem, B. et al. Trained immunity-promoting nanobiologic therapy suppresses tumor growth and potentiates checkpoint inhibition. *Cell* **183**, 786–801 (2020)

IN BRIEF

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.

ORIGINAL ARTICLE Livanos, A. E. et al. Gastrointestinal involvement attenuates COVID-19 severity and mortality. Preprint at medRxiv <https://doi.org/10.1101/2020.09.07.20187666> (2020)

COVID-19

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.

ORIGINAL 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 medRxiv <https://doi.org/10.1101/2020.08.31.20185082> (2020)

COVID-19

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.

ORIGINAL 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/10.1101/2020.08.25.265561> (2020)

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