DNmt1 fails to keep up with rapid cells functions as a tumour suppressor.

DNmt1 activity, in premalignant BmRs, that RTe activation, owing to limiting all mice developed large tumours.

However, when recipient mice were xenograft cells with cGAS knockdown, proliferation of premalignant cells.

nude mice was repressed by DNmt1 expression, which was consistent with reduced immune cell infiltrates observed in the intestinal epithelium of HFD-fed mice.

The downregulation of antigen presentation that evades anti-tumour immune responses is a common feature of many cancers. Using inducible inactivation of the Apc tumour suppressor gene as a model of tumorigenesis, the authors showed that Apcflox/flox LGR5+ ISCs had twofold greater tumorigenicity after in vivo transplantation if they lacked MHC class II expression, but that this difference between MHC class II negative and positive transplanted ISCs was not observed in recipient mice lacking B cells and T cells. Two further mouse models of intestinal tumorigenesis involving inducible deletion of MHC class II confirmed that loss of MHC class II specifically by LGR5+ ISCs was associated with greater numbers of intestinal tumours. Thus, a HFD seems to disrupt MHC class II-dependent immune surveillance of tumour-initiating ISCs through effects on the intestinal microbiome.

Kirsty Minton

Epitope mapping of spike identifies variant-resistant antibodies

One of the biggest concerns in the ongoing COVID-19 pandemic is the potential emergence of SARS-CoV-2 variants that evade immunity. A report in Science now presents a comprehensive map of antibody binding sites of the SARS-CoV-2 spike protein, which was generated using several hundred monoclonal antibodies (mAbs). Among 186 mAbs targeted at the receptor binding domain (RBD) of spike, the authors (a global consortium) identified seven mAb communities with distinctive footprints and competition profiles. Using pseudovirus-based neutralization assays to test mAb binding to mutant spike proteins (with either individual mutations or combinations of mutations, including those corresponding to variants a–e), they were able to identify key classes of RBD-targeted antibodies that maintained neutralization activity against these mutants. The study may allow to predict and interpret the effect of new mutations and inform the selection of antibody cocktails against new variants.

Lucy Bird

Cross-reactive tissue-resident CD8+ T cells may provide first line of defence against SARS-CoV-2

Cross-reactive CD4+ T cells, likely induced by common cold coronavirus infections, are detected in 20–50% of peripheral blood samples from SARS-CoV-2 unexposed individuals. However, cross-reactive CD8+ T cells are rarely detected in these samples. To study whether this may be because CD8+ memory T cells are mostly located in tissues, Niesl at al. examined peripheral blood and tonsillar tissue samples from pre-2019. Indeed, they detected SARS-CoV-2 reactive CD8+ memory T cells in 32% of tissue samples. Cross-reactive CD8+ cells were detected at similar levels in blood and tissue, whereas cross-reactive memory CD8+ T cells were largely absent in matched blood samples. Tissue-resident cross-reactive CD8+ memory T cells displayed markers of follicular homing and tissue residency, and the authors speculate that these may enable rapid sentinel immune responses to SARS-CoV-2.

Lucy Bird

Fc-optimized monoclonal antibodies show superior efficacy

Monoclonal antibody (mAb) therapies have shown some use in patients with mild to moderate COVID-19, but have limited efficacy in preventing complications or death in patients with severe COVID-19. Reporting in Nature, Ravetch, Bournazos and colleagues now demonstrate that optimizing mAbs for the engagement of activating Fcγ receptors (FcγRs) significantly improves their ability to confer full protection in SARS-CoV-2 challenge models. Moreover, these mAbs are also highly potent at reducing mortality post-infection in animal models of severe COVID-19. These findings illustrate the importance of FcγR-mediated pathways in antibody-mediated antiviral immunity and have important implications for the development of more effective mAb therapeutics.

Yamin, R. et al. Fc-engineered antibody therapeutics with improved anti-SARS-CoV-2 efficacy. Nature https://doi.org/10.1038/s41586-021-04017-w (2021)