Credit: S. Bradbrook/Springer Nature Limited

Consistent with the loss of CD47, mice infused with CpG-treated RBCs had higher levels of erythrophagocytosis by splenic red pulp macrophages than mice infused with control RBCs. Mice infused with CpG-treated RBCs also had neutrophil infiltration of the spleen, increased splenic expression of interferon signalling pathway genes and increased plasma levels of IFNγ and IL-6, which are indicative of both local and systemic immune activation. In critically ill patients with sepsis, those who were anaemic had higher levels of RBC-associated mtDNA than those who were not anaemic, which also supports increased erythrophagocytosis in response to DNA binding by RBCs. In erythrocyte-specific *Tlr9*-knockout mice compared with wild-type mice, IL-6 levels were attenuated after CpG administration or in a caecal slurry model of sepsis.

Together, the results suggest that when plasma CpG DNA levels increase beyond homeostatic norms, such as during sepsis or infection, TLR9-dependent binding to RBCs results in erythrophagocytosis, with consequent anaemia and innate immune activation. Anaemia and high cytokine levels are common features of multiple inflammatory pathologies, so further investigation of this pathway could have important therapeutic implications. Indeed, this study also reported that in hospitalized patients with COVID-19 pneumonia, the amount of RBC-bound mtDNA correlated with both anaemia and disease severity.

Kirsty Minton

ORIGINAL ARTICLE Lam, L. K. M. et al. DNA binding to TLR9 expressed by red blood cells promotes innate immune activation and anemia. *Sci. Transl Med.* **13**, eabj1008 (2021)

have a conditional deletion of *Ifngr2* in EGCs — were infected with *H. polygyrus*, by 7 days post-infection (d.p.i.) they showed bleeding at sites of the worm and by 28 d.p.i. they exhibited markedly increased intestinal pathology, characterized by more and larger granulomas, higher accumulation of inflammatory cells and aberrant gut peristalsis. Helminth-infected *Ifngr2*$^{\Delta EGC}$ mice also had fewer CD8$^+$ T cells at 7 d.p.i. than controls, but showed no differences in CD4$^+$ T cell, γδ T cell and natural killer cell numbers or in terms of worm or egg burdens.

To better understand the IFNγ–EGC axis, the authors used UMAP analysis of TM cells from uninfected or helminth-infected control or *Ifngr2*$^{\Delta EGC}$ mice. Interestingly, in uninfected *Ifngr2*$^{\Delta EGC}$ mice, several cell clusters (including mesothelial cells, macrophages and fibroblasts) showed upregulation of inflammatory pathways. In line with this, ~25% of naive *Ifngr2*$^{\Delta EGC}$ mice showed signs of TM inflammation. During helminth infection, both control and *Ifngr2*$^{\Delta EGC}$ mice showed increased immune cell representation in the TM and induction of type 2 immune genes, such as *Arg1*, *Retnla* and *Chil3*. However, the induction of type 2 genes was markedly reduced in *Ifngr2*$^{\Delta EGC}$ mice compared with controls, suggesting that glia-specific ablation of IFNγ signalling impairs tissue healing responses in the gut.

Early in the infection, the authors observed that *H. polygyrus* drives the recruitment of IFNγ-producing cells that promote upregulation of *Cxcl10* by EGCs. Notably, *Cxcl10*$^{\Delta EGC}$ mice infected with *H. polygyrus* developed a similar exaggerated inflammatory pathology to that seen in the *Ifngr2*$^{\Delta EGC}$ mice. Therefore, CXCL10 production by EGCs is an important component of the IFNγ-driven tissue healing response during helminth infection. The authors suggest that this IFNγ–EGC–CXCL10 axis could also be relevant to the pathogenesis of other gastrointestinal disorders, including inflammatory bowel disease.

Yvonne Bordon

ORIGINAL ARTICLE Progatzky, F. et al. Regulation of intestinal immunity and tissue repair by enteric glia. *Nature* https://doi.org/10.1038/s41586-021-04006-z (2021)

IN BRIEF

COVID-19

Foetal sex affects maternal and placental immune responses to SARS-CoV-2

Immune responses to SARS-CoV-2 show sex-specific differences, with males at higher risk of severe COVID-19. Now, Andrea G. Edlow and colleagues have examined whether foetal sex affects immune responses to SARS-CoV-2 in pregnant women. The authors examined maternal and placental immune responses in 38 women with mild or moderate COVID-19 during pregnancy, as well as a control cohort. They found reduced maternal SARS-CoV-2-specific antibody titres as well as reduced transplacental transfer of these antibodies in women carrying male foetuses. Moreover, they observed a sexually dimorphic expression of placental Fc receptors, differences in antibody fucosylation and an upregulation of interferon response genes in male placentas. These results demonstrate that foetal sex affects maternal humoral immune responses as well as placental innate and adaptive immune responses to SARS-CoV-2.

ORIGINAL ARTICLE Bordt, E. A. et al. Maternal SARS-CoV-2 infection elicits sexually dimorphic placental immune responses. *Sci. Transl Med.* https://doi.org/10.1126/scitranslmed.abi7428 (2021)

COVID-19

SARS-CoV-2 Delta variant excels at membrane fusion, but not immune evasion

The SARS-CoV-2 Delta variant has become the dominant strain worldwide. It is around twice as transmissible as its ancestral strain, with a shorter incubation period and higher viral load during infection. Now, Bing Chen and colleagues show that mutations in spike protein of Delta allow for faster membrane fusion than Alpha, Beta, Gamma and Kappa variants, and that Delta is more efficient at infecting cells with very low expression of the ACE2 entry receptor. However, the mutations found in the Delta variant had less impact on its sensitivity to neutralizing antibodies compared to those of the Gamma and Kappa variants. Neutralizing antibodies predominantly target the N-terminal domain (NTD) or the receptor binding domain (RBD) of the spike protein. The authors found different arrangements of the antigenic surface of the NTD in the different variants, but only local changes in the RBD, indicating that therapeutic antibodies or universal vaccines should be targeted at the latter.

ORIGINAL ARTICLE Zhang, J. et al. Membrane fusion and immune evasion by the spike protein of SARS-CoV-2 Delta variant. *Science* https://www.science.org/doi/10.1126/science.abl9463 (2021)

COVID-19

Comparing neurological complications after COVID-19 vaccination and SARS-CoV-2 infection

A large, population-based study of over 30 million people in the UK examined rare adverse neurological events 28 days after vaccination with ChAdOx1nCoV-19, BNT162b2 or a positive test for SARS-CoV-2. Overall, the authors identified a small but increased risk of hospital admission for Guillain–Barré syndrome, Bell's palsy and myasthenic disorders after ChAdOx1nCoV-19 vaccination, and for haemorrhagic stroke after BNT162b2 vaccination. However, they found that infection carries a much greater risk of neurological complications. For example, the authors estimated 38 excess cases of Guillain–Barré syndrome per 10 million doses of ChAdOx1nCoV-19 and 145 excess cases per 10 million positive SARS-CoV-2 tests.

ORIGINAL ARTICLE Patone, M. et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. *Nat. Med.* https://doi.org/10.1038/s41591-021-01556-7 (2021)