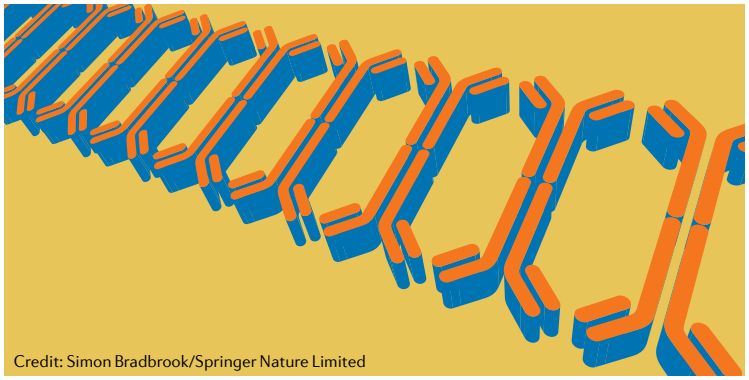

Credit: Simon Bradbrook/Springer Nature Limited

largely nocturnal feeding pattern), whereas light-fed mice had a reversal of the IgA secretion pattern and of metabolism-associated gene expression by plasma cells. Moreover, mice fed a high-fat diet had a complete loss of IgA rhythmicity after 6 weeks, which suggests that nutrient availability might be a rate-limiting factor for antibody production. In support of this, the IgA secretory capacity of plasma cells ex vivo was sensitive to the availability of glucose and leucine in the culture medium.

Lastly, the authors identified IgA-dependent oscillations in commensal bacteria and their metabolism. Using mice that lack the ability to secrete antibodies, they identified several bacterial genera that lost circadian rhythmicity in the absence of IgA. Mice lacking secreted antibody also had a near-complete loss of oscillatory bacterial expression of genes related to glycolysis and gluconeogenesis. Furthermore, time-of-day differences in faecal and blood glucose levels were attenuated in these mice.

Thus, the results suggest that increased nutrient availability after feeding enables intestinal plasma cells to secrete increased levels of IgA, which regulates commensal bacteria for optimal release of nutrients from the diet, as well as potentially other homeostatic functions.

Kirsty Minton

ORIGINAL ARTICLE Penny, H. A. et al. Rhythmicity of intestinal IgA responses confers oscillatory commensal microbiota mutualism. *Sci. Immunol.* **7**, eabk2541 (2022)

phosphorylation of RIG-I and MDA5 to a similar extent as PP1α/γ deletion, suggesting PPP1R12C supports the dephosphorylation of RLRs. In agreement with this, depletion of PPP1R12C impaired IFNβ induction in cells stimulated with synthetic dsRNA or infected with SARS-CoV-2, Zika virus or vesicular stomatitis virus (VSV). Similar findings of impaired IFNβ induction and antiviral gene expression were seen in *PPP1R12C* knockout cells, and in response to VSV infection, *Ppp1r12c*-deficient mice showed impaired innate immune responses, enhanced viral replication and higher mortality.

Further experiments showed that infection with various RNA viruses causes PPP1R12C binding to RIG-I and MDA5. PPP1R12C also showed increased PP1 binding following virus infection, and the authors found that it recruits PP1 phosphatases to the RLRs through the formation of PP1–PPP1R12C–RLR complexes.

PPP1R12C regulates cytoskeleton dynamics as part of the myosin phosphatase complex; therefore, the authors hypothesized that actin cytoskeleton disturbance may displace PPP1R12C from F-actin to promote PP1–PPP1R12C–RLR complex formation. They confirmed this idea using both viral and non-infectious triggers of cytoskeleton disturbance. Notably, the authors found that full activation of RLRs requires both RNA binding and actin cytoskeleton disturbance. They showed that inducible expression of immunostimulatory RNA in cells only led to antiviral gene expression if cells were also treated with agents that disturb the cytoskeleton and cause relocalization of PPP1R12C.

These findings challenge the current view that the presence of immunostimulatory RNA is sufficient for RLR activation. Instead, the authors propose that full RLR activation requires two key trigger steps: first, actin cytoskeleton disturbance to prime RLRs via PP1–PPP1R12C–RLR complex formation, and second the detection of immunostimulatory RNA.

Yvonne Bordon

ORIGINAL ARTICLE Acharya, D. et al. Actin cytoskeleton remodeling primes RIG-I-like receptor activation. *Cell* https://doi.org/10.1016/j.cell.2022.08.011 (2022)

IN BRIEF

IMMUNOTHERAPY

Boosting cytotoxic T cells for immunotherapy

Two papers in *Nature* provide insights into the synergistic activity of PD-1-targeted checkpoint inhibitors and IL-2 or IL-2 receptor (IL-2R) agonists. In a mouse model of LCMV infection, Hashimoto et al. show that the binding of IL-2 to CD25 (the IL-2Rα chain) tweaks the differentiation programme of antigen-experienced PD-1$^+$TCF1$^+$ 'stem-like' CD8$^+$ T cells. In contrast to PD-1 inhibition alone, which expands a population of transitory effector T cells that eventually become exhausted, PD-1 blockade combined with IL-2R signalling results in transcriptionally and epigenetically distinct T cells with superior antiviral activity. Codarri Deak et al. achieved similar effects with PD-1-IL2v, which combines PD-1 blockade with an agonist to IL-2Rβγ. This molecule enables highly specific targeting of antigen-experienced PD-1$^+$ T cells and avoids CD25-mediated side effects, such as the preferential activation of regulatory T cells and lung endothelial cells. PD-1-IL2v showed promising activity in preclinical cancer models, including a model of pancreatic cancer.

ORIGINAL ARTICLE Hashimoto, M. et al. PD-1 combination therapy with IL-2 modifies CD8$^+$ T cell exhaustion program. *Nature* https://doi.org/10.1038/s41586-022-05257-0 (2022) | Codarri Deak, L. et al. PD-1-*cis* IL-2R agonism yields better effectors from stem-like CD8$^+$ T cells. *Nature* https://doi.org/10.1038/s41586-022-05192-0 (2022)

IMMUNE MEMORY

How do smallpox-specific memory B cells survive?

Memory B cells (MBCs) can persist for a lifetime, but how they do this is poorly understood. Chappert et al. isolated vaccinia-specific MBCs from individuals who were vaccinated more than 40 years ago — and as smallpox was eradicated in 1980, these cells have not been re-stimulated, providing a unique opportunity to study their longevity. The antigen-specific cells were enriched in a splenic CD21^{hi}CD20^{hi} IgG$^+$ MBC subset and had limited intra-clonal diversity. They had also undergone extensive affinity-based selection and had elongated telomeres. The analysis further suggested that early MBCs in germinal centres are imprinted with long-lasting potential through telomere elongation and that a regular transit into a splenic niche provides the crucial stimuli that enable these cells to stay functional over many decades.

ORIGINAL ARTICLE Chappert, P. et al. Human anti-smallpox long-lived memory B cells are defined by dynamic interactions in the splenic niche and long-lasting germinal center imprinting. *Immunity* https://doi.org/10.1016/j.immuni.2022.08.019 (2022)

NEUROIMMUNOLOGY

Effect of prenatal stress on the developing brain

Maternal environmental factors such as poor nutrition, immune activation and aberrant microbiome can affect the prenatal brain. Hayes et al. now investigate how the environment affects the microglia that infiltrate the neuroepithelium in early embryonic development. In a mouse model of maternal immune activation (MIA), the authors show that inflammatory stress leads to the long-term blunting of microglia immune reactivity in the adult offspring, with microglia showing changes in chromatin structure, transcription factor occupancy and transcriptional regulation. They also detected dysfunctional connectivity of the ventral striatal circuit in MIA-exposed offspring, but this could be averted by prenatal replacement of microglia with a physiological infiltration of naive microglia. Thus, prenatal stress can affect neuronal network formation via microglia.

ORIGINAL ARTICLE Hayes, L. N. et al. Prenatal immune stress blunts microglia reactivity, impairing neurocircuitry. *Nature* https://doi.org/10.1038/s41586-022-05274-z (2022)