In support of GM-CSF-producing T_H cells being a disease-specific signature population, the authors performed further validation in other patient cohorts and, using a prediction model, they could stratify patients versus controls based on presence of the signature population.

To understand the contribution of the signature subset to disease pathology, the authors studied the effects of the immunomodulatory drug dimethyl fumarate (DMF). In addition to expected changes in systemic lymphocyte composition, DMF-treated patients had a strong decrease in IFNγ- and GM-CSF-producing T_H cell frequencies in the blood. Moreover, the MS signature cell subset was also expanded in cerebrospinal fluid and present in inflamed CNS tissue of untreated patients with RRMS, which together support an important role for this subset in MS pathology.

Lucy Bird

ORIGINAL ARTICLE Galli, E. et al. GM-CSF and CXCR4 define a T helper cell signature in multiple sclerosis. *Nat. Med.* https://doi.org/10.1038/s41591-019-0521-4 (2019)

other branches of the same axon in the surrounding skin. Using an optical shield to prevent light dispersion during photostimulation, they showed that cytokine mRNA levels were increased at adjacent skin sites as well as the photostimulated site. After epicutaneous infection of TRPV1-Ai32 mice, *C. albicans* burden was significantly reduced at both the photostimulated and adjacent skin sites, with the protection of adjacent skin sites being inhibited by an agent that blocks nerve impulses.

Finally, it was shown using wild-type mice that intradermal injection of heat-killed *C. albicans* (which remains local to the injection site) before epicutaneous infection with live *C. albicans* reduced the fungal burden both at the injection site and in the surrounding tissue but not in the presence of the nerve blocker. This shows that neuronal activation can provide an 'anticipatory' host defence response.

Kirsty Minton

ORIGINAL ARTICLE Cohen, J. A. et al. Cutaneous TRPV1$^+$ neurons trigger protective innate type 17 anticipatory immunity. *Cell* https://doi.org/10.1016/j.cell.2019.06.022 (2019)

EARLY LIFE IMMUNITY

Bacterial metabolites shape neonatal immune system

There is growing evidence that allergic disorders may be linked to disturbances in the maternal or neonatal microbiota. Two recent studies in *Nature Microbiology* and *Nature Communications* provide further insight into how microbiota-derived metabolites can shape regulatory T (T_{reg}) cell development in early life, thereby affecting susceptibility to allergy.

Credit: S. Bradbrook/Springer Nature Limited

Infants who are at high risk of developing allergy show distinct changes in their gut microbiota. Their faeces also lack anti-inflammatory bacterial metabolites, such as short-chain fatty acids (SCFAs), and are enriched in monohydroxy fatty acids, including 12,13-diHOME. 12-13-diHOME is a poorly characterized metabolite of linoleic acid (a fatty acid humans derive from the diet) and was shown to be induced in the airways of asthmatics following exposure to allergens; it was also found to inhibit T_{reg} cell induction by dendritic cells (DCs) in vitro. The source of faecal 12,13-diHOME in high-risk neonates is unknown, but Levan et al. hypothesized that it may be derived from the microbiota and influence susceptibility to allergy by affecting DC induction of T_{reg} cells.

In preliminary experiments, Levan et al. showed that 12,13-diHOME can reach the lungs after peritoneal injection and that this treatment leads to fewer T_{reg} cells, increased serum IgE and exacerbated airway inflammation in a mouse model of allergic airway disease. They also detected higher concentrations of 12,13-diHOME in the stools of 1-month-old infants who subsequently developed asthma or allergy. Linoleic acid is initially metabolized to 12,13-EpOME and then converted to 12,13-diHOME by epoxide hydrolase (EH) enzymes, which are encoded by humans, bacteria and fungi. The authors used shotgun metagenomic sequencing to screen neonatal stool samples for sequence reads with EH homology. They did not detect any human or fungal EH genes in the stool samples but found ~1,400 putative bacterial EH genes. Notably, bacterial EH genes were more abundant in the stools of the infants who developed allergy.

They selected 11 of the most frequently detected bacterial genes for functional analyses and found that only 3 of these (1 gene from *Enterococcus faecalis* and 2 genes from *Bifidobacterium bifidum*) could convert 12,13-EpOME to 12,13-diHOME. When they orally delivered *Escherichia coli* strains that had been engineered to overexpress these three functional EH (3EH) genes and linoleic acid to mice, the animals showed higher plasma concentrations of 12,13-diHOME as well as increased inflammation and decreased T_{reg} cell numbers in a model of allergic airway inflammation. Finally, the authors screened samples from two human cohorts and found that a higher 3EH copy number in neonatal faeces is associated with the development of allergy and asthma during childhood.

The study by Hu et al. examined the link between metabolites from the maternal microbiota and fetal immune development in pre-eclampsia, a condition that has been associated with higher rates of allergy in the offspring. They found that fetal thymic development and output of T_{reg} cells is impaired in pre-eclampsia, with follow-up studies showing that this T_{reg} cell deficiency was still seen after 4 years in children born to mothers with pre-eclampsia. They additionally observed that lower maternal levels of serum acetate (a microbiota-derived SCFA that has been shown to support tolerogenic immune responses) were associated with the development of pre-eclampsia. Experiments in germ-free mice indicated that supplementation of mothers with acetate could rescue thymic cellularity and increase FOXP3 expression in T_{reg} cells in pups. Therefore, disturbances in the maternal microbiota that affect the generation of acetate may impair T_{reg} cell development, thereby increasing the risk of pre-eclampsia in the mother and allergic disorders in infants.

Both of these studies indicate how early-life exposure to microbial metabolites can have a crucial role in shaping the immune system.

Yvonne Bordon

ORIGINAL ARTICLE Levan, S. R. et al. Elevated faecal 12,13-diHOME concentration in neonates at high risk for asthma is produced by gut bacteria and impedes immune tolerance. *Nat. Microbiol.* https://doi.org/10.1038/s41564-019-0498-2 (2019) | Hu, M. et al. Decreased maternal serum acetate and impaired fetal thymic and regulatory T cell development in preeclampsia. *Nat. Commun.* **10**, 3031 (2019)

FURTHER READING Skelly, A. N. et al. Mining the microbiota for microbial and metabolite-based immunotherapies. *Nat. Rev. Immunol.* **19**, 305–323 (2019)