cells in vitro. Also, 5-OP-RU was detected in the thymus after cutaneous application or oral gavage, showing that an external source can reach thymic cells.

The results indicate that thymic MAIT17 cell development depends on the remote production of 5-OP-RU by commensal bacteria at mucosal surfaces. This was confirmed using commensal bacterial species that do (*Enterococcus hirae*) or do not (*Enterococcus faecalis*) produce 5-OP-RU, as well as genetically engineered *Escherichia coli* strains that lack enzymes of the vitamin B_2 pathway upstream or downstream of 5-OP-RU production. However, 5-OP-RU alone was not sufficient to promote MAIT cell development in germ-free mice, which suggests that other, as yet unknown, microbial factors are also involved.

Kirsty Minton

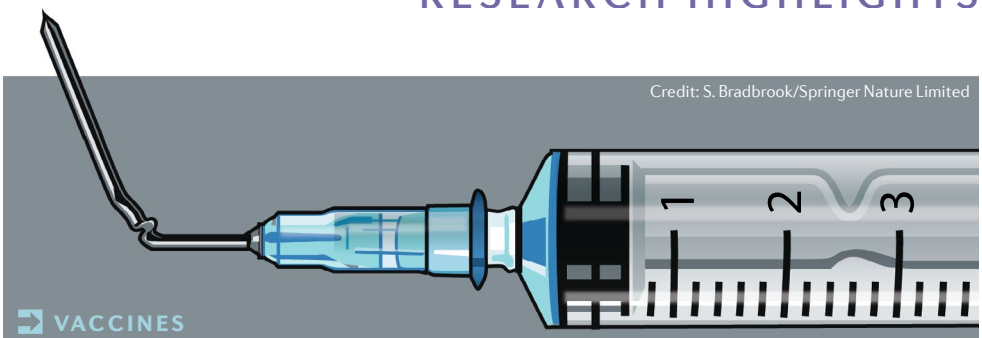
ORIGINAL ARTICLE Legoux, F. et al. Microbial metabolites control the thymic development of mucosal-associated invariant T cells. *Science* https://doi.org/10.1126/science.aaw2719 (2019)
RELATED ARTICLE Toubal, A. et al. Mucosal-associated invariant T cells and disease. *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-019-0191-y (2019)

when analysing UVB-irradiated B2905 tumours in mice over time, the authors found no change in their clonal composition, indicating that no such outgrowth occurs. Instead, they propose that tumours with a high ITH can escape immune surveillance because particular tumour neoantigens undergo 'dilution' within the tumour, thereby leading to weaker antitumour immunity and less immune cell infiltration.

Although the mechanisms underlying the modulation of antitumour immunity by ITH require further investigation, this study shows that assessing the ITH in melanoma patients might be useful as a prognostic indicator for response to immunotherapy. Moreover, it indicates that antigen-specific immunotherapy approaches need to be targeted at antigens present in a large number of clones and that agents that increase the TMB may also increase tumour heterogeneity, which should be avoided.

Alexandra Flemming

ORIGINAL ARTICLE Wolf, Y. et al. UVB-induced tumor heterogeneity diminishes immune response in melanoma. *Cell* **179**, 219–235 (2019)



VACCINES

Antibiotics can impede flu vaccines

Perturbations in the gut microbiota have been shown to affect various immune components and impair the efficacy of treatments such as cancer immunotherapy. Now, work from the group of Bali Pulendran shows that antibiotic-mediated disruption of the gut microbiota can impair the effectiveness of seasonal influenza vaccination in individuals with low levels of pre-existing immunity.

Most studies exploring how the microbiota shapes immune function have used animal models. To examine the effects of the microbiota on the human immune system, Hagan et al. vaccinated antibiotic-treated or control subjects with the seasonal trivalent inactivated influenza vaccine (TIV). They initially enrolled 22 healthy adults and subjected 11 individuals to a 5-day broad-spectrum antibiotic regimen (commencing 3 days before vaccination and ending 1 day after) and collected biological samples regularly until 1 year after vaccination. Antibiotic-treated subjects showed a marked reduction in bacterial loads and profound changes in microbial community composition, chiefly characterized by an over-abundance of Enterobacteriaceae and reduced proportions of Lachnospiraceae, Ruminococcaceae, Bacteroidaceae and Veillonellaceae. This restriction in bacterial diversity was apparent for at least 6 months after cessation of antibiotics administration.

In this initial study, the authors did not see any differences between the TIV-induced antibody responses of antibiotic-treated and control individuals. However, many individuals showed high baseline antibody titres; therefore, in a subsequent study the authors enrolled additional subjects with low pre-existing titres of antibody against influenza. In this follow-up study using individuals with limited pre-existing immunity, antibiotic treatment markedly impaired binding and neutralization antibody responses against the H1N1 A/California strain of influenza (although not against the other two strains targeted by the vaccine) following TIV vaccination. Specifically, the antibiotic-treated subjects showed markedly impaired production of IgG1 and IgA1 specific for H1N1 A/California following vaccination.

The authors found that antibiotic treatment alone was associated with increased expression of gene modules linked with pro-inflammatory signalling and dendritic cell activation, similarly to what had previously been observed in elderly subjects. These changes normalized following cessation of antibiotics, suggesting they were linked with perturbations in the gut microbiota. As the gut microbiota plays an important role in dietary metabolism, the authors examined changes in the blood metabolomes of the different groups. They found that antibiotic treatment was associated with metabolite changes, including changes in bile acid and tryptophan metabolism. The gut microbiota is responsible for converting liver-derived primary bile acids into secondary bile acids; notably, treatment with antibiotics led to a dramatic reduction in levels of secondary bile acids. Accordingly, the authors found prominent differences in the metabolic response to TIV between the antibiotic-treated and control subjects.

Analyses by the authors suggested an inverse correlation between the levels of individual secondary bile acids and expression of various inflammatory modules. In particular, the secondary bile acid lithocholic acid (LCA) showed a 1,000-fold reduction in the plasma of antibiotic-treated subjects and downregulation of LCA was associated with increased expression of inflammasome signalling genes. Further gene network analyses by the authors suggested that the increased inflammatory signalling associated with secondary bile acid disturbances and the impaired IgG1 response to TIV vaccination arise as independent effects of antibiotic-mediated disturbance of the microbiota.

Virtually all humans have been previously exposed to influenza virus and this study indicates that, where pre-existing immunity exists, the immune system can maintain appropriate responses to pathogens despite significant metabolic disturbances arising from transient dysbiosis. However, in situations where immunity may be less mature (such as in adults with low pre-existing immune memory or in infants), dysbiosis may have a greater impact on the development of an appropriate immune response.

Yvonne Bordon

ORIGINAL ARTICLE Hagan, T. et al. Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. *Cell* **178**, 1313–1328 (2019)