recombinant HMGB1 to 7-day-old mice led to microglial activation, a decrease in MBP expression and an accumulation of ROS within the hippocampus.

To investigate whether the brain can be protected from the consequences of microglia activation during NEC by counteracting ROS, they coupled the antioxidant *N*-acetyl-L-cysteine (D-NAC) to dendrimers, which are known to accumulate in microglia in models of neuroinflammation. Oral administration of D-NAC–dendrimers 48 hours after the experimental induction of NEC led to reduced microglial activation and prevented brain injury.

These experiments shed light on the molecular connection between gut and brain pathology in NEC and point to potential novel therapeutic approaches to protect infants with NEC from neurocognitive injury.

Alexandra Flemming

ORIGINAL ARTICLE Nino, D. F. et al. Cognitive impairments induced by necrotizing enterocolitis can be prevented by inhibiting microglial activation in mouse brain. *Sci. Transl Med.* **10**, eaan0237 (2018)

licensing factor, the authors screened various cytokines and alarmins known to be associated with tissue damage. IL-18, despite being generally associated with type 1 responses, was found to be particularly potent in eliciting the release of both IL-5 and IL-13 from ex vivo T cells pre-committed to the type 17 programme. Indeed, a single injection of IL-18 licensed IL-5 and IL-13 production by commensal-specific T_C17 and T_H17 cells, and type 2 licensing following chitin injection was dependent on IL-18 receptor expression by T cells.

Finally, in a model of skin wounding, it was shown that IL-13 neutralization or *Il13* deficiency impaired *S. epidermidis*-accelerated tissue repair. This suggests that the poised type 2 potential of commensal-specific T cells allows for tissue adaptation to injury, thereby promoting repair.

Lucy Bird

ORIGINAL ARTICLE Harrison, O. J. et al. Commensal-specific T cell plasticity promotes rapid tissue adaptation to injury. *Science* https://doi.org/10.1126/science.aat6280 (2018)

Credit: Steve Davey Photography/Alamy

TUMOUR IMMUNOLOGY

Containment strategy

A new study from Mackay, Waithman, Gebhardt and colleagues has detailed how tissue-resident memory $CD8^+$ T cells (T_{RM} cells) protect against tumour outgrowth in the skin. Rather than completely eliminating melanoma cells through cytolytic mechansims, T_{RM} cells promote a melanoma–immune equilibrium that contains the melanoma cells in the epidermis and prevents cancer progression.

As most cancers originate in epithelial layers, the authors were interested in examining antitumour immune responses at these sites. Recirculating T cells are mainly excluded from the epidermis of non-inflamed tissues, but a distinct population of sessile $CD69^+CD103^+$ T_{RM} cells persists here following infection or inflammatory challenge. To explore whether these cells can protect against epidermis-derived cancers, Park et al. used a transplantable model of skin cancer in which B16 melanoma cells were targeted to the epidermis. They generated B16 cell variants that expressed the herpes simplex virus (HSV) glycoprotein gB — termed B16.gB cells — in order to track transgenic gB-specific $CD8^+$ T cells (gBT-I cells) that were responding to the melanomas. Whereas subcutaneous injection of B16.gB cells led to rapid tumour development in wild-type mice, epicutaneous injection of B16.gB cells led to delayed tumour formation and tumours showed variable growth and reduced penetrance. Approximately 40% of mice did not develop any tumours by 4 weeks following epicutaneous injection of B16.gB cells (designated 'non-developers'), and experiments in various lymphocyte-deficient systems showed that this spontaneous protection was immune-mediated.

The fact that some tumours developed much later in some of the non-developers suggested that these mice could harbour microscopic melanomas for long periods. The authors confirmed the presence of occult melanomas in many of the non-developer mice using luciferase-labelled B16.gB cells and through the detection of B16-derived genomic DNA. Therefore, although some mice show immune-mediated tumour suppression following epicutaneous injection of B16.gB cells, a subgroup of these animals still harbour occult melanoma cells and do not achieve melanoma eradication.

To explore $CD8^+$ T cell responses to the melanoma cells, the authors adoptively transferred gBT-I cells into mice before injection with B16.gB cells. The gBT-I cells became activated and expanded in skin-draining lymph nodes and distributed to the tumour-challenged skin and spleen by 2 weeks after injection of B16.gB cells. gBT-I cells also accumulated within tumours and in peritumoural skin, with most peritumoural cells showing a T_{RM} cell phenotype. Notably, mice that remained tumour-free had higher densities of T_{RM} cells in their skin than tumour-bearing mice.

Importantly, the authors found that CD69-deficient mice and CD103-deficient mice (which are deficient in T_{RM} cell generation) were more susceptible to melanoma formation. In addition, mice with pre-existing T_{RM} gBT-I cells (owing to prior HSV infection or local transfer) were protected from tumour development. By contrast, antibody-mediated deletion of these T_{RM} cells triggered tumour outgrowth in previously tumour-free mice. Using intravital two-photon microscopy, the authors were able to visualize T_{RM} cells dynamically interacting with melanoma cells in the skin. Experiments in various knockout mice suggested that tumour necrosis factor (TNF), but not IFNγ or perforin, played a dominant role in T_{RM} cell-mediated tumour suppression. In support of this, TNF-deficient gBT-I T_{RM} cells were shown to be less efficient in suppressing tumour outgrowth.

Therefore, T_{RM} cells can suppress tumour growth by maintaining a cancer–immune equilibrium rather than by killing cancer cells. Although previously proposed, this mechanism has been difficult to study at the cellular level. The authors note that such a containment strategy is also seen in T_{RM} cell control of latent viruses, such as HSV and Epstein–Barr virus. They suggest that non-cytolytic mechanisms of control should be considered in future cancer immunotherapies.

Yvonne Bordon

ORIGINAL ARTICLE Park, S. L. et al. Tissue-resident memory $CD8^+$ T cells promote melanoma–immune equilibrium in skin. *Nature* https://doi.org/10.1038/s41586-018-0812-9 (2018)