Finally, in a cohort of patients who had reactivated latent HCMV after haematopoietic stem cell transplantation, the frequency of NK cells with an 'adaptive' phenotype was greatest in those patients infected with VMAPRTLFL-encoding HCMV. Together, the results show that strain-specific recognition of different UL40 peptides contributes to determining the proliferation and activation of NKG2C$^+$ NK cells during HCMV infection.

The stabilization of HLA-E by UL40 functions as a viral strategy to inhibit NK cell responses through NKG2A. As the inhibitory function of NKG2A was less dependent on peptide sequence variation, the authors suggest that immune pressure mediated by NKG2C$^+$ NK cells could explain the relative rarity of HCMV strains encoding VMAPRTLFL.

Kirsty Minton

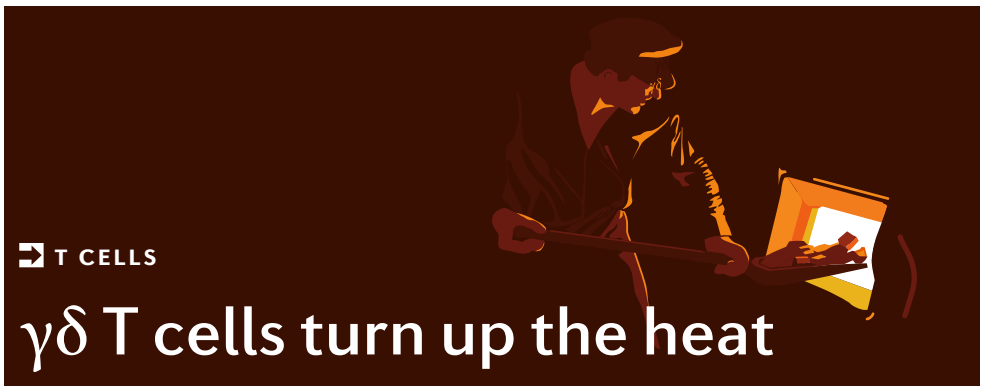
ORIGINAL ARTICLE Hammer, Q. et al. Peptide-specific recognition of human cytomegalovirus strains controls adaptive natural killer cells. *Nat. Immunol.* https://doi.org/10.1038/s41590-018-0082-6 (2018)

transcriptional changes in myeloid cells. By analysing various epigenetic marks, the authors observed striking differences in microglia from control and LPS-treated animals. In particular, mice receiving one LPS injection showed an enrichment of active enhancers for hypoxia-inducible factor 1α (consistent with a trained inflammatory response), whereas mice treated with four doses of LPS showed activated enhancers for phagocytic function (consistent with a tolerized response). These differences were also reflected at the mRNA and protein levels, indicating that epigenetic modifications directly affected gene expression. Interestingly, some enhancers for inflammatory signalling were activated in microglia from non-treated APP mice, suggesting that brain pathology alone can lead to epigenetic reprogramming of microglia.

So, this study suggests that innate immune memory in the brain could affect the severity of any neurological disease with an inflammatory component.

Lucy Bird

ORIGINAL ARTICLE Wendeln, A.-C. et al. Innate immune memory in the brain shapes neurological disease hallmarks. *Nature* **556**, 332–338 (2018)



T CELLS

γδ T cells turn up the heat

The important contributions of γδ T cells to immunity at barrier surfaces are well-established, but now Kohlgruber et al. report that γδ T cells have vital roles in immune homeostasis and thermogenesis in adipose tissues.

First, the authors found that γδ T cells are abundant in various visceral adipose depots in mice, whereas they are less abundant in other organs (for example, the lungs, liver and spleen). In addition, parabiosis experiments in mice and flow cytometry analysis of human omentum demonstrated that γδ T cells are long-lived residents of adipose tissue.

The authors found that adipose-tissue-resident γδ T cells can be differentiated into two populations based on their expression levels of promyelocytic leukaemia zinc finger protein (PLZF), a transcription factor that is known to induce innate-like characteristics in some lymphocytes (such as invariant natural killer T (iNKT) cells and mucosal-associated invariant T (MAIT) cells). Innate-like PLZF$^+$ γδ T cells represent the majority (two-thirds) of γδ T cells in adipose tissue and produce tumour necrosis factor (TNF) and IL-17A, whereas PLZF$^-$ γδ T cells mostly produce interferon-γ (IFNγ). Importantly, the combination of TNF and IL-17A (but not either alone) produced by PLZF$^+$ γδ T cells induced the production of IL-33 by adipose stromal cells in mice and in primary human preadipocytes; IL-33 is known to have an important role in non-shivering thermogenesis, a metabolic adaptation to cold temperatures.

Kohlgruber et al. then demonstrated that adipose-tissue-resident γδ T cells and IL-17A are important for regulatory T (T_{reg}) cell homeostasis in adipose tissue. T_{reg} cells are known to accumulate in adipose tissue in 20-week-old mice, which is mirrored by γδ T cells. Importantly, this accumulation of T_{reg} cells was absent in TCRδ-deficient (*Tcrd*$^{-/-}$) mice that lack γδ T cells. In addition, in *Il17a*$^{-/-}$ mice or mice deficient for two T cell receptor-γ genes (*Vg4*$^{-/-}$*Vg6*$^{-/-}$ mice, which lack IL-17A-producing γδ T cells), T_{reg} cells expressing the IL-33 receptor ST2 were specifically depleted in adipose tissue, but not in the lungs or spleen.

Next, the authors examined the physiological roles of γδ T cells and IL-17A in adipose tissue. Interestingly, in *Tcrd*$^{-/-}$ mice and *Vg4*$^{-/-}$*Vg6*$^{-/-}$ mice, IL-33 protein and mRNA levels were lower in two adipose depots that are important for thermogenesis, namely brown adipose tissue (BAT) and inguinal white adipose tissue (iWAT), respectively, than in wild-type mice after cold challenge. Furthermore, lipid levels in brown adipocytes were higher in *Tcrd*$^{-/-}$ mice and *Vg4*$^{-/-}$*Vg6*$^{-/-}$ mice than in wild-type mice, suggesting that these knockout mice are defective in lipolysis. Additionally, the induction of thermogenic genes in both BAT and iWAT, and the level of the key thermogenesis regulator mitochondrial brown fat uncoupling protein 1 (UCP1) in BAT, were also lower in *Tcrd*$^{-/-}$ mice and *Vg4*$^{-/-}$*Vg6*$^{-/-}$ mice than in wild-type mice.

Importantly, these molecular defects had serious physiological consequences — in response to cold challenge, the body temperature of *Tcrd*$^{-/-}$ mice dropped more rapidly than that of wild-type mice, as the *Tcrd*$^{-/-}$ mice were unable to increase their energy expenditure. The frequency of γδ T cells in BAT and iWAT of wild-type mice increased substantially 8 h after cold challenge, and γδ T cells were the predominant source of IL-17A production in situ. Furthermore, like *Tcrd*$^{-/-}$ mice and *Vg4*$^{-/-}$*Vg6*$^{-/-}$ mice, *Il17a*$^{-/-}$ mice did not upregulate UCP1 in BAT or iWAT, and they had more lipids in brown adipocytes as well as lower expression of thermogenic genes than wild-type mice after cold exposure. Indeed, all *Il17a*$^{-/-}$ mice had to be rescued from death 5–12 h after cold challenge because of their inability to increase energy expenditure. As the frequency of other cell types important for thermogenic responses was unchanged in BAT and iWAT of *Tcrd*$^{-/-}$ mice, the thermogenic defects in γδ T cell-deficient animals are likely independent of other immune cell types.

In summary, this study uncovers a new, crucial role for γδ T cells in thermogenic responses in adipose tissues through their production of IL-17A and TNF.

Grant Otto

ORIGINAL ARTICLE Kohlgruber, A. C. et al. γδ T cells producing interleukin-17A regulate adipose regulatory T cell homeostasis and thermogenesis. *Nat. Immunol.* **19**, 464–474 (2018)