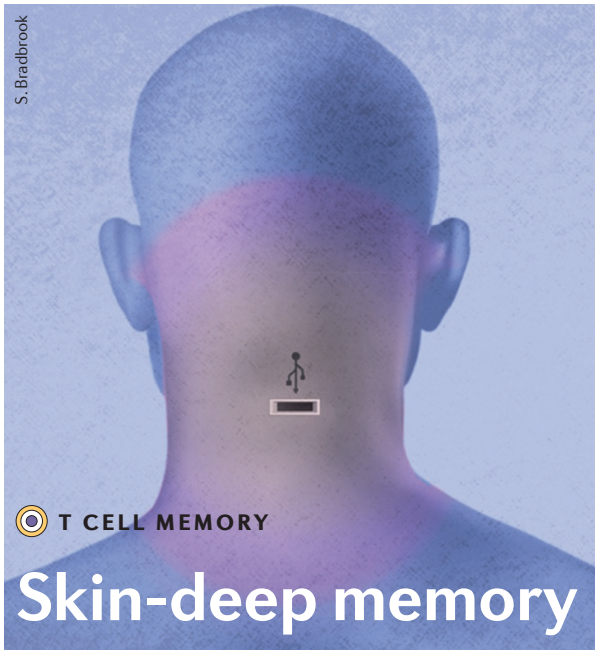

Skin-deep memory

Protective memory T cells have long been thought to reside in the blood and lymph nodes, but a new study in *Nature* shows that a population of memory CD8$^+$ T cells exists permanently in the skin, where these cells provide protection against cutaneous re-infection. In a related paper published in *Science Translational Medicine*, it was shown that these skin-resident memory T cells, but not circulating malignant T cells, were spared in patients with T cell malignancies who were treated with the T cell-depleting antibody alemtuzumab and could continue to mediate immune protection in the skin.

> skin-resident T_{EM} cells protect against pathogens even in the absence of T cell recruitment from the circulation

An accumulation of CD8$^+$ T cells in the skin was observed following localized skin infection of mice with vaccinia virus. After resolution of cutaneous infection (day 30), virus-specific central memory CD8$^+$ T (T_{CM}) cells were detected in the lymph nodes and effector memory CD8$^+$ T (T_{EM}) cells were present in the skin. When these infected mice were surgically joined to mice that had not been previously infected to generate parabiotic pairs, the numbers of T_{CM} cells in the spleen and lymph nodes were similar in both parabionts, which indicates that these cells circulate in the blood. However, no T_{EM} cells were detected in the skin of the non-infected parabiont, even after prolonged periods, which indicates that T_{EM} cells are non-circulating, long-lasting residents of the skin.

To determine the relative roles of the two memory T cell populations in protection from infection, the parabionts were separated and then challenged with vaccinia virus infection of the skin. The virus was cleared much more efficiently in previously infected mice, which had both T_{CM} cells and skin-resident T_{EM} cells, than in the parabionts that had not been previously infected, which had only T_{CM} cells. Interestingly, skin-resident T_{EM} cells were also highly effective at rapidly eliminating the virus at distant skin sites, which indicates that they populate the entire skin surface and provide protection against re-infection independently of T_{CM} cells.

These findings have clinical implications for the treatment of leukaemic cutaneous T cell lymphoma (L-CTCL), which is a malignancy of T_{CM} cells, and of mycosis fungoides, which is a malignancy of skin-resident T_{EM} cells. Clark *et al*. report that low-dose alemtuzumab (a monoclonal antibody specific for CD52) effectively treats patients with L-CTCL but not mycosis fungoides. Indeed, alemtuzumab depleted all T cells from the blood, including skin-homing T_{CM} cells, but did not deplete skin-resident T_{EM} cells. Failure of alemtuzumab to deplete skin-resident T_{EM} cells was not due to poor skin penetration of the drug or loss of expression of CD52 by T_{EM} cells, but is thought to result from the scarcity of neutrophils in the skin to mediate T cell depletion through antibody-dependent cell-mediated cytotoxicity. Importantly, alemtuzumab-treated patients did not suffer from increased infections, which is consistent with the idea that skin-resident T_{EM} cells protect against pathogens even in the absence of T cell recruitment from the circulation.

Lucy Bird

ORIGINAL RESEARCH PAPERS Jiang, X. *et al.* Skin infection generates non-migratory memory CD8$^+$ T_{RM} cells providing global skin immunity. *Nature* **483**, 227–231 (2012) | Clark, R. A. *et al.* Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. *Sci. Transl. Med.* **4**, 117ra7 (2012)