T CELL MEMORY

Warning — here comes a pathogen!

Tissue-resident memory CD8$^+$ T cells (T_{RM} cells) are important for the control of reinfection, but the mechanisms behind this have been unclear. Now, two studies published in *Science* show that following their activation, pathogen-specific T_{RM} cells rapidly induce a tissue-wide response that not only protects against the pathogen for which they are specific but also against unrelated pathogens.

Ariotti *et al.* investigated how a small number of T_{RM} cells can confer rapid protection of local tissue. They generated T_{RM} cells specific for a herpes simplex virus type 1 (HSV1) peptide in mice. To investigate if the T_{RM} cells had any effects on the surrounding tissue, the skin area harbouring the T_{RM} cells was challenged with the same HSV1-derived peptide or an ovalbumin control peptide. The transcriptional profiles from the entire skin tissue revealed differential expression of 89 genes between the two groups of mice. Of note, this differential gene expression was observed as early as 3 hours after antigen administration. Thus, reactivation of skin T_{RM} cells confers a rapid change in gene transcription in the entire skin tissue.

The authors found that the HSV1-derived peptide induced an increase in the level of expression of genes involved in inflammation and immunity. Further analysis indicated that interferon-γ (IFNγ) controls most of the transcriptional changes that are seen in the reactivated skin tissue. Indeed, the transcriptional response following T_{RM} cell reactivation in IFNγ-deficient mice was much lower than in control mice. Furthermore, the tissue response was lost in mice in which only the T_{RM} cells expressed the receptor for IFNγ. This indicates that reactivated T_{RM} cells express IFNγ that acts on other skin-resident cells.

> “reactivation of T_{RM} cells led to the maturation of dendritic cells”

Schenkel *et al.* used a similar experimental setup to study the mechanisms of T_{RM} cell-mediated immune responses to viral reinfection. They found that reactivation of T_{RM} cells led to increased expression of vascular cell adhesion molecule 1 (VCAM1) — which has a role in lymphocyte migration — on the local vascular endothelium. Similarly to Ariotti *et al.*, the altered gene expression in response to T_{RM} cell reactivation depended on IFNγ, as VCAM1 was not upregulated when T_{RM} cells were reactivated in IFNγ-deficient mice.

Next, B cells were shown to co-localize with T_{RM} cells within 12 hours of local T_{RM} cell reactivation and the number of B cells increased >100-fold by 48 hours. This recruitment was dependent on the production of IFNγ by locally reactivated T_{RM} cells and the induction of VCAM1 expression. Intracellular cytokine staining showed that T_{RM} cells also expressed tumour necrosis factor (TNF) after reactivation. Thus, reactivated T_{RM} cells may alert other immune cells to the presence of infection by producing cytokines. In fact, Schenkel *et al.* found that reactivation of T_{RM} cells led to the maturation of dendritic cells within 12 hours, which depended on TNF. Hence, activated T_{RM} cells can function as potent inducers of both adaptive and innate immune responses.

Finally, both research groups found that when reactivated T_{RM} cells were challenged with an unrelated pathogen the host showed protection against this secondary infection. Thus, they concluded that activation of T_{RM} cells depends on antigen recognition, but the genes that are upregulated in response to reactivation leads to local immune responses against antigenically unrelated pathogens.

Together, these studies show that the activation of T_{RM} cells induces tissue conditioning that leads to enhanced pathogen control. Furthermore, the results indicate that T_{RM} cells can sense previously encountered peptides and can broadcast that there is an infection without having to contact every infected cell. Thus, T_{RM} cells function as a bridge between the adaptive and innate immune systems.

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ORIGINAL RESEARCH PAPERS Ariotti, S. *et al.* Skin-resident memory CD8$^+$ T cells trigger a state of tissue-wide pathogen alert. *Science* http://dx.doi.org/10.1126/science.1254803 (2014) | Schenkel, J. M. *et al.* Resident memory CD8$^+$ T cells trigger protective innate and adaptive immune responses. *Science* http://dx.doi.org/10.1126/science.1254536 (2014)

FURTHER READING Farber, D. L., Yudanin, N. A. & Restifo, N. P. Human memory T cells: generation, compartmentalization and homeostasis. *Nature Rev. Immunol.* **14,** 24–35 (2014)