T CELL MEMORY

New insight on old-timers

Memory T cells ensure that the immune response is more effective against re-infecting pathogens. Two key distinctions between memory $CD8^+$ T cells and their naive counterparts are crucial for this: first, memory T cells have distinct migratory patterns; and second, they survive for longer. New studies by Steinert *et al.* and Cui *et al.* offer fresh insight into both of these aspects of memory.

Memory $CD8^+$ T cells have been divided into distinct subsets on the basis of putative trafficking and functional properties. Central memory T (T_{CM}) cells are suggested to be long-lived memory cells that recirculate via secondary lymphoid organs (SLOs), whereas effector memory T (T_{EM}) cells are thought to primarily recirculate between the blood and non-lymphoid tissues and respond rapidly to re-infecting pathogens. A further set of tissue-resident memory T (T_{RM}) cells have been described that are retained in non-lymphoid tissues and do not recirculate. The relative contribution of each subset to immune memory has been unclear; to address this, Steinert *et al.* developed a quantitative immunofluorescence microscopy (QIM) method. In a mouse model of lymphocytic choriomeningitis virus (LCMV) infection, standard protocols for cell isolation markedly underestimated the frequencies of LCMV-specific memory $CD8^+$ T cells in tissues, particularly in non-lymphoid sites, when compared with QIM. Indeed, QIM analyses suggested that more memory $CD8^+$ T cells are found in the blood and peripheral tissues than in SLOs.

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Parabiosis experiments showed that most memory $CD8^+$ T cells in peripheral tissues do not recirculate. This suggests that the majority of memory $CD8^+$ T cells in non-lymphoid tissues are T_{RM} cells, rather than T_{EM} cells, although bona fide T_{EM} cells could be detected exiting tissues via lymphatics. CD69 expression is often used to define T_{RM} cells, but the authors found that a substantial number of resident memory $CD8^+$ T cells do not express this marker. Furthermore, many of the memory $CD8^+$ T cells that entered peripheral tissues (a migratory behaviour associated with T_{RM} cells or T_{EM} cells) expressed the lymph node-homing molecule CD62L, which is typically used to define T_{CM} cells. In fact, adoptive transfer experiments showed that purified T_{CM} cells and T_{EM} cells were equally efficient at migrating to inflamed peripheral tissues. These data suggest that tissue-resident memory $CD8^+$ T cells markedly outnumber those that are recirculating and that our current paradigms of memory T cell subsets require revision.

Cui *et al.* explored how metabolic processes regulate longevity in memory $CD8^+$ T cells. They compared gene expression profiles of naive, effector and memory $CD8^+$ T cells and found that the glycerol channel aquaporin 9 (AQP9) was selectively expressed by memory $CD8^+$ T cells. These cells were shown to upregulate AQP9 in response to stimulation with interleukin-7 (IL-7) — and, to a lesser extent, in response to IL-15 — and deficiency of AQP9 impaired the survival of memory but not effector $CD8^+$ T cells during LCMV infection.

Further experiments suggested that AQP9 deficiency impairs memory $CD8^+$ T cell survival by preventing glycerol uptake, which is required for the synthesis of triglycerides. Triglycerides serve as a source of fatty acids for fatty acid oxidation, a metabolic process that generates energy for memory T cell survival. Consistent with this, AQP9-deficient memory $CD8^+$ T cells had reduced ATP levels, and the overexpression of genes involved in triglyceride synthesis prolonged their survival. Additional analyses showed that IL-7 also increases the expression of genes involved in triglyceride synthesis in previously activated but not naive $CD8^+$ T cells. Therefore, IL-7 promotes memory $CD8^+$ T cell survival not only through the induction of anti-apoptotic genes but also by supporting their metabolic activities.

Yvonne Bordon

ORIGINAL RESEARCH PAPERS Steinert, E. M. *et al.* Quantifying memory CD8 T cells reveals regionalization of immunosurveillance. *Cell* **161**, 737–749 (2015) | Cui, G. *et al.* IL-7-induced glycerol transport and TAG synthesis promotes memory $CD8^+$ T cell longevity. *Cell* **161**, 750–761 (2015)

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