T CELL MEMORY

Keeping energy levels up

A recent study published in *Nature* suggests that the generation of a long-lived memory CD8$^+$ T cell population depends on a switch in energy metabolism from glucose to fatty acid metabolism. Modulation of this metabolic transition shows promise as an approach to boost vaccine efficacy.

To explore the mechanisms regulating memory T cell development, Pearce *et al*. studied mice with a T cell-specific deletion of TNFR-associated factor 6 (TRAF6), which is known to negatively regulate antigen-specific T cell activation. These mice mounted normal antigen-specific effector CD8$^+$ T cell responses following bacterial infection, but few memory CD8$^+$ T cells could be detected 60 days after infection, and the mice failed to respond robustly to re-infection. The defect in memory T cell generation was shown to be CD8$^+$ T cell intrinsic and not a result of insufficient CD4$^+$ T cell help.

Using a systems biology approach to compare gene expression in wild-type and TRAF6-deficient CD8$^+$ T cells, the authors found that TRAF6-deficient T cells had a defect in the expression of genes involved in several metabolic pathways, including fatty acid metabolism. *In vitro* experiments revealed that, unlike wild-type T cells, TRAF6-deficient CD8$^+$ T cells had a reduced capacity to oxidize fatty acids after the withdrawal of interleukin-2 (IL-2). Withdrawal of growth factors such as IL-2 is known to induce metabolic stress in haematopoietic cells, and this causes cells to switch from glycolytic metabolism to catabolic metabolism (such as a fatty acid oxidation and autophagy) to generate energy that is necessary for survival. So the authors proposed that the inability of TRAF6-deficient T cells to switch to fatty acid metabolism impairs their chances of survival when metabolic stress is induced following the peak of the immune response, perhaps owing to limiting growth factors such as IL-2.

Consistent with this hypothesis, TRAF6-deficient CD8$^+$ T cells generated lower levels of active AMP-activated kinase (AMPK), which is a key regulator of fatty acid oxidation, after IL-2 withdrawal compared with wild-type CD8$^+$ T cells. Moreover, exposure to the widely prescribed anti-diabetic drug metformin, which promotes AMPK activation, enhanced fatty acid metabolism in TRAF6-deficient CD8$^+$ T cells. Importantly, daily administration of metformin or rapamycin, another drug that promotes fatty acid metabolism, to mice 1 week following TRAF6-deficient T cell transfer and bacterial infection mitigated the defects in memory T cell development and promoted the survival of both the endogenous and transferred CD8$^+$ T cells. Finally, the pharmacological potential of modulating fatty acid metabolism using metformin was further shown by the finding that metformin treatment of mice increased the efficacy of an experimental cancer vaccine; the increased survival of metformin-treated mice following injection with an otherwise lethal tumour was associated with increased memory CD8$^+$ T cell numbers.

This study highlights a previously unappreciated link between metabolic transition and cell fate determination and suggests that metabolism-altering drugs may be useful for boosting memory T cell responses.

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ORIGINAL RESEARCH PAPER Pearce, E. L. *et al.* Enhancing CD8 T-cell memory by modulating fatty acid metabolism. *Nature* 3 Jun 2009 (doi:10.1038/nature08097)
FURTHER READING Hotamisligil, G. S. & Erbay, E. Nutrient sensing and inflammation in metabolic diseases. *Nature Rev. Immunol.* **8**, 923–934 (2008)