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> S1P promotes naive T cell survival by supporting mitochondrial function

The chemoattractant sphingosine 1-phosphate (S1P) promotes T cell egress from lymph nodes and is important for T cell recirculation through secondary lymph nodes. Reporting in *Nature*, Mendoza *et al.* describe a previously unappreciated role for S1P and its transporter SPNS2 in supporting the survival of naive T cells.

Previous work had shown that mice deficient in SPNS2 (which transports S1P to the lymph) have a markedly reduced number of naive T cells in their secondary lymphoid organs. This was thought to reflect defective export of T cells from the thymus. To test this, Mendoza *et al.* generated *Spns2*Δ mice, in which SPNS2 is not expressed by lymphatic endothelial cells but is still expressed by the blood vessel endothelial cells that regulate T cell egress from the thymus. Despite T cells egressing normally from the thymus, naive T cell numbers were still markedly reduced in the lymph nodes and spleens of the *Spns2*Δ mice. Naive T cell numbers were not increased in other tissues of *Spns2*Δ mice, and these cells did not appear to undergo spontaneous activation or have reduced levels of homeostatic proliferation, suggesting that their survival may be impaired.

In support of this idea, naive $CD4^+$ T cells from the spleens and lymph nodes of *Spns2*Δ mice showed increased rates of cell death and apoptosis compared with controls. Increased rates of naive $CD4^+$ T cell death were also seen in *Spns2*Δ mice reconstituted with wild-type bone marrow. When the authors co-transferred T cells from wild-type mice or *BCL2*-transgenic mice (which are resistant to the mitochondrial pathway of apoptosis) into wild-type or *Spns2*Δ mice, equal numbers of each T cell population were detected in the lymph nodes of wild-type recipients, but more *BCL2*-transgenic T cells were recovered from the lymph nodes of *Spns2*Δ recipients. Therefore, naive T cells seem to be more prone to apoptosis when lymphatic endothelial cells lack functional SPNS2.

The authors tested whether restoring S1P exposure without restoring T cell recirculation in *Spns2*Δ mice could prevent the loss of naive T cells. Indeed, experiments using an inhibitor of the S1P-degrading enzyme S1P lyase suggested that S1P supports T cell survival independently of its role in promoting egress. They next generated *S1pr1*Δ mice, in which the S1P receptor S1PR1 can be inducibly deleted. Experiments using these animals implicated a cell-intrinsic role for S1PR1 signalling in mediating naive T cell survival — naive T cells from *S1pr1*Δ mice show downregulation of transcripts associated with cell survival and upregulation of transcripts associated with cell death.

S1PR1 signalling did not seem to support T cell survival by regulating their access to IL-7 and self-peptide–MHC complexes in the lymph node. Instead, T cells from *S1pr1*Δ mice showed signs of mitochondrial dysfunction, including a 40% reduction in both total and functional mitochondria. Furthermore, *S1pr1*Δ T cells had lower oxygen consumption rates than controls, and activated *S1pr1*Δ T cells showed lower levels of proliferation when relying on oxidative phosphorylation, but proliferated similarly to controls when able to use glycolysis.

These findings show that S1P promotes naive T cell survival by supporting mitochondrial function. The authors propose that given the high energy costs of constant recirculation, it is efficient for naive T cells to use the same signals to support recirculation and mitochondrial function.

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