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T CELLS

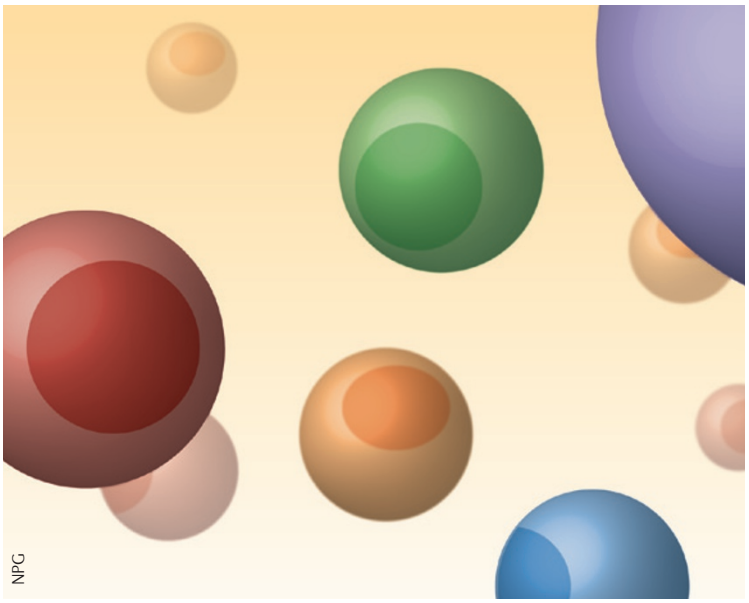
Maintaining T cell homeostasis

> SHP1 seems to control the IL-4-driven proliferation of memory-phenotype T cells

SH2 domain-containing protein tyrosine phosphatase 1 (SHP1; encoded by *PTPN6*) negatively regulates immune signalling, and mice with inactivating mutations in *Ptpn6* (also known as *motheaten* mice) suffer from severe inflammation and autoimmune disease. SHP1 is expressed by all haematopoietic cells, so Johnson *et al.* generated transgenic mice with a T cell-specific deletion of *Ptpn6* (*Ptpn6*$^{fl/fl}$*Cd4*–Cre mice) to study the T cell-intrinsic roles of SHP1.

Studies using *motheaten* mice had previously indicated that SHP1 negatively regulates T cell receptor (TCR) signalling, thereby affecting T cell development and function. However, T cell development was found to be normal in *Ptpn6*$^{fl/fl}$*Cd4*–Cre mice, which — unlike *motheaten* mice — also lacked any signs of inflammation or autoimmunity.

In the periphery, the percentage of CD44^{hi} T cells was increased in naive *Ptpn6*$^{fl/fl}$*Cd4*–Cre mice compared with control *Ptpn6*$^{fl/fl}$ mice (in which SHP1 was not deleted). SHP1-deficient CD44^{hi} T cells had a memory phenotype and could be classified into central and effector memory T cell subsets. As these memory-like T cells developed even in the absence of a specific endogenous antigen, the authors suggest that SHP1 might suppress the expansion of the naturally occurring memory-phenotype T cell population in the steady state.



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TCR sensitivity was found to be normal in peripheral SHP1-deficient CD44^{low} T cells, as assessed using *in vitro* proliferation and cytokine production assays, which indicated that SHP1 has a TCR-independent homeostatic role. Notably, *in vitro* culture of SHP1-deficient T cells for 3 days in the presence of interleukin-2 (IL-2) resulted in increased numbers of IL-4-producing T cells compared with control SHP1-sufficient T cells. The preferential differentiation towards the T helper 2 cell phenotype in the absence of SHP1 was due to defective dephosphorylation of signal transducer and activator of transcription 6 (STAT6) downstream of IL-4 receptor (IL-4R) signalling. This skewing was also reflected by the high levels of IgE in *Ptpn6*$^{fl/fl}$*Cd4*–Cre mice.

Finally, analysis of chimeric mice showed that SHP1 deficiency promoted expansion of the CD44^{hi} T cell population in a cell-intrinsic manner. Moreover, the increase in the number of SHP1-deficient CD44^{hi} T cells could be rescued by the deletion of IL-4. Thus, SHP1 seems to control the IL-4-driven proliferation of memory-phenotype T cells through the negative regulation of IL-4R signalling. Future studies are needed to clarify whether SHP1 has additional roles in antigen-stimulated T cells.

Maria Papatriantafyllou

ORIGINAL RESEARCH PAPER Johnson, D. J. *et al.* Shp1 regulates T cell homeostasis by limiting IL-4 signals. *J. Exp. Med.* **210**, 1419–1431 (2013)