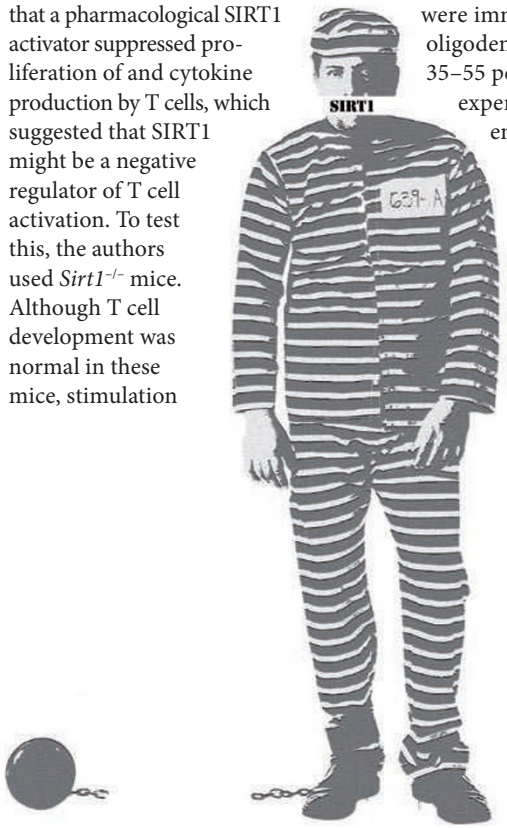
TOLERANCE

SIRT1 keeps escapees quiet

Although self-reactive T cells can escape deletion in the thymus, they are controlled in the periphery by mechanisms that induce tolerance, such as clonal anergy, by which T cells become unresponsive following suboptimal stimulation. The heterodimeric transcription factor activator protein 1 (AP1) is required for T cell activation and is selectively inhibited during peripheral T cell tolerance, but the factors governing this inhibition are not known. Zhang *et al.* now show that NAD-dependent deacetylase sirtuin 1 (SIRT1), a type III histone deacetylase, maintains anergy in T cells by inhibiting acetylation of JUN, a component of AP1.

Previous studies showed that a pharmacological SIRT1 activator suppressed proliferation of and cytokine production by T cells, which suggested that SIRT1 might be a negative regulator of T cell activation. To test this, the authors used *Sirt1*$^{-/-}$ mice. Although T cell development was normal in these mice, stimulation of *Sirt1*$^{-/-}$ T cells *in vitro* and *in vivo* led to greater proliferation and more interleukin-2 production than stimulation of T cells from *Sirt1*$^{+/-}$ littermates. Interestingly, *in vitro* stimulation of *Sirt1*$^{-/-}$ T cells with CD3-specific antibodies without co-stimulation, which induces anergy in wild-type T cells, resulted in full T cell activation, suggesting that SIRT1 might function as an anergic factor. A four- to fivefold increase in *Sirt1* expression levels in anergic wild-type T cells compared with naive wild-type T cells provided further evidence of a role for SIRT1 in anergy.

To determine whether SIRT1 was required to maintain T cell peripheral tolerance to self antigen *in vivo*, *Sirt1*$^{-/-}$ and *Sirt1*$^{+/-}$ mice were immunized with myelin oligodendrocyte glycoprotein 35–55 peptide to induce experimental autoimmune encephalomyelitis (EAE). More *Sirt1*$^{-/-}$ mice showed signs of EAE after immunization, disease onset occurred earlier and the average clinical score was higher than for the *Sirt1*$^{+/-}$ mice. So, the authors concluded that SIRT1 prevented activation of autoreactive T cells and the development of autoimmunity.



Because SIRT1 had previously been shown to suppress several transcription factors, the authors looked at whether SIRT1 could suppress AP1 activity in T cells. They showed that overexpression of SIRT1 inhibited AP1 transcriptional activity in a dose-dependent manner. As SIRT1 is a deacetylase and JUN requires acetylation for its activity it was suggested that SIRT1 might inhibit AP1 by suppressing JUN acetylation. Indeed, there was more acetylation in *Sirt1*$^{-/-}$ T cells than in *Sirt1*$^{+/-}$ T cells and overexpression of SIRT1 inhibited JUN acetylation in transfected HEK-293 cells.

Thus, the findings that SIRT1 is an inhibitor of T cell activation and is required for tolerance suggest that SIRT1 activators could have therapeutic potential for the treatment of T cell-mediated autoimmune diseases and other T cell-mediated inflammatory conditions.

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