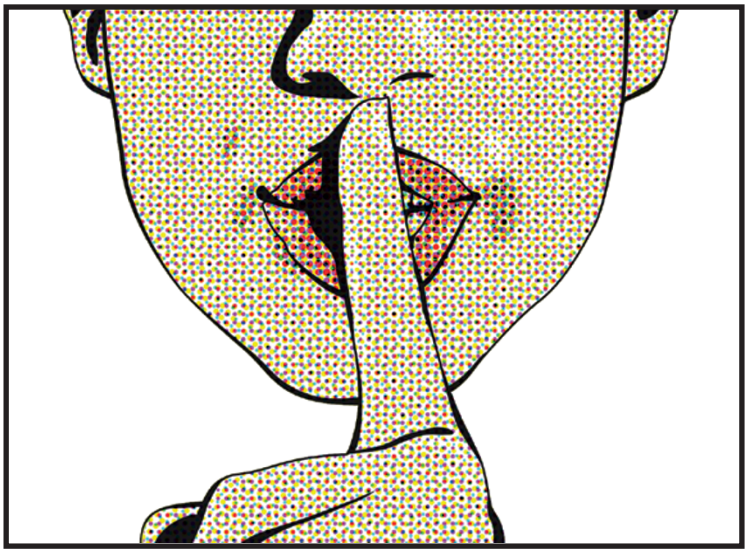
T CELLS

CiShh...

Harnessing the antitumour activities of $CD8^+$ T cells to treat cancer is often limited by tolerogenic processes that occur in the tumour microenvironment and restrain T cell function. Reporting in the *Journal of Experimental Medicine*, Restifo and colleagues identify a key negative regulator of T cell receptor (TCR) signalling — known as cytokine-inducible SH2-containing protein (CISH) — that could be targeted to override tumour tolerance.

CISH is a member of the suppressor of cytokine signalling (SOCS) family and is induced in T cells after TCR stimulation. Using a TCR-transgenic tumour model, the authors show that CISH expression is upregulated in TCR-transgenic T cells that infiltrated tumours expressing their cognate antigen. *In vitro* analyses revealed that $CD8^+$ T cell populations isolated from wild-type mice and stimulated through the TCR did not expand as well as T cells from *Cish*$^{-/-}$ mice, owing to increased apoptosis of the wild-type cells. Moreover, in the absence of CISH, T cells produced larger amounts of cytokines, and more cells produced multiple cytokines following TCR stimulation, together suggesting that CISH limits T cell population expansion and cytokine polyfunctionality.

To test the functional implications of CISH deficiency *in vivo*, the authors adoptively transferred melanoma-specific wild-type or *Cish*$^{-/-}$ T cells into melanoma-bearing mice, together with a recombinant vaccine and interleukin-2. Unlike wild-type T cells, the transferred *Cish*$^{-/-}$ T cells induced marked and long-lasting regression of the established melanomas and extended the survival of mice by 60 days.



S. Bradbrook/NPG

> “*Cish*$^{-/-}$ T cells induced marked and long-lasting regression of the established melanomas”

Next, the authors explored the mechanism of inhibition of TCR signalling by CISH. Microarray analysis suggested that CISH regulated early TCR signalling events, and phosphotyrosine analysis revealed a significant increase in the phosphorylation of the TCR signalling intermediate phospholipase Cγ1 (PLCγ1) in the absence of CISH. The increase in PLCγ1 phosphorylation in *Cish*$^{-/-}$ T cells was associated with a greater magnitude of calcium signalling and the activation of downstream transcription factors compared with wild-type T cells. Accordingly, CISH was found to physically associate with PLCγ1, targeting it for degradation via polyubiquitylation.

So, CISH hushes T cell function through the inhibition of TCR signalling and compromises the antitumour activity of these cells. Overriding this inhibitory pathway could be used to improve adoptive cancer immunotherapy.

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ORIGINAL RESEARCH PAPER Palmer, D. C. *et al.* Cish actively silences TCR signaling in $CD8^+$ T cells to maintain tumor tolerance. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20150304 (2015)

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