Credit: KTSDESIGN/Getty

increased expression of IL-17 at 39.5 °C were abrogated. Deficiency of SUMOylation pathway enzymes or SMAD4 mutation to prevent SUMOylation also abolished the effects of febrile temperature on T_H17 cell differentiation. Indeed, ~37% of the total 1,083 genes that were upregulated in T_H17 cells at 39.5 °C were shown to depend on SMAD4 and many of these were directly bound by SMAD4.

To confirm the indispensable role of SMAD4 in vivo, the authors used an experimental autoimmune encephalomyelitis (EAE) model, in which mice lacking *Smad4* expression in $CD4^+$ T cells or mice with $CD4^+$ T cells expressing the SMAD4 SUMOylation mutant had delayed disease onset and reduced disease scores, associated with reduced numbers of $IL\text{-}17^+$ T cells in the central nervous system. In the same EAE model, aspirin treatment reduced disease in wild-type mice in a similar manner to SMAD4 deficiency.

Together, the results show that a fever-induced heat shock response promotes 'pathogenic' T_H17 cell responses in a SMAD4-dependent manner, which could have implications for the pathogenesis of autoimmunity. The authors also showed that a temperature of 38.5 °C has similar effects on T_H17 cell differentiation and thus the results are relevant to milder fevers.

Kirsty Minton

ORIGINAL ARTICLE Wang, X. et al. Febrile temperature critically controls the differentiation and pathogenicity of T helper 17 cells. *Immunity* https://doi.org/10.1016/j.immuni.2020.01.006 (2020)

BCL-2, respectively, and inhibit cell death. Accordingly, proliferation of *Cd80*$^{-/-}$ *Cd86*$^{-/-}$ and wild-type T cells was similar but *Cd80*$^{-/-}$*Cd86*$^{-/-}$ T cells showed reduced accumulation after 3 days, suggesting that they had poorer survival. By culturing cells in u-bottomed plates (that enforce close proximity) or flat-bottomed plates, the authors showed that cell density correlated with IL-2 concentration, which is consistent with quorum regulation.

Thus, CD28-driven IL-2 promotes cluster growth, which drives further IL-2 and CD80 expression, establishing a positive-feedback circuit. So what keeps the system in check and allows T cell population contraction? CD28 and IL-2 not only promote T cell population expansion but also drive T cell expression of CTLA4, which competes with CD28 for binding to CD80 and CD86 and inhibits IL-2 production, resulting in T cell apoptosis. CTLA4 expression correlated with cell density, thereby providing an antagonistic feedback loop linked to cell density.

Mathematical modelling confirmed that antagonistic feedback loops operating via CD28, IL-2 receptor and CTLA4 explain T cell population dynamics and supported the notion that signalling between T cells enables them to promote and inhibit their own population expansion (depending on the relative expression of CD28 and CTLA4).

Finally, they investigated whether mutual regulation of T cells occurred in vivo. Infection-induced expansion of adoptively transferred *Icam1*$^{-/-}$ T cells was half that of control cells, suggesting that reduced cluster formation limited their survival. Moreover, adoptive transfer of *Icam1*-transgenic or *Il2*-transgenic $CD8^+$ T cells supported the expansion of endogenous $CD8^+$ T cells whereas transfer of *Ctla4*-transgenic $CD8^+$ T cells suppressed expansion. This indicates that $CD8^+$ T cells coordinate their behaviour in vivo and establishes T cell quorum regulation as an additional layer of regulation beyond the effects mediated by DCs and regulatory T cells.

Lucy Bird

ORIGINAL ARTICLE Zenke, S. et al. Quorum regulation via nested antagonistic feedback circuits mediated by the receptors CD28 and CTLA-4 confers robustness to T cell population dynamics. *Immunity* **52**, 313–327 (2020)

Journal Club

A NEW LIFE FOR SELF-REACTIVE T CELL PRECURSORS

Although it is not the focus of my research, the establishment of thymic (central) tolerance has been for me one of the most puzzling aspects of T cell development. In the mid-1990s, as I started my postdoc, the conventional view was that thymic tolerance was mediated by negative selection (deletion) of self-reactive cells, with much experimental support from results gathered in previous years. But how could all or most self-reactive thymocytes be deleted, given the limited time that they spend in the thymus and the multiplicity of self-antigens? Neonatal thymectomy experiments had suggested another mechanism of tolerance, through the generation of 'regulatory' T cells with suppressive activity, but the relationship between these putative cells and thymic selection was unclear.

A major step forward came in 1995 with the identification by Shimon Sakaguchi and colleagues of CD25 as a marker for such regulatory T (T_{reg}) cells. This was followed by the findings that T_{reg} cells are indeed of thymic origin and that their absence accounts for the autoimmune disease that arises after neonatal thymectomy in mice. Thus, there was another mechanism for thymic tolerance. The question became whether it was related to self-reactivity.

A paper by Jordan et al. published in 2001 gave a crucial clue to the answer. The key findings of this elegant study were that $CD25^+$ T_{reg} cells can be selected on self-peptides and that their development requires high-affinity interactions between the T cell receptor and antigen. Thus, the emerging idea, validated by subsequent studies, was that self-reactive thymocytes could not only be deleted (negative selection) but also diverted to an immunosuppressive fate and therefore contribute to tolerance in *trans*.

Together with the demonstration of widespread expression of tissue-specific antigens by medullary thymic epithelial cells (Derbinski et al., 2001), the paper by Jordan et al. provided important insights into T cell tolerance. But the story is far from over. Although subsequent studies deciphered the mechanisms of both T_{reg} cell differentiation and tissue-specific antigen expression in the thymus, much remains to be understood as to what directs thymocytes towards deletion or conventional versus regulatory T cell differentiation.

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ORIGINAL ARTICLE Jordan, M. S. et al. Thymic selection of $CD4^+CD25^+$ regulatory T cells induced by an agonist self-peptide. *Nat. Immunol.* **2**, 301–306 (2001)
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