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REGULATORY T CELLS

Subset-specific suppression

Functionally distinct subsets of CD4$^+$ effector T cells are defined by the expression of key transcription factors, such as T-bet for T helper 1 (T_H1) cells, GATA3 for T_H2 cells and RORγt for T_H17 cells. Subsets of FOXP3$^+$ regulatory T (T_{reg}) cells also express these transcription factors, but it has been unclear whether these subsets have stable differences in function. Rudensky and colleagues show that induced T-bet$^+$ T_{reg} cells in mice form a stable population that specifically inhibits T-bet$^+$ effector T cells.

The authors generated mice expressing red fluorescent protein (RFP) and a tamoxifen-inducible Cre recombinase under the control of the *Tbx21* locus (which encodes T-bet), as well as a recombination reporter that permanently tags cells that have expressed Cre with yellow fluorescent protein (YFP). Under steady-state conditions, 30–70% of effector T_{reg} cells in lymphoid and non-lymphoid tissues of these mice were RFP$^+$ (and hence T-bet$^+$). At 3 weeks, 3 months and 7 months after tamoxifen administration, the majority of YFP-tagged T_{reg} cells continued to express RFP, which indicates that T-bet$^+$ T_{reg} cells have intrinsic long-term stability. Furthermore, when the mice were infected with the T_H2 cell-inducing helminth *Nippostrongylus brasiliensis* 3 weeks after tamoxifen administration, YFP$^+$ T_{reg} cells did not lose RFP expression, which indicates that the T-bet$^+$ T_{reg} cell population is maintained even under non-permissive conditions.

> “the T-bet$^+$ T_{reg} cell population is maintained even under non-permissive conditions”

Next, Rudensky and colleagues looked at the increase in the number of T-bet$^+$ T_{reg} cells in response to a T_H1 cell-polarizing infection. When tamoxifen was administered to the reporter mice 3 weeks before challenge with *Listeria monocytogenes*, the number of RFP$^+$ T_{reg} cells increased markedly whereas the number of YFP$^+$ cells did not. This indicates that T-bet$^+$ T_{reg} cells differentiate from T-bet$^-$ precursors during infection rather than arising from an expansion of the steady-state T-bet$^+$ T_{reg} cell population. To preferentially tag the infection-induced T-bet$^+$ cells with YFP, tamoxifen was administered at the peak of the primary response to *L. monocytogenes*. By day 65 after primary infection, 90% of the YFP$^+$ cells continued to express T-bet and had a greater proliferative response to re-infection than did the bulk RFP$^+$ T_{reg} cell population. Thus, a T_H1 cell-polarizing environment induces the *de novo* differentiation of a stable population of T-bet$^+$ T_{reg} cells that have a strong recall response to the inducing conditions.

Ablation of *Foxp3* in T-bet$^+$ T_{reg} cells resulted in lymphadenopathy, T cell activation and immune infiltration of the lungs in 8-week-old mice. The majority of effector T cells in these mice were RFP$^+$ (T-bet$^+$) and levels of interferon-γ (IFNγ) and IL-2 production were increased compared with levels in control mice, which indicates that T-bet$^+$ T_{reg} cells might be involved in specific suppression of T_H1 cell responses. There was no effect on the T_H2 cell response to *N. brasiliensis* in these mice. Similar results in bone marrow chimaeric mice showed that diphtheria toxin-mediated punctual ablation of T-bet$^+$ T_{reg} cells resulted in T_H1 cell-mediated inflammation. By contrast, mice with selective ablation of T-bet$^-$ T_{reg} cells had suppressed IFNγ production, but unrestrained production of T_H2 and T_H17 cell cytokines.

Thus, T-bet$^+$ T_{reg} cells are a stable subset with T_H1 cell-specific suppressive activity. Further studies are required to determine whether GATA3$^+$ and RORγt$^+$ T_{reg} cell subsets have analogous roles in the suppression of T_H2 and T_H17 cell responses, respectively.

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