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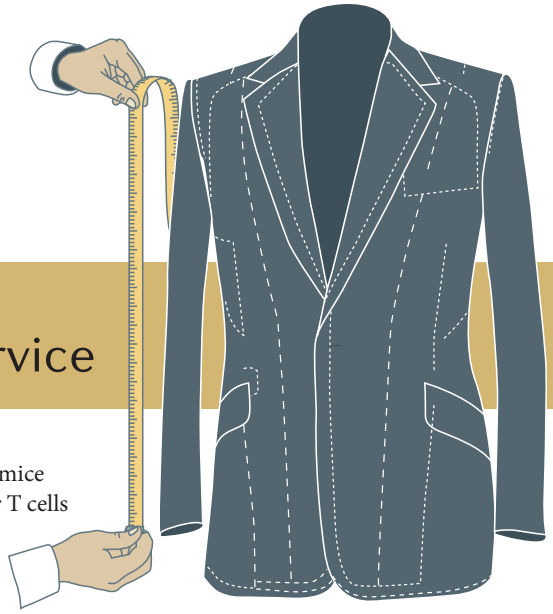

IMMUNE REGULATION

T_{Reg} cells offer a bespoke service

Regulatory T (T_{Reg}) cells provide tailor-made control of the immune response, according to new research by Alexander Rudensky and colleagues. Effector $CD4^+$ T cells differentiate into functionally distinct T helper (T_H) cell populations — T_H1, T_H2 and T_H17 cells — depending on the environmental milieu; these same conditions are now shown to induce the differentiation of a corresponding T_{Reg} cell population to specifically regulate these T_H cells.

The differentiation of T_H17 cells involves the activation of signal transducer and activator of transcription 3 (STAT3). The authors found that phosphorylated (activated) STAT3 also has a function in T_{Reg} cells by binding forkhead box P3 (FOXP3), which is a crucial transcription factor for T_{Reg} cell development. Mice with a conditional deletion of *Stat3* in only their T_{Reg} cells (*Foxp3*^{Cre}*Stat3*$^{fl/fl}$ mice) developed splenomegaly and enlargement of the mesenteric lymph nodes draining the gastrointestinal tract by 6 weeks of age, which progressed to inflammatory bowel disease by 12–14 weeks of age. In contrast to the systemic lymphoproliferative disorder of T_{Reg} cell-deficient mice, pathology in *Foxp3*^{Cre}*Stat3*$^{fl/fl}$ mice was limited to the intestinal mucosa, which indicates that only a subset of T_{Reg} cell functions are affected by deficiency of STAT3.

The *Foxp3*^{Cre}*Stat3*$^{fl/fl}$ mice had more $CD4^+$ effector T cells producing the T_H17 cell cytokine interleukin-17 (IL-17) in the gut, whereas the production of T_H1 and T_H2 cell cytokines was similar in *Foxp3*^{Cre}*Stat3*$^{fl/fl}$ and control mice. IL-17 production was shown to be the initial trigger for colitis induction in *Foxp3*^{Cre}*Stat3*$^{fl/fl}$ mice. The co-transfer of STAT3-sufficient T_{Reg} cells completely abrogates the systemic, multi-organ autoimmunity that results from transfer of effector $CD4^+$ T cells to immunodeficient mice. By contrast, the co-transfer of STAT3-deficient T_{Reg} cells with effector $CD4^+$ T cells prevented systemic disease but resulted in an increased frequency of IL-17-producing $CD4^+$ T cells in the gut and the development of colitis, which supports the selective dysregulation of T_H17 cell responses in *Foxp3*^{Cre}*Stat3*$^{fl/fl}$ mice.

These results show that STAT3 expression by T_{Reg} cells is required for the control of T_H17 cell responses, and the authors suggest several possible mechanisms for this by comparing the expression patterns of FOXP3-dependent genes in STAT3-sufficient and -deficient T_{Reg} cells. First, STAT3 is required for the production of suppressor molecules such as IL-10 and IL-35 that are important for preventing colitis. Second, STAT3-dependent expression of the receptors for IL-1 and IL-6 could enable T_{Reg} cells to compete with T_H17 cells for essential activation cues. Third, the expression of CC-chemokine receptor 6 by T_{Reg} cells, as well as T_H17 cells, in a STAT3-dependent manner controls their migration to and therefore their spatial proximity in the gut. Finally, STAT3 activation in T_{Reg} cells inhibits the expression of soluble mediators of T_H17 cell differentiation, such as transforming growth factor-β and vasoactive intestinal peptide.

So, this study not only confirms that T_{Reg} cells can directly suppress T_H17 cell responses but also shows that transcription factors such as STAT3 can integrate environmental cues to provide 'class-specific' immune regulation.

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ORIGINAL RESEARCH PAPER Chaudry, A. *et al.* $CD4^+$ regulatory T cells control T_H17 responses in a Stat3-dependent manner. *Science* 1 Oct 2009 (doi:10.1126/science.1172702)