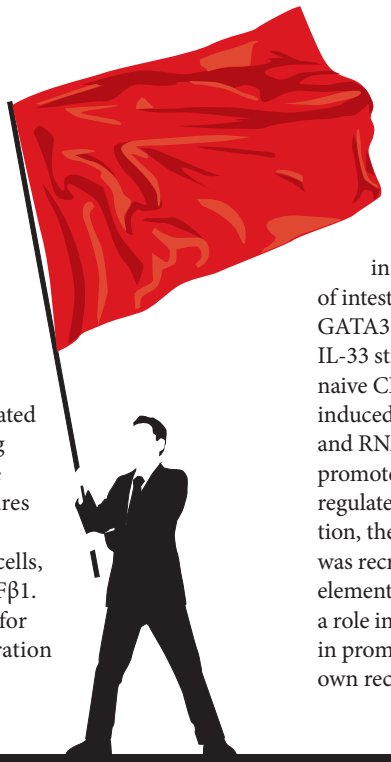
REGULATORY T CELLS

Alarmin(g) control

Regulatory T (T_{Reg}) cells expressing the transcription factor forkhead box P3 (FOXP3) are important for maintaining immune homeostasis in the intestine, but the key factors that control T_{Reg} cell activity at this site are poorly defined. Now, Fiona Powrie and colleagues show that interleukin-33 (IL-33) — which is an alarmin produced in response to tissue damage — promotes T_{Reg} cell function in the intestine.

The authors set out to identify potential tissue-specific regulators of colonic T_{Reg} cells; mRNA expression profiles of T_{Reg} cells from the mesenteric lymph nodes and the colon of mice showed that one of the genes that was most highly upregulated in colonic T_{Reg} cells was *Il1rl1*, which encodes the IL-33 receptor ST2 (also known as IL-1 receptor-like 1). $ST2^+$ T_{Reg} cells are abundant in the intestine, so the authors hypothesized that IL-33 might modulate T_{Reg} cell differentiation. Naive $CD4^+$ T cells were isolated from *Foxp3*^{gfp} reporter mice and activated in the presence of transforming growth factor β1 (TGFβ1). The addition of IL-33 to these cultures increased the percentage and number of FOXP3-expressing cells, but only in the presence of TGFβ1. Thus, IL-33 is a novel cofactor for TGFβ1-mediated *in vitro* generation of T_{Reg} cells.

> IL-33 ... promotes T_{Reg} cell function in the intestine



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Next, the authors investigated whether IL-33 has a role in the *in vivo* proliferation of thymus-derived T_{Reg} cells, which constitute a substantial proportion of the $ST2^+$ colonic T_{Reg} cells. Indeed, IL-33 induced proliferation in splenic T_{Reg} cells but not in effector T cells. Furthermore, *Il1rl1*$^{-/-}$ T_{Reg} cells showed impaired proliferation after injection of IL-33 into chimeric mice that contained a mixture of wild-type and *Il1rl1*$^{-/-}$ haematopoietic cells. Hence, IL-33 promotes the proliferation and accumulation of thymus-derived T_{Reg} cells *in vivo*.

The T-cell-specific transcription factor GATA-binding protein 3 (GATA3) is known to be important for T_{Reg} cell stability and function, and to regulate ST2 expression in T helper 2 (T_H2) cells. Hence, the authors investigated the role of GATA3 in IL-33-mediated regulation of intestinal T_{Reg} cells and found that GATA3 was phosphorylated after IL-33 stimulation of TGFβ1-activated naive $CD4^+$ T cells. This stimulation induced the recruitment of GATA3 and RNA polymerase II to the *Foxp3* promoter, which indicates that IL-33 regulates *Foxp3* expression. In addition, the authors found that GATA3 was recruited to the *Il1rl1* enhancer element. Thus, IL-33 seems to have a role in *Foxp3* induction, as well as in promoting the expression of its own receptor.

Using the T cell transfer model of colitis, the authors examined the ability of *Il1rl1*$^{-/-}$ T_{Reg} cells to protect mice from disease; naive T cells were injected into *Rag1*$^{-/-}$ mice (which lack the gene encoding recombination-activating gene 1) either alone, or together with wild-type or *Il1rl1*$^{-/-}$ T_{Reg} cells. The ability of *Il1rl1*$^{-/-}$ T_{Reg} cells to prevent colitis was substantially impaired, which indicates that IL-33 signalling is important for the suppressive function of T_{Reg} cells *in vivo*.

Finally, the authors examined whether IL-23 — which can promote intestinal inflammation by inhibiting T_{Reg} cell differentiation — limits T cell responsiveness to IL-33. Indeed, the ability of IL-33 to promote FOXP3 expression *in vitro* in the presence of TGFβ1 was abolished after the addition of IL-23. The authors showed that IL-23 prevents T cells from responding to IL-33 by inhibiting ST2 expression and ST2 signal transduction.

Taken together, this study shows that IL-33 produced in response to tissue damage can enhance local intestinal T_{Reg} cell responses. Notably, IL-23 can limit this regulatory mechanism by inhibiting the responsiveness of T_{Reg} cells to IL-33.

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