Nature Reviews Immunology | Published online 27 Jun 2017; doi:10.1038/nri.2017.72

David R. Frazier Photolibrary, Inc. / Alamy

> mice engineered to have jagged 1-deficient T_{reg} cells had attenuated hair follicle regeneration

Regulatory T (T_{reg}) cells are known for suppressing inflammation, but they are increasingly thought to exert specialized, tissue-dependent functions. It was unclear whether skin-resident T_{reg} cells, which localize to hair follicles, have a role in the hair follicle cycle. Ali *et al.* now show that T_{reg} cells regulate the hair follicle cycle by modulating hair follicle stem cells (HFSCs).

Hair follicles go through cyclic phases of growth (anagen) or quiescence (telogen), which are driven by the proliferation and differentiation of HFSCs. The researchers tested the role of T_{reg} cells by carrying out flow cytometric analyses of cells resident in mouse skin during different phases of hair growth. T_{reg} cells were more abundant in the telogen phase and, furthermore, T_{reg} cells present in telogenic skin had a more activated phenotype. To test the function of skin T_{reg} cells, a mouse model of hair follicle regeneration was used, in which a telogen-to-anagen transition is induced by the removal of hair shafts; wild-type mice regrow hair by 14 days post-depilation. By contrast, transgenic mice, which could be induced to be transiently depleted of T_{reg} cells, did not efficiently enter the anagen phase and had substantially less hair regrowth after depilation. These data suggest a role for T_{reg} cells in hair follicle regeneration.

Next, immunofluorescent microscopy was used to examine the location of HFSCs and T_{reg} cells. Notably, a subset of T_{reg} cells (hair follicle 'bulge'-resident cells) colocalized with HFSCs. Furthermore, intravital microscopy suggested that the bulge T_{reg} cell population may be more dynamically active as they show an increase in protrusive activity. A functional link between HFSCs and T_{reg} cells was established by flow cytometric analyses, which showed that the induction of HFSC proliferation following depilation was attenuated in mice depleted of T_{reg} cells. Moreover, whole transcriptome RNA sequencing (RNA-seq) of bulge HFSCs from T_{reg} cell-depleted mice showed a decrease in the expression of genes that are associated with differentiation. Thus, T_{reg} cells are important for inducing the proliferation and differentiation of HFSCs. Interestingly, this is probably not mediated by T_{reg} cell suppression of inflammation, as mice that were transiently depleted of T_{reg} cells and depilated had no increase in skin markers of inflammation.

To investigate the mechanisms of T_{reg} cell-induced HFSC proliferation, the researchers compared the transcriptome of telogenic skin T_{reg} cells to that of skin-draining lymph node T_{reg} cells and found that jagged 1 (a ligand of the Notch signalling pathway) was one of the most differentially expressed genes. Furthermore, HFSCs isolated after depilation had differential expression of Notch target genes in mice depleted of T_{reg} cells. Finally, mice engineered to have jagged 1-deficient T_{reg} cells had attenuated hair follicle regeneration. These data show the importance of jagged 1-mediated Notch signalling in T_{reg} cell induction of HFSC proliferation.

In summary, hair follicle-resident T_{reg} cells have an important and novel tissue-specific function; they regulate the hair follicle cycle by inducing Notch-dependent HFSC proliferation and differentiation.

Shimona Starling

ORIGINAL ARTICLE Ali, N., *et al.* Regulatory T cells in skin facilitate epithelial stem cell differentiation. *Cell* **169**, 1119–1129 (2017)

© 2017 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.