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MICROBIOTA

Pathobiont peacekeepers

Chronic inflammatory diseases of the gut, such as inflammatory bowel disease, are often potentiated by the same microbial species that colonize healthy individuals, such as the *Helicobacter* species. It has been unclear how the pro-inflammatory effector T cell response to these so-called pathobionts is restrained during normal gut homeostasis. Now, Littman and collegues describe a population of pathobiont-specific peripherally derived regulatory T (pT_{reg}) cells that selectively restrain pathobiont-driven inflammation in healthy mice.

Helicobacter hepaticus stably colonizes the large intestine of wild-type mice but causes T helper 17 (T_H17) cell-mediated inflammation in mice with a deficiency of IL-10-mediated immune tolerance. Using this model, the authors cloned *H. hepaticus*-specific T cell receptor (TCR) sequences from the inflammatory T_H17 cells and identified immunodominant peptide epitopes of *H. hepaticus*. Using mice transgenic for one of the cloned TCRs (for example, HH7-2tg mice) or MHC class II tetramers loaded with *H. hepaticus* peptide, they could track *H. hepaticus*-specific T cells *in vivo*. When naive HH7-2tg T cells were transferred into wild-type mice colonized with *H. hepaticus*, they accumulated in the large intestinal lamina propria and differentiated mainly into forkhead box protein P3 $(FOXP3)^+$ pT_{reg} cells. By contrast, when HH7-2tg T cells were transferred into colonized IL-10-deficient mice, they mainly differentiated into T_H17 cells with pro-inflammatory T_H1 cell-like features. Similar differentiation profiles were observed for the adoptive transfer of other *H. hepaticus*-specific T cell clones.

> MAF is a crucial cell-intrinsic factor for the differentiation of *H. hepaticus*-specific pT_{reg} cells

The transcription factor MAF was shown to be highly enriched in the HH7-2tg pT_{reg} cells. In *H. hepaticus*-colonized mice with a conditional deletion of *Maf* in $FOXP3^+$ cells, the proportion of T_{reg} cells in the large intestine was markedly decreased, with a concomitant increase in the number of T_H17 cells. Furthermore, *H. hepaticus*-specific T cells were mainly T_H17 cells rather than T_{reg} cells in the mice with conditional *Maf* deletion in T_{reg} cells. Most of these T_H17 cells expressed MAF, which indicates that they do not arise from the MAF-deficient T_{reg} cells. Thus, the results suggest that MAF is a crucial cell-intrinsic factor for the differentiation of *H. hepaticus*-specific pT_{reg} cells that control a separate population of *H. hepaticus*-specific T_H17 cells. MAF-deficient pT_{reg} cells were also functionally impaired in terms of defective expression of IL-10 and T_{reg} cell signature genes.

In support of a role for MAF-expressing T_{reg} cells in controlling spontaneous inflammatory responses to pathobionts, *H. hepaticus*-colonized mice with conditional deletion of MAF in T_{reg} cells had signs of spontaneous colitis. Similar results were observed for mice with impaired signal transducer and activator of transcription 3 (STAT3) or transforming growth factor-β signalling in T_{reg} cells, both of which are required for MAF expression. Finally, the authors showed that *H. hepaticus*-specific T_{reg} cells were better at suppressing colitis than polyclonal T_{reg} cells in an adoptive transfer model, which highlights an important role for pathobiont-specific pT_{reg} cells in addition to thymus-derived 'natural' T_{reg} cells in maintaining gut homeostasis.

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ORIGINAL ARTICLE Xu, M. *et al.* c-MAF-dependent regulatory T cells mediate immunological tolerance to a gut pathobiont. *Nature* https://doi.org/10.1038/nature25500 (2018)