MUCOSAL IMMUNOLOGY

Colonic creatures are T_{Reg} teachers

> each of us may possess a unique T_{Reg} cell repertoire that develops in response to our own microbiota

Regulatory T (T_{Reg}) cells can arise both from developing T cells in the thymus and from naive T cells that are activated in a tolerogenic manner in the periphery. Thymic T_{Reg} cells recognize self-antigens, but the specificity of peripherally induced T_{Reg} cells is less well understood. This study suggests that most colonic T_{Reg} cells are specific for antigens derived from commensal bacteria and that each of us may possess a unique T_{Reg} cell repertoire that develops in response to our own microbiota.

CORBIS

Previous work has shown that T_{Reg} cells with specificity for food antigens can be induced in the intestine. Commensal bacteria found in the intestine also promote T_{Reg} cell responses, but it has been unclear whether they do this mainly by inducing 'new' T_{Reg} cells with specificity for bacterial antigens or by expanding pre-existing T_{Reg} cell populations. To overcome the difficulty of assessing a fully polyclonal T cell receptor (TCR) repertoire, the authors used transgenic mice with a fixed TCR β-chain (these mice have a limited polyclonal TCR repertoire that is generated through *Tcra* gene rearrangements). They found that the TCRs expressed by effector or memory T cell populations were quite distinct from those expressed by T_{Reg} cells. Furthermore, T_{Reg} cells isolated from the spleen or peripheral lymph nodes used TCRs that were distinct from those found on colonic T_{Reg} cells. Thus, the TCR repertoire of colonic T_{Reg} cells appears to be shaped significantly by the local antigenic environment.

The authors next used an *in vitro* reporter system to show that cells expressing colonic T_{Reg} cell-associated TCRs (but not cells expressing other TCRs) could be activated via their TCRs when cultured with dendritic cells and autoclaved colonic contents from the transgenic mouse colony. Strikingly, the colonic T_{Reg} cell-derived TCRs could not be activated by colonic contents from germ-free mice or by colonic contents from mice sourced from a distinct mouse unit, unless these animals were first co-housed with the transgenic mouse colony. The colonic T_{Reg} cell TCRs showed specificity for antigens derived from distinct commensal species, including *Parabacteroides* spp., *Bacteroides* spp. and a previously uncharacterized *Clostridiales* species. More than half of the colonic T_{Reg} cell TCRs recognized colonic contents or bacterial isolates, suggesting that the TCR repertoire of T_{Reg} cells in the colon is largely skewed towards the recognition of bacterial antigens. Importantly, thymocytes that were transduced with the colonic T_{Reg} cell TCRs did not develop into T_{Reg} cells in the thymus, suggesting that these TCRs mainly mediate peripheral T_{Reg} cell development.

Finally, the authors showed that T cells with specificity for commensal bacteria can also promote disease. In mice with fixed TCR β-chains that had developed colitis as a result of another immune deficiency (in IL-2, IL-10 or TGFβ), TCRs previously associated with colonic T_{Reg} cells were instead expressed by effector T cells. When the effector cells expressing these TCRs were isolated and transferred to lymphocyte-deficient mice, the recipient animals developed colitis. Taken together, the authors' findings support the concept that when the intestinal environment fails to support T_{Reg} cell induction, components of the commensal microbiota can drive inflammatory disease.

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ORIGINAL RESEARCH PAPER Lathrop, S. K. *et al.* Peripheral education of the immune system by colonic commensal microbiota. *Nature* 21 Sep 2011 (doi:10.1038/nature10434)