

Dissecting the Requirement for Secondary Lymphoid Organs in Peripheral Regulatory T-Cell Development



Intestinal mucosal immunity requires the ability to induce a proinflammatory response to clear invasive pathogens while also maintaining self-tolerance in the face of continuous immune activation by luminal contents. Regulatory T cells (Tregs) expressing the transcription factor Foxp3 promote immunologic homeostasis by suppressing dendritic cells¹ and effector T-cell responses through the production of transforming growth factor β , interleukin (IL) 10, and IL35.² In this manner, Foxp3+ Tregs play a central role in the development of oral tolerance to food antigens and commensal bacteria.

Foxp3+ Tregs develop into 2 main subtypes *in vivo*: thymic Tregs, which arise from hematopoietic precursors in the thymus and are selected by a strong T-cell receptor signal against self-antigen, and peripheral Tregs (pTregs), which differentiate extrathymically from conventional T cells through antigen reactivity. pTregs are generated via C-C chemokine receptor (CCR)7-induced migration of CD11c+ CD103+ dendritic cells from gut-associated lymphoid tissue to the mesenteric lymph nodes where processed antigen is presented to naive CD4+ T cells and local transforming growth factor β and retinoic acid promotes pTreg differentiation.^{3–6} Subsequent up-regulation of CCR9 and $\alpha 4\beta 7$ induces their migration to the intestinal lamina propria where IL10 production by CD11b+ CX3CR1+ macrophages expands the pTreg population. Because of their exposure to local antigens, pTregs are considered the central regulators of oral tolerance in the intestine.

The identification of thymic Treg markers such as neuropilin-1 and Helios has resulted in a more detailed assessment of the individual contribution of Foxp3+ Treg populations within the intestinal mucosa. Although our knowledge regarding the molecular mechanisms involved in Foxp3 Treg differentiation *in vivo* has expanded over the past several years, the requirement for secondary lymphoid organs (SLO), such as the mesenteric lymph nodes and gut-associated lymphoid tissue, in this process has remained unclear. In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Geem et al⁷ showed that the majority of these intestinal Foxp3+ Tregs were Helios+, or thymic in origin. By using lymphotoxin α knockout mice, the investigators found that the overall Foxp3+ Treg number was not affected by the loss of SLO; however, accumulation of Foxp3+ Helios- pTregs was reduced markedly only in the small intestine. In contrast, the number of Foxp3+ Tregs in the intestinal lamina propria was enhanced in the absence of CCR7, which the investigators likely attributed to increased homing ligand expression on splenic Foxp3+ Tregs. The observation that SLOs are necessary for small intestinal, but not colonic, pTreg differentiation

highlights the important differences in the requirements for intestinal Foxp3+ Treg development.


Previous studies have shown that microbiota-derived antigens contribute to the colonic pTreg differentiation,⁸ suggesting that the abundance of commensal bacteria in the colon is sufficient to provide a cytokine-rich environment favorable for pTreg differentiation in the absence of SLOs. Consistent with this, germ-free mice lack colonic pTregs, yet maintain an intact small intestinal pTreg compartment.⁹ The current study along with a recent publication by Kim et al¹⁰ further addressed the immune and antigenic requirements for small intestinal pTreg differentiation. Germ-free mice bred on an elemental antigen-free diet fail to develop small intestinal pTregs,¹⁰ indicating that dietary antigen is essential for small intestinal pTreg differentiation. These data suggest a working model in which dendritic cell presentation of dietary antigen in SLOs promotes pTreg differentiation to maintain tolerance to food antigens. In contrast, colonic commensal bacteria, such as Clostridia, induce pTreg differentiation within the lamina propria independent of SLOs, thus generating a separate microbe-induced population of pTregs. Although further investigation is required to definitively address the mechanism by which SLOs contribute to small intestinal pTreg differentiation, the present findings begin to define the broader context of how enteric antigens contribute to intestinal Foxp3+ Treg compartment.

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References

1. Probst HC, Muth S, Schild H. Regulation of the tolerogenic function of steady-state DCs. *Eur J Immunol* 2014; 44:927–933.
2. Bollrath J, Powrie FM. Controlling the frontier: regulatory T-cells and intestinal homeostasis. *Semin Immunol* 2013; 25:352–357.
3. Worbs T, Bode U, Yan S, et al. Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells. *J Exp Med* 2006;203: 519–527.
4. Jang MH, Sougawa N, Tanaka T, et al. CCR7 is critically important for migration of dendritic cells in intestinal lamina propria to mesenteric lymph nodes. *J Immunol* 2006;176:803–810.

5. Sun CM, Hall JA, Blank RB, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J Exp Med* 2007;204:1775–1785.
 6. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med* 2007;204:1757–1764.
 7. Geem D, Ngo V, Harusato A, et al. Contribution of mesenteric lymph nodes and GALT to the intestinal Foxp3+ regulatory T-cell compartment. *Cell Mol Gastroenterol Hepatol* 2016;2:274–280.
 8. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science* 2011;331:337–341.
 9. Weiss JM, Bilate AM, Gobert M, et al. Neuropilin 1 is expressed on thymus-derived natural regulatory T cells, but not mucosa-generated induced Foxp3+ T reg cells. *J Exp Med* 2012;209:1723–1742, S1.
 10. Kim KS, Hong SW, Han D, et al. Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science* 2016;351:858–863.
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- Conflicts of interest**
The author discloses no conflicts.
- Funding**
Supported by grants R03 DK106484 and K01 DK093627 from the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health, and Karen Edelblum is a Rutgers Biomedical Health Sciences Chancellor Scholar.
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2352-345X
<http://dx.doi.org/10.1016/j.jcmgh.2016.02.004>