

## EDITORIAL

## Moving Beyond the Mouse: Key New Insight Into Human Colonic Dendritic Cells



Dendritic cells (DCs) are components of the innate immune system that regularly integrate cues from distal tissue sites and relay important contextual information to draining lymph nodes. In lymph nodes, DCs are particularly adept at promoting the activation and differentiation of naive T- and B-lymphocytes. Once activated, these lymphocytes emigrate from the lymph nodes and efficiently home to sites of infection or tissue injury. The ability of DCs to orchestrate innate and adaptive immune responses in the steady state and during infection is especially important for barrier defense in the gastrointestinal tract given the constant barrage of food and microbial antigens that exists at this site.

To date, the vast majority of information on intestinal DC phenotype and function has been derived from mouse studies. In mice, the majority of DCs in the small and large intestine lamina propria express high levels of CD11c and CD103. Among these CD103<sup>+</sup> DCs, CD11b<sup>+</sup> DCs are abundant in the small intestine, whereas CD11b<sup>-</sup> DCs predominate in the large intestine. Interestingly, both of these major subsets of mouse intestinal DCs potently induce the differentiation of Foxp3<sup>+</sup> regulatory T cells, whereas CD11b<sup>+</sup> DCs also have been shown to promote the differentiation of Th17 cells.

The capacity of intestinal DCs to generate distinct T-cell responses is heavily influenced by components of the microbiota and their metabolites. For example, *Lactobacillus* and *Clostridium* species have been shown to preferentially induce the differentiation and/or expansion of regulatory T cells expressing Foxp3<sup>+</sup> and interleukin 10. Similarly, short-chain fatty acids, primarily butyrate, have been shown to enhance colonic regulatory T cell expansion and function. Alternatively, other components of the microbiota, namely segmented filamentous bacteria, induce Th17 responses. Thus, the specific composition of the microbiota may create a unique local milieu that ultimately dictates intestinal DC-mediated T-cell differentiation. However, although major advances have been made in the understanding of mouse DC subsets, phenotypes, and functional responses toward the microbiota, a relative paucity of data exist on DCs in the human intestine.<sup>1</sup>

In the present issue of *Cellular and Molecular Gastroenterology and Hepatology*, Bernardo et al<sup>2</sup> provide key new pieces of information detailing the recruitment, phenotype, and functions of DCs in the proximal and distal healthy human colon. The investigators found that the majority of colonic DCs were derived from human blood CD11c<sup>+</sup> myeloid DCs that were recruited into the colon via a Chemokine (C-C Motif) Receptor 2-dependent mechanism. DCs in the

proximal and distal colon expressed high levels of CD11c and signal-regulatory protein alpha (SIRP $\alpha$ ), whereas the CD103<sup>-</sup>SIRP $\alpha$ <sup>+</sup> subset was specifically enriched in the proximal colon and the CD103<sup>+</sup>SIRP $\alpha$ <sup>+</sup> subset (analogous to mouse CD103<sup>+</sup>CD11b<sup>+</sup> DCs) predominated in the distal colon.

Not only were DC subsets unique in the proximal and distal human colon, but these differences were reflected in distinct T-cell stimulatory capacity. Proximal colon DCs showed higher CD4<sup>+</sup> T-cell stimulatory capacity as compared with distal DCs, yet the imprinting of gut-homing receptors on T cells activated by proximal colon DCs was lower than that observed using distal colon DCs. These intriguing differences may be a reflection of the unique microbiota-induced cytokine milieu created in these distinct regions of the colon. Indeed, the investigators found that the mucosa-associated microbiota load was lower in the proximal colon and this was associated with increased cytokine secretion and decreased RALDH2 expression. These factors collectively may contribute to enhance T-cell stimulation and favor effector T-cell differentiation. In the proximal colon, however, more intimate contact with the microbiota appears associated with dampened cytokine responses and augmented RALDH2 expression. Overall, these factors may suppress T-cell stimulation in favor of regulatory anergic-type T-cell responses.

Although much remains to be learned about how DCs regulate immune responses in different regions of the human intestine, the work by Bernardo et al<sup>2</sup> is an important step in defining several key features of the regional specialization of these cells. Future studies examining how these and other DC subsets function during inflammatory conditions, such as Crohn's disease and ulcerative colitis, may provide critical information as to how these cells may be exploited or targeted for therapeutic purposes.

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function between the proximal and distal colon. *Cell Mol Gastroenterol Hepatol* 2016;2:22–39.

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**Conflicts of interest**

The author discloses no conflicts.

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