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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Re-evaluating the Role of Deep Crypt Secretory Cells in Intestinal Homeostasis

The mammalian colon offers a somewhat unique stem cell niche because of its complex but compact architecture, high rate of cellular renewal, and proximity to a high population microbiota. The regenerative capacity of the colonic stem cell niche is supported by a specialized group of cells referred to as deep crypt secretory (DCS) cells, which act in a similar role to Paneth cells maintaining the small intestinal stem cell niche.[1] Although first identified in 1983,[2] DCS cells function beyond this maintenance of the stem cell niche remains understudied and poorly understood. For instance, although DCS cells share some similarities to goblet cells and Paneth cells, such as expression of *Notch*, *EGF,* and *Muc2*, they are a distinct cell type with unique secretory profiles,[1] and whether they too play a role in maintaining homeostasis in response to inflammation has not been determined.

Recent work has shown that the intracellular signalling regulator; Sprouty2, is a regulator of colonic goblet cell differentiation,[3] with deletion of Sprouty2 driving the expansion of goblet cells via an epithelial interleukin (IL)-33/stromal IL-13 axis. Interestingly, this appears to be an endogenously protective pathway because Sprouty2 is down-regulated in acute inflammation, and this is protective in murine models of acute colitis. In contrast, chronic colitis models show up-regulation of Sprouty2, and this is representative of findings in inflammatory bowel disease patients.[3] Building on this work, in the current issue, Schumacher et al[4] demonstrate that DCS cells are also regulated by Sprouty2, highlighting an inflammation-responsive expansion of DCS cells, mediated by IL-13, in the absence of Sprouty2.

Using mice with an intestinal epithelial-specific deletion of Sprouty2 (Spry2ΔIE mice) and colonoid models, the authors show that like colonic goblet cells, in the absence of Sprouty2, DCS cell expansion is mediated by an IL-13 increase facilitated by IL-33. Importantly, single cell RNA sequencing analysis suggests that this IL-13 is exclusively produced by DCS cell-adjacent innate lymphoid cell (ILC) 2 populations within the colonic crypt. This prompts interesting questions as to whether ILC2s have an additional underappreciated role in maintaining colonic homeostasis, because Sprouty2 deletion also drives expansion of colonic tuft cells,[3] which are potent secretors of IL-25, and this would conceivably also drive IL-25 mediated IL-13 secretion by ILC2s.[5,6] Future functional studies may shed light on the dynamic kinetics of IL-25 and IL-33 signalling in this axis and whether they act synergistically or as redundant signalling mechanisms.

Because the primary role of DCS cells is thought to be maintenance of the colonic stem cell niche, their developmental regulation by IL-13 may seem curious; however, further single cell analysis of these cells by Schumacher et al[4] shows that IL-13 drives a specific induction of *Retnlb,* which encodes the human defence protein RELMβ, in DCS cells. In mice, loss of RELMβ decreases intestinal barrier function and increases susceptibility to experimental colitis,[7] and this may in part explain why Sprouty2 deletion is protective in these models. Curiously and in contrast to previous studies,[8,9] both immunofluorescence and transcriptomic profiling implicated DCS cells as the major source of RELMβ under homeostatic conditions. This may be because previous studies have relied on immunohistochemical staining, which is likely insufficient to distinguish between goblet cells and DCS cells. The fact that RELMβ was also shown to induce *Muc2* expression in goblet cells suggests that beyond maintaining the stem cell niche[1] and epithelial barrier, DCS cells may also play a role in goblet cell maintenance. This is potentially an important avenue to explore because previous work has shown that loss of DCS cells leads to a reduction in goblet cells.[1]

Overall, the work of Schumacher et al[4] demonstrates that DCS cells play a role in mucosal homeostasis and protection far beyond maintenance of the stem cell niche. Indeed, the current work shows that DCS cells have unique transcriptional profile, and although similar to goblet cells, DCS cells may arise from a common secretory progenitor in the colon. Further studies characterizing the proteome of the DCS cells will provide further insight into their function and contribution within the colonic stem cell niche and their homeostatic role in controlling inflammation.

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Conflicts of interest
The authors disclose no conflicts.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2023.01.005