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EDITORIAL

Epithelial Traffic Control: IL22 Gives TA Cells the Green Light

The intestinal epithelial barrier is instrumental in the physical separation of gut microbiota from underlying innate and adaptive immune cells and stromal cells.[1] This "barrier" is anything but static, however, with intestinal stem cells (ISCs) tightly controlling regeneration of the epithelial lining along the crypt–villus axis in a coordinated balance between ISC self-renewal and differentiation into transit-amplifying (TA) cells.[2] Although numerous, well-defined growth factor pathways are known to regulate ISC and TA cell expansion dynamics in the steady state, far less is understood about how specific cytokines expressed during tissue injury and inflammation influence this intricate process.

Interleukin (IL)22 is a member of the IL10 family of cytokines, which has received considerable attention because of its pleotropic effects in the intestine.[3] IL22 is expressed constitutively in the small intestine and can be induced in the large intestine during inflammatory conditions. The predominant cell type expressing IL22 in the steady-state intestine appears to be group 3 innate lymphoid cells, although numerous additional cell types including $CD4^+$ (T-helper 17 and T-helper 22 cells), natural killer cells, and neutrophils may produce IL22 during inflammatory conditions.[4] In the intestine, expression of IL22 receptor (IL22R) is restricted mainly to epithelial cells, and signaling via IL22R leads to activation of signal transducer and activator of transcription-3. The IL22/IL22R axis has been shown to promote intestinal barrier defense by inducing antimicrobial peptides such as members of the regenerating islet-derived protein 3 family (RegIIIβ, RegIIIγ), S100 calcium-binding protein family (S100A7, S100A8, S100A9), and β-defensin 2. IL22 signaling to intestinal epithelial cells also promotes mucin 1 production and glycosylation, leading to a firmer inner mucus layer. In addition to inducing antimicrobial peptides and the mucus layer, IL22 supports mucosal healing via potently driving epithelial proliferation and regeneration after damage.[5] However, the precise effects of IL22 on the ISC and TA compartments have remained unclear.

Two studies from Zwarycz et al[6] and Zha et al[7] recently published in *Cellular and Molecular Gastroenterology and Hepatology* provide novel insight into the effects of IL22 on intestinal organoids. Both groups independently identified a Janus-faced role for IL22 in enhancing proliferation of TA cells while concomitantly inhibiting ISC expansion. Zwarycz et al[6] first screened for effects of several inflammatory bowel disease (IBD)-related cytokines, including IL-6, IL-17, IL-21, and IL22 on ileal enteroid growth. Using physiological doses of these cytokines based on computational modeling of microenvironment levels, the authors observed that IL-22 was unique in its ability to enhance enteroid size, while decreasing survival, as assessed by organoid forming efficiency (OFE). Using cutting-edge single-cell RNAseq, the authors further demonstrated that IL22R (*Il22ra1*) was heterogeneously expressed on ISCs and TA progenitors, suggesting that in the steady-state only a subset of these cells are receptive to IL22 stimulation. When freshly isolated ISCs were stimulated with IL22, Zwarycz et al[6] observed a decrease in ISC biomarkers (Lgr5, Olmf4) and inhibition of key Wnt- and Notch-target genes, as well as decreased ISC expansion. Using IL22-trangenic mice, they also noted a clear increase in proliferative cells in the TA zone with negligible effects on ISC numbers. Following the addition of IL22 to mouse jejunal crypts, Zha et al[7] also observed enhanced enteroid size, and but astutely noted a marked reduction in enteroid number. The dose-dependent inhibition of enteroid survival mediated by IL22 was even more evident upon passaging when nearly none of the enteroids survived. Having previously reported that IL22 potently induces the tight junction protein claudin-2 and keenly aware that this protein forms paracellular channels that enhance flux of Na^+ and water and thus cellular volume, Zha et al[7] used claudin-2 transgenic and claudin-2 knockout mice to elegantly show a role for claudin-2 in IL22-driven effects on enteroid size. Subsequently, Lgr5 reporter mice were used to show that IL22 markedly reduced ISC numbers and proliferative capacity in vivo, whereas epithelial proliferation and markers of the TA compartment were increased. The inhibitory effects of IL22 on ISCs could be explained, in part, by IL22 suppressing wnt signaling via down-regulation of the Fzd7 wnt receptor and inducing the Wnt antagonist Dkk1, and Notch signaling also was inhibited.

Collectively, the novel data presented by Zwarycz et al[6] and Zha et al[7] provide an interesting and important new framework for understanding how IL22, and perhaps other cytokines, can play dual roles on neighboring cells types to modulate intestinal epithelial repair and barrier function. Although much remains to be appreciated about the complex nature of cytokine signaling pathways on intestinal epithelial cells during health and disease, these studies highlight that careful investigation of the cytokine expression site, dose, and biological function on specific cell types in addition to cytokine-receptor expression, are all likely to provide additional insight into the highly integrated system of the immune–epithelial dynamic in the intestine.

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Conflicts of interest
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