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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Indian Hedgehog Suppresses Intestinal Inflammation

Hedgehog signaling is an evolutionarily conserved pathway that is important for tissue patterning and repair and has been implicated in inflammatory responses for several tissues. However, the gene and cellular targets of the Hedgehog signaling pathway that orchestrate the inflammatory responses are not clearly defined. Hedgehog signaling is mediated by 3 different ligands (sonic hedgehog [Shh], Indian hedgehog [Ihh], and Desert hedgehog [Dhh]), multiple co-receptors (patched, smoothened, growth arrest-specific 1, cell adhesion molecule-related/down-regulated by oncogenes, and brother of cell adhesion molecule-related/down-regulated by oncogenes), 3 transcriptional effectors (glioma [Gli]-associated oncogene homologs 1, 2, 3), and additional regulatory factors. In the gastrointestinal tract, Shh and Ihh are the major ligands expressed by the epithelium. These ligands activate receptors on several stromal cell types, including myofibroblasts, smooth muscle, immune, neural, lymphatic, and vascular cells. Such complexity in the cellular targets has confounded the precise determination of which cell population mediates the response to a specific environmental challenge.

Several studies have reported that Hedgehog signaling in the intestine suppresses inflammation. In particular, recent studies from Lee et al[1] have shown that Hedgehog signaling induces expression of the anti-inflammatory cytokine interleukin (IL)10 in stromal cells, which in turn activates regulatory T cells through induction of the transcription factor Foxp3. In the current study, Westendorp et al[2] identified a gp38-, smooth muscle actin–, and desmin-positive fibroblast that is critical for mediating the recruitment of inflammatory cells. They showed that the hedgehog ligand Ihh normally suppresses the release of immune chemoattractants such as the chemokine C-X-C motif chemokine ligand 12 (CXCL12) from these fibroblasts. By using immune cell–specific Cre recombinase drivers that delete smoothened from macrophage or dendritic cells, Westendorp et al[2] ruled out the notion that direct Hh signaling in these immune cell populations controls the mucosal inflammatory response. Because they showed that conditional deletion of Ihh in the intestine exacerbates colitis, there is the possibility that dextran sulfate sodium induces inflammation in wild-type mice by suppressing mucosal expression of the Hh ligand during mucosal damage. However, the level of Ihh ligand was not assessed by enzyme-linked immunosorbent assay or Western blot to definitively establish this point.[2]

Collectively, the 2 intestinal studies complement each other by showing that loss of hedgehog signaling leads to increased inflammation by 2 different mechanisms. In the Westendorp et al[2] study, hedgehog ligands suppress CXCL12 expression specifically in fibroblasts, whereas Beachy et al[1] described a pro-reparative pathway mediated by stromal expression of IL10. However, unlike the Westerndorp et al[2] study, the IL10-producing stromal cell was not specified, so it is not clear whether there is overlap in the Hh-targeted cell population described in these 2 studies. It also should be noted that neither study provided evidence using chromatin immunoprecipitation or DNA binding assays that Gli1 directly binds to regulatory regions in genes encoding either of these immune modulatory factors. Thus, the possibility remains that neither CXCL12 nor IL10 are direct gene targets of the Gli1 transcriptional effector.

Interestingly, in contrast to the intestine, myeloid cells in the *Helicobacter*-infected stomach are direct cellular targets of hedgehog ligands. Shh secreted from the parietal cell within 2 days of this gastric infection functions as a myeloid cell chemoattractant.[3] Moreover, Shh ligand is required for polarization of myeloid cells into immunosuppressive myeloid-derived suppressor cells during chronic (~6 months) *Helicobacter* infection, but alone is not sufficient to activate complete T-cell–suppressor function. Rather, Hh signaling synergizes with type 1 interferons to fully polarize myeloid cells within the microenvironment of the stomach.[4] Although the function of Hh-dependent cells in the acutely infected stomach has not been investigated thoroughly, there appears to be some congruence with the immunosuppressive effects in the intestine because Hh signaling in the chronically infected stomach contributes to immunosuppression (polarization to myeloid-derived suppressor cells). Other explanations for differences in the gastric vs intestinal responses might include the type of inflammatory challenge or regional patterning of the stroma. Indeed, studies by Kedinger et al[5] 2 decades ago showed that fibroblasts isolated from the proximal vs distal gut might show different phenotypes and, accordingly, different responses to inflammatory triggers.

The translational implications of defining Hh function in the gut are significant. For example, an exonic polymorphism of *Gli1* that diminishes its transactivation has been shown to be associated with ulcerative colitis in a Northern European population.[6] Moreover, CXCL12 has been shown to be up-regulated in patients with inflammatory bowel disease.[7] Therefore, its role as a chemoattractant might contribute to disease progression. In summary, the report from Westendorp et al[2] suggests that hedgehog signaling promotes intestinal homeostasis by preventing fibroblast expression of a chemokine chemoattractant in response to acute mucosal injury. Thus, activating the hedgehog pathway might provide therapeutic options for patients with inflammatory bowel disease and potentially prevent progression to cancer. However, the anti-inflammatory effects of hedgehog antagonists used to treat non–bowel-related cancers are likely to oppose the potential

beneficial function of endogenous Hh ligands in the gastrointestinal mucosa.

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