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EDITORIAL

GLI-fully Responsive to Inflammatory Cytokines

Chronic *Helicobacter pylori* infection is a primary risk factor for the development of gastric cancer, a leading cause of cancer-related death worldwide. *H pylori* initially colonizes the gastric antrum and, over time, can spread throughout gastric corpus causing oxyntic atrophy. In some human patients, the sustained chronic infection over many decades within the stomach eventually leads to the emergence of advanced gastric pathologies, including intestinal metaplasia, dysplasia, and cancer.

How the sustained inflammatory response toward *H pylori* shapes tissue behavior independent of bacterial virulence factors, including induction of hyperplasia and changes in differentiation throughout the distal stomach, remains an important area of investigation. Defining the relevant cytokines, their direct cellular targets, and the cellular response are important steps to understanding early steps in disease progression. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ding et al[1] explore how interleukin (IL)1β and interferon (IFN)-γ influence tissue and cellular behaviors in the antrum. To accomplish this, they used mouse genetic tools to misexpress the 2 key cytokines associated with *Helicobacter* infection, specifically within the antrum using the gastrin promoter and recapitulated the phenomena in vitro using cell lines.

The authors found that although both IL1β and IFN-γ drive a hyperplastic phenotype within the antrum, they illicit divergent effects on endocrine cell differentiation. IFN-γ increased G-cell numbers and serum gastrin levels, whereas IL1β suppressed overall endocrine cell differentiation, responsible for the suppressed serum gastrin levels. To connect these studies to previous exploration by this group, the authors investigated Hedgehog signaling, which has been implicated in the regulation of gastrin.[2] The authors used mouse models of elevated SHH production, in the context of *Helicobacter felis* infection, to establish that Hedgehog signaling leads to decreased numbers of G-cells in the antrum and reduced serum gastrin levels. Interestingly, increasing SHH production significantly elevated the number of IL1β-expressing inflammatory cells, suggesting Hedgehog signaling might have direct and indirect effects on G-cell differentiation and gastrin levels. To continue to explore the relationship between SHH, IFN-γ, and IL1β on gastrin, Ding et al[1] used a gastrin-producing enteroendocrine mimicking GLUTag cell line. Consistent with their in vivo findings, IFN-γ promoted gastrin secretion, whereas IL1β suppressed it in this cell line. This in vitro system confirms the direct effect of these cytokines on gastrin secretion, as confounding factors, such as gastric pH, are removed.

Primary cilia are an important sensory organelle that plays an essential role in mammalian Hedgehog signaling. To explore whether the suppressive effects driven by IL1β and SHH on gastrin occur through the primary cilia, the authors disrupted cilia by knocking down *Kif3a*, a kinesin required to maintain cilia structure. In the absence of primary cilia, gastrin levels were elevated in GLUTag cells and the suppressive effects of IL1β and SHH on gastrin were lost. To extend this observation in vivo, the authors knocked out *Kif3a* in G-cells. In the absence of primary cilia, serum gastrin levels were elevated, G-cell numbers were increased, and antral hyperplasia was induced.

In the context of the complex inflammatory environment driven by *Helicobacter* infection, individual disease phenotypes likely rely on the specific levels and balance of several cytokines. The findings presented in this study highlight the differential effects of 2 key cytokines, IL1β and IFN-γ, through their regulation of endocrine cell differentiation and function in the antrum. Furthermore, the authors identified the primary cilia as a key nexus for the regulation of gastrin in G-cells through activation of Hedgehog effector GLI2 by SHH and IL1β.

Future studies might explore whether IFN-γ or IL1β play a role in causing oxyntic atrophy and expanding the *Helicobacter* niche through gastrin crosstalk with the corpus. Additionally, it may be possible to modify the function of the Hedgehog pathway, IFN-γ, and IL1β in combinatorial ways in the setting of the initiation of *Helicobacter* infection or chronic disease to find out if this leads to specific disease outcomes.

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