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EDITORIAL

The Novel Role of *Lgr5* as a Regulator of Cell Homeostasis and Disease of the Gastric Oxyntic Mucosa

The stem cell compartment is crucial for driving the replenishment of the gastric epithelium. The leucine-rich, repeat-containing G-protein–coupled receptor 5 (*Lgr5*) was among the first genes identified to mark the stem cells within the gastric mucosa.[1] It is accepted that Lgr5 is located in adult stem cells at the base of the antral glands of the stomach, and are capable of long-term renewal of the epithelium.[1] Recently, using a nonvariegated Lgr5-2A-CreERT2 mouse model, investigators found that Lgr5 is expressed within the chief cells of the corpus and are recruited to function as stem cells to regulate epithelial renewal in response to injury.[2] Thus, Lgr5 cells have been shown to play a fundamental role in gastric homeostasis and regeneration.[1,2] In addition, Lgr5-expressing cells also have been identified as a possible cell-of-origin during the development of gastric cancer, specifically within the corpus.[2] However, the mechanisms that regulate the number and function of Lgr5-expressing cells during gastric inflammation in the context of gastric metaplasia have not been well characterized.

There is the accepted notion that gastric metaplasia associated with cancer may reflect the permanent alteration in the behavior of the stem cells. Among the populations of stem cells within the stomach that may be targeted and may lead to the aberrant epithelial cell proliferation and differentiation and thus metaplasia, are cells expressing Lgr5.[3–5] In support of this idea, human studies have shown that there is enhanced Lgr5 expression in patients with progressive dedifferentiation and metastasis of gastric cancer.[5,6] In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Ye et al[7] elegantly show that inflammation and loss of bone morphogenetic protein (BMP) signaling induces the activation of Lgr5-expressing cells. The investigators used a mouse model expressing an inhibition of Bmp signaling in Lgr5+ve cells (*Lgr5*-Cre;Bmpr1a$^{flox/flox}$ mice) that then was infected with *Helicobacter felis*. Evidence from these studies showed that inhibition of Bmp signaling and infection with *Helicobacter* lead to the activation and expansion of Lgr5-expressing cells that importantly then gave rise to a proliferating and metaplastic cell lineage. Specifically, expansion of this cell lineage expressed markers of spasmolytic polypeptide/trefoil factor 2–expressing metaplasia (SPEM). Importantly, the emergence of SPEM in the oxyntic glands was derived from cells with *Lgr5* transcriptional activity. The investigators emphasized that either infection with *H felis* or inhibition of BMP signaling alone caused only incremental changes in the number of Lgr5-expressing cells. However, Lgr5-derived cell lineage expansion into metaplasia in the presence of *Helicobacter* infection was drastically exacerbated in the presence of the inhibition of BMP signaling. In addition, transgenic mice expressing the BMP signaling inhibitor noggin within the gastric epithelium (H^+,K^+-Nog mice) developed epithelial cell hyperproliferation and extensive SPEM in the context of *H felis*–induced inflammation. Collectively, these experiments underscored the importance of BMP signaling in the regulation of *Helicobacter*-induced gastric pathogenesis and epithelial homeostasis.

In the initial studies of the identity of the gastric Lgr5-expressing cells, it was first reported that this population was located at the base of each glandular unit within the adult pyloric/antral region.[1] In fact, Lgr5-positive cells were reported to be absent from the corpus region of the adult stomach.[1] Then, a recent report documented the existence of an Lgr5-positive population identified as quiescent differentiated chief cells that are recruited to function as stem cells during regeneration after injury.[2] In support of the role of chief cells as a source of a reparative metaplastic lineage, our group has reported the emergence of SPEM at the base of the ulcer margin representing a major reparative lineage responsible for healing after gastric ulceration.[8] The study by Ye et al[7] reinforced the expression of Lgr5 within chief cells and the fundamental role of this cell population in the pathogenesis of metaplasia.

Studies in *Lgr5*-Cre;Bmpr1a$^{flox/flox}$ mice have shown that the Lgr5 cell expansion and metaplasia was located within the lesser curvature of the gastric oxyntic (or corpus) mucosa. The stomach is one of the most structurally diverse organs among mammals.[9] In particular, different regions of the stomach respond differently to early transforming factors. For example, individuals most at risk of developing gastric cancer are those in whom the bacteria colonize the corpus (or oxyntic mucosa) of the stomach, when acid secretion is impaired. In contrast, bacterial colonization of the antrum is associated with low levels of inflammation in the corpus, high acid secretion, and the development of duodenal ulcer disease.[10–12] Thus, the findings reported by Ye et al[7] elucidate a plausible pathophysiological mechanism that leads to the development of metaplasia, which predisposes the stomach to cancer.

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Conflicts of interest
The author discloses no conflicts.

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