EDITORIAL

Moving Up a *NOTCH*: Defining the Stem Cell Niche in the Gastric Antrum

Initially intestinal stem cells in the gastrointestinal tract were identified by their mitotic activity and ability to take up and retain radiolabeled nucleotides (eg, tritiated thymidine, bromodeoxyuridine).[1,2] Wnt signaling was subsequently identified as the proliferative signal in the stem cell niche, with downstream targets (eg, Lgr5) expressed by actively cycling cells.[3,4] Although the site of stem cells in the proximal stomach has been linked to the isthmus or "neck" where there is a transition at the upper one-third of the oxyntic gland between the luminal-facing foveolar cells and the midgland parietal cells, only the stem cells in the antral glands of the stomach adjacent to the proximal small intestine show a pattern of mitotic activity marked by Wnt-dependent *Lgr5* expression analogous to the small intestine.[5] The antral stem cell niche is also anatomically defined by an "isthmus," approximately one-third from the crypt base. In the small intestine, the active stem cell niche is defined by 4–5 Lgr5+-WNT-regulated crypt base columnar cells at the base intercalated between Paneth cells, which generate antimicrobial peptides, such as lysozyme and defensins.[6,7] However, despite the similarity in stem cell niches, the signaling pathways of the gastric antrum, also comprised of mitotically active and nondividing support cells, have been less well defined. In this issue, Samuelson and coworkers extend their prior studies by identifying Delta-like1 (DLL1) as the Notch receptor ligand expressed in the nonmitotic stem cell niche that communicates with the actively cycling Lgr5/Notch1/Sox9-positive cells.[8] Because the Lgr5-positive stem cells at the crypt base express the Notch1 receptor, the authors concluded that nonproliferating mucous cells expressing DLL1 form the antral stem cell niche. Based on prior studies, these GSII lectin-positive niche cells are likely TFF2 and Muc6 positive and contribute to Notch-mediated antral tumors through activation of mTor.[9]

Although *Jagged 1* (*Jag1*) was the most abundant Notch ligand in the antral glands, its expression was restricted to the differentiated cell populations of the mid and upper antral gland marked by Muc5AC and FoxQ1.[8,10] However, the Notch1 receptor transcripts were restricted to the stem cell niche below the isthmus suggesting that Jag1 might interact with a receptor other than Notch1 in the upper glandular compartment.[8] Nevertheless, in prior lineage trace experiments, Samuelson and coworkers demonstrated that Notch 1 but not Notch 2 can be detected in differentiated populations in the upper gland, whereas Notch2 did not trace and was only transiently expressed.[11] By contrast, Notch2 transcripts were more strongly expressed in the endothelial and stromal cells of lamina propria. Collectively, these studies show that DLL1 is restricted to the stem cell niche with a switch in Notch ligands to Jag1 expressed by the differentiated cell populations. Thus, future studies need to explore whether the compartmentalization of Notch ligands is essential for antral gland homeostasis and is perturbed during tumorigenesis.

Unlike the small intestine, the gastric antrum is comprised of only actively cycling cells and 2 types of secretory populations: endocrine or mucous. In the small intestine, active Notch signaling promotes the exit of stem cells from the cell cycle followed by differentiation into the absorptive lineage. Moreover, Notch signaling also contributes to stem cell homeostasis in collaboration with Wnts.[12] The overarching function of sustained Notch signaling becomes apparent once homeostasis is perturbed. For example, Carulli et al[13] demonstrated that Notch signaling is required for restitution of the intestinal stem cell niche after acute injury. Likewise, overexpression of the C-terminal domain of the Notch receptor (Notch intracellular domain, NICD) induces transcriptional targets that mediate crypt fission and tumor formation in the antrum but not in the intestine and colon, raising questions regarding why the antrum is more susceptible to Notch signaling. Clearly in the absence of an absorptive lineage, the stem cells are the primary population responding to the proliferative signal.

In summary, Samuelson and coworkers have provided impactful information on the role of Notch signaling in the stomach especially in the antrum through painstaking analysis of complex mouse models and sophisticated imaging. Pharmacologic and antibody treatments have revealed some of the signaling specificity among the 4 receptors and 6 Notch ligands regarding antral stem cell function. Nevertheless, single cell RNA-sequencing (scRNA-Seq) will be essential for refining the phenotypic signatures of the niche-forming mucous cells expressing DLL1 in the stem cell zone versus Jag1 in the differentiated antral cell compartment. How defined cell populations found in the antrum, such as those secreting the hormone gastrin (G-cells), somatostatin (D cells), and serotonin (enterochromaffin cells), emerge will be important, despite known secretory cell suppression by Notch signaling.[14] Such efforts are essential to understanding the role of Notch signaling during injury, inflammation, and tumor formation, an area that has yet to receive the attention it deserves.

JUANITA L. MERCHANT, MD, PhD
Gastroenterology & Hepatology
Department of Medicine
University of Arizona
Tucson, Arizona

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Correspondence
Address correspondence to: Juanita L. Merchant, MD, PhD, 1501 North Campbell Avenue, PO Box 245028, Tucson, Arizona 85724-5028. e-mail: jmerchant@arizona.edu.

Conflicts of interest
The author discloses no conflicts.

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