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EDITORIAL

The Gastric Epithelium: Slow Starter in the Stem Cell/Lineage Specification Stakes?

Stem cell dynamics and lineage specification form the basis of the understanding of the generation of metaplastic and neoplastic states in the gut. Although our knowledge in the intestine has raced ahead, the stomach lags behind. Here, we highlight some of the problems.

There has been a veritable explosion in our knowledge of stem cell identity, dynamics, and lineage specification in the small intestine, and, to a lesser extent, the colon, particularly in relationship to early neoplasia. In the stomach, progress has been less spectacular: given the importance of the cell and molecular changes within the metaplasia/dysplasia/carcinoma sequence in both gastric and esophageal carcinogenesis, this state of affairs is less than satisfactory. The situation is well illustrated by 3 recent articles in *Cellular and Molecular Gastroenterology and Hepatology*: the first of these, Stomach Organ and Cell Lineage Differentiation: From Embryogenesis to Adult Homeostasis,[1] elegantly surveys the present state of our knowledge. Through a variety of techniques there is now a generally accepted map of lineage relationships in the gastric corpus and antrum, quite different areas in terms of cellular content and specification. It is in our understanding of stem cell identity and dynamics, and the relationship of the contained lineages to these stem cells, that wide gaps in our knowledge exist.

Classically, an undifferentiated, granule-free isthmic cell exists as a multipotent stem cell that gives rise to and renews all of the mature corpus cell lineages. Observations using different labeling and morphologic methods in animals (and human beings) agree that corpus glands are clonal, consistent with what might be termed the *single gastric unit stem cell hypothesis*. However, the finding that stable labeling can be restricted to specific single lineages might indicate the presence of long-lived, lineage-committed progenitors, replenishing 1 or perhaps 2 lineages, such as parietal cells and mucous neck/chief cells. However, it is clear from the manner in which proliferative units in the gut are organized that there will, in all probability, be a tissue-specific stem cell, as yet to be recognized, which currently is the elephant in the room. This is not helped by the finding that the apparently terminally differentiated chief cell can act as stem cells and give rise to all the cell lineages within the corpus glands, a finding seemingly unique to the stomach. Unfortunately, investigators of this tissue are faced with experimental problems: tamoxifen or Cre, used in inducible lineage tracing studies, can give anomalous results.

Momentarily, the antral gland appeared simpler, with *lgr5*+ stem cells located at the base of the gland, to which Cck2r+ cells later were added, apparently equivalent to the intestinal crypt. However, this current article does us a service in underlining the fact that cell flux in the antral (and corpus) gland is bidirectional, with the origin of the flux at the isthmus, where the so-called granule-free cells are seen. Thus, the dynamics of the basal *lgr5*+ cells in relationship to the flux parameter here are likely to be complex and interesting: *lgr5*+ cells are multipotent and relatively rapidly cycling, situated at the base, but cells produced in the isthmus are migrating downward toward the *lgr5*+ progeny, which appear to be migrating upward. Perhaps we should not be too surprised, after all, the first Paneth cells in the small intestinal crypt, formed from *lgr5*+ stem cells at the base, appear at the +4 position and then migrate downward against the prevailing flux, upward from the basal *lgr5*+ stem cells. Perhaps bidirectionality is ubiquitous within gastrointestinal crypts and glands.

The other 2 articles, Epithelial Regeneration After Gastric Ulceration Causes Prolonged Cell Type Alterations[2] and The Development of Spasmolytic Polypeptide/TFF2-Expressing Metaplasia (SPEM) During Gastric Repair is Absent in the Aged Stomach,[3] are related but different. The first article makes use of an old observation that the quality of epithelium that covers a healed ulcer is defective, to show that in mice, after induction of gastric ulcers with acetic acid, 30 days after ulceration the regenerated epithelium included spasmolytic polypeptide (SPEM) lineages. In the second article, the same model was used to show that the development of SPEM during gastric repair in response to injury is absent in the aged stomach, but that organoid transplantation in the aged mice led to the emergence of SPEM and gastric regeneration. There has been considerable debate in recent years about the nature and importance of SPEM: produced in mouse corpus by multiple experimental maneuvers, and seen very commonly in both corpus and antrum in human beings, commonly in ulceration (and labeled pseudopyloric metaplasia), has been labeled as a reparative metaplastic lineage and also as a component part of the metaplasia/dysplasia sequence, either directly or through intestinal metaplasia. With its histogenesis in mice through transdifferentiation from chief cells, it remains an enigma: why is it seen so commonly in ulcerative conditions? Is it merely a reparative cell lineage, secreting large amounts of the multifunctional peptide TFF2 (and other goodies) to advance mucosal healing, or is its presence more sinister, and ticks a box in the progression to gastric cancer? Specifically, these current articles point to its reparative function, and may explain why the aging stomach heals less well.

However, in common with the first article, this underlines how little we know about the cell biology of metaplasia and stem cell dynamics within the stomach, our need for new and better models, and how much we need to

relate our experimental findings to the human condition. Evidently there is a great deal to do.

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