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EDITORIAL

Mind the Gap: Crossing Boundaries to Establish Reparative Metaplasia

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Agoston et al[1] report that, in an esophago-jejuno anastomosed rat model, metaplastic columnar-lined esophagus develops within a wound-healing process in the distal edge of a region of ulceration, starting distally at the esophago-jejuno anastomosis. This ulcer migrated proximally, and the length of the columnar-lined esophagus elongated in the time course after the anastomotic surgery. They also concluded that the columnar-lined esophagus was caused through migration of jejunal cells into the esophagus, as the immunoprofile of columnar-lined esophagus was similar to jejunal crypt epithelium.

These new findings address a number of issues. One is that metaplastic columnar-lined esophagus in this model originated from jejunal crypt progenitor cell migration over the anastomosis. Some researchers may think this is not metaplasia, as there is no reprogramming of the stem cells. However, the definition of metaplasia is an endpoint such that a normal lineage is placed in an abnormal position, and it can be called metaplasia even if it is from budding from a jejunal crypt. Furthermore, metaplasia in mucosal tissues is always associated with some injury and subsequent healing response. In this rat model, the metaplasia arose in the process of ulcer healing and was a typical cause of metaplastic lineages. Ulcer-associated mucosal lineage, as described by Sir Nicholas Wright, was first defined in the same rat reflux model, and it evolves from a new pluripotent cell lineage.[2] Therefore, this new finding, columnar-lined esophagus arising from jejunal budding in rodent surgical model should be considered a metaplasia.

The second issue is whether these rodent models are really mimicking human metaplastic columnar lined esophagus or not. Almost all the reported rodent models for metaplastic columnar-lined esophagus are surgically made reflux models. Some have suggested that the metaplastic columnar-lined esophagus in these models results from reprogramming of squamous esophageal epithelia by induction with gastric or jejunal content.[3] Still-increasing evidence suggests that the Barrett's epithelium likely derives from migration of gastric stem cells of the first gland or proximal fundus into the damaged esophageal mucosa.[4,5] In humans, metaplastic columnar-lined esophagus is usually accompanied with gastroesophageal reflux, so the interposition of the jejunum next to esophagus is not completely analogous. In that sense, these rodent models may be different from human metaplastic columnar-lined esophagus. However, it is common to observe an ulcerated lesion in the proximal front of long-segment Barrett's esophagus in human. Thus, by modeling reflux and ulcerative injury, the model of Agoston et al[1] may reflect the phenotype of human metaplastic columnar-lined esophagus. In a previous report of a surgical esophagojejunostomy, mouse metaplastic columnar-lined esophagus model, ulcers at the anastomosis were not always observed.[6] In that report, 1 mouse developed metaplastic columnar island in the forestomach surrounded by squamous epithelium, distant from anastomotic suture, but still exposed to jejunal reflux. From those results, it is likely that metaplastic columnar-lined esophagus in rodent surgical models does not require ulceration at the anastomosis to effect budding from anastomosed jejunal crypts. Many factors and reflux-dependent damage may be associated with metaplastic columnar-lined esophagus arising in rodent models as well as in humans.

In Agoston et al's[1] model, around half of metaplastic columnar-lined esophagus were positive for Pdx-1 as well as jejunum close to anastomosis. Pdx-1 is normally expressed in the gastric antrum, duodenum, and pancreas, and is absent in the esophagus, gastric fundus, and jejunum. The Pdx-1 positivity in the jejunum close to the anastomosis is interpreted by the authors as supportive for intestinal crypt budding origin of metaplastic columnar-lined esophagus. However, Pdx-1 is originally negative in jejunum. Gastric intestinal metaplasia was reported to be positive for Pdx-1, suggesting duodenal metaplasia than general intestinal metaplasia.[7] The anastomosis between organs not adjacent to each other originally could cause other milieus than natural. The neighboring of Sox2-positive squamous epithelium and Cdx2-positive intestinal glands may cause Pdx-1–positive duodenal reprogramming in mucosa close to the anastomosis, even in the jejunal crypt, without morphological changes. Indeed, pyloric metaplasia can be observed in the context of duodenal ulcer or Crohn's disease, likely synonymous with ulcer-associated mucosal lineage.[8,9] This generalized formation of a pyloric type metaplasia in the face of significant injury may be a ubiquitous solution to severe mucosal damage. Nevertheless, the evidence that stem or progenitor cells from a columnar mucosa can migrate into a region of mucosal damage in the esophagus also demonstrates the potential for such cells to establish metaplastic mucosa as a solution for healing mucosal erosion.

Thus, the studies of Agoston et al[1] have reinforced our knowledge of the ability of mucosae to adopt metaplasia as a healing process through migration of stem or progenitor cells, often through a substantial distance, to affect the establishment of a reparative metaplasia. The establishment of a reparative metaplasia in the face of acute injury is likely separable from eventual carcinogenesis that may occur in the setting of chronic injury and metaplasia.

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Conflicts of interest
The authors disclose no conflicts.


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