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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Of Mice and Men and Metaplasia

Metaplasia, the process in which one type of adult tissue replaces another, is a consequence of chronic tissue injury.[1] In the esophagus, gastroesophageal reflux disease (GERD) is the condition that chronically injures the squamous epithelium and causes its replacement by the intestinal-type, columnar epithelium of Barrett's esophagus.[2] The cell of origin for this columnar metaplasia remains unknown, but a number of candidates have been proposed. For example, GERD might cause mature esophageal squamous cells to change into columnar cells (transdifferentiation) or stimulate immature esophageal progenitor cells (in the squamous epithelium or in the ducts of esophageal submucosal glands) to differentiate abnormally into columnar cells (transcommitment).[3] It also has been suggested that Barrett's metaplasia results when progenitor cells in the gastric cardia or residual embryonic-type cells at the gastroesophageal junction migrate proximally to repair GERD-damaged squamous epithelium.[4,5] Finally, it has been proposed that circulating stem cells from the bone marrow might be recruited to the GERD-damaged esophagus, where they differentiate into columnar cells.[6] Animal models have been used to explore all of these hypotheses.

Animal models of Barrett's esophagus have used dogs, pigs, rats and mice, and most have involved surgical manipulations that induce GERD to produce a Barrett's-like, intestinal metaplasia. Unfortunately, all animal models of human disease have limitations. Large animals such as dogs and pigs are expensive and are not easily manipulated at the genetic level. Rats and mice are less expensive and more readily manipulated genetically, but the rodent foregut structure differs substantially from the human. Unlike humans, rats and mice have a squamous-lined forestomach, and their esophagus is lined by a stratified squamous epithelium that is keratinized, and that lacks stromal papillae and submucosal glands. Esophageal surgery is technically more demanding in mice than in rats, and mice have higher surgical mortality rates and lower rates of metaplasia development than rats do.[7] Consequently, rats have been used most frequently as animal models for Barrett's esophagus. Genetic engineering is far more readily accomplished in mice than in rats, however. Lineage tracing techniques might be especially useful for identifying the Barrett's cell of origin, and the sophisticated genetic engineering that would be required for such studies can be performed readily in C57Bl/6J mice.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Terabe et al[8] report results of their studies on the development of esophageal columnar metaplasia in C57Bl/6J mice subjected to 3 different GERD-inducing operations: (1) esophagogastrojejunostomy (EGJ) in which the jejunum is connected side-to-side to the junction between the esophagus and the stomach, (2) esophagojejunostomy (EJ) in which the esophagus is transected and connected end-to-side to the jejunum with the stomach left intact, and (3) gastrectomy and EJ (GT/EJ) in which the esophagus is transected, the stomach is removed, and the esophagus is connected end-to-side to the jejunum.[8] The operative mortality rate was similar for all 3 operations (approximately 13%). Forty weeks after operation, metaplasia developed in 45.5% of mice treated with EGJ, whereas no mouse in the EJ group developed metaplasia, and only 15.4% in the GT/EJ group developed metaplasia. Dysplasia developed in 21.2%, 0%, and 2.6% of mice in the EGJ, EJ, and GT/EJ groups, respectively. This report documents that, as a mouse model for Barrett's esophagus, EGJ can be performed with relatively low operative mortality and with a reasonable rate of developing metaplasia and dysplasia.

In a Barrett's model such as the EGJ mouse that has an anastomosis between the small intestine and the esophagus, an issue that arises is whether the intestinal metaplasia that develops in the reflux-damaged esophagus merely represents an upgrowth of normal intestine. Although such an expansion of normal epithelium into an abnormal area might be considered a metaplasia (ie, one adult tissue type replacing another), it would differ considerably from human Barrett's metaplasia that must arise from a nonintestinal precursor cell and that exhibits gastric as well as intestinal differentiation. Terabe et al's observation that, in 80% of cases, the esophageal columnar metaplasia in the EGJ mouse expressed PDX1 (pancreatic and duodenal homeobox 1, a transcription factor expressed by duodenum but not by jejunum) indicates that its pathogenesis involves more than just the upgrowth of normal jejunal epithelium. Nevertheless, an intestinal progenitor might well be the cell of origin for the esophageal metaplasia in the EGJ mouse. This, combined with the major interspecies differences mentioned previously, limits the conclusions that can be drawn from this animal model regarding the origin of human Barrett's esophagus.

Despite the limitations, there is much to be learned from Terabe et al's mouse models of Barrett's metaplasia. As mentioned, some earlier mouse models suggested that Barrett's metaplasia develops from progenitor cells in the gastric cardia or from residual embryonic-type cells at the gastroesophageal junction.[4,5] Terabe et al's observation that the mouse esophagus can develop intestinal metaplasia after total gastrectomy, which removes the gastric cardia and gastroesophageal junction, shows that these structures are not necessary prerequisites for esophageal metaplasia. Esophageal submucosal glands also are not prerequisites, as mice lack those submucosal glands. However, the hypotheses proposed to explain Barrett's pathogenesis need not be mutually exclusive. It is certainly conceivable that there are

multiple potential cells of origin for and possible pathways to Barrett's esophagus in animals and in humans. Terabe et al's elegant demonstration of a reasonable C57Bl/6J mouse model of Barrett's metaplasia paves the way for the lineage tracing experiments needed to confirm the identity of Barrett's cells of origin.

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Conflicts of interest
The author discloses no conflicts.

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