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Esophageal Stem Cells, Where Art Thou?:

Are there stem cells in the esophagus or not?

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Replenishing the esophagus

The lumen of the esophagus is lined with a squamous stratified epithelium. In the model of Doupé *et al.* (based on the mouse esophageal epithelium), a single population of epithelial progenitor cells (yellow) is present above the basal lamina. The epithelium is maintained, under basal conditions, by these cells, which divide and produce both more progenitor cells or differentiate into the layers of the stratified epithelium

The stem cell biology of the esophageal epithelium is an unresolved area in biomedical research. The field has major clinical implications, as esophageal cancer is a common cause of malignancy-related death, accounting for more than 500,000 deaths per year worldwide (1). Despite decades of research, there is little consensus regarding how this epithelium is maintained. On page XXX of this issue, Doupé *et al.* (2) show that the esophageal epithelium is generated by a single population of cells that divide randomly into differentiated or proliferative progeny. Their finding contrasts with the prevailing hypothesis that stem cells underlie homeostasis of the tissue.

The esophageal epithelium constitutes the protective lining of the esophagus. The tissue is composed of stratified squamous epithelial layers that arise from above the basal lamina (a basement membrane) and suprabasal cells (more superficial layers -- see the figure). In response to gastroesophageal reflux, the esophageal epithelium undergoes metaplastic change in which squamous epithelium is replaced by columnar and secretory epithelial cells. This condition, known as Barrett's esophagus, is associated with increased risk of esophageal cancer.

Surprisingly little is known about the lineage mechanism of tissue homeostasis in the epithelial lining of the esophagus. Studies of human tissue suggest that stem cells give rise to the esophageal epithelium through asymmetric cell divisions (3). Properties of putative progenitors from human esophagus have been characterized in vitro (4), and a population of cells isolated from the mouse epithelium could be expanded in vitro and contribute to esophageal epithelium when transplanted into injured tissue (5). But the contribution of such candidate stem cells to normal or injured growth of the esophageal epithelium wasn't defined. As a result, their existence and functional importance has remained in doubt (6, 7). If stem cells don't maintain esophageal epithelium, what are the properties of the cells that do?

Doupé *et al.* determined the presence of populations of infrequently dividing cells in the mouse esophageal epithelium by using a technique that labels histones (proteins associated with chromatin in genomic DNA) in vivo. Unexpectedly, the only slow-cycling cells that

retained the label were Langerhan's cells and T lymphocytes. These immune cells are likely present in the esophageal epithelium to perform immune surveillance functions, rather than for tissue replenishment. Notably, candidate stem cell markers observed in previous studies in the esophagus or other tissues were not present in the label-retaining cells or other cells of the esophageal epithelium. This indicates that slowly dividing cells do not contribute to the tissue homeostasis of esophageal epithelium, and further suggests that the tissue is somehow maintained by another lineage mechanism.

To further characterize the kinetics of esophageal epithelium maintenance, Doupé *et al.* labeled (using a genetic approach) a small number of cells in the esophageal epithelium and then followed their fate. Labeling in the basal lamina correlated with the total number of labeled suprabasal cells above, consistent with the idea that the esophageal epithelium is maintained by cell division from cells within the basal lamina (see the figure). The authors also waited for a period after inducing labeling before analysis and observed that the number of labeled cells in the basal lamina increased, implying that the original labeled cells divided to generate more such cells (and thus retained the label). These observations indicate that the epithelium is maintained by random cell division within an apparently homogeneous cell population in the basal lamina. This pattern is consistent with scaling behavior (i.e., scale invariance) observed in a power-law relationship, equivalent to the growth pattern of the inter-follicular epidermis (Clayton...Jones, Nature 2007). Notably, these observations are inconsistent with a stem cell contribution to esophageal epithelium, in which the clone size of labeled cells would not have been expected to progressively increase.

Doupé *et al.* further investigated tissue homeostasis under dynamic (rapid cell growth) conditions. Although treatment of the mouse esophageal epithelium with the growth-accelerating chemical retinoic acid did cause an increase in the number of cells in the stratified epithelium, the lineage relationships of the epithelial cells were the same as those observed under normal conditions. These studies imply that a single population of esophageal progenitors maintains tissue homeostasis during normal and accelerated growth. Doupé *et al.* also modeled wound healing using an endoscopic biopsy technique. They observed a migrating front of proliferating cells that are clonally related, suggesting that highly proliferative cells within the epithelium can participate in tissue regeneration. Complementary histone-labeling studies suggest that virtually all nearby cells participate in regeneration. Wounding preferentially accelerated the cell division rate of these epithelial progenitor cells without altering differentiation. As a result, the authors make the surprising conclusion that wounding leads to an expansion of proliferating daughter cells, thus enabling a single population of epithelial progenitors to effectively switch from normal tissue homeostasis to wound healing.

Homeostasis of tissues such as the esophageal epithelium remains an important field with major clinical implications. Given that basal and regenerative tissue homeostasis appears to be maintained by a single population of esophageal progenitors, a major challenge is to determine the safeguards that maintain normal growth in the esophageal epithelium, and to unravel how such mechanisms fail during oncogenic transformation in the development of esophageal cancer.

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