Biology of Barrett's Esophagus and Esophageal Adenocarcinoma

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- Esophageal adenocarcinoma

Although overall cancer incidence in the United States has decreased in recent years,[1] the number of new cases of esophageal cancer is increasing.[2] According to American Cancer Society estimates, there were 16,470 new cases and 14,530 deaths in this country in 2009 from esophageal cancer.[3] Esophageal cancer has 2 main histologic subtypes: squamous cell carcinoma and adenocarcinoma. In the west, the incidence of the squamous cell carcinoma has remained stable or decreased since the 1970s; the incidence of adenocarcinoma has risen steadily during the same time period.[2] Esophageal adenocarcinoma has now become the more prevalent histologic subtype in the United States.[2]

Esophageal adenocarcinoma typically arises in the distal one-third of the esophagus, and its main risk factors are gastroesophageal reflux disease (GERD) and Barrett's esophagus. For patients with Barrett's esophagus, endoscopic surveillance to detect dysplasia is the primary strategy recommended to decrease morbidity and mortality from esophageal adenocarcinoma.[4] This strategy has not proved effective, as shown by the increasing incidence of esophageal adenocarcinoma and the results of a recent study showing that most patients with this cancer have no prior diagnosis of Barrett's esophagus and, therefore, are not enrolled in surveillance programs.[5]

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Basic investigations that have defined the genetic events underlying colonic carcinogenesis have led to effective strategies for the management and prevention of colorectal cancer.[6] Analogously, it is important to understand the molecular carcinogenesis of Barrett's esophagus to identify specific targets to guide the development of effective diagnostic strategies and novel therapeutic agents. To do this, the molecular events that lead to the replacement of normal esophageal squamous cells by metaplastic Barrett cells must first be understood. Building on this understanding, we can appreciate how the genetic abnormalities acquired by metaplastic Barrett cells disrupt their normal properties so they can take on the morphologic and physiologic features of dysplasia and cancer. This report provides a conceptual basis for how normal esophageal squamous cells undergo columnar metaplasia and how metaplastic Barrett cells progress to dysplasia and carcinoma. Some of the main genetic alterations involved in the development and neoplastic progression of Barrett's esophagus are reviewed; however, these represent a fraction of the genetic changes required for the making of Barrett metaplasia, dysplasia, and esophageal adenocarcinoma.

THE MAKING OF BARRETT METAPLASIA

Most, if not all, esophageal adenocarcinomas arise from Barrett's esophagus, the condition in which the normal squamous cells lining the distal esophagus are replaced by intestinal-type columnar cells.[7] Barrett's esophagus develops through the process of metaplasia, the replacement of one adult cell type by another. Metaplasia is believed to arise as a protective response to chronic tissue inflammation,[8] which in the esophagus is believed to be caused by GERD. Barrett metaplasia can result from either fully differentiated esophageal squamous cells changing directly into intestinal-type columnar cells or from changing the differentiation pattern of esophageal stem cells.[8]

METAPLASIA THROUGH TRANSDIFFERENTIATION

Transdifferentiation is the switch of one fully differentiated cell type directly into another. In general, this switch occurs between cell phenotypes that were present in the organ during embryonic development.[8] During embryogenesis, the esophagus is initially lined by ciliated columnar cells, which are replaced by stratified squamous cells as maturation proceeds (**Fig. 1**).[9,10] Data from ex vivo organ cultures of embryonic mouse esophagus demonstrate direct conversion of the columnar cells lining the esophagus into squamous cells, a process found to be independent of cell proliferation or apoptosis.[11] In theory, a reversal of this normal developmental switch in cell phenotype may occur during the formation of Barrett metaplasia. In support of this hypothesis, studies using scanning electron microscopy have demonstrated a distinctive cell at the squamocolumnar junction in Barrett mucosa that expresses cytokeratin markers and demonstrates morphologic features of both squamous and columnar epithelium; moreover, this distinctive cell has not been detected at the squamocolumnar junction in patients without Barrett mucosa.[12] Once Barrett metaplasia is established, the epithelium must undergo maintenance and self-renewal, processes that are not explained by the transdifferentiation hypothesis, however.

METAPLASIA THROUGH STEM CELLS

Stem cells can proliferate, self-renew, give rise to a variety of cell types, and regenerate tissue after injury.[13] A stem cell origin would account for the persistence and maintenance of Barrett epithelium and could explain the predisposition of this tissue