Barrett's esophagus: recent insights into pathogenesis and cellular ontogeny

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Esophageal adenocarcinoma (EAC) has increased 6-fold in its incidence in the last 2 decades. Evidence supports the hypothesis of stepwise progression from normal squamous epithelium → reflux esophagitis → metaplasia (Barrett's esophagus, BE) → dysplasia → adenocarcinoma. The precursor, BE, stands as the bridge connecting the widespread but naive reflux disease and the rare but fatal EAC. The step of metaplasia from squamous to intestine-like columnar phenotype is perhaps pivotal in promoting dysplastic vulnerability. It is widely accepted that chronic inflammation because of gastroesophageal reflux disease leads to the development of metaplasia, however the precise molecular mechanism is yet to be discovered. Additionally, how this seemingly adaptive change in the cellular phenotype promotes dysplasia remains a mystery. This conceptual void is deterring further translational research and clouding clinical decision making. This article critically reviews theories on the pathogenesis of Barrett's esophagus and the various controversies surrounding its diagnosis. We further discuss unanswered questions and future directions, which are vital in formulating effective preventive and therapeutic guidelines for Barrett's esophagus. (Translational Research 2015;166:28–40)

Abbreviations: AFAP = attenuated familial adenomatous polyposis; Agr2 = anterior gradient protein 2 homolog; BAR-T = telomerase-immortalized, non-neoplastic, human Barrett's cell line; BE = Barrett's esophagus; BMI = body mass index; BMP-4 = bone morphogenetic protein 4; BSG = British Society of Gastroenterology; CCK2 = cholecystokinin B; CDX1 = caudal-type homeobox 1; CDX2 = caudal-type homeobox 2; CLE = columnar-lined esophagus; DCA = deoxycholic acid; EAC = esophageal adenocarcinoma; ESEM = endoscopically suspected esophageal metaplasia; GBE = goblet cell BE; GEJ = gastroesophageal junction; GERD = gastroesophageal reflux disease; GFP = green fluorescent protein; GRCL = gut regenerative cell lineage; HGD = high-grade dysplasia; HH = hedgehog; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; IL = interleukin; LGD = low-grade dysplasia; LSBE = long segment BE; MHC = major histocompatibility complex; MLE = multilayered epithelium; NGBE = nongoblet cell BE; OR = odds ratio; PPI = proton pump inhibitor; PTCH = patched; RA = retinoic acid; RE = reflux esophagitis; SERM = selective estrogen receptor modulator; SMO = smoothened; SSBE = short segment BE; TFF = trefoil factor family; Th1 = T helper cells type 1; Th2 = T helper cells type 2; TLR5 = toll-like receptor 5; USBE = ultrashort segment BE; *Vil1* = villin 1; WNT = wingless

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INTRODUCTION

Esophageal adenocarcinoma (EAC) poses an alarming health risk considering its rising incidence.[1] Despite advances in multimodality treatment, it continues to carry an extremely poor prognosis with a 5-year survival of <20%.[2] EAC is clinically silent in early stages and usually presents at an advanced stage. It is believed that EAC develops through the stages of metaplasia-dysplasia-carcinoma. Barrett's esophagus (BE), the metaplastic stage, is by far the strongest predisposing factor for adenocarcinoma development[3] and arises secondary to long-standing gastroesophageal reflux disease (GERD)-induced chronic inflammation. Rationally, BE has been the threshold for initiating interventions to halt disease progression. However, only 5%–10% of patients with GERD develop BE.[4] In addition, about 0.5%–1% of BE progresses to EAC and only 5%–10% of patients with EAC have a prior diagnosis of BE.[5] This can be attributed to silent character of the lesion but also to the possibility that BE may be an epiphenomenon and have little to do with promoting dysplasia. Although this view stands contrary to the present view, it cannot be completely dispelled until the pathogenic pathways are precisely established. The detection and surveillance of BE stands as a clinical enigma today and elucidating the pathogenesis of BE is vital for formulating effective preventive and therapeutic guidelines for clinical management of BE.

Many new etiologic factors and cell signaling pathways have been found recently to be involved in the pathogenesis of BE. Interestingly, studies have recently revealed close semblance between BE and EAC at the genetic and epigenetic level.[6,7] This evokes interest in investigating the origin and mechanism of the initiation and development of BE to identify the exact stage at which dysplastic vulnerability sets in. BE has been shown to imitate the lining of the embryonic foregut. This has fueled research interest into elucidating dynamics of carcinogenic ignition within this reprogrammed epithelium.

EPIDEMIOLOGY OF BE

BE per se is asymptomatic and given the lack of population wide endoscopic screening, the reported prevalence of BE remains a rough estimate at best. It has been estimated widely to be between 1.6% and 6.8% in the western hemisphere.[8,9] Incidence of EAC in BE was reported in earlier studies to be around 0.5%, but more recently it has been found to be much lower ranging from 0.12% to 0.39%.[10,11]

BE has been shown to have a bimodal distribution with 2 groups being children aged <10 years and adults aged >40 years. This has stemmed 2 differing schools of thought on its etiology, congenital and acquired. No change in BE length even on prolonged follow-up[12] and conceptual similarity with gastric heterotopia in Meckels diverticulum favor congenital etiology. Against this theory is the strong dose-dependent association with reflux and other environmental risk factors and acquisition of BE after Heller myotomy and after esophagectomy because of augmented reflux. Barrett in 1950[13] proposed that the columnar-lined epithelium was part of intrathoracically pulled up stomach mucosa because of a congenitally foreshortened esophagus. A decade later in the early 1960's, Moersch et al[14] were the first to suggest that the columnar lining might be an acquired condition because of reflux esophagitis (RE), which destroys the squamous epithelium. This concept gained wide acceptance when Bremner et al in 1970[15] reported columnar cell regeneration in the distal esophagus in a canine experimental model of chronic gastroesophageal reflux.

A prospective study by Nguyen et al[16] strongly established for the first time that congenital BE is very rare or rather nonexistent. Oezcelik et al[17] threw light on the trend of BE and EAC affecting younger population aged <40 years with salient differences in presentation and aggressiveness of the disease in this population. This subgroup was more asymptomatic and went on to develop dysplasia and cancer earlier compared with those aged >40 years. This may warrant corresponding changes in screening guidelines.

Risk factors. The current understanding of the etiology of BE is derived from epidemiologic studies for its risk factors. These are older age, male gender, Caucasian ethnicity, high socioeconomic status, chronic GERD, smoking, and central adiposity.[18] Risk factors can be subclassified into environmental and host factors.

Genetic risk factors. There is remarkable gender and racial skewing in the incidence and prevalence of BE pointing to the importance of these nonmodifiable risk factors in the development of BE.[18] Increasing number of studies reveal genetic associations with BE. Furthermore, numerous reports show familial clustering of BE cases. Genetic factors are dealt in depth later in the review.

Environmental risk factors. Environmental factors have earned more support, as the environmental changes can be rationally held responsible for the steep escalation in the incidence of BE and EAC. These include rise in obesity, decrease in Helicobacter pylori infections, use of antibiotics and proton pump inhibitors (PPIs), and change in diet composition especially nitrates and minerals. These factors are discussed in detail later in this review.