Is Acid Reflux Important in the Progression from Barrett’s Esophagus to Esophageal Adenocarcinoma?

Weibiao Cao*
Department of Medicine and Pathology, Rhode Island Hospital and Warren Alpert Medical School of Brown University, USA

Esophageal adenocarcinoma (EA) has increased in incidence over the past three decades, and in the last 10 years at a rate exceeding that of any other cancer [1]. EA is characterized by a uniformly poor prognosis, with a median survival time following diagnosis of less than 18 months, and a five-year survival rate of less than 20% in operable tumors [2]. Other than surgical resection of early stage disease, no other therapies alter its clinical course.

Gastro-esophageal reflux disease complicated by Barrett’s esophagus (BE) is a major risk factor for esophageal adenocarcinoma. However, mechanisms of the progression from BE to EA is unknown. Acid reflux and reflux-induced inflammation may play an important role in the progression. Ambulatory pH studies show that the total exposure time of esophageal luminal pH < 4 is 1.5-16 hours per day in BE patients, which is greater than in patients with GERD [3,4]. It has also been reported that acid exposure induces DNA damage in human esophageal cell lines [5,6]. Cultured biopsy specimens of intestinal metaplastic cells demonstrate a significant increase in tritiated thymidine uptake when the explants are briefly exposed to acid, suggesting that in Barrett’s specimens brief, episodic acid exposure is sufficient to promote tumorigenesis by stimulating hyperproliferation [7]. Long-term inhibition of esophageal acid exposure by administration of proton pump inhibitors (PPI) to patients with BE has been shown to decrease proliferation of metaplastic cells [8] and an effective anti reflux surgery may reduce the risk of Barrett’s progression [9]. In addition, a prospective study showed that PPI treatment reduces the risk of EA [10] and significantly reduced the incidence of dysplasia in BE patients, when compared with no therapy or treatment with H2 receptor antagonist [11]. These data are consistent with our experience at RI Hospital. In the RI Hospital GI clinic, 150 patients with BE have been treated with high doses of PPI and followed up for 4-20 years. Only one patient has so far developed high-grade dysplasia on treatment.

In contrast, 14 untreated patients seen over a 4-year period developed high-grade dysplasia or EA, and one of them developed high-grade dysplasia after he stopped using PPI for one year. These data suggest that acid exposure may play an important role in the progression from metaplasia to dysplasia and to EA in patients with BE.

The mechanisms whereby acid reflux may accelerate the progression from BE to EA are not known. Reactive oxygen species (ROS) may be an important factor mediating acid reflux-induced damage. ROS may damage DNA, RNA, lipids and proteins, leading to increased mutation and altered functions of enzymes and proteins. High levels of ROS are present in BE and in EA.

We have shown that NOX5-S is the major isoform of NADPH oxidase, an enzyme producing ROS, present in EA cells [12] and may play an important role in this progression. Acid-induced NOX5-S expression depends on an increase in intracellular calcium and activation of CREB [13]. NOX5-S-derived reactive oxygen species may contribute to increased proliferation, decreased apoptosis [13] and DNA damage [unpublished data] in esophageal adenocarcinoma cells. The mechanisms of NOX5-S-mediated increase in cell proliferation are not fully understood. Two mechanisms may be involved in NOX5-S-mediated increase in cell proliferation. One mechanism may be through activation of cyclooxygenase-2 (COX2) and increase of prostaglandin E2 [14]. A second mechanism may be via p16 hypermethylation which inactivates p16 [12]. Hypermethylation of the p16 gene promoter is present at a much higher frequency in Barrett’s esophagus with dysplasia and EA than in Barrett’s intestinal metaplasia. We have shown that exogenous H2O2 significantly increases p16 promoter methylation and cell proliferation. Acid treatment significantly increases p16 promoter methylation and decreases p16 mRNA level. Acid-induced p16 promoter hypermethylation is mediated by activation of NOX5-S [12]. These data support the second mechanism.

In summary, acid reflux and reflux-induced inflammation may play an important role in the progression from BE to EA. Acid exposure may upregulate NOX5-S in Barrett’s metaplastic cells. NOX5-S-derived ROS enhance PGE2 production via over-expression of COX2 and down-regulate p16 via hypermethylation of p16 gene promoter (Figure 1).

Figure 1: NOX5-S mediates acid-induced increase in cell proliferation and decrease in apoptosis.

*Corresponding author: Weibiao Cao, MD, Department of Medicine and Pathology, Rhode Island Hospital and Warren Alpert Medical School of Brown University, 55 Claverick St, Room 337, Providence, RI 02903, USA, E-mail: wcao@hotmail.com

Received April 08, 2012; Accepted April 10, 2012; Published April 12, 2012

Citation: Cao W (2012) Is Acid Reflux Important in the Progression from Barrett’s Esophagus to Esophageal Adenocarcinoma?. J Gastroint Dig Syst 2: e108. doi:10.4172/2161-069X.1000e108

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1). Upregulation of COX2 and downregulation of p16 increase cell proliferation and decrease apoptosis in these cells. Persistent acid reflux present in BE patients may cause changes including high levels of ROS, increased cell proliferation and decreased apoptosis, which may lead to DNA damage and increased mutations and thereby contribute to the progression from metaplasia to dysplasia and to EA. Therefore, high doses of PPI treatment may be important in preventing the progression.

Acknowledgement

Our studies are supported by NIDDK R01 DK080703.

References