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Review of genomics of Barrett's esophagus and esophageal adenocarcinoma

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Abstract

In Barrett's esophagus, esophageal epithelium is replaced by intestinal type columnar epithelium. Esophagogastroduodenoscopy, endoscopic ultrasonography and biopsy are advanced diagnostic tools for Barrett's esophagus. Histological corroboration of endoscopically visible columnarisation results in highest diagnostic accuracy. Surveillance endoscopy with an intensive biopsy every 3 months is recommended after dysplasia is identified. Endoscopic ablation is the first line therapy in that case. Ablation can result in squamous re-epithelialization although rests of glandular metaplasia may remain beneath the neo-squamous epithelium Thus ablation remains experimental until further prospective randomized studies. Surgical resection alleviates the symptoms of acidic reflux but does not decrease the risk of progression from Barrett's esophagus to esophageal adenocarcinoma. Protein pump inhibitors have been linked to a decreased risk of developing esophageal adenocarcinoma, if they are used for more than 2 to 3 years. However, it is unknown whether they can inhibit progression from Barrett's esophagus to esophageal adenocarcinoma. Linkage between proton pump inhibitors and the genomics of the Barrett's esophagus and esophageal adenocarcinoma is still unclear yet. Studies have focused on the risks of the long term suppression of gastric acidity in the prevention and treatment of Barrett's esophagus. However, only few studies are available regarding genomics of this condition. In this review we discuss the genomics of Barrett's esophagus and esophageal adenocarcinoma. We try here to collect the most recent data on this topic and make it readily available for researchers and reviewers.

Introduction

Barrett's esophagus is defined as metaplasia in the distal esophageal cells; in which normal stratified squamous epithelium is replaced by intestinal type columnar epithelium as an adaptation to the acidic environment of gastric reflux. it can be classified as long segment or short segment. Short segment disease is less than three centimeters in length, and has short symptoms duration, in addition, patients with short segment disease have normal lower esophageal sphincter pressure and experience only upright reflux on a 24 hour pH test. Long segment disease is more than three centimeters in length and has longer symptoms duration. Barrett's esophagus is associated with erosions and ulceration of the normal mucosa [1-5]. This condition is most commonly diagnosed in white males in their 50s with a history of gastroesophageal reflux, pyrosis, acid regurgitation, and sometimes dysphagia. Histological corroboration of endoscopically visible columnarisation results in highest diagnostic accuracy [6].

Barrett's esophagus is present in 1% to 2% of the general population but up to 14% of patients with gastric reflux. It is associated with a 30- to 125-fold increased risk of esophageal adenocarcinoma (EAC) as a result of metaplasia, and low and high grade dysplasia [7]. Once dysplasia is identified, endoscopic ablation is a choice for treatment. Ablation can result in squamous re-epithelialization although rests of glandular metaplasia may remain beneath the neo-squamous epithelium in up to 60% of patients. The significance of these rests is unknown as is the optimal ablative technique, Thus ablation remains experimental until further prospective randomized studies [6]. On the other hand, surgical resection alleviates symptoms from acidic reflux but doesn't decrease the risk of progression from Barrett's esophagus to EAC. EAC is an aggressive tumor with a poor prognosis, it is diagnosed most commonly in white men in their 50s, there is often metastasis at diagnosis [8,9], and the 5 year survival rate is 13.4% while the 10 year survival rate is 10.2% [10,11]. As per the National Cancer Institute the overall 5-year survival rate in the Surveillance, Epidemiology, and end results database is 16.8% [12]. EAC is the eighth most common and the sixth most lethal cancer in the world [13]. In the United States, an estimated 16,470 new cases and 14,530 deaths from this disease were expected in 2009 [14]. The disease's genomic background has been established for many cancers. Barrett's esophagus can be easily visualized and biopsied using endoscopy, the technique makes it easy to monitor this premalignant state and perform endoscopic surveillance, and genomic studies [15,16]. Evidence shows that loss of heterozygosity (LOH, which was used recently to demonstrate that premalignant lesions situated around the tumor consist of different clonal lineages), methylation and mutations that lead to the inactivation of CDKN2A, are early events that lead to clonal expansion in the Barrett's esophagus tissue [17-19]. In the absence of CDKN2A, inactivation of TP53 by mutation and LOH

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Table 1. Summary of genomic findings of Barrett's esophagus.

	Chromosome		
Mutations\Oncogene	**Gain**	**Loss**	**Rearrangement**
TP53	1q	4pq	1p
APC3	3q	5q	3q
CDKN2A	5p	9p	11p
MCC	6p	14q	22q
retinoblastoma 1	7pq	16q	
DCC	8q	17p	
NO MUTATION IN DPC4	11	18q	
ERBB2	12q	21	
EGFR	13q	Y	
SRC	14		
Histidine	15q 17q 18p 20q Xpq		

is subsequently linked to progression, from increased 4N fractions (G2/tetraploidy), to aneuploidy and EAC [20]. A cytogenic analysis of Barrett's esophagus showed losses of chromosomes 4, 18, 21 and Y, and gains of 14 and 20. Nevertheless rearrangements were seen on 1p, 3q, 11p, and 22q [21]. For adenocarcinomas around the gastroesophageal junction in situ hybridization analyses using chromosome-specific centromeric probes showed gains of chromosomes 6, 7, 8, 11, and 12 and losses of 17 and Y [22]. Losses were commonly seen on 4pq, 5q, 9p, 14q, 16q, 17p, 18q, 21q, and Y, and gains were seen on 1q, 3q, 5p, 6p, 7pq, 8q, 12q, 13q, 15q, 17q, 18p, 20q, and Xpq [15-19]. Loss of 14q31-q32.1 was detected at a significantly higher frequency in Barrett's esophagus-related EAC than in gastric cardia cancers [22]. In adenocarcinomas, LOH detected allelic imbalance on 4q, 5q, 9p, 13q, 16q, 17p, and 18q suggesting the involvement of the APC3, MCC, CDKN2A, retinoblastoma 1, TP53, and DCC genes [22-24]. Moreover mutations were detected in TP53 and APC [25]. No mutations were found in DPC4, making the involvement of DPC4 unlikely [22]. Protein expression studies have attempted to determine whether EAC of Barrett's esophagus has elevated expression of ERBB2 and EGFR which are oncogenes, nevertheless these oncogenes were elevated in only a few cases with dysplasia [25,26]. In metaplastic tissue SRC oncogene and histidine triad elevated. Polyploidy and aneuploidy are two other early events in Barrett's esophagus [27-30]. Table 1, summarizes the findings mentioned above. Candidate region analysis, lowresolution conventional comparative genomic hybridization, and low-density single nucleotide polymorphism arrays have identified many of the chromosomal aberrations involved in the progression from Barrett's esophagus to EAC.

Several well-known tumor suppressor genes and oncogenes have been implicated, including p16, p53, p21, APC, Rb, SMAD4, Myc, K-ras, EGFR, cyclins, and CDKs. However, except for the deletion of 9p21 across different histologic stages and the LOH of p53 at later stages, the results for other chromosomal aberrations are highly heterogeneous in terms of stage, frequency, and size.

Conclusion

Currently no specific biological or genetic marker is available for predicting the progression of Barrett's esophagus to EAC although we know that most cases of EAC start as Barrett's esophagus. Although many linkages have been hypothesized, further studies are needed to determine more genetic correlation.

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