Genetic and Epigenetic Alterations in Barrett's Esophagus and Esophageal Adenocarcinoma

Andrew M. Kaz, MD[a,b,c], William M. Grady, MD[b,c,*], Matthew D. Stachler, MD, PhD[d], Adam J. Bass, MD[e]

KEYWORDS

• Barrett's esophagus • Esophageal adenocarcinoma • Cancer genomics • LOH • Aneuploidy • Genomic instability • DNA methylation

KEY POINTS

- Genetic and epigenetic alterations play a central role in the formation of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC).
- Global epigenetic alterations occur early in the BE to EAC sequence.
- Genomic analysis of EAC and BE has revealed a set of commonly altered genes that are likely drivers of cancer formation in the esophagus.
- There is considerable genetic and epigenetic heterogeneity in BE and EAC.

INTRODUCTION

Esophageal cancer can be separated into 2 major histotypes, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma, and is the eighth most

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[a] R&D Department, VA Puget Sound Health Care System, 1660 South Columbian Way, S-111-Gastro, Seattle, WA 98109, USA; [b] Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA, USA; [c] Department of Internal Medicine, University of Washington School of Medicine, 1959 NE Pacific Street, Seattle, WA 98195, USA; [d] Department of Pathology, Brigham & Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; [e] Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA
* Corresponding author. Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, D4-100, Seattle, WA 98109.
E-mail address: wgrady@fhcrc.org

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common cancer worldwide.[1] The incidence of EAC has been rising more rapidly than any other type of solid cancer in the United States for the past several decades, possibly secondary to the increasing prevalence of risk factors, such as obesity.[2] EAC is a particularly lethal cancer, with 5-year survival rates of less than 20%.[3]

EAC develops from Barrett's esophagus (BE), intestinal metaplasia of the lower esophagus, which can then progress through low-grade dysplasia and high-grade dysplasia (HGD) to intramucosal carcinoma and then invasive carcinoma.[4] Several concurrent histologic and molecular changes have been described for BE and EAC.[5–8] The molecular changes observed include structural genomic alterations (amplifications and deletions, translocations), DNA sequence alterations (eg, missense mutations), and epigenetic modifications, primarily in the form of DNA hypermethylation and hypomethylation of CpG dinucleotides.

In light of the increased risk of EAC in those with BE, individuals diagnosed with BE are advised to undergo periodic endoscopic surveillance with biopsies of the affected segment to detect early histologic changes (ie, the presence of dysplasia) thought to confer risk for EAC development. However, because the overall risk of progression to EAC is minimal, a challenge when managing individuals with BE is to balance the risks and costs of endoscopic surveillance with the potential benefit of early identification or prevention of cancer. Assays for molecular alterations in BE samples might ultimately complement histologic, demographic, and/or endoscopic data and provide a more accurate prediction of an individual's risk for dysplasia or cancer. This article summarizes the current understanding of genetic and epigenetic alterations that underpin the development of BE, dysplastic BE, and EAC, with an emphasis on global alterations observed in BE and EAC.

GENETIC ALTERATIONS IN BARRETT'S ESOPHAGUS, BARRETT'S ESOPHAGUS WITH DYSPLASIA, AND ESOPHAGEAL ADENOCARCINOMA

Somatic Genomic Alterations in Barrett's Esophagus

The progression of BE to EAC provides a unique system to characterize the process by which a carcinoma emerges from its precursor state. Genomic studies of BE have revealed that it is not simply a metaplastic tissue; it also harbors frequent somatic alterations. The analysis of the process of BE progression has been greatly enhanced by dramatic improvements in genomic technologies, including tools to examine genetic mutations as well as larger structural alterations in cancer (and precancer) genomes.

Early studies of BE identified frequent loss of heterozygosity (LOH) at 17p, 5q, 9p, and 13q.[9,10] The 17p and 9p harbor the tumor suppressors *TP53* and *CDKN2A*, respectively, and studies have revealed frequent LOH through mutation (*TP53* and *CKN2A*) or promoter methylation (*CDKN2A*). Galipeau and colleagues[11] analyzed a series of esophageal biopsies from patients with BE and HGD without invasive EAC, finding patients commonly develop 9p LOH before the onset of 17p LOH. A 17p LOH was associated with genomic doubling to a 4N state, consistent with the impact of p53 loss upon genomic instability. When multiple biopsies from a single patient and time point were analyzed, 9p LOH was identified frequently in a greater percentage of the overall area of BE. These data contributed to the development of a popular model, where *CDKN2A* loss is thought to be an initiating event in BE progression, whereas *TP53* alterations are later events, associated with neoplastic progression and aneuploidy.

Beyond aneuploidy, BE progression has been associated with increasing clonal diversity.[8] Indeed, the presence of genomically distinct clones in the field of BE has been proposed by some researchers, with data suggesting the potential for certain clones to become dominant over time, that is, a 'clonal sweep.'[8,12,13]