Histology, Anatomy, or Geography? Exome Sequencing Begins to Delineate Somatic Mutational Differences in Esophageal Cancer

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**Summary:** Esophageal carcinoma is composed of squamous cell and adenocarcinoma types, each with geographically distinct incidence. The earliest exome sequences in this disease begin to illuminate the genetic demarcations of these anatomically related cancers. Cancer Discov; 2(10): 870-1. ©2012 AACR.

**Commentary on Agrawal et al., p. 899 (2).**

**INTRODUCTION**

Cancers of the esophagus are a major cause of cancer mortality worldwide. These malignancies remain understudied relative to their clinical impact for many reasons, not least because of their daunting clinicopathologic heterogeneity. Cancers of the esophagus show different risk factors, histologic appearances, anatomic locations, geographic distributions, and responses to therapy. The two main histologies are esophageal squamous cell cancer (ESCC) and esophageal adenocarcinoma (EAC). In high-incidence countries (e.g., China), more than 90% of esophageal cancers are of squamous cell histology (ESCC). ESCCs in China are not as strongly associated with exposure to tobacco and alcohol as they are in Westernized societies (1). A potentially distinct etiology in China is also suggested by recently decreasing incidence, correlated with improved nutrition, refrigeration, and sanitation. On the other hand, EAC predominates in Western countries and is increasing in incidence, possibly because of obesity. Adenocarcinoma of the esophagus typically presents in the mid to lower esophagus, almost always preceded by Barrett esophagus, a squamous to columnar metaplasia of the lower esophagus. The risk of developing EAC is much (about 30×) higher in individuals with Barrett esophagus than the normal population, but the annual conversion of Barrett esophagus to EAC is low, well below 1% per year. Despite extensive efforts, screening patients with Barrett esophagus has not led to a survival benefit.

The known disparate rates and forms of esophageal carcinoma in different anatomic distributions, demographic cohorts, and geographic regions motivated a genomic evaluation of the disease both to explain these differences and educate us as to optimal detection, management, and surveillance efforts.

**FINDINGS**

In this issue of Cancer Discovery, Agrawal and colleagues (2) report comparative exome sequencing of 11 EACs and 12 ESCCs. The current exomes were sequenced at an average depth of greater than 150-fold, revealing more than 50 somatic mutations per exome with substantive allelic fraction, for both EACs and ESCCs. This mutation prevalence translates to around 4,000 mutations per genome, less than sun-exposed cancers, but much higher than that found in most solid visceral malignancies. Notably, no clear signature for the C:G>A:T transversions associated with tobacco smoke was reported, similar to findings in head and neck squamous cell cancer (SCC), despite the clinical correlation.

In recent studies, this group and others have shown recurrent loss-of-function mutations in Notch receptors (in addition to other Notch pathway genes such as IRF6 at lower prevalence) in SCCs of the head and neck, lung, and skin. This study finds Notch (NOTCH1, NOTCH2, NOTCH3) mutations in one fifth of ESCCs, but not EACs, in patients from the United States. Most of these mutations occur in NOTCH1, mirroring results from other SCCs. However, a mutation frequency of about 10% was also observed in NOTCH3, predominated by frameshift and splice-site mutations, findings not yet reported in non-ESCCs. This site-specific mutation spectrum might illuminate tissue-specific functions of the highly related Notch receptors.

Agrawal and colleagues (2) also examined Notch status in a series of 48 esophageal SCCs from China, reporting only one NOTCH1 and one NOTCH3 mutation. These aberrations, while convincingly functional (including nonsense mutations), occur at much lower frequency than reported in any SCC subset to date, suggesting a key role for germline genetic background in squamous cell carcinogenesis.

Sequencing of two Barrett esophagus samples clinically related to two adenocarcinomas showed that more than 75% of mutations present in the cancer were also found in the...
Barrett sample. Concordance of TP53 inactivation or wild-type status was confirmed in these pairs, further calling into question the extent of somatic evolution required to produce a malignancy from a so-called precursor lesion.

**INTERPRETATION**

The findings of Agrawal and colleagues (2) in this issue provide a first look at the sequence of most coding genes in a small cohort of retrospectively collected esophageal carcinomas. The exome findings reinforce themes raised in other studies of squamous cell cancers, such as the high incidence of TP53 mutations and scant evidence for a genomic mutational signature of tobacco exposure. However, the failure to find frequent Notch receptor mutations in Chinese ESCCs echoes other reports of bias in mutational spectrum: for example, the higher mutation prevalence of ARID2 in hepatitis C–associated hepatocellular carcinoma (3). Whether the reported Notch mutation differences stem from genetic background in East Asian populations or from geographically distinct environmental insults, they provide an attractive model in which to study such mutational bias.

Agrawal and colleagues (2) also provide provocative data on the molecular origins of adenocarcinoma of the esophagus, reinforcing the somewhat paradoxical notion that most of the genomic changes in a given cancer have already occurred at the preneoplastic stage of disease (4). Taken in concert with more recent findings that many, if not most, somatic events in some human cancers are the result of age and environmental insult and likely unrelated to the neoplastic process (5), we are forced to rethink the crucial barriers keeping benign precursor lesions (Barrett esophagus, melanocytic nevi, colonic polyps) from progressing to frank malignancy, as genomic instability does not appear to be limiting.

An alternative hypothesis is that although commonalities between precursors exist, the genetic determinants of progression or benignity are preprogrammed from a very early stage in each potential cancer’s life. The meaning of a “precancerous” lesion is less clear in this scenario, as it may well be that most “precursors” are actually endpoints and have very little, if any, malignant potential. Other precursor lesions might be sinister from the start, with a progression program that may pass through, but not pause at, what historically appears identical to the “precursor” stage. Such a preordained model might explain the failure of surveillance attempts to affect survival in Barrett esophagus (6) and other diseases (7). Alternatively, clonal heterogeneity in Barrett esophagus might be important in predicting progression (8). Sorting out these scenarios would require profiling not more carcinomas, but instead more benign lesions, to understand the distribution of genomic abnormalities across the relevant denominator: the precursor lesion Barrett esophagus.

Esophageal carcinoma shows just how different cancers arising in a general anatomic location can be. In clinical practice, this classification has its justifications; the surgical skill set required to conduct a thoracotomy does not depend on the molecular pathogenesis of the cancer being surgically removed. However, as we understand more about the heterogeneity of this disease, our management options will only improve, both through understanding the many different diseases that comprise esophageal carcinoma and comparison to other cancer types.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**REFERENCES**

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