Editorial

Signatures of field cancerization: a step towards earlier detection of esophageal adenocarcinoma

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In the March 2017 issue of *Neoplasia* Reed *et al*. report on a metabolic signature in the normal esophageal squamous tissue in patients with esophageal adenocarcinoma (EAC) arising in a background of Barrett's esophagus (BE). The study utilized ^{1}H-nuclear magnetic resonance (^{1}H-NMR) to assess complex metabolic mixtures within tissue samples from normal squamous, BE- and EAC-affected areas of the esophagus to identify individual metabolites and metabolic signatures associated with each state. A metabolic signature was identified that distinguished normal squamous epithelium from BE patients with EAC (n=30) from normal squamous epithelium from patients with dyspeptic symptoms but no detectable BE or EAC (n=68). The signature produced by a partial least squares discriminant analysis (PLS-DA) model included the metabolites 3-hydroxybutyrate, succinate, formate, acetate, glycerophosphocholine, ADP and lactate. The authors discussed potential rationale for the observed differences in these metabolites in the squamous epithelium of patients with EAC, including the possibility that the elevated levels of formate may be related to ATP and NAD(P)H synthesis as cells adapt to changes in energy requirements in the cancer-bearing state. Additional studies will be required to understand why these particular metabolites are altered in the normal squamous mucosa adjacent to EAC.

The authors conducted mapping studies within patients, which involved evaluating metabolites in normal squamous, non-dysplastic columnar epithelium and EAC. While the sample size was limited to only three pre-chemotherapy matched sets and four post-chemotherapy matched sets, a principal component analysis (PCA) model and a PLS-DA model based on multiple metabolites discriminated normal squamous epithelium from BE and EAC, but did not distinguish BE from EAC. Individual metabolites were statistically different, however, the overall metabolic profiles of BE and EAC were similar. The finding that metabolic profiles of BE mucosa were similar to EAC is consistent with previous studies demonstrating that at the gene expression level BE mucosa is closer to EAC than to normal esophageal squamous tissue (1). The study also compared metabolites in BE tissue from patients with and without EAC. While the sample size of this analysis was small (7 BE patients without EAC, 4 BE patients with concomitant EAC), several metabolites including phosphocholine were altered between the two groups, providing a preliminary indication that metabolites may be useful biomarkers to detect the presence of prevalent EAC. As expected the study reported a strong effect of chemotherapy on the metabolic profile of esophageal tissues from patients with EAC. While larger studies are needed to validate the findings of this study, the results provide further evidence that EAC can be detected by measuring its effects on surrounding normal or non-dysplastic tissue within the esophagus.

The findings of this study are important due to the difficulty in recognizing subtle lesions containing high grade dysplasia (HGD) or EAC in patients with BE, and the resulting need for devices and assays to improve detection rates. Current practice guidelines recommend endoscopic surveillance of BE at time intervals determined by the pathologic grade to aid early detection of dysplasia

and EAC (2). The pathologic diagnosis in BE is limited by observer variation (3), and also by the random sampling of the esophagus on endoscopy, which may miss subtle lesions containing HGD or EAC. Expert endoscopists in high-volume clinical centers have higher rates of detection of such lesions than in the community practice setting (4). However, detection of subtle lesions poses challenges in all clinical settings, and HGD/EAC lesions are frequently missed (5). Field cancerization, or a field effect, has been documented in EAC and many other types of cancer (6-8). An expanded preneoplastic field surrounding lesions may appear histologically normal or non-dysplastic but harbor cancer-associated molecular and cellular changes. An expansion to the definition of field cancerization has recently been proposed that is based on the concept of an etiologic field effect in which etiologic factors and their interactions promote a microenvironment conducive to malignant transformation (9). Field cancerization may be detectable in the columnar epithelium around lesions and also in the cardia and the squamous mucosa around or above the BE mucosa. Detection of these abnormalities in patients with BE may enable earlier diagnosis and treatment of lesions containing HGD or EAC. The study by Reed *et al*. builds on the results of others that have demonstrated molecular and cellular abnormalities in the field surrounding EAC, and also in earlier lesions containing HGD in a background of BE. Yakoub *et al*. also described a panel of metabolites that could distinguish between squamous epithelium from patients with EAC from healthy controls (10), and serum metabolite biomarkers associated with HGD and EAC have also been described (11). Mutations, changes in gene expression and DNA methylation as well as cellular changes have also been described in the expanded preneoplastic field in BE; some of these studies are summarized below. Mutations in *TP53* have been found in biopsies from multiple endoscopic levels in BE patients with HGD, demonstrating an expanded preneoplastic field (6). Selaru *et al*. reported that global gene expression patterns, and expression of individual genes, including histone biomarkers and *HLA-DR*, could distinguish normal squamous epithelium from patients with and without EAC (12). The squamous specimens were taken at least 7 cm away from the BE or EAC, indicating the presence of a wide field of abnormalities that could be sampled to detect EAC. Expression of survivin, an inhibitor of apoptosis that is frequently upregulated in tumor cells, in squamous tissue adjacent to EAC has been shown to be predictive of distant recurrence (13). Aberrant DNA methylation has been detected in the *APC*, *CDH1*, *CDKN2A*, and *ESR1* genes, affecting large areas of non-dysplastic BE tissue adjacent to EAC (14). Nanoscale structural properties of nuclei in the cardia and upper squamous mucosa have been shown to stratify patients with non-dysplastic BE from patients with dysplasia and/or EAC (15), indicating that subtle morphologic changes occur in the expanded preneoplastic field. These changes may not be discernible on manual review of hematoxylin and eosin-stained slides, but can be objectively quantified by image analysis algorithms. A tissue systems pathology approach, which objectively quantifies multiple epithelial and stromal biomarkers in digital images of tissues, has also been shown to detect abnormalities indicating field cancerization in BE biopsies with diagnoses of non-dysplastic and low grade dysplasia in patients with prevalent HGD/EAC (16). These studies and others demonstrate that a field effect is present and detectable in EAC, and manifests in many forms including alterations in metabolites, gene expression, DNA methylation, as well as mutations, stromal changes, and nanoscale changes in nuclear morphology. Detection of the field effect in the clinical setting with validated diagnostic assays based on cost-effective methodology may increase the detection of HGD and EAC. Such assays would be adjunctive to the current pathology workflow to provide physicians with additional quantitative, objective information on biomarkers or multivariable signatures that can detect field cancerization in preneoplastic BE or normal squamous mucosa. This will enable earlier therapeutic intervention with effective endoscopic therapies such as radiofrequency ablation and endoscopic mucosal resection (17,18), which will improve patient outcomes.

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in Cernostics, Inc., which offers a clinical assay for risk prediction in Barrett's esophagus.

References

1. Wang S, Zhan M, Yin J, et al. Transcriptional profiling suggests that Barrett's metaplasia is an early intermediate stage in esophageal adenocarcinogenesis. Oncogene 2006;25:3346-56.
2. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol 2016;111:30-50.
3. Montgomery E, Bronner MP, Goldblum JR, et al. Reproducibility of the diagnosis of dysplasia in Barrett esophagus: a reaffirmation. Hum Pathol 2001;32:368-78.
4. Schölvinck DW, van der Meulen K, Bergman JJ, et al. Detection of lesions in dysplastic Barrett's esophagus by community and expert endoscopists. Endoscopy 2017;49:113-20.
5. Visrodia K, Singh S, Krishnamoorthi R, et al. Magnitude of Missed Esophageal Adenocarcinoma After Barrett's Esophagus Diagnosis: A Systematic Review and Meta-analysis. Gastroenterology 2016;150:599-607.e7.
6. Prevo LJ, Sanchez CA, Galipeau PC, et al. p53-mutant clones and field effects in Barrett's esophagus. Cancer Res 1999;59:4784-7.
7. Guo M, House MG, Hooker C, et al. Promoter hypermethylation of resected bronchial margins: a field defect of changes? Clin Cancer Res 2004;10:5131-6.
8. Heaphy CM, Griffith JK, Bisoffi M. Mammary field cancerization: molecular evidence and clinical importance. Breast Cancer Res Treat 2009;118:229-39.
9. Lochhead P, Chan AT, Nishihara R, et al. Etiologic field effect: reappraisal of the field effect concept in cancer predisposition and progression. Mod Pathol 2015;28:14-29.
10. Yakoub D, Keun HC, Goldin R, et al. Metabolic profiling detects field effects in nondysplastic tissue from esophageal cancer patients. Cancer Res 2010;70:9129-36.
11. Buas MF, Gu H, Djukovic D, et al. Candidate serum metabolite biomarkers for differentiating gastroesophageal reflux disease, Barrett's esophagus, and high-grade dysplasia/esophageal adenocarcinoma. Metabolomics 2017. [Epub ahead of print].
12. Selaru FM, Wang S, Yin J, et al. Beyond Field Effect: Analysis of Shrunken Centroids in Normal Esophageal Epithelia Detects Concomitant Esophageal Adenocarcinoma. Bioinform Biol Insights 2007;1:127-36.
13. Malhotra U, Zaidi AH, Kosovec JE, et al. Prognostic value and targeted inhibition of survivin expression in esophageal adenocarcinoma and cancer-adjacent squamous epithelium. PLoS One;8:e78343.
14. Eads CA, Lord RV, Kurumboor SK, et al. Fields of aberrant CpG island hypermethylation in Barrett's esophagus and associated adenocarcinoma. Cancer Res 2000;60:5021-6.
15. Fasanella KE, Bista RK, Staton K, et al. Nuclear Nano-architecture Markers of Gastric Cardia and Upper Squamous Esophagus Detect Esophageal Cancer "Field Effect". J Cancer 2013;4:626-34.
16. Critchley-Thorne RJ, Davison JM, Prichard JW, et al. A Tissue Systems Pathology Test Detects Abnormalities Associated with Prevalent High-Grade Dysplasia and Esophageal Cancer in Barrett's Esophagus. Cancer Epidemiol Biomarkers Prev 2017;26:240-8.
17. Bulsiewicz WJ, Kim HP, Dellon ES, et al. Safety and efficacy of endoscopic mucosal therapy with radiofrequency ablation for patients with neoplastic Barrett's esophagus. Clin Gastroenterol Hepatol 2013;11:636-42.
18. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. JAMA 2014;311:1209-17.

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