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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

# Esophageal Adenocarcinomas: A Need for Speed Driven by Immune Pathways That Have Druggable Targets

Despite advances in multimodality therapy and the development of agents that target tumor growth–promoting pathways, the 5-year survival of patients with esophageal adenocarcinoma (EAC) remains less than 20%. Most of these targeted agents have been directed at growth factor receptor tyrosine kinases, with clinical trials yielding woefully disappointing results. Genomic studies of EACs have shown amplification of multiple receptor tyrosine kinases and their downstream signaling pathways, showing a complex, diffuse, and redundant spider web of signaling networks that might elude inhibition even by combinations of several molecularly targeted agents.[1] Thus, it is essential to identify alternative druggable targets for this deadly tumor, a goal that should be attainable in this era of genomics and personalized medicine. A deep understanding of tumor biology will be critical for the success of this process.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Duggan et al[2] described their use of a loss-of-function screening approach to identify potential therapeutic targets for EAC. First, they studied the effects of a druggable genome small interfering RNA (siRNA) library (>6000 individual gene-targeting siRNA pools) on the viability of a human high-grade dysplastic Barrett's epithelial cell line (CPD). Roughly 250 promising siRNA pools were identified, and a subset of these hits were verified using an alternative siRNA format. By using The Cancer Genome Atlas Research Network, the investigators cross-referenced their CPD hits with genomic variants associated with gene amplification in human esophageal cancers, reasoning that such amplifications would be ideal molecular targets. This approach identified 49 hits that both affected CPD viability and were associated with somatic variation and gene amplification in human esophageal cancers. Genomic amplifications specific to EACs all were encoded at chromosome 6p21.1, home to the major histocompatibility complex locus, suggesting that immune-associated genes might be promising molecular targets.

In another series of studies, gene ontology analyses of the screening library data showed that cytokine-mediated signaling pathways were among the most significant biologic processes targeted by the siRNAs pools. The investigators used a previously reported microarray of EAC tissues to identify 62 putative siRNA target genes and ranked them by the strength of their effects on CPD viability. Interestingly, the top-ranked candidates were immune-associated genes (*LIF*, *C1QA*, and *TREM2*). Experiments using specific siRNAs, recombinant proteins, and rescues confirmed that these 3 immune-related genes reduced the viability of a panel of EAC cell lines. Proof-of-principle studies targeting the inflammatory/immune pathways of these genes showed profound effects on cell viability in vitro and in mouse xenografts. These elegant studies have shown a cohort of targetable molecules that can kill EAC cells, and highlight the central role of inflammatory/immune signaling in driving EAC growth.

There is a growing body of evidence that inflammatory/immune processes contribute importantly to the pathogenesis of EAC. Gastroesophageal reflux disease (GERD) frequently causes chronic esophageal inflammation in the distal esophagus (ie, reflux esophagitis). In some patients, that reflux esophagitis heals through the process of columnar metaplasia, resulting in Barrett's esophagus. Barrett's esophagus is a premalignant condition that is thought to underlie most, if not all, EACs. Up to 40% of adults in Western countries have reported symptoms of GERD, but only a minority of those individuals develop Barrett's esophagus, and only a minority of those develop EAC. Thus, chronic esophageal inflammation caused by GERD underlies the development of Barrett's esophagus and EAC in susceptible individuals.

Incredible advances in omics techniques such as whole-genome sequencing have revolutionized our understanding of how germline susceptibility modulates disease risk alone or in combination with environmental factors. Genome-wide association studies (GWAS) have found that patients with Barrett's esophagus and those with EAC share substantial overlap of germline genetic variants, suggesting a shared genetic susceptibility for the 2 disorders.[3] Moreover, some of these genetic variants are located in or around the major histocompatibility complex locus that regulates activation of the immune system.[4] GWAS studies also have identified novel gene variant–GERD interactions that appear to modulate the risk of developing Barrett's esophagus, but not the risk of developing EAC itself.

The elegant proof-of-principle studies by Duggan et al[2] have shown the power of integrating functional genomic studies in cell lines with genetic data from patients to provide an unbiased avenue for identifying novel, druggable therapeutic targets. In addition, these studies have shown new insights into how EACs appear to be addicted to an inflammatory-immune drive. As someone not quite addicted to, but certainly very enamored with, the high-performance drive of my sports car, I can understand the vulnerability of EAC cells to the uneven road surfaces imposed by an inflammatory-immune–targeted agent. GWAS have shown that germline susceptibility combined with GERD-induced chronic inflammation modulates the risk of developing Barrett's esophagus, but not EAC per se. Thus, it appears that the addiction to the inflammatory-immune drive begins

early in EAC pathogenesis. As we move toward achieving our goal of finding better treatments for EAC patients, a better understanding of tumor biology is critical if we are to expose key cellular vulnerabilities that might be exploited for molecular targeting. The immune addiction of EACs shown by Duggan et al[2] is one such vulnerability, and we would be happy to help EACs kick their habit!

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**Conflicts of interest**
The author discloses the following: Rhonda F. Souza has served as a consultant and receives research support from Ironwood Pharmaceuticals.

**Funding**
This work was supported by National Institutes of Health grants R01 DK103598, R01 DK063621, and R21 DK111369 (R.F.S.).

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2352-345X
https://doi.org/10.1016/j.jcmgh.2018.01.020