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Fused genes found in esophageal cancer cells offer new clues on disease mechanisms

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Despite years of research, cellular mechanisms contributing to cancers like esophageal adenocarcinoma have remained elusive. What has puzzled researchers was how genes in the healthy cells lining the esophagus turned the normal cells into malignant ones. Now, researchers from Case Western Reserve University School of Medicine have characterized structurally abnormal genes in esophageal adenocarcinoma, the findings of which could pave way for developing new biomarkers in this fatal disease. The National Cancer Institute estimates that nearly 37,000 people are living with esophageal cancer in the United States and nearly $1.6 billion is spent on related care each year.

In the study published in *Cancer Research*, researchers compared biopsies from people undergoing endoscopy for Barrett's esophagus, a common complication of reflux that can increase esophageal adenocarcinoma risk. The researchers were looking for "gene fusions" that can occur when two genes become permanently connected to each other and encode one protein, as opposed to two separate proteins. The researchers looked for small pieces of genetic material called RNAs that were produced from the gene fusions. They wanted to identify potentially harmful RNAs that represented gene fusions and that were found in tumor tissues. After comparing 55 tumor biopsies to 49 non-cancerous ones, they found 21 novel gene fusions in esophageal cancer tissues.

"Ours is the first study identifying expressed gene fusions on a genome-

scale in esophageal adenocarcinomas, offering a comprehensive roadmap of gene fusions and new molecular insights into this lethal cancer," indicated Kishore Guda, DVM, PhD, cancer researcher and assistant professor of general medical sciences (oncology) at Case Western Reserve School of Medicine, and the senior author on this study. "We also performed functional studies on a select gene fusion that we found to be highly associated with poorer patient survival."

Under Guda's leadership, the researchers pared down the list and selected two of the identified gene fusions for validation studies in a larger set of biopsy tissues. One fusion in particular, between RPS6KB1 and VMP1 genes, was found in approximately 10% of esophageal adenocarcinomas. Cancer patients expressing this fusion did not survive as long as patients without the fusion. The researchers concluded that the RPS6KB1-VMP1 fusion, as well as other fusions identified in their study, could serve as potential indicators of aggressive esophageal adenocarcinoma.

"Our study also revealed additional gene fusions that were present in both the tumor and normal tissues, derived from the cancer patients," explained Guda. "We believe that such fusions are highly interesting, as some of these can predispose to subsequent tumor development and can be attractive as early predictive biomarkers of cancer risk in this disease."

To better understand how the RPS6KB1-VMP1 fusion may aid tumor development, the researchers tested whether or not it encoded a working protein and where the protein ended up inside cancer cells. In healthy tissues, VMP1 encodes a protein that helps manage normal cell turnover. The gene fusion includes a shorter version of VMP1 which could make it dysfunctional. Genetically engineered cells with the fusion grew faster in the laboratory than those without the fusion, particularly at high cell densities. The rapid growth patterns suggested to Guda that the fusion

protein could be working inside the cells. But when the researchers looked at the fusion protein under a microscope, they found the truncated protein to be distributed randomly within the cells. This is in contrast to full-length VMP1, which stuck to small pockets characteristic of a normally functioning protein. The unusual distribution of the fusion protein may be one way cancer cells are able to avoid normal cell turnover mechanisms.

Gene fusions occur frequently in cancer cells and can arise when cell machinery rearranges chromosomes or improperly replicates DNA. Proteins produced from gene fusions can disrupt cell function in many ways. Fusion proteins may be part of how cancer cells grow so rapidly and evade self-restraint mechanisms. Guda anticipates further studies to clearly delineate how the RPS6KB1-VMP1 fusion in particular contributes to esophageal adenocarcinoma disease progression, and the biologic role of other gene fusions identified in this study.

More information: *Cancer Research*, DOI: 10.1158/0008-5472

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