# Abnormal gene product associated with prostate cancer generated by unusual mechanism

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Researchers have identified a potential new pathway in prostate cancer cells by which cancer-driving gene products can be generated, according to a study published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Our work shows that cancers have many more tricks than we thought to generate potential cancer-driving genes or gene products," said Hui Li, Ph.D., assistant professor of pathology at the University of Virginia in Charlottesville, and a recipient of an Innovative Research Grant from Stand Up To Cancer (SU2C). The AACR is the scientific partner of SU2C.

Gene fusion is a common characteristic of human cancers. In many cases, the protein products of these gene fusions, which are generated via an RNA intermediate, have a key role in the genesis of the cancer. A well-characterized example of this is the protein that drives chronic myeloid leukemia, BCR-ABL, which is generated via RNA intermediates from a fusion gene formed by chromosomal translocation — an event involving exchange of genomic DNA between two distinct chromosomes.

"For many years, chromosomal translocation was considered the sole way in which single RNAs consisting of copies of parts of two genes, so-called fusion RNAs, could be generated," said Li. "We have shown that

fusion RNAs can be generated without changes to DNA by a new mechanism that we are calling cis-SAGe [cis-splicing of adjacent genes]." Recently, a fusion RNA formed from parts of the SLC45A3 and ELK4 genes was identified in prostate cancer cells in the absence of any DNA alterations. Li and his colleagues confirmed in two prostate cancer cells lines that the SLC45A3-ELK4 fusion RNA could be detected even though there was no evidence of genomic DNA rearrangement.

Detailed molecular analysis of the prostate cancer cell lines indicated that the SLC45A3-ELK4 fusion RNA was generated by cis-SAGe. SLC45A3 and ELK4 are neighboring genes, and cis-SAGe occurred when an RNA that crossed the boundary between the two genes was formed.

The protein CCCTC-binding factor normally acts to insulate SLC45A3 and ELK4 from each other. Li and his colleagues found that levels of this protein at the gene boundary inversely correlated with the amount of SLC45A3-ELK4 fusion RNA generated, providing molecular insight into how the quantity of this fusion RNA could be regulated.

A functional role for the SLC45A3-ELK4 fusion RNA in prostate cancer was suggested by two observations. First, it promoted the growth of the two prostate cancer cell lines in culture. Second, its levels in human prostate samples correlated with prostate cancer disease progression — normal prostate tissue expressed the lowest levels and prostate cancer specimens from men with metastatic disease expressed the highest levels.

"These data are not sufficient to say that the SLC45A3-ELK4 fusion RNA has a causal role in prostate cancer," said Li. "But they are highly suggestive, and I am very excited that this high-risk project, which I would not have been able to pursue without the grant from Stand Up To

Cancer, has uncovered what seems to be a new way in which cancer can be driven."

Provided by American Association for Cancer Research