Potentially targetable fusion RNAs may be more common in metastatic breast cancer than previously realized

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Comprehensive profiling of fusion RNAs present in a large cohort of metastatic breast tumors revealed unique fusion mutations that may be

therapeutically targetable, according to results presented at the San Antonio Breast Cancer Symposium, held December 5–9, 2023.

Fusion mutations occur when a portion of one gene becomes fused to a portion of another, which can create gene products with new functions. They are common in cancer types that are characterized by genomic rearrangements and structural damage to the DNA, including breast cancer.

"Fusion RNAs may serve as biomarkers highly specific to cancer cells, have unique functions which may drive cancer progression, and potentially offer more personalized, cancer-specific targets," explained Nolan Priedigkeit, MD, Ph.D., a medical oncology fellow and postdoctoral scholar at Dana-Farber Cancer Institute and the Broad Institute of MIT and Harvard.

Priedigkeit conducted this study alongside senior author Todd Golub, MD, a professor of pediatrics at Harvard Medical School, the Charles A. Dana Investigator in Human Cancer Genetics at Dana-Farber Cancer Institute, and the Director of the Broad Institute of MIT and Harvard.

Targeted therapies that can inhibit fusion proteins have been approved for use in a wide variety of cancers, but the prevalence and role of fusion RNAs in breast cancer has not been as comprehensively mapped, Priedigkeit said.

He and his colleagues performed a retrospective study using RNA sequencing data from two cohorts of patients with metastatic breast cancer, comprising a total of 466 samples across 423 patients. They ran the sequencing data through a collection of five fusion-finding algorithms; highly expressed fusions identified by two or more algorithms that were not present in normal tissues were considered high-confidence and cancer-specific (HCCS).

The researchers found that around one-third of metastatic breast cancers harbored at least one highly expressed HCCS fusion RNA, a rate much higher than Priedigkeit expected. Fusions were most common among tumors of the basal subtype and least common among tumors of the luminal A subtype.

The analysis showed that 64.5% of patients harboring HCCS fusions had at least one fusion involving a cancer-related gene, as defined by the OncoKB database, suggesting that some of these fusions may be cancer driver mutations. In support of this hypothesis, the most common cancer-related gene involved in fusions was ESR1, encoding the estrogen receptor.

Priedigkeit noted that the analysis uncovered both known and novel ESR1 fusions, many of which occurred during or after endocrine therapy and resulted in the loss of binding sites for estrogen receptor inhibitors. The frequency of ESR1 fusions was approximately 5% in estrogen receptor-positive disease.

Further, researchers identified HCCS fusions involving known cancer-driving kinases, some of which have FDA-approved small molecule inhibitors that may provide new treatment strategies for patients with heavily pretreated disease and few remaining options, Priedigkeit said.

"There may be low-frequency fusions—potentially targetable with drugs we already have—that we are missing with current testing standards, as they are tricky to pick up with traditional sequencing platforms," Priedigkeit said. "There is a critical need to understand optimal testing strategies so that we don't overlook potentially actionable fusions in breast cancer."

While these results are preliminary, and more research will be necessary to determine if these fusions are driving cancer progression, Priedigkeit

and colleagues are exploring innovative strategies using gene therapy techniques to target fusion RNA sequences directly.

"The gene therapy revolution is knocking on our door—and there are new technologies that allow targeting nucleic acids directly rather than their protein products," Priedigkeit said. "We have made several collaborations to credential some of these new technologies to exploit fusion RNAs, especially given how common they appear to be in metastatic breast cancers."

Limitations of this study include its retrospective nature and its exclusive applicability to patients with heavily pretreated, metastatic breast cancer. Further, the patient cohorts were treated prior to the widespread availability of antibody-drug conjugates, which Priedigkeit noted may alter the prevalence of various fusions.

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