Researchers discover promising prognostic marker for aggressive breast cancer

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A team of researchers led by Goutham Narla, MD, PhD, at Case Western Reserve University School of Medicine and University Hospitals Case Medical Center, and collaborators at the Mount Sinai School of Medicine and Erasmus Medical Center, have discovered a gene variant that drives the spread of breast cancer. Published in *Science Translational Medicine* (embargoed Jan. 23 at 2:00 pm ET), the study lays the early foundation for predicting which breast cancer patients may develop more aggressive disease and for designing more effective treatments.

"Breast cancer is a genetically complex disease and it remains a challenge to predict disease outcomes and which patients may benefit from more aggressive treatment," says Dr. Narla, assistant professor at Case Western Reserve University School of Medicine and medical geneticist at UH Case Medical Center Seidman Cancer Center. "Our research has uncovered a promising gene marker that will not only help us better identify tumors that behave badly but provide a basis for developing and 'personalizing' therapies to better treat our patients."

The research team discovered that a mutant gene, KLF6-SV1, was linked to the recurrence and metastasis in women with breast cancer. The incorrect splicing of the KLF6 gene essentially creates a protein that causes cancer cells to spread or metastasize. The researchers examined the tumors of 671 breast cancer patients in a tumor bank at Erasmus University Medical Center (Rotterdam, The Netherlands) and found that those whose tumors expressed high levels of the gene variant were 50

percent more likely to die. Since recurrence and metastasis are the major causes of death in breast cancer, this finding will provide a new direction of research to both identify women at risk and to develop targeted drugs that block the process of metastasis.

"This study presents biological proof that this splice variant can potentially be a marker for determining which early stage breast cancer patients will have disease progression," adds Dr. Narla. "More studies need to be done, but this could provide an important prognostic marker to determine which patients need to be treated more aggressively or watched more closely."

Dr. Narla came to UH Case Medical Center and Case Western Reserve in spring, 2012, from Mt. Sinai and is the first Harrington Distinguished Scholar (Early Career Award). This inaugural award provides physician-scientists with the ability to tap into grant funding and a peer network of innovators and mentors within the infrastructure of the Harrington Discovery Institute at UH Case Medical Center. The Institute is part of the $250 million Harrington Project for Discovery & Development, which was launched in February, 2012, with a $50 million gift to UH from the Harrington family of Hudson, OH.

Dr. Narla's laboratory focuses on the identification and characterization of the genes and pathways involved in cancer metastasis. By studying the functional role of the KLF6 tumor suppressor gene, Dr. Narla and his team have identified new signaling pathways regulated by this gene family thus providing new insight into cancer diagnosis and treatment. The team's research found that KLF6 and FOXO1, both tumor suppressor genes, are turned off as cancer spreads through the body. Since first discovering the KLF6 gene 13 years ago as a medical student at Mount Sinai School of Medicine in the laboratory of Dr. Scott Friedman, Dr. Narla has been involved in the identification and characterization of the gene and its role in cancer development.

"In this new research as well as previous studies, Goutham and his team have uncovered important and previously unrecognized genetic markers in cancer," said Stanton Gerson, MD, Director of the Case Comprehensive Cancer Center and the UH Case Medical Center Seidman Cancer Center. "This work highlights how understanding the basic mechanisms regulating cancer development and progression can lead to significant advances in the treatment of cancer. We are so pleased to have a physician-scientist of his caliber at our cancer center and are excited about the impact of this important work."

Dr. Narla will work with the breast cancer team, led by Lyndsay Harris, MD, to study further KLF6-SV1's potential as a prognostic marker for patients with poor outcomes. The group also will work to develop novel therapeutics that can turn the protein off and cause the cells to become less aggressive.

"We look forward to continuing this work to further define the role of this gene variance and improve our understanding of the molecular basis for tumor progression and metastasis," says Dr. Harris, Director of the Breast Cancer Program at UH Case Medical Center and Professor, Medicine-Hematology/Oncology at the Case Western Reserve School of Medicine. "These findings provide us with an important new tool to be able to distinguish between indolent and lethal early stage disease. This will potentially enable us to develop more "personalized" treatments for patients and thereby reduce breast cancer mortality."

Provided by University Hospitals Case Medical Center