Cancer researchers identify new metastasis suppressor gene

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(Medical Xpress)—Among patients with deadly cancers, more than 90 percent die because of metastatic spread of their disease. Looking to target a key pathway in order to interfere with the processes that lead to tumor spread, a research team led by Irwin H. Gelman, Ph.D., of Roswell Park Cancer Institute (RPCI) has identified a new suppressor of cancer metastasis that may point the way toward development of more effective treatments for prostate cancers and other malignant solid tumors.

Activation of the PI3K/AKT signal pathway is a known driver of the progression of prostate cancer to the castrate-resistant stage, the most lethal form of prostate cancer. Using a genome-wide genetic screen, Dr. Gelman and colleagues identified a previously unknown metastasis suppressor—the FOXO4 protein, which belongs to a family of genes that are produced by all human cells.

"Evidence from several publicly available cancer genomic databanks indicates that FOXO4 is typically turned off in metastatic prostate cancer compared to primary prostate tumors. Our research showed that the FOXO4 gene normally turns off genes that control specific metastatic behavior in malignant tumor cells, such as the ability to invade tissues and then to survive and multiply there," says Dr. Gelman, the John & Santa Palisano Chair in Cancer Genetics at RPCI.

In demonstrating that FOXO4 works to prevent the spread of cancerous tumors by binding to and inhibiting the protein RUNX2, the team

identified a circuit that controls metastatic progression in prostate cancer.

"Our findings underline the importance of RUNX2 in promoting metastasis and suggest that drugs that inhibit its function would prevent or treat prostate cancer metastasis," notes Dr. Gelman. "Given the devastating impact of cancer metastasis and the dire need for therapies to combat tumor spread, we're highly encouraged by these findings and excited about the therapeutic possibilities they open up."

Dr. Gelman's lab is now working with collaborators at the University of Maryland to test the effectiveness of the experimental agent CADD522, an inhibitor of RUNX2 function, in preventing or impeding prostate cancer metastasis.

More information: Su B, Gao L, Baranowski C, Gillard B, Wang J, et al. (2014) "A Genome-Wide RNAi Screen Identifies FOXO4 as a Metastasis-Suppressor through Counteracting PI3K/AKT Signal Pathway in Prostate Cancer." *PLoS ONE* 9(7): e101411. DOI: 10.1371/journal.pone.0101411

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