Scientists uncover a novel cooperative effort to stop cancer spread

November 28 2012

(Medical Xpress)—Scientists from the Florida campus of The Scripps Research Institute (TSRI) have uncovered a group of what have been considered relatively minor regulators in the body that band together to suppress the spread of cancer from its primary site.

The discovery offers a fresh batch of possible therapeutic targets as well as new diagnostic tools with the potential to predict and inhibit the spread of cancer (metastasis) in patients suffering from the disease.

The research, published recently in *The* Journal of Biological Chemistry, was conducted by TSRI Professor Donald G. Phinney, a nationally recognized authority in the study of adult bone marrow-derived stem cells, and a postdoctoral fellow in his laboratory, Christopher L. Haga.

In the new study, the scientists found that a cluster of seven microRNAs (miRNA) function cooperatively to repress a process known as epithelial-to-mesenchymal transition (EMT). While EMT is part of the normal biology of cell development in some parts of the body, the process has recently been implicated in two dangerous aspects of tumor growth—tumor metastasis and the growth of drug-resistant cancer stem cells.

MicroRNAs are tiny fragments of RNA found in all mammalian cells. They bind to messenger RNAs, a process that generally results in gene silencing. This cluster of miRNAs, located in a genetic region known as DLK1-DIO3, suppresses a specific signaling network in human cancers

that primarily affect glands such as breast cancer.

"These results establish the DLKI-DIO3 miRNA cluster as a critical checkpoint regulating tumor growth and metastasis," said Phinney. "Our data shows that when this cluster is silenced, it accelerates tumorogenesis and proliferation by inducing EMT."

Silencing the DLK1-DIO3 genetic region is an early event for tumors, Phinney said, pointing out that micro-metastasis can be detected even in the early stages of breast cancer.

One of the seven miRNAs highlighted in the new study—MiR-544—appears to be potent in its powers of inhibition, repressing cancer cell proliferation by inducing Ataxia telangiectasia mutated (ATM), a protein involved in stopping the cell cycle once DNA damage is detected.

"What's interesting is that MiR-544 blocks cell growth in every tumor cell line we've put it into, so we're looking at it as a potential therapeutic target," Phinney said.

Phinney noted that dozens of miRNAs exist in the same genetic region. "It's possible there are other clusters that work together to affect tumor growth and metastasis," he said.

More information: "MicroRNAs in the Imprinted DLK1-DIO3 Region Repress the Epithelial-to-Mesenchymal Transition by Targeting the TWIST1 Signaling Network," www.jbc.org/content/early/2012 … 0/26/jbc.M112.387761

Provided by Scripps Research Institute