UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern team identifies tumor-specific pathway; finding could lead to new cancer-stopping therapies

DALLAS – Nov. 22, 2011 – A research team led by UT Southwestern Medical Center scientists has identified an atypical metabolic pathway unique to some tumors, possibly providing a future target for drugs that could reduce or halt the spread of cancer.

Dr. Ralph DeBerardinis, senior author of the study published Nov. 20 in *Nature*, likened the newly discovered pathway to traffic that is rerouted during a highway construction project.

"If we hone in on this reverse pathway, then we may be able to prevent the growth of certain types of cancer," said Dr. DeBerardinis, assistant professor of pediatrics and a physician scientist in the Eugene McDermott Center for Human Growth and Development. "It's long been thought that targeting tumor-specific metabolic pathways would lead to an effective way to treat cancer. This is one of the few metabolic pathways that may actually exist specifically in tumors."

The pathway involves the Krebs cycle, a series of chemical reactions that generates energy and is considered one of the most familiar and widely studied processes in biology. In the normal cycle, energy is derived by the breakdown of acetate from ingested carbohydrates, fats and proteins into carbon dioxide and water.

For more than 70 years, biology textbooks have depicted the Krebs cycle as running clockwise in normal cells. UT Southwestern researchers found that in some tumors the cycle runs in reverse.

The discovery is the latest milestone in a long line of scientific inquiry that began in the 1920s when biochemists first recognized metabolic differences between cancer cells and normal cells. Scientists since have thought they could stop the growth of cancer cells with drugs that target only tumor-specific pathways, leaving normal cells unaffected.

Researchers have identified only a few such therapeutic windows, the latest of which appears to be the reverse Krebs cycle pathway identified by Dr. DeBerardinis and colleagues in this investigation.

"There is no pathway that has been more extensively studied over the years than the Krebs cycle," Dr. DeBerardinis said. "The fact that with relatively modest manipulation, it can run in reverse is incredibly fascinating."

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Dr. James K.V. Willson, director of the Harold C. Simmons Comprehensive Cancer Center, said the findings are significant.

"We are learning that certain cancers have previously unrecognized mutations in genes controlling metabolism – and these abnormalities are providing new therapeutic opportunities," he said.

Andrew Mullen, a graduate student in genetics and development at UT Southwestern, was first author of the paper. Other UT Southwestern researchers involved in the study were Dr. Eunsook Jin, instructor in the Advanced Imaging Research Center; Pei-Hsuan Chen, graduate student in integrative biology; and Dr. Tzuling Cheng, a postdoctoral researcher in pediatrics. Scientists from Northwestern University and from the National Cancer Institute also participated.

The project was funded in part with a grant from the Cancer Prevention and Research Institute of Texas.

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