UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern researchers uncover a genetic vulnerability of lung cancer to lay the foundation for new drug options

DALLAS – April 4, 2013 – Physician-researchers at UT Southwestern Medical Center have identified a vulnerability of certain lung-cancer cells – a specific genetic weakness that can be exploited for new therapies.

Although researchers have long known that mutant versions of the KRAS gene drive tumor formation and are key to cell survival in non-small cell lung cancer, the blocking of activated KRAS has proven difficult. For years, investigations have explored stopping lung cancer at this junction, which also would have an impact on many other cancers. KRAS mutations, for instance, account for as much as 50 percent of all colon cancers.

"There is an urgent need to identify 'downstream' pathways that are required to sustain and grow non-small cell lung cancer (NSCLC)," said Dr. Pier Paolo Scaglioni, assistant professor of internal medicine and a member of the Harold C. Simmons Cancer Center. "As we focus on the right pathways, we stand a much better chance of chemically blocking them and stopping tumor growth."

The team's findings are published in the April edition of *Cancer Discovery*, a journal of the American Association for Cancer Research. Dr. Scaglioni served as senior author and Dr. Georgia Konstantinidou, a postdoctoral researcher, was first author.

To identify vulnerabilities in KRAS-mutant tumors, Dr. Scaglioni's group used a mouse model of high-grade lung adenocarcinoma induced by a recombinant transgene that allows activation of mutant KRAS in the respiratory epithelium. This strategy allows the generation of high-grade lung cancers that closely resemble human tumors.

Compared with control tumors, the investigators found that the protein RHOA was specifically required for the survival and growth of high-grade tumors via activation of a focal adhesion kinase (FAK). Consistent with a critical role for this pathway in NSCLC, activation of RHOA and FAK was observed in human NSCLC samples and human lung-cancer cells were found to be highly sensitive to pharmacologic inhibitors of FAK.

FAK is a protein that helps cells stick to each other and their surroundings, and also aids in determining how rigid and mobile the cell's structure is. When FAK is blocked in breast cancer, the cancer cells become less metastastic due to decreased mobility.

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Dr. Scaglioni and his team are now poised to study in clinical trials the pharmacologic blockade of FAK using inhibitor compounds currently under commercial development.

"Our findings provide the rationale for the rapid implementation of genotype-specific targeted therapies utilizing FAK inhibitors in cancer patients," Dr. Konstantinidou said.

Other researchers at UT Southwestern involved in the paper include Dr. Rolf A. Brekken, associate professor of surgery and pharmacology; Dr. Michael T. Dellinger, postdoctoral researcher II in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research; and Rachel E. Ramirez, research assistant I in obstetrics/gynecology. Scientists from the University of Texas MD Anderson Cancer Center in Houston and Memorial Sloan-Kettering Cancer Center in New York also contributed to the investigation.

The research was conducted with support from the American Cancer Society, the Ryan Gibson Foundation, and the Department of Defense.

Please visit the Harold C. Simmons Cancer Center to learn more about oncology at UT Southwestern, including highly individualized treatments for cancer at the region's only National Cancer Institute-designated center.

About UT Southwestern Medical Center

UT Southwestern, one of the premier academic medical centers in the nation, integrates pioneering biomedical research with exceptional clinical care and education. The institution's faculty has many distinguished members, including five who have been awarded Nobel Prizes since 1985. Numbering more than 2,700, the faculty is responsible for groundbreaking medical advances and is committed to translating science-driven research quickly to new clinical treatments. UT Southwestern physicians provide medical care in 40 specialties to nearly 100,000 hospitalized patients and oversee more than 2.1 million outpatient visits a year.

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