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Scientists discover new therapeutic target for lung cancer driven by KRAS

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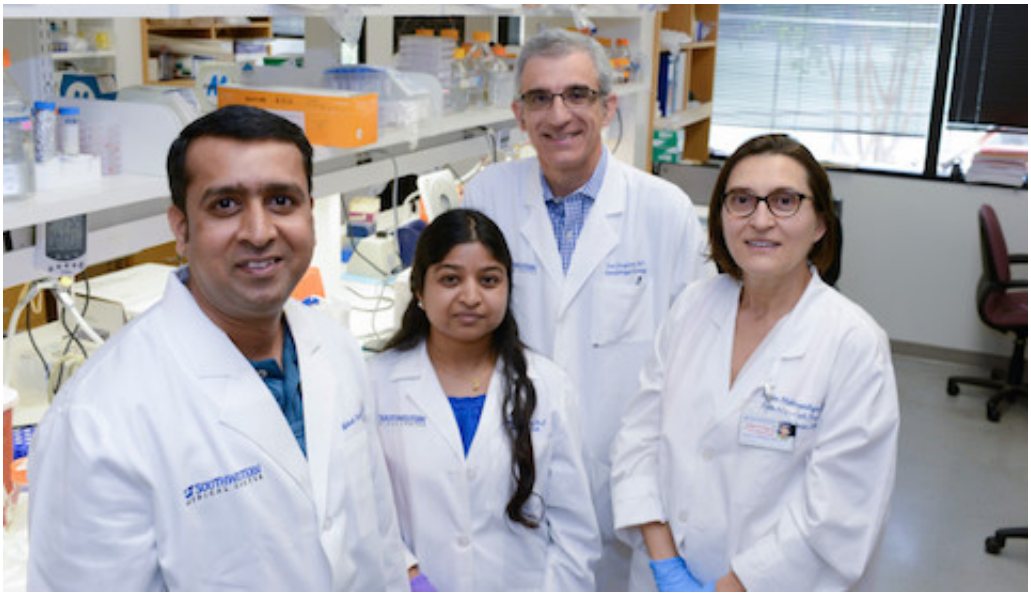

UT Southwestern researchers (left to right) Dr. Mahesh Padanad, Dr. Smita Rindhe, Dr. Pier Paolo Scaglioni, and Dr. Margherita Melegari have found a new way to target lung cancer through the KRAS gene, one of the most commonly mutated genes in human cancer. Credit: UT Southwestern Medical Center

UT Southwestern Medical Center researchers have identified a new way to target lung cancer through the *KRAS* gene, one of the most commonly mutated genes in human cancer and one researchers have so far had difficulty targeting successfully.

Researchers studying the underlying biology of *KRAS* in lung cancer

determined that activity resulting from the *ACSL3* gene is essential for these lung cancer cells to survive, and that suppressing *ACSL3* causes these lung cancer cells to die.

The findings are significant because genetic mutations of *KRAS* occur in about 30 percent of lung cancer cases, and they are associated with aggressive, therapy-resistant disease with a poor prognosis. Lung cancer remains the leading cause of cancer-related deaths in the U.S., according to the National Cancer Institute (NCI).

"Despite some recent advances, mutant *KRAS* remains a very challenging target. There is a dearth of treatment options for tumors initiated by this gene," said senior author Dr. Pier Paolo Scaglioni, Associate Professor of Internal Medicine in the Division of Hematology and Oncology, and a member of the Harold C. Simmons Comprehensive Cancer Center.

The *KRAS* gene (*Kirsten rat sarcoma viral oncogene homolog*), produces proteins called K-Ras that influence when cells divide. Mutations in K-Ras can result in normal cells dividing uncontrollably and turning cancerous.

"Mutant *KRAS* not only promotes the growth of tumors, but also the survival of established lung cancer. Since we have no clinically-relevant effective inhibitors of mutant *KRAS* at this time, there has been an intense clinical interest in developing a treatment that is proven effective," said Dr. Scaglioni, who leads the Cancer Signaling Laboratory at the Simmons Cancer Center.

The team found that the enzymatic activity of *ACSL3* (*Acyl-CoA synthetase long-chain family member 3*) is needed for the mutant *KRAS* gene to promote the formation of lung cancer, and further demonstrated that fatty acids, which are the substrates of ACSL3 enzyme, have a critical role in lung cancer.

"There is an urgent need for discovery of additional targets that inhibit lipid metabolism in cancer cells that could lead to targeted therapies: the discovery of the importance of ACSL3 in lung cancer meets this unmet need," said Dr. Mahesh S. Padanad, first author and part of the UT Southwestern team, which also includes postdoctoral fellow Dr. Smita Rindhe, and Dr. Margherita Melegari, research associate.

The study, published in *Cell Reports*, used several complementary approaches, including cell lines, mice, and human patient tumor samples to understand the biological significance of ACSL3 in lung cancer.

Provided by UT Southwestern Medical Center

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