Study identifies key protein that helps prevent lung cancer tumors from being destroyed

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(Medical Xpress)—Researchers at the Translational Genomics Research Institute (TGen) have discovered a protein, Mcl-1, that helps enable one of the most common and deadly types of cancer to survive radiation and drug treatments.

Non-small cell lung cancer (NSCLC) makes up about 85 percent of the nearly 160,000 Americans expected to die this year from lung cancer, which by far kills more patients than any other type of cancer; accounting for more than 1 in 4 cancer deaths in the U.S. annually. The 5-year survival rate for advanced NSCLC is less than 10 percent.

In the absence of more effective targeted therapies, most lung cancer patients currently rely on platinum-derived chemotherapeutics, such as cisplatin, or radiation therapy.

Previous TGen studies have shown that excessive activation of a cellular signaling mechanism known as TWEAK-Fn14 is linked to the survival and spread of cancer cells.

In a new laboratory study published in the scientific journal *Molecular Cancer Research*, TGen investigators found that a protein called Mcl-1 helps enable TWEAK-Fn14, which in turn helps protect NSCLC tumors from being destroyed by radiation and drugs.

"Our study demonstrates that the expression of Mcl-1 is necessary to promote the TWEAK-mediated survival of NSCLC tumor cells," said Dr. Timothy Whitsett, an Assistant Professor in TGen's Cancer and Cell Biology Division, and the study's lead author. "By deactivating Mcl-1, we believe we can give these lung cancer patients a better response to standard therapy."

Employing a drug called EU-5148, laboratory researchers using lung cancer cell lines found they could block Mcl-1 function and halt the TWEAK-Fn14 cellular signaling mechanism.

"Inhibition of Mcl-1 function enhanced chemo- and radio-sensitivity in NSCLC cells. The depletion of Mcl-1 … was sufficient to abrogate the protective effects conferred on lung tumor cells by TWEAK-Fn14 signaling," according to the study, Mcl-1 Mediates TWEAK/Fn14-induced Non-small Cell Lung Cancer Survival and Therapeutic Response, published online Jan. 27, and awaiting print publication on April 14.

"This work positions both the TWEAK-Fn14 cellular pathway and the Mcl-1 protein as potential therapeutic interventions," said Dr. Nhan Tran, an Associate Professor in TGen's Cancer and Cell Biology Division, and the study's senior author. "Our evidence shows that, if we can bypass these mechanisms, it will be more difficult for these lung cancer cells to evade therapies."

The study concludes that additional research of Mcl-1 and TWEAK-Fn14 mechanism is needed, eventually leading to clinical trials and more effective treatments that could reduce lung cancer mortality.

More information: "Mcl-1 Mediates TWEAK/Fn14-induced Non-small Cell Lung Cancer Survival and Therapeutic Response," Timothy G Whitsett, Jr, Ian T Mathews, Michael H Cardone, Ryan J Lena, William

E Pierceall, Michael Bittner, Chao Sima, Janine LoBello, Glen J Weiss, and Nhan L Tran. *Mol Cancer Res*, molcanres.0458.2013; Published OnlineFirst January 27, 2014; DOI: 10.1158/1541-7786.MCR-13-0458