ZEB1 throttles therapeutic target, protecting KRAS-mutant lung cancer

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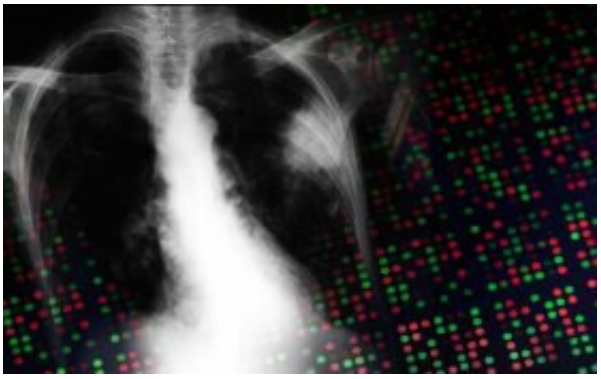

Credit: University of Texas M. D. Anderson Cancer Center

A cellular identity switch protects a cancer-promoting genetic pathway from targeted therapy, researchers at The University of Texas MD Anderson Cancer Center today reported in *Science Translational Medicine*.

Working in cell lines and mouse models of lung cancer, a team led by Don Gibbons, M.D., Ph.D., associate professor of Thoracic/Head and Neck Medical Oncology, demonstrated how the KRAS-driven lung cancer cells defeat treatment by switching from stable, stationary cells into a type of mobile, resistant cell associated with embryonic development. They also found a drug combination that reversed that cellular transition and restored vulnerability to targeted therapy.

About 30 percent of all cancers have an activating mutation of KRAS, which triggers tumor initiation and progression through a signaling pathway called MAPK. While KRAS itself has not been successfully attacked by drugs, targeted therapy has been developed for MEK, one of the downstream proteins triggered by KRAS in the cancer-promoting MAPK cascade.

"MEK inhibitors have been tried in multiple clinical settings, including lung cancer, and the results have not been good," Gibbons said. "They haven't consistently worked for patients with KRAS mutations and it was unclear why."

Gibbons and colleagues set out to identify resistance mechanisms, working through MD Anderson's Lung Cancer Moon Shot, part of its Moon Shots Program, a collaborative effort to accelerate the development of scientific discoveries into clinical advances that save patients' lives.

Triggering epithelial cell shift into dangerous mesenchymal status

A series of cell line experiments and in vivo screens showed that certain cells in tumors have mutant KRAS and activated MAPK signaling, making them potentially vulnerable to MEK inhibition. These epithelial cells—which line or cover the body's organs—are not mobile and perform a specific function.

A second group of experiments established that MAPK signaling is regulated by a protein called ZEB1, which suppressed the IL17RD protein to shut down the signaling pathway in the presence of a KRAS mutation. ZEB1 expression transitions epithelial cells to a different cell type—mesenchymal cells.

This type of mesenchymal cell is normally active during embryonic development, Gibbons explained. As embryonic stem cells produce all the cell types needed for the developing embryo, epithelial cells take on a mesenchymal form that allows, for example, a lung cell to move to join other lung cells. Once in place, the cells revert to epithelial form to stay put and form the organ.

"Mesenchymal cells have a very high migratory and invasive capability because of their normal function during embryogenesis," Gibbons said. "This program, called epithelial to mesenchymal transition (EMT), is known to become activated during the development and progression of tumors."

This firing up of an embryonic process in adult cells has long been associated with cancer progression and metastasis and is a focus of Gibbons' lab.

"You take a well-differentiated epithelial cell that has a normal function, whether it's a kidney cell or a lung cell or a breast cell and they have a function and it's well-defined. All of a sudden you turn on particular EMT gene sets and now those cells behave like a 5-year-old instead of an adult cell because they are no longer regulated in the same way. They run off and begin behaving in a way that is not typical. And that is the epitome of cancer," Gibbons said.

When mouse models with KRAS mutant lung cancer tumors of either epithelial or mesenchymal type were treated with MEK inhibitors, the mesenchymal cells were resistant from the start. Epithelial cells responded well initially, but over 80 percent of the tumors became resistant over time.

"Those tumors that became resistant had undergone a robust epithelial to mesenchymal transition," Gibbons said.

Reversing EMT, restoring MAPK

Previous research by other labs had shown that a type of drug called a histone deacetylase (HDAC) inhibitor can reverse EMT, allowing mesenchymal cells to revert to epithelial cells. In this study, treating cells with an HDAC inhibitor suppressed ZEB1, reversed EMT and restored MAPK activity, making tumors vulnerable to MEK inhibitors.

Combination therapy with an HDAC inhibitor and a MEK inhibitor steeply shrank tumors in mice.

An analysis of several large datasets of human tumors validated a negative correlation between ZEB1 and a measure of MAPK pathway activity.

The team is conducting work on combination therapies to attack both epithelial and mesenchymal cells.

"Mesenchymal cells are not sensitive to MEK inhibitors even though they have mutant KRAS," Gibbons said. "If it's not signaling through MAPK what is the mutant KRAS signaling through, what is it dependent on for its survival?"

Research also focuses on combining a MEK inhibitor with immune checkpoint inhibitors that unleash an immune attack on tumors. Immunotherapy already has had a significant impact on lung cancer and could change the dynamics of cell resistance to MEK treatment.

More information: ZEB1 suppression sensitizes KRAS mutant cancers to MEK inhibition by an IL17RD-dependent mechanism *Science Translational Medicine* 13 Mar 2019: Vol. 11, Issue 483, eaaq1238, DOI: 10.1126/scitranslmed.aaq1238 , stm.sciencemag.org/content/11/483/eaaq1238

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