Researchers inhibit tumor growth in new subtype of lung cancer

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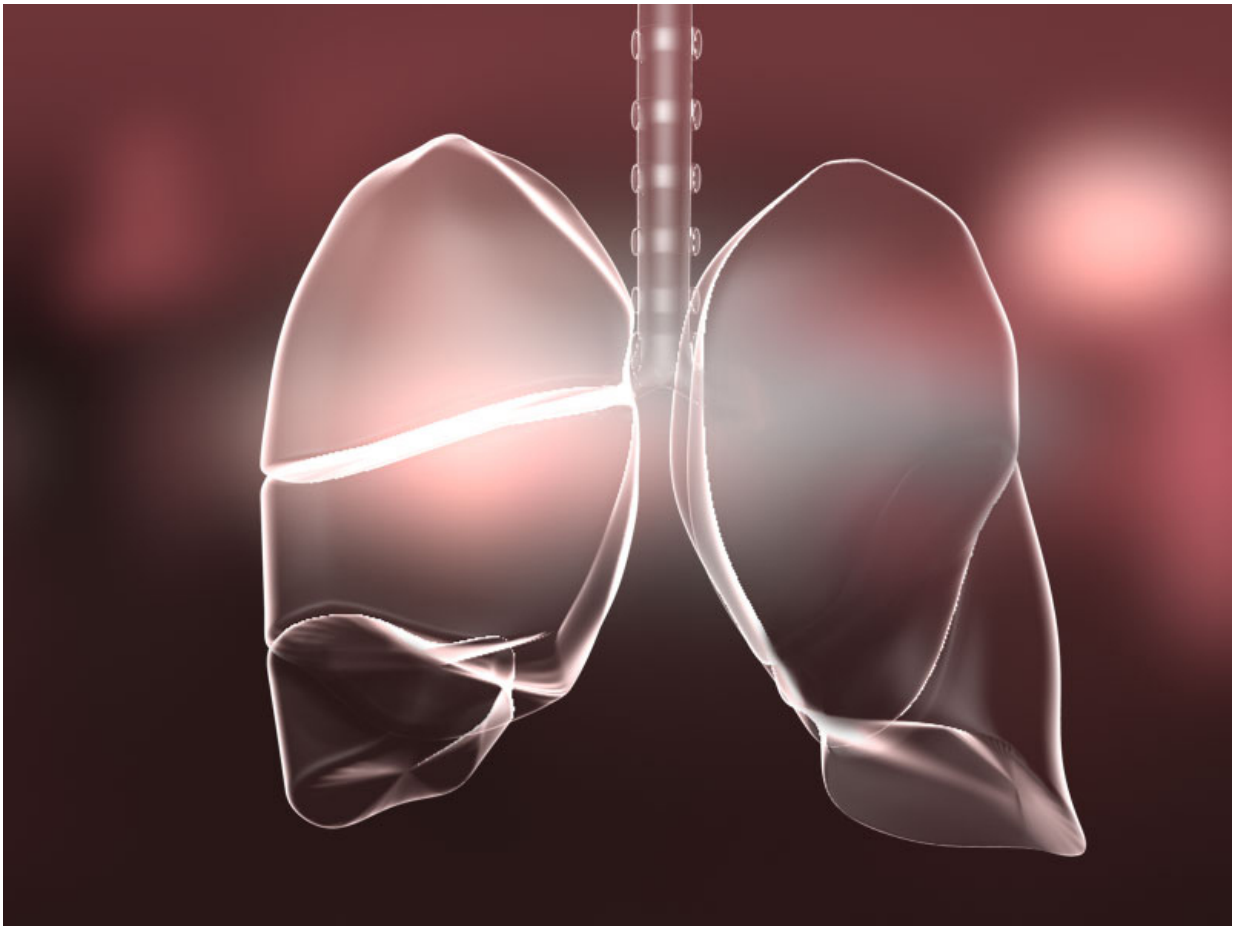

A new study in mice shows that therapy blocking an oncogenic protein, BMI1, may be effective against some forms of non-small cell lung cancer. Credit: Val Altounian, Science Translational Medicine (2016)

Lung cancer is the most common cause of cancer deaths, accounting for about a third of all tumor-related deaths. Adenocarcinomas, a non-small cell lung cancer (NSCLC), account for about 40 percent of cancer diagnoses, but few treatments are available for the disease.

A team of investigators led by Elena Levantini, PhD, a research associate in Hematology-Oncology at Beth Israel Deaconess Medical Center (BIDMC), instructor of medicine at Harvard Medical School and a member of the Harvard Stem Cell Institute, have identified a subtype of human adenocarcinoma. The research could help determine which individuals are at greatest risk of developing lung tumors that may be amenable to a new therapy to inhibit their progression. The results - done in collaboration with the Cancer Science Institute at the National University of Singapore (CSI NUS) - were published today in the journal *Science Translational Medicine*.

"Advances in lung cancer therapy require a greater understanding of the molecular origins of this deadly disease," said last corresponding author Levantini, who is also a researcher at the Institute of Biomedical Technologies at the Italian National Research Council (ITB-CNR). "Understanding the differences among lung cancers also could lead to innovations in treatment strategies and allow us to overcome drug-resistance, relapse and disease progression."

Levantini and colleagues previously showed that NSCLC tumor cells frequently express too little or none of a transcription factor called C/EBPα, a protein that regulates gene expression and cell proliferation in lung tissues. It's also known to play a role in a form of leukemia, as well as liver cancer, squamous cell skin carcinomas, squamous cell cancers of the head and neck and other cancers. In their previous work, the scientists suspected that C/EBPα may act as a tumor suppressant in normal cells, but the mechanism by which its absence promoted lung cancer tumors remained unclear.

In a series of in vitro experiments, the researchers demonstrated that C/EBPα indeed works as a tumor suppressant by restraining the expression of another molecule known to play a role in triggering and maintaining tumor growth. This molecule, called BMI1, is an oncogenic protein that has been implicated in colon cancer, a form of leukemia and breast and gastric cancers.

To determine the relationship between the suspected tumor suppressor (C/EBPα) and the oncogenic protein (BMI1), the researchers first altered a line of human adenocarcinoma cells to overexpress C/EBPα. That led to a marked reduction in the expression of BMI1. When the team analyzed tissues from 261 patients with NSCLC, they found an inverse correlation between the two molecules; that is, more than 80 percent of patient tissues with low levels of the tumor suppressing C/EBPα were positive for BMI1 expression. Likewise, an analysis tissue samples from patients with lung adenocarcinoma with no or low C/EBPα expression revealed that those with lower levels of BMI1 were more likely to survive, a pattern that has prognostic value, the researchers wrote.

"Our findings suggest that the lung cancer subtype defined by the loss of C/EBPα expression might specifically benefit from therapies that inhibit BMI1," the scientists wrote. "Thus, identifying factors that modulate its expression has generated major clinical interest."

The research team was also able to validate its findings in mice. In one set of experiments with mice engineered to express no C/EBPα, the scientists found an inverse relationship between the transcription factor and BMI1 that was nearly identical to its data from human adenocarcinoma. By manipulating BMI1 expression in vivo, the researchers were also able to confirm that decreasing the expression of the oncogenic protein was enough to fully inhibit tumor formation and even significantly arrest tumor growth.

"BMI1 plays a substantial role in many solid tumors, including one of the most aggressive models of lung cancer, and its expression is linked with tumor growth, invasion, metastasis, prognosis and recurrence," Levantini said. "Our findings could help us design better therapies for the subset of adenocarcinoma patients with low C/EBPα and high BMI1 expression pattern."

More information: "Targeted BMI1 inhibition impairs tumor growth in lung adenocarcinomas with low CEBPα expression," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aad6066

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