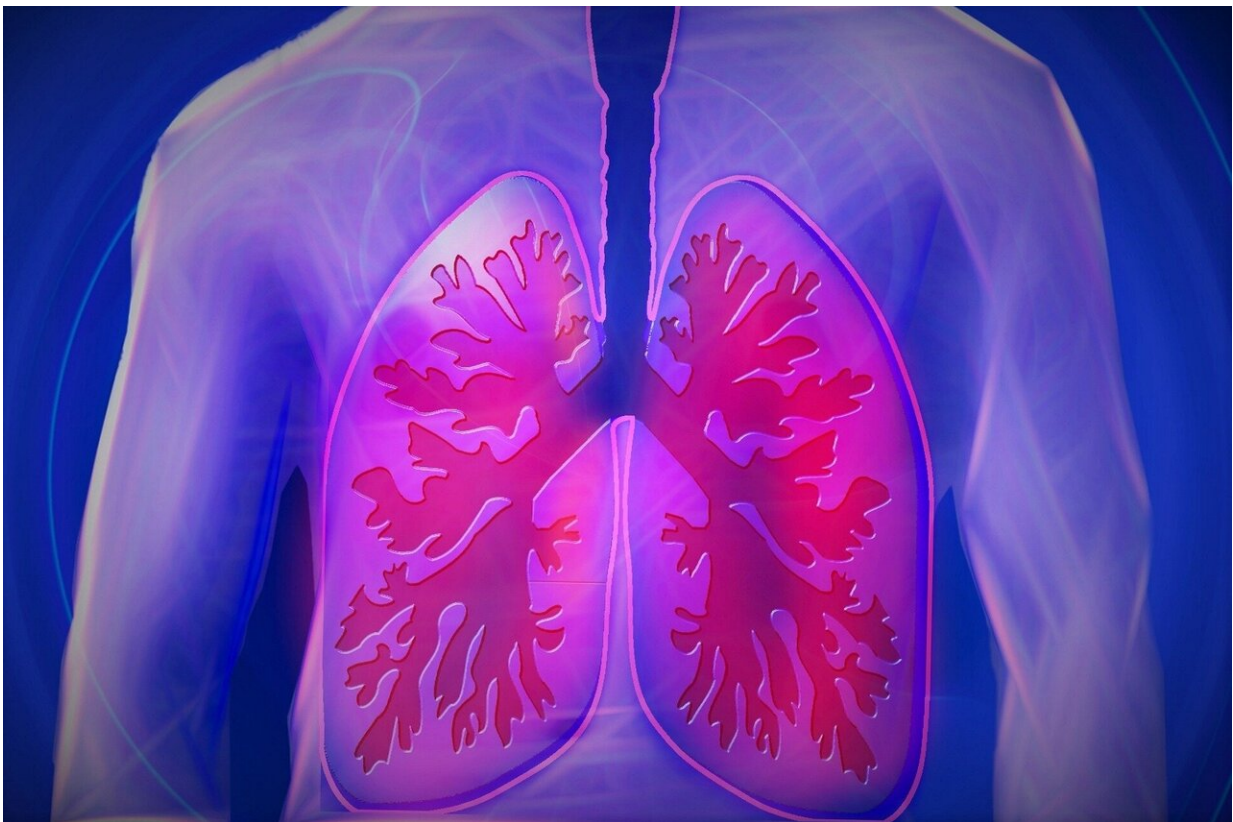


Study could potentially lead to new combination treatments for early-stage lung cancers

November 7 2023



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One of the hallmarks of cancer cell development is its dependence on sugar, especially glucose, to grow and divide. Scientists have long been

studying how to restrict or block this process that promotes tumor growth, called glycolysis, from happening as a possible effective strategy against cancer.

Previously, researchers from the UCLA Health Jonsson Comprehensive Cancer Center identified a specific protein sodium glucose transporter 2, or SGLT2, as a mechanism that lung cancer cells can utilize to obtain glucose.

Drugs that inhibit SGLT2 are already FDA approved for other conditions and the UCLA team found these drugs could also delay the development of lung cancer and improved survival when tested in mice, suggesting these drugs could be repurposed for lung cancer treatment.

However, while inhibiting glycolysis can slow down the growth of tumors, the researchers found it can also make cancer cells more aggressive, making the cancer harder to treat. This led the team to look at other mechanisms of resistance in the tumors that still grow while being treated with SGLT2 inhibition that may link glucose restriction to increases aggression.

Researchers found that by restricting glucose in lung cancer cells, it caused the cells to lose their specialized features, making them more aggressive. This change was linked to alteration in certain molecules and how they modify DNA structure. The study was published in the journal *Cancer Research*

One of those molecules was alpha-ketoglutarate, which plays a pivotal role both in energy metabolism and in gene regulation. Reduced levels of this molecule affected how genes are turned on and off, activating HIF1 α , a transcription factor known to play a role in making cancer cells more aggressive.

This led the researchers to discover a specific set of genes, controlled by HIF1 α , that could predict how aggressive a cancer might be, giving physicians important information that can help guide treatment decisions. The team also found potential ways to block the tumor from becoming more upset, or greedy, when deprived of its nutrients.

"While we still need to further explore the intricacies of this mechanism, our findings point to a potential therapeutic strategy using a combination of treatments involving epigenetic modulators or HIF inhibitors to counter the unintended effects of glucose restriction," said senior author of the study Dr. Claudio Scafoglio, assistant professor of pulmonary and [critical care medicine](#) at UCLA and member of the UCLA Health Jonsson Comprehensive Cancer Center.

This study provides crucial insights into the role of glucose restriction in driving an aggressive phenotype in lung cancer. The discovery suggests a new possible combination approach to treat early-stage lung cancer, using a [glucose](#) inhibitor and an epigenetic inhibitor that are already available for other conditions that can help reduce [tumor growth](#) and offset aggressive behavior. More work is underway to find the right approach to prevent starvation-induced de-differentiation without causing significant side effects.

More information: *Cancer Research* (2023)

Provided by University of California, Los Angeles

Citation: Study could potentially lead to new combination treatments for early-stage lung cancers (2023, November 7) retrieved 27 April 2024 from <https://medicalxpress.com/news/2023-11-potentially-combination-treatments-early-stage-lung.html>

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