Lactate metabolism target halts growth in lung cancer model

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Cancer cells generate energy differently than normal cells, a characteristic that helps them to survive and metastasize. A major goal in the field of cancer metabolism is to find ways to overcome this survival advantage.

Now a research team led by investigators in the Cancer Center at Beth Israel Deaconess Medical Center (BIDMC) has found that targeting the enzyme responsible for the final step of glucose metabolism not only halts tumor growth in non-small-cell lung cancer, but actually leads to the regression of established tumors.

Importantly, the new findings, which appear online April 10 in the journal *Cell Metabolism*, also show that cancer initiating cells –tumor cells that possess stem-cell like characteristics which can give rise to new tumors – are susceptible to LDH-A inhibition.

"We've known for almost 100 years that increased lactate production is associated with aggressive tumors," says the study's senior author Pankaj Seth, PhD, an investigator in the Division of Interdisciplinary Medicine and Biotechnology at BIDMC and Assistant Professor of Medicine at Harvard Medical School (HMS). "So our team had a straightforward question: If you were to inhibit the production of lactate, what would happen? And we found that not only did tumors stop growing, they actually regressed. Most exciting, we also showed that inhibition of LDH-A impacts cancer initiating cells, a population of aggressive tumor cells not targeted by most current therapies."

Altered energy metabolism is a defining biochemical characteristic of cancer cells, and was first observed nearly a century ago by German scientist Otto Warburg in what has now become known as the "Warburg Effect." While normal cells usually produce most of their energy needs from burning fuels using oxygen, cancer's energy production is dependent on sugar or glucose, a process known as fermentative glycolysis.

"Cancer cells rely on anaerobic fermentation for the conversion of glucose to lactate," explains Seth. "This state of fermentative glycolysis is catalyzed by the A form of the LDH enzyme. LDH-A is elevated in cancer cells, and this enables tumor cells to convert the majority of their glucose stores into lactate, regardless of oxygen availability. This shifts the function of glucose metabolites from simple energy production to accelerated cell growth and replication." For this reason, he explains, LDH-A and the possibility of inhibiting its activity has been identified as a promising target in cancer treatments focused on preventing cancer cells from proliferating.

Non-small cell lung cancer (NSCLC) is highly glycolytic, accounts for more than 85 percent of all lung cancers and is the leading cause of cancer deaths. Fermentative glycolysis is promoted in NSCLC through oncogenic mutations in two critical proteins, K-RAS and EGFR. The investigators, therefore, created inducible LDH-A mouse models of non-small cell lung cancer expressing oncogenic K-RAS and EGFR.

"We wanted an established tumor so that we could ascertain how much LDH-A inhibition was needed," says Seth. By genetically adjusting LDH-A levels and comparing the results with that of a small molecule inhibitor, the team showed that when LDH-A was inhibited, not only did the tumors stop growing, they actually regressed in size from the point they were before LDH-A inhibition.

Next, the investigators obtained a small molecule LDH-A inhibitor drug and observed similar effects in cell culture experiments. These results further demonstrated that blocking fermentative glycolysis impacted cancer initiating cells, the small population of tumor-forming, self-renewing cancer cells associated with aggressive disease and poor prognosis.

To investigate the metabolic consequences of LDH-A inhibition, Seth collaborated with co-corresponding author Teresa Fan, PhD, of the University of Kentucky. They conducted a metabolic analysis in which glucose atoms labeled with the stable isotope of carbon were followed as the glucose was converted through the glycolytic pathway into a variety of products. These experiments were carried out in cultured lung cancer cells in the mouse model and in thin slices of human lung tumor tissue.

"The latter is a modern version of Warburg's original experiment," explains Seth. "Together, these experiments showed that LDH-A inhibition affects metabolism, as expected, and underlies the regression of tumors when there is insufficient enzyme to support growth and survival."

"The field of cancer metabolism has seen a resurgence in recent years," adds study coauthor Vikas P. Sukhatme, MD, PhD, BIDMC Chief Academic Officer and Victor J. Aresty Professor of Medicine at HMS. "Findings such as these, conducted in genetically engineered mouse models that are the gold standard by which to judge this data, offer hope that drugs targeting metabolic pathways may one day become part of our armamentarium against this dreadful disease."

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