Study challenges long-standing concept in cancer metabolism

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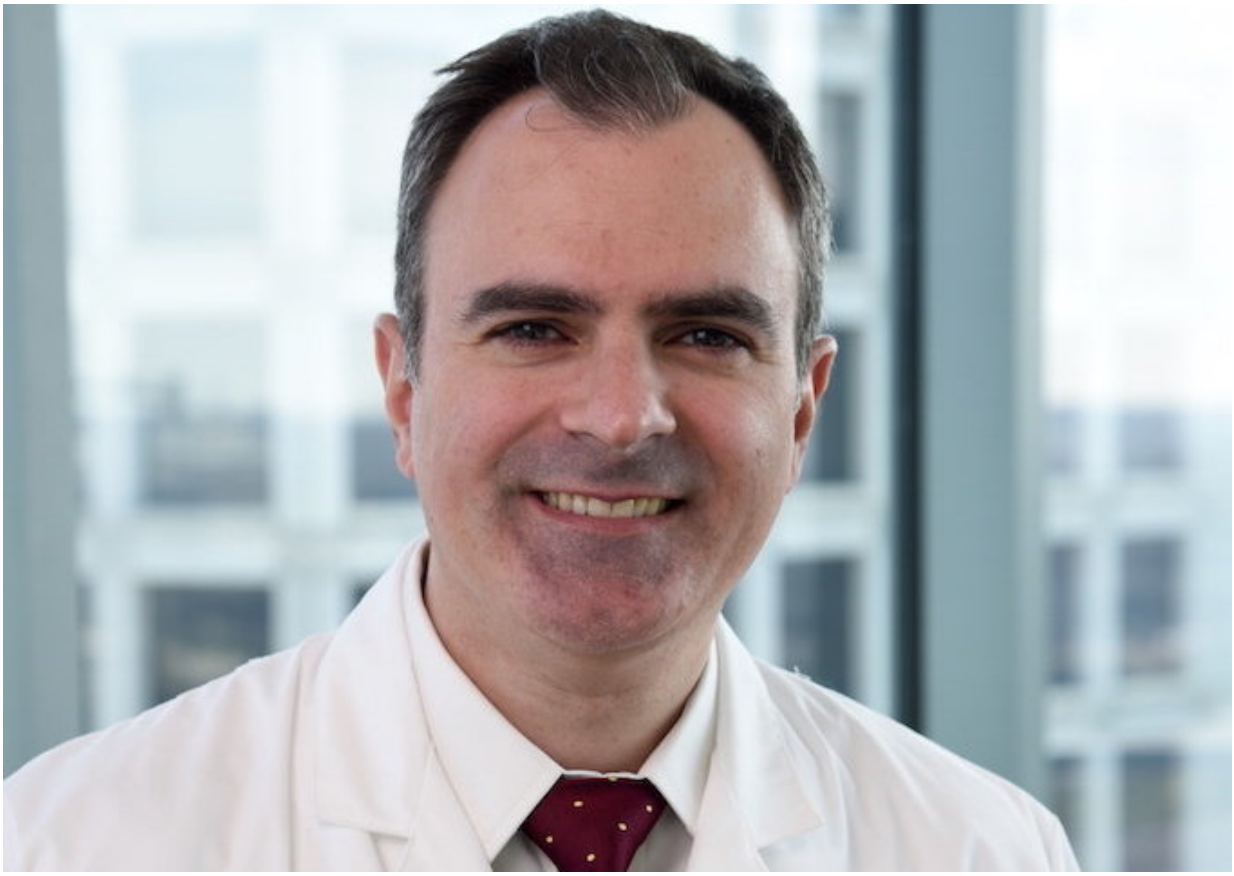

Dr. Ralph DeBerardinis. Credit: UT Southwestern

Scientists at the Children's Medical Center Research Institute at UT Southwestern (CRI) have discovered that lactate provides a fuel for

growing tumors, challenging a nearly century-old observation known as the Warburg effect.

This new finding may represent a major shift in how researchers view cancer metabolism and open a new avenue of study for therapies and imaging techniques for lung cancer, which is the leading cause of carcinoma deaths worldwide.

"We were completely shocked by our findings," said Dr. Ralph DeBerardinis, Professor at CRI, Director of CRI's Genetic and Metabolic Disease Program, and Chief of the Division of Pediatric Genetics and Metabolism at UT Southwestern. "The oldest observation in cancer metabolism, the Warburg effect, says that lactate is a waste product of the tumor. This concept has driven the vast amount of research in the field. Our finding is a fundamental change in how we think about tumor metabolism."

The Warburg effect, named after the German cancer biologist Otto Warburg, has three main components:

- Rapid glucose uptake.
- Reduced glucose oxidation even when oxygen is present.
- Secretion of lactate as a waste product.

In the study published in *Cell*, CRI researchers showed lactate is not only a waste product but also acts as a fuel source consumed by lung cancer cells growing in patients and mice. Combined with a previous study, also published in *Cell*, from the DeBerardinis lab that showed activated glucose oxidation in tumors, the results of this study are challenging the tenets of the Warburg effect.

"We believe that lactate is one of the fuels that supports growth, proliferation, and maybe even lung cancer metastases," Dr. DeBerardinis

said. "Cancer metabolism is clinically actionable, and understanding the lactate pathway could help us find therapeutic targets for lung cancer. Lactate uptake could also have predictive value when used as an imaging tracer."

Additional findings in the study suggest a potential link between lactate use and cancer aggression.

"The findings are preliminary, but we did see a connection between lactate utilization and how quickly the tumors metastasized or recurred. This result suggests that there is something fundamental about the lactate utilization pathway that pertains to the clinical aggressiveness of the tumor," said Dr. Brandon Faubert, a Canadian Institutes of Health Research Fellow at CRI and lead author of the study.

An important factor in these new discoveries was the collaboration between scientists at CRI and the clinical team at UT Southwestern. Working closely with medical personnel in Radiology, Pathology, Pharmacy, Anesthesiology, and the surgical team, researchers were able to analyze the metabolism of tumors during surgeries performed to remove the tumors. This approach provided researchers with vital insights that would not occur in laboratory-based experiments.

More information: Lactate Metabolism in Human Lung Tumors, *Cell* (2017). dx.doi.org/10.1016/j.cell.2017.09.019 , www.cell.com/cell/fulltext/S0092-8674(17)31068-1

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