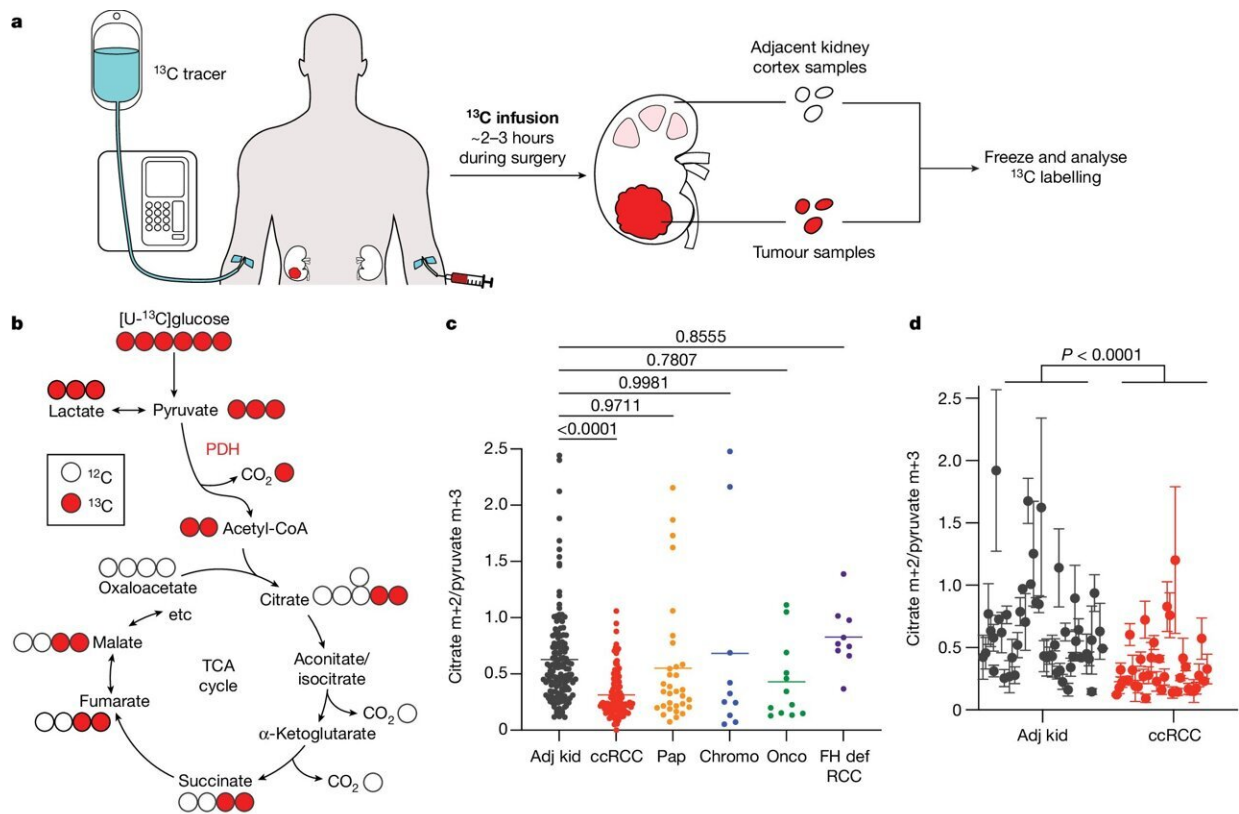


Scientists discover kidney cancers rely on mitochondrial metabolism to metastasize

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Glucose metabolism varies among kidney cancer subtypes. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07812-3

Contrary to how tumors operate while still in the kidney, metastatic kidney cancers rely heavily on mitochondrial metabolism, according to

research from Children's Medical Center Research Institute at UT Southwestern (CRI) published in [Nature](#).

Studying various types of [kidney cancer](#) in 80 UT Southwestern patients, Ralph DeBerardinis, M.D., Ph.D., CRI Professor and Howard Hughes Medical Institute (HHMI) Investigator, and first author Divya Bezwada, Ph.D., collaborated with surgeons from UTSW Department of Urology to track how kidney cancers use sugar and other nutrients from the blood.

Their main discovery is that the mitochondrial electron transport chain, a pathway that allows cells to produce energy from nutrients, is much more active in tumors that have metastasized than in tumors still growing in the kidney.

"Ultimately, the findings could lead to better ways to treat patients with [metastatic cancer](#) or reduce the risk of metastasis in patients with localized cancers at risk of spreading," Dr. DeBerardinis said. "The challenge now is to understand how these key aspects of mitochondrial [metabolism](#) become activated, why they stimulate metastasis, and whether we can safely block them."

These new insights build on earlier CRI discoveries about how some metabolic activities allow [cancer cells](#) to overcome [natural barriers](#) to metastasis, Dr. DeBerardinis added.

"For a century, the dominant idea in [cancer biology](#) was that aggressive tumors turn off mitochondrial metabolism in order to grow and spread. The new research—which studied cancer metabolism directly in patients—shows the opposite: Activating mitochondrial metabolism drives metastasis," Dr. DeBerardinis said.

"Metastasis is the most important cause of cancer-related deaths in

patients with cancers of the kidney and most other organs. Metastatic tumors are the ones we most need to treat."

Vitaly Margulis, M.D., Professor of Urology and a member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern, led the clinical collaboration.

"Most cancer metabolism studies are performed on cells in a dish, which might have little relevance to real tumors. This study is one of the few that examines metabolism where it matters most: in patients," Dr. Margulis said.

"I hope we can move these findings forward for therapy or early prediction of tumors with high metastatic potential. That would add to the personalized cancer management approach we use for every patient with kidney cancer here at UT Southwestern."

The key technology used by CRI scientists involved the intravenous administration of nontoxic, labeled forms of several different nutrients to patients during surgical removal of their tumors.

Samples of the tumors were then analyzed to determine whether the label had moved from the original nutrient to other chemical compounds, a sign that metabolism had occurred. Analysis of several nutrients allowed the team to determine that mitochondrial activity was low in tumors growing in the kidney but higher when these tumors had metastasized to other organs, including the liver, lungs, and brain.

Researchers' findings further suggested mitochondrial activity might stimulate metastasis.

To test this, scientists used mouse models of kidney cancer capable of metastasizing to the lungs. Working with Giannicola Genovese, M.D.,

Ph.D., and Luigi Perelli, M.D., Ph.D., at The University of Texas MD Anderson Cancer Center, Drs. DeBerardinis and Bezwada led a study that discovered inhibiting mitochondrial activity reduces lung metastasis without affecting [tumor](#) growth in the kidney.

On the other hand, activating mitochondrial activity causes the tumors to metastasize much more frequently, even though their growth in the kidney was unaffected.

"This study is an important step to developing metabolic readouts that can predict which patients need more aggressive surveillance, surgery, or other treatments," said Dr. Bezwada, a former DeBerardinis Lab researcher who received her Ph.D. in Cancer Biology from UTSW in 2023.

"We think these new findings will help us understand the metabolic needs of kidney cancer cells growing in patients, and, most importantly, how these needs change during metastasis."

More information: Divya Bezwada et al, Mitochondrial complex I promotes kidney cancer metastasis, *Nature* (2024). [DOI: 10.1038/s41586-024-07812-3](https://doi.org/10.1038/s41586-024-07812-3)

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