Depleted metabolic enzymes promote tumor growth in kidney cancer

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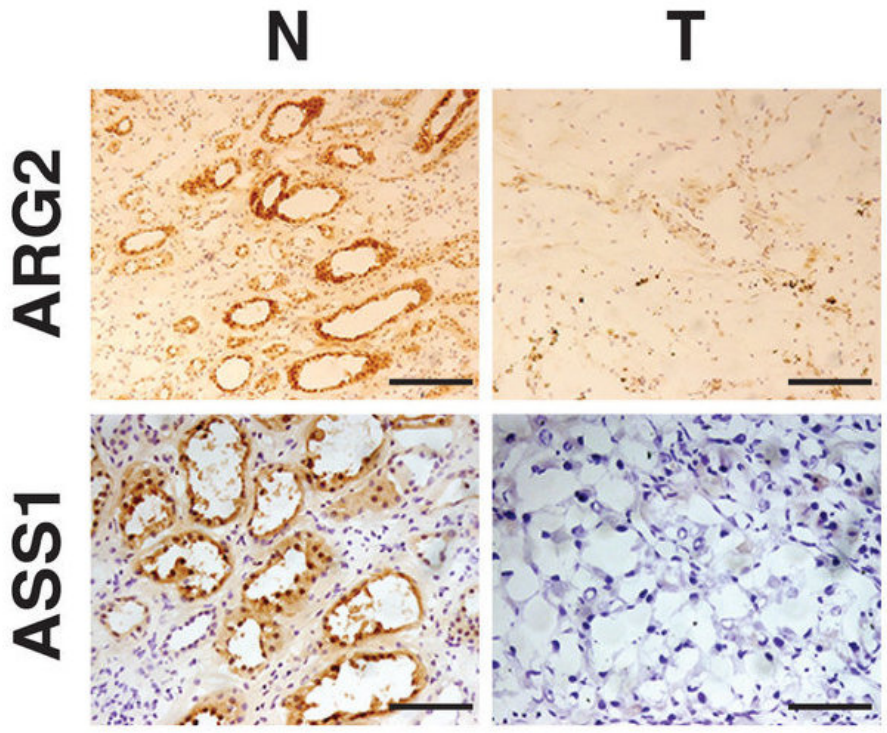

Representative immunohistochemistry images of ARG2 or ASS1 protein in primary ccRCC, N = normal, T = tumor. Scale bars represent 100 microns. Credit: Celeste Simon, Perelman School of Medicine, University of Pennsylvania, *Cell Press*

Kidney cancer, one of the ten most prevalent malignancies in the world, has increased in incidence over the last decade, likely due to rising

obesity rates. The most common subtype of this cancer is "clear cell" renal cell carcinoma (ccRCC), which exhibits multiple metabolic abnormalities, such as highly elevated stored sugar and fat deposition.

By integrating data on the function of essential metabolic enzymes with genetic, protein, and metabolic abnormalities associated with ccRCC, researchers at the Perelman School of Medicine at the University of Pennsylvania determined that enzymes important in multiple pathways are universally depleted in ccRCC tumors. They published their findings this week in *Cell Metabolism*.

"Kidney cancer develops from an extremely complex set of cellular malfunctions," said senior author Celeste Simon, Ph.D., the scientific director of the Abramson Family Cancer Research Institute and a professor of Cell and Developmental Biology. "That's why we approached studying its cause from many perspectives."

Using human tissue provided by the National Cancer Institute's Cooperative Human Tissue Network and Penn Medicine physicians Naomi Haas, MD, an associate professor of Hematology/Oncology, and Priti Lal, MD, an associate professor of Pathology and Laboratory Medicine, the team found that the expression of certain enzymes is strongly repressed in ccRCC tumors. For example, reduced activity of one enzyme, arginase, promotes ccRCC tumor growth through at least two distinct biochemical pathways. One is by conserving a critical molecular cofactor and the second is by avoiding toxic accumulation of organic compounds. The enzymes whose activities are depressed are involved in the breakdown of urea, a byproduct of protein being used in the human body. In addition, loss of these enzymes results in decreased ability of the immune system to eradicate these tumors.

"Pharmacological approaches to restore the expression of urea cycle enzymes would greatly expand treatment options for ccRCC patients,

whose current therapies only benefit a small subset," Simon said.

In the future, the researchers aim to test such epigenetic drugs as HDAC and DNA methylase inhibitors to turn on genes for multiple lost enzymes in renal cancer. The study was completed by researchers at both Penn Medicine and Children's Hospital of Philadelphia who specialize in studying metabolic abnormalities in children.

Provided by Perelman School of Medicine at the University of Pennsylvania