New possible cell target to treat clear cell renal cell carcinoma

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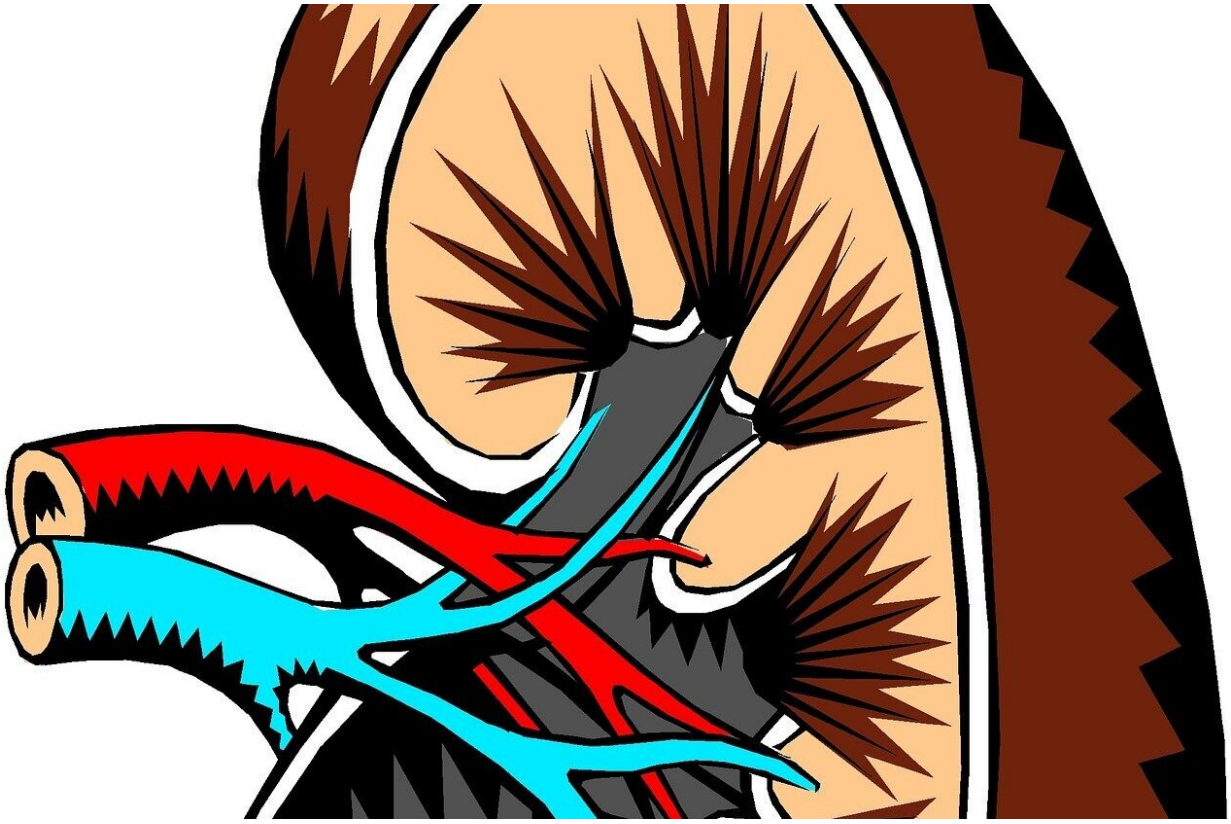

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Clear cell renal cell carcinoma (ccRCC) cells can be destroyed and kept from multiplying by inhibiting the HDL cholesterol receptor SCARB1, according to research from the Perelman School of Medicine at the

University of Pennsylvania. The scientists found the health of these specific cancer cells and tumors are dependent upon cholesterol and this receptor while also showing that medication that specifically targets the receptor could make it impossible for the cancer cells to survive and spread. The research also suggests that controlling cholesterol through diet could minimize the growth of ccRCC tumors. Researchers say future trials can investigate specific therapeutics and diets that can be clinically used to treat ccRCC. The study was published in the journal *Cancer Discovery*.

"Previous studies demonstrated that SCARB1 and cholesterol were both part of the story of ccRCC, but our work here shows a causal role," said lead study author M. Celeste Simon, Ph.D., the Arthur H. Rubenstein, MBBCh Professor in the department of Cell and Developmental Biology and the scientific director of the Abramson Family Cancer Research Institute. "My colleagues and I hope these investigations at the bench can translate to new and successful SCARB1 inhibitors and treatments for people facing this aggressive cancer."

Worldwide, renal cell carcinoma is a common cancer for both men and women, killing 15,000 people in the United States last year. Roughly 70 to 80 percent of renal cell carcinomas are ccRCC. Many are treated by targeted and or immune-based therapies with varying degrees of success. Radiation may also be used.

For this study, the Penn researchers cultured ccRCC cells and put them in environments with varying degrees of cholesterol availability. Cancerous cells, and not normal kidney cells, relied on exogenous cholesterol—or outside cholesterol—in order to grow and survive whereas normal kidney cells are able to synthesize their own cholesterol for typical cellular needs.

"That difference between cancer cells and regular kidney cells is

important because it suggests that kidney cells can create cholesterol they need if cholesterol, available in the body, is restricted," Simon said.

Next, the team identified that there is a greater number of Scavenger Receptors B1 (SCARB1), receptors that import cholesterol for cells, in ccRCC tumors. This led researchers to knock out these receptors in both in vitro and in vivo mouse studies as well as block SCARB1 with a molecule called Block Lipid Transporter-1. ccRCC cells and tumors could not survive without functioning SCARB1.

"There are multiple reasons why the scientific community will likely focus on SCARB1 and the development of SCARB1 inhibitors in the near future," Simon said. A Phase 1 clinical trial was started to investigate the potential for ITX-5061, a SCARB1 inhibitor, to be used as a way to treat hepatitis-C, the researchers said, and other research has tied SCARB1 to the disease progression of SARS-CoV-2.

The research team says that while these results are promising, future work will need to confirm the safety and efficacy of using inhibitors like ITX-5061 to impede SCARB1 and ccRCC in people. They also say the increased incidence of ccRCC in both men and women over the last decade has been suspected to be linked to increased rates of obesity and elevated body mass indices (BMIs) in western populations. This study suggests a causative relationship between obesity, BMI, and circulating HDL cholesterol and likelihood of developing ccRCC that can be further investigated.

More information: Romain Riscal et al, Cholesterol auxotrophy as a targetable vulnerability in clear cell renal cell carcinoma, *Cancer Discovery* (2021). DOI: 10.1158/2159-8290.CD-21-0211