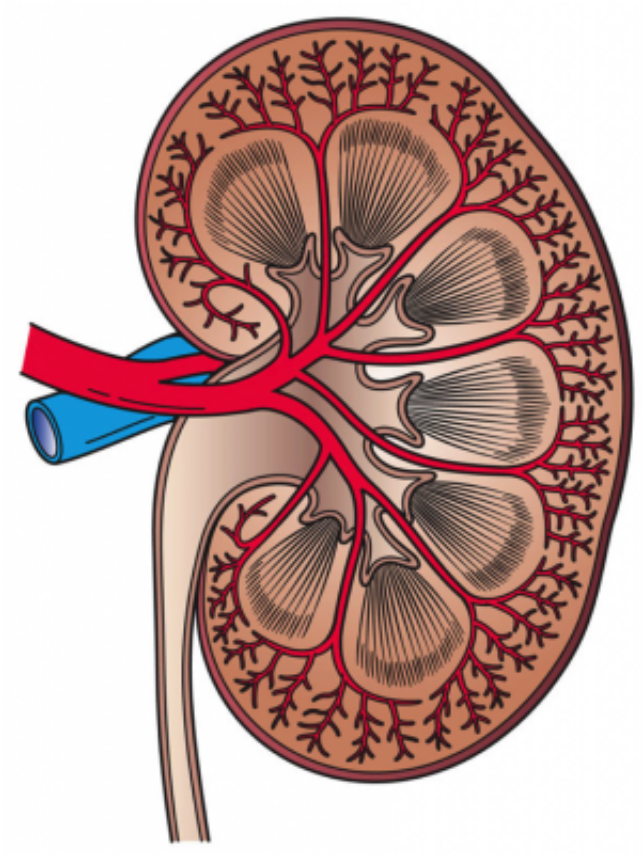
Study offers new understanding of why kidney cancers become metastatic

June 26 2023



This image shows a cross section of a kidney. Credit: Holly Fischer/Wikipedia

Researchers at The University of Texas MD Anderson Cancer have engineered a new model of aggressive renal cell carcinoma (RCC), highlighting molecular targets and genomic events that trigger chromosomal instability and drive metastatic progression.

The study, published in *Nature Cancer*, demonstrates that the loss of a cluster of interferon receptor (IFNR) genes plays a pivotal role in allowing cancer cells to become tolerant of chromosomal instability. This genomic feature may be used to help clinicians predict a tumor's potential to become metastatic and treatment resistant.

Researchers led by Luigi Perelli, M.D., Ph.D., postdoctoral fellow of Genitourinary Medical Oncology, and Giannicola Genovese, M.D., Ph.D., professor of Genitourinary Medical Oncology, used CRISPR/Cas9 gene editing to create a model that faithfully represents RCC in humans, using cross-species analyses to provide further insights into the mechanisms involved in aggressive kidney cancer evolution.

"Until now, there haven't been effective experimental models for metastatic renal cancer progression, but we introduced specific mutations that closely mimic the early stages of human cancers to see how tumors evolve and metastasize," Genovese said. "These tumors become extremely genomically unstable, and, to tolerate this instability, they tend to lose genetic material at a specific site where the interferon genes are located. These insights can help clinicians identify tumors that have the genomic potential to become aggressive."

Renal cell carcinoma is the most common type of kidney cancer, and patients often are treated effectively with surgery, targeted therapy, immunotherapy or a combination of these treatments. However, up to one-third of these patients will have aggressive disease progression, highlighting a need to understand specific mechanisms that drive metastasis in order to identify more effective therapeutic strategies and to predict treatment responses.

One hallmark of cancer is chromosomal instability, which is associated with resistance to many types of therapy and a poor prognosis. However, it is unclear if specific types of chromosomal abnormalities are involved

in driving metastasis and how tumors are able to tolerate them.

The researchers used CRISPR/Cas 9-based genome editing to generate RCC models lacking common tumor suppressor genes. They then targeted cell cycle regulator genes to mimic common chromosomal abnormality associated with metastatic RCC in humans, leading to a phenotype consistent with the human disease. This is the first immunocompetent somatic mosaic model for metastatic RCC, meaning the model has an accumulation of different mutations that result in uncontrolled cell growth but still maintains a functional immune system.

Using genome sequencing and single-cell RNA sequencing to further examine these models, the researchers uncovered molecular drivers of RCC and gained a new understanding of the evolution of chromosomal instability.

Their single cell analyses revealed that a cluster of highly conserved IFNR genes were suppressed in the model, and that this cluster normally functions as a critical gatekeeper, or tumor suppressor, of renal cancer progression.

IFNR gene clusters normally are involved in the immune response. After analyzing various data sets from both mice and humans, the researchers discovered an inverse correlation between the loss of these IFNR genes and aneuploidy, a condition marked by having an abnormal number of chromosomes.

This study suggests that the tumors adapt to high levels of chromosomal instability through the disruption of the IFNR pathway and that this is likely a major biomarker of metastatic potential. It also highlights how renal cancers in different species have followed similar evolutionary patterns that converge around chromosomal instability, which in turn may explain the heterogeneity of these tumors.

In the future, the researchers plan to test drug combinations in these newly generated models to determine how the tumors adapt to various therapies, with the goal of rapidly translating these studies into clinical trials that can help predict treatment response in patients with RCC.

More information: *Nature Cancer* (2023). www.nature.com/articles/s43018-023-00584-1

Provided by University of Texas M. D. Anderson Cancer Center