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Revealing kidney cancer's secret: Tumors gain survival advantage by reprogramming their metabolism

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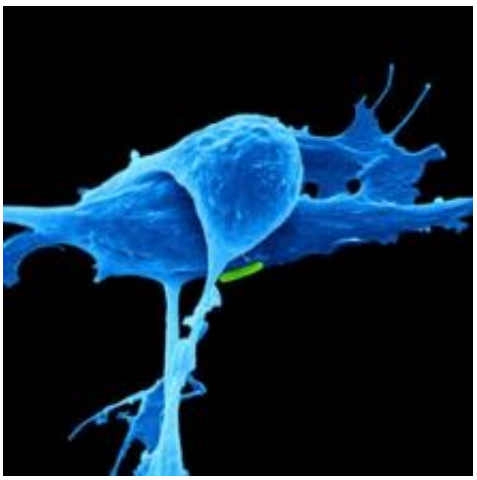

An international team of scientists, led by UC Davis nephrologist Robert Weiss, have used a sophisticated combination of proteomics and metabolomics to show how renal cell carcinoma (RCC) reprograms its metabolism and evades the immune system. In addition, the study found that cancer grade has a major impact on this reprogramming. These results, published in the journal *Cancer Research*, point to new therapeutic options for this particularly deadly cancer.

"The mortality for someone with highly metastatic RCC is somewhere in

the 90 percent range," said Weiss, professor of nephrology and internal medicine at UC Davis and chief of nephrology at the VA Northern California Health System in Sacramento. "We now know this cancer is actually reprogramming its environment to minimize the immune response."

The team used a unique approach to make these discoveries, combining proteomics with metabolomics. The proteomic analyses examined how RCC affects levels of different proteins. Meanwhile, metabolomic studies performed a similar task with metabolites¬—the compounds that remain when larger molecules are broken down or metabolized.

Both proteomic and metabolomic analyses are quite intensive, requiring major computational and statistical firepower. However, combining these two "omics" provided a better view of the mechanisms that govern kidney cancer, like using a wide-angle lens to capture a complete landscape.

"One particular omics technique will tell you part of the story, but it won't give you the whole thing," said Weiss, a scientific member of the UC Davis Comprehensive Cancer Center. "We wanted to combine metabolomics and proteomics and come up with a 'unified field theory' to look at the metabolites in cancer."

This more comprehensive approach paid dividends in several ways. For example, the proteomic analysis showed how RCC increases an enzyme that breaks down the amino acid tryptophan. In turn, the metabolomics studies flagged that tryptophan metabolites suppress the immune system.

A similar story unfolded with glutamine, another amino acid. By manipulating glutamine, kidney cancer removes reactive oxygen species, a key immune system weapon that would usually help destroy the cancer.

"Normally, immune surveillance would shut down the cancer, but RCC has evolved to turn off the immune system, giving it a survival advantage," said Weiss.

The research also uncovered another important story: how cancer grade affects this remodeling. While cancer stage describes how far the disease has progressed through the body—from localized to metastasized—grade describes how abnormal the cancer cells have become. In the case of RCC, higher-grade cancers were remodeling their environments more aggressively.

"We often treat kidney cancers the same, regardless of grade," noted Weiss. "We should think about grade, and not just stage, when we're treating patients."

From a procedural standpoint, the study highlights how combining proteomics and metabolomics can detect cancer mechanisms that either method, by itself, might miss. In addition, this better understanding of how cancer grade affects its ability to alter its surroundings could help oncologists develop more personalize therapies.

But even more importantly, the work points to new therapeutic targets, such as the tryptophan and glutamine pathways, which could help clinicians unleash the immune system against RCC.

"We are going to be testing inhibitors against some of these enzymes so we can stop the tumors from creating these immunosuppressant metabolites," said Weiss.

Provided by UC Davis

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