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Study Uncovers New Driver, Possible Therapeutic Target for Kidney Cancer

By Laura Williamson

The discovery of a second protein that builds up in cells with a common genetic change has opened the door to investigation of an additional therapeutic target for the most common type of kidney cancer.

A study published in *Science* by researchers at the University of North Carolina Lineberger Comprehensive Cancer Center implicates the protein ZHX2 as a driver in clear cell renal cell carcinoma (ccRCC), which accounts for roughly 70% of all kidney cancers. This is the first time ZHX2, previously reported to be a tumor suppressor in liver cancer and lymphoma, has been implicated as a driver in ccRCC, said lead author Qing Zhang, PhD, an assistant professor at the UNC School of Medicine Department of Pathology & Laboratory Medicine and Pharmacology.

"This protein could be a potential therapeutic target used to treat kidney cancer on its own or in combination with other therapies," he said. "The next step is to try to figure out how we can target it therapeutically."

An important predictor of kidney cancer: loss of VHL

Scientists have long known that an important predictor for this type of kidney cancer is the loss of VHL, a gene that suppresses tumors by degrading proteins that are no longer needed, helping to maintain normal cell function. More than 90% of ccRCC patients experience genetic mutations that cause them to lose VHL function.

Previous studies have shown that VHL loss causes a buildup of the protein HIF2α, which turns on the gene VEGF, leading to cancer growth. Most current therapies for ccRCC focus on inhibiting HIF2α or blocking VEGF activity. But these therapies are only partially effective.

The need for alternative treatment pathways

"We have made significant therapeutic advances over the last 10–15 years in kidney cancer," said UNC Lineberger's William Kim, MD, an associate professor of medicine and genetics in the UNC School of Medicine. "No credit should be taken away from that work. There are studies that show that using these VEGF inhibitors prolongs patients' lives. But in the end, a decent number of patients still don't respond to the drugs and rare patients have long-term survival."

Many kidney cancer therapies "have shown great

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Project Aims to Clear Path for Hemodiafiltration in the United States

By Bridget M. Kuehn

A growing number of patients in Europe and Asia are receiving a new form of renal replacement therapy called hemodiafiltration instead of hemodialysis. In fact, about one-third of patients in Europe currently receive hemodiafiltration, and that number is growing by about 6% a year, according to Bernard Canaud, MD, chief medical scientist at Fresenius Medical Care in Germany.

Hemodiafiltration's growing popularity abroad is being driven in part by European studies suggesting that the newer technique leaves patients feeling better with less fatigue and fewer cramps and because of emerging data suggesting that it may also offer cardiovascular benefits, Canaud explained.

Until recently, the U.S. Food and Drug Administration (FDA) had not approved any hemodiafiltration devices, so it hasn't been an option for patients in the United States. But the Kidney Health Initiative (KHI), a public–private partnership that includes the American Society of Nephrology, the FDA, makers of hemodiafiltration

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promise, but 100% response is very uncommon," agreed Armine Smith, MD, director of the Johns Hopkins Urologic Oncology Center at Sibley Memorial Hospital. "They keep the disease stable or shrink the tumor down, but usually the cancer does not go away. The cancer cells overcome the medications in multiple ways. They may shunt the medication out from the cell, or find ways of sequestering the medication inside the cell so it becomes less effective. Or, the cells produce a lot more of the target proteins and that just overcomes the effect of the treatment."

Kidney cancer cells may already be resistant or develop resistance to the pathways currently being targeted, added Pavlos Msaouel, MD, PhD, an assistant professor of genitourinary medical oncology at the University of Texas, MD Anderson Cancer Center.

"If there are other pathways of importance to the cancer cell, separate from the HIF pathway, then those may be keeping those cancer cells alive, despite us targeting HIF," he said. That is, "the cells are using the other pathways instead, so they survive. Or, they learn to rely more on the other pathways. This is a major clinical importance for this paper, in that it identifies emerging new pathways of importance to cancer cells that VHL regulates that are separate from the HIF pathway."

Zhang said he asked himself if "maybe something else played an important role in driving kidney cancer? What else is out there besides HIF2α contributing to this process?"

A comprehensive screening technique narrows focus to ZHX2

To find out, Zhang and his team obtained a genomewide, human cDNA library of 17,000 encoded proteins and, using a comprehensive screening technique, looked "to see if we could find something in there that behaves like HIF2α," he said.

"We wanted to see what other proteins bind to VHL. We found another substrate of VHL," said Kim, explaining that their screening process revealed that "not only is HIF upregulated when VHL is lost, but so is ZHX2."

By examining samples of tumors from seven ccRCC patients with VHL loss, they confirmed that tumors from those patients experienced a buildup of ZHX2. "We showed clinical relevance, because we found it in the patients, as well," said Zhang.

To see whether reducing ZHX2 would shrink or stop tumor growth, the team then introduced tumor cells to the renal capsules of immunodeficient mice. After the tumors began to grow, the mice were fed with a special diet to induce ZHX2 depletion. "The tumors stopped growing and even shrank," said Zhang. "That's what we wanted to see."

The novelty here is that we've found a pathway that's turned on by the most commonly inactivated gene in clear cell kidney cancer.

The authors concluded that "ZHX2 accumulates as a result of VHL loss," said Zhang. "We think this accumulation turns on oncogenic pathways."

New questions to answer

The next step, said Kim, is to look for a drug that can either directly inhibit ZHX2 or a key downstream effector of ZHX2. It will take a lot more investigating to determine what that could be.

"We don't have a known agent or drug that can do this yet," said Zhang. "If we can develop a drug that inhibits ZHX2, we can slow the tumor growth. We have data showing that getting rid of ZHX2 will slow the tumor cell's invasion."

Such a drug could potentially be used in combination with HIF2α inhibitors or other therapies to provide a more effective treatment for ccRCC, the authors said, by targeting multiple pathways at once.

"Studies like this are important, because they delineate the underlying biology of kidney cancer and identify novel, distinct pathways to develop drugs against it," Kim said.

"The novelty here is that we've found a pathway that's turned on by the most commonly inactivated gene in clear cell kidney cancer, a pathway that appears to be completely independent of the HIF pathway. Hopefully in the future, this will allow us to develop a whole new class of inhibitors that can be used independently or combined with current inhibitors."

But that's still a long way off.

"This is basic work," said Kim, "and while exciting, any extrapolation to patient therapy is still a bit away."

One question that needs to be answered in determining whether ZHX2 is an appropriate target, said Msaouel, is whether doing so would cause unintended consequences.

"If ZHX2 functions as a tumor suppressor in different contexts, could inhibiting it promote the development of cancer in other tissues?" he asked. "We don't know. These are clinically relevant questions that we need to elucidate as this pathway is being translationally investigated."

"For example, we may find that it is not as fruitful to target ZHX2, as opposed to other downstream pathways. Finding out will allow us to be a little more precise in targeting this novel pathway," Msaouel said. "In being more precise, we can potentially reduce toxicities and unwanted side effects."

Zhang noted that "there is still some controversy" over whether ZHX2 actually functions as a tumor suppressor in liver cancer and lymphoma because its presence is amplified, or overexpressed, in most other cancers. "So in my mind, there should be more extensive research examining the role of ZHX2 in other cancers."

Researchers may also find that they need to target ZHX2 only in cases of kidney cancer, he said. "It may be important to develop a drug specifically to target ZHX2 in kidney tissue to achieve this selectivity."

"It's promising," said Smith. "I don't think monotherapy for kidney cancer is the answer. This opens up a new avenue. It's definitely exciting."

Hemodiafiltration

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equipment, and other stakeholders have been working to change that.

KHI aims to stimulate innovation and research on kidney diseases, and the treatment of kidney diseases has been one area that has lagged behind in terms of research and new treatment options, said Stephen Ash, MD, a member of the KHI hemodiafiltration work group and medical director at Hemocleanse, Inc. Dialysis.

KHI has brought together nephrologists, regulators, patients, and companies to try to identify and overcome challenges that stand in the way. One of the biggest hurdles to bringing hemodiafiltration to the United States has been that there wasn't a clear pathway for companies to gain clearance from the FDA for marketing hemodiafiltration devices.

"That was the biggest impediment to the improvements in that area," Ash said.

Removing big particles

Hemodialysis was invented in the early part of the 20th century. It is very effective at removing small molecules like urea, creatinine, and potassium from the blood, explained Ash.

In layman's terms, hemodialysis works basically the same way as a tea bag, said Richard Ward, MD, a retired professor of medicine from the University of Louisville, in Kentucky. The small molecules from the blood naturally diffuse through the dialysis membrane to the water on the other side of the membrane. But larger molecules, especially those that are attached to proteins, may not make it through the dialysis membrane.

"There are quite a few larger molecules that accumulate in people without kidney function that are probably contributing to the toxicity of the disease," Ward said. Ash noted that these larger molecules have been linked to hypertension, cardiovascular disease, and ill effects on the immune system.

Hemodiafiltration, developed in the 1980s, was designed to overcome this limitation of dialysis by combining diffusion of molecules across a membrane with convection to help remove some of the larger molecules.

Again, in layman's terms, Ward said, hemodiafiltration works in much the same way a press coffee pot works: by forcing fluid and molecules through a membrane under pressure. The pressure greatly increases the amount of fluid being removed during treatment, Ash said. So instead of removing 2 to 3 liters over 3 to 4 hours as dialysis does, hemodiafiltration removes 20 to 30 liters in the same period. To counteract that large amount of fluid loss, patients are simultaneously infused with an equal amount of sterile fluid. Ash said the intent of hemodiafiltration is to keep patients healthier by creating a renal replacement therapy that more closely resembles the way the kidney works.

"It's really replicating the kind of hemofiltration system that is present in the human body," he said.

Data from four clinical trials have had mixed results, according to a review by the KHI work group.

A Spanish study found that patients treated with hemodiafiltration had a 30% lower risk of cardiovascular disease and of death resulting from all causes. Two other studies failed to show a statistically significant reduction in deaths among individuals receiving hemodiafiltration. A fourth study showed no difference in mortality rates or quality of life in patients over 65 years old, but it did find lower rates of low blood pressure during renal replacement therapy, and fewer muscle cramps. Ash noted that there was a trend toward benefit in all the studies, but some studies may have been too small to enable a statistically significant difference to be found.

"There's no doubt that there's something there that's

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