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Mayo Clinic Researchers Find Genetic Secrets to Common Kidney Cancer

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JACKSONVILLE, Fla. — By examining expression of every human gene in clear cell renal cell carcinoma (ccRCC) compared to normal kidney cells, researchers at Mayo Clinic's campus in Florida have discovered gene signatures they say explain much of the biology of this common and difficult-to-treat kidney cancer.

In the May 18 issue of PLoS ONE, the researchers report they have discovered: a biological pathway signature of ccRCC for a group of altered genes that give this distinct cancer its "clear cell" appearance; other genes that confer stem cell-like properties to the cancer; and a set of master genes lost in ccRCC that they believe likely pushes initial development of the cancer.

"Understanding these genes and the pathways they regulate could provide valuable insight into how to treat ccRCC," says hematologist/oncologist Han W. Tun, M.D., the study's first author.

This cancer makes up 80 percent of all kidney cancer and is often resistant to both chemotherapy and radiation treatment, Dr. Tun says. It accounts for just 3 percent of all cancers in the United States, but is the sixth leading cause of cancer death.

"Up until this point, ccRCC was largely a mystery, but now we have new and exciting clues that seem to reveal the origin and development of this cancer," says senior investigator John Copland, Ph.D., a cancer biologist.

The research team, which included scientists from the University of Texas Medical Branch in Galveston, used a comprehensive genome-wide gene expression analysis to look at expression of about 25,000 genes in the human genome. The gene chip measures the amount of messenger RNA (mRNA) that is transcribed from genes as part of the protein production process.

They used this tool to measure levels of mRNA for each gene in tissue samples taken from kidneys that were removed from 10 ccRCC patients. The kidneys were removed at the time of surgery and contained both normal tissue as well as tumor, so the scientists compared gene expression between the two to see what genes in the cancer were either over- or under-expressed, compared to normal cells.

Researchers found that 13,729 genes had altered expression in the cancer — a figure Dr. Copland calls "just astounding, especially in trying to develop new treatments and in understanding the causes of kidney cancer." They used novel software that grouped these genes into meaningful biological pathways — which helped them discover master genes. Each of these master genes regulates hundreds of "downstream" genes.

Researchers confirmed these gene expression findings in 20 kidneys removed from other ccRCC patients. Then, they validated gene expression at the protein level in kidneys taken from a different group of 50 ccRCC patients. To provide biological relevance, researchers then grew live normal kidney and ccRCC cells in a culture mediuam and conducted experiments.

Among the research findings are:

- The top three biological pathways found included genes regulating normal kidney function and metabolic functions lost in ccRCC. Genes in immune pathways were also over-expressed.
- A gene expression signature responsible for adipogenesis, which is the accumulation of globules of fat inside cells that is the reason for the "clear" appearance of ccRCC. Using a novel cell culture technique, they turned ccRCC cell lines into fat-acquiring "clear cells," mimicking what happens in patients. In patient-matched normal cells, fat is not produced.
- The loss of four developmental transcriptional factor genes in ccRCC that are important for normal kidney development. One of these genes, GATA3, controls many genes through transcriptional regulation of cell growth, immune function and inhibition of adipogenesis. Its loss is known to be critical to development of breast cancer. These four genes are known to control hundreds of other genes.
- That ccRCC cells behave like stem cells — undifferentiated cells that have the ability to become any type of cell in the body. ccRCC, but not normal kidney cells, has the capacity to undergo development of fat-producing cells or bone-making cells, depending on which laboratory culture medium they are placed in.
- A gene expression signature for a biological process called epithelial-mesenchymal transition (EMT), a characteristic feature of invasive cancer and cells undergoing proliferation. EMT may be important for kidney cancer development.

The stem cell-like properties found in ccRCC may explain why this cancer is so resistant to treatment, says Dr. Tun. But it also suggests that newer classes of drugs designed to target stem cells may offer a new alternative to treatment for this cancer, he says.

Additionally, one of the study's biggest surprises is that immune genes are being expressed in ccRCC cells, which may be the reason why ccRCC is one of the few cancers that responds to immunotherapy, says Dr. Tun. One such gene, TLR2, can help control the chronic inflammation that is integral to the disease process. Down-regulating these immune genes may therefore be another good strategy.

"Based on these findings, we propose a cancer model for the development of ccRCC," says Dr. Copland. "Developmentally, kidneys are mesenchymal in origin and develop by biological processes, which include mesenchymal epithelial transition (MET). In our model, normal renal epithelial cells experience loss of normal renal function (dedifferentiation) and EMT as well as preferential adipogenic differentiation.

"We think that these processes turn normal kidney cells into cancer cells with stem cell-like qualities. Since our samples came from patients with early-stage ccRCC, it appears that EMT may play a prominent role in renal carcinogenesis," he says.

The researchers are conducting experiments in which they knock out the four developmental genes from normal kidney cells, to see if cancer develops. They are also introducing these same genes into patient-derived ccRCC cell lines to see if cancer growth stops.

Other authors include Laura A. Marlow, Christina A. von Roemeling, Simon J. Cooper, Ph.D., Pamela Kreinest, Kevin Wu, M.D., Panos Z. Anastasiadis, Ph.D. all from Mayo Clinic; and Bruce A. Luxon, Ph.D., and Mala Sinha, Ph.D., from the University of Texas Medical Branch in Galveston.

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