Researchers find gene they believe is key to kidney cancer

May 20 2010

Researchers at Mayo Clinic's campus in Florida have discovered a key gene that, when turned off, promotes the development of common kidney cancer. Their findings suggest that a combination of agents now being tested in other cancers may turn the gene back on, providing a much-needed therapy for the difficult-to-treat cancer.

Clear cell renal cell carcinoma (ccRCC), the most common kind of kidney cancer, accounts for just 3 percent of all cancers in the United States, but is the sixth leading cause of cancer death. No current treatment has had a measurable effect on the spread of the cancer, oncologists say.

In the May 20, 2010 issue of *Oncogene*, researchers describe a gene called GATA3 that has been silenced in ccRCC and is a key gene also lost in breast cancer. GATA3 controls many genes and proteins that regulate cell growth, and one of them, a receptor known as the type III transforming growth factor-ß receptor (TßRIII), is absent in a number of cancers.

According to the study's senior investigator, John Copland, Ph.D., a cancer biologist at the Mayo Clinic campus at Florida, these findings will surprise many in the cancer field. "Cancer researchers know that GATA3 is essential for immune T cell development and function," he says. "As well, very recent studies show that GATA3 is also critical to breast cancer development, where GATA3 expression is limited to mammary luminal epithelial cells. GATA3 is lost during breast cancer

progression and its loss is a strong predictor of poor clinical outcome in luminal breast cancer. GATA3 also plays an important role in renal development and differentiation during embryogenesis, but little is known about the role of GATA3 in the adult human kidney."

"Now it looks like GATA3 regulates the expression of genes that are critical to cancer control in the kidney, and silencing it appears to be very important to the growth of kidney cancer and probably to others tumors, as well," he says. "No one could have guessed that would be the case in kidney cancer. This is a completely novel finding."

Adds first author Simon Cooper, Ph.D., a molecular biologist at Mayo Clinic, "This research is particularly exciting because GATA3 may be a good therapeutic target. Two classes of drugs known as histone methyltransferase inhibitors and histone deacetylase inhibitors are designed to remove the brakes that cancer puts on key genes, like GATA3, that are silenced during cancer."

The researchers say that GATA3 is silenced through methylation of the GATA3 gene, a chemical modification that commonly occurs in cancer due to a widespread genetic instability that activates methyltransferases and histone deacetylases (HDACs). This process occurs when methyltransferase and HDAC enzymes work together to attach or remove chemical groups from genes, effectively silencing them. The drugs used in this study work together to reverse methylation and deacetylation.

The HDAC inhibitor used in this study is currently being examined in clinical trials for other cancers. It is similar to HDAC inhibitors that are already approved by the Food and Drug Administration for use in cutaneous T cell lymphoma. Dr. Cooper says that data from this study proves that these drugs synergize to restore GATA3 function, but they still need to be tested in kidney cancer animal models to provide a

rationale for proceeding to a cancer clinical trial in kidney cancer.

This study results from a 2003 discovery by Dr. Copland and his team that the loss of TßRIII plays a critical role in kidney cancer cell growth. TßRIII appears to be a tumor suppressor gene that blocks tumor growth. Although it is well known that the ligand, transforming growth factor beta (TGF-ß) binds TßRIII on the cell membrane, TßRIII's growth inhibitory activity is TGF-ß independent, another novel finding.

They found that TßRIII was not expressed in patient ccRCC tissues that they examined; in the laboratory, when it was re-expressed in human ccRCC cell lines, the kidney cancer cells died. "We believe TßRIII is a tumor suppressor which is lost in a number of cancers," says Dr. Copland. "In ccRCC, every patient tumor that we have examined has lost the expression of this receptor as well as GATA3."

"Interestingly, the TßRIII gene is regulated, not by one, but two different promoters. Our team is the first to clone the human TßRIII promoters which allowed us to delete regions and discern how T□RIII expression is regulated," explains Dr. Cooper. They eventually located a region that led to the discovery that GATA3 positively regulates T□RIII expression in normal renal cells. This is the first transcription factor discovered to positively regulate the human TßRIII gene.

"Now that we understand why TßRIII is not expressed in kidney cancer, we can potentially turn the gene back on by reactivating GATA3 using methyltransferase and HDAC inhibitors," Dr. Copland says.

Provided by Mayo Clinic