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URMC discovers new trigger for kidney cancer's invasive behavior

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(PhysOrg.com) -- Scientists have unlocked a strong interaction between two proteins involved in kidney cancer that help to explain the menacing invasiveness of this particular disease, according to a University of Rochester Medical Center study.

The incidence of renal cell carcinoma, the most common type of kidney cancer, has been rising steadily during the past decade. Although early-stage cases have the best prognosis, a lack of early warning signs makes detection difficult. Usually early detection is made by chance during imaging tests for other problems. More often, doctors find kidney cancer when the tumor is larger or has begun to spread. It is also resistant to chemotherapy and radiation.

“We are trying to gain a better understanding of what stimulates renal carcinoma cells to be so invasive, and here we described the ability of a protein receptor, known as RACK1, to act as a scaffold and direct the communication that leads to cellular invasion,” said Guan Wu, M.D., Ph.D., corresponding author of the research published in the journal, *Oncogene*, and an assistant professor of Urology at URMC.

“Eventually we hope to identify more efficient ways to treat kidney cancer metastasis,” Wu said. “At the same time, we are looking for enzymes that might make renal cancer cells more sensitive to existing chemotherapy drugs.”

Mutation of a tumor suppressor gene known as von Hippel-Lindau or

VHL, is a key biological feature of renal cell carcinoma. VHL proteins, while binding to certain targets, are responsible for keeping in check the cycle of oxygen supply to the cells.

When the VHL protein (pVHL) is absent or defective, tumor cells stimulate blood vessel growth quickly (a process called angiogenesis, required for tumor growth), which results in hyper-vascularized tumors, one characteristic of kidney cancer. Newer drugs, such as Sutent and Nexerva, have been fairly successful at choking down blood vessels and suppressing kidney cancer growth in certain patients. However, we do not have a magic bullet yet to target to kidney cancer, Wu said.

Despite a better understanding of VHL and angiogenesis, the major obstacle for scientists has been finding a link between VHL and the high degree of aggressiveness in renal carcinoma, said Xiangrong He, M.D. Ph.D., research associate in the URMC Department of Urology and a fellow at the James P. Wilmot Cancer Center.

Generally the process of metastasis is regulated by insulin-like growth factor-I or IGF-I. In the case of kidney cancer the URMC team discovered that the RACK1 molecule plays a key role in switching on the growth factor activity in renal cancer cells that have the VHL defect.

Researchers also found they could partially disrupt or reverse cellular invasiveness in the laboratory by knocking down expression of RACK1 (receptor for activated C kinase 1). However, because the results showed only a partial blocking of renal cell invasiveness, this suggests that other signaling pathways within the VHL complex might be involved and therefore additional studies must continue, researchers said.

“In the future we hope to be able to genotype a patient and predict how the cancer will behave,” said He, who led the laboratory research.

Meanwhile, Wu is also investigating the clinical outcomes of different surgical techniques used to remove kidney cancers. Surgery to remove all or part of the affected kidney is the primary treatment. Today Wu and colleagues are performing an increasing number of robot-assisted laparoscopic surgeries, resulting in easier recoveries for patients compared to traditional open surgery.

As part of an international consortium, Wu is tracking the survival outcomes of patients who receive a less-invasive robot-assisted partial nephrectomy compared with patients who receive a traditional, open surgery to remove all or part of one kidney after a cancer diagnosis.

“We are attempting to look at all sides of the equation for renal cell carcinoma, from cancer biology to the best surgical techniques, so that we can refine our knowledge and deliver the best possible care to patients,” Wu said.

More information: www.nature.com/onc/journal/vao … ull/onc2010427a.html

Provided by University of Rochester Medical Center

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