

Researchers uncover potentially promising therapeutic combination for renal cell carcinoma

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Renal cell carcinoma (RCC) is the most common form of kidney cancer. In 2018, there were an estimated 403,000 new cases of RCC and

175,000 deaths due to kidney cancer worldwide. Currently, the 5-year survival rate for patients with metastatic RCC is only about 12 percent. Current treatments include inhibitors of the VEGF and PD-1 pathways. However, resistance to therapy occurs in most patients and new combination treatments are still needed to enhance the efficacy of these current approaches.

Now, investigators have demonstrated that ACE2 expression is a good prognostic factor in RCC, that loss of ACE2 mediates resistance to classical treatments, and that in preclinical models, treatment with a drug that is downstream of ACE2 can improve tumor responses in RCC and significantly prolong survival. The team, led by Beth Israel Deaconess Medical Center's (BIDMC) Rupal Bhatt, MD, Ph.D., and University College Cork, Ireland's Thomas Walther, Ph.D., published their findings in the journal *Science Translational Medicine*.

"Our team reported that ACE2 is a new protective molecule for RCC, and building on this finding, we show that angiotensin-(1-7), a small peptide generated by ACE2, can be used to control tumor growth in preclinical models," said co-corresponding Bhatt, a medical oncologist at BIDMC and associate professor of medicine at Harvard Medical School. "Our findings suggest that angiotensin-(1-7) could be developed in clinical trials as a promising therapeutic option in patients with RCC in combination with current standard of care treatments and has a strong potential to improve overall survival."

ACE2 is an enzyme that belongs to the renin-angiotensin system (RAS) and antagonizes the classical angiotensin II/AT1 receptor pathway. Interestingly, it is also the receptor for the SARS-CoV2 spike protein, and its downregulation by the virus leads to the often deadly progression of acute respiratory distress syndrome in COVID-19 patients.

Bhatt, Walther and colleagues show that higher ACE2 expression

correlates with better overall survival in patients with RCC. They also demonstrated that VEGF receptor inhibitors such as sunitinib and axitinib down-regulate ACE2 expression in tumor cells in culture and in tumors in mouse models of RCC. Using novel and innovative methods and techniques, the authors generated multiple lines of evidence that this ACE2 down-regulation can be causative for the resistance to VEGF pathway inhibition, the inevitable consequence of this approved used class of drugs.

The authors also report that angiotensin-(1-7) is the likely mediator of this effect. The authors also showed that triple therapy of VEGF pathway inhibitors and anti-PD-L1 with angiotensin-(1-7) is superior to the actual standard treatment with VEGFR and PD-1 pathway inhibition.

"Our work shows that angiotensin-(1-7) could provide a promising therapeutic option in patients with RCC in combination with VEGF-pathway inhibitors," said co-corresponding author Walther, Professor in Pharmacology at the University College Cork. "Resistance to VEGF-pathway inhibitors is a general problem in cancer treatment and therefore our findings have broader implications for VEGF-pathway inhibitor therapies that beyond RCC could be extended to other types of cancers."

More information: P. Khanna et al., "ACE2 abrogates tumor resistance to VEGFR inhibitors suggesting angiotensin-(1-7) as a therapy for clear cell renal cell carcinoma," *Science Translational Medicine* (2021). stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.abc0170

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