MOLECULAR & CELLULAR ONCOLOGY
2021, VOL. 8, NO. 4, e1918529 (2 pages)
https://doi.org/10.1080/23723556.2021.1918529

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COMMENTARY

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Combining VEGF receptor inhibitors and angiotensin-(1–7) to target renal cell carcinoma

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ABSTRACT

Resistance to tyrosine kinase inhibitors of the vascular endothelial growth factor receptor inevitably develops in most patients with metastatic kidney cancer. Our recent findings demonstrate that addition of angiotensin-(1-7) peptide can be a potential therapy that delays such resistance.

ARTICLE HISTORY
Received 25 March 2021
Revised 13 April 2021
Accepted 13 April 2021

KEYWORDS
ACE2; RCC; Ang-(1–7); VEGFR-TKI; resistance

Renal cell carcinoma (RCC) is one of the 10 most common cancers in both men and women in the United States with clear cell subtype of RCC (ccRCC) constituting about 80% of RCC incidence. Tyrosine kinase inhibitors of the vascular endothelial growth factor receptor (VEGFR-TKI) are a major treatment option for patients with metastatic ccRCC, in the past as single agents and currently also in combination with immune checkpoint inhibitors (ICI) of the programmed death-ligand 1 (PD-L1) pathway.[1,2] However, long-term durable responses occur only in a small subset of patients. Therefore, development of new targets that prolong the response to VEGFR-TKI treatment is important to improve outcomes in patients.

Angiotensin-converting enzyme (ACE) 2 is a peptidase within the renin–angiotensin system (RAS) that generates angiotensin (Ang)-(1–7) by cleaving the eighth amino acid of Ang II. ACE2/Ang–(1–7) form the alternate arm of RAS that antagonizes the classical RAS axis formed by ACE/Ang II. Recent papers have shown increased amounts of ACE2 prevent tumor growth and epithelial-to–mesenchymal transition in preclinical cancer models such as gallbladder cancer, non-small cell lung cancer and hepatocellular cancer.[3–5]

We recently reported that higher levels of ACE2 can abrogate tumor resistance to VEGFR-TKI therapy in ccRCC and that this effect is mediated by Ang-(1–7).[6] We analyzed *ACE2* expression in transcriptomes of 533 ccRCC tumors derived from nephrectomy samples from The Cancer Genome Atlas–Kidney Renal Clear Cell Carcinoma (TCGA-KIRC) and showed that patients with higher *ACE2* expression had improved survival outcomes including overall survival, disease-specific survival and progression-free interval. Multivariate cox regression models adjusting for gender, tumor stage and tumor grade were computed, and the relationship between *ACE2* expression and survival outcomes was found to be independent of gender, stage and grade. In two Von Hippel–Lindau tumor suppressor (*VHL*)-deficient ccRCC cell lines, A498 and 786-O, stable and transient *ACE2* overexpressing cells were generated. Using colony formation assays, we showed that an increase in *ACE2* reduced the number of colonies formed *in vitro*. In an *in vivo* preclinical model of ccRCC, *ACE2* overexpression resulted in reduced tumor formation. 786-O cells stably overexpressing *ACE2* were subcutaneously injected into immunodeficient female athymic nude/beige mice. Following for 6 weeks post injection, only 1 of 15 mice injected with *ACE2* overexpressing cells formed tumors compared to 11 of 15 mice injected with control vector transfected cells.

We subsequently assessed the role of ACE2 in tumor resistance to VEGFR-TKI treatment. Mice bearing A498 cell-derived ccRCC xenografts were treated with either sunitinib (a VEGFR-TKI) or control. We showed that ACE2 protein and RNA expression were downregulated in sunitinib-treated tumors using Western blot analysis, immunohistochemistry, and qRT-PCR. Also, the enzymatic activity measured by quantification of Ang-(1–7) generation in membranes isolated from tumor tissue was significantly lower in sunitinib-treated mice. We also showed that sunitinib treatment did not affect expression of the Ang-(1–7) receptor, MAS in tumor tissue. Together with the findings that blockade of the MAS receptor in colony formation assays with *ACE2* overexpressing cells reversed colony formation suppression, and Ang-(1–7) had a direct effect on *in vitro* colony formation similar to that seen with *ACE2* overexpression, these data suggest that the effects of ACE2 on tumor growth are mediated by Ang-(1–7).

Finally, in mice bearing A498 and 786-O xenografts, combined treatment with sunitinib and Ang-(1–7) suppressed

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tumor growth for a more prolonged period than sunitinib monotherapy. A triple combination with axitinib, anti-PD-L1 and Ang-(1–7) showed improved tumor suppression than axitinib and anti-PD-L1 treatment in immunocompetent mice bearing syngeneic RENCA tumors suggesting that addition of Ang-(1–7) improves treatment efficacy with both VEGFR-TKI monotherapy as well as with VEGFR-TKI and ICI combination.

This study provides evidence that ACE2 is a potent prognostic factor in ccRCC. ACE2 downregulation contributes to tumor resistance against VEGFR-TKI therapy in ccRCC and addition of Ang-(1–7) is a possible therapy to abrogate this tumor resistance. Ang-(1–7) combined with current standard therapy of VEGFR-TKI alone or in combination with ICI is a promising treatment that could provide additional therapeutic benefit in advanced RCC.

Ang-(1–7) has already been studied in phase I and II trials in nonmalignant conditions and has been shown to have a low toxicity profile.[7,8] This study therefore has the potential for rapid translation to early clinical studies in metastatic ccRCC.

Further studies are needed to determine whether patients could be selected for treatment by assessment of circulating ACE2 activity as a biomarker for pathway relevance. Additionally, ACE2 has been shown to suppress tumor growth in multiple other cancers, and resistance to VEGFR-TKI is a general problem in cancer treatment. Our findings may have broader implications for VEGFR-TKI in other cancers where changes to ACE2/Ang-(1–7) may contribute to treatment resistance.

Disclosure of potential conflicts of interest

TW is also scientific advisor of Constant Pharmaceuticals LTD (Boston, USA). A patent by RSB and Beth Israel Deaconess Medical Center has been filed on April 16, 2017, for the "Combination therapy for cancer" outlining combination of VEGFR inhibition with angiotensin pathway molecules. TW and RSB are inventors of the patent "An anti-viral therapeutic strategy" (day of filing: 22.05.2020).

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