Perspective

The therapeutic potential of HIF-2 antagonism in renal cell carcinoma

Olivier Cuvillier

CNRS, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France; Université de Toulouse, UPS, Toulouse, France

Correspondence to: Olivier Cuvillier. IPBS CNRS UMR 5089, 205 Route de Narbonne, 31077 Toulouse Cedex 4, France.

Email: olivier.cuvillier@inserm.fr.

Provenance: This is a Guest Perspective commissioned by Editorial Board Member Dr. Xiongbing Zu, MD, PhD (Department of Urology, Xiangya Hospital, Central South University, Changsha, China).

Comment on: Chen W, Hill H, Christie A, *et al.* Targeting renal cell carcinoma with a HIF-2 antagonist. Nature 2016;539:112-117.

Abstract: Hypoxia, the insufficient delivery of oxygen for the demand of a tissue, contributes to the development of an aggressive phenotype, resistance to radiation therapy and chemotherapy, and is predictive of a poor outcome in numerous tumor types. Adaptation to hypoxia is mediated by hypoxia-inducible factors (HIFs), including HIF-1α and HIF-2α, which regulate genes promoting angiogenesis, increased tumor growth or metastasis. In kidney cancer, HIF-2α is believed to be the most important driver for development and progression of clear cell renal cell carcinoma (ccRCC), highlighting the therapeutic potential of HIF-2 antagonists in this disease. Recent studies show that HIF-2α can be targeted by selective, and orally active new class of inhibitors. In conjunction with the restricted expression of HIF-2α in normal adult physiology, these studies suggest that such therapeutic approach might be favorable for patients with lower toxicity than current anti-angiogenic drugs like sunitinib. However, the differential sensitivity to these HIF-2α antagonists along with the potential mechanisms of resistance reported in these studies advocate for the identification of biomarkers to determine which patients are more likely to benefit from these therapies as well as paving the way for second generation inhibitors or complementary inhibitory approaches.

Keywords: HIF-2; antagonists; clear cell renal cell carcinoma (ccRCC)

Submitted Nov 22, 2016. Accepted for publication Nov 24, 2016.

doi: 10.21037/tau.2017.01.12

View this article at: http://dx.doi.org/10.21037/tau.2017.01.12

Clear cell renal cell carcinoma (ccRCC) accounts for around 3% of adult malignancies. Its prognosis is closely related with disease stage, with 5-year survival rates ranging from almost 90% to less than 10% for stage I and IV disease, respectively. The last decade has witnessed major advances in the understanding of ccRCC biology and a number of effective treatments are available, such as antiangiogenic agents (multitargeted tyrokine kinase inhibitors or anti-VEGF strategies) and mTOR inhibitors (1). More recently, targeted therapy against the PD-1/PD-L1 immune checkpoint pathway has produced encouraging objective response rates in patients with metastatic ccRCC (2).

However, the development of acquired resistance to targeted therapies has heightened the need for investigation of novel approaches for ccRCC management. Hypoxia is a characteristic feature of solid tumors and the adaptation of cancer cells to hypoxia is instrumental in the development of aggressive phenotype and associated with a bad prognostic in patients (3). At the cellular level, the adaptation to hypoxia is mediated by the hypoxia-inducible factors (HIFs), consisting of an oxygen-sensitive α-subunit and a constitutively expressed β-subunit (also known as ARNT for aryl hydrocarbon receptor nuclear translocator), regulating the expression of target genes that promote angiogenesis, glycolysis, metastasis, increased tumor growth and resistance to treatments (3). HIF-1α and HIF-2α are the best characterized HIF-α subunits. Whereas HIF-1α is ubiquitously expressed, HIF-2α has a more restricted expression and is particularly present in highly vascularized organs or hypoxic tissues including kidney epithelial cells (4).

Despite their substantial sequence similarity and co-expression in various cancer cell types, HIF-1α and HIF-2α play non-overlapping roles in tumor progression (5). The distinct roles of HIF-1α and HIF-2α in promoting tumor growth have been mainly defined in ccRCC because a majority of ccRCC patients (50–80%) exhibit a genetic inactivation of von Hippel-Lindau (VHL) gene resulting in the loss of pVHL, which normally mediates ubiquitination of HIF-α and its subsequent degradation, resulting in a constitutive expression of either HIF-1α and HIF-2α or HIF-2α alone (6). The role for HIF-2α as a key driver in the development and progression of the disease has been firmly established (7,8), whereas the activity of HIF-1α has been shown to be dispensable as its expression is often silenced (9).

These data suggest the specific function of HIF-2α in ccRCC highlight the therapeutic potential of HIF-2α antagonists in this disease. Although transcription factors are typically considered "undruggable", the PAS-B domain of the HIF-2α subunit contains a large cavity within its hydrophobic core that provides a singular foothold for small-molecule to disrupt HIF-2α dimerization to ARNT (10,11). Recently published studies show that HIF-2α can be targeted by selective and orally active small-molecule inhibitors, paving the way to a novel strategy to treat ccRCC (12-14). A structure-based design approach developed by Peloton Therapeutics led to the discovery of closely related compounds including PT2399 and PT2385, which were evaluated for their biological activities. Two studies published in Nature clearly established that PT2399 specifically and functionally inhibited the dimerization of HIF-2α (but not HIF-1α) with its partner ARNT. As anticipated, specific HIF-2α target genes including VEGF-A, GLUT1, PAI-1 or CCND1 were significantly reduced demonstrating the on-target effects of PT2399. Using a large repertoire of ccRCC cell models (14), PT2399 was found to cause tumor regression in orthotopic xenografts, which correlated with reduced circulating tumor-derived VEGF. Similar findings were reported in the second study conducted with an extensive panel of patient-derived xenografts (13). However, differential responses to PT23099 were observed in both studies. Cell lines or patient-derived xenografts highly sensitive to PT2399 had stronger HIF-2α levels than poorly sensitive ones, suggesting that assessing HIF-2α activity/expression would be required as a predictive biomarker of efficacy. Importantly, prolonged treatment with PT2399 led to resistance, generated by mutations in both HIF-2α and its binding partner ARNT. Both mutations preserved HIF-2α dimerization despite the presence of PT2399 (13). These findings support the notion that second generation inhibitors and/or complementary approaches (15) would be ineluctable. In addition, acquisition of a p53 mutation might represent another mechanism of resistance to PT2399 as reported in the 786-O ccRCC cells despite their considerable amount of HIF-2α (14). These data suggest that mutations in some genes like p53 may impact response to HIF-2α antagonists similar to what has been observed in patients resistant to VEGF-targeted therapies (16). A third study published in Cancer Research describe the effects of a the related small-molecule inhibitor PT2385 (12). In line with the other studies, PT2385 showed a strong inhibitory on HIF-2α-controlled genes without any effect on HIF-1α-controlled genes, associated with a potent anti-tumor activity in xenograft models and decreased circulating VEGF-A level. Noteworthy, in animal studies, PT2385 did not exhibit the cardiovascular safety concerns observed with anti-VEGF therapies such as hypertension (17). PT2385 might thus represent a novel therapeutic option with more desirable safety profile than current anti-angiogenic approaches. As such, a Phase 1, dose-escalation trial of PT2385 is ongoing in patients with advanced ccRCC (ClinicalTrials.gov Identifier: NCT02293980).

In summary, the validation of HIF-2α as a bona fide target in ccRCC described in these studies in conjunction with the restricted expression of HIF-2α in normal adult physiology suggests that therapeutic approaches based on HIF-2α antagonists might be favorable for patients. However, the differential sensitivity to HIF-2α antagonists along with the potential mechanisms of resistance reported in these studies advocate for a need for companion predictive biomarkers as well as paving the way for second generation inhibitors or complementary inhibitory approaches.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Penticuff JC, Kyprianou N. Therapeutic challenges in renal cell carcinoma. Am J Clin Exp Urol 2015;3:77-90.

2. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
3. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell 2012;148:399-408.
4. Wiesener MS, Jürgensen JS, Rosenberger C, et al. Widespread hypoxia-inducible expression of HIF-2alpha in distinct cell populations of different organs. FASEB J 2003;17:271-3.
5. Keith B, Johnson RS, Simon MC. HIF1α and HIF2α: sibling rivalry in hypoxic tumour growth and progression. Nat Rev Cancer 2011;12:9-22.
6. Kaelin WG Jr. Kidney cancer: now available in a new flavor. Cancer Cell 2008;14:423-4.
7. Rankin EB, Rha J, Unger TL, et al. Hypoxia-inducible factor-2 regulates vascular tumorigenesis in mice. Oncogene 2008;27:5354-8.
8. Gordan JD, Lal P, Dondeti VR, et al. HIF-alpha effects on c-Myc distinguish two subtypes of sporadic VHL-deficient clear cell renal carcinoma. Cancer Cell 2008;14:435-46.
9. Shen C, Beroukhim R, Schumacher SE, et al. Genetic and functional studies implicate HIF1α as a 14q kidney cancer suppressor gene. Cancer Discov 2011;1:222-35.
10. Rogers JL, Bayeh L, Scheuermann TH, et al. Development of inhibitors of the PAS-B domain of the HIF-2α transcription factor. J Med Chem 2013;56:1739-47.
11. Scheuermann TH, Li Q, Ma HW, et al. Allosteric inhibition of hypoxia inducible factor-2 with small molecules. Nat Chem Biol 2013;9:271-6.
12. Wallace EM, Rizzi JP, Han G, et al. A Small-Molecule Antagonist of HIF2α Is Efficacious in Preclinical Models of Renal Cell Carcinoma. Cancer Res 2016;76:5491-500.
13. Chen W, Hill H, Christie A, et al. Targeting renal cell carcinoma with a HIF-2 antagonist. Nature 2016;539:112-117.
14. Cho H, Du X, Rizzi JP, et al. On-target efficacy of a HIF-2α antagonist in preclinical kidney cancer models. Nature 2016;539:107-111.
15. Wu D, Potluri N, Lu J, et al. Structural integration in hypoxia-inducible factors. Nature 2015;524:303-8.
16. Fay AP, de Velasco G, Ho TH, et al. Whole-Exome Sequencing in Two Extreme Phenotypes of Response to VEGF-Targeted Therapies in Patients With Metastatic Clear Cell Renal Cell Carcinoma.J Natl Compr Canc Netw 2016;14:820-4.
17. Hamnvik OP, Choueiri TK, Turchin A, et al. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. Cancer 2015;121:311-9.

Cite this article as: Cuvillier O. The therapeutic potential of HIF-2 antagonism in renal cell carcinoma. Transl Androl Urol 2017;6(1):131-133. doi: 10.21037/tau.2017.01.12

