Unraveling the Role of Hypoxia-Inducible Factor in Renal Cell Carcinoma: A Biological and Therapeutic Perspective

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Summary: The genetic control of hypoxia-inducible factor (HIF) has long been associated with the pathogenesis of clear cell renal cell carcinoma. Only recently have the complex genetics and biology of relevant HIF subtypes been unraveled, leading to potential novel strategies for treating this disease.

A mere decade ago, the practicing oncologist possessed a limited armamentarium for the treatment of metastatic renal cell carcinoma (mRCC). Agents such as interleukin-2 and IFN-α yielded clinical benefit in a relatively small proportion of patients with mRCC, and clinical results with cytotoxic chemotherapy were even more dismal. The landscape changed dramatically as a result of greater biological understanding of clear cell RCC, the dominant subtype of this disease, constituting roughly 80% of this population. Specifically, mutation or hypermethylation events were found in the von Hippel-Lindau (VHL) gene in the majority of patients with clear cell disease. The gene product, pVHL, serves a number of functions, including ubiquitylation of hypoxia-inducible factor (HIF), thereby targeting the entity for proteasomal destruction. Alterations in VHL prevent HIF degradation, thereby facilitating deregulation of HIF target genes, such as VEGF. Overproduction of VEGF, in turn, promotes tumor growth and angiogenesis through a variety of mechanisms.

Within the past 5 years, 6 agents directed at VEGF signaling have been approved by the U.S. Food and Drug Administration. Four of the agents are direct inhibitors of either VEGF ligand (bevacizumab) or the VEGFR tyrosine kinase domain (sunitinib, sorafenib, and pazopanib; ref. 1). An additional 2 agents (temsirolimus and everolimus) abrogate signaling through a downstream moiety, mTOR. The rapid integration of multiple agents into clinical algorithms for mRCC has generated a clinical conundrum. As an illustration, the National Comprehensive Cancer Network recommends up to 7 potential regimens for the patient with treatment-naïve clear cell disease, and 4 of these carry category 1 (i.e., uniform consensus) recommendations (3). Various strategies have been proposed to resolve this state of equipoise. Head-to-head trials ultimately represent the gold standard, but these trials are costly and require immense resources. Numerous combination studies are currently under way, but experiences to date have been marred by significant toxicity without synergistic (or even additive) efficacy.

With these constraints in mind, much attention has shifted toward the identification of novel therapeutic targets that may carry drug development beyond the current plateau. Although targeting HIF represents both an innovative and a logical foray, it is now well established that HIF does not exist as a singular entity, and signaling via distinct subtypes of HIF may be varied and complex. In a cohort of 57 sporadic ccRCC patients, Gordan and colleagues (4) identified 3 molecular subtypes of disease: (1) VHL wild type, with little or no HIF expression (12%); (2) VHL mutant with increased HIF-2α expression (27%); and (3) VHL mutant with both increased HIF-1α and HIF-2α expression (61%). Tumors exclusively overexpressing HIF-2α demonstrated higher expression of c-myc–activated targets (i.e., cyclin D2 and E2F). In contrast, HIF-1α can inhibit c-myc activity, and therefore, tumors expressing both HIF-1α and HIF-2α demonstrated increased expression of a distinct panel of moieties, including Akt2, RhoC, and phospho-S6K.

In this issue of Cancer Discovery, Shen and colleagues (5) provide further evidence of a distinct role for HIF-1α—that of a tumor suppressor. HIF-1α is located on chromosome 14q, and several studies have associated deletions of 14q with a poor prognosis in mRCC (6). Consistent with previous reports, Shen and colleagues (5) have identified absent or truncated HIF-1α mRNA in a variety of RCC cell lines, suggesting copy-number loss or gene rearrangement, respectively. In fact, of 16 cell lines examined, 7 had sustained homozygous deletions in HIF1α exons, and 4 had loss of 1 HIF1α allele in its entirety. In vitro assays using VHL+/− cell lines transfected with inducible HIF-1α expression vectors showed that increased HIF-1α expression led to tumor suppression. Conversely, use of shRNA to downregulate HIF-1α in VHL−/− cell lines expressing both HIF-1α and HIF-2α led to enhanced proliferation.

In subsequent experiments, gene expression profiling and supervised clustering analyses were performed in cell lines expressing both HIF-1α and HIF-2α or HIF-2α alone (5). A resulting commentary on Shen et al., p. 222 (5).
“HIF-1α transcriptional signature” was generated, encompassing a number of known HIF-1α specific targets. Comparison of this signature with gene expression data from 52 VHL–/– clear cell carcinomas supported a diminution of HIF-1α activity in patients with 14q deletions spanning the HIF1α locus.

The potential clinical implications of the work by Shen and colleagues (5) are multifund, albeit complex. HIF-1α expression appears to be highly sensitive to rapamycin and clinically relevant analogues (7, 8). Bearing this in mind, one might anticipate the activity of these agents to be highly contingent upon levels of HIF-1α expression. However, in a phase III study comparing temsirolimus to IFN-α, HIF-1α levels were not found to predict response, progression-free survival, or overall survival in association with temsirolimus therapy (9). These data do not preclude the possibility that other mediators along the HIF-signaling axis may represent valid therapeutic targets. Expression of HIF-1α is driven by both mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2); the former complex exhibits a much higher sensitivity to rapamycin (10, 11). In contrast, HIF-2α expression is driven by mTORC2. Thus, with the evolving role of HIF-1α as a tumor suppressor, inhibiting signaling via mTORC2 (and thereby diminishing HIF-2α expression) may represent a more viable therapeutic strategy. As one potential approach, the agent NVP-BEZ235 (recently examined in a phase I study in solid tumors) antagonizes signaling via both mTORC1 and mTORC2, and further prevents activation of Akt, an mTORC2 substrate (12, 13). Alternatively, direct inhibition of HIF-2α has been postulated as a potential antitumor strategy; several candidate drugs have been identified via high-throughput screens and appear to have activity in preclinical models of RCC (14).

Thus, beyond their immediate conclusions, Shen and colleagues (5) provide a framework for conceptualizing potential therapeutic approaches for mRCC (5). Although the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2). Envisioning the putative link between HIF and RCC biology has been established for more than a decade, only recently are the implications of HIF subtypes being deciphered (2).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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