miR-30c-2-3p and miR-30a-3p: New Pieces of the Jigsaw Puzzle in HIF2α Regulation

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Summary: Clear cell renal cell carcinoma (ccRCC), the most frequent subtype of renal cell cancer, is characterized by mutation of the von Hippel–Lindau (VHL) tumor suppressor gene, which results in stabilization of hypoxia-inducible factor (HIF) α proteins. In this issue of Cancer Discovery, Mathew and colleagues report that miR-30c-2-3p and miR-30a-3p downregulation in ccRCC promotes increased expression of HIF2α.

In this issue of Cancer Discovery, Mathew and colleagues (6) report miR-30c-2-3p and miR-30a-3p as a novel regulatory mechanism responsible for attenuation of the tumor-suppressive role of HIF1α in ccRCC (Fig. 1). miRNA profiling revealed that in tumors expressing both HIF1α and HIF2α, miR-30c-2-3p and miR-30a-3p were repressed as compared with tumors expressing HIF2α exclusively. Regulation of the aforementioned miRs proved to be pVHL-dependent but HIF-independent (6), contradicting the work of Huang and colleagues (7) that showed miR-30c to be regulated by HIF1α. Using cell lines as well as mouse models, Mathew and colleagues (6) showed that ectopic expression of both tested miRs induced downregulation of HIF2α and inhibition of xenograft tumor growth in mice. Moreover, application of a miR-30a-3p antagonim induced a higher tumor-cell proliferation rate and enhanced tumor growth (6).

HIFα proteins belong to the helix-loop-helix PAS family of DNA-binding transcription factors. They bind to HIF target genes at a 5′-RCGTG-3′ (where R is a purine) core sequence and activate their transcription (for review, see ref. 2). HIFα proteins regulate genes in a large variety of tissues and cells; however, expression of their targets may be restricted to specific locations. An example is erythropoietin, which is expressed only in the kidney in adults. Moreover, although HIF1α and HIF2α regulate some of the same genes, their targets are not identical and may differ in different cell types. For example, VEGF is regulated by HIF2α in VHL-deficient RCC cells, but HIF1α is responsible for the transcription of the VEGF gene in breast cancer cells (8). Another level of complexity is added by the fact that HIFα pathway members are targets of various miRNAs. Significant upregulation of hypoxia-related miRNAs, such as miR-21 and miR-210, was reported in ccRCC. On the contrary, miR-200c, which binds multiple targets in the VHL/HIF6 pathway, including VEGF, as well as PI3K/AKT and mTOR pathway members, was shown to be consistently downregulated in numerous ccRCC studies (5, 9).

Despite the frequent mutations occurring within chromosome 14q, to which HIF1A maps, ccRCC tumors often maintain one wild-type HIF1A allele (10). A unique function of the...
HIF1α protein is stimulation of the glycolytic enzymes and suppression of anabolic biosynthesis. Contrary to HIF2α, it inhibits cell-cycle progression by posttranslational inhibition of the c-Myc oncoprotein. In contrast to HIF1α, HIF2α is not involved in glycolytic regulation and may enhance cell-cycle progression by promoting c-Myc–dependent activation of cyclin D2 and E2F1 and repression of p21 and p27. Moreover, c-Myc overexpression promoted by HIF2α was associated with accumulation of DNA damage in early-stage disease that may also contribute to genomic instability in tumors. It was shown that HIF2α is responsible for the growth of human ccRCC xenografts in mice (3). In addition, a single-nucleotide polymorphism within HIF2A was associated with an increased risk of kidney cancer. Similar to restoration of pVHL, blocking HIF2α expression suppresses tumorigenesis, confirming its oncogenic potential (for review, see ref. 2). Hence, genes preferentially regulated by HIF2α have been shown to be especially oncogenic as compared with HIF1α-regulated genes. Mathew and colleagues (6) demonstrated a more pronounced upregulation of HIF2α in tumors expressing both HIF1α and HIF2α compared with tumors expressing HIF2α exclusively. Thus, it was concluded that the elevated levels of HIF2α in HIF1α+/HIF2α-positive tumors are a direct consequence of miR-30c-2-3p and miR-30a-3p downregulation (6).

The standard procedure for ccRCC tumors is partial or complete nephrectomy. The surgical procedure is usually followed by systemic therapy in metastatic RCC. Immunotherapy (e.g., IFN-α and interleukin-2) showed relatively low tumor response, accompanied by significant toxicity. A novel treatment option is so-called targeted therapy with small molecules (e.g., sunitinib and sorafenib) or with monoclonal antibodies (e.g., bevacizumab) that inhibit tumor angiogenesis and cell viability by targeting VEGF and platelet-derived growth factor receptor pathways in endothelial and RCC cells. As has been suggested, tumors expressing HIF1α and HIF2α could be more susceptible to these drugs (3). Systemic therapies may also target the mTOR pathway (e.g., temsirolimus and everolimus). Despite the fact that these treatment options show an improvement in progression-free survival, the response rate is low. Therefore, new therapies for metastatic ccRCC are needed. An increasing number of publications have shown successful reduction of tumor size after application of various miRNAs or antagonirs in in vitro and in vivo systems. Mathew and colleagues (6) elegantly demonstrated that tumors developed in immunocompromised mice were bigger if xenografts originated from miR-30a-3p antagonist–expressing cells compared with control tumors. Therefore, the authors concluded that application of the synthetic miRNAs could be beneficial for patients with ccRCC (6). Although prospective studies are needed, this study sheds light on potential new therapeutic tools for ccRCC treatment.

**Disclosure of Potential Conflicts of Interest**

H. Moch has received a commercial research grant from Pfizer. No potential conflicts of interest were disclosed by the other author.

Published online January 8, 2014.

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