HIF-1α Partners with FoxA2, a Neuroendocrine-Specific Transcription Factor, to Promote Tumorigenesis

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In this issue of *Cancer Cell*, Qi et al. report a novel mechanism by which HIF-1α synergizes with a tissue-specific transcription factor, FoxA2, to promote a transcriptional program that supports prostate tumor formation and progression.

Cellular exposure to hypoxia (low O_2) occurs frequently in various human pathologies, including tumorigenesis (Bertout et al., 2008). During solid tumor formation, hypoxic areas can arise due to insufficient vascularization of rapidly growing lesions. In response to hypoxic stress, tumor cells initiate numerous changes in gene expression, primarily via stabilization of the hypoxia-inducible factors (HIFs) HIF-1α and HIF-2α (Semenza, 2008). Under normoxic conditions, HIFα transcription factors are ubiquitylated by the von Hippel-Lindau (VHL)-E3 ligase complex and rapidly degraded by the 26S proteasome. Ubiquitylation of HIFs is mediated by O_2-dependent prolyl hydroxylases (PHDs). O_2 depletion inactivates PHDs and prevents ubiquitylation of HIF. Stabilized HIF-1α and HIF-2α then dimerize with their constitutively expressed partner HIF-1β, also known as ARNT (aryl hydrocarbon receptor nuclear translocator), and accumulate in the nucleus where they bind hypoxia-responsive elements (HREs) located in the promoter or enhancer regions of target genes. HIF target genes regulate multiple aspects of tumorigenesis, including angiogenesis, metabolism, migration, and invasion (Bertout et al., 2008).

Recently, several studies have demonstrated that HIFα regulation in tumors is not limited to low O_2-dependent stabilization but can also be modulated in some cancers by oncogenic Ras signaling and other stimuli (Blum et al., 2005; Kikuchi et al., 2009). One prevalent tumor associated with elevated HIFα activity is prostate cancer, which expresses elevated HIF-1α protein compared with normal prostate epithelia and benign hyperplasias (Zhong et al., 2004). In prostate tumors, HIFα stability is regulated by multiple inputs including O_2 levels and changes in androgen signaling resulting from loss of ERβ expression, which occurs in high-grade tumors. Initial studies suggested that O_2-mediated HIF-1α stabilization is an early event in prostate cancer, whereas loss of ERβ promotes more advanced disease by stabilizing HIF-1α and driving EMT in a VEGF-dependent manner (Mak et al., 2010).

In this issue, Qi et al. (2010) propose a novel O_2-dependent mechanism wherein HIF-1α cooperates with the forkhead box transcription factor FoxA2 to stimulate a transcriptional program that facilitates neuroendocrine prostate tumor initiation and metastasis. The neuroendocrine phenotype is found in more than 30% of prostate cancers and is associated with a poor clinical outcome. In tumors, HIFs regulate transcription both independently and via crosstalk with factors widely expressed in human tissues, including Notch, c-Myc, and p53 (Gordan et al., 2008). Importantly, Qi et al. have found that in addition to modulating these commonly expressed factors, HIF-1α also mediates tissue-specific transcription by interacting with FoxA2, which is selectively expressed in neuroendocrine tumor tissues.

Qi et al. (2010) used the murine transgenic TRAMP model of metastatic prostate tumors, which is driven by prostate-specific expression of the SV40 T antigen, in their study. To modulate HIF-1α levels in the TRAMP system, the authors silenced the ubiquitin ligase Siah2. In general, Siah2 controls stability of PHDs, which in turn regulate the stability of HIFs (Nakayama et al., 2004). Thus, silencing Siah2 increases HIFα degradation. Neuroendocrine prostate carcinoma formation was significantly decreased in the $TRAMP^{tg}/Siah2^{-/-}$ mice compared to $TRAMP^{tg}/Siah2^{+/+}$ and $TRAMP^{tg}/Siah2^{+/-}$ animals (Figure 1). Metastases to liver, lungs, and lymph nodes were also dramatically decreased in the $TRAMP^{tg}/Siah2^{-/-}$ mice. By using in vitro binding assays and coimmunoprecipitations, the authors determined that under hypoxic conditions, FoxA2, ARNT, and HIF-1α interacted directly in order to synergistically promote transcription via recruitment of the coactivator p300. Interestingly, a limited subset of HIF-1α target genes were specifically upregulated by FoxA2 cooperation including Hes6, Sox9, and Jmjd1a (Figure 1; Qi et al., 2010). Other HIF-1α targets like Glut-1 and VEGF were unaffected. Expression of Hes6, Sox9, and Jmjd1a promoted anchorage-independent growth in soft agar as well the development of a hypoxia-dependent neuroendocrine phenotype in prostate carcinomas. To determine the importance of Hes6, Sox9, and Jmjd1a expression in vivo, the authors expressed these proteins, individually or together, in TRAMP tumor cells while inhibiting Siah2 with the ectopically expressed peptide inhibitor PHYL. These

cells were injected into the prostates of mice. Coexpression of all three genes rescued tumorigenesis in these animals although individual expression of the targets did not. These data suggest that the HIF-1α/FoxA2-mediated transcriptome might contribute to tumor formation and progression through simultaneous activation of multiple pathways. Further experiments revealed that Siah2, FoxA2, Hes6, and Sox9 expression were elevated in high-grade human prostate cancers, that the neuroendocrine phenotype can be triggered by hypoxia, and that this phenotype is associated with metastatic disease. Immunohistochemistry analysis showed that neuroendocrine markers were coexpressed with HIF-1α, FoxA2, Hes6, and Sox9 in advanced human prostate cancer tissue samples.

Several important questions emerge from these findings. (1) Is the mechanism of cooperation between HIF-1α and tissue-specific transcription factors common to other tumors? (2) What other tissue-specific transcription factors interact with HIF-1α to modulate tumorigenic transcription in human cancers? (3) Is there a specific relationship between HIF and Fox family transcription factors that supports tumor formation? (4) Does HIF-2α also synergize with Fox family members in some tumors? Recent findings suggest that HIF and Fox transcription factors coregulate tumorigenesis in other tissues including breast and hepatic cancers (Xia et al., 2009). Additionally, it is known that the effect of HIFα isoforms differs between tumor types, with some tumors utilizing HIF-1α-dependent pathways and others requiring HIF-2α and its downstream effectors (Gordan et al., 2008). Thus, it is possible that the mechanism proposed here by Qi et al. (2010) is widespread in tumors but that the particular isoforms and family members involved are tissue type specific.

With this work, Qi et al. (2010) have further developed a molecular understanding of neuroendocrine prostate carcinoma. Moreover, evaluation of the pathways identified in their studies will provide invaluable information in the development of targeted therapeutics for prostate cancer. Their findings have also raised questions about the role of synergistic HIFα-dependent transcription in other tumor contexts. Hopefully, the identification of additional interacting factors that synergize with HIFα in a tissue-specific manner will help elucidate meaningful druggable targets for treatment of prostate and other cancers.

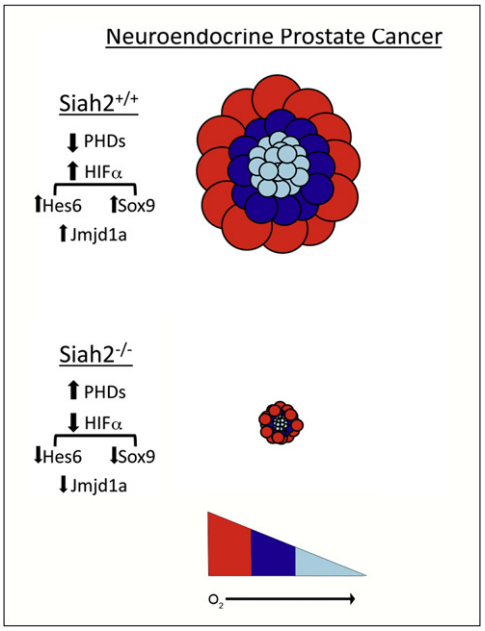

Figure 1. The Effects of Siah2 Inhibition and HIF Stabilization on Prostate Cancer Formation
Deletion of Siah2 results in decreased HIFα and HIF target (Hes6, Sox9, Jmjd1a) expression in the TRAMP model of prostate cancer. HIF-1α synergizes with the neuroendocrine-specific transcription factor FoxA2 to regulate transcription of these genes and drive both tumorigenesis and the neuroendocrine phenotype in a hypoxia-dependent manner.

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