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Review

Exploitation of the HIF Axis for Cancer Therapy

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ABSTRACT

Hypoxia, a reduction in the normal level of tissue oxygen tension, occurs in most solid tumors in regions where tumor growth outstrips new blood vessel formation. Hypoxic cancer cells are resistant to both chemotherapy and radiation and are a major reason for the failure of cancer therapy. The cellular response to hypoxia is mediated through the hypoxia-inducible transcription factor-1 (HIF-1). HIF-1 is critically important for tumor progression and angiogenesis. In fact, HIF-1α is overexpressed in 70% of human cancers and their metastases. Thus, agents that inhibit angiogenesis and tumor growth via inhibition of HIF-1 represent an attractive yet unexplored new modality for cancer treatment. We will overview inhibitors of HIF-1α and will discuss their potential use for cancer therapy.

OXYGEN-DEPENDENT REGULATION OF HIF-1

Hypoxia Inducible Factor 1 (HIF-1) is a transcriptional factor that plays a key role in adaptation to hypoxia and therefore in tumor progression and angiogenesis. HIF-1 is a heterodimer composed of HIF-1α and HIF-1β (also know as a aryl receptor nuclear translocator [ARNT]) subunits. HIF-1β is constitutively expressed, whereas HIF-1α is maintained at low steady-state levels under normoxia through controlled degradative processes in to the presence of oxygen. This control is exerted by a family of specific enzymes known as HIF-1α prolyl-4-hydroxylases (PHD) which are absolutely dependent on oxygen as cosubstrate, providing the molecular basis for the oxygen-sensing function of these enzymes. Hydroxylation of HIF-1α at residues 402 and 564 allows the interaction of HIF-1α with the Von Hippel Lindau protein (pVHL). pVHL acts as an E3 ubiquitin ligase giving the specificity to proteasomal degradation by targeting HIF-1α for ubiquitination. The interaction between HIF-1α and VHL is further accelerated by acetylation of lysine residue 532 through the N-acetyltransferase ARD1.[1] In a second hydroxylation control HIF-1α/VHL complex also recruits Factor Inhibiting HIF-1α (FIH) which has been recently shown to hydroxylate Asn 803 residue. This hydroxylation abrogates the interaction of HIF-1α with the transcriptional coactivator p300/CBP inhibiting in this way HIF-1 transcriptional activity.[2] Interaction of HIF-1α/VHL with FIH also permits the recruitment of histones deacetylases (HDAC), which are known to function as transcriptional corepressors[3] and that may also contribute to the loss of HIF-1α transcriptional activity under nonhypoxic conditions.

PHD depend on oxygen and iron. Under hypoxic conditions PHDs are inhibited resulting in an exponential increase in the HIF-1α protein as the O_2 concentration decreases. Under these conditions HIF-1α heterodimerizes with its partner HIF-1β and binds to the specific enhancer DNA sequences called hypoxia response elements (HRE) activating the transcription of more than 40 genes involved in angiogenesis, metabolic adaptation and survival of cells under hypoxia.[4,5]

OXYGEN-INDEPENDENT REGULATION OF HIF-1

HIF-1α activity is also controlled in an O_2-independent fashion under the regulation of signaling pathways, both via the phosphatidylinositiol 3-kinase (PI3K) and mitogen-activated protein kinase pathways.[6] In contrast to hypoxia regulation, which affects all cells by stabilizing HIF-1α protein leading to an increase in HIF-1 transactivation function, this regulation is cell-type specific and mainly increases the rate of HIF-1α synthesis as well as the stimulation of the HIF-1α transactivation domain function.[7,8] Among the growth factors and cytokines that activate these signal transductions pathways are insulin growth factor 2 (IGF2), transforming growth factor α (TGFα), epidermal growth factor (EGF), fibroblast growth factor 2 (FGF2), heregulin, insulin, insulin-like growth factor 1

and 2. These growth factors induce HIF-1α protein through its interaction with Receptor Tyrosine Kinase that will activate PI3K-AKT-FRAP pathway or MAP kinase pathway resulting in a stimulation of HIF-1α protein synthesis, HIF-1 DNA binding activity and HIF-1α transcription activity.

Induction of HIF-1α under normoxia conditions has been also linked with *Helicobacter pylori*-induced gastric carcinogenesis. Reactive oxygen species (ROS) from *Helicobacter pylori* in gastric epithelial cells has been shown to induce constant HIF-1α expression under normoxia and subsequently activate HIF-1-mediated transcription.[9] However, the precise role that ROS species play on HIF-1α stability is still controversial, since ROS species have been reported to both inhibit HIF-1 (NAPDH oxidase hypothesis)[10] and activate it (mitochondria pathway).[11] In either case, the effectors whose activity is regulated by ROS and transduce the signal directly or indirectly to HIF-1 remains unknown.

HIF-1 AND CANCER

HIF-1 is a critical, genome-wide transcription regulator identified for oxygen homeostasis responsive to hypoxic stress. HIF-1 controls the expression of >40 genes, including VEGF, involved in angiogenesis, glycolysis and invasion.[4]

Several lines of evidence show clearly that overexpression of HIF-1α and HIF-1-dependent genes contribute to the lethal phenotype of many solid tumors especially breast and prostate cancer. These lines of evidence include:

1. HIF-1α expression levels were first shown to correlate with tumor metatstatic potential in the Dunning rat model of metastatic prostate cancer where the metastatic ability of the tumor was proportionate to the amount of HIF-1α expression.[12]
2. In humans, up-regulated HIF-1α expression is found in >70% of human cancers with the highest levels observed in metastases as compared to adjacent normal tissues.[13,14]
3. In addition, HIF-target genes, such as VEGF and endothelin-1 are found overexpressed in many solid tumors and are critically involved in the pathophysiology of the lethal phenotype of prostate and breast cancer and the establishment of bone metastases in prostate.
4. Interestingly, promising new drugs for the treatment of metastatic hormone refractory prostate cancer, currently in Phase II and III clinical trials target individual growth factors, mainly endothelin-1 (ET-1), and VEGF, all of which are under the regulation of HIF-1α via the hypoxia-response elements located 5' to the first exon.

The central hypothesis of exploiting HIF pathway therapeutically is that the inhibition of HIF-1-mediated gene regulation will reduce tumor angiogenesis and prevent the adaptive metabolic response to hypoxia, thus suppressing tumor growth. Small-molecule inhibitors of HIF-1/HRE are expected to lead to the attenuation of HIF-1 transcriptome, retardation of tumor growth and minimal toxicity towards normal tissues.

THERAPEUTIC STRATEGIES TO TARGET HIF

Several strategies have been employed by several groups most of which focus on the identification of small molecules that specifically inhibit HIF and HIF-transcriptome. In addition to the above strategies, agents that inhibit signal transduction pathways like MEK, Raf kinase, mTOR and ERBB2 kinase inhibitors, also result in decreased levels of HIF-1α, most likely due to inhibition of the above pathways. In this review, we will focus on small molecules that target HIF, for which there is significant knowledge on the mechanistic aspects of HIF inhibition.

2ME2 and Microtubule-Disrupting Drugs. 2-Methoxyestradiol (2ME2) is a naturally occurring derivative of estradiol currently in Phase I/II clinical trials as an inhibitor of tumor angiogenesis. 2ME2 is an orally active, well-tolerated small molecule[15,16] whose antiproliferative activity is independent of the estrogen receptors α and β.[17] Moreover, 2ME2 was shown to bind and depolymerize microtubules in vitro, albeit at low affinity, which lead to the presumption that the antitubulin effects of 2ME2 did not contribute to its antitumor and antiproliferative properties.

We have recently reported that 2ME2 potently inhibits the protein levels and transcriptional activity of HIF-1α.[18] Mechanistically, we found that 2ME2 downregulates hypoxia-inducible factor-1 (HIF) at the posttranscriptional level and inhibits HIF-1-induced transcriptional activation of VEGF expression. Inhibition of HIF-1 occurs downstream of the 2ME2/tubulin interaction, as disruption of interphase microtubules is required for HIF-1α downregulation. Most importantly, we showed that 2ME2 inhibits tumor growth and angiogenesis at concentrations that efficiently disrupt tumor microtubules in vivo. In the same study additional microtubule-targeting drugs that either stabilize (taxol) or destabilize microtubules (vincristine) also inhibited HIF-1α levels and HIF-1 transcriptional activity in vitro.[18] Taken together these data provide a solid mechanistic link between the disruption of the microtubule cytoskeleton and inhibition of angiogenesis. While this is an unconventional connection between a nuclear transcription factor and the cytoplasmic chemomechanics of tubulin function, in fact this hypothesis is proven to be correct and is driving a significant amount of interest in the connection between microtubule dynamics and the control of angiogenesis. However, the signaling events that link MT disruption to HIF-1α inhibition have yet to be determined. Especially, since a recent report has shown that microtubule-depolymerizing drugs (vinblastine, colchicine) but not taxol (microtubule-stabilizing) induced HIF-1α protein levels. However, this effect was only transient (1–6 hr treatment), and longer treatments (>7 hr) downregulated HIF-1α.[19] Thus, it is important to take into account the temporal effects of disrupting the chemomechanics of the microtubule network and try to identify the proteins and/or signaling events that link HIF regulation to microtubules.

Topoisomerase-I Inhibitors. Investigators at the Developmental Therapeutics Program-Tumor hypoxia at the NCI has developed a cell-based high throughput screen (HTS) to identify small molecule inhibitors of the HIF-1 transcriptional activity, which may have antiangiogenic and anticancer activities[20] From the approximately 2000 compounds analyzed they have identified two different classes of compounds. The first one is a stable analog of quinocarmycin, a compound identified as having melanoma specificity and that was evaluated in the early 1990s by the NCI and evaluated in phase I clinical trials.[21,22] Its use however, was discontinued because of unexpected and unpredictable toxicicities.[23,24] The second class of compounds represents drugs that inhibit Topoisomerase-I (Topo-I). One is Topotecan and the other two are Camptothecin (CPT) analogs.[20] These compounds have been shown to specifically inhibit the transcriptional activity of HIF-1 and the mRNA of VEGF as well as the DNA binding capacity of HIF-1α. Topo-I inhibitors are chemotherapeutic agents that stabilize complexes formed between Topo-I and DNA, preventing religation of the DNA strand, resulting in single-strand DNA breaks and cell death. Inhibition of Topo-I has

been associated with activation of the NF-kB pathway and inhibition of angiogenesis. Whether direct inhibition of Topo-I is essential for inhibition of HIF-1α protein accumulation and VEGF expression warrants further investigation. It also remains to be determined whether inhibition of HIF-1α is important for the antiproliferative activity of Topo-I inhibitors; especially, since a recent study using mouse embryonic fibroblast (MEF) deficient for HIF-1α (HIF-1α$^{-/-}$) showed that the Topo-I inhibitor SN38 (a camptothecin-derivative) equally impaired cell growth in both the wild-type and HIF-1α$^{-/-}$ fibroblasts.[25] In contrast. the HIF-1α$^{-/-}$ MEFs showed increased sensitivity to carboplatin, etoposide (Topo-II inhibitor) and ionizing radiation (all of them induce DNA double-strand breaks) compared with their wild-type counterparts. However, we have to keep in mind that pharmacologic inhibition of HIF-1α is not the same as genetic inactivation.

Hsp90 Inhibitors. Heat shock protein 90 (Hsp90) is an ATP dependent molecular chaperone that prevents the aggregation of unfolded proteins generated by heat shock, oxidative or ischemic stresses. In addition Hsp90 is a partner of a large, unknown number of substrate proteins including steroid-hormone receptors, protein kinases and transcription factors such as bHLH proteins.[26] Natural inhibitors of the ATPase activity like geldanamycin (GA) and radiciol, block the processing of Hsp90 substrate proteins. Gradin et al. first found the stable interaction between de novo-synthesized HIF-1α and Hsp90,[27], while other groups showed that this interaction is disrupted in hypoxia leading to for HIF-1α stabilization and activation.[28] Geldanamycin and its derivative 17-allyl-aminogeldanamycin (17-AAG) bind to the ATP-conserved pocket in the Hsp90 protein and inhibit its function. Mechanistically, it has been reported that GA promotes ubiquitination and degradation of HIF-1α protein through the proteosomal pathway in a way that is both oxygen- and VHL-independent.[29,30] The GA-induced HIF-1α degradation was reversed in the presence of proteasome inhibitors, however, this strategy failed to restore HIF-1 transcriptional activity.

Accordingly, benzoquinone ansamycin drugs like geldanamycin, radicicol and their derivatives might be considered as HIF-1 inhibitors used in treatment for HIF-1α overexpressing cancers.

YC-1. YC-1 is a newly developed agent that inhibits platelet aggregation and vascular contraction and stimulates soluble guanylate cyclase, which increases intracellular cGMP concentration. Chun et al. have demonstrated that YC-1 blocks the induction of EPO and VEGF mRNAs, and inhibits the DNA-binding activity of HIF-1.[31] It suppresses the hypoxic accumulation of HIF-1α by post-translational mechanism. It has been also recently described that YC-1 inhibits proliferation in cultured HUVEC cells in a dose- and time-dependent manner. YC-1 treatment also induced an increase in the CDK inhibitors p21 and p27 and a decrease in the CDK2 kinase activity that could account for the impairment in the transition from G1 to S phase.[32] In a xenograft human tumors mouse models it is been shown that YC-1 reduced tumor growth and angiogenesis. They also observed that tumors treated with YC-1 expressed low levels of HIF-1α and HIF-1 inducible genes, regardless of tumor type.[33] These observations imply that YC-1 may be a good candidate agent for HIF-1 suppression effective under hypoxic condition and can be developed to block tumor hypoxia-mediated angiogenesis.

NSAIDs. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme now called cyclooxygenase (COX) which leads to the formation of prostaglandins (PGs). There is increasing evidences that NSAIDs may also have a potential role as antiangiogenic agents besides of their cytotoxic effects. Jones et al. have demonstrated that both a nonselective (indomethacin) and a cyclooxigenase-2 (COX-2)-selective (NS-398) NSAIDs reduce HIF-1α protein and that leads to the inhibition of VEGF as well as its specific receptor Flt-1 that both are HIF-1 regulated genes. The authors believe that the effect of NSAIDs on HIF-1α under hypoxia is through increased VHL expression leading to ubiquitination and degradation of HIF-1α.[34] Ibuprofen has also been reported to downregulated HIF-1α and HIF-2α proteins with a subsequent reduction in the HIF-regulated products VEGF and Glut-1. However the authors also report that these effects are more complete under normoxia.[35] Some of the NSAIDs seem to be another class of candidate anti-HIF-1 agents, although the specific biological mechanisms warrant further investigation.

GENE THERAPY

Gene therapy strategies based on selective induction of the HIF-1/HREmediated gene-directed enzyme/prodrug therapy (GDEPT) system or selectively gene expression is in development. The Herpes Simplex Virus thymidine kinase/Ganciclovir (HSVtk/GCV) system is the most characterized enzyme/prodrug strategy in cancer and is currently in a number of clinical trials. Tumor hypoxia can be also exploited using live obligate anaerobes or tumor associated macrophages transfected with retro- or adenoviral vectors might be used to deliver therapeutic HREcontaining genes to hypoxia areas.[36] The use of replication-competent gene therapy viruses has emerged as a viable strategy to specifically kill tumor cells[37] and it has been recently reporter the generation of a hypoxia/HIF-dependent replicative virus (HYPR-ad) to regulate conditionally the replication of an adenovirus in order to target hypoxic cells.[38] Gene transfer (liposome transfection) of an expression plasmid encoding an antisense HIF-1α inhibits VEGF expression and reduces the density of tumor blood vessels. It also induces the rejection of established small (0.1 cm) EL-4 tumors, but does not eradicate large tumors although slows their growth.[39]

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