HIF-1 and human disease: one highly involved factor

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Oxygen homeostasis represents an important organizing principle for human development and physiology. The essential requirement for oxidative phosphorylation to generate ATP is balanced by the risk of oxidative damage to cellular lipids, nucleic acids, and proteins. As a result, cellular and systemic O₂ concentrations are tightly regulated via short- and long-acting response pathways that affect the activity and expression of a multitude of cellular proteins (for review, see Semenza 1999a). This delicate balance is disrupted in heart disease, cancer, cerebrovascular disease, and chronic obstructive pulmonary disease, which represent the most common causes of mortality and account for two-thirds of all deaths in the U.S. (Greenlee 2000). Appreciation of the fundamental importance of oxygen homeostasis for development, physiology, and disease pathophysiology is growing but still incomplete. Knowledge acquisition is presently exponential when one includes areas, such as the role of angiogenesis in ischemic or neoplastic disease, in which investigators are studying oxygen homeostasis even though they may not interpret their studies within this broad physiological context.

Vascular endothelial growth factor (VEGF) plays an essential role in angiogenesis (for review, see Ferrara and Davis-Smyth 1997; Ferrara 1999). The regulation of VEGF expression illustrates how reduced O₂ availability (hypoxia) can elicit physiological responses via multiple molecular mechanisms. VEGF expression is induced when most cell types are subjected to hypoxia, thus providing a mechanism by which tissue perfusion can be optimized to demand. Steady state levels of VEGF mRNA increase in hypoxic cells as a result of increased production (transcriptional activation) and decreased destruction (mRNA stabilization). Whereas overall protein synthesis is inhibited in response to hypoxia, VEGF mRNA is efficiently translated into protein by use of an internal ribosome entry site (Stein et al. 1998). Finally, expression of the VEGF receptor FLT-1 is also induced when endothelial cells are exposed to hypoxia (Gerber et al. 1997).

The essential first step in this process, transcriptional activation, is mediated by the binding of hypoxia-inducible factor 1 (HIF-1) to a cis-acting hypoxia-response element located 1 kb 5’ to the transcriptional start site of the human VEGF gene (Forsythe et al. 1996). HIF-1 is a basic helix–loop–helix PAS protein consisting of HIF-1α and HIF-1β subunits (Wang and Semenza 1995; Wang et al. 1995). HIF-1α expression and HIF-1 transcriptional activity are precisely regulated by cellular O₂ concentration (for review, see Semenza 1999b, 2000a; Wenger 2000). The molecular mechanisms of sensing and signal transduction by which changes in O₂ concentration result in changes in HIF-1 activity are poorly understood, but recent data suggest that the O₂ signal is converted to a redox signal (Chandel et al. 2000; Haddad et al. 2000) that may trigger a kinase cascade and/or regulate HIF-1 directly (for review, see Semenza 1999a,b; Chandel and Schumacker 2000).

The regulation of HIF-1 activity occurs at multiple levels. Whereas HIF-1α mRNA is constitutively expressed in tissue culture cells, it is markedly induced by hypoxia or ischemia in vivo (Yu et al. 1998; Bergeron et al. 1999). HIF-1α protein expression is negatively regulated in non-hypoxic cells by ubiquitination and proteasomal degradation (Salceda and Caro 1997; Huang et al. 1998; Kallio et al. 1999). Under hypoxic conditions, HIF-1α protein levels increase dramatically and the fraction that is ubiquitinated decreases (Sutter et al. 2000). Nuclear localization of HIF-1α may also be induced by hypoxia (Kallio et al. 1998). The carboxy-terminal half of HIF-1α contains two transactivation domains that are also negatively regulated under nonhypoxic conditions (Jiang et al. 1997b; Pugh et al. 1997). The interaction of these domains with the coactivators CBP, p300, SRC-1, and TIF2 is regulated by the cellular O₂ concentration and redox state (Kallio et al. 1998; Ema et al. 1999; Carrero et al. 2000). Finally, species–specific alternative splicing of human and mouse HIF-1α RNA has also been reported (Wenger et al. 1997; Iyer et al. 1998b; Gothie et al. 2000). Hypoxia results in the rapid accumulation of HIF-1α in the nucleus (Wang et al. 1995) where it dimerizes with HIF-1β and binds to the core DNA sequence 5’-RCGTG-3’ (Semenza 2000a), leading to the transcriptional activation of VEGF and several dozen other known target genes (Table 1). HIF-1α and HIF-1β expression are required for embryonic survival in mice (Kozak et al. 1997; Maltepe et al. 1997; Iyer et al. 1998a; Ryan et al. 1998;
ischemia induces VEGF expression (Banai et al. 1994) and the extent to which VEGF is induced in cultured leukocytes exposed to hypoxia ex vivo is correlated with the degree of coronary collateralization induced by myocardial ischemia in vivo (Schulz et al. 1999). HIF-1α mRNA and protein expression are induced and precede VEGF expression during acute ischemia and early infarction in the human heart (Lee et al. 2000). Thus, it is possible that variation in ischemia-induced HIF-1 activity may underlie the observed variation in VEGF expression and represent an important risk factor for myocardial infarction. In addition, therapeutic strategies designed to increase HIF-1α expression may promote angiogenesis within ischemic myocardium. PR39, a macrophage-derived peptide, has been shown to induce myocardial angiogenesis via inhibition of HIF-1 degradation (Li et al. 2000).

Ischemic preconditioning is an experimental phenomenon in which subjecting an animal to a sublethal ischemic challenge results in protection against a subsequent lethal challenge. There is an immediate but short-lived phase of protection within the first 2–3 hr that is followed by a delayed but sustained late phase of protection 12–24 hr later that requires new protein synthesis (Rizvi et al. 1999, and references therein). The late phase of ischemic preconditioning is lost in knockout mice that lack expression of the Nos2 gene encoding inducible nitric oxide (NO) synthase [Guo et al. 1999]. Induction of Nos2 expression in hypoxic cardiac myocytes and vascular endothelial cells may be mediated by HIF-1 (Palmer et al. 1998; Jung et al. 2000). Furthermore, NO has been shown to induce HIF-1α expression under nonhypoxic conditions (Kimura et al. 2000). NO has been proposed to be both a trigger and a mediator of delayed preconditioning [Bolli et al. 1997]. Thus, NO production in response to the preconditioning stimulus may induce HIF-1-mediated Nos2 expression that is protective against a subsequent lethal ischemic challenge. As in the case of ischemia-induced angiogenesis, once the molecular mechanisms of this process are more completely understood it may be possible to identify pharmacologic inducers that would have great therapeutic utility.

### Ischemic cardiovascular disorders

#### Myocardial ischemia

Atherosclerosis leads to arterial stenosis, impaired perfusion of the downstream vascular bed, and ischemia. When oxygen and glucose deprivation irreversibly affect myocardial viability, the end result is an infarction (heart attack). Hypoxia/ischemia has dramatic stimulatory effects on vascularization of coronary and peripheral vascular beds in fetal and juvenile animals whereas angiogenesis is markedly inhibited in aged animals because of impairment of VEGF production and endothelial cell responses to VEGF (Martin et al. 1998; Rivard et al. 1999). The impairment of VEGF production can be attributed to decreased HIF-1 activity in response to hypoxia (Frenkel-Denkberg et al. 1999, Rivard et al. 2000).

Among middle-aged adults there is also variation in the extent to which ischemia induces the development of collateral blood vessels that allow perfusion of myocardium downstream of coronary artery stenosis and that influence the incidence and severity of myocardial infarction (Habib et al. 1991; Sabia et al. 1992). Myocardial ischemia induces VEGF expression (Banai et al. 1994) and the extent to which VEGF is induced in cultured leukocytes exposed to hypoxia ex vivo is correlated with the degree of coronary collateralization induced by myocardial ischemia in vivo (Schulz et al. 1999). HIF-1α mRNA and protein expression are induced and precede VEGF expression during acute ischemia and early infarction in the human heart (Lee et al. 2000). Thus, it is possible that variation in ischemia-induced HIF-1 activity may underlie the observed variation in VEGF expression and represent an important risk factor for myocardial infarction. In addition, therapeutic strategies designed to increase HIF-1α expression may promote angiogenesis within ischemic myocardium. PR39, a macrophage-derived peptide, has been shown to induce myocardial angiogenesis via inhibition of HIF-1 degradation (Li et al. 2000).

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#### Cerebral ischemia

When adult rats are subjected to permanent middle cerebral artery occlusion, HIF-1α mRNA is induced in the penumbra or viable tissue surrounding the infarction (Bergeron et al. 1999). The induction of HIF-1α mRNA is temporally and spatially correlated with the expression of mRNAs encoding glucose transporter 1 and the glycolytic enzymes aldolase A, lactate dehydrogenase A, phosphofructokinase L, and pyruvate kinase M, which are all known HIF-1 target genes [Iyer et al. 1998a; Table 1]. These data suggest that induction of glycolytic metabolism may promote the survival of neurons within the penumbra. Colocalization of HIF-1α and VEGF expression has also been demonstrated in the penumbra and is associated with neovascularization (Marti et al. 2000). In contrast, studies of primary cortical cultures from newborn mouse brains revealed that inhibition of

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**Table 1. Direct HIF-1 target genes**

<table>
<thead>
<tr>
<th>Glucose/Energy Metabolism and Cell Proliferation/Viability</th>
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<tr>
<td>Adenylate Kinase 3, Aldolase A, Aldolase C, Enolase 1 (ENOL1), Glucose Transporter 1, Glucose Transporter 3, Glyceraldehyde-3-phosphate Dehydrogenase, Hexokinase 1, Hexokinase 2, Insulin-like Growth Factor 2 (IGF-2), IGF Binding Protein 1 (IGFBP-1), IGFBP-3, Lactate Dehydrogenase A, Phosphoglycerate Kinase 1, Pyruvate Kinase M, p21, Transforming Growth Factor β3 (TGFβ3)</td>
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**Erythropoiesis and Iron Metabolism**

- Ceruloplasmin, Erythropoietin, Transferrin, Transferrin Receptor

**Vascular Development/Remodeling and Vasomotor Tone**

- α1b-Adrenergic Receptor, Adrenomedullin, Endothelin-1, Heme Oxygenase 1, NitrOxide Synthase 2, Plasminogen Activator Inhibitor 1, Vascular Endothelial Growth Factor (VEGF), VEGF Receptor FLT-1

*References for all HIF-1 target genes are cited in Semenza 2000b, except for TGFβ3 (Caniggia et al. 2000) and ceruloplasmin (Mukhopadhyay et al. 2000).*
HIF-1 activity by overexpression of a dominant negative form of HIF-1α (Jiang et al. 1996) is associated with reduced cell death in response to oxygen and glucose deprivation [Halterman et al. 1999]. Studies of HIF-1α-null embryonic stem cells also implicated HIF-1α in mediating apoptosis in response to oxygen and glucose deprivation [Carmeliet et al. 1998]. These results are consistent with a model in which hypoxia-induced HIF-1α associates with and prevents the degradation of p53 protein [An et al. 1998], which then induces apoptosis of cortical neurons [Banasiak and Haddad 1998].

When newborn rats are subjected to permanent left common carotid artery occlusion and exposed to 8% O₂, cerebral infarction occurs in the hemisphere ipsilateral to the occlusion. Rats exposed to 8% O₂ for 3 hr and then subjected to carotid occlusion and hypoxia 24 hr later are protected against cerebral infarction [Gidday et al. 1994]. As in the case of myocardial preconditioning [Bolli et al. 1997], cerebral preconditioning is blocked by NOS inhibitors [Gidday et al. 1999]. Significant protection can also be achieved by injecting the rats with cobalt chloride or desferrioxamine [Bergeron et al. 2000], which are known inducers of HIF-1 activity [Wang and Semenza 1993]. Exposure of rats to hypoxia alone induces HIF-1α protein expression throughout the brain, whereas combined carotid occlusion and hypoxia result in decreased HIF-1α expression in the ipsilateral cortex and a striking induction within the microvasculature of the ischemic brain [Bergeron et al. 2000]. The physiological significance of this dramatic alteration in HIF-1α expression remains to be determined. In contrast to the data from in vivo studies suggesting that HIF-1α expression may contribute to hypoxic preconditioning, studies of cultured neurons suggest that hypoxic preconditioning ex vivo leads to decreased HIF-1α expression in response to oxygen-glucose deprivation 48 hr later [Ruscher et al. 1998]. Thus, it will be important to definitively establish, for example, by analysis of partially HIF-1α-deficient mice (see below), whether the net effect of HIF-1α in vivo is protective or pathogenic and then to determine which cell types (glia, inflammatory cells, neurons) contribute to this effect.

**Retinal ischemia**

In diabetes, occlusion of retinal vessels leads to ischemia-induced neovascularization, which is a major cause of blindness. Clinical and laboratory studies have demonstrated a critical role of VEGF in this process [for review, see Ferrara 1999]. In a mouse model of ischemic retinopathy, exposure of neonates to hypoxia for five days results in vascular regression and retinal ischemia when the mice are returned to room air [Pierce et al. 1995], conditions similar to those that result in the retinopathy of prematurity. HIF-1α expression is induced during normal retinal development, is downregulated by hypoxia, and upregulated on return to normoxic conditions, a pattern that is temporally and spatially correlated with VEGF expression [Ozaki et al. 1999].

**Pulmonary hypertension**

In some patients with chronic obstructive lung disease, alveolar hypoxia leads to the development of pulmonary hypertension. In this disorder, hypoxia-induced pulmonary arteriolar remodeling results in reduced lumen diameter and increased resistance to blood flow, leading to progressive right heart failure and, ultimately, patient death. Mice exposed to 10% O₂ for three weeks develop right ventricular hypertrophy as a result of increased right ventricular pressure, which is in turn secondary to medial wall hypertrophy within small pulmonary arterioles. This hypoxia-induced vascular remodeling is markedly impaired in mice that are heterozygous for a loss-of-function allele at the Hif1a locus and therefore partially HIF-1α deficient [Yu et al. 1999]. These results suggest that local inhibition of HIF-1 activity in the lung might represent a therapeutic strategy for treating or preventing pulmonary hypertension in at risk individuals.

**Pregnancy disorders: preeclampsia and intrauterine growth retardation**

Preeclampsia is a disorder of unknown etiology that affects 5% of all pregnancies and is a leading cause of fetal and maternal morbidity and mortality [for review, see Norwitz and Repke 2000; Roberts 2000]. A central defect in preeclampsia appears to be the failure of trophoblasts to adequately invade the myometrium and induce remodeling of uterine spiral arteries during early placentation, which results in decreased uteroplacental perfusion [for review, see Aplin 2000]. For most of the first trimester, the human fetus and placenta develop under hypoxic conditions but, at 10–12 weeks, the intervillous space opens and the placenta and fetus are exposed to maternal blood. It is at this stage that trophoblast cells actively invade the maternal decidua, and the developmental switch of trophoblasts from a proliferative to an invasive phenotype is controlled by the cellular O₂ concentration [Genbacev et al. 1996, 1997]. The proliferative, noninvasive trophoblast phenotype appears to be maintained by hypoxia-induced, HIF-1-mediated expression of TGFβ3 because treatment of human villous explants with antisense oligonucleotides against HIF-1α or TGFβ3 induces invasion under hypoxic conditions [Canigglia et al. 2000]. Inhibition of TGFβ3 also induces trophoblast invasion in explants from preeclamptic pregnancies [Canigglia et al. 1999], suggesting that defective downregulation of HIF-1α and/or TGFβ3 may play a major role in the pathogenesis of preeclampsia.

Another leading cause of fetal and neonatal morbidity and mortality is intrauterine growth retardation (IUGR). Decreased placental perfusion, resulting in placental and fetal hypoxia, is believed to be a major cause of IUGR. Fetal and maternal insulin-like growth factors (IGFs) play an important role in regulating fetal growth. IGF-binding protein 1 (IGFBP-1) is a negative regulator of IGF activity. IGFBP-1 expression, which is induced by hypoxia via a HIF-1 binding site in the gene promoter, is greatly increased in the cord blood of newborn children with IUGR [Tazuke et al. 1998].
Cancer

Hypoxia is an important selective force in the clonal evolution of tumors (Graeber et al. 1996) and HIF-1α is overexpressed in common human cancers (Zhong et al. 1999; Zagzag et al. 2000). The involvement of HIF-1 in tumor progression has been reviewed in detail (Semenza 2000b) but the major physiologic and genetic mechanisms leading to HIF-1α overexpression are summarized below.

Angiogenesis and hypoxia

Until primary tumors establish a blood supply, the limited diffusion of O₂ from nearby host vessels limits their growth to no more than a few cubic millimeters because cell division is balanced by cell death. Increased expression of VEGF is essential for the establishment of angiogenesis in most solid tumors. Experimental data (for review, see Semenza 2000b) suggest the following model: Increased VEGF expression is required to initiate and sustain tumor angiogenesis. Increased VEGF levels result from the synergistic effects of tumor hypoxia and tumor-specific genetic alterations [mutations] involving oncogenes and tumor suppressor genes. Increased VEGF expression results in the formation of dysfunctional vasculature that cannot adequately perfuse the entire tumor. Cellular adaptation to hypoxia is therefore a requirement of tumor progression independent of angiogenesis. As a result, most solid tumors have the seemingly paradoxical characteristic that poor clinical outcome is significantly correlated with both vascular density and tumor hypoxia.

In human glialomas, there is a significant association between tumor grade, vascularization, and HIF-1α overexpression [Zagzag et al. 2000]. The highest grade glioma is glioblastoma multiforme [GBM], which is associated with a mean patient survival time of less than one year, regardless of treatment. In this condition, the rapidly proliferating tumor cells outstrip their blood supply resulting in extensive necrosis. The viable tumor cells surrounding necrotic regions express high levels of HIF-1α protein [Zhong et al. 1999; Zagzag et al. 2000] and VEGF mRNA [Plate et al. 1992; Shweiki et al. 1992]. This pattern of expression suggests that the tumor cells are responding to hypoxia by HIF-1-mediated VEGF expression as demonstrated previously in cultured cells and mouse xenografts [Forsythe et al. 1996; Maxwell et al. 1997; Carmeliet et al. 1998; Iyer et al. 1998a; Ryan et al. 1998]. GBMs have multiple mutations that activate tumor suppressor genes, including p14ARF, p16CDKN2A, TP53, and PTEN [Ishii et al. 1999], or activate oncogenes, including CDK4, EGFR, and MDM2 [Holland et al. 1998]. Remarkably, recent studies have established that mutations in oncogenes and tumor suppressor genes which had previously been shown to increase VEGF expression do so by induction of HIF-1α, as described below.

Tumor suppressor genes

Hemangioblastoma is a brain tumor that differs from GBM by a lack of necrosis. This tumor is so well vascularized that, as its name implies, it was originally believed to arise from the progenitor cells for blood and vascular endothelial cells. Instead, hemangioblastomas produce extraordinarily high levels of VEGF that are responsible for inducing extensive vascularization. Remarkably, all hemangioblastomas analyzed overexpressed HIF-1α [Zagzag et al. 2000]. Hypoxia is unlikely to be a stimulus for HIF-1α expression in these cells. The key genetic lesion in hemangioblastoma and in clear cell renal carcinoma, another extensively vascularized tumor type, is functional inactivation of the von Hippel-Lindau (VHL) tumor suppressor [Gnarra et al. 1994; Herman et al. 1994; Kanno et al. 1994; Shuin et al. 1994]. In renal carcinoma cell lines, VHL loss-of-function results in constitutive expression of HIF-1α under nonhypoxic conditions [Maxwell et al. 1999]. VHL is associated with ubiquitin–protein ligase activity [Lisztwan et al. 1999] and loss of VHL function in renal carcinoma cells results in defective ubiquitination of HIF-1α under nonhypoxic conditions [Cockman et al. 2000].

p53 loss-of-function also leads to an increase in HIF-1α and VEGF expression that, although less dramatic than that associated with VHL loss-of-function, affects many more tumors, as loss of p53 activity occurs via one or more molecular mechanisms in the majority of human cancers (for review, see Giaccia and Kastan 1998). Remarkably, p53 also acts to target HIF-1α for ubiquitination but, in contrast to VHL, loss of p53 activity primarily leads to augmented hypoxia-induced HIF-1α and VEGF expression [Ravi et al. 2000]. This is possible because there is considerable ubiquitination of HIF-1α even under hypoxic conditions (Sutter et al. 2000). HIF-1α and p53 directly interact, leading to the recruitment of the ubiquitin-protein ligase MDM2, which binds to p53 [Ravi et al. 2000]. HIF-1α expression increases the stability of p53 [An et al. 1998] whereas p53 decreases the stability of HIF-1α in an MDM2-dependent manner [Ravi et al. 2000], suggesting that within the trimolecular complex HIF-1α is a preferential target of MDM2. HIF-1α-mediated stabilization of p53 may also play a role in hypoxia-mediated apoptosis leading to selection for loss of p53 function in tumor cells (Graeber et al. 1996).

Oncogenes

Dysregulation of signal transduction pathways regulating cell proliferation and viability is a hallmark of cancer. This can occur through gain-of-function mutations in genes encoding receptor tyrosine kinases such as EGFR, HER2neu, or IGF-1R, and nonreceptor tyrosine kinases, such as c-SRC. The prototype oncogene, v-SRC, induces the expression of HIF-1α protein, HIF-1 DNA-binding and transcriptional activity, and mRNAs encoding VEGF and ENO1 [Jiang et al. 1997a]. The biological effects of oncogenic tyrosine kinases occur via activation of the RAS, phosphatidylinositol-3-kinase [PI3K]/AKT [protein kinase B], and/or RAF/MEK/ERK [MAP kinase] pathways. In human prostate cancer cells, HIF-1α and VEGF overexpression are mediated via the PI3K/AKT pathway via the downstream effector kinase FKB/rapa-
mycin-associated protein [FRAP] also known as mammalian target of rapamycin [mTOR] [Zhong et al. 2000]. Exposure of cells to LY294002 or rapamycin, inhibitors of PI3K and FRAP, respectively, completely blocks HIF-1α expression in nonhypoxic cells. In human prostate cancer and glioma cell lines, HIF-1-dependent transcription can be induced by a constitutively active form of AKT or a dominant-negative form of the phosphatase PTEN, which functions as a tumor suppressor by negatively regulating the PI3K/AKT pathway [Zhong et al. 2000; Zundel et al. 2000]. PTEN loss of function is correlated with angiogenesis and advanced tumor stage in human prostate cancer [Giri and Ittmann 1999; McMenamin et al. 1999]. Overexpression of PTEN in glioma cells dramatically reduces the accumulation of HIF-1α [Zundel et al. 2000], suggesting that the PI3K/AKT pathway may also regulate the ubiquitination of HIF-1α.

Oncogenic RAS mutations are also very common in human cancer and can lead to VEGF expression via either the PI3K or MAPK pathway, depending upon the cell type [Rak et al. 2000]. The induction of VEGF promoter activity in H-RAS-transformed NIH 3T3 cells is dependent on PI3K (but not FRAP) activity and the presence of an intact HIF-1-binding site [Mazure et al. 1997]. In CCL-39 fibroblasts, expression ofraf-1 results in phosphorylation of HIF-1α by p42 and p44 ERK, which is associated with increased HIF-1 transcriptional activity but no increase in HIF-1α protein expression [Richard et al. 1999], suggesting an effect on transactivation domain function, but the site of phosphorylation has not been reported. HIF-1α may also be phosphorylated by ERK in HMEC-1 endothelial cells under hypoxic conditions [Minet et al. 2000]. Exposure of mouse embryonic fibroblasts to the organomercurial compound mersalyl induces the expression of HIF-1α protein, HIF-1 DNA-binding and transcriptional activity, and mRNAs encoding VEGF and ENO1, an effect that is dependent on the presence of IGF-1R and MEK activity [Agani and Semenza 1998]. These studies suggest that the MAP kinase pathway can regulate HIF-1α protein stabilization or transactivation in a cell-type or stimulus-specific manner.

Effects of increased HIF-1 activity on tumor biology

Taken together, recent data indicate that HIF-1 activity is increased by both physiologic and epigenetic mechanisms in human cancer. Analysis of isogenic cell lines in nude mouse xenograft assays indicate that loss of HIF-1 activity results in increased tumor latency and decreased vascular density [Jiang et al. 1997a; Maxwell et al. 1997; Carmeliet et al. 1998; Ryan et al. 1998], whereas overexpression of HIF-1α results in decreased tumor latency and increased vascular density, volume, and permeability [Ravi et al. 2000]. Known HIF-1 target genes provide a molecular basis by which HIF-1 overexpression may promote key aspects of tumor progression [Table 1]: Glucose transporters and glycolytic enzymes promote metabolic adaptation to hypoxia, NOS2 and VEGF promote angiogenesis; IGF-2 promotes cell survival and prolifera-

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References


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