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The role of Hypoxia-inducible factors in Tumourigenesis: A Review

Obeagu Emmanuel Ifeanyi
Diagnostic Laboratory Unit,University Health Services,Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria.
*Corresponding author: *emmanuelobeagu@yahoo.com, obeagu.emmanuel@mouau.edu.ng*

Abstract

HIFs facilitate both oxygen delivery and adaptation to oxygen deprivation by regulating the expression of genes that are involved in many cellular processes, including glucose uptake and metabolism, angiogenesis, erythropoiesis, cell proliferation, and apoptosis. Under normoxia, HIFs are targeted for proteasomal degradation by the von Hippel–Lindau (VHL) tumor suppressor, pVHL. It has been shown that pVHL is the substrate recognition component of an E3 ubiquitin ligase complex that interacts with HIF-*α* in an oxygen-dependent manner. Hypoxia is the best-characterized mechanism of HIF activation in tumors. It has been estimated that 50–60% of solid tumors contain areas of hypoxic and/or anoxic tissues that develop as a result of an imbalance between oxygen supply and consumption in proliferating tumors. Low oxygen concentrations may result from increased metabolic activity and oxygen consumption and/or increased tumor cell distance from local capillaries and blood supply. One mechanism by which HIF-2 controls cellular proliferation is through modulation of C-Myc activity. C-Myc promotes cellular proliferation by regulating the expression of genes involved in cell cycle control including cyclins (cyclin D2) and cyclin kinase inhibitors.

Keywords: Role, Hypoxia, Hypoxia inducible factors, Tumuorgenesis

Introduction

Hypoxia-inducible factors

HIFs facilitate both oxygen delivery and adaptation to oxygen deprivation by regulating the expression of genes that are involved in many cellular processes, including glucose uptake and metabolism, angiogenesis, erythropoiesis, cell proliferation, and apoptosis. They are members of the PAS (PER-ARNT (arylhydrocarbon receptor nuclear translocator)-SIM) family of basic helix-loop-helix (bHLH) transcription factors that bind to DNA as heterodimers composed of an oxygen-sensitive *α* subunit and a constitutively expressed *β* subunit, also known as ARNT. To date, three HIFs (HIF-1, -2, and -3) have been identified that regulate transcriptional programs in response to low oxygen levels.

HIF-1 was the first HIF family member to be characterized. Using DNA affinity purification, HIF-1 was identified as a hypoxic-induced factor that bound an 18-nt fragment of the *EPO* enhancer required for the hypoxic activation of *EPO* in Hep3B cells. Structural analysis of the HIF-1*α* protein revealed that HIF-1*α* contains four distinct domains including a bHLH domain for DNA binding and dimerization, a PAS domain for dimerization and target gene specificity, an oxygen-dependent degradation domain (ODD) required for degradation by the ubiquitin–proteasome pathway, and two transactivation domains located in the C-terminal portion of the protein(Pugh et al.,1997).

Notably, HIF-1 has emerged as a critical regulator of the cellular response to hypoxia since it is ubiquitously expressed and induces the expression of many hypoxia-inducible genes(Wenger et al.,1996).

Oxygen-Dependent Regulation of HIF

Under normoxia, HIFs are targeted for proteasomal degradation by the von Hippel–Lindau (VHL) tumor suppressor, pVHL. It has been shown that pVHL is the substrate recognition component of an E3 ubiquitin ligase complex that interacts with HIF-*α* in an oxygen-dependent manner. Hydroxylation of conserved proline residues within the HIF-*α* ODD by prolyl-4-hydroxylase domain (PHD)-containing proteins mediates pVHL binding and degradation.. Under hypoxia, HIF-*α* subunits are stabilized and translocate to the nucleus, where they heterodimerize with ARNT and bind to HREs located within regulatory elements of HIF target genes. Cell culture studies have shown that HIF stabilization and DNA-binding activity is induced at oxygen concentrations below 6% oxygen and is maximal at 0.5% oxygen tensions(Jiang et al.,1996). Once stabilized, the HIF-*α*/ARNT heterodimer activates transcription by recruiting the transcriptional activators p300 and CBP. The interaction between HIF and p300/CBP is also regulated in an oxygen-dependent manner by factor inhibiting HIF-1 (FIH-1), a member of the 2-oxoglutarate and Fe(II)-dependent oxygenase superfamily. FIH hydroxylates asparagine residues located within the HIF-*α* C-terminal transactivation domain (CTAD) and prevents p300/CBP binding. Thus, full activation of HIF transcriptional activity requires both HIF*α* stabilization and CTAD activation (Lando et al.,2002).

Hypoxia Inducibel Factor Activation in Cancer

A recent survey of malignant and normal tissues found that the expression of both HIF-1*α* and HIF-2*α* are commonly increased in a variety of human tumors, including bladder, breast, colon, glial, hepatocellular, ovarian, pancreatic, prostate, and renal tumors. In clinical specimens, elevated HIF-1 expression correlates with poor patient outcome in head and neck cancer, nasopharyngeal carcinoma, colorectal, pancreatic, breast, cervical, osteosarcoma, endo-metrial, ovarian, bladder, glioblastoma, and gastric carcinomas, while elevated HIF-2 expression correlates with poor patient outcome in hepatocellular, colorectal carcinoma, melanoma, ovarian, and non-small cell lung cancers (Giatromanolaki et al.,2001). Collectively, these findings highlight that HIF activation is a common event in cancer and suggest that HIF may play a role in tumorigenesis.

Hypoxia is the best-characterized mechanism of HIF activation in tumors. It has been estimated that 50–60% of solid tumors contain areas of hypoxic and/or anoxic tissues that develop as a result of an imbalance between oxygen supply and consumption in proliferating tumors. Low oxygen concentrations may result from increased metabolic activity and oxygen consumption and/or increased tumor cell distance from local capillaries and blood supply. Consistent with tumor hypoxia as a mechanism of HIF activation, HIF protein is commonly detected in perinecrotic regions of sporadic tumors and overlaps with staining for known hypoxic markers(Kim et al.,2005).

HIF can also be activated in tumors under normoxic conditions through genetic alterations in its oxygen-signaling pathway. As described earlier, VHL plays a central role in regulating HIF transcriptional activity. Inactivation of VHL results in HIF stabilization and increased target expression irrespective of oxygen concentrations. VHL-mediated regulation of HIF transcriptional activity has important implications for tumor development. Germ-line mutations in *VHL* results in VHL disease, a familial tumor syndrome that predisposes patients to the development of highly vascularized neoplasms, including hemangioblastomas of the retina and central nervous system, renal cell carcinomas (RCCs), endocrine and exocrine pancreatic tumors, as well as pheochromocytomas(Latif et al.,1993). VHL is also inactivated in the majority of sporadic RCC and hemangio-blastomas, highlighting the importance of VHL tumor suppressor activity.

Multiple lines of evidence suggest that activation of the PI-3 kinase signaling pathway can also induce HIF activity. Subsequently, it was found that activation of the PI-3 kinase/Akt pathway through enhanced growth factor signaling or inactivation of negative regulators including PTEN or TSC2 also increased HIF activity. In many cell types, PI-3 kinase/Akt signaling regulates HIF activity in an mTOR-dependent manner. Although the exact mechanism by which mTOR regulates HIF activity is unclear, evidence suggests that it may have both transcriptional and post-translational effects on HIF(Hudson et al.,2002).

Hypoxia Inducible Factor Functions in Cancer

Tumorigenesis involves a number of alterations in cell physiology that contribute to malignant growth. Importantly, HIFs have been found to promote key steps in tumorigenesis, including angiogenesis, metabolism, proliferation, metastasis, and differentiation.

Angiogenesis

Neovascularization is critical for tumor progression since the supply of oxygen and nutrients becomes limited in tumor cells that are located more than 100 μm away from a blood vessel. The ability of tumor cells to induce angiogenesis occurs through a multistep process, termed the 'angiogenic switch,' which ultimately tips the balance toward pro-angiogenic factors. HIF can directly activate the expression of a number of pro-angiogenic factors, including VEGF, VEGF receptors FLT-1 and FLK-1, plasminogen activator inhibitor-1 (PAI-1), angiopoietins (ANG-1 and -2), platelet-derived growth factor B (PDGF-B), the TIE-2 receptor, and matrix metalloproteinases MMP-2 and -9 (Figure 3, for a recent review). Of all the proangiogenic factors induced by HIF, VEGF-A is particularly noteworthy since it has potent angiogenic properties and is expressed in a large number of human tumors(Dvorak,2002).

List of HIF-regulated genes that promote key aspects of tumorigenesis. HIF regulates the expression of over 100 genes that regulate key aspects of tumorigenesis, including angiogenesis, metabolism, proliferation, invasion, and metastasis. ALDA, aldolase **...**

In both human cell lines and murine model systems, HIF signaling has been shown to be required for the regulation of VEGF and tumor angiogenesis. However, the relative contribution of individual HIF family members in this process is controversial. A proangiogenic role has been reported for HIF-1. Notably, HIF-1-deficient ES cells formed significantly smaller teratocarcinomas that exhibited reduced tumor vessel density and VEGF levels compared to teratocarcinomas derived from wild-type ES cells.VEGF expression and angiogenesis were also found to be HIF-1 dependent in hypoxic astrocytes providing further evidence for HIF-1-mediated angiogenesis. Recent studies suggest that HIF-2 can also regulate angiogenesis. Raval *et al*.(2005) observed that VEGF expression was preferentially induced by HIF-2 in VHL-deficient RCC cells that expressed both HIF-1 and -2. To directly compare the relative contributions of HIF-1 and -2 in tumorigenesis, Covello *et al*.(2005) generated teratocarcinomas derived from ES cells in which HIF-2α was knocked into the HIF-1α locus, thereby expanding HIF-2 expression. Teratomas derived from HIF-2α knock-in ES cells were larger and exhibited increased vascularity and VEGF expression compared to wild-type (HIF-1α expressing)-derived teratomas, suggesting that HIF-2 plays an important role in promoting tumor angiogenesis and growth. Collectively, these findings demonstrate that both HIF-1 and -2 can activate VEGF and tumor angiogenesis; however, their individual contributions appear to be cell-type dependent. These differences may be attributed to different levels of HIF-1 and -2 in individual cell types and may be affected by cell-specific cofactors that modulate HIF activity.

Metabolism

It was noted over 70 years ago that cancer cells shift glucose metabolism from oxidative to glycolytic pathways. This process known as the Warburg effect, involves decreased mitochondrial respiration and increased lactate production even in the presence of oxygen. It is well established that HIF, in particular HIF-1, directly regulates the expression of a number of genes involved in glycolytic metabolism, including glucose transporters, glycolytic enzymes, lactate production, and pyruvate metabolism in both hypoxic and normoxic (e.g. VHL deficient) cells Recent studies using transformed cell lines show that HIF-1 can also regulate cellular metabolism by controlling mitochondrial respiration. Zhang *et al*.(2007) observed that HIF-1 negatively regulates mitochondrial mass and oxygen consumption in VHL-deficient RCC cells. The mechanism by which HIF mediates these effects appears to be through inhibition of C-Myc activity. HIF-1 was found to negatively regulate C-Myc activity and mitochondrial respiration through transcriptional activation of the C-Myc repressor, MXI-1, and through regulation of C-Myc protein stability. Collectively, these findings demonstrate that HIF controls multiple aspects of metabolism through direct transcriptional activation of genes involved in glucose metabolism and indirectly by regulating C-Myc activity. These observations indicate that HIF is an important mediator of metabolism in cancer.

Proliferation

HIF-2 plays an important role in promoting tumor growth. In VHL-deficient RCC cells, HIF-2 is both necessary and sufficient to maintain tumor growth(Kondo et al.,2003). Furthermore, tumors generated from RCC cell lines overexpressing HIF-2 grow at a faster rate compared to HIF-1-overexpressing tumors. Covello *et al*.(2005) demonstrated that teratomas derived from ES cells with HIF-2α in the place of the HIF-1α locus are larger and exhibit increased proliferation rates compared to wild-type (HIF-1α expressing) teratomas. While HIF-2 may facilitate tumor growth through multiple mechanisms, recent studies indicate that HIF-2 can positively regulate cell proliferation.

One mechanism by which HIF-2 controls cellular proliferation is through modulation of C-Myc activity. C-Myc promotes cellular proliferation by regulating the expression of genes involved in cell cycle control including cyclins (cyclin D2) and cyclin kinase inhibitors (p21 and p27).73 Unlike HIF-1, HIF-2 promotes C-Myc-dependent activation of cyclin D2 and repression of p27 in RCC cells.74 How HIF-2 preferentially promotes C-Myc activity remains unclear, but may occur through alterations in C-Myc interactions with transcriptional cofactors, including Sp1, Miz1, and Max.74

HIF-2 may also drive cell cycle progression through the activation of cyclin D1.Cyclin D1 is a well-characterized cell cycle regulatory protein that is upregulated in many cancers. Recent studies have shown a correlation between HIF-2-mediated cyclin D1 expression and tumor growth in RCC cells(Bindra et al.,2002).Whether cyclin D1 is a direct HIF target remains to be determined.

Metastasis

Metastasis is a critical step in tumor pathogenesis and is the primary cause of human cancer deaths. It occurs in a series of distinct steps that include tumor cell invasion, intravasation, extravasation, and proliferation. HIF activation correlates with metastasis in multiple tumors and can promote metastasis through the regulation of key factors governing tumor cell metastatic potential, including E-cadherin, lysyl oxidase (LOX), CXCR4, and stromal-derived factor 1 (SDF-1).

E-cadherin is a key factor governing metastatic potential in the majority of epithelial cancers. It is a cellular adhesion molecule that regulates cell–cell adhesion and stimulates antigrowth signals through cytoplasmic interactions with β catenin. The importance of E-cadherin in regulating metastasis is underscored by the findings that E-cadherin inactivation enhances metastatic potential and forced expression of E-cadherin in cancer cells inhibits metastasis. HIF has recently been described as a critical factor for the regulation of E-cadherin expression in ovarian carcinoma and VHL-deficient renal cells. It has been proposed that HIF mediates repression of E-cadherin expression through the upregulation of E-cadherin-specific repressors, including Snail and SIP1(Evans et al.,2007).

HIF also promotes metastasis through activation of the extracellular matrix protein LOX(Erler et al.,2006). LOX is an amine oxidase involved in extracellular matrix formation. Increased LOX expression is correlated with decreased distant metastasis-free survival and overall survival in patients with breast and head and neck cancer. In addition, LOX activation promotes the invasive and metastatic potential of breast cancer cells. Erler *et al*.(2006) recently reported that LOX is a direct HIF target in hypoxic tumor cells and that genetic and pharmacologic inhibition of LOX is sufficient to prevent hypoxia-induced cell invasion and metastasis *in vitro* and *in vivo*. These findings indicate that LOX is a critical factor in hypoxia-induced metastasis.

Interactions between the chemokine receptor CXCR4 and its ligand SDF-1 play an important role in the directional migration of metastatic tumor cells. CXCR4 is the most common chemokine expressed in tumors and SDF-1 is highly expressed at sites of metastasis, including the lung, bone marrow, and liver. Studies have shown that HIF is a potent inducer of both CXCR4 and SDF-1 expression in a variety of cell types, including VHL-deficient RCCs, non-small cell lung cancer, glioblastomas, and endothelial cells.

Differentiation

Accumulating evidence suggests that cancer stem cells are important mediators of tumor growth. According to the ‘cancer stem cell’ hypothesis, tumors are thought to originate from a small population of proliferating cells that maintain the ability to self-renew and differentiate into a heterogeneous population.. It is well documented that hypoxia and

HIF promotes an undifferentiated state in a variety of cell types. Hypoxia has been shown to prevent the differentiation of progenitor cells and promote dedifferentiation of cancer cells. Gustafsson *et al*.(Gustafsson et al.,2005) has provided evidence to suggest that Notch plays an important role in maintaining a dedifferentiated state under hypoxia in multiple cell types, including cortical neural stem cells, myogenic satellite cells, and C2C12 cells. In these cells, hypoxia enhanced Notch signaling in a HIF-dependent manner, whereby HIF-1α interacts with and stabilizes the Notch ICD domain. In addition to regulating Notch, HIF could also promote an undifferentiated state by directly activating the expression of genes involved in stem cell maintenance. Evidence suggests that primitive hematopoietic and embryonic stem (ES) cells reside in an hypoxic micro-environment, suggesting that low oxygen tensions may play a role in maintaining stem cell fate. In support of this notion, hypoxia has been shown to maintain human ES (hES) cells in an undifferentiated state and maintain stem cell pluripotency. Interestingly, maintenance of a dedifferentiated state in hypoxic hES cells correlated with the expression of Oct4, transcription factor involved in maintaining an undifferentiated state in ES that has recently been identified as one of four factors sufficient to reprogram fibroblasts to a cell that exhibits ES cell morphology and growth properties.

HIF and Tumor Inhibition

Despite HIF's protumorigenic properties, HIF has also been reported to inhibit tumor growth. In addition, HIF activation has been reported to inhibit tumor growth in additional cell types, including glioblastomas and VHL-deficient fibrosarcomas(Mack et al.,2003). While all of these tumor models confirmed a positive role for HIF in tumor angiogenesis, tumor growth inhibition was associated with decreased proliferation and increased apoptosis.

Recent studies have elucidated mechanisms by which HIF-1 can negatively regulate tumor growth. First, HIF-1 can indirectly induce cell cycle arrest by inhibiting Myc activity. It has been proposed that a physical interaction between HIF-1α and Myc prevents Myc-mediated repression of the cyclin kinase inhibitor p21. Second, HIF can induce apoptosis through both direct and indirect mechanisms. It has been reported that HIF-1 can directly induce the expression of the proapoptotic genes BNIP3 and NIX in a variety of human cancer cell lines, macrophages, and endothelial cells(Sowter et al.,2001).

The mechanisms of BNIP3-mediated cell death under hypoxia are not well understood. A recent report suggests that BNIP3 is required for hypoxia-induced macroautophagy(Tracy et al.,2007). Autophagy is generally thought of as a cellular survival mechanism that involves recycling of amino acids and fatty acids to produce energy under conditions of nutrient deprivation and stress; however, sustained autophagy can result in autophagic cell death. Whether macroautophagy is induced by HIF as a mechanism for cellular survival and or cell death remains to be determined. HIF can also indirectly induce apoptosis by promoting glucose deprivation.

Conclusion

HIFs facilitate both oxygen delivery and adaptation to oxygen deprivation by regulating the expression of genes that are involved in many cellular processes, including glucose uptake and metabolism, angiogenesis, erythropoiesis, cell proliferation, and apoptosis. Under normoxia, HIFs are targeted for proteasomal degradation by the von Hippel–Lindau (VHL) tumor suppressor, pVHL. It has been shown that pVHL is the substrate recognition component of an E3 ubiquitin ligase complex that interacts with HIF-α in an oxygen-dependent manner. Hypoxia is the best-characterized mechanism of HIF activation in tumors. It has been estimated that 50–60% of solid tumors contain areas of hypoxic and/or anoxic tissues that develop as a result of an imbalance between oxygen supply and consumption in proliferating tumors. Low oxygen concentrations may result from increased metabolic activity and oxygen consumption and/or increased tumor cell distance from local capillaries and blood supply. Despite HIF's protumorigenic properties, HIF has also been reported to inhibit tumor growth. In addition, HIF activation has been reported to inhibit tumor growth in additional cell types, including glioblastomas and VHL-deficient fibrosarcomas.

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