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L.-M. Chen, I. Choi, G. G. Haddad and W. F. Boron  
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## Hydroxylation of HIF-1: Oxygen Sensing at the Molecular Level

The ability to sense and respond to changes in oxygenation represents a fundamental property of all metazoan cells. The discovery of the transcription factor HIF-1 has led to the identification of protein hydroxylation as a mechanism by which changes in  $P_{O_2}$  are transduced to effect changes in gene expression.

Gregg L. Semenza

Program in Vascular Cell Engineering; Departments of Pediatrics, Medicine, Oncology, and Radiation Oncology; and Institute of Genetic Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205  
gsemenza@jhmi.edu

Multicellular life on Earth is based on the use of  $O_2$  for the efficient generation of high-energy compounds, and  $O_2$  consumption increases with the mass and metabolic activity of the organism. However, exposure to  $O_2$  must be limited due to the damaging effects of reactive oxygen species (ROS) on cellular macromolecules. Thus all of the major physiological systems of mammals participate in complex homeostatic mechanisms that are designed to maintain the  $O_2$  concentration to which each cell is exposed within a narrow range (FIGURE 1). The study of these systems has occupied physiologists for centuries. During the course of the past century, these studies have been extended to the cellular level. Finally, research over the past decade has produced dramatic insights into the molecular mechanisms underlying oxygen homeostasis during both prenatal and postnatal life.

### Control of Oxygen-Regulated Gene Expression by HIF-1

Physiological responses involve changes in gene expression. The blood  $O_2$ -carrying capacity is maintained by the  $O_2$ -regulated production of erythropoietin (EPO), which stimulates the proliferation and survival of red blood cell progenitors. Analysis of *cis*-acting sequences required for increased transcription of the *EPO* gene in response to hypoxia led to the identification (70), biochemical purification (81), and molecular cloning (79) of hypoxia-inducible

factor-1 (HIF-1). EPO is produced primarily within a rare cell type in the kidney. However, HIF-1 is expressed in all cell types and functions as a master regulator of oxygen homeostasis by playing critical roles in both embryonic development and postnatal physiology. HIF-1 has been identified in all metazoan species that have been analyzed from *Caenorhabditis elegans* to *Homo sapiens* (organisms whose cell numbers differ by more than 10 orders of magnitude), suggesting that the appearance of HIF-1 represented an adaptation that was essential to metazoan evolution.

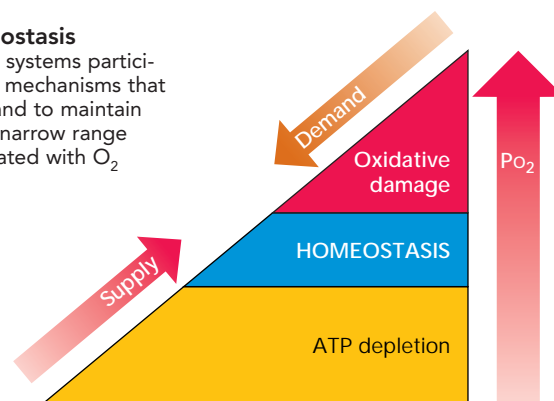
The expression of over 70 genes is known to be activated at the transcriptional level by HIF-1, and specific HIF-1 binding sites have been identified for many of these genes. Although the list of HIF-1 target genes is extensive (FIGURE 2), it probably underestimates the total number of genes regulated by HIF-1 by at least an order of magnitude. The battery of genes regulated by HIF-1 is different in each cell type, and, for some genes, expression can be induced or repressed by HIF-1 depending on the cell type (34). Among the critical physiological processes regulated by HIF-1 target genes are erythropoiesis, angiogenesis, and glycolysis, which are examples of systemic, local tissue, and intracellular adaptive responses to hypoxia, respectively (30).

HIF-1 is a heterodimeric protein that is composed of HIF-1 $\alpha$  and HIF-1 $\beta$  subunits. The amino-terminal half of each subunit consists of basic helix-loop-helix and Per-ARNT-Sim (PAS) domains that mediate heterodimerization and DNA binding. The carboxy-terminal half of HIF-1 $\alpha$  contains two transactivation domains that mediate interactions with coactivators such as CREB binding protein (CBP) and p300 (30, 31, 59). Coactivators interact with both sequence-specific DNA binding proteins such as HIF-1 and with the general transcription factors associated with RNA Polymerase II (reviewed in Ref. 69). Coactivators also have histone acetyltransferase activity that is required to make the DNA embedded in chromatin accessible to the polymerase complex for transcription into RNA.

The HIF-1 $\beta$  subunit is constitutively expressed, whereas the expression and activity of the HIF-1 $\alpha$  subunit are precisely regulated by the cellular  $O_2$

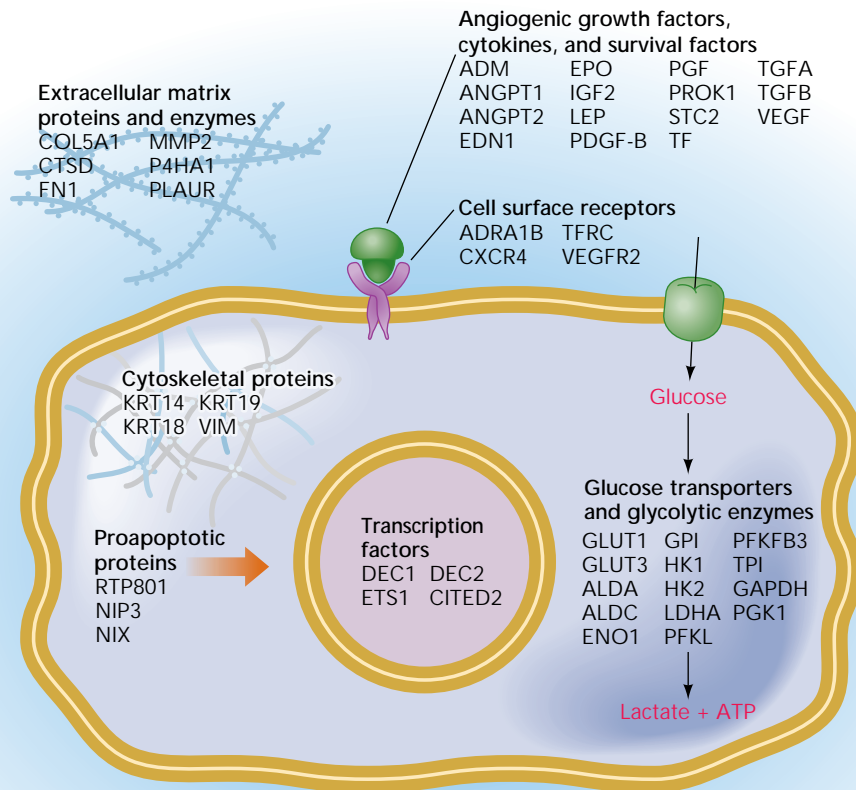
#### FIGURE 1. Oxygen homeostasis

All of the major physiological systems participate in complex homeostatic mechanisms that regulate  $O_2$  supply and demand to maintain cellular oxygenation within a narrow range that balances the risks associated with  $O_2$  deficiency and excess.



**FIGURE 2. Representative HIF-1 target genes**

Hypoxia inducible factor-1 (HIF-1) activates the transcription of genes encoding secreted signaling proteins, including angiogenic growth factors and survival factors, cell surface receptors, extracellular matrix proteins and modifying enzymes, transcription factors, cytoskeletal proteins, proapoptotic proteins, and glucose transporters and glycolytic enzymes. ADM, adrenomedullin; ADRA1B,  $\alpha_{1B}$ -adrenergic receptor; ALD, aldolase; ANGPT, angiopoietin; CITED, CREB binding protein (CBP)/p300-interacting transactivator; COL5A1, collagen V  $\alpha$ 1-subunit; CTSD, cathepsin D; CXCR, chemokine receptor; DEC, differentiated embryo chondrocyte expressed; EDN, endothelin; ENO, enolase; EPO, erythropoietin; ETS, erythroblastosis virus transforming sequence; FN, fibronectin; GLUT, glucose transporter; GPI, glucose phosphate isomerase; HK, hexokinase; KRT, keratin; LDHA, lactate dehydrogenase A; LEP, leptin; MMP, matrix metalloproteinase; NIP, BCL2/adenovirus E1B 19-kDa-interacting protein; NIX, NIP3-like; P4HA1, prolyl-4-hydroxylase  $\alpha$ 1-subunit; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3; PFKL, phosphofructokinase L; PGF, placental growth factor; PGK, phosphoglycerate kinase; PLAUR, urokinase-type plasminogen activator receptor; PROK, prokineticin (endocrine gland-derived VEGF); STC, stanniocalcin; TF, transferrin; TFRC, transferrin receptor; TGFA and TGFB, transforming growth factor- $\alpha$  and - $\beta$ ; TPI, triose phosphate isomerase; VEGFR, VEGF receptor; VIM, vimentin.



concentration. HIF-1 $\alpha$  accumulates instantaneously under hypoxic conditions and on reoxygenation is rapidly degraded, with a half-life of <5 min in posthypoxia tissue culture cells (28, 79). This represents an overestimate of the half-life, because it includes the time required for O<sub>2</sub> to diffuse out of the culture medium. In an isolated, perfused, and ventilated lung preparation subjected to hypoxia and reoxygenation, the half-life of HIF-1 $\alpha$  is <1 min (85). No protein has been shown to have a shorter half-life.

In addition to HIF-1 $\alpha$ , a structurally and functionally related protein designated HIF-2 $\alpha$ , which is the product of the *EPAS1* gene, can also heterodimerize with HIF-1 $\beta$  (77). HIF-1 $\alpha$ :HIF-1 $\beta$  and HIF-2 $\alpha$ :HIF-1 $\beta$  heterodimers appear to have overlapping but distinct target gene specificities (22, 73). Unlike HIF-1 $\alpha$ , HIF-2 $\alpha$  is not expressed in all cell types, and when expressed it can be inactive as a result of cytoplasmic sequestration (56). A third protein, designated HIF-3 $\alpha$ , has also been identified (18). Its role has not been well defined, although a splice variant, designated IPAS, has been shown to bind to HIF-1 $\alpha$  and inhibit its activity (45, 46).

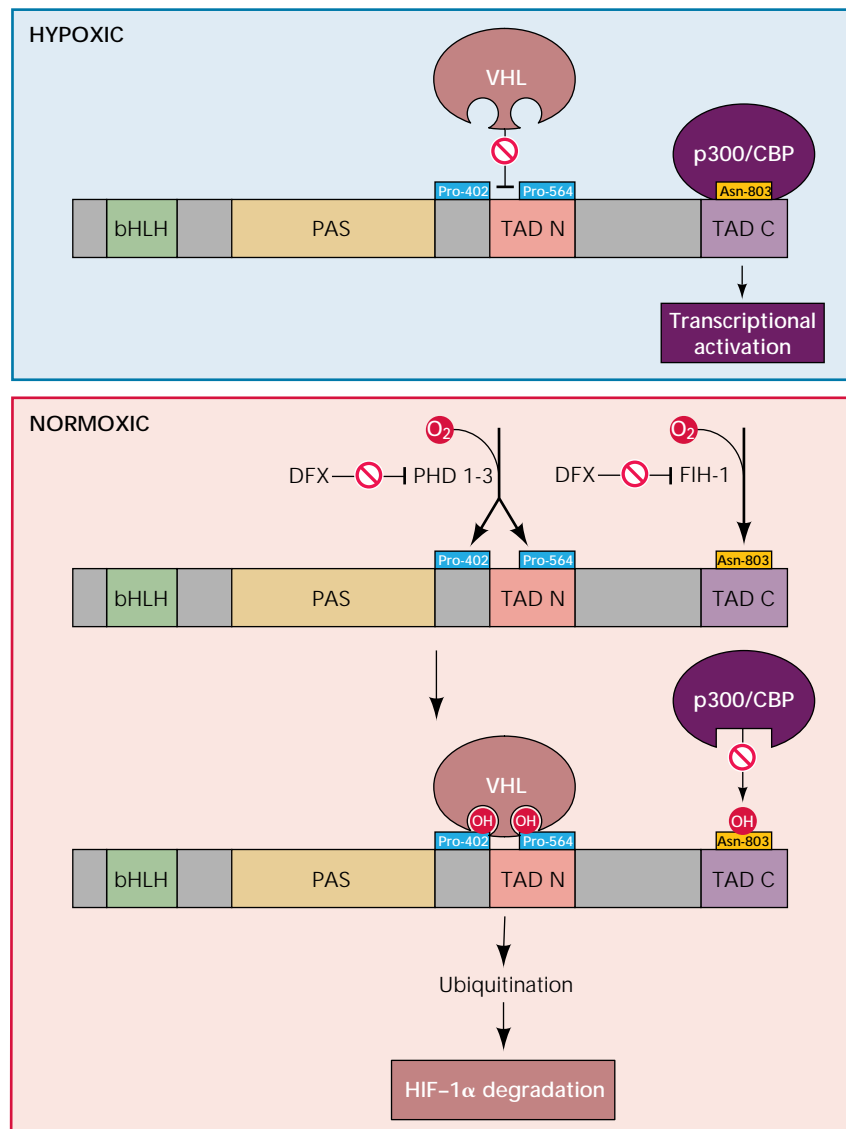
### Molecular Mechanisms of Oxygen Sensing

The mechanism underlying the dramatic regulation of HIF-1 $\alpha$  protein expression was a

source of great debate, with several models proposed that invoked, for example, the functioning of an O<sub>2</sub>-binding hemoprotein or an ROS-generating NADPH oxidase as central to the oxygen sensing that determined HIF-1 $\alpha$  levels (reviewed in Ref. 66). Among the observations used to support these models was the finding that HIF-1 DNA binding activity and target gene expression were induced in cells exposed to the iron chelator desferrioxamine or to cobalt chloride (80). Remarkably, HIF-1 $\alpha$  transactivation domain function is also induced in cells exposed to hypoxia, iron chelation, or cobalt chloride (30, 31, 59), suggesting a common mechanism for regulating both HIF-1 $\alpha$  expression and activity.

The O<sub>2</sub>-dependent degradation of HIF-1 $\alpha$  involves ubiquitination and degradation by the 26S proteasome (23, 32, 61). The von Hippel-Lindau tumor suppressor protein (VHL) is required for this process (FIGURE 3), because renal carcinoma cells lacking functional VHL constitutively express HIF-1 $\alpha$  and HIF-1 target genes under nonhypoxic conditions (6, 49). VHL forms a complex with elongin B, elongin C, cullin 2, and RBX1 to form an E3 ubiquitin-protein ligase capable of functioning with E1 ubiquitin-activating and E2 ubiquitin-conjugating enzymes to mediate the ubiquitination of HIF-1 $\alpha$  (33).

A region of HIF-1 $\alpha$  encompassing amino acid residues 400–600 is necessary and sufficient for O<sub>2</sub>-regulated ubiquitination and degradation (23, 32,



**FIGURE 3. Oxygen sensing by hydroxylation of HIF-1 $\alpha$**

The amino-terminal half of HIF-1 $\alpha$  consists of basic helix-loop-helix (bHLH) and Per-ARNT-Sim homology (PAS) domains. The carboxy-terminal half contains the transactivation domains (TAD-N and TAD-C). The HIF-1 $\alpha$  prolyl hydroxylases (HPH)/prolyl hydroxylase domain proteins (PHD) 1–3 hydroxylate Pro-402 and Pro-564. Factor inhibiting HIF-1 (FIH-1) hydroxylates Asn-803. Proline hydroxylation is required for the interaction of HIF-1 $\alpha$  with the von Hippel-Lindau tumor-suppressor protein (VHL), which is the recognition component of an E3 ubiquitin-protein ligase that targets HIF-1 $\alpha$  for proteasomal degradation. Asparagine hydroxylation prevents the interaction of HIF-1 $\alpha$  with the coactivators CBP and p300. The enzymes, which contain Fe(II) at the active site, can be inactivated by desferrioxamine (DFX) and other iron chelators. O<sub>2</sub> appears to be a rate-limiting substrate for the hydroxylases under physiological conditions, thus providing a mechanism for the direct regulation of the stability and activity of HIF-1 $\alpha$  as a function of the cellular O<sub>2</sub> concentration.

74). VHL interacts, via its  $\beta$ -domain, with amino acid residues 532–585 of HIF-1 $\alpha$  (55, 75). Because the ubiquitination and degradation of other key regulatory proteins such as I $\kappa$ B are regulated by phosphorylation, great effort was made to identify phosphorylatable (serine, threonine, tyrosine) residues of HIF-1 $\alpha$  that were important for regulation of protein half-life, but to no avail. Instead, Pro-564 is hydroxylated in an O<sub>2</sub>-dependent manner, and this modification is required for VHL binding (25, 27, 87). Pro-402 represents a second site of hydroxylation and VHL binding (48). Pro-402 and Pro-564 are each contained within a similar amino acid sequence (LXXLAP, where A is alanine, L is leucine, P is proline, and X is any amino acid). HIF-2 $\alpha$  and HIF-3 $\alpha$  expression are also regulated by prolyl hydroxylation and VHL binding (20, 49, 50).

Three prolyl hydroxylases were identified in mammalian cells and shown to use O<sub>2</sub> as a substrate to generate 4-hydroxyproline at residue 402 and/or 564 of HIF-1 $\alpha$  (2, 13, 24). These proteins are

homologues of EGL-9, which was identified as the HIF-1 $\alpha$  prolyl hydroxylase in *C. elegans* by genetic studies (13). Alternative designations for the three mammalian homologues include EGLN, prolyl hydroxylase domain protein (PHD), and HIF-1 $\alpha$  prolyl hydroxylase (HPH) 1–3. The hydroxylation reaction also requires 2-oxoglutarate ( $\alpha$ -ketoglutarate) as a substrate and generates succinate as a side product. Ascorbate is required as a cofactor. The prolyl hydroxylase catalytic site contains an Fe(II) ion that is coordinated by two histidine and one aspartate residue. Unlike heme-containing proteins, the Fe(II) in 2-oxoglutarate-dependent oxygenases can be chelated or substituted by Co(II), rendering the enzyme inactive. Most importantly, these prolyl hydroxylases have a relatively high  $K_m$  for O<sub>2</sub> that is slightly above its atmospheric concentration, such that O<sub>2</sub> is rate limiting for enzymatic activity under physiological conditions (13, 20). As a result, changes in the cellular O<sub>2</sub> concentration are directly transduced into

changes in the rate at which HIF-1 $\alpha$  is hydroxylated, ubiquitinated, and degraded. However, a thorough analysis of the relationship between O<sub>2</sub> concentration and enzyme activity for each of the PHDs in living cells, and a comparison with the corresponding dose-response curve for HIF-1 $\alpha$  expression (29), has not yet been reported. In particular, the plot of HIF-1 $\alpha$  protein levels as a function of O<sub>2</sub> concentration in HeLa cells yielded a sigmoidal curve suggestive of cooperativity (29), a finding that is not readily explained by the known biochemistry of the HIF-1 $\alpha$  prolyl hydroxylases.

Remarkably, HIF-1 $\alpha$  transactivation domain function is regulated by O<sub>2</sub>-dependent hydroxylation of Asn-803, which blocks the binding of the coactivators CBP and p300 (41). Factor inhibiting HIF-1 (FIH-1), which was identified in a yeast two-hybrid screen as a protein that interacts with and inhibits the activity of the HIF-1 $\alpha$  transactivation domain (44), functions as the asparaginyl hydroxylase (19, 40). As in the case of the prolyl hydroxylases, FIH-1 appears to use O<sub>2</sub> and 2-oxoglutarate and contain Fe(II) in its active site (11, 42, 51), although it has a  $K_m$  for O<sub>2</sub> that is three times lower than the prolyl hydroxylases (37).

Spectroscopic analyses of a peptide from the HIF-1 $\alpha$  transactivation domain complexed with the interacting domain of CBP or p300 revealed that Asn-803 is present within an  $\alpha$ -helix that is buried deep within the protein interface, where it participates in multiple hydrogen-bonding interactions that are predicted to stabilize the complex (9, 12, 15). Hydroxylation of Asn-803 is predicted to disrupt these protein-protein interactions. Similarly, hydroxylation of Pro-564 has been shown to also function as a molecular switch to positively regulate the interaction of HIF-1 $\alpha$  and VHL (21, 53). Thus hydroxylation provides a mechanism for regulating protein-protein interactions, similar to the effect of phosphorylation and other posttranslational modifications. However, what sets hydroxylation apart is that the modification occurs in an O<sub>2</sub>-dependent manner, thus establishing a direct link between cellular oxygenation and HIF-1 activity.

One remarkable aspect of the O<sub>2</sub>-sensing system described above is its plasticity. Although O<sub>2</sub> may be the limiting substrate for hydroxylation under physiological conditions, it appears that under pathophysiological conditions iron or ascorbate may also be limiting (36). Furthermore, the expression of the PHDs varies from one cell type to another as well as in response to various physiological stimuli, including hypoxia (1, 10, 13, 52). Thus the O<sub>2</sub> dose-response curve may be shifted to the left or right under different developmental or physiological conditions. Alternative splicing of the primary RNA transcripts for two of the PHDs provides yet

another mechanism for modulating prolyl hydroxylase activity (20). Finally, the transcriptional response elicited by a hypoxic stimulus also demonstrates a remarkable degree of plasticity, because the battery of target genes that is regulated by HIF-1 is unique to each cell type (34). Thus the identification of the molecular components of the O<sub>2</sub>-sensing system represents a milestone, rather than a finish line, on the course to defining the physiology of oxygen homeostasis.

### Developmental and Physiological Consequences of HIF-1 Activity

The identification of HIF-1, VHL, FIH-1, and the PHDs over the past decade has delineated a pathway by which cells sense O<sub>2</sub> and respond to changes in oxygenation with changes in gene expression, a property that is fundamental to the cells of all metazoan species. Coincident with these dramatic molecular discoveries have been equally dramatic discoveries regarding the remarkable variety of biological processes in which HIF-1 plays an important role. Analyses of mice, in which expression of HIF-1 $\alpha$  has been lost either in all cells (germline knockout) or a single cell lineage (conditional knockout), have identified multiple aspects of development and physiology that are dependent on HIF-1 (TABLE 1). Indeed, the study of HIF-1's role in development and physiology provides a basis for unifying these two central areas of biology. O<sub>2</sub> delivery to cells of the developing embryo becomes limited by diffusion such that establishment of a functioning circulatory system is required for embryonic survival by embryonic

**TABLE 1. Developmental and physiological roles of HIF-1 as established by analysis of HIF-1 $\alpha$ -null mice and cell lines**

Role(s)	References
Development	
Cardiovascular development, embryonic survival	7, 26, 39, 60
Chondrogenesis/skeletal development	62
Adipogenesis	88
B lymphocyte development	38
Mammary gland development	64
Physiology	
Angiogenesis	5, 34, 60
Hypoxia-induced glycolysis	26, 65
Hypoxia-induced apoptosis	5
Hypoxia-induced erythropoiesis	86
Hypoxia-induced pulmonary vascular remodeling	71, 86
Carotid body sensing of arterial PO <sub>2</sub>	35
Myeloid cell-mediated inflammation	8
Hypoxia-induced myocardial preconditioning	4
Hypoxia-induced cell cycle arrest	17
HIF, hypoxia-inducible factor	

day 9 (E9) in the mouse. In wild-type mouse embryos, HIF-1 $\alpha$  expression increases dramatically between E8.5 and E9.5, whereas embryos that lack HIF-1 $\alpha$  expression die between E9.5 and E10.5 and show cardiac malformations, vascular regression, and massive cell death (7, 26, 39, 60). Complete HIF-2 $\alpha$  deficiency is also associated with embryonic lethality (58, 76), and because the embryos survive longer than *Hif1 $\alpha$ <sup>-/-</sup>* mice, effects on multiple organ systems can be demonstrated (63).

Whereas complete HIF-1 $\alpha$  deficiency results in developmental defects, partial HIF-1 $\alpha$  deficiency is sufficient to result in impaired responses to physiological stimuli. A particularly dramatic example is the loss of O<sub>2</sub> sensing in the carotid body of *Hif1 $\alpha$ <sup>-/-</sup>* mice (35). Although the carotid bodies are anatomically and histologically normal and depolarize normally in response to cyanide application, they show essentially no response to hypoxia. Thus partial HIF-1 $\alpha$  deficiency in the carotid body results in a complete loss of the ability to sense and/or respond to changes in the arterial Po<sub>2</sub> by stimulation of the central nervous system cardiorespiratory centers. HIF-2 $\alpha$  is also expressed in the mouse carotid body (76), which suggests that HIF-1 $\alpha$  and HIF-2 $\alpha$  play distinct roles in this organ. The HIF-1 target genes that are critical for O<sub>2</sub> sensing and/or efferent responses by the carotid body have not been identified. Remarkably, in the intact animal, other chemoreceptors are less sensitive to *Hif1 $\alpha$*  gene dosage and compensate for the loss of carotid body activity in *Hif1 $\alpha$ <sup>-/-</sup>* mice (35).

Another dramatic phenotype is the complete inability of *Hif1 $\alpha$ <sup>-/-</sup>* myeloid cells (granulocytes and macrophages) to respond to inflammatory stimuli (8). Myeloid cells are dependent on glycolysis for ATP generation, perhaps reflecting the hypoxic microenvironment that is often associated with inflammation and infection. HIF-1 $\alpha$  deficiency results in ATP deficiency, which impairs critical myeloid cell functions such as aggregation, motility, invasion, and bacterial killing. The role of HIF-1 in immunity is not restricted to myeloid cells, because HIF-1 also plays critical roles in B lymphocyte development (38) and T lymphocyte activation (47). The ability to create mice in which HIF-1 $\alpha$  deficiency is restricted to a limited number of cell types (8, 62, 64) is likely to result in the identification of an increasing number of developmental and physiological processes that are regulated by HIF-1.

### Medical Consequences of HIF-1 Activity

The preceding sections provide a brief summary of the critical role of HIF-1 in understanding oxygen sensing, development, and physiology. HIF-1 plays

an equally important role in disease pathophysiology, including ischemic cardiovascular disease (3, 67) and cancer (68, 82), the most common causes of mortality in the US population. As a result, there is considerable interest in HIF-1 as a therapeutic target in these disorders (16, 68, 82). In the case of cardiovascular disease, increased HIF-1 activity induced as a result of HIF-1 $\alpha$  gene therapy (34, 72, 78), small molecule inhibitors of prolyl hydroxylase activity (20, 24, 43), or inhibitors of HIF-1 $\alpha$ -VHL interaction (83) may provide a means to stimulate neovascularization of ischemic tissue. In contrast, small-molecule inhibitors of HIF-1 activity may be useful as anticancer agents (84). However, because HIF-1 functions as a global regulator of oxygen homeostasis, it may not be a useful therapeutic target if the treatment results in unintended and undesirable side effects. An alternative approach may be to focus on the products of HIF-1 target genes. For example, erythropoietin administration may reduce ischemia-induced apoptosis in patients presenting with acute cerebral or myocardial infarction (4, 14, 54, 57). The translation of a rapidly growing body of basic science data into clinical applications looms as the most challenging and most important goal in this exciting field. ■

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