Regulation of Oxygen Homeostasis by Hypoxia-Inducible Factor 1

Metazoan organisms are dependent on a continuous supply of O2 for survival. Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that regulates oxygen homeostasis and plays key roles in development, physiology, and disease. HIF-1 activity is induced in response to continuous hypoxia, intermittent hypoxia, growth factor stimulation, and Ca2+ signaling. HIF-1 mediates adaptive responses to hypoxia, including erythropoiesis, angiogenesis, and metabolic reprogramming. In each case, HIF-1 regulates the expression of multiple genes encoding key components of the response pathway. HIF-1 also mediates maladaptive responses to chronic continuous and intermittent hypoxia, which underlie the development of pulmonary and systemic hypertension, respectively.

The complexity of metazoan life is sustained by energy generated through the oxidative metabolism of glucose and fatty acids in the mitochondria, which results in the production of reducing equivalents that are used to maintain an electrochemical gradient that drives ATP synthesis. This highly efficient mechanism for producing ATP is dependent on the utilization of O2 as the terminal electron acceptor at complex IV of the respiratory chain. When electrons react with O2 prematurely (e.g., at complex III), reactive oxygen species (ROS) are generated. Tonic, low-level ROS production represents a signal that mitochondrial function is intact, whereas increased ROS production, resulting from reduced or fluctuating O2 availability, is a danger signal that the cell is at risk of oxidative damage and, if uncorrected, death. Our understanding of the mechanisms by which cells and organisms sense hypoxia has dramatically advanced over the last two decades, principally through the discovery of hypoxia-inducible factor 1 (HIF-1) and the delineation of its role as a master regulator of oxygen homeostasis. This paper will provide an update on advances that have occurred in the field of oxygen biology since it was last reviewed in the inaugural issue of Physiology (70).

**Oxygen Sensing and Signal Transduction**

Increased or decreased O2 availability results in hypoxia or hypoxia, respectively. Hypoxia occurs physiologically as a result of excessive (“overshoot”) angio genesis (80) and clinically when O2 is delivered to patients at inappropriately high concentrations. Hypoxia is a fundamental physiological stimulus that occurs in response to tissue growth during normal development (11, 38, 80, 91, 92) and in disease states, such as anemia, hemorrhage, and pneumonia, that have afflicted humans and their ancestors throughout time and therefore have exerted selective pressure for the evolution of adaptive responses. In addition, modern man is afflicted by novel scourges associated with living long and/or unwisely, such as tobacco-related lung disease, atherosclerotic cardiovascular disease, and cancer, that have not exerted selective pressure due to their late onset, both with respect to reproduction of the individual and evolution of the species. Hypoxia can occur continuously or intermittently and be either acute or chronic in duration. Whereas chronic continuous hypoxia may occur either in a physiological or pathological context, chronic intermittent hypoxia only occurs in a pathological context. The distinction between physiological and pathological responses to hypoxia is important and will be delineated in greater detail below.

**Continuous hypoxia**

HIF-1 is a heterodimeric protein that is composed of a constitutively expressed HIF-1α subunit and an O2-regulated HIF-1α subunit (88). Under normoxic conditions, the HIF-1α subunit is synthesized and subjected to hydroxylation on proline residue 402 and/or 564 by prolyl hydroxylase domain (PHD) proteins (principally PHD2) that use O2 and α-ketoglutarate as substrates (FIGURE 1A) to catalyze a dioxygenase reaction in which one oxygen atom is inserted into the proline residue and the other oxygen atom is inserted into α-ketoglutarate to form succinate and CO2 (12, 30). The protein OS-9 binds to both PHD2 and HIF-1α, thereby facilitating hydroxylation (4). Prolyl hydroxylation is required for the binding of the von Hippel-Lindau protein (VHL), which interacts with Elongin C and thereby recruits a ubiquitin ligase complex (30, 31). The protein SSAT2, which interacts with HIF-1α, VHL, and Elongin C, stabilizes the interaction of VHL with Elongin C, thereby facilitating ubiquitination of HIF-1α (2). Ubiquitination marks...
HIF-1α for degradation by the proteasome (68). FIH-1 binds to HIF-1α and negatively regulates transactivation function (49) by hydroxylating asparagine residue 803, which blocks the interaction of the HIF-1α transactivation domain with the co-activator p300 or CBP (41). Thus both the stability and transcriptional activity of HIF-1α are negatively regulated by O2-dependent hydroxylation (FIGURE 1A).

When cells are acutely subjected to hypoxia, the hydroxylase reactions are inhibited as a result of substrate (O2) deprivation and/or increased mitochondrial production of ROS, which may inhibit the hydroxylases by oxidizing a ferrous ion in the catalytic site (24, 30). The loss of hydroxylase activity increases HIF-1α stability and transactivation function, leading to its dimerization with HIF-1β, binding of HIF-1 to its recognition sequence 5'-/(A/G)CGTG-3' (71) in target genes, and increased transcription of target gene sequences into mRNA. When cells are acutely subjected to hypoxia, the hydroxylation reactions are inhibited as a result of substrate (O2) deprivation and/or increased mitochondrial production of ROS, which may inhibit the hydroxylases by oxidizing a ferrous ion in the catalytic site (24, 30). The loss of hydroxylase activity increases HIF-1α stability and transactivation function, leading to its dimerization with HIF-1β, binding of HIF-1 to its recognition sequence 5'-/(A/G)CGTG-3' (71) in target genes, and increased transcription of target gene sequences into mRNA.

Intermittent hypoxia

Brief episodes of hypoxia and reoxygenation (intermittent hypoxia) are known to occur during swimming as a consequence of apneas triggered by the naso-pharyngeal reflex (60). Of greater concern is the chronic intermittent hypoxia that occurs as a result of obstructive sleep apnea and causes cardiovascular disease (34), as will be discussed below. Despite the fact that intermittent hypoxia involves short (15–30 s) episodes of hypoxia followed by longer (e.g., 5 min) periods of reoxygenation, HIF-1 activity is induced, albeit by mechanisms that are distinct from those regulating its activity under conditions of chronic hypoxia (96). The signal transduction pathways by which intermittent hypoxia activates HIF-1 have been delineated in the PC12 rat pheochromocytoma cell line, in which hypoxia was previously (13) shown to induce membrane depolarization and increased intracellular Ca2+ ([Ca2+]i). When these cells were exposed to 60 cycles of intermittent hypoxia, the hydroxylation reactions are inhibited as a result of substrate (O2) deprivation and/or increased mitochondrial production of ROS, which may inhibit the hydroxylases by oxidizing a ferrous ion in the catalytic site (24, 30). The loss of hydroxylase activity increases HIF-1α stability and transactivation function, leading to its dimerization with HIF-1β, binding of HIF-1 to its recognition sequence 5'-/(A/G)CGTG-3' (71) in target genes, and increased transcription of target gene sequences into mRNA.

1.5% O2 for 30 min induced and increased HIF-1α protein and mRNA in these cells, indicating a kinase-dependent phospholipase activity, involving the PI3K/AKT/mTOR pathway (42). FIGURE 2A depicts the signal transduction pathways that have been identified to mediate the hypoxia-induced expression of HIF-1α. The PI3K/AKT/mTOR pathway is an important signaling pathway that is activated by growth factors and mitogens and that regulates a wide range of cellular processes, including cell growth, proliferation, survival, and metabolism. Inhibition of the PI3K/AKT/mTOR pathway with PI3K inhibitors, such aswortmannin, has been shown to reduce HIF-1α expression in various cell types, including cancer cells (43). The PI3K/AKT/mTOR pathway is also involved in the regulation of the hypoxia-inducible factor (HIF) family of transcription factors, which are key regulators of oxygen homeostasis and are activated under conditions of low oxygen tension. HIF-1α is the most well-studied member of the HIF family and plays a critical role in the adaptive response to hypoxia, mediating the expression of genes that are essential for survival under low oxygen conditions. The PI3K/AKT/mTOR signaling pathway is a major regulator of HIF-1α expression, as inhibition of this pathway results in reduced HIF-1α levels, indicating a negative feedback mechanism that helps to maintain oxygen homeostasis. Additionally, the PI3K/AKT/mTOR pathway is closely linked to the regulation of glucose metabolism, cell growth, and survival, which are important for the proliferation and survival of cancer cells. Therefore, targeting the PI3K/AKT/mTOR pathway may provide a therapeutic strategy for the treatment of hypoxia-dependent diseases, such as cancer, where oxygen supply is limited and hypoxia is a common feature.
1.5% O2 for 30 s followed by 20% O2 for 5 min, HIF-1α protein and HIF-1 transcriptional activity were induced and increased further after 120 cycles (95). In these cells, intermittent hypoxia triggered NADPH oxidase-dependent ROS production, which induced phospholipase C activity, leading to the generation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (Figure 1B). Binding of IP3 to its cognate receptor led to mobilization of intracellular Ca2+, which activated calcium-calmodulin kinase (CamK) and, together with diacylglycerol, induced protein kinase C (PKC) activity. PKC stimulated mTOR-dependent HIF-1α synthesis and inhibited PHD2-dependent degradation of HIF-1α (96). CamK phosphorylated the coactivator p300, thereby promoting its interaction with HIF-1α, leading to transcriptional activation (95). In contrast to continuous hypoxia, in which HIF-1α is rapidly degraded (t1/2 < 5 min) on reoxygenation (88), HIF-1α levels remain persistently elevated following intermittent hypoxia due to the persistent activation of mTOR (96), a finding that has significance in the context of obstructive sleep apnea, in which pathological cardiovascular and respiratory responses persist for hours after the termination of intermittent hypoxia (63).

Oxygen-Independent Mechanisms for Regulating HIF-1α

In addition to the O2-dependent pathways described above, O2-independent pathways regulating the synthesis and the degradation of HIF-1α have been delineated. These pathways appear to be particularly important in the context of cancer.

**Regulation of HIF-1α degradation**

Although the PHD2-VHL pathway is the critical mechanism regulating HIF-1α stability in response to changes in O2 concentration (Figure 1A), recent studies have revealed that the RACK1 protein can bind to HIF-1α and interact with Elongin C, thereby recruiting an E3 ubiquitin–protein ligase complex (46). RACK1 can substitute for VHL to promote ubiquitination and

**FIGURE 2.** Oxygen-independent regulation of HIF-1α protein levels.

A: the regulation of HIF-1α protein stability by RACK1 is shown. RACK1 binding is increased by treatment with the heat shock protein 90 (HSP90) inhibitor 17-allylamino-17-demethoxygeldanamycin (17-AAG) or by the calcineurin inhibitor cyclosporine A (CsA). Binding of Ca2+ to calmodulin (Cam) activates calmodulin phosphatase activity, which inhibits RACK1 dimerization. B: the regulation of HIF-1α protein synthesis by the PI3K-AKT-mTOR (purple) and MAP kinase (orange) pathways, which mediate phosphorylation of key regulators of translation (red), is shown. Arrow and blocked arrow indicate activation and inhibition, respectively.
degradation of HIF-1α (FIGURE 2A), with the critical distinction that RACK1-HIF-1α interaction is not O2 regulated. Although RACK1 was originally identified as a protein that stabilized interactions between PKC and its substrates, PKC activity is not required for RACK1-mediated ubiquitination and degradation of HIF-1α (46).

RACK1-mediated HIF-1α degradation has been demonstrated in two contexts. First, heat shock protein 90 (HSP90) is known to bind to HIF-1α, and HSP90 inhibitors have been shown to inhibit tumor growth and to induce proapoptotic degradation of HIF-1α even in cells lacking VHL (28). RACK1 was shown to compete with HSP90 for binding to the PAS-A subdomain of HIF-1α (46). Treatment with an HSP90 inhibitor such as 17-allylamino-17-demethoxygeldanamycin results in unopposed RACK1 binding leading to increased ubiquitination and degradation of HIF-1α. The ability of HSP90 inhibitors to induce HIF-1α degradation is dependent on RACK1 expression (46). These studies have delineated a novel mechanism of action contributing to the anti-cancer effect of HSP90 inhibitors.

RACK1 also appears to contribute to the mechanism of action of another important drug, cyclosporine A, which is an immunosuppressant that prevents tissue rejection following transplantation by inhibiting calcineurin, a Ca2+/calmodulin-dependent serine/threonine protein phosphatase (44). Cyclosporine A has been shown to inhibit hypoxia-induced HIF-1α expression (14, 37). RACK1 consists of seven copies of the tryptophan-aspartate-rich WD40 repeat domain on separate RACK1 monomers such that dimerization is required for RACK1 to recruit Elongin C to HIF-1α that dimerization is required for RACK1 to recruit Elongin C to HIF-1α (which, like HIF-1α, is an O2-dependent degradation). Ionomycin, a calcium ionophore, was shown to increase HIF-1α activity (45). The ionophore, cyclosporine A, which is an immunosuppressant that prevents tissue rejection following transplantation by inhibiting calcineurin, a Ca2+/calmodulin-dependent serine/threonine protein phosphatase (44).

Elongin C (SSAT2, which stabilizes the interaction of VHL and HIF-1α/H9251) also binds to HIF-1α and thereby inhibits dimerization and RACK1-dependent ubiquitination and degradation (3). However, in contrast to the interaction of HIF-1α with RACK1 (FIGURE 2A), the paralogs SSAT1 and SSAT2 play complementary roles in promoting O2-independent and O2-dependent degradation of HIF-1α, respectively.

**Regulation of HIF-1α synthesis**

The principal mechanism for transducing extracellular signals to the nucleus is by the binding of growth factors, cytokines, and other ligands to cognate receptors. HIF-1α is regulated by the mammalian target of rapamycin (mTOR). Strongly associated with their inhibition of HIF-1α (50, 83).

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**HIF-1α-Mediated Adaptive Responses to Hypoxia**

HIF-1α mediates cell autonomous, tissue-restricted, and systemic homeostatic responses to hypoxia. An illustrative example of each of these is described below.

**ERYTHROPOIESIS**

Red blood cells function to deliver O2 from the lungs to every cell in the body. Acute blood loss, ascent to high altitude, and pneumonia each result in a reduction in the blood O2 content. The ensuing tissue hypoxia induces HIF-1α activity in cells throughout the body, including specialized cells in the kidney that produce erythropoietin (EPO), a glycoprotein hormone that is secreted into the blood and binds to its cognate receptor on erythroid progenitor cells, thereby stimulating their survival and differentiation (29). Analysis of the sequences regulating hypoxia-induced EPO gene transcription has shown.

**ERYTHROPOIESIS**

Erythropoiesis is a systemic hypoxic response that local tissue requirements for oxygen and HIF-1 activity are pre-emptive growth responses to hypoxia. An illustrative example of each of these is described below.

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transcription led to the discovery of HIF-1 (72). Subsequently, HIF-1 has been shown to orchestrate erythropoiesis by coordinately regulating the expression of multiple genes encoding proteins responsible for the intestinal uptake, tissue recycling, and delivery of iron to the bone marrow for its use in the synthesis of hemoglobin (FIGURE 3A), including transferrin (66), transferrin receptor (48, 81), ceruloplasmin (53), and hepcidin (59). In addition, HIF-1 also activates transcription of the EPO receptor (51).

Erythropoiesis is impaired in Hif1a–/– (homozygous HIF-1α-null) embryos and the erythropoietic defects in HIF-1α-deficient erythroid colonies could not be corrected by cytokines, such as vascular endothelial growth factor (VEGF) or EPO, but were ameliorated by administration of Fe-salicylaldehyde isonicotinoylhydrazone, a compound that can deliver iron into cells independently of iron transport proteins, which was consistent with reduced levels of transferrin receptor in HIF-1α-deficient embryos and yolk sacs (93). In contrast, deficiency of HIF-2α (which, like HIF-1α, is O2 regulated, dimerizes with HIF-1β and activates target gene expression) has a major effect on EPO production in adult mice (23).

Angiogenesis

Erythropoiesis represents an adaptive response to systemic hypoxia. In contrast, angiogenesis represents a local tissue response to decreased oxygenation. As cells grow and proliferate, their consumption of O2 increases and HIF-1 activity is induced, either as a result of preemptive growth factor-mediated induction (FIGURE 2B) or as a result of tissue hypoxia (FIGURE 1A). HIF-1 then coordinately activates the transcription of multiple genes encoding angiogenic growth factors and cytokines (FIGURE 3B), including vascular endothelial growth factor (VEGF), stromal-derived factor 1 (SDF-1), placental growth factor (PLGF), angiopoietin 1 and 2, and platelet-derived growth factor B (5, 8, 18, 32, 76), which bind to cognate receptors on vascular endothelial and smooth muscle cells as well as on endothelial progenitor cells, mesenchymal stem cells, and other bone marrow-derived angiogenic cells (FIGURE 3B). In addition, HIF-1 regulates the expression of CXCL4 (78), which is the receptor for SDF-1, and VEGFα (22, 101).
mitochondrial metabolism even in the tissue exposed to hypoxia (Figure 3C), which are all encoded by HIF-1 target genes (27, 67, 69, 71).

Induction of PDK1 expression will inhibit the oxidative metabolism of AcCoA derived from glucose but will not affect the oxidative metabolism of AcCoA derived from fatty acids. The most draconian response to persistent hypoxia is the active destruction of mitochondrial components (20). Remarkably, mice embryos lacking COX-4 (27, 67), whereas littermates (heterozygous Hif1a+/–), which are all encoded by HIF-1 target genes (27, 67, 69, 71).

The adaptive significance of these metabolic responses to hypoxia were revealed by the finding that HIF-1α-deficient MEFs die when cultured under hypoxic conditions for 72 h due to dramatically increased ROS levels (35, 69). The cells can be rescued by overexpression of PDK1 or BNIP3, or by treatment with free-radical scavengers (35, 69). It has long been known that mitochondrial ROS production increases under hypoxic conditions (87). However, recent studies have demonstrated that acute hypoxia also leads to increased mitochondrial ROS production, which is required for the inhibition of HIF-1α hydroxylase activity (24). Exposure of wild-type (WT) MEFs to hypoxia for 48 h results in reduced ROS levels, in contrast to Hif1a–/– MEFs in which ROS levels are markedly increased (35, 97).

The following conclusions can be drawn regarding the metabolic adaptation to hypoxia. The increase in glycolysis and decrease in respiration that occur in response to hypoxia do not represent a passive effect of substrate (O2) deprivation but instead represent an active response of the cell to counteract the reduced efficiency of respiration under hypoxic conditions, which is contrary to the regulation of mitochondrial respiration by hypoxic conditions in vivo. This ability to maximize ATTP production without increasing ROS levels. Finally, analysis of lung tissue from non-hypoxic Hif1a–/– mice, which are heterozygous for a HIF-1α-null allele and thus partially HIF-1α deficient, revealed an ~50% decrease in mitochondrial mass compared with WT littermates (97). This remarkable finding indicates that HIF-1 regulates mitochondrial metabolism even in the tissue exposed to the highest Po2..."
HIF-1-Mediated Pathological Responses to Hypoxia

Continuous hypoxia and pulmonary hypertension

The only organ to receive 100% of cardiac output is the lungs, which receive the blood that is pumped from the right ventricle. The pulmonary arterial circulation functions to load erythrocytes with O2. Blood is then returned to the left heart from which it is pumped through the systemic circulation to all tissues of the body. The systemic circulation dilates in response to hypoxia, which is an autoregulatory device to maintain tissue oxygenation. In contrast, arterioles in the pulmonary circulation constrict in response to hypoxia to shunt blood away from lung tissue that is not oxygenated. Whereas this is an adaptive response in the setting of pneumonia, it is maladaptive in the setting of chronic lung disease, in which alveolar hypoxia is widespread. The right ventricle is forced to pump against greater resistance (pulmonary hypertension), resulting in ventricular hypertrophy and ultimately heart failure. HIF-1 plays a key role in this maladaptive response as determined in a mouse model in which animals are maintained in an ambient O2 concentration of 10% for 3 wk (94).

HIF-1 mediates multiple pathogenic responses of pulmonary artery smooth muscle cells (PASMCs) to hypoxia. HIF-1 inhibits the expression of the voltage-gated potassium channels Kv2.1 and Kv1.5 (90) and activates expression of the TRPC1 and TRPC6 store-operated calcium channels (89). Increased [K+]i and [Ca2+]i in PASMCs promote cell proliferation. Finally, HIF-1 induces PASMC hypertrophy through mechanisms that have yet to be delineated (74). The combination of PASMC hypertrophy, constriction, and proliferation causes the reduction in the luminal diameter of pulmonary arterioles that underlies pulmonary hypertension (FIGURE 4A).

Acute hypoxia (77). This phenotype is a striking complement to the impaired pulmonary vasoconstrictive and cardiorespiratory responses to chronic hypoxia that are observed in Hif1a+/– mice (36, 94).

Chronic intermittent hypoxia and systemic hypertension

Whereas chronic continuous hypoxia induces pulmonary hypertension, chronic intermittent hypoxia (CIH) induces systemic hypertension. CIH occurs in individuals with obstructive sleep apnea (OSA), in which airway occlusion results in cessation of breathing leading to hypoxemia, which then arouses the individual to breathe. OSA may be a contributing factor in 30% of patients with essential hypertension (43).

The carotid body is a small chemosensory organ located at the bifurcation of the internal and external carotid arteries that senses arterial Pao2. CIH induces signaling from the carotid body that activates the symmetrical rise in production of systemic hypertension induced in response to chronic intermittent hypoxia is shown. EDN1, endothelin 1; Kv1.5, voltage-gated potassium channel 1.5; NHE1, sodium-hydrogen exchanger 1; TRPC1, transient receptor potential protein C1.
pathetic nervous system, leading to increased cate-
cholamine secretion, which increases arterial tension, leading to hypertension (43, 61). Exposure of HIF-1α-
mice and their WT littermates to CIH for 10 days results in marked increases in systolic and diastolic blood pressures and a significant elevation in plasma norepinephrine concentration in the WT mice, where-
as their HIF-1α-littermates are unaffected (58). Remarkably, the carotid bodies of mice, although structurally and histologically normal, do not respond to hypoxia, although they respond nor-
to CO2 and cyanide (36, 38).

CIH induces ROS production in rodents (62) and humans (16) and induces HIF-1α expression (58). Administration of the superoxide scavenger manganese tetrakis[1-methyl-4-pyridyl]porphyrin pentachloride to WT mice blocks CIH-induced ROS production (57), hypertension (39), and HIF-1α induction (58). Remarkably, in HIF-1α-mice, there is a complete loss of CIH-induced HIF-1α expression and ROS production (58). These results indicate that ROS production is required for HIF-1α induction and that HIF-1α induction is required for ROS production, sug-
gest a feed-forward mechanism in which ROS induces HIF-1α, which induces more ROS, leading to higher HIF-1α expression (FIGURE 4B).

In contrast to the physiological response to contin-
uous hypoxia observed in MEFs described above, in which HIF-1α-activation ameliorates increases in ROS lev-
els, the pathological response to CIH is characterized by a HIF-1-dependent increase in ROS levels. OSA is a complication of obesity and, like other complications of excessive hypoxia observed in MEFs described above, in HIF-1α-expressing cells, triggers increases in ROS levels that promote oxygen-dependent degradation of HIF-1α (58).


2. Brahimi-Horn MC, Chiche J, Pouysségur J. Hypoxia and can-


6. Brahmi-Horn MC, Chiche J, Pouysségur J. Hypoxia and can-


8. Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas GL. Progenitor cell trafficking is regulated by hypoxic gradi-


