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 (78).

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”) anoxogensis (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 (80). 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 hydroxylation 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 is negatively regulated by O2-dependent hydroxylation (FIGURE 1A).

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-1α 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, HIF-1α protein and induced and inhibited these cells, intermittent HIF-1α protein and induced protein and inhibited these cells, intermittent hypoxia due to fi finding the...
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 degradation of HIF-1α (97). In addition, the PI3K-AKT-mTOR (purple) and MAP kinase (orange) pathways, which mediate phosphorylation of key regulators of translation (red), are 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 (26). 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-asparagine-rich WD40 repeat domain and forms dimers through homotypic interactions between the fourth WD40 (WD4) repeat domain (84). HIF-1α and Elongin C bind to the WD7 repeat domain on separate RACK1 monomers such that dimerization is required for RACK1 to recruit Elongin C to HIF-1α (47). Phosphorylation of RACK1 promotes its dimerization, and the catalytic subunit of calcineurin binds to RACK1 and mediates its dephosphorylation, thereby inhibiting dimerization and RACK1-dependent HIF-1α degradation (FIGURE 2A). Ionomycin, a calcium ionophore, was shown to increase HIF-1α levels even in BCC1 cells, which lack functional VHL (47). Thus calcineurin activation represents another mechanism, in addition to those identified in the response to intermittent hypoxia (FIGURE 1B), by which calcium signaling can increase HIF-1α activity (FIGURE 2A).

SSAT1, which shares 46% amino acid identity with SSAT2, also binds to HIF-1α and promotes its ubiquitination and degradation (3). However, in contrast to SSAT2, which stabilizes the interaction of VHL and Elongin C (FIGURE 1A) and thereby promotes O2-dependent ubiquitination (2), SSAT1 acts by stabilizing the interaction of HIF-1α with RACK1 (FIGURE 2A). Thus the paralogs SSAT1 and SSAT2 play complementary roles in promoting O2-dependent and O2-independent 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. Activated receptor tyrosine kinases and G-protein-coupled receptors on the cell surface, leading to the activation of the phosphatidylinositol-3-kinase (PI3K) and MAP kinase pathways (FIGURE 2B). Signal transduction through these pathways stimulates cell survival, growth, and proliferation. An inevitable consequence of cell growth and proliferation is increased O2 consumption, and it is perhaps notable that transduction pathways induce what can be considered pre-emptive HIF-1 activity because it occurs in an O2-independent manner (19, 82, 98).

Treatment of MCF-7 human breast cancer cells with heregulin, which binds to heterodimers composed of the human epidermal growth factor receptor family members HER2 and HER3, activates PI3K, which phosphorylates the serine-threonine kinase Akt (protein kinase B). Activated Akt phosphorylates and activates the mammalian target of rapamycin (mTOR). mTOR phosphorylates two key regulators of translation, p70S6 kinase (p70S6K) and 4E-BP1. Activated p70S6K phosphorylates ribosomal protein S6, whereas phosphorylation of 4E-BP1 blocks its ability to interact with and inhibit eIF-4E, a critical regulator of cap-dependent mRNA translation (FIGURE 2B), and these actions of mTOR increase the rate of translation of a subset of cellular mRNAs (25, 28). Heregulin treatment increases the synthesis of HIF-1α protein in MCF-7 cells, and this effect is blocked by rapamycin, which is a specific inhibitor of mTOR activity (42). As in the case of HSP90 inhibitors (FIGURE 2A), rapamycin and its derivatives are a class of drugs currently in clinical trials as anti-cancer agents, and their anti-cancer effects are strongly associated with their inhibition of HIF-1 (58, 83).

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

HIF-1 mediates cell autonomous, tissue-restricted, and systemic host regulatory 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 results 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 showed that RACK1 is a target of hypoxia-inducible factor (HIF) transcription factors, which bind to the hypoxia-responsive element (HRE) in the EPO promoter (66). The ability of Hsp90 inhibitors to induce HIF-1α and mTOR activity thereby potentiate the transcriptional response to hypoxia.

**Angiogenesis**

Erythropoietin (EPO)-mediated angiogenesis in response to local tissue hypoxia is one consequence of how HIF-1α activity promotes cell growth and proliferation. An inevitable consequence of increased O2 consumption is increased proliferation. An inevitable consequence of cell growth and proliferation is increased O2 consumption, and it is perhaps notable that transduction pathways induce what can be considered pre-emptive HIF-1 activity because it occurs in an O2-independent manner (19, 82, 98).

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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-1α 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 preempive 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 CXCR4 (79), which is the receptor for SDF-1, and VEGFR1 (22, 84).

Responses

Increased HIF-1 activity

An illustration of the adaptive responses of the lungs to high altitudes is shown below. An illustration of the adaptive responses of the lungs to hypoxia is shown below. Weight loss is produced by a hormone that is stimulated by stimulating the α2-adrenergic receptor on the body, which produces a reduction in O2 consumption.

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This remarkable finding indicates that HIF-1 regulates mitochondrial metabolism even in the tissue exposed to the highest $P_{O_2}$...
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. Continuous hypoxia also dilates the pulmonary microvasculature (MEFs) culminating in the reduced pulmonary vascular tone, and augmented pulmonary vasoreactivity as determined in a mouse model in which animals are maintained in an ambient O₂ concentration of 10% for 3 wk (94).

HIF-1 regulates the expression of the sodium-hydrogen exchanger NHE1, which increases intracellular pH (73). Increased [H+]i and [Ca 2+]i in PASMCs promote hypoxia-inducible factor (HIF)-1 also induces expression of the sodium-hydrogen exchanger NHE1, which increases intracellular pH (73). Increased [H+]i and [Ca 2+]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).

Mice heterozygous for a knockout allele at the locus encoding HIF-1α (94) or HIF-2α (95) have increased basal ventilation and pulmonary vascular tone, and augmented pulmonary vasconstrictive and cardiorespiratory responses to acute hypoxia (77). This phenotype is a striking complement to the impaired pulmonary vasconstrictive 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 P/O₂. CIH induces signaling from the carotid body that activates the sympathetic nervous system and leads to hypertension.

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pathetic nervous system, leading to increased catecholamine secretion, which increases arterial tone, 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 HIF-1α mice, although structurally and histologically normal, do not respond to hypoxia, although they respond normally to CO2 and cyanide (36, 54). 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 (58), 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, suggesting a feed-forward mechanism in which ROS induces HIF-1α, which in turn further increases ROS levels, leading to higher HIF-1α expression (FIGURE 4B).

In contrast to the physiological response to continuous hypoxia observed in MEFs described above, in which HIF-1α activity ameliorates increases in ROS levels, 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 obesity, has not been subject to evolutionary selection (15406–15411, 2003). Although structurally and histologically normal, do not respond to hypoxia, although they respond normally to CO2 and cyanide (36, 54), CIH induces ROS production in rodents (62) and humans (16) and induces HIF-1α expression (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, suggesting a feed-forward mechanism in which ROS induces HIF-1α, which in turn further increases ROS levels, leading to higher HIF-1α expression (FIGURE 4B).

Summary and Perspective

This review has summarized a small sample of the tremendous progress that has been made recently in understanding the molecular physiology of oxygen homeostasis and how it is dysregulated in various disease processes. The interested reader is encouraged to consult the many recent reviews that discuss other important aspects of hypoxic adaptation, which are not covered here due to space limitations (6, 15, 17, 21, 282: 33358–33366, 2007; 29. Jelkmann W. J Biol Chem 283: 10393–10398, 2008).

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mice against polycythemia GL. OS-9 interacts with the RACK1 and pro-1 ligase complex to maintain oxygen species in vivo. Exp Physiol 91: 117–119, 2006.


27. Hays JD, Rabbitts TP. 40S ribosomal subunit P1 eukaryotic initiation factor-1α expression by 10.220.33.1 on October 19, 2017 http://physiologyonline.physiology.org/ Downloaded from
68. Salazar S, Cao J. Hypoxia-inducible factor 1α (HIF-1α) protein is rapidly degraded by the ubiquitin-proteasome system under normoxic conditions. Its stabilization by hypoxia depends on redox-induced changes. **J Biol Chem.** 272: 22642-22647, 1997.