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Review article

Hypoxia-inducible factor 1, a master transcription factor of cellular hypoxic gene expression

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One of the most important goals of patient management in operation theaters and intensive care units is to maintain appropriate oxygen homeostasis in patients. It is essential to understand the strategies of living body against O_2 imbalance, especially O_2 deficiency (hypoxia). Adaptation to hypoxia and maintenance of O_2 homeostasis involve a wide range of responses that occur at different organizational levels in the body [1]. Not only is O_2 homeostasis essential for survival, but also hypoxia plays a critical role in the pathogenesis of major causes of mortality, including cerebral and myocardial ischemia and chronic heart and lung disease. Investigating the molecular mechanisms of O_2 homeostasis therefore represents not only an effort to delineate fundamental aspects of human physiology, but also a means of gaining new insights about, and potentially new therapeutic approaches to, the most important public health problems of the present day.

To place the molecular advances in a physiological and pathophysiological context, it is useful to think about the ways that our bodies are equipped to deal with hypoxia. We experience rapid breathing, increased circulation, and the accumulation of muscle lactic acid when exposed to hypoxia and will exhibit an increase in red blood cell (RBC) and hemoglobin counts and a proliferation of blood capillaries if hypoxia is prolonged. Such responses are designed to decrease cellular O_2 need and dependence on O_2 and to increase tissue O_2 supply. Some of the responses are intrinsic to all hypoxic cells, indicating that each cell has its own O_2-sensing system [1–4], whereas other responses are mediated by more specialized sensors in the body that monitor global O_2 levels and cause system-wide changes in tissue O_2 delivery [5]. For example, when cells of the carotid body detect subnormal O_2 levels in the carotid arteries, they propagate dopaminergic signals to the brain to increase breathing and thus the O_2 saturation of the blood [5,6]. To give another example, cells of the developing liver and adult kidney regulate the O_2-carrying capacity of the blood by secreting the glycoprotein hormone erythropoietin (EPO), which stimulates RBC and hemoglobin production [7,8]. The Pasteur effect is the substantial increase in carbohydrate consumption that occurs to compensate for its inefficient utilization under anaerobic conditions [9]. When O_2 is unavailable as the final electron acceptor in the respiratory chain, the cell must abandon oxidative phosphorylation and rely solely on glycolysis for energy production. The switch to anaerobic metabolism is considered to be regulated by energy pathway metabolites acting on glycolytic enzymes [9]. For example, phosphofructokinase is allosterically inhibited by ATP, and the inhibition is reversed by AMP. This is, however, just a small part of the way in which each cell deals with inadequate O_2 supply. Hypoxic cells sense diminishing O_2 levels directly well before their ATP pools are depleted, and they respond with a self-imposed strict program to suppress their energy usage by shutting down nonessential cell functions [1,3,10]. Hypoxia is not only a signal for energy conservation, but also in the past few years it has been found to trigger expression of a select set of genes [7]. These include specific isoforms of glycolytic enzymes and glucose transporters that function better at low O_2. Another is the EPO gene, and it is the study of this gene that has led to a considerably expanded view of the hypoxic response [7,8,11].

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Cellular responses to hypoxia can be acute or chronic [3,4,12]. Acute responses rely mainly on ion channels, which mediate adaptive changes in cell excitability, contractility, and secretory activity. This review will specifically focus on responses to subacute or chronic hypoxia that involve changes in gene expression that are mediated by the transcriptional regulator hypoxia-inducible factor 1 (HIF-1) [7,13]. General aspects of HIF-1 structure, function, and regulation will be described, and data supporting the relevance of HIF-1 to human embryology and (patho)physiology will be summarized. The clinical implications of these findings also will be discussed.

Molecular biology of HIF-1

HIF-1 is a heterodimer of α and β subunit

The discovery of HIF-1 as a global regulator of O_2 homeostasis initially resulted from analysis of the molecular mechanisms by which EPO gene transcription was activated in response to hypoxia. A small (ca. 50-bp) DNA sequence that functions as a hypoxia response element (HRE) was identified in the 3′-flanking region (regulatory region of the gene expression) of the human EPO gene [14,15]. HIF-1 was cloned as a cellular factor that was detected in hypoxic cells, but not in nonhypoxic cells [16,17]. HIF-1 is a transcription factor and a heterodimer consisting of HIF-1α and HIF-1β subunits [17–19]. The amino-terminal half of each subunit contains basic helix-loop-helix (bHLH) and PER-ARNT-SIM homology (PAS) domains. The bHLH domain defines a large superfamily of dimeric eukaryotic transcription factors in which the bHLH domain mediates dimerization and the basic domain contacts DNA. HIF-1β is identical to ARNT (aryl hydrocarbon receptor nuclear translocator), which was shown to dimerize with the aryl hydrocarbon receptor after activation of the latter by binding of aryl hydrocarbons such as dioxin [20]. In contrast, human HIF-1α was a previously unidentified protein. Comparison of complementary DNAs encoding human, mouse, and rat HIF-1α reveals more than 90% amino acid sequence identity [19,21,22]. Factors homologous to HIF-1α that dimerize with HIF-1β have been described and designated HIF-2α (also known as endothelial PAS domain 1 [EPAS1], HIF-1α-like factor, HIF-related factor, and member of PAS superfamily 2) and HIF-3α [21,23]. HIF-2α and HIF-3α constitute HIF-2 and HIF-3 with corresponding β subunits.

HIF-1α and HIF-1β mRNA are expressed in most, if not all, human and rodent tissues. In contrast, HIF-2 shows a more restricted pattern of expression. For example, mRNA encoding HIF-2α is expressed specifically in developing vascular endothelium, fetal lung, and catecholamine-producing cells [24,25]. It appears that HIF-1 plays a very general role by signaling the existence of hypoxia to the transcriptional machinery in the nucleus of all cells, whereas HIF-2 plays more limited or specialized roles in O_2 homeostasis.

Regulation of HIF-1 activity

The biological activity of HIF-1 is determined by the expression and activity of the HIF-1α subunit [7]. The regulation of HIF-1α expression and activity in vivo occurs at multiple levels, including mRNA expression [26–28], protein expression [29–32], intracellular localization [33], and transactivation [31,34,35]. Among them, the most intensively studied is the regulation of steady-state HIF-1α protein levels.

In normoxic conditions, there was barely detectable HIF-1α protein. When cells were transferred to hypoxic conditions, HIF-1α expression was detected as early as 2 min and peaked after 4 to 8 h of hypoxia [10]. When cells were exposed to hypoxia for 4 h and returned to normoxia, HIF-1α protein expression levels decayed with a half-life of less than 5 min. Above a critical intracellular oxygen tension, HIF-1α is rapidly degraded in proteasomes after its ubiquitination [30,36]. Three recent reports proposed that a proline residue of HIF-1α is hydroxylated by putative proline hydroxylases that require oxygen and iron for their activation, and that this modification plays a critical role in ubiquitination of HIF-1α under normoxic conditions [37–39]. Epstein et al. reported molecular cloning of the proline hydroxylases of Caenorhabditis elegance and human beings [13,40]. They also showed that the proline hydroxylases require iron for their activity [40]. This strongly suggests that the proline hydroxylases are putative oxygen sensors in living cells in the context of HIF-1 activation. Further description of details of the O_2 sensing mechanism is beyond the scope of this review.

The DNA-binding activity of HIF-1 and expression of HIF-1α and HIF-1β protein were analyzed in HeLa cells, an established cell line derived from human cervical carcinoma, exposed to a broad range of O_2 concentrations [31]. HIF-1α protein expression as determined by immunoblot assay parelleled HIF-1 DNA-binding activity. There was about a twofold increase in HIF-1α expression as O_2 concentration declined from 20% to 6%, and then a 10-fold increase between 6% and 0.5% O_2. The response was maximal at 0.5% and half-maximal at 1.5%–2% O_2. The characteristics of the response curve are of particular interest because of their physiological relevance: PO_2 measured in renal cortex was 20–30 mmHg (3%–4%); in the liver, venous PO_2 ranged from 30 to 35 mmHg [41]; and in the heart, epicardial microvascular and myocardial PO_2 measure-

Table 1. Genes whose hypoxia-induced expression is mediated by HIF-1

Energy metabolism and glycolysis	
	Adenylate kinase 3, aldolase A (ALDA), aldolase C (ALDC), enolase 1 (ENO1), glucose transporter (GLUT) 1, GLUT 3, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), hexokinase 1 (HK1), hexokinase 2 (HK2), insulin-like growth factor 2, IGF binding protein 1, lactate dehydrogenase A (LDHA), phosphofructokinase L (PFKL), phosphoglycerate kinase 1 (PGK1), pyruvate kinase M (PKM)
Apoptosis	
	p21, Nip, anti-apoptotic protein (AIP-2)
Iron metabolism and erythropoiesis	
	Ceruloplasmin, Erythropoietin, heme oxygenase-1, transferrin, transferrin receptor
Vascular genesis/remodeling and vasomotor activity	
	α_{1B}-Adrenergic receptor, adrenomedullin, endothelin-1, HO-1, nitric oxide synthase 2 (iNOS), plasminogen activator inhibitor 1, vascular endothelial growth factor (VEGF), VEGF receptor

ments of 17 and 12 mmHg, respectively, have been reported [42], and occlusion of a distal branch of the left anterior descending artery for 1 min resulted in an O_2 concentration of near zero in the ischemic core and an O_2 gradient as distance from the core increased [42]. Kietzmann et al. demonstrated that HIF-1α protein was expressed predominantly in the perivenous zone of rat liver in situ [43]. Taking account of the evidence that HIF-1 activation occurs at less than 5% O_2 [31], the expression pattern is correlated with O_2 tension gradient in the liver sinusoids. These data suggest that any reduction of tissue oxygenation in vivo would occur along the steep portion of the HIF-1 response curve, thus providing a mechanism for a graded transcriptional response to hypoxia. Interestingly, a line of reports clearly demonstrates that stimuli including insulin, insulin-like growth factors (IGF) 1 and 2, and epidermal growth factor also increase HIF-1α protein level as well as HIF-1 activity in certain cell types, even under nonhypoxic conditions [44–46]. In addition, in vascular smooth muscle cells, a range of different extracellular receptor agonists, including angiotensin II, platelet-derived growth factor, and thrombin, have been shown to induce VEGF expression in an HIF-1-dependent manner [47]. The nitric oxide (NO) donors NOC-18, S-nitroso-acetylpenicillamine (SNAP), and nitrosoglutathione (GSNO), but not sodium nitroprusside (SNP), induced HIF-1α protein expression and HIF-1 activity under nonhypoxic condition in pulmonary artery endothelial cells and hepatocytes [48,49].

Hypoxia signal transduction may also require kinase/phosphatase activity, because treatment of cells with genistein, a tyrosine kinase inhibitor, or sodium fluoride, a serine/threonine phosphatase inhibitor, blocked hypoxia-induced HIF-1α expression [50]. In certain cell types, phosphatidylinositol 3-kinase inhibitors such as LY294002 or wortmannin also block hypoxia-induced HIF-1α expression [46,51,52]. In vitro, HIF-1α is a target of mitogen-activated protein kinase (MAPK) [53,54]. In addition to phosphorylation/dephosphorylation, the activity of HIF-1 is under cellular redox status. Treatment with H_2O_2, NO, or CO inhibits hypoxia-induced HIF-1 activation. Treatment with reducing reagents or enzymes with reducing activity has been shown to increase HIF-1 DNA-binding activity and HIF-1-dependent gene expression [29,34].

HIF-1 target genes

A lines of studies has identified HREs containing essential HIF-1 binding sites in genes encoding proteins that mediate a variety of essential adaptive responses to hypoxia [7]. The presence of at least one intact HIF-1 binding site is necessary, but not sufficient, for these elements to mediate transcriptional activaiton. Analysis of embryonic stem (ES) cells deficient in HIF-1α- [55,56] or HIF-1β [57] found that the normal induction of VEGF mRNA expression in response to hypoxia was absent in these cells. The number of target genes activated by HIF-1 continues to increase, and includes genes whose protein products are involved in angiogenesis, energy metabolism, erythropoiesis, cell proliferation and viability, vascular remodeling, and vasomotor responses (Table 1). HIF-1 thus plays a very critical role in increasing O_2 delivery to cells, as well as adaptation to decreased O_2 availability.

Involvement of HIF-1 in physiological and pathophysiological processes

Glucose and energy homeostasis and HIF-1

The Pasteur effect refers to the increase in carbohydrate consumption that is observed under anaerobic conditions and is associated with inhibition of oxidative metabolism. The regulation of glycolysis under anaerobic conditions has been regarded as being meditated by glycolytic metabolites and high-energy intermediates. HRE has been identified in a number of genes encoding

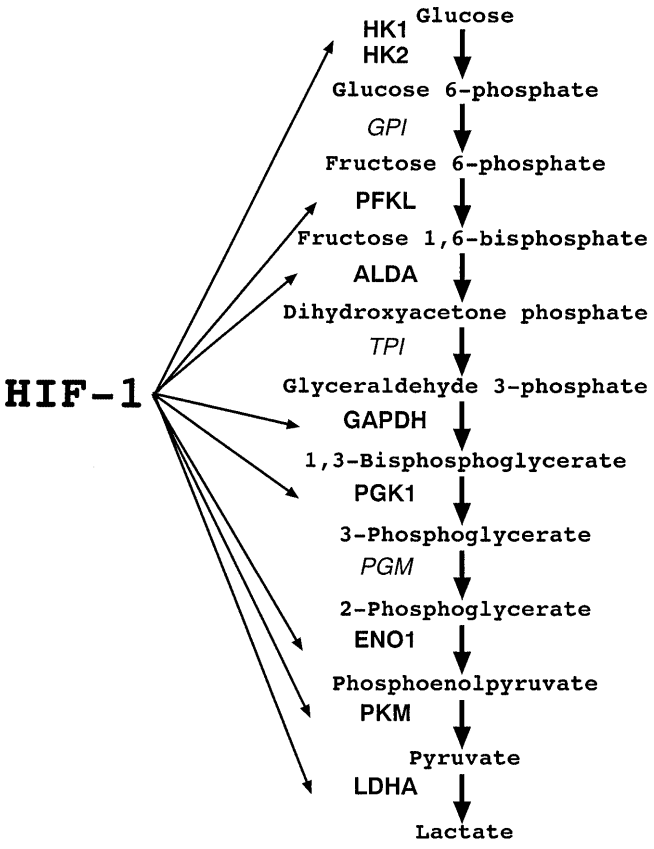

Fig. 1. Transcriptional regulation of glycolytic enzymes by HIF-1. Hypoxia-induced expression of most glycolytic enzymes is transcriptionally regulated by HIF-1. *TPI*, Triose phosphate isomerase; *PGM*, phosphoglycerate mutase, phosphoglucose isomerase (*GPI*)

glycolytic enzymes that are required for anaerobic catabolism of glucose. The promoters of genes encoding aldolase-A, enolase-1, lactate dehydrogenase-A, PFK, and phosphoglycerate kinase-1 contain HIF-1 consensus binding sites that can bind HIF-1 [58]. In fact, induction of almost all glycolytic enzymes is dependent on HIF-1 (Fig. 1). In addition, transcriptional regulation of genes related to glucose metabolism such as glucose transporter 1 (GLUT1) and IGF-2 and IGF-binding protein are also HIF-1 dependent. In turn, insulin, IGF-1, and IGF-2 all induce HIF-1α expression in cultured cells [44–46]. Using genetically manipulated cells, Seagroves et al. clearly demonstrated that HIF-1 plays an essential role in the establishment of the Pasteur effect. Cells lacking HIF-1α exhibit decreased growth rates during hypoxia, as well as decreased levels of lactic acid production and decreased acidosis [59]. They also show that this decrease in glycolytic capacity results in dramatically lowered free ATP levels in HIF-1α-deficient hypoxic cells. Thus, HIF-1 activation is an essential control element of the metabolic state during hypoxia.

Iron metabolism and HIF-1

Iron is an essential trace metal in all living organisms. Both iron overload and iron depletion can severely affect physiological processes such as development, erythropoiesis, and biochemical metabolism. The liver represents the major organ of iron storage in the body and is most susceptible to injuries due to iron overload. Thus, iron homeostasis has to be tightly balanced, and, as a consequence, free iron occurs only transiently in the serum. When iron is absorbed from the small intestine into the blood, it immediately binds apotransferrin to form transferrin (Tf) 1, which is then transported by the plasma to all tissues of the body. Delivery of iron occurs by binding of Tf to the Tf receptor (TfR), followed by endocytosis. In erythroblasts, iron is primarily required for heme synthesis in mitochondria. Transcription of the genes for Tf and TfR is stimulated by hypoxia, and an HRE in the Tf or TfR promoter is critically involved in this response [60,61]. The induction of ceruloplasmin 1, a 132-kDa copper protein that is abundant in serum, is also regulated by HIF-1 [62].

Vascular tone regulation and HIF-1

Originally described as the endothelial-derived relaxing factor, NO has been shown to have a diverse range of biological activities, including regulation of vascular tone, neurotransmission, and modulation of immune functions. NO is generated by a family of NO synthases (NOSs). The inducible form of NOS, iNOS, produces large amount of NO in response to cytokines and endotoxin. Interferon gamma (IFN-γ) can increase the transcription of the iNOS gene in epithelial cells. This response can be enhanced by proinflammatory stimuli, including tumor necrosis factor α (TNF-α) and lipopolysaccharide (LPS). Hypoxia increases INF-γ-induced iNOS gene transcription. Moreover, transcription of the iNOS gene in murine macrophages is increased through an HRE in the iNOS promoter [63,64]. Another stress-associated protein whose expression is stimulated by hypoxia is heme oxygenase-1 (HO-1). HO-1, a microsomal membrane enzyme, catalyzes the first and rate-limiting reaction in heme catabolism, the oxidative cleavage of b-type heme molecules to yield equimolar quantities of biliverdin, carbon monoxide (CO), and iron. CO is a gaseous mediator of intracellular and intercellular signal transduction as well as NO. Experiments using living rat and rat aortic vascular smooth muscle cells demonstrate that HO-1 is induced in response to hypoxia in lung, liver, aorta, and heart and that this induction is dependent on HIF-1 [65].

In addition to NO and CO, bioactive peptides such as endothelin and adrenomedullin play pivotal roles in vascular tone regulation. Endothelin 1 (ET-1) is a 21-residue polypeptide synthesized and secreted by vascu-

lar endothelial cells [66]. It is a member of a family of structurally related polypeptide hormones and is the most potent endogenously produced vasoconstrictor known. The enhanced secretion of ET-1 during myocardial ischemia has been linked with enhanced contractility in the failing heart as well as with the progression of heart failure. The combined actions of ET-1 and NO may be important in regulating vascular tone and blood pressure. In addition to its vasomodulating activity, ET-1 has been shown to modulate multiple cell functions, including proliferation, protooncogene and protein kinase activity, induction of inotropy and hypertrophy in cardiac muscle, and activation of cardiac-specific genes [67,68]. There is an HRE in the regulatory region of the ET-1 gene [69–71], and induction of ET-1 in response to hypoxia is dependent on HIF-1 as well as AP-1 (activating protein 1) and GATA-2 [72]. Adrenomedullin is a recently described hypotension-inducible peptide, originally isolated from a human pheochromocytoma, that is an important regulator of the renal and cardiovascular systems [73]. The peptide has been shown to increase glomerular filtration rate, increase natriuresis, and cause hypotension in rats. Adrenomedullin was identified as an HIF-1 responsive gene in cultured adult rat ventricular cardiomyocytes [74–76]. The finding of elevated adrenomedullin levels in humans with congestive heart failure suggests a role for this protein in ischemic heart disease [77,78].

Apoptosis and HIF-1

Several recent studies have provided evidence in support of the hypothesis that HIF-1 mediates the death and life of cultured cells subjected to O_2 and/or glucose deprivation, possibly by associating with, and preventing the degradation of, p53, which plays a critical role in cellular life and death, and ES cells derived from *Hif-a*(−/−) (homozygous for the knockout allele) mice show no induction of p53 protein or apoptosis in response to O_2 deprivation [79]. One study, which utilized mouse ES cells, implied that HIF-1 has a pro-apoptotic role in tumor cells, a conclusion that appears unfounded, especially in advanced cancers with loss of function of p53 [80]. Another study, which utilized cultured cortical neurons, implied that HIF-1 promotes cell death in the context of cerebral ischemia [81,82]. However, after occlusion of the middle cerebral artery in rats, increased expression of mRNA encoding HIF-1 and glycolytic enzymes was induced in the penumbra, which is the viable cortical tissue surrounding the infarct [27,83]. Further studies are required to determine whether this response contributes to the survival of these cells. Moreover, expression of genes regulating apoptosis, such as Nip3 and antiapoptotic protein 2, is mediated by HIF-1 [84,85].

Hypoxic pulmonary hypertension and HIF-1

In contrast to *Hif1a*(−/−) mice, which have their development arrested by E9.0 and die by E10.5 [55,56,80], *Hif1a*(+/−) (heterozygous for knockout allele) mice develop normally and are indistinguishable from wild-type littermates. However, when they are exposed to 10% O_2 for 1–6 weeks, classic (patho)physiological responses to hypoxia, such as increases in hematocrit, right ventricular mass, and right ventricular pressure, are impaired in *Hif1a*(+/−) mice relative to their wild-type littermates. To investigate the effects of HIF-1α deficiency on remodeling of pulmonary arterioles, histological sections of lungs from *Hif1a*(+/−) and *Hif1a*(+/+) mice exposed to 10% O_2 for 3 weeks were prepared for morphometric analysis. The proportions of nonmuscularized, partially muscularized, and completely muscularized pulmonary arterioles in *Hif1a*(+/−) and *Hif1a*(+/+) mice were significantly different, with fewer completely muscularized and more nonmuscularized arterioles in the lungs of the *Hif1a*(+/−)mice. The wall thickness of completely muscularized pulmonary arterioles was also significantly reduced in *Hif1a*(+/−) mice. These results indicate not only that under chronically hypoxic conditions *Hif1a*(+/−) mice have fewer completely muscularized pulmonary arterioles, but also that the degree of muscularization in such vessels is reduced. Hypoxia has effects on the pulmonary circulation, including vasoconstriction and ventilation/perfusion mismatch. In a rat model of chronic hypoxia, there is an increase in iNOS transcripts in lung endothelial cells in situ hybridization [86]. Exposure of bovine pulmonary artery endothelial cells to hypoxia in vitro induces binding of HIF-1 to the iNOS promoter [86–88]. Thus HIF-1 plays a major role in mediating pulmonary vascular remodeling in response to chronic hypoxia. Several known HIF-1 target genes, including EPO, ET-1, IGF-2, iNOS, and VEGF, may be involved in these responses, and others will probably be identified in future studies. Local inhibition of HIF-1 activity in the lung by inhalation therapy may provide a means of preventing or retarding the development of this lethal complication of chronic lung disease in at-risk individuals.

Respiratory regulation and HIF-1

The carotid body, as well as the neuroepithelial body, is capable of transducing changes of O_2 pressure in arterial blood into nervous signals that are used to regulate respiration and circulation in an attempt to avoid hypoxic situations in the body [6]. A generally accepted concept defines this process as PO_2-dependent transmitter release from carotid body type I or glomus cells, which generates action potentials in postsynaptic nerve

endings of the sinus nerve. Catecholamines, especially dopamine, are most abundantly expressed in glomus cells, although it is established that glomus cells release multiple substances as neurotransmitters. Interestingly, the expression of tyrosine hydroxylase, which is an essential enzyme for neosynthesis of catecholamines, under hypoxic conditions is regulated by HIF-1 [89]. In addition to catecholamines, NO and CO are also deeply involved in synaptic transmission [90]. As described in this review, induction of iNOS and HO-1 in response to hypoxia is dependent on HIF-1. This evidence strongly suggests that HIF-1 may regulate respiratory adaptation to hypoxia.

Ischemic cardiovascular disorders and HIF-1

Atherosclerosis leads to arterial stenosis, impaired perfusion of the downstream vascular bed, and ischemia. When O_2 and glucose deprivation irreversibly affect myocardial viability, the end result is an infarction. Hypoxia/ischemia has dramatic stimulatory effects on the vascularization of coronary and peripheral vascular beds in fetal and juvenile animals, whereas angiogenesis is markedly inhibited in aged animals. The impairment of VEGF production can be attributed to decreased HIF-1 activity in response to hypoxia. Among middle-aged adults, there is also variation in the extent to which ischemia induces the development of collateral blood vessels that allow perfusion of the myocardium downstream of coronary artery stenosis and that influence the incidence and severity of myocardial infarction. Myocardial ischemia induces VEGF expression, and the extent to which VEGF is induced in cultured leukocytes exposed to hypoxia ex vivo is correlated with the degree of coronary collateralization induced by myocardial ischemia in vivo. Expression of HIF-1 mRNA and protein is induced and precedes VEGF expression during acute ischemia and early infarction in the human heart. Thus, it is possible that variation in ischemia-induced HIF-1 activity may underlie the observed variation in VEGF expression and represent an important risk factor for myocardial infarction [83,91,92].

When adult rats are subjected to permanent middle cerebral artery occlusion, HIF-1 mRNA is induced in the penumbra or viable tissue surrounding the infarction region. The induction of HIF-1 mRNA is temporally and spatially correlated with the expression of mRNAs encoding GLUT-1 and the glycolytic enzymes, including aldolase A, lactate dehydrogenase A, phosphofructokinase L, and pyruvate kinase M. These data suggest that induction of glycolytic metabolism may promote the survival of neurons within the penumbra. Colocalization of HIF-1 and VEGF expression has also been demonstrated in the penumbra and is associated with neovascularization. In contrast, studies of primary cortical cultures from newborn mouse brains revealed that inhibition of HIF-1 activity by overexpression of a dominant negative form of HIF-1 is associated with reduced cell death in response to oxygen and glucose deprivation [82]. In the central nervous system, neurons express EPO receptor and astrocytes produce EPO. EPO has been shown to protect primary cultured neurons from *N*-methyl-D-aspartate receptor-mediated glutamate toxicity [93]. Infusion of EPO into the lateral ventricles of gerbils prevented ischemia-induced learning disability and rescued hippocampal CA1 neurons from lethal ischemic damage [93].

Inflammation and HIF-1

Tissue hypoxia and reperfusion injury stimulate local and systemic inflammatory responses [94]. The concept of a perioperative tissue O_2 debt resulting in organ dysfunction, which need not be clinically manifest until several days after an operation, is now accepted. Many high-risk patients cannot mount an adequate hemodynamic response to the stress of surgery, and this may be compounded by unrecognized hypovolemia and poor organ perfusion. Tissue hypoxia and reperfusion injury both fuel the subsequent systemic inflammatory response [94].

The mRNA for HIF-1α subunit was increased three- to four-fold by Northern blot analysis after cells had been incubated for 3 h in the presence of IL-1 [95]. In addition, IL-1 increased the binding of the heterodimer HIF-1 to the HIF consensus sequence. Interestingly, HIF-1α is selectively up-regulated by IFN-α and -β, but nor IFN-γ [96]. In addition, TNF-α or IL-1β stimulates HIF-1 activation not only under normoxic conditions but also under hypoxic conditions [97]. Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone-binding proteins that regulate transcriptional responses to peroxisome proliferators and structurally diverse fatty acids. PPARs have been implicated in a wide variety of functions, including lipid homeostasis and inflammatory responses. Narravula and Colgan suggested that HIF-1 is involved in negative regulation of PPAR expression in response to hyoxia [98]. These results suggest that HIF-1 might have a role in inflammation.

After wounding, HIF-1α, GLUT-1, and phosphoglycerate kinase (PGK-1) mRNAs were detectable in basal keratinocytes at the wound edge [99,100]. Expression of all three genes increased to maximum levels in reepithelializing basal keratinocytes and then diminished to near undetectable levels after wound epithelialization. Although VEGF mRNA similarly increased and decreased during the wound-healing process, its expression pattern was more punctate; the most intense hybridization signals were detected in the upper spinous

and granular layers of reepithelializing keratinocytes and in dermal cells morphologically similar to macrophages. HIF-1 is activated under hypoxic conditions, resulting in the up-regulation of its target genes plasminogen activator inhibitor-1 (PAI-1) and VEGF. PAI-1 and VEGF are also induced in response to vascular injury, which is characterized by the activation of platelets and the coagulation cascade. Thrombin [101], platelet-derived growth factor-AB [47], angiotensin II [47], and TGF-β_1 [47] up-regulated HIF-1α protein in cultured and native vascular smooth muscle cells. These data suggest stage-specific and spatiotemporal control of HIF-1α and HIF-1 target gene expression in wound healing [99].

Shock and HIF-1

Derangements in critical organ perfusion occur in critically ill patients. The resulting imbalance between O_2 supply and demand may play a pivotal role in the pathogenesis of hemorrhagic and septic shock [102]. Shock initiates an inflammatory response that includes increased expression of iNOS and production of prostaglandins [94]. Hierholze et al. showed that the lungs of living rats subjected to hemorrhagic shock had a twofold increase in HIF-1 activation and an increase in expression of iNOS mRNA as compared with sham controls [103]. Mucosal organs such as the intestine are supported by a rich and complex underlying vasculature. For this reason, the intestine, and particularly the barrier-protective epithelial cells, are susceptible to damage related to diminished local blood flow and tissue hypoxia. Failure of barrier function may result in organ failures. Expression of the gene for human intestinal trefoil factor (ITF), an intestine-specific barrier factor, is dependent on HIF-1 [104]. HIF-1-dependent induction of ITF may provide an adaptive link for maintenance of function of the intestine barrier during hypoxia.

Aging and hypoxic response

One of the major characteristics of aging is the decline in the capacity to respond to stress. Hypoxia is a typical stress to which senescent organisms respond poorly. One example of this phenomenon in humans is a decreased ability to tolerate and adapt to ischemic vascular disease in the elderly. Recently, it has been demonstrated that this decrease is in part due to a decrease in the amount of angiogenesis responsible for collateral blood vessel development. This age-dependent impairment of angiogenesis was shown to be mediated by a decline in the production of VEGF. One of the mechanism of this impairment is the reduction of HIF-1α protein expression and DNA binding activity of HIF-1 [105,106]. Thus, age-dependent reduction in hypoxia-induced VEGF expression partly results from reduced HIF-1 activity and may explain the previously described age-dependent impairment of angiogenesis in response to ischemia.

Summary and implications

In summary, I have described pivotal roles of the transcriptional factor HIF-1 in cellular and systemic hypoxic responses (Fig. 2). HIF-1 is required for the establishment of key physiological systems during development and their subsequent utilization in fetal and postnatal life. HIF-1 also appears to play a key role in the pathology of many human diseases. This review omits the critical roles of HIF-1 and its target genes in cancer. Future studies on pharmacological modulation of HIF-1 activity by drugs used during the perioperative period may produce new insights into the anesthetic management of patients. We recently found that the volatile anesthetic halothane significantly blocks HIF-1 activity and downstream target gene expression induced by hypoxia in the human hepatoma-derived cell line,

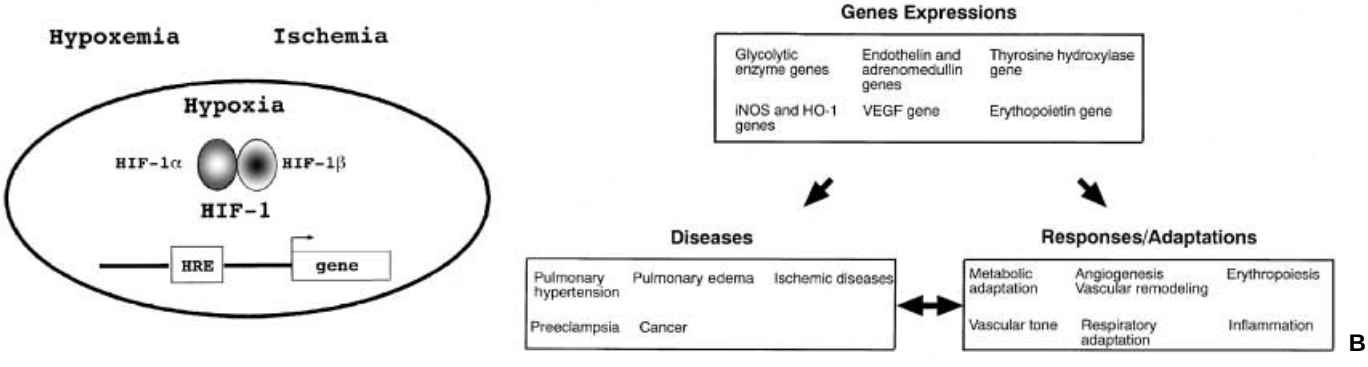

Fig. 2. Involvement of HIF-1 in key physiological and pathophysiological processes. **A** HIF-1 participates in essential physiological processes via transactivation of target genes. **B** HIF-1 transactivation of target genes also contributes to either protective or pathologic responses in several major disease

Hep3B [107]. Because the involvement of HIF-1 in the hypoxic response is not limited to the liver, investigations are indicated of the effects of halothane in other tissues or organs, such as brain, kidney, lung, and blood vessels, and of other anesthetics, both volatile and those administrated intravenously.

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