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REVIEW ARTICLE MECHANISMS OF DISEASE

Oxygen Sensing, Homeostasis, and Disease

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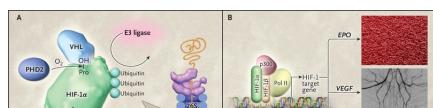
Introduction

HYPOXIA PLAYS CRITICAL ROLES IN THE PATHOBIOLOGY OF HEART DISEASE, CANCER, STROKE, AND chronic lung disease, which are responsible for 60% of deaths in the United States. This review summarizes advances in our understanding of how cells sense and respond to changes in oxygen availability and the physiologic or pathologic consequences of these responses in the context of chronic diseases. The role of hypoxia in inflammatory disorders was recently reviewed in the Journal¹ and is therefore not discussed here.

Mechanisms of Signal Transduction in Hypoxia

Humans have evolved complex circulatory, respiratory, and neuroendocrine systems to ensure that oxygen levels are precisely maintained, since an excess or deficiency may result in the death of cells, tissue, or the organism. As discussed below, oxygen homeostasis represents an organizing principle for understanding evolution, development, physiology, and disease. Historically, oxygen sensing was thought to be limited to specialized cells, such as the glomus cells of the carotid body, which depolarize within milliseconds in response to hypoxemia by means of incompletely understood mechanisms.² We now recognize that all nucleated cells in the body sense and respond to hypoxia. Under conditions of reduced oxygen availability, hypoxia-inducible factor 1 (HIF-1) regulates the expression of genes that mediate adaptive responses.³⁻⁶ In hypoxic cells, the transcription of several hundred messenger RNAs (mRNAs) is increased, and the expression of an equal number of mRNAs is decreased. The changes are dependent on HIF-1 in both cases, but HIF-1 binding is detected only at genes with increased expression. HIF-1 decreases mRNA expression indirectly by regulating transcriptional repressors and microRNAs.³⁻⁶

Figure 1.

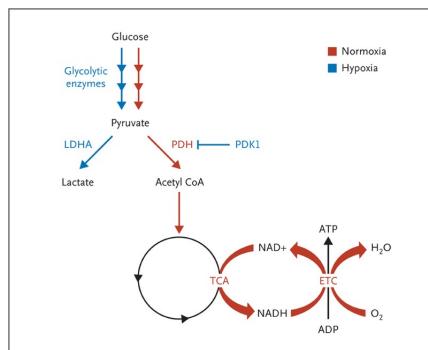


HIF-1 was first identified in human cells as a regulator of erythropoietin, the hormone that controls red-cell production; vascular endothelial growth factor (VEGF), which stimulates angiogenesis; and glycolytic enzymes, which adapt cell metabolism to hypoxic conditions (Figure 1A).⁶ HIF-1 is composed of a constitutively expressed HIF-1 β subunit and an oxygen-regulated HIF-1 α subunit.⁷ Under aerobic conditions, HIF-1 α is hydroxylated by prolyl hydroxylase domain proteins (PHDs), which use oxygen and α -ketoglutarate as substrates and contain Fe²⁺ in their catalytic center.⁸ Hydroxylated HIF-1 α interacts with the von Hippel–Lindau (VHL) protein, the substrate-recognition subunit of a ubiquitin-protein ligase that targets HIF-1 α for proteasomal degradation (Figure 1B). Under hypoxic conditions, hydroxylation is inhibited and HIF-1 α accumulates. HIF-1 transcriptional activity is regulated by factor-inhibiting HIF-1 (FIH-1), an asparaginyl hydroxylase that blocks the interaction of HIF-1 α with the coactivator protein p300.^{6,8} Thus, HIF-1 α hydroxylation provides a mechanism for transducing changes in oxygen availability to the nucleus as changes in gene transcription.

HIF-1 $\alpha^{-/-}$ mouse embryos, which lack HIF-1 α , are arrested in their development at midgestation and die from cardiac and vascular defects and decreased erythropoiesis, indicating that all three components of the circulatory system are dependent on HIF-1 for normal development.^{9,12} Hypoxic responses are also mediated by HIF-2, a heterodimer composed of HIF-1 β and HIF-2 α (a parologue of HIF-1 α that is also regulated by oxygen-dependent hydroxylation). HIF-1 α is present in all nucleated cells of all metazoan species, whereas HIF-2 α expression is restricted to certain cell types within vertebrate species and plays an important role in both erythropoiesis and vascularization.¹³

Regulation of Cellular Metabolism by HIF-1

Figure 2.



Regulation of Glucose Metabolism in Response to Changes in Cellular Oxygen Levels.

Even the simple roundworm *Caenorhabditis elegans*, which consists of about 1000 cells and contains no specialized systems for oxygen delivery, expresses HIF-1, indicating that the primordial function of HIF-1 was to mediate adaptive responses that allow cells to survive oxygen deprivation. One way in which HIF-1 promotes cell survival under hypoxic conditions is by mediating a switch from oxidative to glycolytic metabolism. The glycolytic enzymes convert glucose to pyruvate, which can be converted either to acetyl coenzyme A (CoA) for oxidation in the tricarboxylic acid cycle or to lactate as a glycolytic end product (Figure 2). HIF-1 activates the expression of lactate dehydrogenase A and pyruvate dehydrogenase kinase 1 (PDK1), thus tipping the balance from oxidative to glycolytic metabolism.^{14,15}

As compared with glycolysis, oxidative metabolism yields 18 times as much ATP per mole of glucose consumed. Although it is the conventional wisdom that cells respire until oxygen is depleted, at which point they switch to glycolysis, we now know that this model of metabolic regulation is incorrect. HIF-1 $\alpha^{-/-}$ fibroblasts are incapable of switching from oxidative to glycolytic metabolism when shifted from aerobic conditions of 95% air and 5% carbon dioxide (20% oxygen, with a partial pressure of oxygen [PO₂] of about 140 mm Hg) to hypoxic conditions (1% oxygen, with a PO₂ of about 7 mm Hg).¹⁶ ATP levels are higher in HIF-1 $\alpha^{-/-}$ cells at 1% oxygen than in HIF-1 $\alpha^{+/+}$ cells at 20% oxygen, indicating that 1% oxygen does not limit ATP production.¹⁶ However, HIF-1 $\alpha^{-/-}$ fibroblasts maintained at 1% oxygen or less will die owing to toxic levels of reactive oxygen species.^{14,16} Under aerobic conditions, electrons are transferred from NADH and flavin adenine dinucleotide (FADH₂) (generated by oxidation of acetyl CoA) to

superoxide,¹⁷ which is then converted to hydrogen peroxide and other toxic reactive oxygen species. Thus, there is sufficient oxygen for oxidative phosphorylation to occur in hypoxic fibroblasts, but at the cost of a loss of redox homeostasis. The extent to which these findings apply to disease states, such as cancer and pulmonary hypertension, remains to be determined.

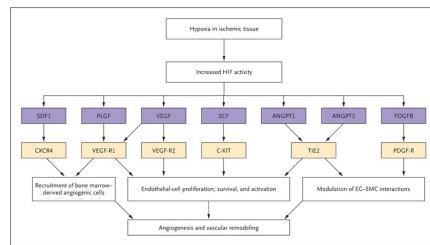
The PHD–VHL–HIF Axis in Hereditary Erythrocytosis

Hereditary erythrocytosis (congenital polycythemia) is a disorder characterized by excess red-cell production. At high hematocrit levels, capillary blood flow is impaired, placing affected persons at increased risk for cerebral and peripheral vascular thrombosis. Persons with Chuvash polycythemia are homozygous for a missense mutation that partially impairs binding of the VHL protein to hydroxylated HIF-1 α subunits, resulting in HIF activity that is inappropriately elevated at any given level of PO₂.¹⁸ Hypoxia-induced changes in respiration and pulmonary vascular tone occur at higher PO₂ levels in affected persons than in controls, reflecting a generalized defect in oxygen sensing.¹⁹ Cases of hereditary erythrocytosis due to a missense mutation in PHD protein 2 (PHD2) or HIF-2 α , which impairs the hydroxylation of HIF-1 α , HIF-2 α , or both, have also been described.^{18,20,21} Thus, the PHD–VHL–HIF pathway has been saturated with mutations, indicating its key role in erythropoiesis and other physiological systems designed to maintain oxygen homeostasis.

Failed Adaptation to Hypoxia in Ischemic Cardiovascular Disease

Atherosclerotic stenosis of arteries in the heart and legs results in cardiac and limb ischemia, respectively, as blood flow downstream of the stenosis becomes restricted. In young, healthy mice, femoral-artery ligation results in the local induction of HIF-1, followed by the transcriptional activation of genes that encode VEGF and other angiogenic factors within the ischemic limb, and after several weeks, normal perfusion is restored.²² This adaptive vascular response is impaired by aging²² and diabetes,^{23,24} which are major risk factors for coronary artery disease and peripheral arterial disease. Whereas HIF-1 $\alpha^{-/-}$ mice are subject to embryonic death, HIF-1 $\alpha^{+/-}$ mice develop normally but have impaired recovery of perfusion and more severe tissue damage after arterial ligation.²²

Figure 3.



Regulation of Vascular Response to Hypoxia by HIF-1.

VEGF and other secreted factors (Figure 3) activate vascular cells to promote angiogenesis (the budding of new capillaries from existing vessels) and arteriogenesis (the remodeling of collateral blood vessels to accept increased flow, thus bypassing stenotic regions of the conduit arteries).^{25,26} Angiogenic factors also reach the circulation and stimulate the mobilization of bone marrow–derived angiogenic cells (BMDACs), which home to ischemic tissue and participate in angiogenesis and arteriogenesis.^{22,27} Although originally described as endothelial progenitor cells, most BMDACs are myeloid cells. Instead of differentiating into cells that are incorporated into the remodeling vessels, myeloid cells produce paracrine factors that stimulate vascular remodeling.^{28,29} To promote vascular remodeling, BMDACs must be mobilized from bone marrow and other tissues and enter the peripheral blood, home to ischemic tissue, be retained within the ischemic tissue by adherence to the vascular endothelium and extravasation from the vessel, and survive long enough within this tissue to initiate vascular responses.

With aging, the loss of ischemia-induced expression of angiogenic factors leads to a failure of BMDAC mobilization and homing.²² After arterial ligation in mice 2 to 8 months of age, intramuscular administration of a recombinant adenovirus encoding a form of HIF-1 α engineered to have constitutive activity ($\Delta dC\Delta 5$) is sufficient to stimulate BMDAC mobilization and homing, improving the

model for type 2 diabetes.³⁰ AdCA5 is not sufficient to recover perfusion in mice 13 to 17 months of age; in these mice, AdCA5 gene therapy followed by intravenous administration of BMDACs results in recovery of blood flow but only when the BMDACs have been pretreated with dimethyloxalylglycine (DMOG), an α -ketoglutarate antagonist that induces HIF-1 activity by inhibiting prolyl hydroxylation.^{31,32} HIF-1 activation in BMDACs leads to the expression of β_2 integrins that promote vascular adherence and tissue retention,³¹ as well as metabolic enzymes, membrane transporters, and pH regulators that promote BMDAC survival in ischemic tissue.³²

HIF-1 also plays an important role in coronary artery disease. HIF-1 α induction occurs early in the course of myocardial infarction, as shown by examination of ventricular-biopsy specimens obtained from patients with acute infarction.³³ Transgenic mice with myocardial HIF-1 α overexpression have reduced infarct size, improved cardiac function, and increased capillary density after coronary-artery ligation.³⁴ Collateral vessels are identified on angiography in approximately two thirds of patients with critical coronary artery disease in which the degree of arterial stenosis ($\geq 70\%$) is sufficient to cause symptoms (angina). The factors that determine whether collaterals will develop in patients with critical stenosis have not been identified. However, when plaque rupture causes total coronary occlusion and myocardial infarction, patients with collateral vessels have smaller infarcts and are more likely to survive than those without collateral vessels.^{35,36} Single-nucleotide polymorphisms at the HIF-1 α locus are associated with an absence of coronary collateral vessels in patients with critical stenosis³⁷ and in patients with acute coronary syndromes who present with stable angina rather than infarction.³⁸ Thus, genetic variation may affect HIF-1 activity and thereby alter the presentation of coronary artery disease.

In mice, HIF-1 is required for ischemic preconditioning, a phenomenon in which exposure of the heart to several short (e.g., 5-minute) episodes of ischemia and reperfusion provides protection against the injurious effects of a subsequent prolonged (e.g., 30-minute) episode of ischemia.^{39,40} Mice with increased levels of cardiac HIF-1 α and HIF-2 α due to decreased PHD2 activity are protected against myocardial infarction in the absence of preconditioning.⁴⁰⁻⁴² These results suggest that HIF-1 not only regulates perfusion and oxygen delivery but also plays a critical role in the ability of the heart to survive episodes of oxygen deprivation, which may involve changes in energy metabolism (described above) and adenosine production.⁴³ In rodent stroke models, pretreatment with pharmacologic inducers of HIF activity results in a reduction in cerebral infarct size, and several HIF target genes are candidates for mediating neuroprotection.⁴⁴⁻⁴⁷ Among high-altitude residents in Switzerland, death from coronary artery disease or stroke is less common than it is in the general population, suggesting that living in chronic hypoxia provides some protection.⁴⁸

Preclinical data linking activation of the PHD–HIF system with ischemic adaptation provide a basis for therapeutic attempts to increase HIF or decrease PHD activity in patients with coronary artery disease and peripheral arterial disease. In a study of patients with critical limb ischemia (a condition in which perfusion is inadequate to maintain tissue viability), HIF-1 α levels were found to be increased in vascular endothelial cells but not in the ischemic muscle cells,⁴⁹ suggesting an impaired physiological response to ischemia. In phase 1 clinical trials, patients with peripheral arterial or coronary artery disease were given a recombinant adenovirus encoding a chimeric protein that contained the N-terminal half of HIF-1 α fused to the VP16 herpesvirus transactivator protein. There were no adverse consequences reported in these two studies in which intramuscular injections were administered to 34 patients with critical limb ischemia and in which intramyocardial injections were administered to 10 patients at the time of coronary-artery bypass grafting.^{50,51} However, there have been no reports of the efficacy of such treatment in patients with peripheral arterial or coronary artery disease, possibly because the chimeric protein does not retain all the activities of HIF-1 α ; gene therapy alone is insufficient to mediate a vascular response in such patients, who tend to be elderly; or the adenoviral proteins or VP16 induces a confounding inflammatory response.

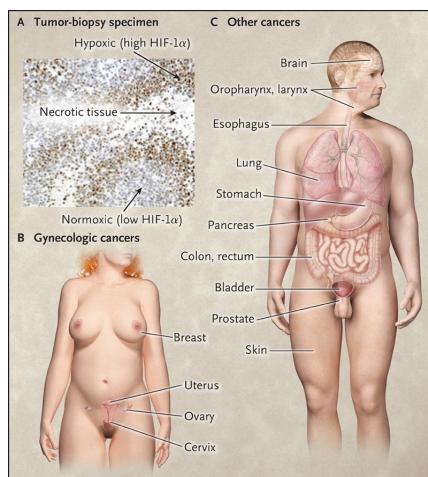
An alternative strategy for treating peripheral arterial disease,⁵² cerebral ischemia,⁴⁴⁻⁴⁷ and other ischemic disorders would be the development of drugs that inhibit the prolyl hydroxylases and thereby activate HIF.^{47,53} These drugs either chelate iron, which is present in the catalytic center of the hydroxylases, or, like DMOG, compete with α -ketoglutarate for binding to the catalytic site. More than 60 different dioxygenases use iron and α -ketoglutarate,⁵⁴ and the development of inhibitors specific to a particular hydroxylase (e.g., one of the PHDs) would be highly desirable for clinical applications. However, in patients with Chuvash polycythemia, even modestly increased HIF signaling that is prolonged and systemic has pathologic effects.⁵⁵ Therefore, the clinical application of such agents must be approached in a careful and conservative manner.

Another alternative strategy would be the use of HIF target-gene products as therapeutic agents, which brings us back to where the story began, with the cloning of the erythropoietin gene^{56,57} and the production of recombinant human erythropoietin for administration in patients with chronic renal failure whose kidneys do not make sufficient erythropoietin to sustain a normal red-

multiple HIF-dependent angiogenic factors.²² One potential advantage of using downstream proteins as therapeutic agents is that they act immediately, whereas the effects of HIF-1 α gene therapy or PHD inhibitors are delayed because they require transcription and translation of target-gene products. In animal models, erythropoietin, which functions as a survival factor for many cell types, has improved recovery from an ischemic event when administered immediately before or after the event.⁵⁹⁻⁶² Positive results were reported in a small clinical trial of erythropoietin in patients with acute ischemic stroke,⁶³ but follow-up studies failed to demonstrate efficacy, and the use of erythropoietin in combination with tissue plasminogen activator resulted in increased mortality.^{64,65} PHD inhibitors, which induce the expression of multiple survival and angiogenic factors, may be more efficacious, but clinical trials are needed to confirm this hypothesis.

Co-opted Adaptation to Hypoxia in Cancer

Figure 4.



Hypoxia, Hypoxia-Inducible Factor 1 (HIF-1), and Cancer.

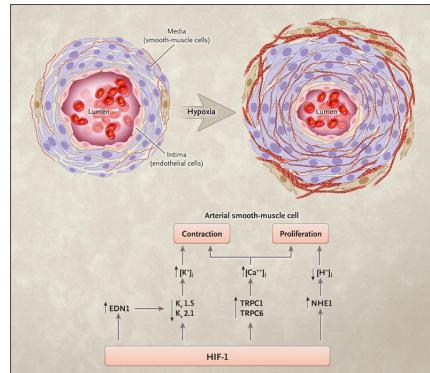
In ischemic cardiovascular disease, the induction of HIF activity is adaptive, and therapeutic efforts are directed toward augmenting the response. In cancer, co-optation of the physiologic responses to hypoxia plays a major role in disease progression, and therapeutic efforts are directed toward inhibiting HIF. Folkman established the critical role of angiogenesis in the growth of primary tumors and their metastasis.⁶⁶ Tumor vessels are structurally and functionally abnormal, and even highly vascularized cancers may contain areas of severe hypoxia. In breast cancer, the mean PO₂ is 10 mm Hg (as compared with >60 mm Hg in normal breast tissue), and a PO₂ of less than 10 mm Hg in the primary tumor is associated with increased risks of metastasis and death.⁶⁷ HIF-1 α overexpression in the primary tumor is also associated with increased mortality in breast cancer and other common cancers (Figure 4).⁶⁸ HIF-1 activates the transcription of genes that play critical roles in angiogenesis,⁶⁹ genetic instability,⁷⁰ immune evasion,⁷¹ metabolic reprogramming,⁷²⁻⁷⁴ invasion and metastasis,^{75,76} radiation resistance,⁷⁷ and stem-cell maintenance.⁷⁸ Although HIF-1 has the potential to regulate hundreds of target genes, only a subset will be regulated by HIF-1 in any given cancer. As with any protein implicated in cancer, one can find contradictory examples suggesting that HIF-1 is involved in limiting tumor growth or has no effect at all. The challenge is to understand the role of HIF-1 in a particular patient's cancer in order to determine whether it might be targeted therapeutically, and if so, how.

Intratumoral hypoxia is a major mechanism by which HIF-1 is activated in human cancers, but HIFs are also activated as a consequence of tumor-suppressor loss of function or oncogene gain of function.⁶⁸ The most dramatic example of this is VHL loss of function, which results in the constitutive overexpression of HIF-1 α and HIF-2 α .⁷⁹ Unlike persons with Chuvash polycythemia, who are homozygous for a missense mutation in VHL that partially impairs its ability to ubiquitinate HIFs, many persons with the VHL syndrome (type 1, 2A, or 2B) are heterozygous for a mutation that results in loss of function. Somatic mutation or epigenetic inactivation of the other allele blocks HIF ubiquitination and degradation. These patients are at high risk for tumors (particularly clear-cell renal carcinomas and cerebellar hemangioblastomas) that are highly vascularized owing to high levels of VEGF and other HIF-regulated angiogenic factors.⁷⁹

when given at lower doses on a daily basis, they inhibit HIF-1 and downstream pathways such as angiogenesis in tumor xenograft models.⁸⁰ Several drugs that were used previously for the treatment of diseases other than cancer, including cardiac glycosides such as digoxin, have been shown to inhibit HIF-1 activity and to block tumor growth in mice,⁸¹ but whether they will do so within the limited dose range tolerated by humans is not known. Other HIF-1-blocking agents that are being investigated in clinical trials of cancer treatment (inhibitors of histone deacetylases, heat-shock protein 90, and mammalian target of rapamycin [mTOR]) inhibit the activity of many other proteins; the extent to which inhibition of HIF-1 contributes to their therapeutic efficacy is unknown but may vary greatly from one patient to another. Including a drug that inhibits HIF-1 as part of a multiagent chemotherapeutic regimen will probably benefit a subset of patients with cancer, but the difficulty in matching patient populations with appropriate drug combinations remains the greatest obstacle to the effective treatment of metastatic disease.

Maladaptive Responses to Hypoxia in Pulmonary Hypertension

Figure 5.



Pathogenesis of Hypoxic Pulmonary Hypertension.

Hypoxic pulmonary hypertension is a progressive and often fatal complication of chronic lung disease. Unlike systemic arterioles, which dilate in response to hypoxemia in order to increase tissue perfusion, pulmonary arterioles constrict in order to shunt blood away from regions of the lung that are not ventilated. This is an adaptive response in patients with lobar pneumonia but not in those with chronic lung disease, in whom alveolar hypoxia occurs throughout the lungs, with pulmonary hypertension leading to right heart failure and progressive hypoxemia. HIFs regulate target genes that play key roles in the pathogenesis of pulmonary hypertension (Figure 5).⁸²⁻⁸⁴ As compared with their wild-type littermates, HIF-1 $\alpha^{+/-}$ or HIF-2 $\alpha^{+/-}$ mice have less severe pulmonary hypertension when subjected to prolonged hypoxia.^{85,86} In contrast, persons with hereditary erythrocytosis due to mutations that stabilize the HIF-2 α protein have elevated pulmonary arterial pressures under normoxic conditions.⁸⁷ HIF-1-mediated alterations in the energy metabolism of pulmonary arterial smooth-muscle⁸⁸ and endothelial⁸⁹ cells may play an important pathogenic role in hypoxic pulmonary hypertension (World Health Organization [WHO] group III) and idiopathic pulmonary hypertension (WHO group I). Altered redox homeostasis also plays an important role in pulmonary hypertension.^{90,91} Epigenetic inactivation of superoxide dismutase 2 expression has been implicated in the induction of HIF-1 α expression in pulmonary arterial smooth-muscle cells from fawn-hooded rats, which are a model for idiopathic pulmonary hypertension.⁹⁰

Evolutionary Adaptation of Tibetans to High Altitude

For thousands of years, humans have lived on the Tibetan plateau at altitudes that exceed 3000 m. As compared with residents at sea level, where the atmospheric PO₂ is 150 mm Hg, residents of the Tibetan highlands, where the PO₂ is 110 mm Hg or less, live under conditions of chronic hypoxia and have evolved unique adaptations to their environment. Normally, when the lungs are subjected to high-altitude hypoxia, increased pulmonary vascular tone becomes a maladaptive response that leads to hypoxemia and heart failure. When hypoxemia is due to anemia, erythrocytosis is an adaptive response, whereas when it is due to ambient hypoxia, further increases in red-cell mass cannot correct the problem and may make it worse, owing to hyperviscosity associated with polycythemia. In adapted Tibetans, these responses to hypoxia are blunted, and many Tibetans have normal pulmonary

With the advent of powerful DNA-sequencing methods, it became possible to identify loci at which genetic selection has occurred in Tibetan highlanders relative to the lowland population from which they arose. Remarkably, the strongest evidence of selection was found at the locus encoding HIF-2 α .⁹³⁻⁹⁵ Evidence for selection at loci encoding PHD2, factor-inhibiting HIF-1 (FIH-1), and HIF target genes has also been reported.^{95,96} How the selected genetic variants alter the function of these proteins is not known. The variants may result in reduced activity of PHD2 and HIF-2 α , the net effect of which would be to alter the balance between HIF-2 α , which mediates vascular and erythropoietic responses to hypoxia, and HIF-1 α , which mediates metabolic as well as vascular responses. In any case, these findings underscore the central role of the PHD–HIF system in maintaining oxygen homeostasis.

Conclusions

Oxygen-sensing and HIF-dependent responses to hypoxia are essential for prenatal development and postnatal physiology. They can play either protective or pathogenic roles in the chronic diseases that are the most common causes of death in the U.S. population, as well as in many other conditions (including ocular neovascularization^{97,98} and organ transplantation^{99,100}) that cannot be discussed in this short review. The targeting of HIFs and PHDs represents a novel strategy for treating these diseases, provided that therapeutic effects can be obtained without untoward side effects. These conditions will be most easily met if the therapy is local, is of short duration, and is combined with other treatments that selectively amplify the consequences of modulating HIF activity in diseased tissue.

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[Disclosure forms](#) provided by the author are available with the full text of this article at NEJM.org.

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Supplementary Material

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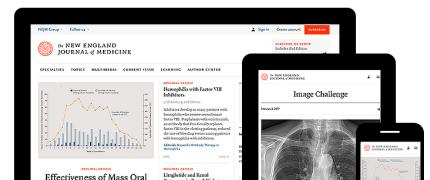
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