INVITED REVIEW

HIGHLIGHTED TOPIC | Oxygen Sensing in Health and Disease

Analysis of expression and posttranslational modification of proteins during hypoxia

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Kumar, Ganesh K., and Jon B. Klein. Analysis of expression and posttranslational modification of proteins during hypoxia. J Appl Physiol 96: 1178–1186, 2004; 10.1152/japplphysiol.00818.2003.—The cellular responses to hypoxia are complex and characterized by alterations in the expression of a number of genes, including stress-related genes and corresponding proteins that are necessary to maintain homeostasis. The purpose of this article is to review previous and recent studies that have examined the changes in the expression and posttranslational modification of proteins in response to chronic sustained and intermittent forms of hypoxia. A large number of studies focused on the analysis of either the single protein or a subset of related proteins using one-dimensional gel electrophoresis to separate a complex set of proteins from solubilized tissues or cell extracts, followed by immunostaining of proteins using antibodies that are specific to either native or posttranslationally modified forms. On the other hand, only a limited number of studies have examined the global perturbations on protein expression by hypoxia using proteomics approach involving two-dimensional electrophoresis coupled with mass spectrometry. Results derived from specific protein analysis of a variety of tissues and cells showed that hypoxia, depending on the duration and severity of the stimulus, affects the level and the state of posttranslational modification of a subset of proteins that are associated with energy metabolism, stress response, cell injury, development, and apoptosis. Some of these earlier findings are further corroborated by recent studies that utilize a global proteomics approach, and, more importantly, results from these proteomics investigations on the effects of hypoxia provide new protein targets for further functional analysis. The anticipated new information stems from the analysis of expression, and posttranslational modification of these novel protein targets, along with gene expression profiles, offers exciting new opportunities to further define the mechanisms of cellular responses to hypoxia and to control more effectively the clinical consequences of prolonged or periodic lack of oxygen.

chronic sustained hypoxia; intermittent hypoxia; two-dimensional electrophoresis; mass spectrometry; hypoxia-associated proteins

Molecular oxygen is essential for the survival of mammals due to its critical role as an electron acceptor during ATP production via oxidative phosphorylation. Hypoxia, i.e., lack of oxygen, is a pervasive physiological stimulus that affects all organisms in unique ways, depending on their intrinsic cellular macromolecular constituents and their reaction products. The cellular responses to hypoxia are complex and characterized by alteration in the expression of a number of genes, including stress-related genes and corresponding proteins that are necessary to maintain homeostasis. A broader understanding of hypoxia-induced alterations in cellular or organ function could be better achieved from a combined knowledge derived from the concerted application of genomic and proteomics approaches.

Genomics and proteomics may be broadly defined as the characterization of all of the genes and proteins, respectively, expressed by a genome in a specified cell type, tissue, or organ and comparison of potential alterations in their expression in response to environmental perturbations. Although genomic changes during hypoxia have been extensively investigated, hypoxia-induced changes in the proteome of mammalian cells are in their early phase of investigations. Although a large number of studies have focused on the influence of hypoxia on the expression and posttranslational modification of a single protein of interest or a subset of functionally related proteins, only a few reports have really examined proteome-wide alterations during hypoxia (23, 35, 46, 85). In this review, we will briefly address the recent technical advances in the analysis of proteome and focus on the present status of the impact of various forms of hypoxia, i.e., chronic sustained (SH) and intermittent hypoxia (IH), on the expression and posttranslational modification of proteins in tissues and cells. In the first
part of this review, the findings on SH- and IH-induced alterations in protein expression will be presented, whereas, in the second part, findings from studies that specifically address changes in posttranslational modification of proteins during hypoxia will be discussed. Several excellent reviews on various aspects of proteomics techniques are available (2, 4, 13, 57), and these aspects, therefore, will be discussed only briefly.

METHODS FOR THE ANALYSIS OF PROTEIN EXPRESSION

Analysis of Expression of Individual Protein(s)

Thus far, in a majority of studies that have examined the impact of decreased availability of oxygen on protein expression in a tissue or a cell model, the changes in the level of a specific protein of interest following hypoxia have been measured. In general, two methods have been used to assess any qualitative or quantitative change in protein expression during hypoxia. These methods have employed monoclonal or polyclonal antibodies specific to native or posttranslationally modified form of proteins, thus permitting either immunocytochemical or ELISA or immunoblot analysis of control and test samples. In a few studies, new protein synthesis has been assessed by one-dimensional SDS-PAGE separation, coupled with autoradiographic analysis of proteins that are metabolically labeled with \[^{35}\text{S}]\text{methionine. Using these simple and relatively inexpensive methods, the potential impact of hypoxia on the expression of a wide range of proteins that reside either in the cytosol or membrane fraction or nucleus or mitochondria has been analyzed in specific tissues and cultured cells. Both the duration and the severity of hypoxia varied among these studies. However, antibody-based techniques are limited by being able to identify known proteins for which specific antibodies exist and to a relatively small number of proteins that can be simultaneously identified.}

Proteomics Analysis (Global Analysis of Protein Expression)

Proteomics analysis can provide information pertaining to compensatory changes occurring at the level of protein expression as a consequence of prior transcriptional and translational alterations in response to environmental perturbations. In scheme 1 (Fig. 1), the various steps associated with proteomics analysis of tissues or cells are presented. For the analysis, often a cell–free extract of the tissue or the cell is used, either as such or along with subcellular fraction(s) derived from differential centrifugation of the cell-free extract. A variety of complementary procedures for the global analysis of protein expression have been described. These include two-dimensional (2D) PAGE (2DE) coupled with mass spectrometry (MS) (10, 11, 40, 41), multidimensional chromatography coupled with tandem MS (19, 54, 81), and chip technologies coupled with either antigens (56, 92) or antibodies (29, 44, 55, 91). Among them, 2DE coupled with matrix-assisted laser desorption/ionization MS is the most extensively used approach for identifying the proteins and quantifying changes in protein expression (10, 11). On the other hand, the multidimensional chromatography, coupled with tandem MS strategy and isotope-labeled affinity tags, may permit more sensitive separation and quantification of proteins than that achieved by 2DE (28, 32). Irrespective of the approach, a typical proteomics analysis consists of the following steps: 1) sample preparation, 2) optimal separation of protein species, 3) imaging, 4) identification of protein species and their charge variants (posttranslational modification), 5) quantification, and 6) data assessment using protein databases that can be either web-based or locally maintained. Also, for protein identification, peptides are generated with one or more of the proteolytic enzymes, and the resultant peptides are analyzed by MS. Depending on the complexity of the samples to be analyzed, there are several variations in each one of the above steps, but the details of these variations will not be presented here due to space constraint; however, they can be found in Refs. 28, 39, 69, 70, 73, 74, and 84.

Protein separation in 2DE is achieved in two steps. In the first step (first dimension), proteins extracted from either cells or tissues are subjected to isoelectric focusing, which permits separation of proteins on the basis of differences in the isoelectric point. In the subsequent step (second dimension), the proteins are transferred to either a slab or vertical SDS polyacrylamide gel, and proteins are resolved based on the molecular weight differences among proteins with a similar isoelectric point. Once the components of a protein mixture have been separated on the second-dimension gel, a staining method appropriate for the eventual analysis must be chosen. Ideally, a staining method should confer three properties to the resulting image: 1) sensitivity, 2) range, and 3) linearity. The staining technique must respond to extremely low levels of protein and must clearly distinguish the protein’s presence. The intensity of the image must not become “saturated” by regions of the gel with high concentrations of protein. There must be a proportional relationship between the image intensity and the protein concentration per unit area of gel to allow quantification of expression.

In comparing the quantitative changes in protein expression between the control and experimental samples, it is essential that equal amounts of proteins are used for proteomics analysis. Traditionally, the separated proteins occurred as discrete spots in the 2D profiles and were visualized by Coomassie

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**Fig. 1. Scheme 1: general steps involved in proteomics analysis. 2D, two-dimensional; MS, mass spectrometry.**
brilliant blue or silver staining, and the relative abundance of each protein and alteration in their level were assessed by densitometric scanning analysis. More recently, chemiluminescent fluorescing stains have been used that exhibit better linearity and dynamic range than silver or Coomassie stains. The chemical identity of the selected proteins was determined by MS analysis of protein spots eluted from the 2D protein profile, in conjunction with Web-based protein databases such as Swiss-PROT.

These basic proteomics techniques have been applied in two general approaches. The first, expression proteomics, attempts to identify the protein expression of a biological system in terms of its response to the environment. It is most commonly practiced as a differential proteome analysis following the application of some experimental stimulus or the presence of a disease state. Expression proteomics requires not only the identification of expressed proteins, but also estimates of their quantity. The second approach, functional proteomics, uses proteomics techniques to study the interaction between proteins. Mapping these interactions provides information about signaling pathways, modules, and complex biosynthesis and degradation networks. Proteomics mapping, combined with affinity capture techniques, allows the identification of the components of such interactive complexes.

ANALYSIS OF EXPRESSION OF PROTEINS DURING HYPOXIA

Several investigations have focused on the adjustments in protein expression in response to chronic SH as well as IH by the analysis of protein expression either at the single-protein level (38, 49) or recently throughout the proteome (23, 46, 85). A comparative analysis of these studies suggests that hypoxia upregulates a subset of proteins in a cell-type- or tissue-dependent manner. These hypoxia-evoked proteins can be arbitrarily classified into the following groups: 1) nucleus resident proteins such as transcriptional factors, 2) proteins of energy metabolism including glycolytic enzymes, 3) stress-related proteins like heat shock proteins (HSPs) and cell death factors, 4) membrane-bound proteins that include transporters and receptors, and 5) other cytosolic proteins, including antioxidants and proteins associated with signaling cascade.

Nuclear Resident Proteins

Few studies have examined the effects of SH on the expression of nuclear resident proteins such as hypoxia-inducible factor (HIF)-1α. HIF-1α is a basic helix-loop-helix containing member of the PER-ARNT-SIM family of transcription factors and plays a central role in the response to hypoxia. It has been demonstrated that HIF-1α, HIF-2α/endothelial PER-ARNT-SIM domain protein, and HIF-3α protein levels are increased during SH (59, 75, 76). Furthermore, the increased expression of HIF-1α during SH seems primarily due to increased protein stabilization via decreased ubiquitination-mediated degradation of HIF-1α protein (59, 75, 76). The elevated level of HIFs, in turn, coordinately activates the expression of many target genes whose protein products, including erythropoietin and angiogenic factors, facilitated cell survival during lack of oxygen.

The 14-3-3 signaling/adapter proteins have been shown to be involved in a variety of cellular processes. The effect of SH (2% O2) on the expression of isoforms of 14-3-3 signaling/adapter proteins in cytrophoblasts, the specialized epithelial cells of fetal origin and extra-embryonic lineage, was investigated by a proteomics approach involving 2D PAGE coupled with MS (35). Proteomics analysis of cytrophoblast revealed that hypoxia had no significant effect on the overall expression level of 14-3-3 adapter proteins, especially that of ε- and ζ-isoforms (35). However, hypoxia specifically induced the translocation of 14-3-3 ε- but not the ζ-isoform to the nucleus. These findings suggest that ε-isoform of 14-3-3 protein may be involved in hitherto unknown but novel oxygen-regulated nuclear processes, including transcription (8) and signal transduction (20, 34).

GAPDH is a glycolytic enzyme. Recent studies have shown that, in addition to its role in energy production in the cytosol, GAPDH is also involved in DNA repair and replication in the nucleus (21, 79). In endothelial cells, hypoxia, via activation of gene expression (18), augments GAPDH proteins not only in the cytosolic fraction but also in the nuclear fraction (89), consistent with its multiple roles in various cellular compartments.

Proteins of Energy Metabolism

Molecular oxygen is essential for cellular ATP production. Consequently, hypoxia profoundly influences energy metabolism, and the overall effect seems to be dependent on cell type. Vascular endothelial cells, the first within the vasculature to encounter decreases in blood oxygen concentration, are more hypoxia tolerant than other cell types. SH has been shown to upregulate a set of stress proteins (93) in vascular endothelial cells. These proteins are often referred to as hypoxia-associated proteins (HAPs) and include the glycolytic enzyme GAPDH. In addition to GAPDH, the level of nonneuronal enolase protein was also increased in endothelial cells exposed to SH (1). However, it should be noted that HAPs are distinct from the stress proteins evoked in response to either heat shock (i.e., HSPs) or glucose deprivation (i.e., glucose-regulated proteins) (1, 25, 27, 86, 93). GAPDH, in addition to its role in energy production in the cytosol, also has been shown to be involved in translational regulation and endocytosis in the membrane compartment (60, 79, 80). Although SH increased the enzyme activity, it was not proportional to the increase in protein level, suggesting that GAPDH is involved not only in increased glycolysis for increased energy production during hypoxia but also in other cellular processes associated with the nucleus or membranes. Interestingly, HAPs are not induced by hypoxia in other hypoxia-sensitive cell types. Furthermore, carbon monoxide, which inhibits hypoxia-induced erythropoietin expression, had no effect on the augmentation of HAPs by hypoxia in endothelial cells (25). Taken together, these studies suggest that hypoxia-induced expression of GAPDH, nonneuronal enolase, and other HAPs are unique to endothelial cells and that this enhanced HAP expression is causally linked to the ability of endothelial cells to tolerate and to adapt to lack of oxygen.

The effect of SH on the expression of enzymes of glycolysis of cytrophoblasts was investigated with a proteomics approach (35). The phenotype induced by exposing cytrophoblasts to hypoxia in vitro resembles features of pregnancy complications such as preclampsia. The results showed that cytrophoblast protein repertoire was discretely altered by hypoxia. Notably, the expression of enzymes of glycolysis,
such as triosphosphate isomerase and phosphoglycerate mutase, was increased, consistent with the increased glucose consumption in human term cytotrophoblast during hypoxia (16, 17) and the hypoxia-evoked augmentation of glycolysis reported in endothelial cells (26).

Stress-Related Proteins

One of the ways by which cells protect against stress induced by environmental cues is by enhanced synthesis and accumulation of several members of functionally and compartmentally distinct families of HSPs, such as HSP70, HSP90, HSP60, and HSP27. In most cells, hypoxia induces the expression of HSP70, thus enabling their survival during episodes of low oxygen. However, in hypoxia-tolerant endothelial cells, sustained reduction of PO2 reduces the expression of HSP70 protein while stimulating the activity and expression of glycolytic enzymes (24, 27, 66). Interestingly, in astrocytes, metabolic labeling studies have shown that hypoxia upregulates the expression of protein with sequence identity to the glucose-regulated protein of 78 kDa (36).

IH, unlike SH, significantly reduced atrial HSP70 and HSP90 protein expression, whereas their levels remained unaltered in the ventricle (64). This reduced level of expression of stress-related proteins in IH atria remained downregulated, even after exposure to acute hypoxia. Therefore, it seems that increased resistance of the isolated atria of IH animals to a subsequent anoxic insult may be due, in part, to reduction in hypoxia-induced HSP protein expression. Furthermore, Edmondson et al. (14), applying a functional proteomics approach, have identified HSPs in a PKC-ε signaling complex that confers resistance to cardiac ischemia. In addition to HSP proteins, IH has also been shown to affect the expression of a number of other stress-related proteins. For example, exposure of rats to alternating cycles of hypoxia (10% O₂ for 90 s) and normoxia (21% O₂ for 90 s) for up to 14 days has been shown to selectively upregulate protein expression and activity of cyclooxygenase (COX)-2, but not COX-1, in cortical regions of rats to alternating cycles of hypoxia (6.0–7.5% O₂) and 3 min of normoxia (21% O₂) for 8 h/day for 28 days. IH exposure decreased the expression of sodium/hydrogen exchanger (NHE) isoform 1 and sodium-bicarbonate cotransporter proteins in the central nervous system and especially in the cerebellum. On the other hand, the level of isoform 3 of NHE, which is expressed only in the cerebellum, was also reduced. Interestingly, IH decreased the protein expression of anion exchanger 3 in most of the brain regions. These results demonstrate that IH downregulates the acid-extruding capacity of many neurons, thus rendering them more susceptible to acidic insult and subsequent neuronal injury. However, it remains to be established whether IH-induced reduction in NHE isoform 1 and NHE isoform 3 is causally related to protein destabilization. On the other hand, in cytotrophoblast, SH increased the level of annexin II, a calcium/lipid binding protein, which has been implicated to play a functional role in defining the proliferative capacity of cells (61).

Other Cytosolic Proteins

Proteins of cardiovascular function. The expression of nitric oxide (NO) synthase (NOS) isoforms, at both the mRNA and protein levels, was examined in lungs of rats exposed to 3 wk of normobaric hypoxia (10% O₂) (50). Overall, the expression of both endothelial (eNOS) and inducible forms of NOS protein was increased. Specifically, hypoxia facilitated de novo synthesis of eNOS proteins in the microvascular endothelium. Studies in cultured porcine pulmonary artery endothelial cells showed that the expression of PDGF B chain but not that of the A chain was increased by hypoxia (3% O₂) (51). More importantly, hypoxia further facilitated the translocation of PDGF B chain from the nuclear region to the cytoplasmic and perinuclear region. Taken together, these results support the idea that both NÖ and PDGF may contribute to vascular remodeling during hypoxic pulmonary hypertension. On the other hand, IH (8–8.5% O₂ for 12 h/day for 21 days) decreased the expression of neuronal NOS by ~52% in the right atria of the guinea pig (64). The above finding is consistent with the enhanced sympathetic nerve activity during IH and further supports the important role of NO in the regulation of cardiovascular function during IH.

Antioxidants. Proteomics analysis of cytotrophoblast (35) showed that the expression of antioxidants, Mn SOD and 1-Cys peroxiredoxin, was decreased during SH. The reduction in antioxidant expression is in accord with the downregulation of Cu/Zn SOD in cytotrophoblasts in preeclampsia, a pregnancy complication that is thought to occur as a result of placental hypoxia (58).

Neurotrophic factors. It has been shown that, during IH, episodic serotonin receptor activation increases spinal protein synthesis, especially that of the brain-derived neurotrophic factor, a neurotrophin involved in many forms of synaptic function.
plasticity (63). The increased brain-derived neurotrophic factor expression during IH has been proposed to enhance glutamatergic synaptic currents in phrenic motoneurons and increase their responsiveness to bulbo-spiral inspiratory inputs.

HYPOXIA AND INDUCTION OF POSTTRANSLATIONAL MODIFICATIONS

There are several instances wherein hypoxia, in addition to affecting protein expression, also alters the function of existing proteins via posttranslational modification(s) of specific amino acid residues. A large number of studies have focused on the phosphorylation-dephosphorylation reactions occurring during hypoxia. A partial list of proteins that undergo posttranslational modification(s) during hypoxia is shown in Table 1. From a comparative analysis of these proteins, it is evident that acute hypoxia (15, 45) or SH (5, 62, 83, 87) or IH (49) facilitates either phosphorylation or dephosphorylation of a large number of proteins, including transcription factors (5, 62, 83, 87), translation initiation factors (47, 72), protein kinases (6, 33, 48), cell adhesion and cytoskeletal proteins (9, 15, 43, 88, 90), cytosolic and mitochondrial enzymes (3, 15, 45, 77), cell surface receptors (30, 31, 78), and neurotransmitter-related proteins and synthetic enzymes (37, 49, 65, 78).

Acute hypoxia has been shown to increase the phosphorylation of glycogen phosphorylase and pyruvate dehydrogenase in a perfused rat heart preparation (15). Furthermore, in pulmonary microvascular endothelial cells, there was an increase in the phosphorylation of xanthine dehydrogenase/oxidase after 4 h of acute hypoxia (45). Similarly, SH facilitated cAMP response element binding protein (CREB) phosphorylation in type I cells of the rat carotid body (87), in the cerebral cortex of the newborn piglets (62), and in undifferentiated PC12 cells (5). On the other hand, in endothelial cells, SH decreased the level of TAL1/SCL transcription factor but increased specific phosphorylation of Ser122 of TAL1/SCL (83).

Among protein kinases, hypoxia facilitated the phosphorylation of glycogen synthase kinase-3, Akt, and endothelial PAS domain protein 1 in PC12 cells (6). Also, hypoxia increased the phosphorylation of PKC-α in Chinese hamster V79 cells (33) and p38 MAPK in cardiomyocytes (48). However, in porcine heart, hypothermic hypoxia for 10 h resulted in increased dephosphorylation of phosphofructokinase (68).

Interestingly, hypoxia, in a pattern-dependent manner, differentially affected the phosphorylation of myosin light chain. Whereas SH decreased 20-kDa myosin light chain phosphorylation in carotid artery muscle, it augmented the phosphorylation of 20-kDa myosin light chain in pulmonary arterial muscle (90).

Several studies have shown that SH facilitates protein dephosphorylation via activation of specific phosphatases. Thus SH reduced the phosphorylation of eNOS and Akt in neonatal rabbit heart (78), connexin-43 in cultured astrocytes (53), and phosphofructokinase in porcine heart (68). In the rat brain and synaptosomal preparation, hypoxia-ischemia facilitated tyrosine phosphorylation of N-methyl-D-aspartate receptor NR2B (31), whereas it increased the dephosphorylation of serine residue of synapsin-1 (65) and Ser41/Thr72 of neuro-modulin/growth-associated protein-43 (37). Similarly, there was a decrease in the phosphorylation of focal adhesion proteins during hypoxia-reoxygenation of kidney proximal tubules (88). However, the identity of phosphatases that mediate hypoxia-induced dephosphorylation has not yet been determined.

Also, there are examples wherein hypoxia altered the protein function without affecting the level of protein expression. Thus, in both left and right ventricles, SH did not affect the expression of G_{o,2} and G_{s} proteins, whereas it significantly decreased the functional activity of G_{s} (42), thereby contributing to desensitization of catecholamines. It is not known whether the altered posttranslational modification of G_{s} might have contributed to the observed decrease in activity. IH, unlike SH (62), increased the dephosphorylation of CREB in aged rat brain (22). However, in PC12 cells, IH (alternating cycles of hypoxia, i.e., 1% O_{2} for 15 s, and normoxia, i.e., 21% O_{2} for 3 min) markedly increased the phosphorylation of tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine biosynthesis (49). Notably, IH did not alter TH protein level, whereas it increased TH enzyme activity. Furthermore, removal of endogenous catecholamines bound to TH and in vitro phosphorylation of TH in cell-free extracts with the catalytic subunit of PKA resulted in enhanced TH activity in normoxic, but not in IH, cells. These findings indicate potential induction of TH phosphorylation and removal of endogenous inhibition of TH by IH. This possibility was further supported by the observations that, in IH cells, 1) there is an increase in total serine and Ser40-specific phosphorylation of TH, and 2) the increases in TH activity, total serine, and Ser40-specific phosphorylation of TH resulting from IH exposure are attenuated selectively by CaMK and PKA-specific inhibitors. Together, these results provide evidence that IH activates TH in PC12 cells via phosphorylation of serine residues, especially Ser40, in part by CaMK and PKA, without affecting TH protein expression. IH preconditioning was also reported to increase the phosphorylation of the CREB in the hippocampus (72).

In addition to phosphorylation, a limited number of studies examined the effect of hypoxia on protein glycosylation. In rats, hypobaric hypoxia (380 mmHg) differentially altered the degree of glycosylation of plasma proteins. Whereas hypoxia increased the fucosylation of transferrin, it resulted in a decrease of fucosylation of IgG (71). Thus far, nearly 300 posttranslational modifications have been documented. It will be of interest to determine whether other types of posttranslational events are also recruited in response to chronic SH and IH.

SUMMARY AND FUTURE DIRECTIONS

Hypoxia affects a variety of cellular processes and is also recognized as a major contributing factor in a variety of pathological processes. Single or proteomewide analysis of expression and posttranslational modification of proteins in response to hypoxia revealed that complex adjustments are made in multiple cellular compartments to cope with the reduced oxygen availability for maintaining cellular function. Only in the past few years have proteomics techniques been applied to assess the effect of hypoxia in cells or tissues. Although a large body of information is already available, there are still several gaps in our knowledge on the mechanism(s) by which hypoxia affects protein expression. Except for a few proteins, there is a paucity of information regarding whether hypoxia-induced upregulation of protein(s) is due to either de novo synthesis or increased protein stabilization or via translocation of proteins to specific cellular compartments.
Thus far, studies examining the influence of hypoxia on protein expression have been restricted to those proteins that show enhanced expression. However, only a few studies have examined the proteins whose expression is downregulated by either SH or IH. Future proteomics studies establishing the identity of these proteins whose expression is reduced during hypoxia are necessary to assess their relative importance in oxygen-sensing mechanisms, as well as to further elucidate the compensatory mechanism(s) associated with cellular remodeling during hypoxia. Recently, it has been demonstrated that one or more of the complexes of the electron transport chain of the mitochondria are involved in the oxygen-sensing mechanism(s) associ-
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