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HIF-1 as a Marker of Age-Related Diseases Associated with Tissue Hypoxia

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Abstract—The data on the role of hypoxia-inducible factor, HIF-1, in the development of immunopathology (infectious, inflammatory, and autoimmune diseases), cancer (of the lung, brain, female reproductive system, urinary bladder, and pancreas), diabetes mellitus, and Alzheimer's disease are analyzed. The data on the genes involving cell differentiation, apoptosis, and proliferation, the expression of which is regulated by HIF-1, are described. HIF-1 activates the expression of the telomerase gene and increases the replicative lifetime of human lung fibroblasts under hypoxic conditions. HIF-1 may be a molecular marker of cell aging and metabolism, as well as a potential therapeutic target for the treatment of age-related diseases.

Keywords: HIF-1, hypoxia, diabetes mellitus, oncogenesis, immunopathology, neuropathology, aging
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INTRODUCTION

Aging at the levels of cells and tissues is often induced by hypoxia, which is characteristic of many pathological states associated with stress and disturbances in cardiovascular functioning. The successful adaptation of the body to hypoxia includes, in particular, certain changes in the expression of a group of genes, the products of which modulate cell metabolism, differentiation, proliferation, and apoptosis. Cell aging interferes with many of these processes. Hypoxia-inducible factor (HIF-1) is a key regulator in the expression of the genes responsible for the tissue response to oxygen deficiency. This molecule provides a rapid and adequate response to hypoxic stress. In the human lung fibroblasts, HIF-1 activates the expression of telomerase gene (Nishi et al., 2004), which, in turn, increases the replicative life of fibroblasts under hypoxia (Bell et al., 2007). In addition, the HIF-1 overexpression extends the life of *C. elegans* (Zhang et al., 2009).

Immune pathology, carcinogenesis, neurodegenerative diseases, and diabetes mellitus are among the key are-related diseases with HIF-1 as an important player in their pathogenesis. This protein enhances cell survival at a lowered level of oxygen, necessary for their vital activities. Expression dysregulation of the HIF-1 transcription factor is one of the causes for development of neoplasms as well as disturbances of vascularization, angiogenesis, energy metabolism, cell proliferation, and differentiation. HIF-1 induces transcription of over 90 genes involved in oxygen delivery to hypoxic areas, cell renovation, and glucose metabolism. In the human lung fibroblasts, HIF-1 activates expression of the telomerase gene and prolongs their replicative lifespan under hypoxia. HIF-1 can be a molecular marker of cell aging and metabolism as well as a potential therapeutic target for treatment of the age-related diseases.

The goal of this review is to analyze the role of HIF-1 in development of several pathological states associated with age.

CHARACTERIZATION OF HIF-1 FUNCTION

HIF-1 is a dimeric protein complex involved in the regulation of tissue functions upon a decreased oxygen concentration (Ziello et al., 2007). For the first time, this transcription factor was visualized by Semenza and his colleagues at Johns Hopkins University in Baltimore, United States, in 1992 as the regulator of erythropoietin expression (Semenza and Wang, 1992). HIF-1 regulates the expression of the genes enhancing cell adaptation and survival in hypoxia (Bhat et al., 2010). This protein is among the key factors involved in the immune response and the homeostatic processes increasing vascularization in hypoxic tissues. HIF-1 can be regarded as a major component for the antihypoxic therapeutics (Wenger, 2002).

The HIF-1 transcription complex is a heterodimer comprising α- and β-subunits. The *hif* gene encodes

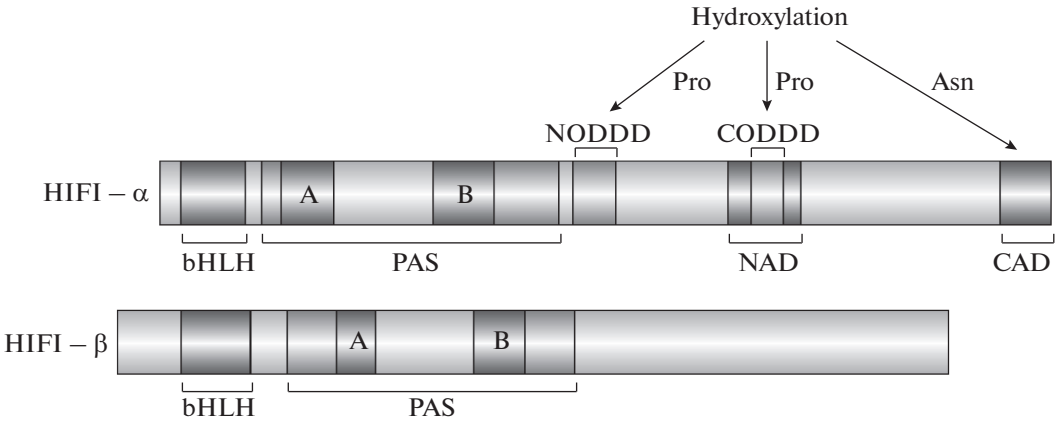

Fig. 1. Structure of the α- and β-subunits of the HIF-1 transcription factor (according to Schofield and Ratcliffe, 2004, with some modifications). See text for explanation (here and in Figs. 2–4).

HIF-1 α-subunit and resides in human chromosome 14. HIF-1 belongs to the PER-ARNT-SIM (PAS) subfamily of the transcription factors with a helix–loop–helix (bHLH) domain (Yang et al., 2005). The HIF-1 α- and β-subunits are similar in their structure, both containing PAS and bHLH domains (Fig. 1). The N terminal of α- and β-subunits contains a bHLH domain; thus, HIF-1 belongs to the dimeric eukaryotic transcription factor family, in which HLH domain performs the function of DNA binding, is involved in dimerization, and interacts with RNA polymerase (Semenza, 2004). PAS, the central domain, enhances heterodimerization. PAS proteins have been discovered in most eukaryotes and prokaryotes, thereby suggesting their evolutionary conservation (Fig. 1).

Hydroxylation of the Pro^{402} and Pro^{564} in the N-terminal transactivation domain (NAD) leads to binding of the Von Hippel–Lindau (VHL) protein, which is a component in the recognition of ubiquitin (Ub) ligand, thereby enhancing HIF-1α ubiquitination and proteasomal degradation under aerobic conditions. Hydroxylation of Asn^{803} in the C-terminal transactivation domain (CAD) blocks the binding of the co-activators p300 (EP300, E1A binding protein p300) and CBP (CREB-binding protein, CREBBP). The hydroxylation reactions are inhibited under hypoxic conditions, leading to an increase in the HIF-1 half-life and transcription activation.

The HIF-1β subunit is the product of the *ARNT* (aryl hydrocarbon receptor nuclear translocator) gene (Lando et al., 2002). HIF-1β is an oxygen-independent nuclear protein and can heterodimerize with HIF-1α or aryl hydrocarbon receptor (AhR). AhR is involved in induction of the enzymes responsible for metabolism of xenobiotics (Gu et al., 2001). While HIF-1β is the subunit common for several heterodimeric transcription factors and is constantly expressed in the tissues, HIF-1α is unique and definitive HIF-1 subunit and its expression level depends on the tissue oxygen saturation.

HIF-1 exists as several isoforms of α-subunits (HIF-1α, HIF-2α, and HIF-3α), displaying different biological properties. The oxygen-sensitive HIF-1α subunit is of the greatest interest (Fig. 2). While HIF-1α subunit is expressed in all mammalian tissues, the expression of HIF-2α is confined to several cell types. In addition, some key target genes are activated only according to the HIF-1α pathway (Prabhakar and Semenza, 2012). Presumably, the HIF-2α molecule emerged during vertebrate evolution (Epstein et al., 2001; Prabhakar and Semenza, 2012). In hypoxia in rats, the HIF-2α expression is induced in the brain, heart, intestine, kidney, liver, and pancreas cells (Wiesener et al., 2003).

The expression of the HIF-3α gene is induced by HIF-1 in hypoxia, suggesting a negative feedback for inhibiting the HIF-1 activity. HIF-3α may assist in the maintenance of corneal avascularization by blocking the HIF-1 dependent expression of angiogenic growth factors. In rats, this mechanism plays a negative role in the adaptation to hypoxia, since inhibition of HIF-3α expression leads to an increase in physical stamina (Drevytska et al., 2012; Prabhakar and Semenza, 2012; Fig. 2).

HIF-1α contains two transactivation (stimulating transcription) regions—amino-terminal N-TAD and carboxy-terminal C-TAD (Ruas et al., 2002). The C-TAD interacts with the coactivator proteins CBP (CREB) and p300 (Lando et al., 2002). CREB regulates transcription of the genes encoding *c-fos*, neurotrophin, tyrosine hydroxylase, and various neuropeptides (somatostatin, encephalin, corticoliberin, etc.). Along with HIF-1, the proteins CREB and p300 interact with other transcription factors and enhance upregulation of target genes. In addition, HIF-1α also carries an oxygen-dependent degradation domain,

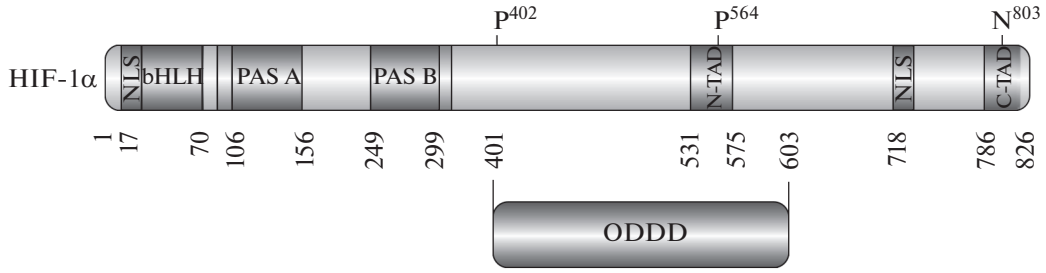

Fig. 2. Structure of HIF-1α (according to Schofield and Ratcliffe, 2004, with some modifications).

ODDD, making this subunit oxygen-sensitive and resistant to denaturation (Taie et al., 2009).

It was shown that HIF-1α is expressed in all human and mouse tissues and activates the compensatory physiological responses under hypoxic conditions, including erythropoiesis, glycolysis, and angiogenesis (Semenza, 2009). The HIF-1α activity is regulated by posttranslational modifications, namely, hydroxylation, acetylation, and phosphorylation (Lee et al., 2004). HIF-1α can be activated with the help of both the hypoxic and nonhypoxic stimuli. There are several stages of HIF activation by oxygen that should be considered, namely, HIF-1 regulated synthesis, processing, stabilization, nuclear localization, dimerization, and interaction with transcription coactivators (Schofield and Ratcliffe, 2004).

Thus, the HIF-1α isoform involved in the mechanism underlying protection of organs and tissues from hypoxia is of the highest significance in terms of molecular biology and medicine.

Under normal oxygen conditions, HIF-1α subunits are constantly present in the cell but have a short half-life of approximately 1–5 min. Their content is maintained at a low level as a result of triggering several biochemical reactions, first and foremost, prolyl and asparagine hydroxylation (Bhat et al., 2011; Fig. 3).

The hydroxylation at Pro^{402} and Pro^{564} is catalyzed by intracellular prolyl hydroxylase (PHD) family. Four PHDs have been identified but only three of them (PHD1, PHD2 and, PHD3) have been characterized and are regarded as HIF-modulating enzymes (Uden et al., 2008). These three enzymes have different patterns of maximum expression. During hydroxylation, HIF-1α and 2-oxoglutarate are stoichiometrically decarboxylated in the presence of oxygen and iron to give CO_2 and succinate. Prolyl hydroxylation makes the complex HIF-1α–OH recognizable to VHL protein, a component of ubiquitin protein ligase E3. VHL protein interacts with the protein elongin C and is subsequently recognized by the ubiquitin ligase complex. The attachment of ubiquitin marks the HIF-1α molecule for further degradation in a proteasome (Vakhitova et al., 2016; Semenza, 2009).

Hydroxylation of the Asn^{803} in the HIF-1 N-terminal transactivation domain blocks its interaction with the transcription coactivators p300 and CBP. This reaction is regulated by the asparagine hydroxylase FIH-1 (factor-inhibiting HIF-1).

Thus, the enzymes FIH-1 and PHD inactivate HIF-1α in the presence of oxygen by inhibiting HIF-1 dependent expression of target genes. With a decrease in oxygen concentration, the hydroxylation reactions are inhibited and the PHD and FIH activities also decrease, thereby decreasing the HIF-1α degradation and causing its accumulation in the cell, which is followed by its dimerization with HIF-1β (Huang and Bunn, 2003; Pugh and Ratcliffe, 2003). The resulting HIF-1 dimer is translocated to the nucleus to bind the consensus sequence 5'-(A/G)CGTG-3' of a hypoxia response element (HRE) in the promoter or enhancer of the hypoxia-sensitive target genes, thereby activating their transcription (Semenza, 2009). The HIF-1 transcription activity appears in full after the binding of the transcription coactivators CBP, p300, SRC-1, or TIF-2, which acetylate histones and remodel the chromatin structure in HRE. The coactivators interact with HIF-1α in the C-terminal transactivation domain, C-TAD, rich for redox-sensitive cysteine residues, which is controlled by the nuclear redox factor-1, Ref-1 (Carrero et al., 2000); next, a large number of hypoxia-dependent genes are activated (Fig. 3).

In total, over 90 putative HIF-1 target genes have been identified (Zheng et al., 2015), including the genes involved in angiogenesis due to the of vascular endothelial growth factor, in the upregulation of erythropoietin synthesis, and in the activation of the systems of glucose transport, cytoprotection by neurotrophic factors, and in normalization of the cell cycle and metabolism at the level of mitochondria, in particular, the activity of antioxidant enzymes, superoxide dismutase, and catalase (Huang and Bunn, 2003; Bhat et al., 2011). The totality of these effects allow implementation of the adaptive response to a hypoxic impact. In addition, HIF-1 influences the state of many neurotransmitter systems via activating γ-aminobutyrate type A receptor-binding protein, GABARBP (Park et al., 2014) and increasing the tyrosine

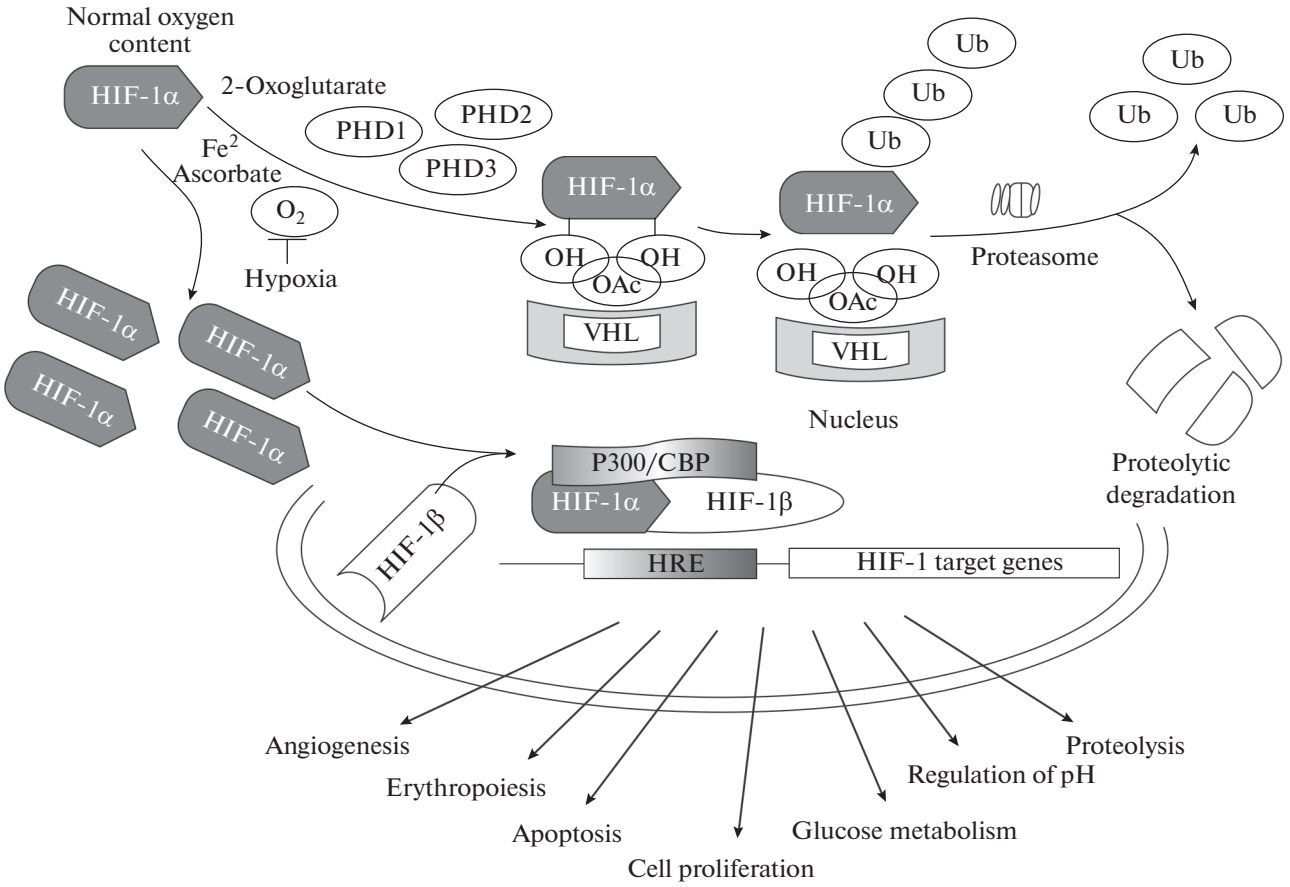

Fig. 3. HIF-1α reaction cascade under normal oxygen supply conditions and hypoxia (according to Petousi and Robbins, 2014, with some modifications).

hydroxylase activity (Schnell et al., 2003). The HIF-1 interaction with choline receptors has been described (Hirota et al., 2004). Presumably, 1 to 5% of all human genes are expressed in response to hypoxia by the HIF-dependent mechanism, as shown in Fig. 4 (Semenza, 2004).

Each of the target gene functions potentially enhances cell survival under hypoxia (Table 1).

Along with a hypoxic stimulation, there are oxygen-independent HIF-1 activation pathways.

HIF-1 is activated by growth factors, transcription factors, and oncogenes. They stimulate cell proliferation and survival as well as influence the interrelation of tissue growth processes and their supply with oxygen. The phosphorylation cascades (phosphatodylinositol 3-kinase, PI3K, and mitogen-activated protein kinase, MAPK, metabolic pathways) are activated by TGF, a growth factor, and activate the HIF-1 response to hypoxia with the help of posttranslational and translational control (Nangaku and Fujita, 2008). The PI3K signaling pathway is triggered by the tyrosine kinase receptor and induces the expression of HIF-1α subunit.

The MAPK pathway upregulates HIF-1 transcription activity without any effect on the HIF-1α protein expression, presumably by decreasing the HIF-1α binding with FIH-1 (Gunaratnam and Bonventre, 2009). The HSP90 chaperone influences de novo HIF-1α synthesis and induces its structural alterations necessary for dimerization with ARNT (Semenza, 2009). Desferrioxamine, an iron chelator, or cobalt chloride, which inhibits prolyl hydroxylase, can increase the HIF-1α level in the brain (Peyssonnaux et al., 2005). Nitric oxide and many reactive oxygen species also increase the HIF-1α content in tissues (Kimura et al., 2002; Bell et al., 2007).

After a trauma, HIF-1α is cleaved by PHD. It was shown that PHD regulation of HIF-1α inhibition enhances the restoration of injured tissues in mammals, leading to wound healing and scarring (Zhang et al., 2015). HIF-1α expression increases in rat skin fibroblasts in immobilization stress. Note that this is accompanied by upregulation of VEGF and glucose transporter-1 syntheses (Goto et al., 2017). The HIF-1α expression activates the synthesis of angiotensin-2 and endothelin-1, which enhance te development of lung hypertension (Semenza, 2009). It was shown that

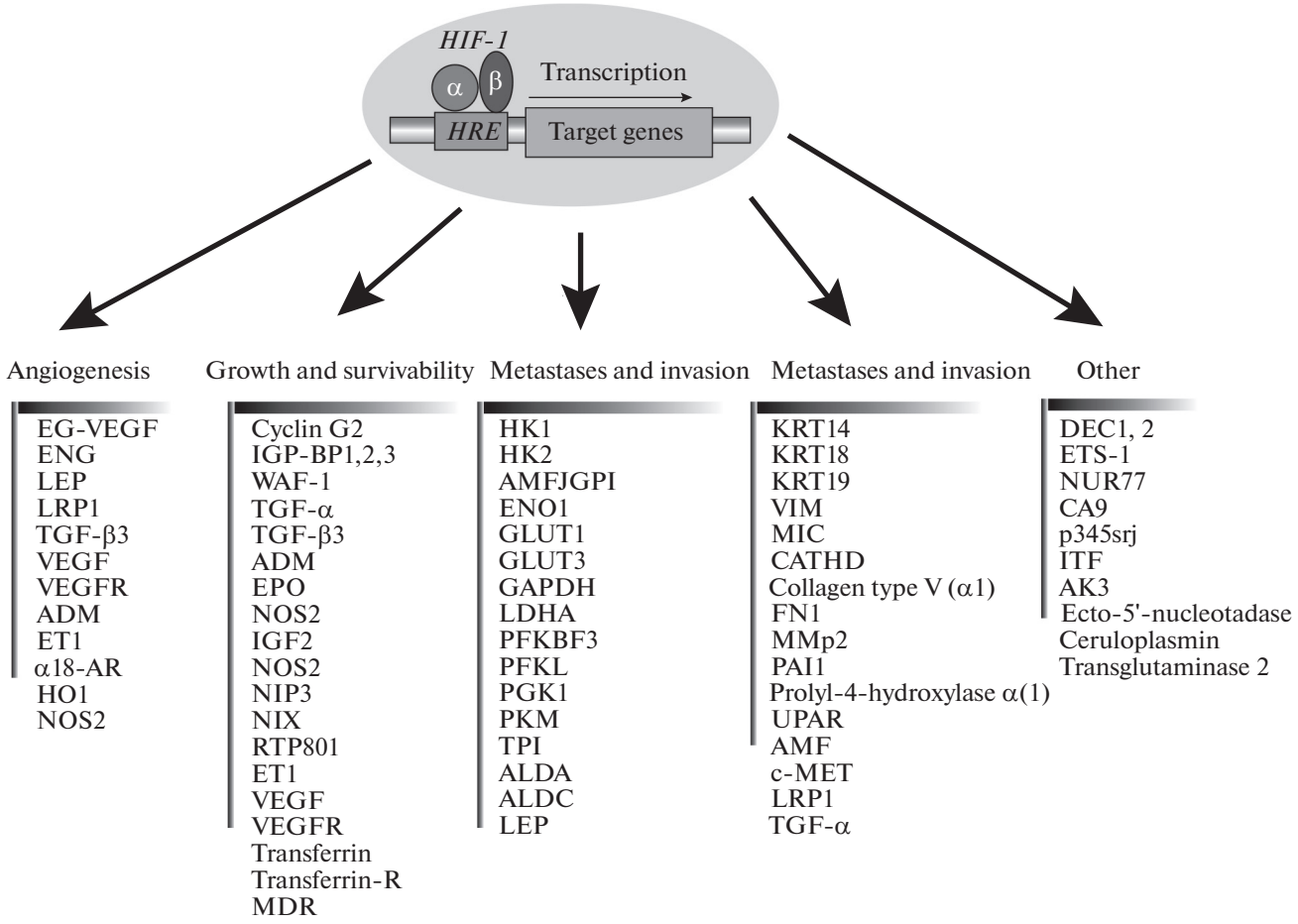

Fig. 4. HIF-1 target genes (according to Hong et al., 2004, with some modifications).

HIF-1 is involved in many pathophysiological processes and has both protective and injuring effects.

HIF-1 AND IMMUNOPATHOLOGY

HIF-1α expression in immune cells may be induced not only by hypoxia but also by other pathological states, such as inflammation and infectious diseases (Jiang et al., 2010; Goggins et al., 2013). HIF-1α expression is upregulated in the glomerular and tubulointerstitial tissues in lupus nephritis. HIF-1α can promote mesangial cell proliferation (Deng et al., 2014) and is shown to mediate the prostate hyperplasia during inflammation (Kim H.J. et al., 2013). The

Table 1. Classification of HIF-1 regulated genes

Process	Product of HIF-1 regulated gene
Angiogenesis	VEGF, vascular endothelial growth factor, and its receptor, VEGFR1; TGF, transforming growth factor; and plasminogen activator inhibitor
Vasomotor control	Endothelin-1, NO synthase-2, heme oxygenase-1, α1B-adrenoreceptor, and adrenomedullin
Erythropoiesis	Erythropoietin, transferrin, ceruloplasmin, and transferrin receptor
Energy metabolism	Lactate dehydrogenase A, glyceraldehyde-3-phosphate dehydrogenase, hexokinases-1 and -2, aldolases A and C, phosphofructokinase L, phosphoglycerate kinase-1, pyruvate kinase, enolase, and glucose transporters 1 and 2
Regulators of cell proliferation, differentiation, and apoptosis	p21; Bcl-2/EIB; NIP3-like protein X; IGF, insulin-like growth factor; and IGF-binding proteins 1, 2, and 3
Other	Carbonic anhydrase 9, tyrosine hydroxylase, collagen prolyl hydroxylase, p35, and adenylate kinase 3

HIF-1α expression increases in the synovial fluid in rheumatoid arthritis (Brouwer et al., 2009). HIF-1α also plays an important role in fibrosis and inflammation in adipose tissue (Kim et al., 2014) and skin (Kim et al., 2011), wound healing (Zampell et al., 2012), progression of reflux esophagitis (Pawlik et al., 2014), systemic lupus erythematosus (Feng et al., 2014), and inflammation of the lower respiratory tract. HIF-1α is involved in arsenite-induced inflammation of bronchial epithelial cells (Xu et al., 2013) and plays an important role in protection against pulmonary *Aspergillus fumigates* infection (Shepardson et al., 2014). HIF expression changes during allergic and eosinophilic inflammations of the lower airways (Crotty Alexander et al., 2013; Lee et al., 2014). In addition, HIF-1α also plays an important role in the pathogenesis of nasal inflammations, including polyp development and chronic sinusitis (Cheng et al., 2016).

HIF transcription factors are key elements in the control of immune cell metabolism and functions, and they as play an important role in innate and adaptive immunities (Palazon et al., 2014). HIF activates the functions of T cells, dendritic cells, macrophages, neutrophils, and epithelial cells (Scholz and Taylor, 2013; Guan et al., 2017).

TNF-α activates HIF-1 via several pathways, including the production of reactive oxygen species and nitric oxide and activation of the transcription factor NF-κB (Brüne and Zhou, 2007; Remels et al., 2015). IL-1β upregulates HIF-1α synthesis at the level of translation. During inflammation, bacterial cell components may stimulate the HIF-1 protein accumulation and activation via increasing the level of the corresponding mRNA (Frede et al., 2006; Jantsch et al., 2008). This mechanism is mainly induced by NF-κB, which is a major transcription regulator in inflammation and is activated with the help of Toll-like receptor (Karin, 2006; Dehne and Brüne, 2009; Willam, 2014; Yang et al., 2014).

HIF regulates the activity of macrophages and dendritic cells (Imtiyaz and Simon, 2010). Macrophages coordinate inflammation and, together with dendritic cells, coordinate the innate and adaptive immune responses (Dehne and Brüne, 2009). It is known that hypoxic responses regulate the biological activity of macrophages. Moreover, HIF-1α is necessary for direct macrophage maturation. HIF-1α can also mediate the macrophage inflammatory responses and act as a transcription factor that regulates hypoxic gene expression in macrophages (Fang et al., 2009). Hypoxia and HIF-1α are also able to modulate the maturation, activation, and antigen-presenting functions of immune cells (Jantsch et al., 2008).

HIF can coordinate the functions of neutrophils, key mediators in the innate immune response (Campbell et al., 2014). HIF-1α and HIF-2α are necessary for the survival of neutrophils in hypoxia and inflammation. According to the model of lipopolysaccharide-mediated lung damage, the HIF-1α deficiency is associated with the apoptosis of neutrophils (Elks et al., 2011). HIF-1 plays an important role in a negative regulation of the T-cell function in vivo and in vitro (McNamee et al., 2013; He et al., 2015).

Studies of the mechanism underlying the leukocyte action in inflammatory processes demonstrate that HIF-1α regulates the transcription of cationic antimicrobial polypeptides, an increase in the synthesis of free radicals, and the induction of NO synthase (Remels et al., 2015). The substances that activate HIF-1α in vitro (mimosine, desferrioxamine, and cobalt chloride) are known to upregulate the production of nitric oxide and cationic antimicrobial polypeptides by increasing the synthesis of endogenous antibiotics (Yang et al., 2014).

HIF-1 AND CARCINOGENESIS

The metabolic profile of most tumor cells differs from the norm, including higher cytosol glycolysis, higher glucose absorption, and excess production of lactic acid. HIF-1α is responsible for an increased glycolytic activity in most cancer cells, which allows these cells to survive. Its activation is necessary for the cancer cells to display the Warburg effect, since this elevates the activities of the overwhelming majority of the enzymes involved in aerobic glycolysis even in the case of a normal oxygen supply. The HIF-1α inhibition has been repeatedly proposed as a therapeutic target against cancer, since its key role in the Warburg effect can provide the control of tumor growth (Sanchez-Sanchez et al., 2015).

Under different conditions, HIF-1α promotes formation or apoptosis of malignant tumors by influencing their growth via the regulation of angiogenesis and metabolism (Talks et al., 2000; Kung et al., 2004). HIF-1α and VEGF are regarded as the key markers in lung cancer. The levels of serum and pleural HIF-1α in lung cancer are considerably higher as compared with tuberculosis patients. HIF-1α expression in the pleural fluid allows for differential diagnosis of benign and malignant lung neoplasms (Shen et al., 2015; Shrestha et al., 2017). HIF-1α overexpression is associated to a considerable degree with tumor progression and metastases through its involvement in the initiation of angiogenesis and VEGF expression (Bos et al., 2003). Hypoxia enhances the apoptosis of normal and tumor cells (Semenza, 2003; Vaupel and Mayer, 2007). It was shown that chetomin, a HIF-1α inhibitor, efficiently inhibits the growth of malignant peripheral nerve sheath tumor cells (Fukushima et al., 2017).

Increased HIF-1 expression was observed in the majority of the examined tumors, including colon cancer, breast carcinoma, pancreatic carcinoma, renal carcinoma, prostatic cancer, ovarian carcinoma, brain cancer, and bladder cancer (Talks et al., 2000; Kim, K.J. et al., 2013). An increase in the HIF-1 level in the

tumors, such as cervical cancer, non-small-cell lung cancer, breast cancer (both LV positive and negative), oligodendroglioma, and oropharyngeal, ovarian, endometrial, esophageal, head and neck, and stomach cancers, is associated with an aggressive progression of the tumor; thus, HIF-1 is regarded as a prognostic marker of the tolerance of x-ray therapy and chemotherapy, as well as of increased mortality (Semenza, 2003; Bos et al., 2003).

In the development of hypoxia, the overexpression of p53, a tumor suppressor, may be associated with HIF-1α dependent pathway of apoptosis activation (Vaupel and Mayer, 2007). The research into epithelial ovarian carcinoma showed that HIF-1α and p53 correlate with low levels of tumor cell apoptosis and predict unfavorable outcome of the disease (Birner et al., 2001). In addition, photodynamic therapy was shown to be ineffective at the early stages of esophageal cancer with both HIF-1α overexpression and without BCL2 expression (Koukourakis et al., 2001).

Despite the many years of ongoing research to develop therapeutics intended for the destruction of hypoxia-induced tumor cells, the blockage of HIF-1α signaling pathways has not been confirmed as an effective means to slow the progression of tumor growth and angiogenesis (Liu, 2014).

HIF-1 AND NEUROPATHOLOGY

HIF-1α modulates hypoxic and ischemic injuries to the brain by elevating the level of neuroglobin (NGB), a neuroprotective agent. Both proteins can be used as prognostic markers of acute ischemic stroke (Xue et al., 2017).

A decrease in the oxygen and glucose supply to the brain in aging or hypoxia is a hypometabolic factor. Peptide Aβ42 is accumulated during Alzheimer's disease (AD) in the hypometabolic brain regions. The amyloid peptide Aβ42 and hypoxia can induce inflammation, oxidative stress, and neuron death. HIF-1α is one of the transcription factors involved in the compensatory mechanisms for the maintenance of neuron survivability. Maintenance of the HIF-1α level by PHD inhibition decreased the injury of brain neurons during hypoxia and slowed AD progression (Liu et al., 2017; Ashok et al., 2017). It was shown that iron chelators and heavy metals (cobalt and nickel) enhance the maintenance of HIF-1α expression in nerve cells. According to other data, a decrease in HIF-1α expression and, as a consequence, a decrease in the rate of glycolysis, leads to the activation of astrocytes and development of neurodegenerative diseases (Schubert et al., 2009; Ashok et al., 2017).

HIF-1α was shown to have an antiapoptotic effect on hippocampal neurons, both in vitro and in vivo. It was demonstrated that HIF-1 is a protective agent during hypoxic–ischemic brain injury (Minhas et al., 2017; Ashok et al., 2017). A decrease in the HIF-1 level in the brain of AD patients is associated with impaired regulation of the GLUT-1 and GLUT-3 glucose transporters. A decline in the glucose metabolism leads to a decrease in the level of O-linked N-acetylglucosamine (O-GlcNAc) and further hyperphosphorylation of τ-protein and decrease in its activity, which, in turn, induces the formation of neurofibrillary tangles and neuron degeneration in AD patients (Liu et al., 2009; Ashok et al., 2017).

HIF-1α coordinates the cell response to hypoxia; its level is elevated in the microcirculatory portion of the bloodstream of AD patients (Yin et al., 2010; Grammas et al., 2011). In addition, the brain microvessels of AD patients contain numerous inflammatory factors that are involved in vessel activation and angiogenesis, including TNF-α, IL-1β, IL-6, IL-8, VEGF, and angiopoietin-2. HIF-1α regulates not only angiogenesis but also the transcription of the genes encoding proinflammatory cytokines (Imtiyaz and Simon, 2010; Grammas et al., 2011). These data suggest that the hypoxia-induced increase in HIF-1α and angiogenic/inflammatory proteins is a specific feature of the microcirculation of AD patients.

The putative role of HIF-1α as a neuroprotector during AD is currently under discussion (Kliushnik et al., 2017).

HIF-1 AND DIABETES MELLITUS

It was shown that HIF-1α can be a predictor of diabetes mellitus at a rate of 70%. Defects in hypoxia-mediated neovascularization in the myocardium, skeletal muscles, nerves, and skin are characteristic of diabetes mellitus (Martin et al., 2003). An inadequate formation of the compensatory collateral vessels in response to ischemia increases the risk for cardiovascular morbidity and mortality in diabetes mellitus patients (Thangarajah et al., 2010). Such diabetic microvascular defects may result from an insufficient production of angiogenic cytokines and VEGF (Lerman et al., 2003; Thangarajah et al., 2010). Many researchers believe that a decrease in the hypoxia-induced VEGF expression in diabetes mellitus patients results from disturbed HIF-1α transactivation (Semenza, 2003; Thangarajah et al., 2009, 2010). HIF-1α expression increases in patients at stages 3 and 4 as compared with stages 1 and 2 (Sayed and Mahmoud, 2016). This agrees with the data from Yan and Su (2014), who demonstrated that HIF-1α expression increases with the diabetes progression, since it is accompanied by hypoxia. In addition, a direct correlation is observed between the expression of HIF-1α and VEGF at different diabetes mellitus stages.

Although HIF-1 is a major mediator in the cell response to hypoxia, it was shown that the expression of HIF classical targets, such as VEGF, can also utilize some HIF-independent mechanisms. These observa-

tions explain why the growth in new blood vessels can be impaired within a single tissue (Arany et al., 2008).

It was demonstrated that the hypoxia-induced VEGF expression declines in the muscle fibroblast culture grown at a high glucose concentration, as well as in fibroblasts isolated from the type 2 diabetes mellitus patients. This is caused by a glucose-induced defect in the HIF-1 transactivation, which, in turn, results from a decrease in the HIF-1α binding with the p300 protein (Thangarajah et al., 2010). The interaction of HIF-1α with coactivator p300 is a key stage in the transcription of a HIF-mediated gene. A weakened association of HIF-1α and p300 at a high glucose concentration leads to a decrease in HIF-1 activity. The prevention of HIF-1α and p300 association may result from a p300 covalent modification caused by methylglyoxal, a reactive oxygen-containing dicarbonyl metabolite, produced via glycolysis. The level of methylglyoxal in the blood increases in oxidative stress because of an increase in the intracellular glucose concentration (Brownlee, 2001).

The use of deferoxamine (DFO) allows for a decrease in the degree of the glucose-mediated disturbance of HIF-1 transactivation via prevention of the formation of reactive oxygen species catalyzed by iron, which reduces the methylglyoxal formation. A local DFO administration also promotes diabetic wound healing in mice. The DFO ability to level the disturbances in HIF-1 transactivation correlates with an increase in VEGF expression and activation of vascular proliferation (Thangarajah et al., 2010).

Diabetic retinopathy is among the most severe diabetes mellitus complications, which is observed in 90% of diabetes patients. This pathology may be caused by the oxidative stress that develops during the progression of metabolic syndrome (Curtis et al., 2009; Özdemir et al., 2014). Diabetes mellitus causes an increased expression of the factors enhancing angiogenesis, such as VEGF, HIF-1α, and pigment epithelium-derived factor, PEDF (Özdemir et al., 2014).

The concept that HIF functional activity can be disturbed in diabetic states is similar to that of bodily aging. It was shown that aging is accompanied by hypoxia in various tissues and a decrease in VEGF production. A decline in angiogenesis during aging in animals is associated with a decrease in the VEGF expression and lower HIF-1α levels (Chang et al., 2007).

Intermittent normobaric hypoxia on the human glucose metabolism have been observed to have favorable effects (Tekin et al., 2010; Chen et al., 2016; Serebrovska et al., 2017). It was shown that prehypoxia enhances increases in glycolytic enzyme activity, the number of mitochondria in skeletal muscles, and insulin sensitivity (Mackenzie et al., 2012; Tian et al., 2016; Serebrovska et al., 2017). Normobaric hypoxia leads to a decrease in the blood glucose level in diabetes mellitus patients (Morishima et al., 2015), which is especially important for elderly patients with a high risk for diabetes development.

Moderate levels of intermittent hypoxia activate an intracellular signaling cascade, which comprises manifold receptors, mitochondrial respiration chain, and superfamilies of the inducible and activating transcription factors involved the initiation of hypoxic tolerance. One of the key regulators of the oxygen homeostasis in hypoxia is HIF, which initiates the transcriptional activation of numerous target genes for improving the oxygen delivery and utilization (Semenza, 2004; Serebrovska et al., 2017), and it has emerged that it is directly involved in normalization of glucose homeostasis (Han et al., 2014; Chen et al., 2016).

One of the HIF-1α target genes is the gene encoding glucose transporter 1 (GLUT-1), which is present in most human cells (Mueckler, 1994) and is the only glucose transporter in the brain (Maher et al., 1994). GLUT-1 enhances the glucose transport through the plasma membrane of mammalian cells (Wang et al., 2007). GLUT-1 is activated in hypoxia and its activity depends on the degree of hypoxic impact (He et al., 2014; Park et al., 2016).

Another HIF-1α target gene involved in the regulation of glucose homeostasis is insulin receptor, INSR (Serebrovska et al., 2017). An elevation in the INSR level can decrease insulin resistance. An increased INSR quantity is observed with hypoxic stress (Tian et al., 2015), while overexpression of this gene promotes obesity and the development of diabetes mellitus in mice (Sasaki et al., 2015).

CONCLUSIONS

Thus, transcription factor HIF-1 is involved in the regulation of over 90 genes involved in angiogenesis, vasomotor control, erythropoiesis, energy metabolism, and cell proliferation, differentiation, and apoptosis in the nervous, immune, and endocrine organs. All effects of HIF-1 are involve the adaptation to and maintenance of the functions of tissues and organs in hypoxia. Since disturbances of cardiovascular functions and the resulting hypoxia are characteristic of elder-age cohorts, HIF-1 molecule may be regarded as a marker of the compensatory mechanism for the maintenance of normal blood circulation and the functioning of the organs of neuroimmunoendocrine system during aging. In addition, HIF-1 in human fibroblasts activates the telomerase gene expression, which also indicates a high significance of this protein in the regulation of cell aging.

It was demonstrated that transcription factor HIF-1 is involved in the signaling cascades that act in different pathologies, including those characteristic of the elderly and senile cohorts. These diseases include various immune pathologies (fibrosis, inflammation of adipose tissue, systemic lupus erythematosus, inflammation of the respiratory tract, and autoimmune dis-

eases), gastroesophageal reflux disease, neuropathologies (Alzheimer's disease and brain ischemia of different geneses), cancer (cervical, lung, breast, ovarian, endometrial, esophageal, head and neck, gastric, and nervous tissue cancers), and diabetes mellitus.

Since HIF plays a key role in the pathogenesis of different socially significant diseases, this molecule is a potential therapeutic target for diagnosis and treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement on the welfare of animals. This article does not contain any studies involving animals performed by any of the authors.

REFERENCES

Arany, Z., Foo, S.Y., and Ma, Y., HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1, *Nature*, 2008, vol. 451, pp. 1008–1112.

Ashok, B.S., Ajith, T.A., and Sivanesan, S., Hypoxia-inducible factors as neuroprotective agent in Alzheimer's disease, *Clin. Exp. Pharmacol. Physiol.*, 2017, vol. 44, no. 3, pp. 327–334.

Bell, E.L., Klimova, T.A., Eisenbart, J., et al., Mitochondrial reactive oxygen species trigger hypoxia-inducible factor-dependent extension of the replicative life span during hypoxia, *Mol. Cell Biol.*, 2007, vol. 27, pp. 5737–5745.

Bhat, P.J., Darunte, L., Kareenhalli, V., et al., Can metabolic plasticity be a cause for cancer? Warburg–Waddington legacy revisited, *Clin. Epigenet.*, 2011, vol. 2, no. 2, pp. 113–122.

Birner, P., Schindl, M., Obermair, A., et al., Expression of hypoxiainducible factor 1alpha in epithelial ovarian tumors: its impact on prognosis and on response to chemotherapy, *Clin. Cancer Res.*, 2001, vol. 7, no. 6, pp. 1661–1668.

Bos, R., van der Groep, P., Greijer, A.E., et al., Levels of hypoxia-inducible factor-1alpha independently predict prognosis in patients with lymph node negative breast carcinoma, *Cancer*, 2003, vol. 97, no. 6, pp. 1573–1581.

Brouwer, E., Gouw, A.S., Posthumus, M.D., et al., Hypoxia inducible factor-1-alpha (HIF-1α) is related to both angiogenesis and inflammation in rheumatoid arthritis, *Clin. Exp. Rheumatol.*, 2009, vol. 27, pp. 945–951.

Brownlee, M., Biochemistry and molecular cell biology of diabetic complications, *Nature*, 2001, vol. 414, pp. 813–820.

Brune, B. and Zhou, J., Nitric oxide and superoxide: interference with hypoxic signaling, *Cardiovasc. Res.*, 2007, vol. 75, pp. 275–282.

Campbell, E.L., Bruyninckx, W.J., Kelly, C.J., et al., Transmigrating neutrophils shape the mucosal microenvironment through localized oxygen depletion to influence resolution of inflammation, *Immunity,* 2014, vol. 40, pp. 66–77.

Carrero, P., Okamoto, K., Coumailleau, P., et al., Redox-regulated recruitment of the transcriptional coactivators CREB-binding protein and SRC-1 to hypoxia-inducible factor 1α, *Mol. Cell. Biol.,* 2000, vol. 20, pp. 402–415.

Chang, E.I., Loh, S.A., Ceradini, D.J., et al., Age decreases endothelial progenitor cell recruitment through decreases in hypoxia-inducible factor 1α stabilization during ischemia, *Circulation*, 2007, vol. 116, pp. 2818–2829.

Chen, X., Zhao, T., Huang, X., et al., Intermittent hypoxia maintains glycemia in streptozotocin-induced diabetic rats, *Cell Stress Chaperones*, 2016, vol. 21, pp. 515–522.

Cheng, K.J., Bao, Y.Y., and Zhou, S.H., The role of hypoxia inducible factor in nasal inflammations, *Eur. Rev. Med. Pharmacol. Sci.*, 2016, vol. 20, no. 24, pp. 5067–5076.

Crotty Alexander, L.E., Akong-Moore, K., Feldstein, S., et al., Myeloid cell HIF-1α regulates asthma airway resistance and eosinophil function, *J. Mol. Med.*, 2013, vol. 91, pp. 637–644.

Curtis, T.M., Gardiner, T.A., and Stitt, A.W., Microvascular lesions of diabetic retinopathy: clues towards understanding pathogenesis, *Eye*, 2009, vol. 23, pp. 1496–1508.

Dehne, N. and Brüne, B., HIF-1 in the inflammatory microenvironment, *Exp. Cell Res.*, 2009, vol. 315, pp. 1791–1797.

Deng, W., Ren, Y., Feng, X., et al., Hypoxia inducible factor-1α promotes mesangial cell proliferation in lupus nephritis, *Am. J. Nephrol.*, 2014, vol. 40, pp. 507–515.

Drevytska, T., Gavenauskas, B., Drozdovska, S., et al., HIF-3α mRNA expression changes in different tissues and their role in adaptation to intermittent hypoxia and physical exercise, *Pathophysiology*, 2012, vol. 19, no. 3, pp. 205–214.

Elks, P.M., van Eeden, F.J., Dixon, G., et al., Activation of hypoxia-inducible factor-1α (HIF-1α) delays inflammation resolution by reducing neutrophil apoptosis and reverse migration in a zebrafish inflammation model, *Blood,* 2011, vol. 118, pp. 712–722.

Epstein, A.C., Gleadle, J.M., McNeill, L.A., et al., *C. elegans* EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation, *Cell*, 2001, vol. 107, pp. 43–54.

Fang, H.Y., Hughes, R., Murdoch, C., et al., Hypoxia-inducible factors 1 and 2 are important transcriptional effectors in primary macrophages experiencing hypoxia, *Blood,* 2009, vol. 114, pp. 844–859.

Feng, C.C., Ye, Q.L., Zhu, Y., et al., Lack of association between the polymorphisms of hypoxia-inducible factor α (HIF1α) gene and SLE susceptibility in a Chinese population, *Immunogenetics*, 2014, vol. 66, pp. 9–13.

Frede, S., Stockmann, C., Freitag, P., and Fandrey, J., Bacterial lipopolysaccharide induces HIF-1 activation in human monocytes via p44/42 MAPK and NF-κB, *Biochem. J.*, 2006, vol. 396, pp. 517–527.

Fukushima, S., Endo, M., Matsumoto, Y., et al., Hypoxia-inducible factor 1 alpha is a poor prognostic factor and potential therapeutic target in malignant peripheral nerve sheath tumor, *PLoS One*, 2017, vol. 12, no. 5, p. e0178064.

Goggins, B.J., Chaney, C., Radford-Smith, G.L., et al., Hypoxia and integrin-mediated epithelial restitution during mucosal inflammation, *Front. Immunol.,* 2013, vol. 4, pp. 272.

Goto, K., Sakamoto, J., Nakano, J., et al., Development and progression of immobilization-induced skin fibrosis through overexpression of transforming growth factor-.1 and hypoxic conditions in a rat knee joint contracture model, *Connect. Tissue Res.*, 2017, pp. 1–11.

Grammas, P., Tripathy, D., Sanchez, A., et al., Brain microvasculature and hypoxia-related proteins in Alzheimer's disease, *Int. J. Clin. Exp. Pathol.*, 2011, vol. 4, no. 6, pp. 616–627.

Gu, Z., Jiang, Q., and Zhang, G., Extracellular signal-regulated kinase and c-Jun N terminal protein kinase in ischemic tolerance, *Neuroreport*, 2001, vol. 12, pp. 3487–3491.

Guan, F., Lu, X.J., Li, C-H., and Chen, J., Molecular characterization of mudskipper (*Boleophthalmus pectinirostris*) hypoxia-inducible factor-1α (HIF-1α) and analysis of its function in monocytes/macrophages, *PLoS One*, 2017, vol. 12, p. 5.

Gunaratnam, L. and Bonventre, J.V., HIF in kidney disease and development, *J. Am. Soc. Nephrol.*, 2009, vol. 9, no. 20, pp. 1877–1887.

Han, X., Sun, S., Zhao, M., et al., Celastrol stimulates hypoxia-inducible factor-1 activity in tumor cells by initiating the ROS/Akt/p70S6K signaling pathway and enhancing hypoxiainducible factor-1alpha protein synthesis, *PLoS One*, 2014, vol. 9, pp. 112–170.

He, L.Y., Li, L., Guo, M.L., et al., Relationship between $CD4^+CD25^+$ Treg and expression of HIF-1α and Ki-67 in NSCLC patients, *Eur. Rev. Med. Pharmacol. Sci.*, 2015, vol. 19, pp. 1351–1355.

He, Q., Yang, Q.C., Zhou, Q., et al., Effects of varying degrees of intermittent hypoxia on proinflammatory cytokines and adipokines in rats and 3T3-L1 adipocytes, *PLoS One*, 2014, vol. 9, pp. 86–96.

Hirota, K., Ryo Fukuda, R., Takabuchi, S., et al., Molecular mechanism underlying the action of substituted Pro-Gly dipeptide Noopept, *J. Biol. Chem.*, 2004, vol. 279, no. 40, pp. 41521–41528.

Hong, S., Lee, H., and Kim, K.-W., HIF-1α: a valid therapeutic target for tumor therapy, *Cancer Res. Treat.*, 2004, vol. 36, no. 6, pp. 343–353.

Huang, L.E. and Bunn, H.F., Hypoxia-inducible factor and its biomedical relevance, *J. Biol. Chem.*, 2003, vol. 278, pp. 19575–19578.

Imtiyaz, H.Z. and Simon, M.C., Hypoxia-inducible factors as essential regulators of inflammation, *Curr. Top. Microbiol. Immunol.*, 2010, vol. 345, pp. 105–120.

Jantsch, J., Chakravortty, D., Turza, N., et al., Hypoxia and hypoxia-inducible factor-1α modulate lipopolysaccharide-induced dendritic cell activation and function, *J. Immunol.,* 2008, vol. 180, pp. 4697–4705.

Jiang, H., Zhu, Y.S., Xu, H., et al., Inflammatory stimulation and hypoxia cooperatively activate HIF-1α in bronchial epithelial cells: involvement of PI3K and NF-κB, *Am. J. Physiol. Lung Cell Mol. Physiol.*, 2010, vol. 298, pp. 660–669.

Karin, M., Nuclear factor–κB in cancer development and progression, *Nature*, 2006, vol. 441, pp. 431–436.

Kim, H.J., Park, J.W., Cho, Y.S., et al., Pathogenic role of HIF-1α in prostate hyperplasia in the presence of chronic inflammation, *Biochim. Biophys. Acta*, 2013, vol. 1832, pp. 183–194.

Kim, K.J., Choi, J.S., Kang, I., et al., Melatonin suppresses tumor progression by reducing angiogenesis stimulated by HIF-1 in a mouse tumor model, *J. Pineal Res.,* 2013, vol. 54, no. 3, pp. 264–270.

Kim, M., Neinast, M.D., Frank, A.P., et al., ERα upregulates Phd3 to ameliorate HIF-1 induced fibrosis and inflammation in adipose tissue, *Mol. Metab.*, 2014, vol. 3, pp. 642–651.

Kim, Y., Kim, B.H., Lee, H., et al., Regulation of skin inflammation and angiogenesis by EC-SOD via HIF-1α and NF-κB pathways, *Free Radical Biol. Med.*, 2011, vol. 51, pp. 1985–1995.

Kimura, M., Suzuki, H., and Ishihama, A., Formation of a carboxyterminal domain phosphatase (Fcp1)/TFIIF/RNA polymerase II (pol II) complex in *Schizosaccharomyces pombe* involves direct interaction between Fcp1 and the Rpb4 subunit of pol II, *Mol. Cell Biol.*, 2002, vol. 22, no. 5, pp. 1577–1588.

Klyushnik, T.P., Androsova, L.V., Mikhailova, N.M., et al., Systemic inflammatory markers in age-associated cognitive impairment and Alzheimer's disease, *Zh. Nevropatol. Psikhiatr. im. S.S. Korsakova*, 2017, vol. 117, no. 7, p. 74–79.

Koukourakis, M.I., Giatromanolaki, A., Skarlatos, J., et al., Hypoxia inducible factor (HIF-1α and HIF-2α) expression in early esophageal cancer and response to photodynamic therapy and radiotherapy, *Cancer Res.*, 2001, vol. 61, no. 5, pp. 1830–1832.

Kung, A.L., Zabludoff, S.D., France, D.S., et al., Small molecule blockade of transcriptional coactivation of the hypoxia-inducible factor pathway, *Cancer Cell,* 2004, vol. 6, no. 1, pp. 33–43.

Lando, D., Peet, D.J., Whelan, D.A., et al., Asparagine hydroxylation of the HIF transactivation domain a hypoxic switch, *Science*, 2002, vol. 295, pp. 858–861.

Lee, J.W., Bae, S.H., Jeong, J.W., et al., Hypoxia-inducible factor (HIF-1)α: its protein stability and biological functions, *Exp. Mol. Med.*, 2004, vol. 36, no. 1, pp. 1–12.

Lee, S.H., Kim, C.H., Yang, K.S., et al., Increased expression of vascular endothelial growth factor and hypoxia inducible factor-1α in lung tissue of patients with chronic bronchitis, *Clin. Biochem.*, 2014, vol. 47, pp. 552–559.

Lerman, O.Z., Galiano, R.D., Armour, M., et al., Cellular dysfunction in the diabetic fibroblast: impairment in migration, vascular endothelial growth factor production, and response to hypoxia, *Am. J. Pathol.*, 2003, vol. 162, pp. 303–312.

Liu, X., Q6, a novel hypoxia-targeted drug, regulates hypoxiainducible factor signaling via an autophagy-dependent mechanism in hepatocellular carcinoma, *Autophagy,* 2014, vol. 10, pp. 111–122.

Liu, F., Shi, J., and Tanimukai, H., Reduced O-GlcNAcylation links lower brain glucose metabolism and tau pathology in Alzheimer's disease, *Brain*, 2009, vol. 132, pp. 1820–1832.

Liu, Y., Xu Y., Zhang, L., et al., Down-regulated drebrin aggravates cognitive impairments in a mouse model of

Alzheimer's disease, *Int. J. Mol. Sci.*, 2017, vol. 18, no. 4, pp. 800.

Mackenzie, R., Maxwell, N., Castle, P., et al., Intermittent exercise with and without hypoxia improves insulin sensitivity in individuals with type 2 diabetes, *J. Clin. Endocrinol. Metab.*, 2012, vol. 97, pp. 546–555.

Maher, F., Vannucci, S.J., and Simpson, I.A., Glucose transporter proteins in brain, *FASEB J.*, 1994, vol. 8, pp. 1003–1011.

Martin, A., Komada, M.R., and Sane, D.C., Abnormal angiogenesis in diabetes mellitus, *Med. Res. Rev.,* 2003, vol. 23, pp. 117–145.

McNamee, E.N., Korns, J.D., Homann, D., and Clambey, E.T., Hypoxia and hypoxia-inducible factors as regulators of T cell development, differentiation, and function, *Immunol. Res.*, 2013, vol. 55, pp. 58–70.

Minhas, G., Mathur, D., Ragavendrasamy, B., et al., Hypoxia in CNS pathologies: emerging role of miRNA-based neurotherapeutics and yoga based alternative therapies, *Front. Neurosci.,* 2017, vol. 11, pp. 273.

Morishima, T., Hasegawa, Y., Sasaki, H., et al., Effects of different periods of hypoxic training on glucose metabolism and insulin sensitivity, *Clin. Physiol. Funct. Imaging*, 2015, vol. 35, pp. 104–109.

Mueckler, M., Facilitative glucose transporters, *Eur. J. Biochem.,* 1994, vol. 219, pp. 713–725.

Nangaku, M. and Fujita, T., Activation of the renin-angiotensin system and chronic hypoxia of the kidney, *Hypertens. Res.*, 2008, vol. 31, no. 2, pp. 175–184.

Nishi, H., Nakada, T., Kyo, S., et al., Hypoxia-inducible factor 1 mediates upregulation of telomerase (hTERT), *Mol. Cell Biol.*, 2004, vol. 24, pp. 6076–6083.

Özdemir, G., Ergün, Y., Bakariş, S., et al., Melatonin prevents retinal oxidative stress and vascular changes in diabetic rats, *Eye*, 2014, vol. 28, no. 8, pp. 1020–1027.

Palazon, A., Goldrath, A.W., Nizet, V., and Johnson, R.S., HIF transcription factors, inflammation, and immunity, *Immunity*, 2014, vol. 41, pp. 518–528.

Park, H.S., Kim, J.H., Sun, B.K., et al., Hypoxia induces glucose uptake and metabolism of adipose-derived stem cells, *Mol. Med. Rep.*, 2016, vol. 14, pp. 4706–4714.

Park, S.H., Kim, B.R., Lee, J.H., et al., GABARBP downregulates HIF-1α expression through the VEGFR-2 and PI3K/mTOR/4E-BP1 pathways, *Cell Signal.*, 2014, vol. 26, no. 7, pp. 1506–1513.

Pawlik, M.W., Kwiecien, S., Pajdo, R., et al., Esophagoprotective activity of angiotensin-(1–7) in experimental model of acute reflux esophagitis: evidence for the role of nitric oxide, sensory nerves, hypoxia-inducible factor-1alpha and proinflammatory cytokines, *J. Physiol. Pharmacol.*, 2014, vol. 65, pp. 809–822.

Petousi, N. and Robbins, P.A., Human adaptation to the hypoxia of high altitude: the Tibetan paradigm from the pregenomic to the postgenomic era, *J. Appl. Physiol.*, 2014, vol. 116, no. 7, pp. 875–884.

Peyssonnaux, C., Datta, V., Cramer, T., et al., HIF-1α expression regulates the bactericidal capacity of phagocytes, *J. Clin. Invest.,* 2005, vol. 115, pp. 1806–1815.

Prabhakar, N.R. and Semenza, G.L., Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2, *Physiol. Rev. Publ.*, 2012, vol. 92, no. 3, pp. 967–1003.

Pugh, C.W. and Ratcliffe, P.J., Regulation of angiogenesis by hypoxia: role of the HIF system, *Nat. Med.*, 2003, vol. 9, no. 6, pp. 677–684.

Remels, A.H., Gosker, H.R., Verhees, K.J., et al., TNF-α-induced NF-κB activation stimulates skeletal muscle glycolytic metabolism through activation of HIF-1α, *Endocrinology,* 2015, vol. 156, pp. 1770–1781.

Ruas, J.L., Poellinger, L., and Pereira, T., Functional analysis of hypoxia-inducible factor-1-mediated transactivation—identification of amino acid residues critical for transcriptional activation and/or interaction with CBP, *J. Biol. Chem.,* 2002, vol. 277, pp. 38723–38730.

Sanchez-Sanchez, A.M., Antolin, I., and Puente-Moncada, N., Melatonin cytotoxicity is associated to Warburg effect inhibition in Ewing sarcoma cells, *PLoS One*, 2015, vol. 10, p. 8.

Sasaki, T., Kuroko, M., Sekine, S., et al., Overexpression of insulin receptor partially improves obese and diabetic phenotypes in db/db mice, *Endocrinol. J.*, 2015, vol. 62, pp. 787–796.

Sayed, Kh.M. and Mahmoud, A.A., Heat shock protein-70 and hypoxia inducible factor-1α in type 2 diabetes mellitus patients complicated with retinopathy, *Acta Ophthalmol.*, 2016, vol. 94, no. 5, pp. 361–366.

Schnell, P.O., Ignacak, M.L., Bauer, A.L., et al., Regulation of tyrosine hydroxylase promoter activity by the von Hippel–Lindau tumor suppressor protein and hypoxia-inducible transcription factors, *J. Neurochem.*, 2003, vol. 85, no. 2, pp. 483–491.

Schofield, C.J. and Ratcliffe, P.J., Oxygen sensing by HIF hydroxylases, *Nat. Rev. Mol. Cell Biol.,* 2004, vol. 5, no. 5, pp. 343–354.

Scholz, C.C. and Taylor, C.T., Targeting the HIF pathway in inflammation and immunity, *Curr. Opin. Pharmacol.*, 2013, vol. 13, pp. 646–653.

Schubert, D., Soucek, T., and Blouw, B., The induction of HIF-1 reduces astrocyte activation by amyloid beta peptide, *Eur. J. Neurosci.*, 2009, vol. 29, pp. 1323–1334.

Semenza, G.L., Targeting HIF-1 for cancer therapy, *Nat. Rev. Cancer*, 2003, vol. 3, no. 10, pp. 721–732.

Semenza, G.L., Hydroxylation of HIF-1: oxygen sensing at the molecular level, *Physiology* (Bethesda), 2004, vol. 19, pp. 176–182.

Semenza, G.L., Involvement of oxygen-sensing pathways in physiologic and pathologic erythropoiesis, *Blood,* 2009, vol. 114, no. 10, pp. 2015–2019.

Semenza, G.L. and Wang, G.L., A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site 96 required for transcriptional activation, *Mol. Cell Biol.*, 1992, vol. 12, pp. 5447–5454.

Serebrovska, T.V., Portnychenko, A.G., Drevytska, T.I., et al., Intermittent hypoxia training in prediabetes patients: beneficial effects on glucose homeostasis, hypoxia tolerance and gene expression, *Exp. Biol. Med.*, 2017, vol. 242, no. 15, pp. 1542–1552.

Shen, H., Feng, G., Cui, J., et al., Clinical implications of serum hypoxia inducible factor-1α and vascular endo-

thelial growth factor in lung cancer, *Tumori J.*, 2015, vol. 101, no. 4, pp. 404–411.

Shepardson, K.M., Jhingran, A., Caffrey, A., et al., Myeloid derived hypoxia inducible factor 1-α is required for protection against pulmonary *Aspergillus fumigatus* infection, *PLoS Pathog.*, 2014, vol. 10, pp. 36–65.

Shrestha, P., Davis, D.A., Veeranna, R.P., et al., Hypoxia-inducible factor-1α as a therapeutic target for primary effusion lymphoma, *PLoS Pathog.*, 2017, vol. 13, no. 9, pp. 89–96.

Taie, S., Ono, J., Iwanaga, Y., et al., Hypoxiainducible factor-1α has a key role in hypoxic preconditioning, *J. Clin. Neurosci.*, 2009, vol. 16, no. 8, pp. 1056–1060.

Talks, K.L., Turley, H., Gatter, K.C., et al., The expression and distribution of the hypoxia-inducible factors HIF-1α and HIF-2α in normal human tissues, cancers, and tumor-associated macrophages, *Am. J. Pathol.,* 2000, vol. 157, no. 2, pp. 411–421.

Tekin, D., Dursun, A.D., and Xi, L., Hypoxia inducible factor 1 (HIF-1) and cardioprotection, *Acta Pharmacol. Sin.*, 2010, vol. 31, pp. 1085–1094.

Thangarajah, H., Yao, D., Chang, E.I., et al., The molecular basis for impaired hypoxia-induced VEGF expression in diabetic tissues, *Proc. Nat. Acad. Sci. U.S.A.*, 2009, vol. 106, pp. 13505–13510.

Thangarajah, H., Vial, I.N., Grogan, R.H., et al., HIF-1α dysfunction in diabetes, *Cell Cycle*, 2010, vol. 9, no. 1, pp. 75–79.

Tian, Y., Yao, J., Liu, S., et al., Identification and expression analysis of 26 oncogenes of the receptor tyrosine kinase family in channel catfish after bacterial infection and hypoxic stress, *Comp. Biochem. Physiol., Part D: Genomics Proteomics*, 2015, vol. 14, pp. 16–25.

Tian, Y.M., Liu, Y., Wang, S., et al., Anti-diabetes effect of chronic intermittent hypobaric hypoxia through improving liver insulin resistance in diabetic rats, *Life Sci.*, 2016, vol. 150, pp. 1–7.

Uden, P., Kenneth, N.S., and Rocha, S., Regulation of hypoxia-inducible factor-1α by NF-κB, *Biochem. J.*, 2008, vol. 412, no. 3, pp. 477–484.

Vakhitova, Yu.V., Sadovnikov, S.V., Borisevich, S.S., et al., Molecular mechanism underlying the action of substituted Pro-Gly dipeptide Noopept, *Acta Nat.*, 2016, vol. 8, no. 1 (28), pp. 82–89.

Vaupel, P. and Mayer, A., Hypoxia in cancer: significance and impact on clinical outcome, *Cancer Metastasis Rev.*, 2007, vol. 26, no. 2, pp. 225–239.

Wang, B., Wood, I.S., and Trayhurn, P., Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes, *Pflugers Arch.*, 2007, vol. 455, pp. 479–492.

Wenger, R.H., Cellular adaptation to hypoxia: O_2-sensing protein hydroxylases, hypoxia-inducible transcription factors, and O_2-regulated gene expression, *FASEB J.*, 2002, vol. 16, pp. 1151–1162.

Wiesener, M.S., Jurgensen, J.S., Rosenberger, C., et al., Widespread hypoxia-inducible expression of HIF-2α in distinct cell populations of different organs, *FASEB J.*, 2003, vol. 17, pp. 271–273.

Willam, C., HIF meets NF-κB signaling, *Kidney Int.*, 2014, vol. 85, pp. 232–234.

Xu, Y., Zhao, Y., Xu, W., et al., Involvement of HIF-2α-mediated inflammation in arsenite-induced transformation of human bronchial epithelial cells, *Toxicol. Appl. Pharmacol.*, 2013, vol. 272, pp. 542–550.

Xue, L., Chen, H., Lu, K., et al., Clinical significance of changes in serum neuroglobin and HIF-1α concentrations during the early-phase of acute ischemic stroke, *J. Neurol. Sci.*, 2017, vol. 375, pp. 52–57.

Yan, H.T. and Su, G.F., Expression and significance of HIF-1α and VEGF in rats with diabetic retinopathy, *Asian Pac. J. Trop. Med.*, 2014, vol. 7, pp. 237–240.

Yang, J., Zhang, L., Erbel, P.J., et al., Functions of the Per/ARNT/Sim domains of the hypoxia-inducible factor, *J. Biol. Chem.*, 2005, vol. 43, pp. 36047–36054.

Yang, S., Yu, M., Sun, L., et al., Interferon-γ-induced intestinal epithelial barrier dysfunction by NF-κB/HIF-1α pathway, *J. Interferon Cytokine Res.*, 2014, vol. 34, pp. 195–203.

Yin, X., Wright, J., Wall, T., and Grammas, P., Brain endothelial cells synthesize neurotoxic thrombin in Alzheimer's disease, *Am. J. Pathol.*, 2010, vol. 176, pp. 1600–1606.

Zampell, J.C., Yan, A., Avraham, T., et al., HIF-1α coordinates lymphangiogenesis during wound healing and in response to inflammation, *FASEB J.*, 2012, vol. 26, pp. 1027–1039.

Zhang, Y., Shao, Z., Zhai, Z., et al., The HIF-1 hypoxia-inducible factor modulates lifespan in *C. elegans, PLoS One*, 2009, vol. 4, no. 7, pp. 563–569.

Zhang, Y., Strehin, I., Bedelbaeva, K., et al., Drug-induced regeneration in adult mice, *Sci. Transl. Med.*, 2015, vol. 7, p. 290.

Zheng, H., Fridkin, M., and Youdim, M., New approaches to treating Alzheimer's disease, *Perspect. Med. Chem.*, 2015, vol. 7, pp. 1–8.

Ziello, J.E., Jovin, I.S., and Huang, Y., Hypoxia-inducible factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia, *Yale J. Biol. Med.*, 2007, vol. 80, no. 2, pp. 51–60.

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