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Роль фактора, индуцируемого гипоксией, 1α при адаптации к гипоксии в патогенезе новой коронавирусной болезни 2019

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АННОТАЦИЯ

Введение. Новый коронавирус (англ.: *severe acute respiratory syndrome-related coronavirus 2*, SARS-CoV-2) появился в декабре 2019 г. и быстро распространился по миру, вызвав пандемию респираторного заболевания. Этот высокопатогенный вирус способен поражать лёгочную ткань и нарушать газообмен, приводя к острому респираторному дистресс-синдрому и системной гипоксии. В условиях гипоксии происходит активация адаптационных механизмов, в т. ч. фактора, индуцируемого гипоксией 1α (англ.: *hypoxia-inducible factor*, HIF-1α). HIF-1α вовлечён в регуляцию таких ключевых процессов, как, например, пролиферацию клеток, их метаболизм и ангиогенез. Помимо этого, уровень экспрессии HIF-1α связан с интенсивностью ответа иммунной системы организма, в т. ч. врождённого звена, опосредующего воспалительную реакцию. Поэтому понимание особенностей механизмов, лежащих в основе патогенеза этого заболевания, имеет большое значение для эффективной терапии коронавирусной болезни 2019 (англ.: *COronaVIrus Disease 2019*, COVID-19).

Цель. Анализ актуальных данных о HIF-1α и его влиянии на патогенез и прогрессирование COVID-19.

Проведен анализ актуальных отечественных и зарубежных литературных источников по разделам: HIF-1α как ключевой фактор адаптации к гипоксии, мишени воздействия HIF-1α в аспекте патогенеза COVID-19, нарушение HIF-1α опосредованной адаптации к гипоксии как элемент патогенеза гиперактивации иммунных клеток.

Заключение. HIF-1α препятствует проникновения вируса SARS-CoV-2 в клетку и проявляет себя главным регулятором провоспалительной активности в месте воспаления в окружении гипоксии. В условиях нарушенной метаболической гибкости высокий уровень HIF-1α обуславливает избыточный воспалительный ответ со стороны клеток иммунной системы. Высокий уровень HIF-1α в клетках в очаге воспаления ассоциирован с повышением продукции факторов ангиогенеза, опосредующих сосудистую проницаемость и процесс капиллярной утечки. Это сопровождается повреждением тканей и органной недостаточностью. В то же время, HIF-1α может опосредовать противовоспалительный эффект благодаря активации аденозинового рецептор-зависимого пути, что рассматривается как возможная защита клеток и органов от повреждения гиперактивными иммунными клетками.

Ключевые слова: *COVID-19; гипоксия; HIF-1α; цитокиновый шторм; механизмы адаптации*

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Role of Hypoxia-Inducible Factor 1α in Adaptation to Hypoxia in the Pathogenesis of Novel Coronavirus Disease 2019

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ABSTRACT

INTRODUCTION: A novel coronavirus (*severe acute respiratory syndrome-related coronavirus 2* (SARS-CoV-2)) emerged in December 2019 and rapidly spread over the world having provoked a pandemic of respiratory disease. This highly pathogenic virus can attack the lung tissue and derange gas exchange leading to acute respiratory distress syndrome and systemic hypoxia. Hypoxic conditions trigger activation of adaptation mechanisms including *hypoxia-inducible factor-1α* (HIF-1α) which is involved in the regulation of the key processes, e. g, proliferation and metabolism of cells and angiogenesis. Besides, the level of HIF-1α expression is associated with the intensity of the immune response of an organism including that of the innate immunity mediating inflammatory reaction. Therefore, understanding the peculiarities of the mechanisms underlying the pathogenesis of this disease is of great importance for effective therapy of *coronavirus disease 2019* (COVID-19).

AIM: Analysis of the current data on HIF-1α and its effect on the pathogenesis and progression of COVID-19.

The analysis of the relevant domestic and international literature sources was performed in the following sections: HIF-1α as a key factor of adaptation to hypoxia, targets for HIF-1α in the aspect of the pathogenesis of COVID-19, disorders in HIF-1α-mediated adaptation to hypoxia as an element of the pathogenesis of hyperactivation of the immune cells.

CONCLUSION: HIF-1α prevents penetration of SARS-CoV-2 virus into a cell and primarily acts as the main regulator of the proinflammatory activity at the inflammation site surrounded by hypoxia. In the conditions of the deranged metabolic flexibility, a high level of HIF-1α evokes an excessive inflammatory response of the immune cells. A high HIF-1α level in cells of the inflammation focus is associated with enhanced production of the factors of angiogenesis mediating vascular permeability and capillary leakage process. This is accompanied by tissue damage and organ failure. At the same time, HIF-1α can mediate the anti-inflammatory effect through activation of adenosine receptor-dependent pathway, which is considered as a probable protection of cells and organs against damage by hyperactive immune cells.

Keywords: *COVID-19; hypoxia; HIF-1α; cytokine storm; adaptation mechanisms*

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LIST OF ABBREVIATIONS

ACE-2 — angiotensin-converting enzyme 2
ADAM — a disintegrin and metalloproteinase domain
ALV — artificial lung ventilation
ARDS — acute respiratory distress syndrome
ATP — adenosine triphosphoric acid
A2AR — adenosine A2A receptor
CBP — cyclic AMP response element binding protein
CCL — chemokine (C-C motif) ligand
COVID-19 — coronavirus disease 2019
FIH — factor inhibiting HIF
GLUT — glucose transporter
HIF — hypoxia-inducible factor
HK — hexokinase
HREs — hypoxia response elements
IL — interleukin
LDHA — lactate dehydrogenase A
mRNA — matrix ribonucleic acid
NDRG — N-myc downstream-regulated gene
NETosis — neutrophil extracellular traps
NF-kB — nuclear factor kappa-light-chain-enhancer of activated B cells
PDK — pyruvate dehydrogenase kinase
PHD — prolyl hydroxylase
REDD — regulated in development and DNA damage response
RNA — ribonucleic acid
ROS — reactive oxygen species
SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2
TAC — tricarbonic acid cycle
TMPRSS — transmembrane protease, serine
TNF — tumor necrosis factor
VEGF — vascular endothelial growth factor
VHLp — von Hippel-Lindau protein

INTRODUCTION

In December 2019, an outburst of a deadly disease caused by a new coronavirus 2 associated with severe acute respiratory syndrome (SARS-CoV-2) was recorded in Wuhan (province Hubei, China) [1]. Subsequently, the disease was named Coronavirus Disease 2019 (COVID-19). SARS-CoV-2 is a highly contagious (index 1.4–2.5 [2]) and highly pathogenic infectious agent spread through airborne droplets in direct contact with infected patients and is potentially transmitted through fecal-oral way as well [3]. Infection with SARS-CoV-2 causes acute respiratory disease, with the common symptoms as fever, cough, shortness of breath and increased fatigue. The disease is associated with the threatening complications such as pneumonitis, acute respiratory distress-syndrome (ARDS), respiratory failure, shock, multiorgan failure [4].

An important pathological feature characteristic of patients with moderate, severe and extremely severe form of COVID-19 infection is a progressing systemic hypoxia [3].

Hypoxia is a stimulus that launches adaptation mechanisms associated with changes in cell metabolism, organ perfusion, and erythropoiesis and iron metabolism [5]. Hypoxia-inducible transcription factor 1α (HIF-1α) is considered nowadays to be a sensor that perceives hypoxia at the cell level [6]. HIF-1α permits cells to survive in severe hypoxic conditions, however, in case of extremely severe hypoxia as observed in a severe course of COVID-19 infection, HIF-1α can convert from a factor of adaptation into a factor of maladaptation: it is established that its excessive accumulation in cells of the innate immune system slows down their natural clearance and mediates the uncontrolled synthesis of proinflammatory cytokines [3, 7].

The activity of HIF-1α is known to mediate the activation of proangiogenic and proinflammatory factors, which is associated with diffuse damage into the alveolar-capillary barrier characteristic of ARDS in COVID-19 infection [8].

ARDS is an acute diffuse inflammatory lesion of the lung parenchyma that develops as a non-specific reaction to various damaging factors leading to acute respiratory failure due to damage to the lung tissue and reduction in the mass of airy lung tissue [9].

A subgroup of patients with COVID-19 and ARDS infection is characterized by overfilling of the pulmonary arteries with venous blood, and by severe hypoxemia, significant hemocoagulation disorders and rapid development of shock [10]. This *atypical* form of ARDS is characterized by a significant pulmonary shunt and abnormal respiratory mechanics with the underlying hypoxic pulmonary vasoconstriction and hypercoagulation associated with local microvascular thrombosis in the pulmonary circulation and with the addition of microvascular lesions of the kidneys, brain and other vital organs [11].

Despite the steps undertaken to treat respiratory failure, more than 80% of patients with severe COVID-19 infection who received ventilation die by day 28 from the onset of the disease [12]. The high mortality rate of patients and the atypical course of ARDS in patients with COVID-19 infection provide the ground to suggest that COVID-19 infection creates *preconditions for*

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dysfunction of the body's adaptation mechanisms to hypoxic conditions [13].

The **aim** of this study to analyze the current data on the hypoxia-inducible factor 1α and its effect on the pathogenesis and progression of coronavirus disease 2019.

HIF-1α as Key Factor in Adaptation to Hypoxia

HIF-1α is a conservative heterodimeric transcription factor that allows the body to adapt to changes in the concentration and availability of oxygen in the blood [6]. The HIF-1 heterodimer comprises an oxygen-dependent HIF-1α subunit and a constitutively expressed HIF-1β subunit [14]. The HIF-1β subunit is continuously expressed in the cell, regardless of the oxygen level in the cell. The expression of HIF-1α gradually increases under hypoxic conditions. There exist 3 isoforms of HIF-α possessing specific properties: HIF-1α, HIF-2α and HIF-3α. Isoforms of HIF-α subunits regulate 5 groups of genes (Table. 1) [15, 16].

Таблица 1. Изоформы фактора, индуцируемого гипоксией, 1α [15, 16]

Isoform	Group of Genes
HIF-1α	Genes of glycolysis enzymes — phosphofructokinase, phosphoglycerate kinase and lactate dehydrogenase
HIF-2α	Genes of TGF-α and erythropoietin
HIF-3α	sqrdl, zp3v2 genes, whose products are involved in the regulation of metabolism and embryonic development
HIF-1α and HIF-2α	VEGF, IL-6 and GLUT1 genes
HIF-1α and HIF-3α	REDD1 gene which product is involved in the stimulation of autophagy in hypoxia

Notes: IL — interleukin, GLUT — glucose transporter (unidirectional glucose transporter protein), REDD — gene regulated during development and reaction to DNA damage, TGF — transforming growth factor, VEGF — vascular endothelial growth factor

The expression of α-subunits of the transcription factor enhances in response to both acute and chronic hypoxia [16]. HIF-1α is most active in conditions of acute, short-term (2–24 hours) and severe hypoxia or anoxia. HIF-2α isoform is responsible for adaptation to moderate chronic hypoxia [14]. HIF-3α is assumed to be a negative regulator of HIF-1α and HIF-2α activity due to competition for binding to HIF-1β subunits [15]. At the same time, the biological role of HIF-3α remains poorly understood and continues to be actively investigated. Thus, the ability of HIF-3α subunit to stabilize upon selective binding to oleoylethanolamide has recently been demonstrated, which, according to researchers, points to the function of HIF-3α as a sensor of endogenous lipids [17].

Under normoxic conditions, HIF-1α interacts with and binds to the von Hippel–Lindau (VHL) protein, which activates the ubiquitin ligase system and leads to proteasomal degradation of HIF-1α. Hydroxylation of prolin residues in HIF-1α is vital for VHL protein binding and depends on α-ketoglutarate-dependent dioxygenases, prolyl hydroxylases (PHD) and asparaginyl hydroxylase, a factor inhibiting HIF (FIH) [14]. Under hypoxic conditions, prolyl hydroxylases are inhibited, which leads to stabilization of HIF-1α and dimerization with HIF-1β. After dimerization, HIF moves to the nucleus to bind to hypoxia response elements (HREs) in the promoter region with the participation of co-activators of CREB-binding protein (cyclic AMP response element binding protein, CBP). At the same time, HIF activates genes that control cell oxygen homeostasis, including genes involved in oxygen consumption, erythrocyte production, angiogenesis, iron metabolism and mitochondrial metabolism [18]. It has been established that activation of these genes is associated with changes in the metabolism of a wide range of cells and their proliferation, vasomotor control and immune regulation [18, 19] (Figure 1).

Prolyl hydroxylation of HIF-1α is associated with the utilization of α-ketoglutarate (a NAD-dependent substrate of the tricarbonic acid cycle (TAC)), while another TAC substrate — succinate, is an allosteric inhibitor of this process [20]. In normoxia, succinate is converted to fumarate with the participation of succinate dehydrogenase, which is involved in both the TAC and the electron transfer chain in mitochondria. The loss of succinate dehydrogenase activity creates preconditions for the accumulation of succinate in cells. Therefore,

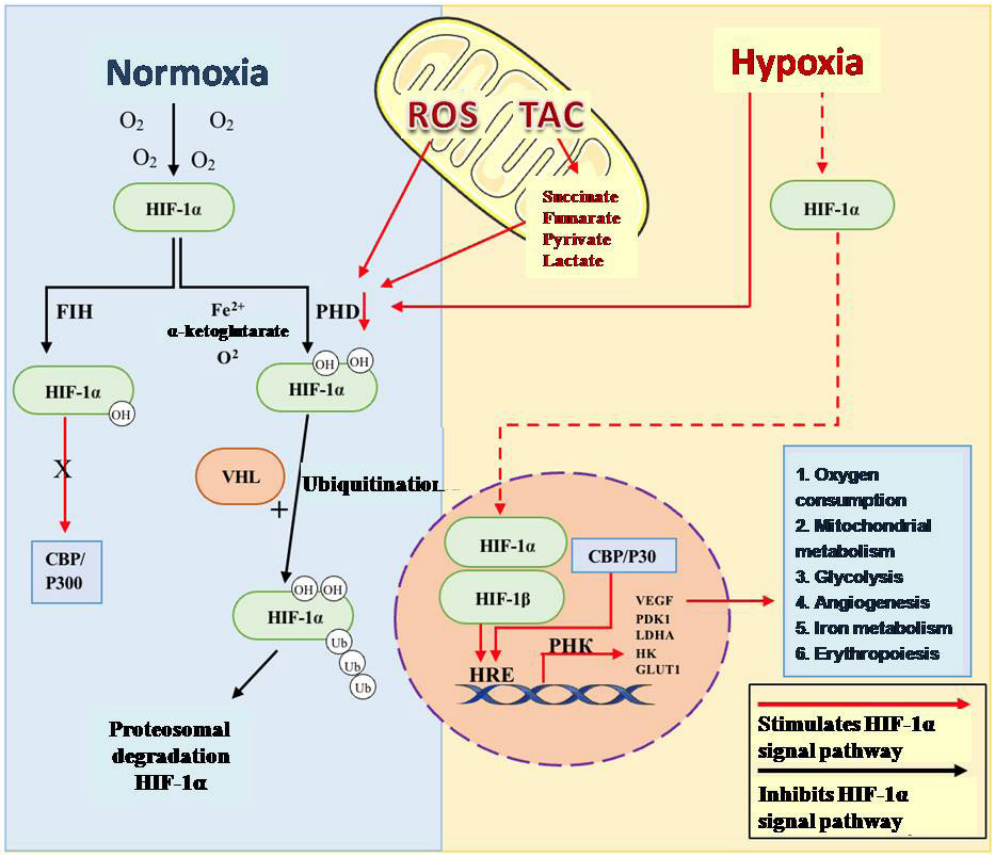

Fig. 1. Regulation of the hypoxia-inducible factor, 1α [18, 19].

Notes: ROS — reactive oxygen species, TAC– tricarbonic acid cycle, RNA — ribonucleic acid, CBP — cyclic AMP response element binding protein (co-activators of CREB-binding protein), FIH — factor inhibiting HIF; GLUT — glucose transporter, HIF — hypoxia-inducible factor, HK — hexokinase, HREs — hypoxia response elements, LDHA — lactate dehydrogenase A, PDK — pyruvate dehydrogenase kinase, VEGF — vascular endothelial growth factor, VHL — von Hippel–Lindau suppressor protein.

elevated levels of cellular succinate are linked with dysfunction of the electron transport chain complex II associated with increased production of reactive oxygen species (ROS) [21], dysregulation of proliferation and migration genes [22], posttranslational modification of proteins by the succinylation type [23].

On the other hand, a number of researchers have demonstrated an important role of succinate in the mechanisms of adaptation to hypoxia [24]. There are two phases of the formation of adaptation mechanisms: the phase of induction of adaptation and the phase of formation of genome-dependent reactions of long-term adaptation [24]. The phase of rapid adaptation to hypoxia is associated with the active use of succinate as an energy substrate, while the phase of long-term adaptation to hypoxia is characterized by expression of a number of enzymes, membrane transporters, regulators of the mitochondrial life cycle and other biomolecules under the influence of transcription factors (HIF-α family) [20].

The level of intracellular lactate is another important aspect participating in the mechanisms of adaptation to hypoxia. Intracellular lactate has been found to regulate the hypoxic response of the cell by stabilizing HIF-1α, HIF-2α and N-myc downstream regulated gene (NDRG) 3 through inhibiting PHD [25]. It is noteworthy that the stabilization of HIF-1α can occur under normoxic conditions, irrespective of oxygen concentration, which is commonly referred to as the pseudohypoxic state of the cell. In this case, the stabilization of HIF-1α occurs due to a disorder of PHD, deficit of their substrate α-ketoglutarate or cofactors — Fe^{2+} and ascorbate [23]. Finally, increased deubiquitinase activity may also contribute to the stabilization of HIF-1α in normoxia [26]. In hypoxia or pseudohypoxia, the concomitant increase in HIF-1α activity activates

pyruvate dehydrogenase kinase (PDK) 1 and lactate dehydrogenase A (LDHA), additionally directing pyruvate metabolism towards lactate formation [14].

Among other TAC metabolites capable of mediating the stabilization of HIF-1α, the role of 2-hydroxylglutarate, fumarate and pyruvate is also noted [23]. In this regard, it seems promising to study the role of TAC metabolites and enzymes involved in their metabolism to evaluate them as possible biomarkers and therapeutic targets in the mechanisms of adaptation to hypoxia for clinical practice.

Targets for HIF-1α in the Aspect of COVID-19 Pathogenesis

Angiotensin converting enzyme (ACE) 2 is expressed in various human cells, including vascular epithelium, lungs, kidneys and intestine, and plays a significant role in the mechanisms of vasodilation [27]. The participation of ACE-2 as a receptor for the penetration of the SARS-CoV-2 virus into the cell has been established [8]. For the virus to penetrate into a host cell, the viral particle binds to ACE-2 receptor and membrane-bound serine protease (TMPRSS) 2 through a receptor-binding domain. ACE-2 acts as a receptor for SARS-CoV-2 by binding to the spike protein of the viral capsid, while TMPRSS2 triggers spike protein priming [28]. Therefore, SARS-CoV-2 is most tropic to cells that express both ACE-2 and TMPRSS2 on the surface of the cell membrane. The activity of ACE-2 can be regulated through the expression of mRNA or protein, as well as through the cleavage of the cell membrane, which is mediated by a disintegrin and metalloproteinase domain (ADAM) 17 [29].

To date, a number of studies have been conducted to determine the role of HIF-1α in the penetration of the SARS-CoV-2 virus into human cells [30]. In a model of hypoxic pulmonary hypertension, the authors demonstrated that HIF-1α can produce an inhibitory effect on the penetration of the virus through ACE-2 through let-7b microRNA [31]. In a study on the mechanism of prostate cancer cell resistance to therapy, it was found that HIF-1α suppresses TMPRSS2 [32]. It has been demonstrated that HIF-1α can also increase the expression of ADAM17, which cleaves ACE-2 off the surface of alveocytes thereby preventing the penetration of SARS-CoV-2 into the cell [29]. Thus, a change in the level of HIF-1α can significantly affect susceptibility of the body to infection with the SARS-CoV-2 virus (Figure 2).

A study on cell lines demonstrated that hypoxia and the prolyl hydroxylase inhibitor HIF-1α (roxadustate) reduce the expression of ACE-2 and inhibit the penetration and replication of SARS-CoV-2 in lung epithelial cells through the HIF-1α-dependent pathway, which is considered a potential approach for the treatment of COVID-19 by the authors [33]. Therefore, HIF-1α is of great importance in the pathogenesis of COVID-19 infection and requires further research as a potential application point for the development of therapeutic strategies.

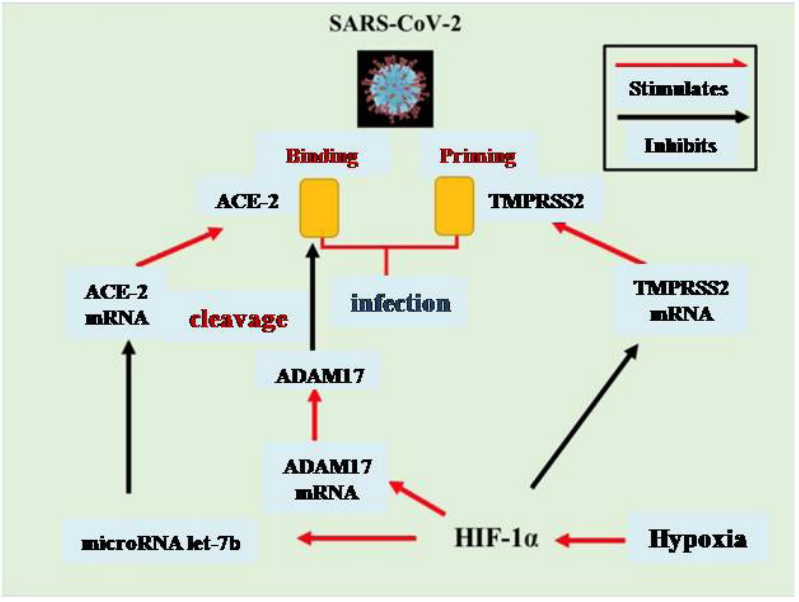

Fig. 2. Activation of hypoxia-inducible factor 1α signal pathway associated with reduction of the expression of ACE-2 and TMPRSS2 and an increase in the activity of ADAM17 metalloproteinase.

Notes: SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2, HIF — hypoxia-inducible factor, ACE — angiotensin-converting enzyme, TMPRSS — serine transmembrane protease, ADAM — a disintegrin and metalloproteinase domain, mRNA — matrix ribonucleic acid.

Disorder in HIF-1α-Mediated Adaptation to Hypoxia as an Element of the Pathogenesis of Hyperactivation of Immune Cells

Metabolic flexibility, known as metabolic adaptation, depends on both nutrient availability and oxygen levels [34]. Hypoxic conditions are associated with production of ROS, which leads to damage and dysfunction of mitochondria [35]. Many studies confirm the idea of dysregulation of mitochondrial functions underlying a decrease in metabolic flexibility [34]. Examples of diseases where this occurs may be type 2 diabetes mellitus, obesity, metabolic syndrome, systemic inflammation, malignant tumors, which, in turn, is associated with metabolic reprogramming of cells of the immune system [36].

Metabolic flexibility coordinates metabolic reprogramming, which is characterized by a shift in energy production from mitochondrial oxidative phosphorylation to aerobic glycolysis while maintaining a normal level of partial tension of oxygen in the blood; this aerobic glycolysis is called the Warburg effect [34–37].

It is known that the shift to the glycolytic phenotype in tumor cells is explained by the action of HIF-1α and its effect on glucose metabolism [38]. In immune cells, such as neutrophils, HIF-1α signaling also regulates glucose uptake and oxygen consumption [39]. According to some authors, the progression of COVID-19 infection is similar to the progression of a malignant tumor, and an important role here is played by HIF-1α [40].

Metabolic reprogramming of immune cells in hypoxia may occur in different ways. Thus, S Rajasundaram, et al. (2018) suggest that the realization of HIF-1α-mediated mechanism of adaptation to hypoxia can produce an anti-inflammatory effect through activation of the adenosine receptor-dependent pathway [41]. Hypoxic conditions stimulate increased release of adenosine with activation of the adenosine signaling system. Thus, adenosine receptors are involved in the release of IL-10 from monocytes/macrophages, and are also involved in inhibiting the proliferation and secretion of tumor necrosis factor (TNF) α, interferon-γ, IL-2, IL-4 and IL-5. The authors suggest that this pathway may be life-saving, as it can protect inflamed tissues of vital organs from damage by hyperactive immune cells [41].

On the other hand, S Galván–Peña, et al. (2014) note that in the progression of inflammation, the effect of hypoxic conditions becomes more noticeable [42]. HIF-1α is important for the formation of the proinflammatory phenotype of M1 macrophages, since its transcriptional activity conditions the metabolic switching of macrophages to glycolysis through the induction of expression of glycolytic genes and glucose transporters [42].

Macrophages, like neutrophils, are involved in inflammatory processes being the earliest immune cells penetrating inflammatory tissues [42]. Staying in the inflammatory microenvironment, macrophages can act depending on the predominant local stimuli either as pro-inflammatory (M1) or anti-inflammatory (M2) agents. After exposure to local stimuli, M1 and M2 macrophages release a wide range of immune mediators.

M1 macrophages possess a proinflammatory cytotoxic effect and produce ROS, cytokines (TNF, IL-1, IL-6, IL-12 and IL-23) and chemokines (chemokine ligand 5, CCL-5; chemokine (C-X-C motif) ligand 9, CXCL9; chemokine (C-X-C motif) ligand 10, CXCL10; chemokine (C-X-C motif) ligand 5, CXCL5) [43]. On the contrary, M2 macrophages mediate anti-inflammatory functions (wound healing, tissue remodeling, angiogenesis) and produce VEGF, epidermal growth factor, transforming growth factor-β, IL-4, IL-13 and IL-10 [43].

Activation of the HIF-1α signaling pathway results in the formation of a proinflammatory phenotype of M1 macrophages, which in severe cases of COVID-19 infection leads to excessive production of proinflammatory cytokines the phenomenon of a cytokine storm [40].

To date, it has been established that the cytokine storm determines the severity of the disease in patients with COVID-19 infection to a greater extent than the degree of lung damage [44]. Cytokine storm is a disorder in the adequate cytokine production by cells of both innate and adaptive immunity. Dysregulation of the immune system leads to over-intensive activation of more leukocytes, which release inflammatory cytokines including IL-1β and IL-6, which eventually leads to multiple organ failure [44]. The cytokine profile, directly related to the severity of COVID-19 infection, is characterized by an increase in IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α and TNF [44].

Besides, the state of hypoxia and stabilization of HIF-1α can provoke or intensify a cytokine storm, since the level of VEGF secretion increases under the action of HIF-1α [20]. VEGF and VEGF receptors are directly involved in the migration of circulating inflammatory cells into tissues and in increase in the vascular permeability, which is associated with the progression of the severity of the condition in patients with COVID-19 infection [45].

It should also be added that systemic hypoxia in COVID-19 infection impairs neutrophil turnover [3].

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Hypoxia contributes to the reduction of neutrophil apoptosis through HIF-1α, nuclear factor kappaB and macrophage inflammatory protein 1α [46]. It was established that instead of natural clearance, the excessive intravascular activation of neutrophils occurs with subsequent NETosis (neutrophil extracellular traps) [47]. The result is a launch of blood clotting and damage to the vascular wall with the development of vasculitis [47].

Thrombosis in the microcirculatory system (small arteries, small veins and capillaries) can cause damage to vital organs, which aggravates the condition of patients with COVID-19 [5, 48]. In addition, hypoxia is one of the important factors contributing to coagulopathy [5]. Thus, genes associated with HIF-1α-mediated adaptation to hypoxia induce production of prothrombotic factors such as plasminogen activator inhibitor-1 and tissue factors, and at the same time activation of antithrombotic factors takes place such as thrombomodulin, protein S and tissue factor pathway inhibitor [49]. The study of the effect of HIF-1α signaling pathway, as a biological marker of adaptation to hypoxia, for the activation of various prothrombotic and antithrombotic factors in patients with COVID-19 infection requires further study [5].

CONCLUSION

Systemic hypoxia, which accompanies all stages of coronavirus disease 2019, plays a significant role in its pathogenesis and outcome of the disease. Hypoxia-inducible factor 1α allows cells to adapt to adverse hypoxic conditions, however, being over-stimulated, it can turn from a factor of adaptation into a factor of maladaptation, since its excessive accumulation in cells of the innate immune system disrupts apoptosis of neutrophils in acute respiratory distress syndrome and leads to a cytokine storm.

Summarizing the data, it can be assumed that hypoxia-inducible factor 1α prevents the penetration of the SARS-CoV-2 virus into cells. It also functions as the main regulator of proinflammatory activity at the site of inflammation surrounded by hypoxia. However, in conditions of impaired metabolic flexibility, as, for example, in diabetes mellitus, metabolic syndrome, a high level of hypoxia-inducible factor 1α induces an excessive inflammatory response from the cells of the immune system. A high level of hypoxia-inducible factor 1α in cells in the inflammation focus is associated with an increased production of angiogenesis factors mediating vascular permeability and the capillary leakage process. This is accompanied by tissue damage and organ failure. At the same time, it was found that hypoxia-inducible factor 1α can mediate the anti-inflammatory effect through activation of the adenosine receptor-dependent pathway, which is considered to be a possible protection of cells and organs from damage by hyperactive immune cells.

Further study of the contribution of hypoxia-induced factor 1α to adaptation of the body to hypoxic conditions and its role in the formation of an inflammatory response in the pathogenesis of coronavirus disease 2019 is of particular value. The prospects of correcting the systemic inflammatory response in patients with coronavirus disease 2019 are associated with the determination of ways to control the level of hypoxia-inducible factor 1.

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