https://doi.org/10.33647/2074-5982-15-1-48-61

THE ROLE AND REGULATION OF HYPOXIA-INDUCIBLE TRANSCRIPTION FACTOR-1 AND SUCCINATE RECEPTOR-1 IN TYPE 2 DIABETES: A LINK TO VASCULAR COMPLICATIONS

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Type 2 diabetes is a major metabolic disorder that leads over time to serious complications. Tight glycemic control is considered to be an essential strategy for preventing diabetes-related complications. However, randomized clinical trials accrued over last decades have demonstrated no significant benefit of glycemic control in terms of decreasing micro- and macrovascular complications, except for a 15% reduction in the risk of nonfatal myocardial infarction. Emerging evidence suggests that vascular complications of diabetes correlate with a dysregulation of the angiogenic response governed by hypoxia-inducible transcription factor 1 (HIF-1) and succinate receptor 1 (SUCNR1). Type 2 diabetes affects HIF-1 activity at several levels, including HIF-1α subunit transcription, mRNA translation into the HIF-1α protein, degradation of the HIF-1α protein and binding of the HIF-1α protein to co-activators, which eventually results in a dysregulation of the adaptive angiogenic response to hypoxia. Both hyperglycemia and insulin resistance are involved in these impairments. Diabetes affects SUCNR1 signaling in a tissue-specific manner. A cross-talk between HIF-1 and SUCNR1 signaling explains, at least partially, paradoxical tissue-specific changes in the angiogenesis in diabetic microvascular complications, an excessive formation of blood vessels in the retina and a deficiency in small blood vessels in peripheral tissues, such as the skin. As a conclusion, targeting HIF-1 and SUCNR1 signaling seems to represent a novel promising approach for the prevention and treatment of diabetes-related vascular complications.

Keywords: Type 2 diabetes, hyperglycemia, insulin, hypoxia inducible factor 1 (HIF-1), succinate receptor 1 (SUCNR1), microvascular complications, macrovascular complications
Conflict of interest: the authors declare no conflict of interest.
Funding: The work was supported by the Russian Foundation for Basic Research, grant RFBR No. 18-015-00450.
For citation: Pomytkin I.A., Karkischenko V.N. The Role and Regulation of Hypoxia-Inducible Transcription Factor-1 and Succinate Receptor-1 in Type 2 Diabetes: a Link to Vascular Complications. *Biomedicine.* 2019;15(1):48–61. https://doi.org/10.33647/2074-5982-15-1-48-61

Submitted 01.02.2019
Revised 11.02.2019
Published 10.03.2019

РОЛЬ И РЕГУЛЯЦИЯ ИНДУЦИРУЕМОГО ГИПОКСИЕЙ ФАКТОРА ТРАНСКРИПЦИИ-1 И СУКЦИНАТНОГО РЕЦЕПТОРА-1 ПРИ ДИАБЕТЕ ТИПА 2: СВЯЗЬ С СОСУДИСТЫМИ ОСЛОЖНЕНИЯМИ

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Диабет 2 типа является основным метаболическим заболеванием, которое со временем приводит к серьезным осложнениям. Жесткий контроль уровней глюкозы в крови считается важной мерой, позволяющей предотвратить осложнения диабета. Однако рандомизированные клинические испытания, проведенные за последние десятилетия, не выявили существенной пользы гликемического контроля для предотвращения микро- и макрососудистых осложнений диабета, за исключением снижения риска нефатального инфаркта миокарда на 15%. В то же время появляются данные, что существует корреляция между возникновением сосудистых осложнений сахарного диабета и нарушениями в регуляции ангиогенеза управляемой индуцируемым гипоксией фактором 1 (HIF-1) и сукцинатным рецептором 1 (SUCNR1). Диабет 2 типа влияет на активность HIF-1 на нескольких уровнях, включая транскрипцию субъединицы HIF-1α, трансляцию мРНК в белок HIF-1α, деградацию белка HIF-1α и связывание белка HIF-1α с коактиваторами, что в итоге приводит к нарушению адаптивного ангиогенного ответа на гипоксию. Гипергликемия и инсулиновая резистентность участвуют в этих нарушениях. Кроме того, диабет влияет на передачу сигналов сукцинатного рецептора 1 тканеспецифическим образом. Перекрестное взаимодействие между HIF-1 и SUCNR1 объясняет, по крайней мере частично, парадоксальные тканеспецифические изменения ангиогенеза при диабетических микрососудистых осложнениях, а именно чрезмерное образование кровеносных сосудов в сетчатке и дефицит мелких кровеносных сосудов в периферических тканях, таких как кожа. В заключение, терапевтическое воздействие на сигнальные системы HIF-1 и SUCNR1 может стать новым многообещающим подходом к профилактике и лечению сосудистых осложнений диабета 2 типа.

Ключевые слова: сахарный диабет 2 типа, гипергликемия, инсулин, индуцируемый гипоксией фактор 1 (HIF-1), сукцинатный рецептор 1 (SUCNR1), микрососудистые осложнения, макрососудистые осложнения
Конфликт интересов: авторы заявили об отсутствии конфликта интересов.
Финансирование: Работа выполнена при поддержке РФФИ: Грант РФФИ № 18-015-00450.
Для цитирования: Помыткин И.А., Каркищенко В.Н. Роль и регуляция индуцируемого гипоксией фактора транскрипции-1 и сукцинатного рецептора-1 при диабете типа 2: связь с сосудистыми осложнениями. *Биомедицина*. 2019;15(1):48–61. https://doi.org/10.33647/2074-5982-15-1-48-61

Поступила 01.02.2019
Принята после доработки 11.02.2019
Опубликована 10.03.2019

Introduction

Diabetes mellitus (DM) is a major metabolic disorder with a global prevalence of 8.5% [1]. Type 1 diabetes and type 2 diabetes are the two chronic forms of DM, formerly known as insulin-dependent and non-insulin-dependent diabetes mellitus, respectively. Type 2 diabetes accounts for approximately 90% of all diabetes cases and leads over time to serious complications. In 1993, the Diabetes Control and Complications Trial demonstrated the benefit of tight glycemic control for delaying the onset and slowing the progression of diabetic retinopathy, nephropathy, and neuropathy, as well as for reducing the risk of macrovascular diseases in patients suffering from type 1 diabetes [2]. In 1998, the UK Prospective Diabetes Study Group showed that intensive blood-glucose control could substantially decrease the risk of microvascular complications, rather than macrovascular diseases, in patients with type 2 diabetes [3]. Practice guideline recommendations and clinical care standards have since focused on achieving tight glycemic control to prevent

complications in patients with both type 1 and type 2 diabetes. Contrary to the emerged consensus, findings from the ACCORD randomised trial (n=10,251) have demonstrated that intensive glucose lowering therapy does not reduce the risk of advanced measures of microvascular outcomes [4], nor does it reduce major cardiovascular events, while resulting in increased mortality [5]. Evidence from randomized clinical trials accrued over last decades and recent meta-analyses has led to scepticism about the value of tight glycemic control for the prevention of complications in patients with type 2 diabetes, since no significant benefit of such a therapy has been shown in terms of patient-important micro- and macrovascular outcomes, with the exception of a 15% reduction in the risk of nonfatal myocardial infarction [6]. These findings spur the need to explore other factors beyong glycemic control in order to discover new therapeutic approaches for the prevention of vascular complications caused by type 2 diabetes.

An impaired adaptive response to hypoxia is a key pathological characteristic of type 2 diabetes. In general, the adaptive response is mediated by signaling of two oxygen sensors, i.e. hypoxia-inducible transcription factors (HIFs) and succinate receptor 1 (SUCNR1). Growing evidence suggests that type 2 diabetes results in dysregulation of HIFs and SUCNR1 signaling. It may contribute to vascular complications, given that the angiogenic response is an essential part of HIFs and SUCNR1 action. This review summarizes the role and regulation of hypoxia-inducible transcription factors and SUCNR1 in type 2 diabetes, as well as the vascular complications thereof.

Hypoxia-inducible transcription factors

Hypoxia-inducible transcription factors were originally discovered as oxygen sensors that play key roles in the transcriptional response to hypoxia [7, 8]. HIFs are heterodimeric proteins consisting of a unique O_2-regulated alpha subunit (HIF-1α, HIF-2α or HIF-3α) and an oxygen-independent HIF-1β subunit. HIF-1α is ubiquitously expressed in the body, whereas expression of a structurally similar HIF-2α is restricted to certain cell types, mainly endothelial and epithelial cells, as well as neurons [9, 10]. There is a consensus that HIF-1 and HIF-2 are activators of the transcriptional response to hypoxia, while HIF-3 is generally viewed as a negative regulator of HIF-1/HIF-2 activity [11]. The most knowledge about the roles of HIFs in adaption to hypoxia was obtained from studies on HIF-1. Upon activation, HIF-1 directly regulates the expression of more than 1,000 human genes in a cell type-specific manner [12, 13]. In particular, HIF-1 activates expression of genes encoding glucose transporters 1 (GLUT1) and 3 (GLUT3) and virtually all glycolytic enzymes to provide a metabolic shift from oxidative phosphorylation towards glycolysis. In addition, HIF-1 upregulates expression of a set of angiogenic factors, mainly vascular endothelium growth factor (VEGF), as well as receptors and signaling molecules involved in angiogenesis, vascular remodeling and vascular response (Table 1). Therefore, HIF-1 plays a key role in vascularization of body tissues, and its dysregulation may lead to vascular complications in type 2 diabetes.

Regulation of HIF-1 activity

HIF-1 activity is controlled by a steady-state level of the HIF-1α protein through a tight regulation of the balance between its synthesis and degradation. Insulin stimulates HIF-1α synthesis via activation of the canonical phosphatidylinositol-3-kinase PI3K/AKT/mTOR signaling pathway that increases the rate of HIF-1α mRNA translation into the HIF-1α protein [25, 26, 27]. Certain cytokines and growth factors, including insulin-like growth factor 1 (IGF-1) and 2 (IGF-2) [28, 29], increase HIF-1α synthesis in a manner similar to that for insulin [30].

HIF-1α degradation is a key process in the regulation of the cellular response to hypoxia.

Table 1. *Examples of HIF-1 target genes encoding angiogenic factors*
Таблица 1. *Примеры генов-мишеней HIF-1, кодирующих факторы ангиогенеза*

Encoding protein	Gene	Refs
Adrenomedullin	*ADM*	[14][15]
Angiopoietin 1	*ANGPT1*	[16] [17]
Angiopoietin 2	*ANGPT2*	[17] [18]
Apelin	*APLN*	[19]
Endothelin 1	*EDN1*	[20] [21]
Placental growth factor	*PGF*	[17]
Platelet-derived growth factor B	*PDGFB*	[17]
Vascular endothelial growth factor	*VEGF*	[22]
VEGF receptor 1	*FLT1*	[23] [24]

Table 2. *IC_{50} values for inhibition of 4-prolyl hydroxylases with succinate and fumarate*
Таблица 2. *Значения IC_{50} для ингибирования 4-пролилгидроксилаз с сукцинатом и фумаратом*

4-Prolyl hydroxylase	IC50, μM		Km, μM
	Succinate [39]	Fumarate [39]	2-Oxoglutarate [32]
PHD1	830	120	60
PHD2	510	80	60
PHD3	570	60	55

Under normoxia, hydroxylation of HIF-1α at one or two proline residues with 4-prolyl hydroxylases (PHDs) triggers ubiquitination and a rapid proteasomal degradation of the HIF-1α protein. The degradation is rapid, with a half-life of HIF-1α being less than 5 min at 21% O_2 in well-oxygenated cells [31]. 4-Prolyl hydroxylases act as oxygen sensors, since their activity directly depend on oxygen concentrations. All three isoforms — PHD1, PHD2 and PHD3 — utilize O_2 and 2-oxoglutarate, the metabolite of the citric acid cycle, as substrates with the Km values of 230-250 μM and 55-60 μM, respectively [32]. Since the Km values for O_2 are slightly above the atmospheric concentration of O_2 (about 200 μM), even a small shift to hypoxia dicreases the activity of PHDs and slows the rate of HIF-1α degradation. Accumulated HIF-1α dimerizes with HIF-1β, binds to the hypoxia response element (HRE), recruits the transcriptional co-activators p300/CBP and activates the transcription of target genes [33, 15]. In parallel, hypoxia unlocks the HIF-1α/p300 interaction via downreguling HIF-1α protein hydroxylation at the asparagine residue with a factor inhibiting HIF-1 (FIH-1) [34, 35].

Among the three isoforms of 4-prolyl hydroxylases, PHD2 is the major negative regulator for HIF-1α and the most abundant isoform in normoxic cells [36]. PHD2 is the major negative regulator for VEGF [37] and the most potent inhibitor of vascular growth in tissues [38]. Therefore, PHD2 is considered to be a promising target for therapeutic interventions, and several PHD2 antagonists are currently under development as drug candidates.

Succinate and fumarate — intermediates of the citric acid cycle — are metabolic inhibitors of 4-prolyl hydroxylases [39]. The half-maximal inhibitory concentrations (IC_{50}) values for succinate- and fumarate-induced inhibition of 4-prolyl hydroxylases in comparison with Km values for 2-oxoglutarate are presented in Table 2.

Fumarate is a competitive inhibitor of 4-prolyl hydroxylases due to its structural similarity with 2-oxoglutarate. The fumarate IC_{50} value

for PHD2 inhibition is close to Km values for 2-oxoglutarate, suggesting that fumarate can prevent a PHD2-induced degradation of the HIF-1α protein and may play a role in the regulation of HIF-1 activity under physiologically relevant conditions.

Succinate is characterized by a much weaker inhibiting activity compared to fumarate, with its IC_{50} values of > 500 μM being distinct from its range of physiological concentrations. For the reference, succinate levels in human plasma vary from 1 to 9 μM at rest and increase up to 125 μM under hypoxic conditions (treadmill running or breath-hold diving) [40, 41]. Therefore, succinate plays a role in the inhibition of HIF-1α degradation only in cases of severe ischemia, when succinate levels can rise up to millimolar values [42].

Succinate receptor 1

Succinate receptor 1 (SUCNR1) is an alternative oxygen sensor that triggers an angiogenic response to hypoxia. SUCNR1 is a member of the rhodopsin-like G protein-coupled receptor family (GPCRs) [43]. It was discovered in 2001 as a GPR91 receptor and was initially viewed as a new purinergic receptor due to its similarity with such molecules [44]. Later, the receptor was established to be highly specific towards succinate [45], subsequently being re-named as succinate receptor 1. Half-maximum potency (EC_{50}) values for the succinate-induced SUCNR1 activation vary within the 17-56 μM range, depending on the type of cells transfected with human SUCNR1 and assay methods [45, 46, 47]. The EC_{50} value for succinate in the SUCNR1-mediated calcium mobilization is at least by one-order lower compared to that for such intermediates of the citric acid cycle as oxaloacetate (171 μM), L-malate (207 μM), 2-oxoglutarate (7.3 mM) and fumarate (>1 mM) [45, 48]. Upon binding, succinate triggers the activation of the SUCNR1/MAPK/ERK signaling pathway, calcium mobilization and the Gi protein-mediated inhibition of cAMP production [43]. Under hypoxia, when succinate concentrations rise, the SUCNR1 receptor triggers angiogenesis in a way alternative to HIF-1. The succinate/SUCNR1 signaling pathway upregulates the expression of VEGF, angiopoietins 1 and 2, as well as other angiogenic genes in a tissue-specific manner, which results in re-vascularization of hypoxic tissues [49]. Therefore, dysregulation of SUCNR1 signaling may lead to vascular complications of type 2 diabetes.

SUCNR1 expression in murine tissues was originally considered to be limited to the kidney, liver, spleen and small intestine [45]. However, later studies have shown SUCNR1 to be ubiquitously expressed, although its amount varying greatly between types of cells. The highest expression of SUCNR1 mRNA and protein was observed in the peripheral white adipose tissue and the kidney, followed by organs of various functional systems including the respiratory, urinary, digestive, reproductive, central and peripheral nervous systems [50, 51]. At the organ level, SUCNR1 expression is cell-specific. In the kidney, SUCNR1 localizes to the renal vascular lumen, in particular the afferent arteriole and the glomerular vasculature, as well as in the luminal membrane of multiple segments of the renal tubules [52, 46]. In the liver, SUCNR1 is exclusively expressed in quiescent hepatic stellate cells [53]. In the heart, SUCNR1 expression is low [51], while some studies have demonstrated that SUCNR1 is expressed in the ventricular cardiomyocytes, mainly in the sarcolemma membrane and T-tubules [54, 55, 56]. In the retina, SUCNR1 is predominantly expressed in the cell bodies of the retinal ganglion cell layer [57]. In the brain, SUCNR1 is expressed in cortical neurons, astrocytes [49], and neural stem cells [58]. SUNCR1 plays a key role in haematopoiesis. Stimulation of SUCNR1 on hematopoietic progenitor cells (HPC) of the bone marrow induces the proliferation of erythroid and megakaryocyte progenitor cells [59]. SUCNR1 is expressed in human plate-

lets [60], dendritic cells, [61], T lymphocytes (CD4+ and CD8+) and B (CD19+) cells [62].

Diabetes affects an adaptive angiogenic response to hypoxia

VEGF is the major angiogenic factor that mediates the HIF-1- and SUCNR1-induced adaptive response to hypoxia. VEGF induces vascular permeability and drives the proliferation and migration of vascular endothelial cells [63]. In 2002, Chou et al discovered that diabetes affects the VEGF-mediated angiogenesis in microvascular and cardiac tissues in an opposite manner [64]. The expression of mRNA and protein for VEGF and its receptors in diabetic rats was as twice as low in the myocardium, while being as twice as high in the retina and glomeruli [64]. The differential regulation function of VEGF has since been shown for other diabetic tissues.

1. Cardiovascular complications of diabetes

Cardiovascular complications of diabetes mellitus are the leading causes of diabetes-related morbidity and mortality [65]. Growing evidence suggests that coronary vessel anomalities correlate with a reduced HIF-1 and VEGF signaling in the diabetic heart. In the coronary circulation, impaired collateral vessel formation has been demonstrated in the hearts of patients with diabetes [66, 67, 68]. A two-fold decrease in the VEGF mRNA and VEGF receptor 2 (VEGFR-2) mRNA levels was observed in cardiac samples from patients with type 1 and 2 diabetes compared to non-diabetic donors [64]. Ventricular biopsy specimens from type 2 diabetic patients showed a decrease in the HIF-1α and VEGF levels in comparison with a non-diabetic control group [69]. Animal experiments have demonstrated that the HIF-1α reduction in ventricular cardiomyocytes leads to a significant reduction of vessel counts in the myocardium compared with controls [70], and that such an altered HIF-1 signaling coincides with the left and right coronary artery anomalies [71]. Collectively, these findings indicate that a reduction in HIF-1/VEGF signaling in the diabetic heart correlates with cardiovascular complications and seems to underlie a diminished adaptive response to hypoxia. The mechanisms behind the HIF-1α cardiac reduction in diabetes have been found to be of metabolic origin and driven by increased fatty acids [72] and hyperglycemia [73].

2. Diabetic nephropathy

Diabetic nephropathy (DN) is a leading cause of end-stage renal disease that accounts for the increased mortality rate in type 1 and type 2 diabetes [74, 75]. Hypoxia represents an early event in the development and progression of DN. HIF-1 has been shown to mediate the metabolic responses to renal hypoxia [76]. Renal expression of the HIF-1 target genes, VEGF and its receptors was up-regulated in experimental animals and patients with type 1 and type 2 diabetes, especially early in the course of diabetes [77]. Hyperglycemia upregulates HIF-1α transcription in the glomeruli of diabetic model mice through a glucose-responsive carbohydrate-responsive element-binding protein (ChREBP) [78, 79]. It still remains controversial whether HIF-1 activation exerts a beneficial or harmful role in the development of diabetic nephropathy [80]. Evidence suggests that activation of HIF-1 may even prevent diabetic nephropathy [81, 82], whereas impairement of HIF-1 signaling accelerates progression of kidney disease [83]. A short, but not prolonged, therapeutic activation of HIF-1 has been proposed as a promising protective approach to the treatment of kidney disease in patients with diabetes [76].

3. Diabetic retinopathy

Diabetic retinopathy remains a leading cause of blindness in persons with diabetes [84]. VEGF upregulation has been considered to be a major cause of retinal neovascularization and vascular leakage that lead to the progression of proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME)

[85, 86]. The reduction of VEGF in diabetic retina is believed to be an effective therapy against DME and PDR. In line with this, multiple anti-VEGF drugs are widely used as the first line of treatment [87]. The increase of HIF-1α correlates temporally and spatially with increased retinal VEGF levels in hypoxic retina [88]. However, SUCNR1-dependent, rather than HIF-1 dependent, VEGF production is considered to be the major cause of proliferative diabetic retinopathy. SUCNR1 is predominately expressed in retinal ganglion cells, with its activation triggering the release of pro-angiogenic factors, such as VEGF and angiopoietins [57]. Succinate levels rise regionally in retina in response to hyperglycemia. Mean succinate concentrations in the vitreous fluid of patients with proliferative diabetic retinopathy were 1.7-fold higher than those in non-diabetic control groups [89]. A local rise in retinal succinate triggers VEGF expression through the SUCNR1/ERK1,2/EBP β (c-Fos) and ERK1/2-COX-2/PGE2 signaling pathways [90, 91]. The inhibition of retinal SUCNR1 signaling prevents a high glucose-induced VEGF protein production [90], identifying SUCNR1 as a promising target in the treatment of proliferative diabetic retinopathy.

4. Diabetic foot ulceration

Diabetic foot ulceration (DFU) is a chronic major complication of diabetes mellitus characterized by impaired wound healing that frequently leads to the lower limb amputations [92]. Hypoxia is an essential feature of a wound, thus being a critical stimulus for normal wound healing [93]. Transcutaneous oxygen tension has been shown to be predictive of ulcer healing in patients with diabetes and chronic foot ulcers [94]. Emerging evidence suggests that impaired cellular response to hypoxia is a causative factor for delayed wound healing in diabetic patients. Biopsy specimens from patients with DFU demonstrated lower HIF-1α protein levels in comparison with those from patients with chronic venous ulcers [95]. Fibroblasts from the dermis of diabetic db/db mice exhibited a seven-fold decrease in the basal VEGF production ($P < 0.001$) compared to wild-type fibroblasts, thus having lost responsiveness to hypoxia [96]. Markedly lower levels of VEGF expression in the skin were found in streptozotocin (STZ)-induced mice and db/db mice following cutaneous ischemia compared to wild-type mice [97]. Dermal fibroblasts from patients with type 2 diabetes demonstrated a two-fold decrease in the production of VEGF protein in respose to hypoxia (0.5% O_2) compared to age-matched nondiabetic control, which effect was linked to hyperglycemia [97, 98]. Hyperglycemia is believed to be central to the repression of HIF-1 signaling in diabetic wounds. In vitro studies in primary human dermal fibroblasts and endothelial cells, as well as in db/db mouse primary fibroblasts [99], have demonstrated hyperglycemia to destabilize HIF-1α protein and down-regulate the transcription of several HIF-1 target genes essential for wound healing, including heat shock protein 90, VEGF-A, VEGF-R1, stromal cell-derived factor (SDF)-1α and stromal cell factor (SCF) [99]. Non-selective inhibitors of 4-prolyl hydroxylases counteract the hyperglycemia-induced repressive effect on HIF-1 functions and improve wound healing in db/db mice [99]. PHD2 silencing improves diabetic murine wound closure [100]. The molecular basis for the repression of HIF-1 signaling under hyperglycemia is still debated. The glyoxalase 1 (GLO1) substrate methylglyoxal was shown to modify HIF-1α and co-activator p300 under hyperglycemia, hampering its interaction critical for the activation of transcription of HIF-1 target genes [101, 97].

Mechanisms underlying diabetes-induced impairment of the adaptive response to hypoxia

The aforepresented data demonstrate the dysregulation of HIF-1 and SUCNR1 signal-

ing to correlate with both an impaired adaptive response to hypoxia and vascular complications in type 2 diabetes. Reduced HIF-1 levels are a major factor in vascular complications in type 2 diabetes, with the exception of proliferative diabetic retinopathy caused by SUCNR1 overactivity.

Type 2 diabetes affects HIF-1 signaling at least at five regulatory points (Figure).

Hyperglycemia upregulates HIF-1α transcription through the glucose-responsive carbohydrate- responsive element-binding protein (ChREBP) [78, 79], but destabilizes the HIF-1α protein under hypoxia [95, 99]. This destabilizing effect is mediated by methylgyoxal, a highly reactive metabolite of spontaneous decomposition of triose phosphate intermediates in glycolysis, which levels increase under hyperglycemia [73]. Additionally, methylglyoxal modifies the arginine and lysine residues in proteins involved in HIF-1 signaling, such as HIF-1α and co-activator

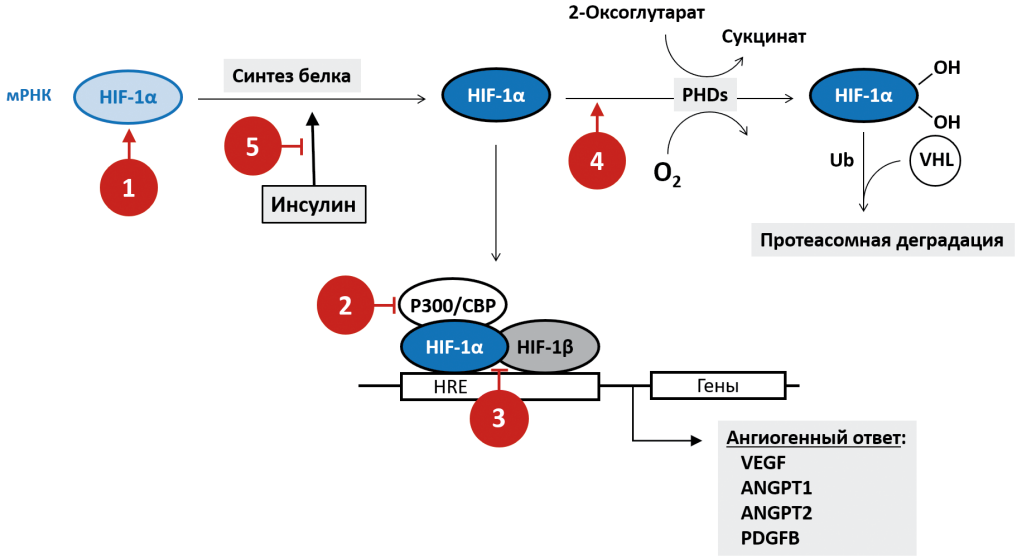

Fig. *Type 2 diabetes affects the HIF-1-mediated angiogenic response to hypoxia.*
Under hypoxic conditions, the HIF-1α protein accumulates, dimerizes with HIF-1β, recruits co-activators p300/CBP and binds to hypoxia response elements (HREs) to activate the transcription of target genes encoding angiogenic factors. Type 2 diabetes affects the HIF-1-mediated angiogenic response at least at five levels. Red circles indicate regulatory points at which HIF-1 signaling is affected by type 2 diabetes. ① *— Hyperglycemia upregulates transcription of HIF-1α mRNA;* ②,③ *— Methylglyoxal/hyperglycemia downregulates transcription of HIF-1 target genes, preventing HIF-1α/HIF-1β and HIF-1α/p300 interactions within the transcription complex;* ④ *— Methylglyoxal/hyperglycemia downregulates HIF-1α accumulation, promoting degradation of HIF-1α protein;* ⑤ *— Insulin resistance presumably downregulates HIF-1α protein synthesis, affecting the insulin-stimulated translation of HIF-1α mRNA to protein.*
Рис. *Диабет 2 типа влияет на ангиогенный ответ на гипоксию опосредованный HIF-1.*
В условиях гипоксии белок HIF-1α накапливается, образует димер с HIF-1β, рекрутирует ко-активаторы p300 / CBP и связывается с HIF-чувствительными элементами в промоторах (HRE) и, так, активирует транскрипции генов-мишеней, кодирующих факторы ангиогенеза. Диабет 2 типа влияет на HIF-1-опосредованный ангиогенный ответ, по меньшей мере, на пяти уровнях. Красным отмечены регуляторные точки, в которых диабет 2 типа влияет на передачу сигналов HIF-1. ① *— Гипергликемия активирует транскрипцию мРНК HIF-1α субъединицы.* ②, ③ *— Метилглиоксаль / гипергликемия подавляют транскрипцию генов-мишеней HIF-1, предотвращая взаимодействия между HIF-1α / HIF-1β и HIF-1α / p300 в транскрипционном комплексе.* ④ *— Метилглиоксаль / гипергликемия способствуют деградации белка HIF-1α и, так, подавляют накопление HIF-1α при гипоксии.* ⑤ *— Инсулиновая резистентность подавляет синтез белка HIF-1α, влияя на стимулированный инсулином процесс трансляции мРНК HIF-1α.*

p300, which results in hampering interactions between HIF-1α, HIF-1β and p300 within the transcription complex and inhibiting activation of the transcription of HIF-1 target genes [101, 97].

Insulin resistance is a hallmark of type 2 diabetes. The Consensus Development Conference on Insulin Resistance has defined insulin resistance as an impaired biological response to insulin, which should not be confined solely to glucose metabolism parameters, but should apply to all biological actions of insulin [102]. Previous studies have demonstrated that insulin directly upregulates HIF-1α protein synthesis, leading to HIF-1α accumulation even under normoxic conditions [25, 26, 27]. However, the effect of insulin resistance on HIF-1α protein synthesis in type 2 diabetes is yet to be revealed. It seems likely that insulin resistance can downregulate HIF-1α protein synthesis. In this context, insulin resistance and hyperglycemia, acting as pathologic factors in type 2 diabetes, will both lead to a reduction in HIF-1α protein, although by two different mechanisms. Hyperglycemia affects HIF-1α degradation, while insulin resistance is likely affect HIF-1α protein synthesis. The undervalued role of insulin resistance in HIF-1-mediated angiogenic response seems to explain why tight glycemic control alone is not sufficient for the prevention of vascular complications in type 2 diabetes.

Succinate deficiency caused by a switch to free fatty acid metabolism has been shown to be an alternative factor behind the HIF-1α reduction in diabetic hearts, in view that succinate can promote HIF-1α accumulation through inhibition of regulatory 4-prolyl hydroxylases (Table 2) [72].

Conclusion and prospects

In general, a tissue-specific dysregulation of the HIF-1-mediated angiogenic response to hypoxia correlates with micro- and macrovascular complications of type 2 diabetes. The retina-specific overactivation of succinate/SUCNR1 signaling explains, at least partially, paradoxical tissue-specific changes in the angiogenesis in diabetic microvascular complications, an excessive formation of premature blood vessels in the retina and a deficiency in the formation of small blood vessels in peripheral tissues, such as the skin.

Although current research is mainly focused on the role of hyperglycemia in the vascular complications of diabetes, hyperglycemia seems to be not the sole factor causal to dysregulation of HIF-1 signaling in type 2 diabetes. There is strong evidence that insulin directly upregulates HIF-1α protein synthesis. Therefore, local insulin resistance might downregulate the HIF-1-mediated response to hypoxia, thus contributing to the development of vascular complications in type 2 diabetes. This seems to explain, at least partially, recent findings that have showen no significant benefit of tight glucose control in terms of patient-important micro- and macrovascular outcomes, with the exception of a 15% reduction in the relative risk of nonfatal myocardial infarction [6]. Future research should aim at veryfying the hypothesis about the role of insulin resistance in the HIF-1 related angiogenic response in type 2 diabetes.

In addition, the improvement of insulin receptor signaling at target hypoxic regions seems to be a novel promising approach to the treatment of vascular complications caused by type 2 diabetes.

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