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Destabilization of HIF-1a by Diabetes, Oxidative Stress, Obesity and Other Related Disorders

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Abstract

One of the most fundamental molecular processes in response to hypoxia is the activation and stabilization of a transcriptional factor called hypoxia induced factor 1a (HIF-1a), which is responsible for the regulation of many downstream effector genes. Multiple key biological pathways such as proliferation, energy metabolism, invasion, and metastasis are governed by these genes. This article discusses the role of hypoxia-inducible factor 1a (HIF-1a) in metabolic and pathological processes, particularly in adipose tissue, oxidative stress, inflammation, diabetes and cancer. HIF1A is a basic helix-loop-helix PAS domain containing protein, and is considered as the master transcriptional regulator of cellular and developmental response to hypoxia. HIF-1a regulates the expression of genes involved in angiogenesis, glucose metabolism, inflammation and oxidative stress. In obesity, adipose tissue hypoxia leads to increased expression of HIF-1a, which can lead to chronic inflammation and adipose tissue dysfunction. Another field that HIF-1a is also involved in cancer pathogenesis pathways, such as proliferation, invasion, angiogenesis, and metastasis, and is considered a potential therapeutic target for metabolic/genetic diseases and cancer. Direct and indirect HIF-1 inhibitors have been identified, but only a few have entered clinical trials due to their multiple side effects.

Keywords

HIF-1a, Diabetes, Oxidative Stress, Obesity, Cancer, Angiogenesis, Mitochondria

1. Introduction

HIF-1a is a basic helix-loop-helix PAS domain containing protein and is thought to be a transcriptional master regulator of cellular and developmental responses

to hypoxia [1] [2]. Dysregulation and overexpression of HIF-1a due to hypoxia or genetic alterations is strongly implicated in cancer biology and many other pathophysiology, especially in the areas of angiogenesis, energy metabolism, cell survival and tumor invasion [3].

HIF-1a contains a basic helix-loop-helix domain near the C-terminal, followed by two distinct PAS domains (PER-ARNT-SIM), and a PAC domain (PAS-associated C-terminal) [1] [4]. The HIF-1a polypeptide also contains a nuclear localization signaling motif, two transactivation domains, CTAD and NTAD, and an intervening inhibitory domain (ID) that can suppress the transcriptional activity of CTAD and NTAD. Although there is a total of three HIF, isoforms formed by alternative splicing, however isoform 1 was chosen as the canonical structure and that is the most extensively studied isoform in structure and function [5].

The transcription factor HIF-1a plays an important part in cellular responses to systemic oxygen levels in mammals [6] [7]. HIF-1a and its activity is regulated by various post-translational modifications (hydroxylation, acetylation, and phosphorylation). HIF-1a is known to induce transcription of over 60 genes, including VEGF and erythropoietin, involved in biological processes such as angiogenesis and erythropoiesis [3] [8] [9]. HIF-1a also induces transcription of genes involved in cell proliferation and survival, and glucose and iron metabolism. Consistent with its dynamic biological role, HIF-1 undergoes conformational changes and responds to systemic oxygen levels by binding to the HRE regions of the promoters of hypoxia-responsive genes and inducing transcription [10] [11] [12] [13] [14].

HIF-1a stability, subcellular localization and transcriptional activity are particularly affected by oxygen level. The α subunit forms a heterodimer with the β subunit. Under normoxic conditions, the VHL-mediated ubiquitin protease pathway rapidly degrades the HIF1-1a. However, under hypoxia, degradation of the HIF-1a protein is prevented and HIF-1a levels accumulate to associate with HIF-1b and plays a transcriptional role on target genes as it is presented in **Figure 1** [15] [16]. The enzymes prolyl hydroxylase (PHD) and HIF prolyl hydroxylase (HPH) are involved in specific post-translational modifications of HIF-1a proline residues (P402 and P564 within the ODD domain) that enable binding of VHL and HIF-1a [14]. The enzymatic activity of oxygen sensor dioxygenase PHD is dependent on oxygen level as it requires oxygen as one of the major substrates to be transferred to the proline residues of HIF-1a [11] [17]. The hydroxylated proline residues of HIF-1a are then recognized and embedded in the hydrophobic core of the von Hippel-Lindau tumor suppressor protein (VHL), which is itself part of the ubiquitin ligase enzyme [18] [19]. Hydroxylation of HIF-1a proline residues also regulates the ability to bind coactivators under hypoxia (**Figure 1**) [20] [21].

HIF-1a gene function can be effectively studied based on independent validation by siRNA knockdown [22]. The HIF-1 transcription factor is formed by heterodimerization of HIF-1a and HIF-1b [1] [23]. The role of HIF-1 in hypoxic

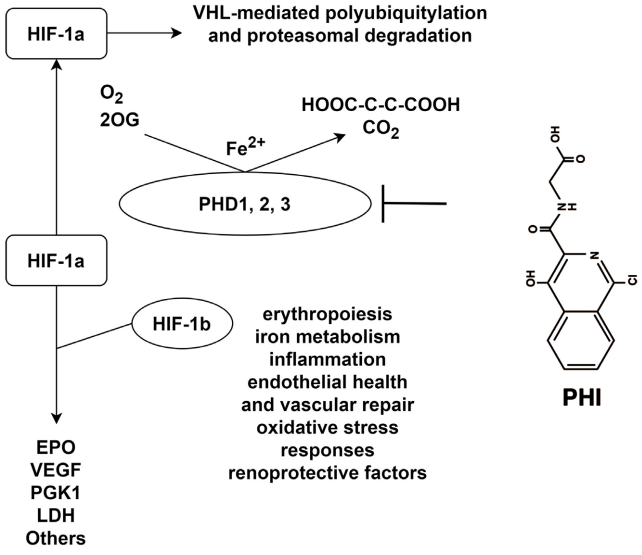

Figure 1. Schematic overview of the PHD/HIF pathway. The oxygen sensitive HIF-1a is constitutively synthesized but it is rapidly degraded under normoxic conditions. However, under hypoxia cellular levels of HIF1-a increase and HIF1-a translocates to the nucleus, where it forms a heterodimer with HIF1-b. Proteasomal degradation of HIF-a is mediated by the pVHL-E3 ubiquitin ligase complex and requires HIF-a prolyl-4-hydroxylation by oxygen and iron dependent PHD dioxygenases (PHD1-3). Decarboxylation of 2-oxoglurate (2OG) produces hydroxylated HIF1-a, succinate and CO_2. Inhibition of PHD or VHL is associated with increased transcription of HIF-regulated genes such as vascular endothelial growth factor (VEGF), erythropoietin (EPO), phosphoglycerate kinase 1 (PGK1), lactate dehydrogenase (LDH) and other genes involved in the regulation of hypoxia responses, including cellular metabolism and mitochondrial function, inflammation, vascular function and oxidative stress and other responses. The chemical structure of a PHD inhibitor (PHI) that can effectively stimulate endogenous EPO production in hemodialysis patients are presented (Haase 2017).

responses were firstly reported by the seminal 1992 and 1993 papers by Wang and Semenza [24] [25].

As it is known, sufficient oxygen is essential for many metabolic processes, including mitochondrial generation of energy production from glucose (stored as ATP) [26]. HIF-1a is essential for normal development. Systemic knockout is embryonic lethal with abnormal placental development and cardiac and vascular abnormalities [27].

In the short term, humans respond to hypoxia by cells in the carotid body sensing lower oxygen and driving increased respiration. Heterozygous HIF-1a null mice demonstrate that HIF-1 plays an important role in carotid body development [28]. HIFs are also the most important factors in mediating the intermediate to long-term response to hypoxia.

Thus, it is not surprising that HIF-1a is regulated by many factors, as it plays a key role in oxygen sensing and hypoxia response [10] [13] [29]-[34]. In unstressed cells, HIF-1a is synthesized, but it has a half-life of seconds to minutes [15]. In the presence of oxygen, iron, and 2-oxoglutarate (*a*-ketoglutarate), HIF-1a is hydroxylated on two proline residues by prolyl hydroxylase domain

(PHD) proteins (also called P4H proteins) [35]. These PHDs function as oxygen sensors to regulate HIF degradation. Another level of regulation is provided by enzymatic asparagine hydroxylation by one factor inhibiting HIF (FIH). Hydroxylated HIF-1a binds to the von Hippel-Lindau (VHL) protein, leading to its ubiquitination and proteolysis [36]. This interaction is inhibited by cobalt. Absence of sufficient oxygen, iron, or 2-oxoglutarate inhibits hydroxylation and thereby inhibits degradation. Likewise, lack of PHDs, FIH, or VHL reduce HIF-1a degradation.

Unproteolyzed HIF-1a binds to HIF-1b, which facilitates translocation to the nucleus, recruitment of transcriptional coregulators, and regulation of gene expression [37].

2. Hypoxia-Inducible Factor 1 Alpha and Diabetes

Hypoxia can be defined as the relative lack of oxygen reaching the tissues. Hypoxia-inducible factors (HIFs) are key regulators of the mammalian response to hypoxia. Under normal circumstances, HIF-1a protein turnover is rapid and hyperglycemia further destabilizes the protein. HIFs are implicated in development of the microvascular and macrovascular complications of diabetes in addition to their role in diabetes pathogenesis [38].

The prevalence of diabetes rapidly rising. In 2017 it was estimated that there were over 450 million people with diabetes worldwide [39]. Diabetes is a leading cause of preventable blindness, end-stage renal failure, and preventable lower limb amputation [40]. It is also associated with increased risk of cardiovascular disease and reduced life expectancy [41].

Insulin is the major hormone produced by β-cells in the islets of Langerhans of the pancreas. It lowers blood glucose levels by stimulating its uptake into tissues such as muscle and fat. Glucose transporter 4 (GLUT4) is largely responsible for this effect [42] [43] [44]. In type 1 diabetes (T1D), β cells are lost as a result of autoimmune-mediated destruction [45] [46]. In type 2 diabetes (T2D), β-cells are unable to release sufficient insulin to regulate glucose due to cell loss, decreased function, or both. Obesity increases the risk for of T1D [47] and T2D [48] [49] [50] in part by reducing insulin sensitivity.

All mammals have processes to sense, respond to, and correct hypoxia. The most important component of this response is mediated by the hypoxia inducible factors (HIFs) [47].

Studies have found that HIF-1b mRNA is reduced in islets of T2D patients and is critical for normal β-cell function [51] [52]. With the heterodimeric composition of the active transcription factors, these findings led us to consider the partner or partners that are important for β cell function [53]. Studies show the role of HIF-1a in β cell function and survival was also shown by observations of improved glucose tolerance in mice fed a high-fat diet and an iron chelator to increase HIF-1a protein stability [54]. Improved glucose tolerance was due to better β-cell function. In mice with β-cell specific deletion of HIF-1a, iron chelation had no beneficial effect on β-cell function [55].

Pancreatic islets, especially β-cells, "sense" glucose by metabolizing it and increasing ATP. This sensing requires cellular glucose uptake and subsequent metabolism. Deletion of HIF-1a in β-cells decreased basal and glucose-stimulated ATP concentrations [53]. Decreased ATP production, even when glucose is elevated, provides a mechanism for impaired glucose-stimulated insulin secretion impairment accompanied by decreased HIF-1 factor expression. Higher intracellular ATP leads to closure of the inwardly rectifying potassium channel Kir6.2, causing the opening of voltage dependent calcium channels, especially L-type channels, in β-cells. The resulting calcium influx stimulates fusion of insulin vesicles with the plasma membrane and insulin release [54].

First-phase insulin release is defined as the release of insulin within 10 min after stimulation. The second phase of insulin release occurs after 10 min. First phase secretion is important for maintaining normal glucose tolerance. The loss of first-phase releases predicts future development of T1D and T2D [55] [56] [57] [58]. Mice lacking HIF-1a in β-cells have a marked loss of first phase insulin release [53]. Interestingly, loss of β-cell HIF-1a increases the risk of T1D. NOD mice (a model of T1D) have low rates to develop diabetes after exposure to the β-cell toxin streptozotocin or to viruses associated with human diabetes [59]. In NOD mice, loss of HIF-1a in β-cells makes β-cells more susceptible to death and increases the risk of spontaneous T1D and the risk of T1D after exposure to streptozotocin or coxsackievirus [59].

Increasing HIF-1a has different effects on glucose tolerance depending on the method used. These contradictory results are discussed below.

Prolyl hydroxylase requires 2-oxoglutarate for its activity, but its regulation is more complex. Other tricarboxylic acid intermediates (succinate and fumarate) compete with 2-oxoglutarate for the binding pocket of PHDs and inhibit their function [60], allowing HIF-1a stability. Pyruvate also inhibits PHD mediated hydroxylation of HIF-1a thereby increasing availability of protein [61].

Together, these effects can be predicted to increase the availability of HIF-1a in hyperglycemia. However, the opposite happens. The presence of β-cell dysfunction leads glucose levels to rise and HIF-1a protein is destabilized [62]. Briefly, increases in 2-methylglyoxal that accompany hyperglycemia stimulate HIF-1a catabolism and inhibit transcriptional activity. 2-Methylglyoxal inhibits HIF-1a and HIF-1b dimer formation and recruitment of the p300/CBP regulatory complex [63]. Therefore, hyperglycemia reduces HIF-1a activity.

Lack of HIF-1a has been associated with decreased β-cell function and survival and glucose induced inhibition of HIF-1a protein stability is also likely to rush distortion in β-cell function and speed progression to diabetes (**Figure 2**) [64].

In addition to the effects of glucose and its metabolites, insulin signaling upregulates HIF-1a through the PI3K and MAPK phosphorylation pathways. Since insulin resistance is present in at least 80% of patients with type 2 diabetes, impaired insulin signaling contributes to the reduction in HIF-1a seen in diabetes [53]. Insulin deficiency associated with β-cell dysfunction or death would further reduces HIF-1a in diabetic hyperglycemia.

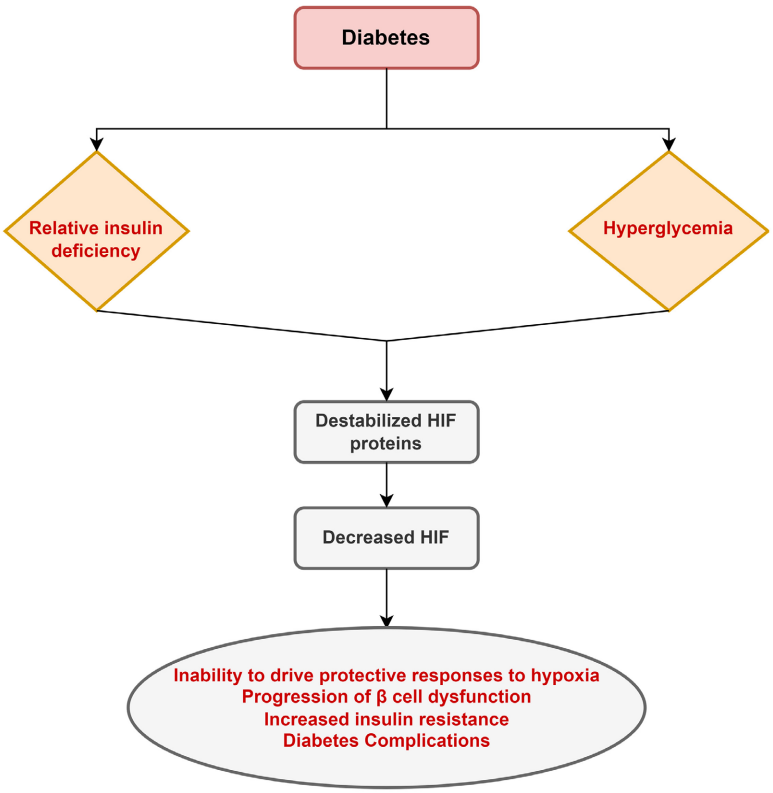

Figure 2. Schematic Interactions between diabetes and HIFs. Insulin resistance and deficiency in diabetes are associated with destabilization of HIF proteins. These concurrent outcomes mediate complex effects on diabetes progression and complications (Cheng, Ho *et al.* 2010).

Furthermore, to the effects of glucose on β-cell function (often called glycotoxicity) and HIF-1a protein stability, lipids affect both β-cell function (lipotoxicity) and HIF-1a [64]. Metabolism of fatty acids, especially palmitic acid, reduces succinic acid. Since succinate inhibits prolyl hydroxylation of HIF-1a, so decreased succinate allows for increased HIF-1a proteolysis. This is also consistent with the hypothesis that glycolipotoxicity is responsible for the increased prevalence of diabetes observed in obesity.

In addition to changes in β-cell function and gene expression seen with β-cell specific deletion of HIF-1a and with HIF-1a knockdown [53] [60], HIF-1a dysfunction is involved in many of the metabolically important tissues and in many chronic complications of diabetes [61].

3. HIF-1a in Muscle

Muscle plays an important role in the development of insulin resistance, being the primary tissue in the body for insulin-stimulated glucose uptake [26] [65] [66]. Insulin increases GLUT4 translocations to the myocyte cell membrane [43] [44]. Muscle contraction during exercise increases oxygen utilization, causing to muscle hypoxia and induction of HIF-1a protein [67] [68].

Muscle exercise and/or hypoxia increase glycolysis, and chronic hypoxia can

decrease mitochondrial content, hypothesizing that most of the energy supply is due to glycolysis [69]. Along with muscle contraction, HIF-1a is important in maintaining muscle function and metabolism in hypoxic conditions [67]. However, HIF-1b is apparently unnecessary for normal muscle fiber type designation and insulin sensitivity, suggesting that an alternate HIF-1a partner is active in muscle [70].

Knockdown of HIF-1a in C2C12 cultured myocytes worsen GLUT4 translocation and glucose uptake [71]. Mice with a muscle specific HIF-1a deletion have a shift from glycolysis with lactate export during exercise to complete oxidation of glucose, but at the expense of extensive muscle damage in the long term [72]. When young, athletic performance increases, but the reverse occurs when muscles are damaged.

The MRL/Mpj mouse strain shows improved HIF-1a-dependent muscle function [73]. In mouse models, inhibiting PHDs to increase HIFs, improves the muscle response to exercise-induced injury [74] and to cryoinjury [75]. In humans, the Pro582Ser polymorphism produces HIF-1a that is relatively resistant to degradation and enhances HIF-1a activity. This polymorphism is common in athletes, especially high endurance athletes [76].

Similar to the above observations in β-cells, increasing HIF-1a due to hypoxia or VHL deletion has detrimental effects on muscle, but increasing HIF-1a with FIH or PHD deletion appears to be beneficial [77]. Taken together, the data indicate that myocyte HIF-1a is required for normal muscle glucose uptake, insulin sensitivity, and prevention of muscle damage. Given these features, it is surprising that there appear to be few published data describing muscle HIF-1a levels in diabetes.

4. HIF-1a and Adipose Tissue

Effects in adipose tissue suggest that the relative hypoxia observed in obesity associated with increased HIF-1a protein leads to increased adipose fibrosis [78] [79]. A similar increase in fibrosis is observed by overexpression of a constitutively active HIF-1a [80].

In one study, reducing HIF-1a using a dominant-negative HIF-1a mutant improved obesity on a high fat diet [81]. This study reported that the HIF inhibitor PX-478 improved fat fibrosis and suppressed high fat diet-induced weight gain. In contrast, another group showed that reducing HIF-1a activity, also with a dominant-negative HIF-1a mutant, increased obesity with loss of normal brown adipocyte phenotype in the interscapular brown fat pad [82]. Both groups overexpressed HIF-1a with a deletion of the DNA-binding domain containing amino acids 30 - 389, and the reasons for the different results remain unclear. Deletion of HIF-1a in adipocytes using the Cre-lox system containing aP2-Cre causes mice to resist to weight gain, have smaller fat pads, and improve insulin sensitivity [83].

The metabolic effects of increasing HIF-1a in adipose tissue were also examined. Mice with VHL deletion of adipocytes (mediated by aP2-Cre) are not

viable and die between embryonic day 14 and 18 [84]. Death was due to extensive hemorrhages involving the brain, liver and skin. VHL-deficient embryos showed increased expression of VEGF, which promotes angiogenesis. Using a β-galactosidase reporter, the aP2-Cre driver showed strong embryonic expression in the hindbrain and spine [84]. This suggests that interpretation of aP2-Cre driven mice and dominant negative aP2-driven overexpression experiments may be complicated by its expression outside of adipose tissue [85].

5. HIFs as Therapeutic Targets for Diabetes and Diabetes Complications

As mentioned above, impaired adaptive responses to hypoxia and hypoxia due to insufficient HIF-1 activation in diabetic tissues are fundamental pathogenic factors in the development of diabetes and diabetic complications. Therefore, future strategies to increase HIF-1 signaling may lead to promising therapeutic modalities for the treatment of diabetes and its complications [86].

Pharmacological induction of HIF-1 promotes wound healing in experimental models of diabetes [85] [86] [87]. Recent preclinical studies in diabetic animal models have shown that PHD inhibition prevents the progression of diabetic nephropathy [88] [89] and atherosclerosis [90], ischemic heart [64] [91] and peripheral neurons [92], also improves cognitive function [93]. Several studies have also shown that PHD inhibition is beneficial for the prevention and treatment of metabolic disorders and obesity [94] [95] and for improving beta cell function [37].

The prolyl hydroxylase inhibitor (HIF-PH inhibitor) roxadustat (FG-4592) was recently approved for the treatment of anemia due to chronic kidney disease [96] and several other HIF stabilizers have clinical trials underway. However, the clinical therapeutic effects of PHD inhibitors on diabetes and diabetic complications need more investigation.

Although topical application of HIF inducers in diabetic foot ulcers has only minimal systemic effects, further mechanistic and translational studies are required in order to identify the right dose, the temporal window and tissue specific application for systemic use of HIF inducers to minimize potential side effects. Further efforts to elucidate the regulation of HIF-1 signaling in diabetes may provide new and more specific therapeutic targets as well as efficient biomarkers for identifying individuals who are most likely to benefit from HIF-targeting therapy [96].

6. HIF-1a Oxidative Stress Protection by Directly Targeting Mitochondria

Hypoxia has also been reported to be associated with increased production of reactive oxygen species (ROS) and cause oxidative stress [97]. ROS is a double-edged sword. Low ROS levels are important signaling molecules in many pathophysiological processes. Excess ROS, on the other hand, damages cellular components and initiating cell death [98]. HIF-1, a key transcription factor in

cellular responses to hypoxia, is a heterodimer composed of a constitutively expressed β-subunit and an O_2-regulated α subunit. Under normoxia, α subunit levels are regulated by ubiquitin dependent proteasomal degradation. Conserved proline residues in the subunits are hydroxylated by O_2-dependent prolyl hydroxylases (PHDs) and modified residues are then ubiquitinated by the pVHL containing E3 ubiquitin ligase complex and degraded by the proteasome [99].

However, under hypoxia, the HIF-1a subunit is stabilized by inhibition of PHDs and accumulates in the cell nucleus [99]. HIF-1 binds to hypoxia response elements and regulates the transcription of hundreds of genes involved in diverse processes as diverse as erythropoiesis, angiogenesis, metabolic reprogramming, cell proliferation and apoptosis or survival in response to hypoxia [100].

Mitochondria are the powerhouses of the cell, as well as acting as O_2 sensors. Moreover, mitochondria are the major source of intracellular ROS in hypoxic cells [101]. As such, mitochondria play an important role in determining cell fate under hypoxia. When O_2 levels fall, the flow of O_2 and electrons in the respiratory chain becomes unbalanced, resulting in overproduction of ROS in the respiratory chain complex, increased oxidation of macromolecules, and subsequent cellular dysfunction or death. Several studies have shown that HIF-1 reduces cellular ROS production by switching energy production from oxidative phosphorylation to glycolysis as **Figure 3** shows [102]. HIF-1 inhibits mitochondrial

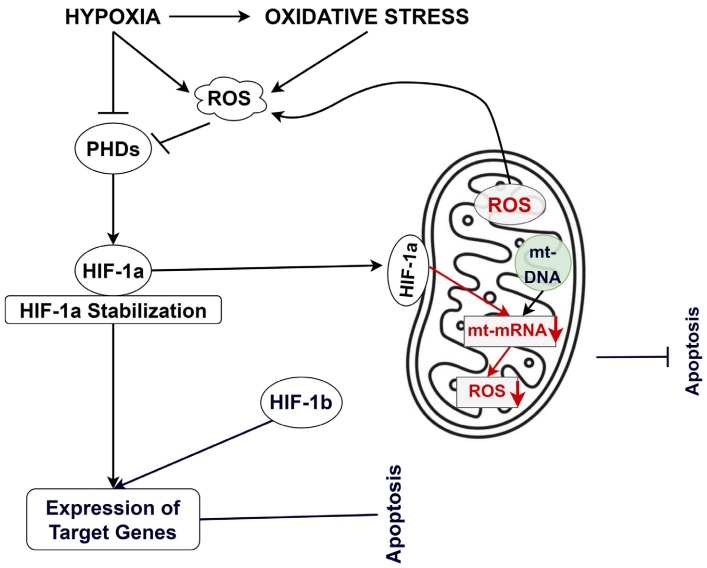

Figure 3. After exposure to hypoxia or H_2O_2 treatment a small fraction of HIF-1a is translocated to the mitochondria. Expression of mito-HIF-1a is sufficient to attenuate apoptosis in-duced by exposure to hypoxia or H_2O_2 induced oxidative stress. Moreover, mito-HIF-1a expression reduced the production of reactive oxygen species, the collapse of mitochon-drial membrane potential, and the expression of mitochondrial DNA-encoded mRNA in response to hypoxia or H_2O_2 treatment independently of nuclear pathways. According to the above, mitochondrial HIF-1a protects against oxidative stress induced-apoptosis independently of its well-known role as a transcription factor (Li, Zhou *et al.* 2019).

respiration and electron transport chain activity by activating the transcription of the microRNA miR-201 downregulating the expression of the iron-sulfur cluster assembly proteins ISCU1/2 and NDUFA4L2, thereby reducing complex I activity [103]. HIF-1 also activates transcription of genes encoding glucose transporters and glycolytic enzymes, increasing glucose flux to lactate [104]. Furthermore, HIF-1 activates the apoptotic protein BNIP3 and induces mitochondria-selective autophagy under hypoxia [105]. Until recently, HIF-1 dependent regulation of mitochondrial function was thought to be directly or indirectly dependent on the nuclear translocation of HIF-1. However, several studies have reported that HIF-1a accumulates in mitochondria after hypoxic exposure or preconditioning [106]. Also, studies have found that a small fraction of HIF-1a trafficked to the mitochondria after chemical or hypoxic stabilization in a highly reproducible manner [107].

7. Regulation of HIF-1a Activity in Adipose Tissue by Obesity-Associated Factors

A hypoxic response of adipose tissue during obesity has been reported by several laboratories [108]. This finding provides a cellular mechanism underlying chronic inflammation and dysfunction of adipose tissue in obesity [109] [110]. Hypoxia in adipose tissue has led the attention to hypoxia marker genes such as hypoxia-inducible factor 1a (HIF-1a) and vascular endothelial growth factor (VEGF). HIF-1a, a transcription factor whose activity is induced by hypoxia, has been used as an indicator of hypoxia in adipose tissue [80] [111] [112] [113]. Its suitability as a hypoxia-specific marker in obesity has yet to be evaluated. HIF-1 is composed of two protein subunits with a basic helix-loop-helix structure. The a-subunit (HIF-1a) determines the transcriptional activity of HIF-1 and its protein abundance increases in response to hypoxia. The a-subunit protein (HIF-1a) is constitutively expressed and known to be the nuclear translocator of aryl hydrocarbon receptors [114].

Coactivators include p300 and CBP, which catalyze the acetylation of histone proteins and the initiation of gene transcription [115] [116]. Corepressor activity is determined by histone deacetylases (HDACs) [117], which have multiple isoforms. It is not clear which HDAC isoform specifically inhibits HIF-1 activity [118] [119] [120]. VEGF is a key target gene of HIF-1. VEGF promotes angiogenesis, a process that is required for adipocyte discrimination and adipose tissue development [121] [122] [123]. Angiogenesis inhibitors suppress adipose tissue growth in animal models [124] [125] [126] and represent a potential class of anti-obesity agents. Interestingly, adipocytes express increased levels of VEGF [127] [128], which provides a molecular mechanism for the high capacity of fat tissue to induce angiogenesis. However, the molecular mechanisms of VEGF expression in adipocytes remain poorly understood. Studies have shown that the three factors that are able to induce HIF-1a protein are preadipocyte differentiation, insulin, and hypoxia [129].

8. HIF-1a and Cancer Angiogenesis

Although HIF-1a has the ability to heterodimerize with HIF-1b and bind to hypoxia-inducible genes bearing hypoxia response elements motif, it shows a different specificity for their transcriptional targets. VEGF and GLUT-1 are regulated by HIF-1a [130]. The endothelial mitogen VEGFA is the most note-worthy of all of these HIF-1 targets, as it is thought to be the master regulator of angiogenesis in tumors. Due to its well-established role in tumor angiogenesis, HIF-1 is considered an attractive therapeutic target for cancer therapy [131]. Direct HIF-1 inhibitors that affect the expression or function of HIF-1, and indirect HIF-1 inhibitors that act on other molecules in related pathways have been identified. The former class of inhibitors targets HIF through various mechanisms, including inhibition of mRNA expression, protein synthesis, dimerization, DNA binding and transcriptional activity. However, only a few of them are in clinical trials, because of their multifaceted side effects [132] [133].

9. Conclusions

Regulation of HIF-1a activity seems to play an important role in multiple metabolic procedures within muscles, adipose tissue, oxidative stress/ROS, proinflammatory cytokines and their complications such as obesity, diabetes, leading very often to cardiovascular diseases and cancer. Furthermore, HIF-1a could be also considered as a potential therapeutic target for many metabolic/genetic disorders.

Recently, a great focus has been also placed on elucidating the role of HIF-1 in cancer pathogenesis pathways, such as proliferation, invasion, angiogenesis, and metastasis, since HIF-1a is directly involved in the shift of cancer tissues from oxidative phosphorylation to aerobic glycolysis (Warburg effect).

Regarding diabetes, by improving glucose control, increases HIF-1a protein and provides a range of benefits, some of which are at least partially mediated by HIF-1a. However, most strategies to improve diabetes and its complications by regulating HIF-1a have yet to be proved clinically useful. The intersection of HIF biology with diabetes is a complex area in which a lot of questions remain, especially regarding the well conducted studies clearly describing discrepant effects of different/contradictory methods of increasing HIF-1a, even within the same tissues.

Authors' Contributions

Investigation, writing original draft preparation AK; supervision, project administration, PK, MT, CF, GAK. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors of this article certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria;

educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this article.

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