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The Roles of Hypoxia-inducible Factors: Potential Clinical Target in Cardiovascular Diseases

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Abstract:

Cardiovascular diseases (CVDs) are among the top causes of death in many countries, and hypoxia is an important factor in the emergence of CVDs. Hypoxia-inducible factors (HIFs) are the essential transcription components responsible for responding to hypoxic opinions, and HIF and its family coordinate the assembly of multiple proteins to regulate HIF pathways, such as the metabolism of glycolysis, the proliferation and migration of endothelial cells, the control of reactive oxygen species, and angiogenesis. According to the duration of inducible hypoxia in CVDs, acute and chronic oxygen deprivation conditions are distinguished. Four typical CVDs, atherosclerosis, and myocardial ischemia as examples of acute hypoxic conditions, and pulmonary hypertension and heart failure as examples of chronic hypoxic states, were chosen to demonstrate that the HIF and its related pathways play important roles in pathogenesis, cellular metabolism, and clinical application. This paper aims to enhance treatment options for medical diagnosis by examining the molecular control of HIFs in CVDs. To further understand the regulation of cellular reactions and the hypoxic-related signaling pathways concerned, HIF could be researched as a novel potential medical target for treating and preventing CVDs.

Keywords: Hypoxia, HIF, cardiovascular disease

1. Introduction

Even though the results of cardiovascular disease (CVD) have improved with the development of medicine, it is still one of the major reasons for high levels of morbidity and mortality around the world, particularly in middle-income countries [1, 2]. Disorders impacting the heart or blood vessels are collectively referred to as CVD, and they include hypertension, coronary artery disease, valvular disease, coronary microvascular dysfunction, and sudden cardiac death, occasionally leading to disease in other organs, such as chronic kidney disease (CKD) [3]. Cardiovascular systems require oxygen to keep cells in homeostasis. Still, the body will experience hypoxia, and the cells will be compelled to engage in anaerobic respiration if the amount of oxygen available cannot keep up with the requirement for energy within the cells [4]. Hypoxia is an important trigger for CVDs because it causes cellular malfunction and death.

Cells produce and increase hypoxia-inducible factor (HIF) in the hypoxia response, and it regulates the majority of the transcriptional responses of the cells to hypoxia [4]. Two main subunits are involved in the HIF family: oxygen-sensitive α subunit (HIF-1α) and expressed consistently and steadily β subunit (HIF-1β). In the presence of oxygen, prolyl hydroxylase domain (PHD) is hydroxylated at the particular proline residues to control HIF-1α protein at the level of post-translational, and system of von Hippel-Lindau (VHL) ubiquitin ligase identifies the hydroxylated HIF-1α protein then triggers proteolytic degradation [5]. Conversely, PHD restraint regulated HIF-1α stability and degradation process is reduced in the absence of oxygen circumstances, and HIF-1α migrates into the nucleus to be with HIF-1β then to form a heterodimer, which triggers the hypoxia-inducible genes transcription by connecting the hypoxia response element (HRE) [4, 6]. Furthermore, under hypoxic conditions, the HIF-1α protein boosts the production of glycolytic enzymes to sustain the amounts of ATP in the mitochondrial respiration procedure and promote glycolytic metabolism, which influences vascular endothelial cells (EC) [7]. To preserve cardiovascular homeostasis, encourage tissue growth and repair, and control the diffusion of nutrients and oxygen, ECs create an external barrier [8]. These barriers supported angiogenesis and enabled tissue healing by requiring glycolysis for the generation of energy to withstand hypoxic injury, and the ability of glycolytic reliance of ECs is strengthened by HIFs in the low oxygen levels [8]. Var-

ious hypoxia-inducible genes, including those linked to cellular metabolism, angiogenesis, and inflammation, are regulated by HIF [4]. Moreover, by controlling its downstream targets and pertinent signaling pathways in cardiovascular systems, HIF can trigger adaptation processes to reduced levels of oxygen and orchestrate protection mechanisms in hypoxic environments [4]. This one reviews the roles of HIF and its related mechanisms in glycolytic metabolism and ECs and also pays attention to the regulation of the HIF pathway at classical hypoxia-related cardiovascular diseases, including atherosclerosis (AS), myocardial ischemia (MI), pulmonary hypertension (PH), and heart failure (HF), and discuss the possible about HIF may develop as a potentially new clinical target for therapy in the course of treatment and preventing CVDs.

2. The Family of HIFs

As a heterodimeric transcription factor, HIF has two well-known subunits, which are HIF-α and HIF-β; at the same time, HIF-β or HIF-1β, also called aryl-hydrocarbon receptor nuclear translocator (ARNT) due to it was discovered to be an aryl-hydrocarbon receptor dimerization companion when aryl hydrocarbons are accumulation [4]. Three isoforms of the HIF-α subunit found in mammals are HIF-1α, HIF-2α, and HIF-3α, and all of them could connect with HIF-1β. In the presence of oxygen, HIF-1α hydroxylation caused by the PHD family, including PHD1, PHD2, and PHD3, and hydroxylation enhance HIF-1α connected with VHL protein, a part of the E3 ubiquitin ligase complex, to polyubiquitination and quickly proteasomal degradation [7]. Moreover, factor inhibiting HIF-1 (FIH-1) is another element to hydroxylate HIF-1α under a normoxic environment. Hydroxylation of HIF-1α occurs in the asparagine residue of the HIF-1α C-terminal transactivation domain to prevent it from attaching to the coactivator histone acetyltransferase p300's CH1 domain [4, 7].

In the absence of oxygen, HIF-1α becomes stable and accumulates, migrating from cytosol to the nucleus to dimerize with HIF-1β subunit to be HIF-1 that links with HRE in the area of interest gene's enhancer or promoter, and then controlling the production of molecules to facilitate ECs angiogenesis, such as vascular endothelial growth factor (VEGF), and regulate the reaction of cells to hypoxia as shown in Fig. 1 [4, 8]. At the same time, hypoxic situations cause HIF-1α to stimulate specific genes involved in glucose metabolism control and to induce glycolysis, and HIF-2α is mainly produced by mammal pulmonary ECs, which have a variety of physiological and pathological roles [8]. HIF-3α can be swiftly triggered at the level of mRNA at mild oxygen deprivation, which suggests HIF-3α is more responsive to hypoxia than either HIF-1α and HIF-2α, and HIF-3α suppresses the target genes that are downstream of both HIF-1α and HIF-3α to avoid their activation [4].

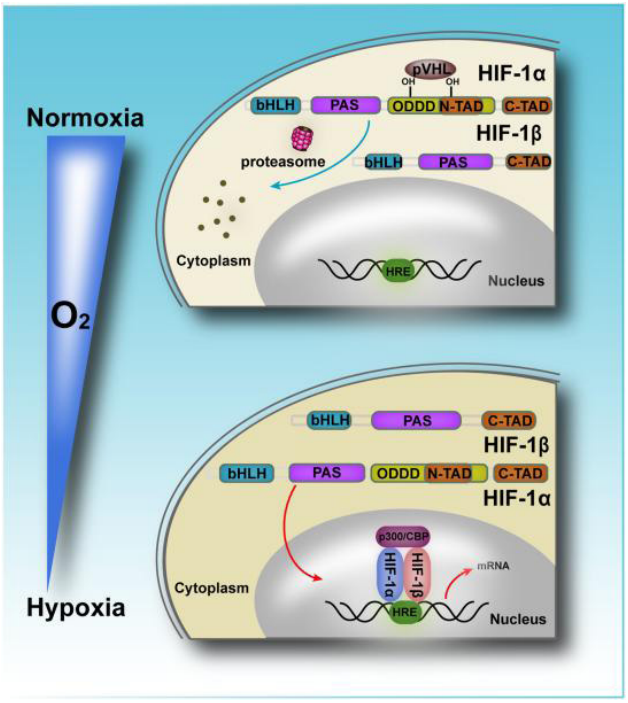

Fig. 1 Activation of HIF-1 under hypoxia conditions [4]. The VHL protein-coupled HIF-1 with polyubiquitin results in proteasomal proteolysis in normoxic circumstances, but HIF accesses the nucleus and triggers the transcription of genes carrying HRE in hypoxic settings.

3. HIF-1 Regulated under the Glycolytic Metabolism

In the presence of oxygen, glycolysis converts glucose into pyruvate in the cytoplasm, then the cycle of tricarboxylic acid (TCA) subsequently coverts the pyruvate in the mitochondria and supplies the transporters of electrons to the electron transport chain (ETC) to produce enough ATP to satisfy the bioenergetic demands of the cells or tissues in the human body and hence preserve homeostasis [7]. However, the activity of mitochondria is substantially impaired in hypoxic environments, and oxygen deficiency prevents the movement of electrons and OXPHOS, which lowers the amount of ATP generated, so the need to keep adequate ATP synthesis through the glycolytic channel without oxygen to meet bioenergetic demands [6, 7].

The HIF family controls glucose metabolism to impact the response of the heart in the human body in situations of lack of oxygen. Under the fewer molecules of oxygen

concentration, HIFs regulate the activity of target genes, and all stages of metabolic processes in cells are impacted via these targets, which promote glycolysis and inhibit oxidative phosphorylation inside the mitochondria [4]. Additionally, reactive oxygen species (ROS) are produced throughout the absence of oxygen as a result of the ETC being disrupted and a disturbed redox state. [4]. While oxygen has a primary role in maintaining HIFs strength, angiopoietin-2 activity and association with ROS generated by stressors from the environment also play a role in preserving HIF equilibrium [8]. Upon accumulation in reaction to a lack of oxygen, HIFs trigger the regulation of numerous genes associated with glycolysis, such as glucose transport. HIF-1 binds to the HRE in the genes encoding these proteins to encourage their enhanced expression, which in turn promotes the activity of such transporter of glucose transporters and enzymes for glycolysis [7].

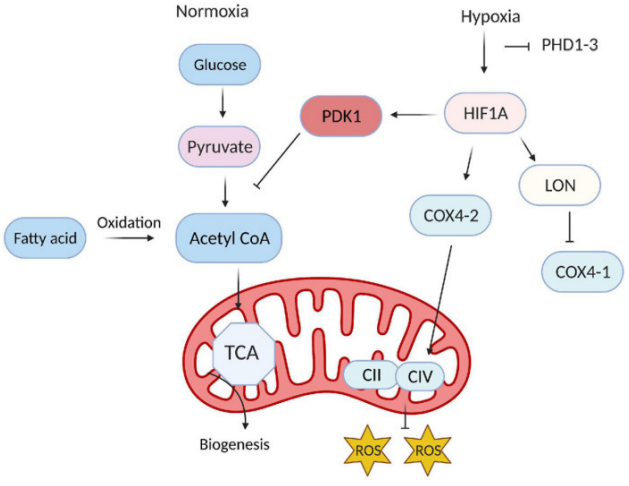

Fig. 2 HIFs stimulate the metabolism of glycolysis in ECs [8]. In normal oxygen-level circumstances, just a small fraction of the byproducts of glycolysis in ECs undergo synthesis into acetyl CoA and reach the TCA cycle. The majority of acetyl-CoA is produced through fatty-acid metabolism and consumed for the generation of energy. In low-oxygen environments, HIFs increase ECs' reliance on glycolysis by promoting the production of PDK1, which blocks the pyruvate from being converted to acetyl-CoA.

HIF increases the activity of PDK, which phosphorylates pyruvate dehydrogenase and prevents pyruvate from being converted to acetyl-CoA. Because acetyl-CoA is the main source of the TCA, HIF suppresses TCA-induced OXPHOS, which further strengthens ECs' reliance on glycolytic metabolism, as shown in Fig. 2 [8]. Thus, the mechanism triggered by HIF equilibrium is the processes of metabolism to produce energy, such as ATP, and the active pathway of cells survives, preserving the heart under hypoxic stress [4]. Furthermore, the regulation of HIF-1 could protect the heart when the metabolism shifts, and HIF-1 stimulation encourages the oxidation of glucose and glycolysis to cause the preservation of cells [5]. Moreover, the level of ROS grows sharply under a lack of oxygen or ischemia conditions, and overexpression alters the levels of hormones and behavior in cardiovascular diseases [5].

4. Roles of HIFs in ECs

ECs control the flow of oxygen as well as nutrients across the human body to facilitate the development of tissues and wound healing. ECs in individuals with good health tend to remain inactive for periods in regular physiological circumstances. Nevertheless, ECs are triggered by angiogenic communication systems with a reaction to damage or illnesses, such as CVDs [8]. ECs have a very low mitochondrial concentration, and the majority of ECs rely on their glycolysis to produce up to a larger number of ATP regardless of environments with enough oxygen [8]. Moreover, there are greater resources accessible for sustaining the activity of perivascular cells since ECs don't need a comparable amount of oxygen, and anaerobic metabolism lowers ROS production and allows ECs to vascularize oxygen-deficient tissues in addition to protecting them from hypoxic injury [8]. To increase the total oxygenation of tissues, ECs under glycolytic metabolism can stimulate angiogenesis under hypoxia [7]. Even though ECs are at nearly enough oxygen condition, reduced OXPHOS produces a lesser level of ROS to expose them to less oxidative damage and shield them from apoptosis regulated by ROS [7].

Oxygen-deprived circumstances cause the proliferation of ECs, which is triggered by HIF-1α. The vascular ECs underwent death as a result of HIF-1α knockdown (KD), and HIF-1α undergoes degradation by PHD and FIH, and then those two hydroxylases KD encourage angiogenesis [5]. HIF-1 has multiple targets associated with the proliferation of ECs. In recent research, by upregulating VEGF expression, microRNA-210, which is increased by HIF-1α, can regulate the reaction of ECs towards the hypoxic environment; also, HIF-1α and microRNA-211 both control the expression of VEGF receptors (VEGFRs) on ECs, and they could together cause ECs to proliferate [5]. Coordinated movement of vascular ECs is required for angiogenesis and vasculogenesis, besides their proliferation. Another research suggested the part that oxygen deprivation plays in the movement of ECs, HIF-1α increases cell motility by reducing VE-cad-herin expression, hence limiting the connection between cells [5].

Typically, a key contributing component to the destruction of vascular homeostasis that results in numerous cardiovascular illnesses is hypoxia. To help cells adjust to a low-oxygen environment, HIFs trigger in hypoxic ECs and afterward modulate many target genes, such as HIF-1α and HIF-2α both regulate the ECs transcriptional reaction through the process of regulation of transcription under hypoxic conditions [4]. In combination, the metabolism of glycolysis promotes the activity of EC's angiogenesis, and HIF-1 also regulates the proliferation and migration of ECs.

5. HIFs in CVDs

For different CVDs, producing more HIFs could protect the heart in ischemia or hypoxia situations. The following cardiac restoration depends just as much on HIF-1 function in ECs under a hypoxic or ischemic environment, and HIF-1 not only has regulation oxygen-sparing benefits on the endothelium but also promotes the production of angiogenic molecules, which in turn drives the angiogenic reaction to hypoxia [9]. Moreover, by changing angiogenesis, vascular reconstruction, glycolysis metabolism, ECs proliferation, and migration, HIF-1α stimulation increases the longevity of cells in low-oxygen conditions [10]. The fact that HIFs may stimulate genes for a variety of purposes highlights how crucial they are as regulators in CVDs under the hypoxic circumvent, and different CVDs could divided by the duration of hypoxia destruction to acute and chronic hypoxic states [11].

Acute pathologic hypoxic states result from a rapid decrease in blood supply to tissues, which may endure for several hours or even days. To make up for the absence condition, some pathways are activated, including enhanced circulation and oxygen transportation and delivery, and permanent damage results when the compensatory systems are overpowered by a lack of oxygen [11]. However, decreased supply of oxygen to tissues can occur in chronic hypoxic states, which can persist for days or years [11]. Next, AS and MI will be the characterized cases of acute hypoxic states, and PH and HF will be the examples of chronic hypoxic states to be discussed.

5.1 HIFs in AS

AS is a common occurrence of a cardiovascular condition linked to hypoxia, and it is most frequently linked to signs like heart attacks, claudication, strokes, and angina pectoris due to disruptions in arterial circulation [6, 8]. A system of capillaries extends from the adventitial vasa vasorum into the lesion's intimal layer, causing the buildup of macrophages, inflammatory cells, lipids, and nutrients in the artery membrane, and this process is thought to be the mechanism by which lesions caused by AS spread [8]. Moreover, because inflammatory cells consume a substantial number of oxygen molecules, and their inner layer thickens to prevent the transport of oxygen, there is less oxygenation available locally, which encourages neovascularization and stimulates HIF [8]. AS causes both HIF-1α and HIF-2α to build up in the human body, and the development of early-phase lesions into later-phase lesions is also correlated with a rise in HIF availability [8].

Furthermore, one important aspect of AS is angiogenesis; a variety of genes that encourage angiogenesis in the plaque, such as VEGF, are expressed through the mediation of HIF-1α [12]. HIF-1α promotes not just VEGF but also the VEGFRs on ECs, such as VEGFR1 and VEGFR2, and the interaction between VEGF with its receptors influences changes in the permeability and growth of ECs that are associated with AS [12]. In the mice atherosclerosis-prone (ApoE-/-) model, HIF amplification boosted lesions, while HIF suppression lowered the production of VEGF and neointimal proliferation [8].

Moreover, one research provided that HIF-1α stimulates the expression of miR-19a under controls and monocyte conformity to damaged ECs, which in turn promotes AS in ECs [5]. In addition, Krüppel-like factor 2, which inhibits PFKFB3 to block activity at glycolytic metabolism in ECs, declines throughout AS; this explains why the absence of oxygen improves the assimilation of glucose in atherosclerotic plaques [8]. Furthermore, another research suggested that AS is caused by endothelial dysfunction and is associated with the absence of oxygen environments, particularly superoxide; the production of ROS under oxygen deprivation is responsible for the onset of endothelial dysfunction [6]. Because of the foregoing, one important participant in the pathophysiology of AS is HIF-1α. Thus, to achieve the goal of modifying the HIF pathway in AS, further knowledge of the cellular localization and duration of HIF-1α in the plaque is necessary [12].

5.2 HIFs in MI

When the cardiac muscle's requirement for oxygen and blood circulation surpasses what is available, a condition known as MI arises and is caused by intracoronary thrombus, which obstructs the circulation of blood to the heart, it results in the diminished synthesis of ATP [4, 8]. Under ischemia or lower oxygen situations, the cardiovascular system produces more HIF to play the role of cardioprotection and elevated HIF-1α in the peri-infarct regions of the ischemic heart [4]. At the same time, the absence of oxygen also causes cardiac ECs to enhance both the levels of HIF-1α and HIF-2α, thereby improving ischemia resistance and encouraging the formation of vessels by many angiogenic factors expression, including VEGF and such ANGPT1 and ANGPT2 angiopoietins [8]. Furthermore,

rebuilding the vascular plexus calls for angiopoietins, and the growth of ECs and the flow of glucose molecules is promoted by VEGF, which assists fresh capillaries in forming [8].

Ischemia-reperfusion injury (IRI) may result from a rise in the generation of ROS and inflammation following an extended state of ischemia, and it largely results from apoptosis-induced cellular death, which is detrimental to ECs more in the human body. Thus, endothelial dysfunction is frequently seen in those who are recuperating from MI [8]. IRI could harm the body's tissues through multiple pathways; there is an overall increase in ROS generation and a decrease in NO bioavailability, in addition to a fall in intracellular concentrations of cAMP followed by a boost in blood leakage and permeability [8]. An increase of infarct throughout is linked to HIF-2α omissions distinctness to monocytes, while HIF-2α stimulation by the epithelial growth factor amphiregulin shrinks the impairment caused by IRI to the myocardium [8]. Recent research provided HIF targets utilize the metabolism of nucleotide to preserve the heart; the stabilization of HIF-1α blocks the expression of CD73 and raises the level of extracellular adenosine via A2B adenosine receptor selectively under MI condition in the lab mouse, which in turn diminished the magnitude of myocardial infarct [4].

5.3 HIFs in PH

When the average blood pressure of the pulmonary is maintained above 25 mmHg at rest situation, it occurs PH. It is caused by hypoxic pulmonary vasoconstriction (HPV) and restructuring of blood vessels [6]. The lungs use HPV as their primary oxygen delivery mechanism when the oxygen level is insufficient in the human body, and this mechanism underlying the reaction is an increase in calcium infiltration brought on by ROS activation [6]. Excessive ROS triggers the sarcoplasmic reticulum and distributes calcium ions into the smooth muscle cells at the pulmonary arteries then promoting vasoconstriction [6]. To keep a standard export from the heart, this mechanism raises blood pressure in the pulmonary vasculature, and a raised systolic pressure is required to occur at the right ventricle [6]. As an acknowledged response in PH, an elevated systolic pressure at the right ventricular is going to result in a drop in artery supply at the right coronary as well as a boost in vascular tension and oxygen consumption [6]. If neglected, PH can induce elevated hypoxemia, and pressure at the pulmonary arterial and right ventricular, which eventually contributes to HF and even death [13].

HIF's function may also influence the onset or advancement of PH in the metabolism of ECs; thus, new PH treatment strategies may include HIFs to regulate the networks of ECs and related targets in the downstream pathway [8]. HIF-1 affects the equilibrium of calcium in vascular cells by controlling multiple calcium-mediated pathways, which contributes to the emergence of PH [5]. In addition, HIF-1α triggers VEGF in the process of controlling activities of ECs, including immigration, differentiation, and proliferation, to enhance angiogenesis throughout pulmonary arterial hypertension (PAH), thus, VEGF plays a crucial role in the regulation of EC [4].

Pulmonary arterial smooth muscle cells (PASMCs) play essential roles during PAH is widely known, as opposed to PASMCs, where HIF-1α is crucial, and pulmonary arterial endothelial cells (PAECs) require HIF-2α [13]. One recent research pointed out that when exposed to prolonged lack of oxygen mice heterozygous for knockout (KO) alleles the Epas1 gene at HIF-2α encoding or Hif1a gene at HIF-1α encoding is shielded from developing PAH, however, when ECs have KOPHD2, PAH emerges during oxygen circumstances [13]. This may be prevented by KO of HIF-2α in the same cells, whereas not HIF-1α, indicating significant pathogenesis of HIF-2α in PAECs; at the same time, PAH regulated by hypoxia is prevented when HIF-2α in ECs is KO in mice model [13]. In light of this, the loss of PHD2 in PAECs worsens PAH, and encourages remodeling of the vascular system, therefore, PHD2's modulation of HIF-2α and its expression are key components in the formation of PAH [11].

5.4 HIFs in HF

HF is an advancing illness, it refers to the heart's incapacity to continue contracting, which results in inadequate blood supply to the extremities and symptoms of hypoxia and ischemia, and the culmination of nearly all cardiac conditions, including AS, MI, and PH, which all linked to a high death rate [4, 6]. The myocardium is burdened more by excessive pressure and elevated heartbeats, which exacerbates the imbalance between oxygen availability and demand, and it causes the heart's hypoxic responses to become persistently active [4]. According to a single report, HIF-1α helps the myocardium develop and become accustomed to stress excess; nevertheless, excessive pressure builds up p53 gradually to restrict the trigger HIF-1α and damages heart angiogenesis and systolic operation, ultimately resulting in HF [4].

Hypoxia-induced alterations in mitochondria are a primary cause and characteristic of HF indicated by previous research on the pathophysiology of HF, and a rapid drop in electrical power brought on by oxygen deprivation and the ensuing malfunction of the mitochondria can seriously harm the function of cardiomyocytes [6]. Additionally, excessive production of ROS may potentially cause cardiomyocyte apoptosis by negatively impacting cell

structure and performance, and the significant reduction in myocardial cells may result in contractile dysfunction and ventricular restructuring [6]. Because of this, malfunction of the left ventricle will result in a drop in cardiac flow and perhaps an infarction of the myocardium, and it is an essential phase in the onset of HF [6].

A tiny Rho GTPase and proangiogenic factor involved in the controlling of the HIF-1α-VEGF signaling chain is Rnd3, and it stimulates the development of ECs tubes and the production of vascular endothelial growth factor A (VEGFA) through its interaction and stabilization of HIF-1α [4]. Treatment with cobalt chloride, which is a stabilizing agent of HIF-1α, substantially rescues the phenotype of angiogenesis deficit and HF, indicating that Rnd3 plays an essential function in stress-responsive angiogenesis; moreover, Rnd3 functions as a new proangiogenic factor engaged in heart reactive angiogenesis via the stimulation of HIF-1α-VEGFA signaling pathway was confirmed [4].

5.5 HIFs in Potential Treatment

According to the activation of the HIFs signaling pathway and their related metabolism in various cardiovascular diseases, scientists research HIFs as a fresh potential target to treat heart diseases. Via the application of ischemic pre-conditioning, HIF-1 induction has been demonstrated previously to offer medicinal benefits in the setting of myocardial ischemia, and short bursts of ischemia-reperfusion before an ischemic insult have been shown to boost tissue staying alive, and this has been associated with an activation of the HIF regulatory mechanism [9]. By using the PHD suppression, iron chelators including hydralazine and desferrioxamine have been demonstrated to exhibit the stabilizing characteristics for HIF-1α [9]. Also, some researches provide that PHD inhibitors are found with characteristics of stabilization of HIF and a few PHD inhibitors have been used to treat such anemia associated with CKD.

Recently research provided that lower levels of serum cholesterol, and atherosclerotic plaque areas were the outcomes of FG-4497, which is a PHD inhibitor medicine [5]. Nevertheless, another scientist pointed out that systemic PHD inhibitors could make the disease worse, such as PH. Except activation of HIF-1 and inhibition of PHD, there are still other potential methods, such as ROS and VEGF. For example, Asiatic acid, an organic substance, improves the activity of mitochondria by lowering intracellular calcium ion levels while reducing the formation of ROS to keep the ability of cardiomyocytes; at the same time, by controlling the application of miR-1290, Asiatic acid reduces HIF-3α and raises HIF-1α production levels, which in turn reduces cell death stimulated by low-oxygen condition [10]. Moreover, given that VEGF is intimately linked to angiogenesis, sevoflurane pretreatment could raise the level of VEGF to promote angiogenesis by triggering the AKT/HIF-1α/VEGF regulatory mechanism to achieve the purpose of preserving the heart [10].

6. Conclusion

Cardiovascular disorders are one kind of the primary urgent for treatment due to their high morbidity and mortality in many countries, and one common feature of those diseases is hypoxia. Undoubtedly, the mechanism of HIFs is essential to the cellular reaction, such as the metabolism of glycolysis and ECs, under the hypoxic environment. Moreover, the HIFs could transcript many genes to promote angiogenesis and regulate cellular metabolism, such as VEGF, to protect the heart from hypoxia and cardiovascular disease. Thus, the HIF family and its related molecular pathway play a key role in cellular metabolism, homeostasis, and cardiovascular disorders. Here, four classic cardiovascular diseases according to the duration of the disease are reviewed, they are atherosclerosis, myocardial ischemia, pulmonary hypertension, and heart failure. Those four hypoxic-induced diseases are all regulated in the HIF molecular mechanisms, and the role of ECs and ROS are also discussed in the diseases, and designed to enhance treatment strategies for medical diagnosis.

There are already many methods found by scientists to treat hypoxic-induced diseases by using targets in the HIF pathway, such as activation of HIF-1α, inhibition of PHD, reducing the accumulation of ROS, and increasing the transcription of VEGF to promote angiogenesis or vessel formation. In those proven ways, the discovery of PHD inhibitors has already assisted scientists solve many hypoxic-induced disorders, such as CKD anemia. However, there still are limits to treatment in those methods. To date, HIF focusing on drugs has primarily targeted the kidney in their design and less related clinical medicine to treat heart disease. Even though many small molecular PHD inhibitors have been found and proven to be used in clinical treatment, PHD inhibitors are presently only used in animal models of cardiovascular diseases, and their progress is slow and challenging. Furthermore, hypoxia-related molecular pathways apart from HIF, such as triggering AMPK, could possibly offer another potential clinical strategy in cardiovascular diseases.

These discoveries may support the creation of alternative medical therapies for the regulation of HIF molecular pathways and related cellular reactions, hence promoting the advancement of diseases associated with hypoxia, especially in cardiovascular diseases. In summary, since HIF-1 and its family are fairly fresh fields of study, additional investigation is necessary to fully understand its

signal pathway, operation, and possible therapeutic uses in cardiovascular disorders.

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