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Molecular Mechanism of the Protective Effect of Hypoxia on Cardiomyocytes

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Abstract. Hypoxia causes damage to the heart and blood vessels that is not directly related to the extent of hypoxia. Therefore, moderate hypoxia may be protective, but severe hypoxia is harmful. Systematic reviews have explored the molecular mechanisms of cardioprotection by hypoxia at the three levels of the hypoxia-inducible factor-1α (HIF-1α) transcription factor, reactive oxygen species signalling, and myocardial calcium ion regulation, in addition to studying mitochondrial membrane channel behaviour under hypoxia. HIF is the master transcription factor that senses changes in oxygen and thus regulates the stability of its α-subunit through oxygen-dependent prolyl hydroxylases. The concentration of ROS in the ROS signalling pathway has a dual nature: at physiological levels, it serves as a second messenger to activate pathways such as JAK2/STAT3 through reversible oxidative modifications; under subchronic hypoxia, the level of ROS first rises and then falls. Otherwise, NO is increased, and antioxidant genes regulated by nuclear factor E2-related factor 2 (Nrf2) are also expressed to help convert oxidative damage into protective adjustment. Intermittent low-pressure hypoxia pretreatment restores the function of SERCA2a by activating the ROS-JAK2/STAT3-Bcl-2 signaling pathway during early reperfusion to quickly relieve Ca^{2+} overload, and simultaneously, transcription factors such as CREM drive long-term changes in gene expression that affect sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a). In short, the protective effect of hypoxia on cardiomyocytes is a complex endogenous adaptation network formed by the joint operation of multiple signaling pathways at different times and places.

Keywords: Hypoxia, Protective Effect, Cardiomyocytes, HIF, ROS

1. Introduction

Hypoxia is often considered a serious disruption of homeostasis in the previous model of physiology. Based on recent data from the population and some initial research, the old mode of life is starting to be reshaped. More than 400 million people live in high-altitude areas above 1,500 meters around the world, and hundreds of millions of low-altitude residents travel to these high-altitude areas for work, tourism or religious reasons each year [1]. The large number of people provides a first-hand natural observation base for researching the impact of reduced atmospheric pressure and oxygen deficiency on the heart and blood vessels. A special case is that people living at medium elevations have a lower risk of death from heart disease compared with those in lowlands.

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A national cohort study in Switzerland showed that for every 1,000-metre increase in altitude, the mortality rate of coronary heart disease and stroke dropped by 22% and 12%, respectively; this protective effect was observed even after controlling for typical confounders such as lipid levels and blood pressure [1]. Austria and the United States have also presented similar evidence [1]; it is proposed that mild hypoxia, in conjunction with other high-altitude environmental factors such as increased ultraviolet radiation and lower temperatures, may collectively activate an endogenous protective mechanism of the cardiovascular system to prolong life. Certainly, these altitude-related advantages are not without deficiencies; at a certain point, severe extreme hypoxia will cause an increase in the death rate [1]. Based on the above classic bidirectional dose-response curve, it can be deduced that the impact of hypoxia on the heart is subject to fluctuations between risk and adaptive defence.

At the time of acute exposure, there is a restrictive and remodeling injury to the heart. Due to a drop in arterial oxygen content, the body promptly stimulates the sympathetic nervous system via the carotid bodies to raise both breathing and heart rates significantly in an effort to restore oxygen delivery [1]. However, due to the physiological limitations of the body at high altitudes, the upper limit of the heart rate (HRmax) is lower. When the altitude is over 2000-3500 metres, there will be a significant reduction in this reserve clinically [1]. Therefore, using heart rate standards for low-altitude environments to evaluate or guide high-altitude exercise may fail to accurately reflect the actual physiological stress placed on the body during exercise and thus be unsafe. Oxygen supply and contractile performance of the functionally intact heart are relatively unchanged at rest and under submaximal load. The above feature offers a relatively safe system for gradually introducing therapeutic exercise under hypoxia.

Combination of controlled hypoxic exposure and moderate exercise is gradually appearing as a new mode of cardiovascular rehabilitation. Both have similar mechanisms; that is, under conditions of hypoxia and exercise, local tissue metabolism increases the production of vasodilators, such as nitric oxide, which act to counteract the systemic vasoconstrictive effect of the sympathetic nervous system and thus achieve what is referred to as "functional sympathetic vasodilation" [1]. Under the above haemodynamic conditions, there will be an improved distribution of blood flow during exercise and strong physiological support for the extended amelioration of vascular endothelial dysfunction and the formation of collateral circulation. In light of the above, research needs to be conducted on the molecular mechanism by which cardiomyocytes sense hypoxic stress and trigger powerful endogenous anti-injury programmes to exploit the protective effect of hypoxia. It provides support for the construction of a new system of treatment. Therefore, an organized collection of all the above evidence from epidemiological, organ-physiological, and molecular regulatory perspectives needs to be carried out to reveal the whole structure of this complex adaptive network. Based on the above, this paper will explore how high-altitude hypoxic exposure affects the cardiovascular system and investigate the molecular mechanisms by which cardiomyocytes respond to hypoxia and how these protective pathways help protect against ischemic injury.

2. Hypoxia-inducible factor (HIF)

The first type of gene regulated by HIF is a common transcription factor for dealing with oxygen-starved conditions. HIF serves as a general regulatory mechanism for maintaining oxygen homeostasis in the body, and is required at many stages in various tissues during embryonic development, life, injury or disease [2]. HIF is a protein product that enables cells to adapt to low-oxygen environments and thus initiates numerous responses under conditions of danger to life, such as cancer development and the onset of heart and blood vessel diseases. Therefore, HIF has

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gradually gained attention in recent years and is now the focus of biomedical research and potential drug treatment.

From a molecular structure perspective, HIF belongs to the basic helix-loop-helix (bHLH)-PAS superfamily, and as a heterodimeric transcription factor, it is composed of an oxygen-sensitive α subunit and a constitutively expressed β subunit (also known as the aromatic hydrocarbon receptor nuclear translocation protein, ARNT) [3]. The three types of the α subunit are HIF-1α, HIF-2α and HIF-3α. Among them, HIF-1α is distributed relatively broadly throughout most tissue cells, while HIF-2α is mainly expressed in endothelial cells, cardiomyocytes and some other parenchymal cells. Several functional domains of the protein structure of the α subunit include the bHLH and PAS domains, which bind to DNA and dimerize with the β subunit; an oxygen-dependent degradation domain (ODD) acts as the core region for oxygen regulation, containing proline residues that can be recognized and hydroxylated by prolyl hydroxylase (PHD); and the N-terminal and C-terminal trans-activation domains recruit transcription coactivators to start target gene expression [4]. The above particular structural modules are able to detect changes in the partial pressure of oxygen and respond precisely through transcription of the HIF system.

The essential regulatory route of HIF activity involves regulating the oxygen-sensitive stability of the α subunit [3]. Under normal oxygen partial pressure (aerobic conditions), specific proline residues in the ODD domain of HIF-α are hydroxylated by PHD enzymes, and this process requires oxygen, Fe^{2+}, and α-ketoglutarate as cofactors. Hydroxylated HIF-α is specifically recognized by the von Hippel-Lindau (VHL) tumor suppressor protein, which serves as an E3 ubiquitin ligase complex; as a result, it is rapidly polyubiquitinated and subsequently degraded by the 26S proteasome. Therefore, the HIF pathway is functionally silenced in the presence of oxygen, and its half-life is less than 5 minutes [4]. In addition, under aerobic conditions, the HIF inhibitor (FIH-1) hydroxylates the asparagine residue in the C-terminal trans-activation domain of the α subunit, thus preventing its binding to the transcription coactivator p300/CBP and further inhibiting the function of residual HIF-α at the transcriptional level [4]. A multi-level, multi-node inhibitory mechanism is employed to keep the HIF pathway firmly in the 'off' state when oxygen levels are normal.

Cells in a hypoxic environment will no longer be inhibited by the above mechanisms. As the catalytic activity of PHD enzymes is dependent on oxygen, hypoxia will cause a reduction in PHD activity, fail to hydroxylate proline residues on HIF-α, and thus prevent it from being recognized and degraded by VHL. Thus, the HIF-α protein can be quickly stabilised and accumulated [3]. Stabilised HIF-α translocates to the nucleus and, along with the constitutive HIF-β subunit, forms an active heterodimer. This dimer specifically recognizes and binds to hypoxia-responsive elements (HREs; core sequence: 5′-RCGTG-3′) located in the promoter or enhancer region of the target gene. Under the co-activation of co-activators such as p300/CBP, a transcriptional program for the downstream gene is initiated [4]. A cascade of these signals goes from "oxygen sensing" to "transcriptional response", and HIF can regulate the expression of more than 100 target genes within hours of hypoxia. HIF is involved in many essential biological functions, including the development of red blood cells, regulation of blood vessels, glucose transport, change in glycolytic metabolic pathways, angiogenesis, changes in mitochondrial function, autophagy, cell proliferation and apoptosis, and thus forms an all-encompassing network of hypoxia-inducible factor responses [5].

The complexity of the HIF system also includes a sensitive oxygen-sensing mechanism, as well as various functions and spatio-temporal regulations for all of its α subtypes [3]. HIF-1α and HIF-2α have high structural similarity and are both regulated by oxygen levels, but their target genes and other biological functions differ considerably (see Table 1). The first type of functional division of this subgroup is its response to hypoxia in the cardiovascular system: HIF-1α is quickly upregulated

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upon acute hypoxia to induce metabolic adjustment and regulate vascular permeability, while HIF-2α is formed when hypoxia persists over a long period or occurs chronically to carry out widespread cell protection and vascular reconstruction. This mechanism has a relay-style spatiotemporal switching mechanism, high plasticity, and fine regulatory control under all types of hypoxic stress [3].

The biological effects of HIF are very sensitive to the characteristics of the hypoxic microenvironment, such as the degree and extent of hypoxia, the time and rate of hypoxia, and specific traits of the injured tissue [5]. Under conditions of severe acute hypoxia, such as myocardial infarction, there is an abrupt reduction in oxygen supply to the ischemic core; this rapidly leads to the accumulation and transcriptional activation of HIF-1α, and a quick-onset protective mechanism is triggered that includes metabolic restructuring and the stimulation of erythropoiesis. However, after the restoration of blood supply and reperfusion, the combination of oxygen-free radical bursts and inflammatory cascade reactions may inhibit the function of HIF; that is, although it provides protection through antioxidant defence and anti-apoptotic pathways, it can also cause additional damage to the tissue due to an overactive inflammatory response. Heck-Swain and Koeppen have published research on the paradox of hypoxia-induced erythropoiesis and found that the overall effect of HIF in myocardial ischemia-reperfusion injury depends on its differential regulation in different tissues and the time pattern of induction [6]. Moderate HIF activation maintains the life of cardiomyocytes by increasing glycolysis and mitochondrial autophagy; in endothelial cells, HIF promotes the expression of angiogenic factors such as VEGF to build collateral circulation; and in infiltrating inflammatory cells, HIF regulates the production of inflammatory cytokines and thus has both pro-damage and pro-repair effects simultaneously [6].

Table 1. Functional differences between HIF-1α and HIF-2α in the hypoxic response

Comparison dimension	HIF-1α	HIF-2α
Tissue expression distribution	Widely expressed in almost all tissue cells	Relatively confined to endothelial cells, cardiomyocytes, and specific parenchymal cells
Priority regulatory target gene	Encode glycolytic enzymes (e.g., phosphoglycerate kinase, lactate dehydrogenase A)	Genes involved in dry state maintenance and vascular remodeling (e.g., Oct4, erythropoietin)
Main Biological Functions	Acute shift in the metabolic drive mode from oxidative phosphorylation to glycolysis	Mediates long-term adaptive responses, such as vascular remodeling and cellular protection
Hypoxic Response Chronology	Rapid upregulation during acute hypoxia	Gradual accumulation under persistent or chronic hypoxic conditions

HIF has a variety of functions in cardiovascular diseases caused by chronic hypoxia, and these functions also vary in different circumstances. The myocardium in chronic heart failure is continuously under relative hypoperfusion and energy metabolism impairment. Sustained low-level activation of the HIF signalling pathway is expected to serve as a compensatory adjustment mechanism by sustaining glycolytic energy supply, promoting angiogenesis and regulating mitochondrial quality [5]. However, too much HIF is activated in pulmonary hypertension, and thus the disease is aggravated by vascular remodelling and right ventricular hypertrophy. A prolonged increase in HIF-2α in the endothelial cells of the pulmonary blood vessels is associated with disease. The two forms of effect are protective and pathological, and this phenomenon occurs in HIF

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biology; therefore, tailored countermeasures must be designed according to the type of disease and hypoxia [5].

With a nucleus-organelle function and other regulatory roles, the HIF family is closely involved in the pathogenesis of hypoxia-induced diseases, so drugs that inhibit the HIF pathway are being developed now. It has been proposed that pharmacological intervention can target HIF-1α through various routes: promoting the degradation of the HIF-1α protein, inhibiting the transcription of its mRNA and blocking protein synthesis, preventing binding to HREs on DNA, and disrupting protein-protein interactions with transcriptional co-activators such as p300/CBP [4]. These inhibitors have shown good anti-cancer properties by blocking HIF-1α-driven glycolytic metabolism, angiogenesis and tumour invasion/metastasis in cancer cells [2, 4]. HIF will be activated at a lower level and thus act as a protector against damage from ischemia in the heart and blood vessels. HIF prolyl hydroxylase inhibitors (PHD inhibitors) can stabilise the HIF-α protein by mimicking hypoxic conditions, and have been used in the treatment of renal anaemia; they show promise for reducing infarct size and improving cardiac function in ischemic diseases, such as myocardial infarction, in preclinical studies [6]. The two treatments of "inhibition" and "activation" have different functions in the HIF pathway in tumours and ischaemic diseases.

3. Reactive oxygen species signaling pathway

The two biological effects of the concentration-dependent rise in reactive oxygen species (ROS) signals in this way are distinct. Hong et al. have systematically studied this "double-edged sword" characteristic and found that ROS at physiological concentrations regulate the activity of signaling proteins by reversibly oxidizing the thiol groups of cysteine residues in these proteins. Oxidative modification has the same specificity and reversibility as phosphorylation; therefore, ROS can also function as second messengers to precisely regulate downstream effector molecules [7]. However, if the concentration of ROS is too high, non-specific oxidative damage will occur in the cell, including lipid peroxidation, protein cross-linking and denaturation, DNA oxidative damage, etc., all of which directly threaten cell viability [7].

The range of effect of ROS signalling is highly dependent on where and how much of the cell it has. Mitochondria are a typical source of reactive oxygen species (ROS) in the cell, and other ROS-producing enzymes include NADPH oxidases (NOX) and xanthine oxidase. Mitochondria-derived ROS serve as the essential trigger for both ischemia preconditioning and postconditioning cardioprotection; after transient reperfusion, a certain quantity of ROS generated by the respiratory chain activates signaling molecules, such as protein kinase C (PKC) and tyrosine kinases, through oxidative modification to promote the opening of mitochondrial ATP-sensitive potassium channels and inhibit the pathological opening of the mitochondrial permeability transition pore (mPTP). Thus, it will be unable to withstand the next period of heart attack.

ROS signalling is not isolated, but also connects to the nitric oxide (NO) signalling system for cardiac protection. Singh et al. have conducted many experiments on the ROS/NO interaction in a rat heart under subchronic hypobaric hypoxia [8]. The study found that over time, during the first period of oxygen deprivation, the heart significantly increased its production of ROS, showed an increase in oxidative stress indicators such as malondialdehyde, and reduced the activity of antioxidant enzymes; however, after an extended period of oxygen deprivation in the subacute stage, nitric oxide (NO) levels continued to rise significantly, ROS levels dropped considerably, and lipid peroxidation damage also decreased [8]. The change from a "ROS-dominant" to a "NO-dominant" state can be considered a molecular hub that switches the heart from an oxidative injury phase to a

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protective-adaptation phase. At the same time, the expression of the endogenous antioxidant genes HO-1 and MT also increased significantly [8].

Most of the end products of ROS signalling are regulated by transcription factors that are then activated. When the cells sense an increase in ROS, a group of redox-sensitive transcription factors is activated to start a whole-body protection gene expression system. Hong et al. have introduced the research results on this transcriptional regulatory network [7]. Among the above, nuclear factor E2-related factor 2 (Nrf2) is the most important transcription factor in the oxidative stress response. Nrf2 is in its inhibitory state in the cytoplasm, bound to Kelch-like ECH-associated protein 1 (Keap1), and is subject to constitutive ubiquitination and subsequent degradation; an increase in ROS oxidatively modifies specific cysteine residues of Keap1, altering its structure to liberate Nrf2. Nrf2 then moves to the nucleus, binds with the antioxidant response element (ARE), and induces the transcription of several antioxidant enzyme and phase II detoxification gene systems, such as superoxide dismutase, catalase, heme oxygenase-1, and glutathione-S-transferase [7]. Differential Effects of ROS signalling under various hypoxia are shown in Table 2.

Table 2. Effect characteristics of ROS signaling under different hypoxic conditions

Type of hypoxia	ROS level changes	Main signaling pathway	Biological consequences
Early stage of acute hypoxia	Significantly elevated (oxidative stress)	Inhibition of antioxidant enzyme activity	Lipid peroxidation injury, cellular stress
Subacute hypoxia	First elevation followed by decline; compensatory increase in NO	Upregulation of HO-1 and MT, activation of HIF-1α	From oxidative damage to protective adaptation
Ischemic preconditioning	Moderately elevated (signaling)	Activates PKC and tyrosine kinase	Triggers the opening of mitoKATP and inhibits mPTP

4. Regulation of calcium ions in the myocardium

Regulation of intracellular calcium (Ca^{2+}) in cardiomyocytes at the level of homeostasis is required to regulate cardiac muscle contraction and relaxation electrically and molecularly. Physiologically, excitation-contraction coupling in cardiomyocytes is mediated by the endoplasmic reticulum (ER) to sequester cytoplasmic Ca^{2+} through SERCA2a (SERCA2a), and this calcium is released from the ER during diastole. However, during ischemia-reperfusion (I/R) injury, severe Ca^{2+} overload frequently occurs in cardiomyocytes due to ATP depletion, oxidative stress and acid-base imbalance; as a result, contractile dysfunction, arrhythmias and even cell death can occur. Therefore, one of the main goals of the study in cardiac protection research has been to explore the endogenous protective mechanisms that can regulate or restore calcium homeostasis. Intermittent hypobaric hypoxia (IHH) is a non-pharmacological model of ischemic preconditioning that can mitigate the effects of I/R injury, such as Ca^{2+} overload and contractile dysfunction. Based on the above studies [9, 10], at least two molecular mechanisms of hypoxia protection have been identified: firstly, a prompt protective effect that is induced by reactive oxygen species (ROS) during early reperfusion, and this pathway involves the JAK2/STAT3 signal cascade; secondly, prolonged adaptive regulation mediated by transcription factors such as the cAMP response element regulatory molecule (CREM) (see Table 3).

At the level of rapid protection mechanisms, a leading study in 2015 clearly showed that ROS produced during the initial period of reperfusion are not only harmful but also act as essential signaling factors for the cardioprotective effects of IHH pre-treatment [9]. Based on the results of this study, during the first few minutes after restoring blood flow in the area of transient ischaemia, the IHH-treated group showed a small increase in ROS, and this weak oxidative stress activated the

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JAK2/STAT3 pathway. The protective effect of IHH pretreatment was lost after adding ROS scavengers or JAK2 inhibitors; thus, it was confirmed that the ROS-JAK2/STAT3 signalling pathway was required [9]. Other research has shown that the activated STAT3 transcription factor can promote the physical association of the anti-apoptotic protein Bcl-2 with SERCA2a at the sarcoplasmic reticulum. The binding has produced a functional connection, not just a co-occurrence: Bcl-2 reactivates the activity of SERCA2a that was inhibited by ischaemia/reperfusion injury (I/R), increases the calcium-uptake capacity of the sarcoplasmic reticulum (SR) from the cytoplasm [9].

Table 3. Comparison of rapid protection and long-term adaptation in myocardial calcium homeostasis regulation

Characteristic dimension	Quick protection mechanism	Long-term adaptation mechanism
Trigger Factor	An appropriate amount of ROS is produced during the early reperfusion phase.	Transcriptional reprogramming induced by intermittent hypoxia exposure
Key signaling molecule	JAK2/STAT3 pathway	CREM and other transcription factors
Effect Target	SERCA2a physically binds to Bcl-2, restoring its activity.	Reprogramming of gene expression for SERCA2a, PLB, CaMKII, and other genes
Time course of action	Rapid activation occurs within minutes after reperfusion	Transcriptional level adjustment lasting from several hours to several days
Functional Consequences	Reduce diastolic cytoplasmic Ca^{2+} levels and reverse Ca^{2+} overload	Establishing a calcium homeostasis "baseline" with enhanced tolerance to I/R injury

In 2005, another group of scientists made some progress in understanding the changes at the molecular level in heart muscle by studying the regulation of calcium-binding proteins by transcription factors [10]. Specifically, in transgenic mice overexpressing the human cardiac-specific CREM (CREM-IbΔC-X) in their hearts, ectopic expression of this transcription factor severely damaged the cardiac calcium regulation network, resulting in pronounced atrial enlargement, atrioventricular hypertrophy, atrial fibrillation and an increased risk of premature death [10]. Notably, the diseased mouse hearts showed a compensatory enhancement of left ventricular contractility, and at the molecular level, this was due to the up-regulation of SERCA2a and β-adrenergic receptors [10]. The two reasons for this are: first, CREM and its regulated cAMP response element serve as key transcriptional hubs to regulate the expression level of Ca^{2+}-related proteins (SERCA2a) in cardiomyocytes; second, the functional impact of either moderate or pathological up-regulation of SERCA2a is modified by the entire regulatory network. Based on the above results, it is proposed that hypoxic protection mechanisms may be regulated at the level of gene expression, induced by remodeling of calcium-regulation-related genes, such as SERCA2a, phospholipid-binding protein (PLB) and calcium/calmodulin-dependent protein kinase (CaMKII), through modulation of CREM or other transcription factors; thus, a transcriptional "baseline" that promotes enhanced calcium homeostasis resistance to ischemia/reperfusion injury may be established [10].

5. Other mechanisms

Jointly regulated by the two essential pathways in the mitochondrial membrane, the mitochondrial ATP-sensitive potassium channel (mitoKATP) and the mitochondrial permeability transition pore (mPTP) also play a protective role against myocardial ischaemia/reperfusion injury. MitokoKATP is a potassium-selective channel located in the inner mitochondrial membrane, and its opening causes a

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modest release of ROS that serves as a signaling molecule to activate downstream protective kinase pathways [11]. mPTP is, on the other hand, a non-selective channel in the mitochondrial inner membrane that irreversibly opens early in the reperfusion phase due to calcium overload and an increase in ROS; this results in mitochondrial swelling, loss of membrane potential, release of pro-apoptotic factors, and is now considered the final common pathway for reperfusion injury [11].

Activation of mitoKATP reduces the opening of mPTP. At the molecular level, mitoKATP opens to reduce the accumulation of calcium in the mitochondria by regulating ion concentrations in the matrix; thus, moderate ROS signals activate PKCε and PI3K/Akt, as well as other Reperfusion Injury Rescue Kinases (RISKs), which indirectly inhibit mPTP; at the same time, mitochondrial tubule structure and ATP synthase activity are maintained, providing support for the recovery of energy metabolism [11].

NO and protein S-nitrosylation mediated by it are involved in this process. Lee et al. reviewed that moderate restoration of eNOS-derived NO during the early reperfusion phase inhibits mPTP by two ways: first, NO directly S-nitrosylates the mPTP component CypD and prevents its assembly and opening; second, NO activates mitoKATP via S-nitrosylation to enhance the protective signaling axis mentioned above [12]. Protecting effects of NO are both time- and concentration-dependent: a relatively small amount of physiological NO exists in the very early hours after reperfusion, and high concentrations of NO can be harmful to the cells and thus lose protective function [12].

6. Conclusion

Hypoxia offers all sorts of defence mechanisms for cardiomyocytes, and all of these protective effects are caused by a complex network of signal transduction pathways operating in different areas and at various times. The core of oxygen-sensing HIF systems coordinates all types of protective responses, from acute metabolic adaptation to chronic vascular remodelling, through subtype-specific division of labour and temporal switching of HIF-1α and HIF-2α. ROS signalling is a dialectical phenomenon that requires both concentration and origin; therefore, medium-level ROS function as protective triggers to promote the expression of anti-apoptotic and antioxidant genes by activating the JAK2/STAT3 and Nrf2 pathways, and at the same time, their co-occurrence with NO signals determines whether an oxidative injury will lead to adaptation or death. At the level of calcium homeostasis, hypoxic protection has a dual-regulation mechanism that includes a rapid response (ROS-JAK2/STAT3-Bcl-2 → SERCA2a functional restoration) and a long-term effect (CREM transcription factors remodeling calcium-regulated gene expression). At the mitochondrial level, the mitoKATP-mPTP interaction axis and S-nitrosylation modification of NO are also the final execution nodes of protective signals. The above are various methods for protecting heart muscle cells against ischaemia-reperfusion damage. Based on this understanding, molecular theories of cardiovascular protection can be developed for hypoxia mimetics, HIF stabilizers and mitochondrial channel modulators, as well as precise control over signal intensity, timing and target cell specificity of interventions to avoid pro-injury effects. Future research should focus on elucidating the spatiotemporal coordination of these signaling pathways and employing multimodal imaging along with genetically encoded probes to monitor dynamic processes in real time. Building on this foundation, combining drugs or gene therapies with different mechanisms of action holds promise for achieving multi-target, temporally precise treatment against myocardial ischemia-reperfusion injury.

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