

HIF-1 α in myocardial ischemia-reperfusion injury (Review)

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Abstract. Myocardial ischemia-reperfusion injury (MIRI) is a severe injury to the ischemic myocardium following the recovery of blood flow. Currently, there is no effective treatment for MIRI in clinical practice. Over the past two decades, biological studies of hypoxia and hypoxia-inducible factor-1 α (HIF-1 α) have notably improved understanding of oxygen homeostasis. HIF-1 α is an oxygen-sensitive transcription factor that mediates adaptive metabolic responses to hypoxia and serves a pivotal role in MIRI. In particular, previous studies have demonstrated that HIF-1 α improves mitochondrial function, decreases cellular oxidative stress, activates cardio-protective signaling pathways and downstream protective genes and interacts with non-coding RNAs. The present review summarizes the roles and associated mechanisms of action of HIF-1 α in MIRI. In addition, HIF-1 α -associated MIRI intervention, including natural compounds, exosomes, ischemic preconditioning and ischemic post-processing are presented. The present review provides evidence for the roles of HIF-1 α activation in MIRI and supports its use as a therapeutic target.

Contents

1. Introduction
2. Molecular characteristics of HIF-1 α
3. HIF-1 α -mediated transcriptional responses to hypoxia

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4. Roles of HIF-1 α in MIRI
5. Involvement of HIF-1 α in the myocardial protective effects of natural compounds against MIRI
6. Roles of HIF-1 α in myocardial ischemic pre- and post-conditioning
7. Future perspectives

1. Introduction

Ischemic heart disease is a major cause of mortality and disability in high-income countries, followed by cerebrovascular disease (1). The mortality rate for ischemic heart disease in China is increasing at an annual rate of 5.05% (2,3). The recanalization of obstructed vessels (reperfusion therapy) by thrombolytic drug treatment, percutaneous coronary intervention (PCI) and coronary artery bypass grafting are considered to be the most effective therapeutic strategies for myocardial ischemia (4). In 2017, 753,142 patients in mainland China accepted coronary artery intervention, representing a 13% increase compared with 2016. The vast majority of patients undergo interventional surgery through the radial artery, and the mortality rate following PCI is low (0.23%) (2). However, there is accumulating evidence that reperfusion therapy may cause further tissue damage, referred to as myocardial ischemia-reperfusion injury (MIRI) (5). Oxidative stress, inflammatory responses, mitochondrial damage and calcium overload, as well as cell death and cell survival-associated signaling pathways are involved in the pathophysiology of MIRI (6). Therefore, the development of therapies targeting the molecular mechanism underlying MIRI development is of significance for the treatment of ischemic heart disease and the prevention of MIRI.

Hypoxia-inducible factor (HIF) is a heterodimeric transcription factor that serves a pivotal role in mediating adaptive responses to hypoxia (7). It consists of an oxygen-sensitive HIF- α subunit and a HIF- β subunit. The latter is also termed aryl hydrocarbon receptor nuclear translocator (ARNT). Mammals have three isoforms of the HIF- α subunit (HIF-1 α , HIF-2 α and HIF-3 α). HIF-1 α is a key factor in the oxygen-sensing pathway initially identified by Semenza *et al* (8) in 1991 and is particularly important for the maintenance of oxygen homeostasis in mammalian cells (9). In cancer, ischemic heart disease or chronic obstructive pulmonary disorder, tissue partial pressure of oxygen is decreased, resulting in the activation of

HIF-1 α (10). Under hypoxic conditions, HIF-1 α protein is does not undergo degradation by the oxygen-dependent ubiquitin proteasome system and is stably expressed. HIF-1 α accumulates in the cytoplasm and is translocated to the nucleus and subsequently forms a dimer with ARNT to regulate target gene transcription (11). The activation of HIF-1 α improves cell survival in a hypoxic environment by altering energy metabolism, proliferation, angiogenesis and vascular remodeling. HIF-1 α is essential for cardioprotection against MIRI (12). Stable expression stabilization of HIF-1 α allows cells or tissues to adapt to hypoxic responses during MIRI, protects cardiomyocytes from ischemic heart disease and improves patient prognosis.

2. Molecular characteristics of HIF-1 α

HIF-1 is the first identified nuclear transcription factor with a highly specific regulatory role in oxygen homeostasis. Both HIF-1 α and HIF-1 β exhibit basic helix-loop-helix (bHLH) motifs and belong to the bHLH-Per-ARNT-Sim (PAS) homology protein family. The bHLH domain is a DNA-binding domain that can bind to hypoxia response elements (HRE) of target genes. The HLH motif mediates dimerization with other proteins. The PAS domain is the only conserved domain among all members of the bHLH-PAS protein family, including HIF-1 α , ARNT, aryl hydrocarbon receptor (AhR) and PAS (13,14).

The protein stability, subcellular localization and transcriptional activity of HIF-1 α can be regulated by the intracellular oxygen concentration. This regulatory association is primarily due to the unique structure of the oxygen-dependent degradation domain (ODDD) (Fig. 1). Under normoxic conditions, the two proline sites (Pro402 and Pro564) of the ODDD of HIF-1 α are hydroxylated by oxygen-dependent prolyl hydroxylase domain (PHD)-containing proteins including the prolyl hydroxylases PHD1, 2 and PHD3 (15). Hydroxylated HIF-1 α is recognized by von Hippel-Lindau (VHL) and degraded by the oxygen-dependent ubiquitin-proteasome pathway (15,16). Therefore, the half-life of HIF-1 α is very short under normal oxygen levels, <5 min.

3. HIF-1 α -mediated transcriptional responses to hypoxia

Under hypoxic conditions, the inhibition of oxygen-dependent PHD1, -2 and -3 enzyme activity results in the degradation of HIF-1 α via the ubiquitin-proteasome pathway. HIF-1 α accumulates and is translocated to the nucleus, where it binds to ARNT to form a heterodimeric complex that binds to HRE. Thus, transcription of target genes is regulated by HIF-1 α via the core sequence of HRE (5'-RCGTG-3') contained in the promoter region (17). The recruitment of CREB-binding protein/p300 results in the induction of the transcription of >100 downstream target genes, such as vascular endothelial growth factor (*VEGF*), erythropoietin, induced nitric oxide synthase (*iNOS*) and glucose transporter (*GLUT*), thereby regulating the response to hypoxia at the cellular and systemic levels (7,18-20). In addition to hypoxia, HIF-1 α can be activated by other factors, such as growth factors, acetylcholine and angiotensin II (10) (Fig. 2). HIF-1 α target genes associated with ischemic heart disease and their roles are listed in Table I.

4. Roles of HIF-1 α in MIRI

Matsushima *et al* (21) demonstrated that HIF-1 α may protect cardiac fibroblasts from apoptosis and represent a potential therapeutic target for heart remodeling following hypoxic injury. Additionally, a number of studies have confirmed that HIF-1 α prevents MIRI and has a cardioprotective effect (22,23).

Protective effect on mitochondrial function. Mitochondria are the main sites for aerobic respiration and are also primary targets for ischemic injury. Mitochondrial dysfunction plays a crucial role in MIRI (24,25). During ischemia, decreased oxygen levels impair mitochondrial ATP production and induce an increase in intracellular Ca²⁺. During reperfusion, the concentration of intracellular Ca²⁺ increases further, resulting in a calcium overload in the cytoplasm and mitochondria. Simultaneously, hypoxia damages the mitochondrial electron transport chain (ETC), resulting in increased reactive oxygen species (ROS) production. The increases in ROS and Ca²⁺ levels lead to the opening of non-selective, highly conductive permeability transition pores (PTPs) in the mitochondrial inner membrane, as well as changes in mitochondrial membrane permeability (26). PTP opening further increases mitochondrial Ca²⁺ and ROS levels and stimulates the oxidation of proteins and lipids in mitochondria (27). Calcium overload and oxidative stress may cause mitochondrial dysfunction, which in turn induces cardiomyocyte apoptosis or necrosis. On the one hand, the decrease in the intracellular oxygen concentration can activate HIF-1 α by inhibiting PHD proteins during ischemia. On the other hand, HIF-1 α can regulate the expression levels of mitochondria-specific genes to adapt to hypoxic stress and improve mitochondrial function (28). Nanayakkara *et al* (29) suggested that HIF-1 α could transcriptionally regulate frataxin expression levels in response to hypoxia and acted as a cardioprotective factor against ischemic injury. Increased levels of frataxin can mitigate mitochondrial iron overload and subsequent ROS production, thereby preserving mitochondrial membrane integrity and the viability of cardiomyocytes. Thus, HIF-1 α preserves the integrity of the mitochondrial membrane, promotes cell survival and protects against MIRI. Moreover, HIF-1 α can also improve mitochondrial respiratory function by activating different cardioprotective signaling pathways, such as the PI3K/AKT and Janus kinase 2/STAT3 pathways, to protect the heart following IRI (30). Additionally, some studies have suggested that mitochondria can regulate HIF-1 α stability and that ROS produced by the mitochondrial ETC can stabilize HIF-1 α under hypoxic conditions (16). Mitochondria-derived ROS have multiple, opposing effects. They can impair mitochondrial function and promote cardiomyocyte death or stabilize HIF-1 α to improve mitochondrial function (31). However, this finding is controversial and may be associated with oxygen levels, as oxygen concentration affects both mitochondrial function and HIF-1 α stability and activity. The determination of the oxygen levels required to optimize mutual beneficial effects of mitochondria and HIF-1 α may provide a novel direction for the treatment of MIRI.

Maintenance of cellular redox balance. ROS are generally considered to be toxic by-products of aerobic metabolism and

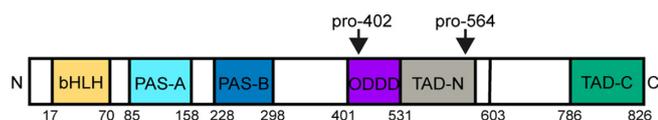


Figure 1. Schematic illustration of the domain structure of HIF-1 α . HIF-1 α consists of a bHLH motifs and a PAS domain in the NH₂-terminal, which are necessary for heterodimerization and DNA binding to hypoxia response elements. The two TADs, which stimulate transcription, are present in the COOH-terminal of HIF-1 α . TAD-C interacts with coactivators such as CREB-binding protein/p300 to activate gene transcription. HIF-1 α also contains an ODDD, which promotes proteasomal degradation of HIF-1 α by PHD-containing enzymes and factor inhibiting HIF. HIF-1 α , hypoxia-inducible factor-1 α ; bHLH, basic helix-loop-helix; PAS, Per-ARNT-Sim homology; TAD, transactivation domains; TAD-N, transactivation domain N terminal; TAD-C, transactivation domain C terminal; ODD, oxygen-dependent-degradation; PHD, prolyl hydroxylase domain.

are the primary cause of macromolecular destruction (32,33). However, it has been demonstrated that ROS also contribute substantially to numerous physiological and pathological conditions (34). In MIRI, ROS generation begins during ischemia, and large amounts of ROS are produced during reperfusion. Excessive ROS accumulation in cells is one of the primary causes of MIRI. This deleterious effect is mediated by the oxidative modification of proteins, lipids and histone-free mitochondrial DNA (35). Therefore, the elimination of excessive ROS in cells and the alleviation of oxidative stress in cardiomyocytes can promote myocardial cell survival and decrease the severity of MIRI (36,37).

The mitochondrial ETC is an important source of ROS and may contribute to MIRI (38). In ischemia, an abnormal increase in ROS causes the accumulation of succinate, resulting in decreased ETC complex activity. Following reperfusion, succinate is rapidly oxidized to generate large amounts of ROS. A notable increase in ROS and IR-induced Ca²⁺ influx leads to mitochondrial PTP opening, which decreases ETC activity and further increases the formation of ROS. In addition, the NADPH oxidase (Nox) family produces large amounts of ROS. The Nox2 and Nox4 isoforms are major components of the Nox family that produce reactive oxidants in the heart, leading to MIRI. Decreased ROS production by mitochondria and Nox can attenuate the severity of MIRI, whereas low levels of ROS can also modulate HIF-1 α expression levels (32,39).

HIF-1 α contributes to MIRI through numerous mechanisms. It can activate the HIF pathway, thereby activating target genes involved in the regulation of the redox state of cells as well as decreasing ROS production and apoptosis in the cardiomyocytes of patients with IRI (6). Additionally, HIF-1 α stabilizes mitochondrial function and promotes the production of mitochondrial antioxidants in cells. For instance, HIF-1 α can enhance the antioxidant capacity of cells through the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and by upregulating the synthesis of the antioxidant tripeptide glutathione and superoxide dismutase 2 (32,40,41). Furthermore, HIF-1 α mediates a shift from oxidative metabolism to glycolysis (thus decreasing the production of mitochondrial oxidants), decreases ETC activity and attenuates mitochondrial ROS production, thereby avoiding cell death (42). HIF-1 α mediates ROS production by mitochondria and the Nox family and regulates the redox state of cells, which decrease the severity of MIRI (36).

A number of studies support the beneficial effects of HIF-1 α on the maintenance of cellular redox balance (43-45). However, this view is also somewhat controversial. Tang *et al* (46) demonstrated that during MIRI, the polyol pathway increases the cytosolic NADH/NAD⁺ ratio, resulting in HIF-1 α activation and transferrin receptor upregulation, which exacerbates oxidative damage and increases lipid peroxidation. However, the effect of HIF-1 α on oxidative stress was not evaluated separately in this previous study. Further investigation is needed to determine the dynamic regulatory effects of HIF-1 α on different types of redox indicators at different time points in MIRI.

HIF-1 α signaling pathway. Since the first reported target gene of HIF-1 α (erythropoietin), hundreds of downstream targets have been identified, demonstrating the complexity and importance of the HIF-1 α signaling pathway (15). In MIRI, HIF-1 α can regulate and participate in a number of signaling pathways that protect the heart (47). MIRI initially leads to hypoxia, resulting in AKT phosphorylation and activation of HIF-1 α and numerous protective genes (48). Dong *et al* (49) demonstrated that sevoflurane pretreatment can increase the expression levels of VEGF by activating the AKT/HIF-1 α /VEGF signaling pathway. VEGF is closely associated with angiogenesis. In MIRI, increased angiogenesis can effectively improve hypoxia in lesions, thereby protecting the heart (50). *iNOS* acts downstream of HIF-1 α and has a cardioprotective effect in MIRI (51,52). In addition, heme oxygenase-1 (HO-1), adiponectin, insulin-like growth factor-2, GLUT and other loci are involved in the protective effect of HIF-1 α against MIRI (18).

In MIRI, HIF-1 α can also act by directly or indirectly regulating numerous signaling pathways (42,49). In terms of mitochondria, HIF-1 α can directly or indirectly influence mitochondrial function, decrease mitochondrial damage and attenuate the severity of MIRI (53). HIF-1 α can induce myocardial mitochondrial autophagy via the HIF-1 α /Bcl2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) signaling pathway, thereby promoting myocardial cell survival following MIRI. However, this is limited to HIF-1 α -mediated mitochondrial autophagy in the early stage of IR, which may lead to protective responses, whereas prolonged autophagy may promote cardiomyocyte death. In terms of oxidative stress, HIF-1 α also plays a significant role. For instance, HIF-1 α can upregulate Nrf2, which then activates antioxidant enzymes to protect cells by enhancing intrinsic ROS clearance (23,53). In terms of inflammation, the phosphorylation of I κ B α during hypoxia results in the degradation of I κ B α and activation of NF- κ B (48). However, HIF-1 α activation can inhibit the NF- κ B pathway and induce HO-1, thereby attenuating the production of pro-inflammatory cytokines, inhibiting tissue inflammation and decreasing the severity of MIRI. In addition, HIF-1 α can regulate numerous signaling pathways, such as GSK3 β /mitochondrial PTP, β -catenin, ERK1/2, Bcl-2, PI3K/AKT and mTOR, which are involved in the regulation of broad-spectrum cell functions, and thus can decrease the severity of MIRI (54-57).

Crosstalk between HIF-1 α and non-coding RNAs. MicroRNAs (miRNAs or miRs) are small non-coding RNA molecules ~22 nucleotides in length. They primarily bind to the 3'

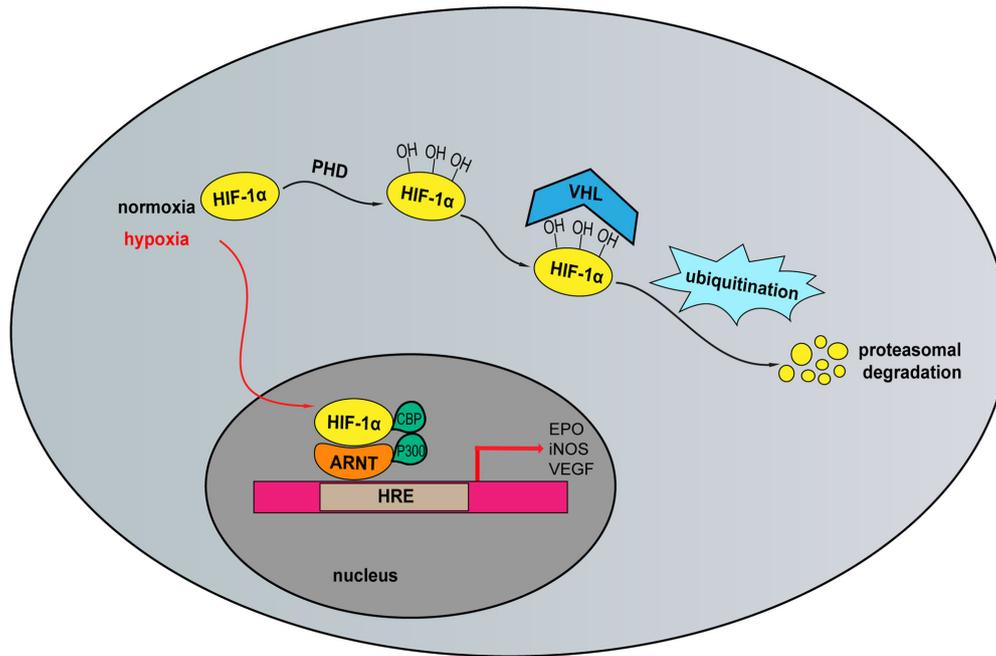


Figure 2. Oxygen-dependent regulation of HIF-1 α . In normoxic conditions, HIF-1 α protein is hydroxylated by prolyl hydroxylases PHD1, PHD2, and PHD3. Hydroxylated HIF-1 α is recognized by VHL and degraded by the ubiquitin-proteasome pathway. In hypoxic conditions, HIF-1 α accumulates and translocates to the nucleus where it binds to ARNT to form a heterodimeric complex that binds to the promoter region of the HRE. CBP/p300 recruitment induces transcription of downstream target genes. HIF-1 α , hypoxia-inducible factor-1 α ; PHD, prolyl hydroxylases; VHL, von Hippel-Lindau; ARNT, aryl hydrocarbon receptor nuclear translocator; HRE, hypoxia-response element; CBP, CREB-binding protein; EPO, erythropoietin; iNOS, inducible nitric oxide synthase; VEGF, vascular endothelial cell growth factor; PHD, prolyl hydroxylase domain.

untranslated region of mRNAs to control stability and translation, thereby decreasing protein levels. More than 30% of genes in the human genome are regulated by miRNAs. A number of studies have reported that miRNAs serve a vital role in cardiovascular disease (58). Sheng *et al* (59) suggested that the overexpression of miR-7b inhibits IR-induced apoptosis in H9C2 cells by targeting the HIF-1 α /phosphorylated-P38 pathway. *In vivo* experiments have demonstrated that overexpression of miR-335 enhances the transcriptional activity of HIF-1 α , increases the expression levels of HO-1 and iNOS and inhibits the opening of mitochondrial PTP, thereby decreasing myocardial infarct size and myocardial apoptosis as well as improving MIRI (41). Liu *et al* (60) demonstrated that sirtuin 1 (SIRT1) also acts as a transcriptional repressor to suppress the expression levels of miR-138 in adult sensory neurons in response to peripheral nerve injury. Therefore, miR-138 and SIRT1 can form a mutual negative feedback regulatory loop, which provides a novel mechanism for controlling intrinsic axon regeneration. The overexpression of miRNA-138 can decrease apoptosis following myocardial IR by decreasing the expression levels of HIF-1 α . This may be explained by the difference between early and prolonged hypoxia (60). During early hypoxia, changes in miRNA levels may contribute to the accumulation of HIF-1 α and maintain the steady-state levels of HIF-2 and HIF-3 (61). In addition, HIF-1 α can act as a modulator of miRNA function. Wu *et al* (62) demonstrated that the accumulation of HIF-1 α following myocardial infarction leads to a decrease in miRNA-10b-5p, which mediates the apoptosis of cardiomyocytes. Although the number of known miRNAs associated with HIF-1 α is increasing, the majority of studies have concentrated on cancer cell lines, and relatively little is

known about their role in cardiovascular disease, particularly in MIRI (63,64).

Long non-coding RNAs (lncRNAs) are >200 nucleotides in length and have no protein-coding properties; they mediate numerous biological processes, such as cell proliferation, cell differentiation and apoptosis (65). lncRNAs negatively or positively regulate the expression levels of protein-coding genes by numerous modes of action. For example, one type of lncRNA, referred to as competitive endogenous RNAs (ceRNAs) (66) decrease the availability of functional miRNAs by acting as a complementary sequence for miRNA binding. lncRNAs are closely associated with a number of biological functions and pathological processes (e.g. cardiovascular diseases) (67). There is increasing evidence that lncRNAs serve a significant role in the regulation of the myocardial IR process (68). For example, Ren *et al* (69) investigated the effect of lncRNA nuclear enriched abundant transcript 1 (lnc-NEAT1) on cell proliferation and apoptosis in MIRI and observed that lnc-NEAT1 is overexpressed in MIRI compared with levels in normal cardiomyocytes. Downregulation of lnc-NEAT1 enhances cell proliferation and inhibits cell apoptosis by targeting miR-193a in IR injury H9C2 cells (69). Li *et al* (70) assessed the role of lncRNA H19 in the regulation of MIRI and suggested that H19 expression levels are downregulated in IR hearts of mice and cardiomyocytes treated with H₂O₂. They also demonstrated that H19 functions as a ceRNA, decreasing the expression levels of miR-877-3p via the aforementioned base-pairing mechanism. However, the association between HIF-1 α and lncRNAs has not yet been fully elucidated. Yang *et al* (71) assessed the association between HIF-1 α and hypoxia-responsive lncRNA-p21 and demonstrated that lncRNA-p21 is essential for enhancing cell glycolysis under

Table I. HIF-1 α target genes.

Function	HIF-1 α target	(Refs.)
Angiogenesis	Vascular endothelial growth factor	(7,48)
Erythropoiesis	Erythropoietin	(19)
Vascular tone	Induced nitric oxide synthase	(20)
	Heme oxygenase-1	(47)
Glucose metabolism	Glucose transporter	(18)
Mitochondrial function	Frataxin	(29)
Mitochondrial function	Bcl-2 and adenovirus E1B 19-kDa-interacting protein 3	(52)
Anti-oxidation	Nuclear factor erythroid 2-related factor 2; superoxide dismutase 2	(39)
	Nox2, Nox4	(38)
	GSK3 β	(53)
Apoptosis	Phosphorylated-P38; Bcl-2	(58)
Remote ischemic preconditioning	Interleukin-10	(82)

HIF-1 α , hypoxia-inducible factor-1 α ; Nox, NADPH oxidase.

hypoxic conditions. VHL-mediated HIF-1 α ubiquitination is attenuated and leads to the accumulation of HIF-1 α , promoting glycolysis under hypoxic conditions (72). Xue and Luo (73) investigated the mechanism by which lncRNA HIF-1 α -antisense RNA 1 (AS1) regulates cytokine signaling inhibitor 2 (SOCS2) via miR-204 in MIRI ventricular remodeling: The silencing of HIF1 α -AS1 and upregulation of miR-204 inhibited apoptosis, and lncRNA HIF1A-AS1 served as a ceRNA to adsorb miR-204, thereby inhibiting miR-204 and increasing SOCS2 expression levels. The downregulation of HIF1A-AS1 and upregulation of miR-204 can attenuate ventricular remodeling and improve cardiac function in mice following MIRI by regulating SOCS2. There is extensive evidence that interactions between HIF-1 α and lncRNA play pivotal roles in many diseases (73); however, further research on their involvement in MIRI is needed. In-depth studies of the specific mechanisms of action may provide a new direction for the treatment of MIRI.

5. Involvement of HIF-1 α in the myocardial protective effects of natural compounds against MIRI

Several studies have demonstrated that certain natural compounds alleviate MIRI, and the therapeutic effect is mediated by HIF-1 α . For example, Liu *et al* (74) demonstrated that saponins of *Panax notoginseng* had protective effects against MIRI via the HIF-1 α /Bcl-2/BNIP3 pathway, which increases mitochondrial autophagy. In addition, Shen *et al* (75) suggested that *Panax notoginseng* saponin Ft1 could increase the expression levels of HIF-1 α and growth factor secretion, thereby activating the PI3K/AKT and Raf/MEK/ERK signaling pathways. Asiatic acid is another natural compound that decreases ROS accumulation, enhances mitochondrial membrane potential and decreases the intracellular Ca²⁺ concentration to improve mitochondrial function (76). In H9C2 oxygen/glucose deprivation/reoxygenation *in vitro* models, asiatic acid protects against MIRI, which is mediated by the AKT/GSK-3 β /HIF-1 α signaling pathway (76). Moreover, asiatic acid decreases HIF-3 α by regulating miR-1290 targeting, thereby increasing HIF-1 α expression levels, resulting in decreased hypoxia-induced

apoptosis (62). Lastly, several other natural compounds, such as ginsenoside Rg1, paclitaxel, dihydrotanshinone I and protocatechuic aldehyde, can protect against MIRI by affecting mitochondria, ROS, angiogenesis and cell survival through increases in HIF-1 α expression levels (77,78).

6. Roles of HIF-1 α in myocardial ischemic pre- and post-conditioning

Ischemic preconditioning (IPC) aims to enhance resistance to subsequent ischemic injury by transient ischemia. Post-IPC protection is divided into two time periods: Immediately following IPC and 12-24 h after IPC. Cai *et al* (79) evaluated the role of HIF-1 α in the acute phase of IPC and suggested that compared with wild-type mice, cardiac function was improved in mice expressing the HIF-1 α gene following IPC, and that infarct size and cell death decreased. These findings indicated that the reduced severity of MIRI following IPC is HIF-1 α -dependent. Jia *et al* (80) demonstrated that IPC could activate HIF-1 α , upregulating miRNA-21 at the transcriptional level and ultimately decreasing the production of proinflammatory cytokines and apoptosis in target organs. IPC can also protect the heart by upregulating myocardial iNOS expression levels, which is also mediated by HIF-1 α . Furthermore, HIF-1 α plays a key role in remote IPC (81). In remote IPC, transient IR in the arm or leg protects the heart from long-term coronary occlusion and reperfusion. Cai *et al* (82) demonstrated that remote IPC increases plasma IL-10 levels and decreases myocardial infarct size in wild-type mice, but not in HIF-1 α knockout mice. Their study further revealed that HIF-1 is necessary and sufficient for induction of IL-10 gene transcription in cultured mouse myocytes, indicating that the protective effect of remote IPC on MIRI depends on HIF-1 α (82). Late IPC can also increase the expression levels of HIF-1 α and IL-10 in the heart, thereby activating the cardiomyocyte anti-apoptosis and survival signals and thus serving an anti-MIRI role (83).

Previous studies have suggested that ischemic post-conditioning can improve myocardial function, decrease

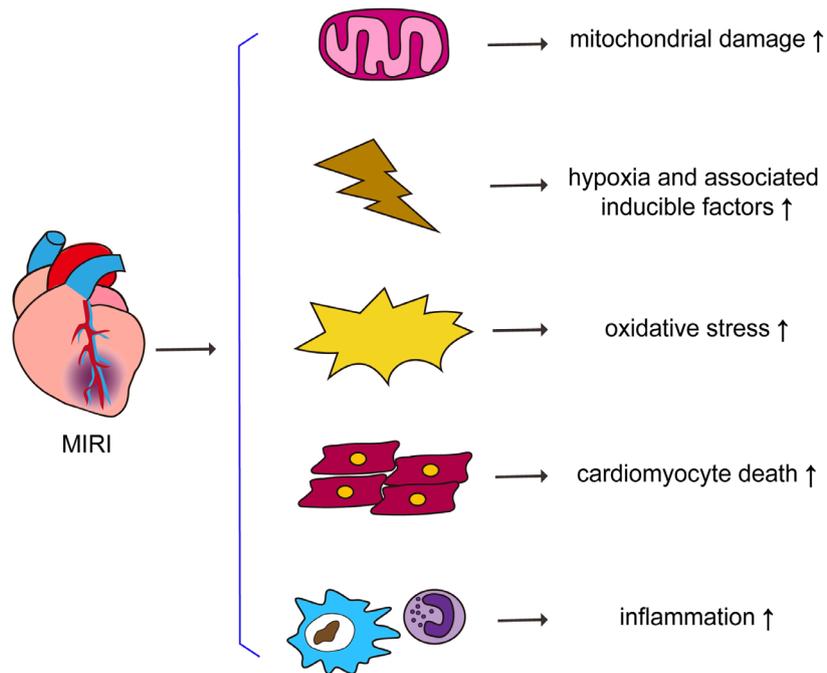


Figure 3. Pathophysiological mechanisms involved in MIRI. Oxidative stress, inflammatory responses, mitochondrial damage and calcium overload, as well as hypoxia-associated factors contribute to the pathophysiology of MIRI. MIRI, myocardial ischemia-reperfusion injury.

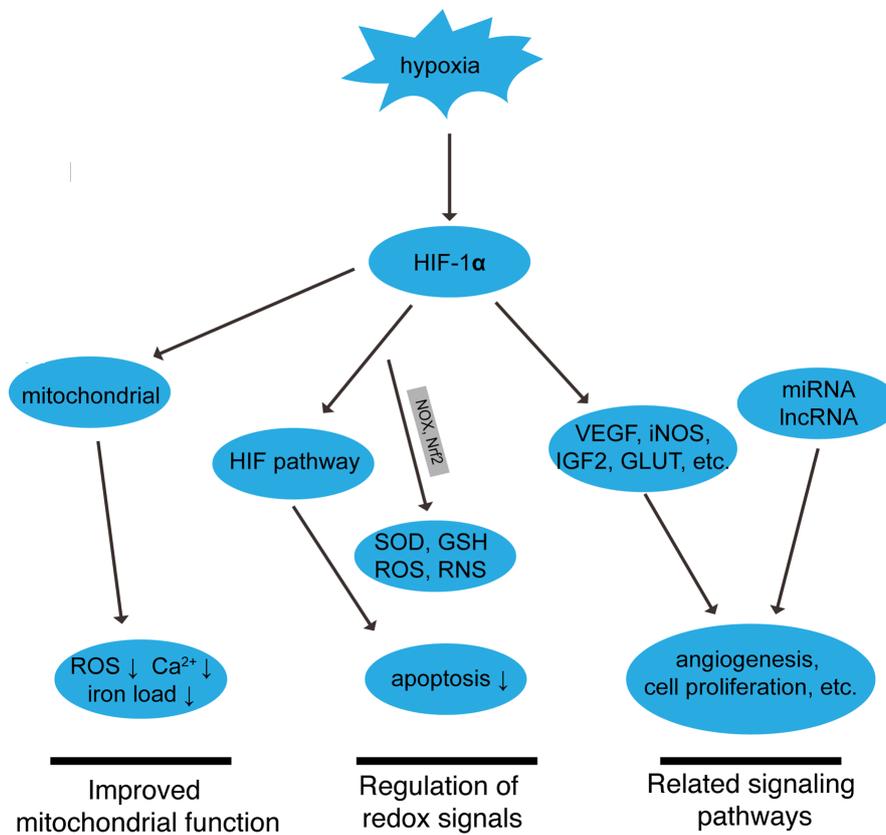


Figure 4. Roles of HIF-1 α in MIRI. The upward-facing arrow indicates enhancement. The downward-facing arrow indicates inhibition. MIRI, myocardial ischemia reperfusion injury; HIF-1 α , hypoxia-inducible factor-1 α ; miRNA, microRNA; lncRNA, long non-coding RNA; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; iNOS, induced nitric oxide synthase; IGF2, insulin-like growth factor 2; GLUT, glucose transporter; Nox, NADPH oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; glutathione; ROS, reactive oxygen species; RNS, reactive nitrogen species, RNS.

myocardial infarct size, and protect cardiomyocytes against MIRI. For example, Wan *et al* (84) reported that ischemic

postconditioning can enhance HIF-1 α activity in the heart of rats following MIRI, and that HIF-1 α can act on miR-214

to relieve MIRI. In addition, remote ischemic postconditioning can notably decrease the degree of MIRI severity. Wang *et al* (85) demonstrated that the cardioprotective effects of remote ischemic postconditioning are primarily associated with macrophage migration inhibitory factor (MIF). Remote ischemic postconditioning confers protection against MIRI through the MIF-AMPK signaling pathway. However, MIF also plays a role in remote ischemic postconditioning through the HIF-1 α -dependent humoral pathway, which inhibits HIF-1 α and leads to a decrease in plasma MIF and concomitant increase in cardiac MIF, thereby reducing its cardioprotective effects. In summary, HIF-1 α serves critical roles in IPC, including remote IPC, late IPC and their post-conditioning, and may thus represent an important target for MIRI treatment.

7. Future perspectives

With the rapid development of biomedical research in the past decade, the mechanisms underlying MIRI have been extensively studied. MIRI is mediated by multiple factors. Cardiomyocyte death may be promoted by a number of synergistic mechanisms throughout the pathophysiological process. Numerous molecular targets associated with MIRI and cardioprotection have been identified (86,87). HIF-1 α is one of the most promising targets (88). HIF-1 α can mitigate MIRI by various complex mechanisms (Figs. 3 and 4). However, although a previous study has demonstrated that inhibiting HIF-1 α in the early stage of cerebral IR injury in rats can decrease infarction volume and mortality by inhibiting apoptosis, it is unclear whether a similar process might occur in MIRI (89). The mechanisms underlying the protective effect of HIF-1 α in MIRI, including the roles of genes involved in glycolysis, mitochondrial function, cell survival, apoptosis and oxidative stress, are still poorly characterized. HIF-1 α regulates multiple target genes and may thus play different roles at different stages of MIRI progression via different mechanisms. Further research on the role of HIF-1 α in the pathophysiology of MIRI and the underlying mechanisms is therefore essential.

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Authors' contributions

CC and YH conceived and designed the review. JZhe retrieved the relevant literature and wrote the manuscript. HC constructed the figures. PC, JZho and YC reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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