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

JIE ZHENG[1*], PEIER CHEN[1*], JIANFENG ZHONG[2], YU CHENG[1], HAO CHEN[1], YUAN HE[1] and CAN CHEN[3]

[1]Laboratory of Cardiovascular Diseases, Guangdong Medical University, Zhanjiang, Guangdong 524000; [2]Guangdong Key Laboratory of Age-related Cardiac and Cerebral Diseases, The Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524001; [3]Department of Cardiology, The Second Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524003, P.R. China

Received January 31, 2020; Accepted August 20, 2020

DOI: 10.3892/mmr.2021.11991

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-1α (HIF-1α) have notably improved understanding of oxygen homeostasis. HIF-1α 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-1α improves mitochondrial function, decreases cellular oxidative stress, activates cardioprotective 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-1α in MIRI. In addition, HIF-1α-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-1α activation in MIRI and supports its use as a therapeutic target.

Contents

Correspondence to: Professor Yuan He, Laboratory of Cardiovascular Diseases, Guangdong Medical University, 57 Renmin Southern Road, Xiashan, Zhanjiang, Guangdong 524000, P.R. China
E-mail: heyuan@gdmu.edu.cn

Professor Can Chen, Department of Cardiology, The Second Affiliated Hospital of Guangdong Medical University, 12 Minyou Road, Xiashan, Zhanjiang, Guangdong 524003, P.R. China
E-mail: chencan-21@163.com

*Contributed equally

Key words: hypoxia-inducible factor-1α, ischemic heart disease, myocardial ischemia-reperfusion injury, mitochondrial function

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-1α, HIF-2α and HIF-3α). HIF-1α 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-1α (10). Under hypoxic conditions, HIF-1α protein is does not undergo degradation by the oxygen-dependent ubiquitin proteasome system and is stably expressed. HIF-1α 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-1α improves cell survival in a hypoxic environment by altering energy metabolism, proliferation, angiogenesis and vascular remodeling. HIF-1α is essential for cardioprotection against MIRI (12). Stable expression stabilization of HIF-1α 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-1α

HIF-1 is the first identified nuclear transcription factor with a highly specific regulatory role in oxygen homeostasis. Both HIF-1α and HIF-1β 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-1α, ARNT, aryl hydrocarbon receptor (AhR) and PAS (13,14).

The protein stability, subcellular localization and transcriptional activity of HIF-1α 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-1α are hydroxylated by oxygen-dependent prolyl hydroxylase domain (PHD)-containing proteins including the prolyl hydroxylases PHD1, 2 and PHD3 (15). Hydroxylated HIF-1α is recognized by von Hippel-Lindau (VHL) and degraded by the oxygen-dependent ubiquitin-proteasome pathway (15,16). Therefore, the half-life of HIF-1α is very short under normal oxygen levels, <5 min.

3. HIF-1α-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-1α via the ubiquitin-proteasome pathway. HIF-1α 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-1α 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-1α can be activated by other factors, such as growth factors, acetylcholine and angiotensin II (10) (Fig. 2). HIF-1α target genes associated with ischemic heart disease and their roles are listed in Table I.

4. Roles of HIF-1α in MIRI

Matsushima *et al* (21) demonstrated that HIF-1α 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-1α 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 Ca^{2+}. During reperfusion, the concentration of intracellular Ca^{2+} 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 Ca^{2+} 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 Ca^{2+} 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-1α by inhibiting PHD proteins during ischemia. On the other hand, HIF-1α 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-1α 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-1α preserves the integrity of the mitochondrial membrane, promotes cell survival and protects against MIRI. Moreover, HIF-1α 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-1α stability and that ROS produced by the mitochondrial ETC can stabilize HIF-1α under hypoxic conditions (16). Mitochondria-derived ROS have multiple, opposing effects. They can impair mitochondrial function and promote cardiomyocyte death or stabilize HIF-1α 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-1α stability and activity. The determination of the oxygen levels required to optimize mutual beneficial effects of mitochondria and HIF-1α 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

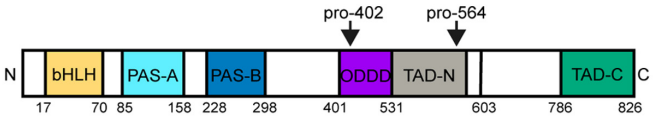

Figure 1. Schematic illustration of the domain structure of HIF-1α. HIF-1α consists of a bHLH motifs and a PAS domain in the NH_2-terminal, which are necessary for heterodimerization and DNA binding to hypoxia response elements. The two TADs, which stimulate transcription, are present in the COOH-terminal of HIF-1α. TAD-C interacts with coactivators such as CREB-binding protein/p300 to activate gene transcription. HIF-1α also contains an ODDD, which promotes proteasomal degradation of HIF-1α by PHD-containing enzymes and factor inhibiting HIF. HIF-1α, hypoxia-inducible factor-1α; 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 Ca^{2+} 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-1α expression levels (32,39).

HIF-1α 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-1α stabilizes mitochondrial function and promotes the production of mitochondrial antioxidants in cells. For instance, HIF-1α 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-1α mediates a shift from oxidative metbolism to glycolysis (thus decreasing the production of mitochondrial oxidants), decreases ETC activity and attenuates mitochondrial ROS production, thereby avoiding cell death (42). HIF-1α 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-1α 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-1α activation and transferrin receptor upregulation, which exacerbates oxidative damage and increases lipid peroxidation. However, the effect of HIF-1α on oxidative stress was not evaluated separately in this previous study. Further investigation is needed to determine the dynamic regulatory effects of HIF-1α on different types of redox indicators at different time points in MIRI.

HIF-1α signaling pathway. Since the first reported target gene of HIF-1α (erythropoietin), hundreds of downstream targets have been identified, demonstrating the complexity and importance of the HIF-1α signaling pathway (15). In MIRI, HIF-1α 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-1α 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-1α/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-1α 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-1α against MIRI (18).

In MIRI, HIF-1α can also act by directly or indirectly regulating numerous signaling pathways (42,49). In terms of mitochondria, HIF-1α can directly or indirectly influence mitochondrial function, decrease mitochondrial damage and attenuate the severity of MIRI (53). HIF-1α can induce myocardial mitochondrial autophagy via the HIF-1α/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-1α-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-1α also plays a significant role. For instance, HIF-1α 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 IκBα during hypoxia results in the degradation of IκBα and activation of NF-κB (48). However, HIF-1α activation can inhibit the NF-κB 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-1α can regulate numerous signaling pathways, such as GSK3β/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-1α and non-coding RNAs. MicroRNAs (miRNAs or miRs) are small non-coding RNA molecules ~22 nucleotides in length. They primarily bind to the 3'

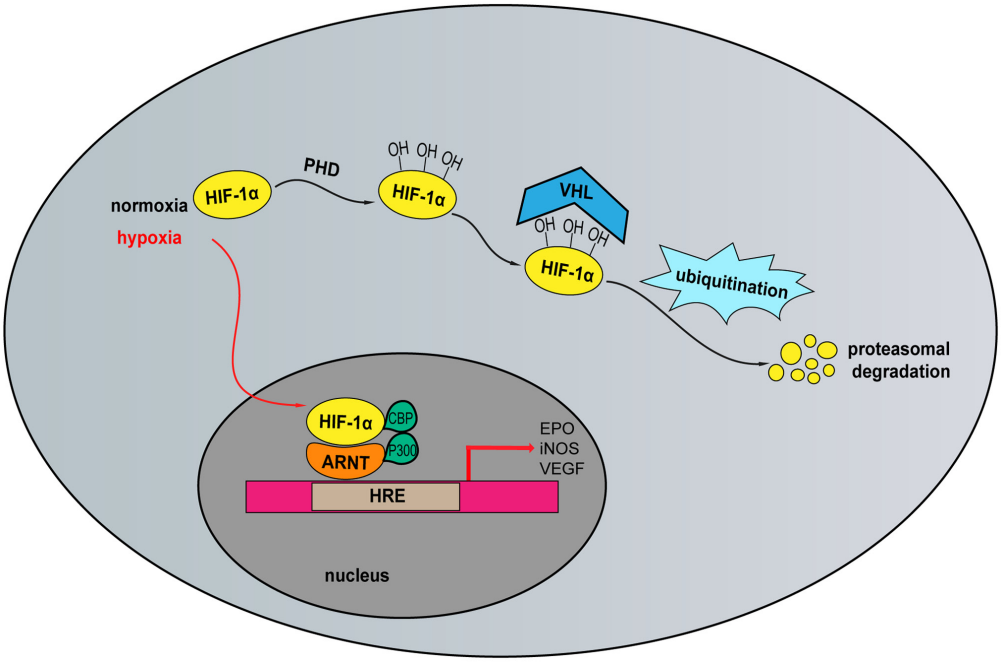

Figure 2. Oxygen-dependent regulation of HIF-1α. In normoxic conditions, HIF-1α protein is hydroxylated by prolyl hydroxylases PHD1, PHD2, and PHD3. Hydroxylated HIF-1α is recognized by VHL and degraded by the ubiquitin-proteasome pathway. In hypoxic conditions, HIF-1α accumulates and translocates to 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-1α, hypoxia-inducible factor-1α; PHD, prolyl hydroxylases; VHL, von Hippel-Lindau; ARNT, aryl hydrocarbon receptor nuclear translocator; HRE, hypoxia-response element; CBP, CREB-binding protein; EPO, erythropoietin; iNOS, inductible 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-1α/phosphorylated-P38 pathway. *In vivo* experiments have demonstrated that overexpression of miR-335 enhances the transcriptional activity of HIF-1α, 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-1α. 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-1α and maintain the steady-state levels of HIF-2 and HIF-3 (61). In addition, HIF-1α can act as a modulator of miRNA function. Wu *et al* (62) demonstrated that the accumulation of HIF-1α following myocardial infarction leads to a decrease in miRNA-l0b-5p, which mediates the apoptosis of cardiomyocytes. Although the number of known miRNAs associated with HIF-1α 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 H_2O_2. 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-1α and lncRNAs has not yet been fully elucidated. Yang *et al* (71) assessed the association between HIF-1α and hypoxia-responsive lncRNA-p21 and demonstrated that lncRNA-p21 is essential for enhancing cell glycolysis under

Table I. HIF-1α target genes.

Function	HIF-1α 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)
	GSK3β	(53)
Apoptosis	Phosphorylated-P38; Bcl-2	(58)
Remote ischemic preconditioning	Interleukin-10	(82)

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

hypoxic conditions. VHL-mediated HIF-1α ubiquitination is attenuated and leads to the accumulation of HIF-1α, promoting glycolysis under hypoxic conditions (72). Xue and Luo (73) investigated the mechanism by which lncRNA HIF-1α-antisense RNA 1 (AS1) regulates cytokine signaling inhibitor 2 (SOCS2) via miR-204 in MIRI ventricular remodeling: The silencing of HIF1α-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-1α 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-1α 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-1α. For example, Liu *et al* (74) demonstrated that saponins of *Panax notoginseng* had protective effects against MIRI via the HIF-1α/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-1α 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 Ca^{2+} 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-3β/HIF-1α signaling pathway (76). Moreover, asiatic acid decreases HIF-3α by regulating miR-1290 targeting, thereby increasing HIF-1α 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-1α expression levels (77,78).

6. Roles of HIF-1α 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-1α in the acute phase of IPC and suggested that compared with wild-type mice, cardiac function was improved in mice expressing the HIF-1α gene following IPC, and that infarct size and cell death decreased. These findings indicated that the reduced severity of MIRI following IPC is HIF-1α-dependent. Jia *et al* (80) demonstrated that IPC could activate HIF-1α, 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-1α. Furthermore, HIF-1α 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-1α 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-1α (82). Late IPC can also increase the expression levels of HIF-1α 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

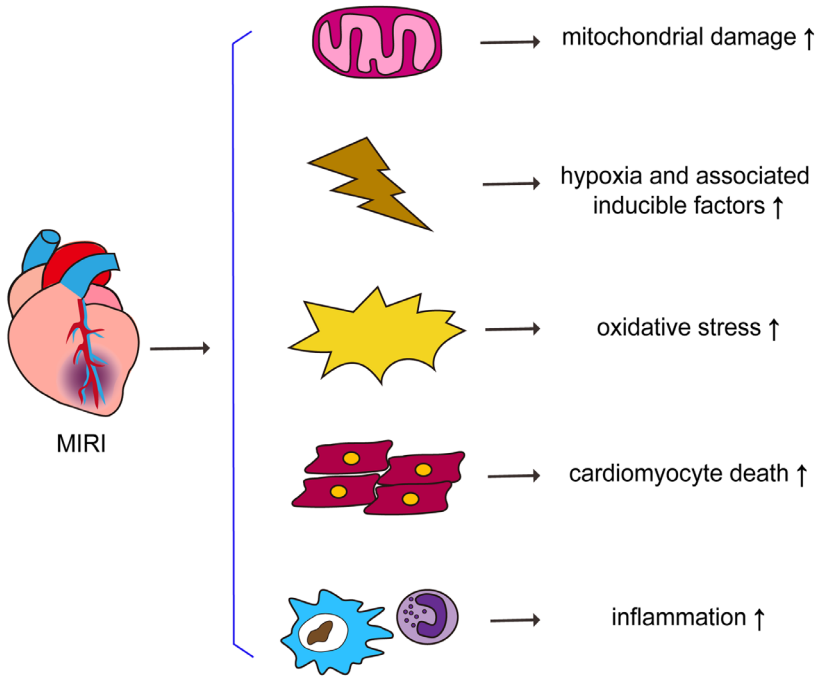

Figure 3. Pathophysiological mechanisms involved in MIRI. Oxidative stress, inflammatory responses, mitochondrial damage and calcium overload, as well as hypoxia-associated factors contribute to the pathophysiology of MIRI. MIRI, myocardial ischemia-reperfusion injury.

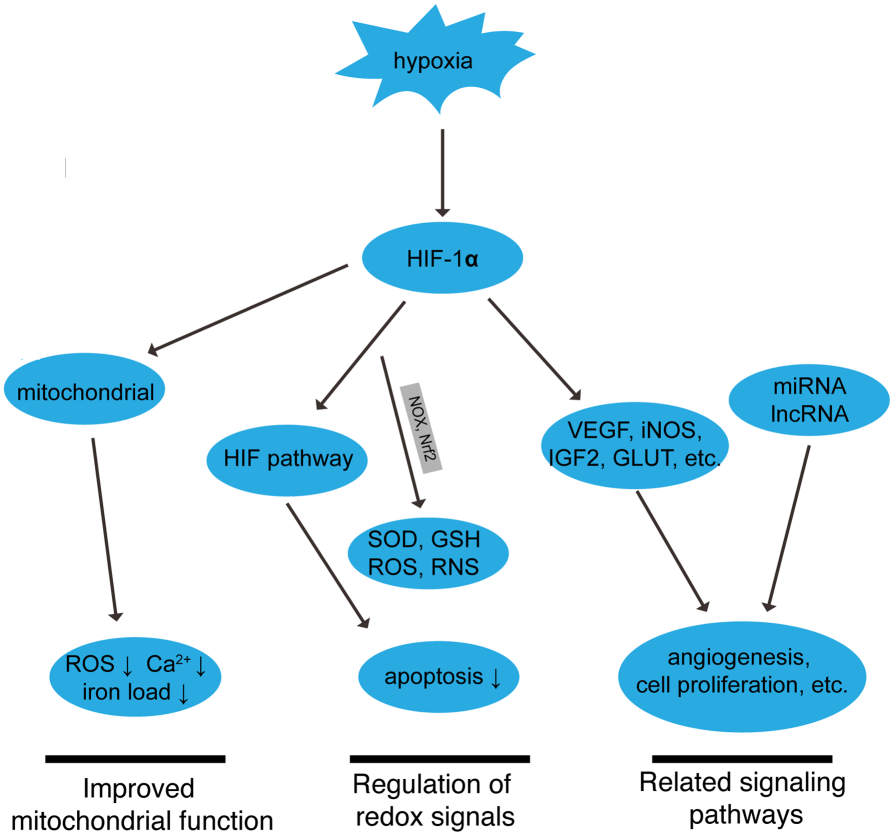

Figure 4. Roles of HIF-1α in MIRI. The upward-facing arrow indicates enhancement. The downward-facing arrow indicates inhibition. MIRI, myocardial ischemia reperfusion injury; HIF-1α, hypoxia-inducible factor-1α; miRNA, microRNA; lncRNA, long non-coding RNA; ROS, reactive oxygen species; VEGF, vascular 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-1α activity in the heart of rats following MIRI, and that HIF-1α 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-1α-dependent humoral pathway, which inhibits HIF-1α and leads to a decrease in plasma MIF and concomitant increase in cardiac MIF, thereby reducing its cardioprotective effects. In summary, HIF-1α 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-1α is one of the most promising targets (88). HIF-1α can mitigate MIRI by various complex mechanisms (Figs. 3 and 4). However, although a previous study has demonstrated that inhibiting HIF-1α 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-1α in MIRI, including the roles of genes involved in glycolysis, mitochondrial function, cell survival, apoptosis and oxidative stress, are still poorly characterized. HIF-1α 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-1α in the pathophysiology of MIRI and the underlying mechanisms is therefore essential.

Acknowledgements

Not applicable.

Funding

The present paper was supported by the National Natural Science Foundation of China (grant no. 81700269).

Availability of data and materials

Not applicable.

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.

References

1. Kaski JC, Crea F, Gersh BJ and Camici PG: Reappraisal of ischemic heart disease. Circulation 138: 1463-1480, 2018.
2. Ma LY, Chen WW, Gao RL, Liu LS, Zhu ML, Wang YJ, Wu ZS, Li HJ, Gu DF, Yang YJ, *et al*: China cardiovascular diseases report 2018: An updated summary. J Geriatr Cardiol 17: 1-8, 2020.
3. Zhao D, Liu J, Wang M, Zhang X and Zhou M: Epidemiology of cardiovascular disease in China: Current features and implications. Nat Rev Cardiol 16: 203-212, 2019.
4. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ and Smith PK: ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: A report of the American college of cardiology appropriate use criteria task force, American association for thoracic surgery, American heart association, American society of echocardiography, American society of nuclear cardiology, society for cardiovascular angiography and interventions, society of cardiovascular computed tomography, and society of thoracic surgeons. J Am Coll Cardiol 69: 2212-2241, 2017.
5. Ibáñez B, Heusch G, Ovize M and Van de Werf F: Evolving therapies for myocardial ischemia/reperfusion injury. J Am Coll Cardiol 65: 1454-1471, 2015.
6. Bellanti F: Hypoxia-inducible factor-1 in myocardial ischaemia/reperfusion injury. Acta Physiol (Oxf) 221: 93-94, 2017.
7. Choudhry H and Harris AL: Advances in hypoxia-inducible factor biology. Cell Metab 27: 281-298, 2018.
8. Semenza GL, Nejfelt MK, Chi SM and Antonarakis SE: Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene. Proc Natl Acad Sci USA 88: 5680-5684, 1991.
9. Chee NT, Lohse I and Brothers SP: mRNA-to-protein translation in hypoxia. Mol Cancer 18: 49-49, 2019.
10. Masoud GN and Li W: HIF-1α pathway: Role, regulation and intervention for cancer therapy. Acta Pharm Sin B 5: 378-389, 2015.
11. Majmundar AJ, Wong WJ and Simon MC: Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell 40: 294-309, 2010.
12. Eckle T, Köhler D, Lehmann R, El Kasmi K and Eltzschig HK: Hypoxia-inducible factor-1 is central to cardioprotection: A new paradigm for ischemic preconditioning. Circulation 118: 166-175, 2008.
13. Jiang BH, Rue E, Wang GL, Roe R and Semenza GL: Dimerization, DNA binding, and transactivation properties of hypoxia-inducible factor 1. J Biol Chem 271: 17771-17778, 1996.
14. Wang GL and Semenza GL: Purification and characterization of hypoxia-inducible factor 1. J Biol Chem 270: 1230-1237, 1995.
15. Sousa Fialho MDL, Abd Jamil AH, Stannard GA and Heather LC: Hypoxia-inducible factor 1 signalling, metabolism and its therapeutic potential in cardiovascular disease. Biochim Biophys Acta Mol Basis Dis 1865: 831-843, 2019.
16. Ong SG and Hausenloy DJ: Hypoxia-inducible factor as a therapeutic target for cardioprotection. Pharmacol Ther 136: 69-81, 2012.
17. Mole DR, Blancher C, Copley RR, Pollard PJ, Gleadle JM, Ragoussis J and Ratcliffe PJ: Genome-wide association of hypoxia-inducible factor (HIF)-1alpha and HIF-2alpha DNA binding with expression profiling of hypoxia-inducible transcripts. J Biol Chem 284: 16767-16775, 2009.
18. Lee JW, Bae SH, Jeong JW, Kim SH and Kim KW: Hypoxia-inducible factor (HIF-1)alpha: Its protein stability and biological functions. Exp Mol Med 36: 1-12, 2004.
19. Singh L, Aldosary S, Saeedan AS, Ansari MN and Kaithwas G: Prolyl hydroxylase 2: A promising target to inhibit hypoxia-induced cellular metabolism in cancer cells. Drug Discov Today 23: 1873-1882, 2018.

20. Abe H, Semba H and Takeda N: The roles of hypoxia signaling in the pathogenesis of cardiovascular diseases. J Atheroscler Thromb 24: 884-894, 2017.
21. Matsushima S, Kuroda J, Ago T, Zhai P, Ikeda Y, Oka S, Fong GH, Tian R and Sadoshima J: Broad suppression of NADPH oxidase activity exacerbates ischemia/reperfusion injury through inadvertent downregulation of hypoxia-inducible factor-1α and upregulation of peroxisome proliferator-activated receptor-α. Circ Res 112: 1135-1149, 2013.
22. Zhou YH, Han QF, Wang LH, Liu T, Meng XY, Wu L, Li T, Jiao YR, Yao HC and Zhang DY: High mobility group box 1 protein attenuates myocardial ischemia reperfusion injury via inhibition of the p38 mitogen-activated protein kinase signaling pathway. Exp Ther Med 14: 1582-1588, 2017.
23. Zhu N, Li J, Li Y, Zhang Y, Du Q, Hao P, Li J, Cao X and Li L: Berberine protects against simulated ischemia/reperfusion injury-induced H9C2 cardiomyocytes apoptosis in vitro and myocardial ischemia/reperfusion-induced apoptosis in vivo by regulating the mitophagy-mediated HIF-1α/BNIP3 pathway. Front Pharmacol 11: 367, 2020.
24. Lesnefsky EJ, Chen Q, Tandler B and Hoppel CL: Mitochondrial dysfunction and myocardial ischemia-reperfusion: Implications for novel therapies. Annu Rev Pharmacol Toxicol 57: 535-565, 2017.
25. Hausenloy DJ, Garcia-Dorado D, Bøtker HE, Davidson SM, Downey J, Engel FB, Jennings R, Lecour S, Leor J, Madonna R, *et al*: Novel targets and future strategies for acute cardioprotection: Position paper of the european society of cardiology working group on cellular biology of the heart. Cardiovasc Res 113: 564-585, 2017.
26. Bernardi P and Di Lisa F: The mitochondrial permeability transition pore: Molecular nature and role as a target in cardioprotection. J Mol Cell Cardiol 78: 100-106, 2015.
27. Jang S, Lewis TS, Powers C, Khuchua Z, Baines CP, Wipf P and Javadov S: Elucidating mitochondrial electron transport chain supercomplexes in the heart during ischemia-reperfusion. Antioxid Redox Signal 27: 57-69, 2017.
28. Chowdhury A, Aich A, Jain G, Wozny K, Lüchtenborg C, Hartmann M, Bernhard O, Balleiniger M, Alfar EA, Zieseniss A, *et al*: Defective mitochondrial cardiolipin remodeling dampens HIF-1α expression in hypoxia. Cell Rep 25: 561-570, 2018.
29. Nanayakkara G, Alasmari A, Mouli S, Eldoumani H, Quindry J, McGinnis G, Fu X, Berlin A, Peters B, Zhong J and Amin R: Cardioprotective HIF-1α-frataxin signaling against ischemia-reperfusion injury. Am J Physiol Heart Circ Physiol 309: H867-H879, 2015.
30. Fuhrmann DC and Brüne B: Mitochondrial composition and function under the control of hypoxia. Redox Biol 12: 208-215, 2017.
31. Cadenas S: ROS and redox signaling in myocardial isch-emia-reperfusion injury and cardioprotection. Free Radic Biol Med 117: 76-89, 2018.
32. Deshwal S, Antonucci S, Kaludercic N and Di Lisa F: Measurement of mitochondrial ROS formation. Methods Mol Biol 1782: 403-418, 2018.
33. Garlick PB, Davies MJ, Hearse DJ and Slater TF: Direct detection of free radicals in the reperfused rat heart using electron spin resonance spectroscopy. Circ Res 61: 757-760, 1987.
34. Boengler K, Bornbaum J, Schlüter KD and Schulz R: P66shc and its role in ischemic cardiovascular diseases. Basic Res Cardiol 114: 29, 2019.
35. Boengler K, Lochnit G and Schulz R: Mitochondria 'THE' target of myocardial conditioning. Am J Physiol Heart Circ Physiol 315: H1215-H1231, 2018.
36. Chen J, Luo Y, Wang S, Zhu H and Li D: Roles and mechanisms of SUMOylation on key proteins in myocardial ischemia/reperfusion injury. J Mol Cell Cardiol 134: 154-164, 2019.
37. Kurian GA, Rajagopal R, Vedantham S and Rajesh M: The role of oxidative stress in myocardial ischemia and reperfusion injury and remodeling: Revisited. Oxid Med Cell Longev 2016: 1656450, 2016.
38. Bertero E and Maack C: Calcium signaling and reactive oxygen species in mitochondria. Circ Res 122: 1460-1478, 2018.
39. Cadenas S: ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. Free Radic Biol Med 117: 76-89, 2018.
40. Jiang L, Zeng H, Ni L, Qi L, Xu Y, Xia L, Yu Y, Liu B, Yang H, Hao H and Li P: HIF-1α preconditioning potentiates antioxidant activity in ischemic injury: The role of sequential administration of dihydrotanshinone I and protocatechuic aldehyde in cardioprotection. Antioxid Redox Signal 31: 227-242, 2019.
41. Semenza GL: Hypoxia-inducible factors: Coupling glucose metabolism and redox regulation with induction of the breast cancer stem cell phenotype. EMBO J 36: 252-259, 2017.
42. Thomas LW and Ashcroft M: Exploring the molecular interface between hypoxia-inducible factor signalling and mitochondria. Cell Mol Life Sci 76: 1759-1777, 2019.
43. Adeyemi OS, Eseola AO, Plass W, Otuechere CA and Elebiyo TC: New imidazoles cause cellular toxicity by impairing redox balance, mitochondrial membrane potential, and modulation of HIF-1α expression. Biochem Biophys Res Commun 529: 23-27, 2020.
44. Gyongyosi A, Terraneo L, Bianciardi P, Tosaki A, Lekli I and Samaja M: The impact of moderate chronic hypoxia and hyperoxia on the level of apoptotic and autophagic proteins in myocardial tissue. Oxid Med Cell Longev 2018: 5786742, 2018.
45. Watanabe Y, Cohen RA and Matsui R: Redox regulation of ischemic angiogenesis-another aspect of reactive oxygen species. Circ J 80: 1278-1284, 2016.
46. Tang WH, Wu S, Wong TM, Chung SK and Chung SS: Polyol pathway mediates iron-induced oxidative injury in ischemic-reperfused rat heart. Free Radic Biol Med 45: 602-610, 2008.
47. Zhang S, Ma K, Liu Y, Pan X, Chen Q, Qi L and Li S: Stabilization of hypoxia-inducible factor by DMOG inhibits development of chronic hypoxia-induced right ventricular remodeling. J Cardiovasc Pharmacol 67: 68-75, 2016.
48. Lee JW, Ko J, Ju C and Eltzschig HK: Hypoxia signaling in human diseases and therapeutic targets. Exp Mol Med 51: 1-13, 2019.
49. Dong J, Xu M, Zhang W and Che X: Effects of sevoflurane pretreatment on myocardial ischemia-reperfusion injury through the Akt/hypoxia-inducible factor 1-alpha (HIF-1α)/vascular endothelial growth factor (VEGF) signaling pathway. Med Sci Monit 25: 3100-3107, 2019.
50. Li J, Zhou W, Chen W, Wang H, Zhang Y and Yu T: Mechanism of the hypoxia inducible factor 1/hypoxic response element pathway in rat myocardial ischemia/diazoxide post-conditioning. Mol Med Rep 21: 1527-1536, 2020.
51. Wu N, Zhang X, Du S, Chen D and Che R: Upregulation of miR-335 ameliorates myocardial ischemia reperfusion injury via targeting hypoxia-inducible factor 1-alpha subunit inhibitor. Am J Transl Res 10: 4082-4094, 2018.
52. Si J, Wang N, Wang H, Xie J, Yang J, Yi H, Shi Z, Ma J, Wang W, Yang L, *et al*: HIF-1α signaling activation by post-ischemia treatment with astragaloside IV attenuates myocardial ischemia-reperfusion injury. PLoS One 9: e107832, 2014.
53. Zhang Y, Liu D, Hu H, Zhang P, Xie R and Cui W: HIF-1α/BNIP3 signaling pathway-induced-autophagy plays protective role during myocardial ischemia-reperfusion injury. Biomed Pharmacother 120: 109464, 2019.
54. Liu DW, Zhang YN, Hu HJ, Zhang PQ and Cui W: Downregulation of microRNA-199a-5p attenuates hypoxia/reoxygenation-induced cytotoxicity in cardiomyocytes by targeting the HIF-1α-GSK3β-mPTP axis. Mol Med Rep 19: 5335-5344, 2019.
55. Adluri RS, Thirunavukkarasu M, Dunna NR, Zhan L, Oriowo B, Takeda K, Sanchez JA, Otani H, Maulik G, Fong GH and Maulik N: Disruption of hypoxia-inducible transcription factor-prolyl hydroxylase domain-1 (PHD-1$^{-/-}$) attenuates ex vivo myocardial ischemia/reperfusion injury through hypoxia-inducible factor-1α transcription factor and its target genes in mice. Antioxid Redox Signal 15: 1789-1797, 2011.
56. Yao HC, Zhou M, Zhou YH, Wang LH, Zhang DY, Han QF, Liu T, Wu L, Tian KL and Zhang M: Intravenous high mobility group box 1 upregulates the expression of HIF-1α in the myocardium via a protein kinase B-dependent pathway in rats following acute myocardial ischemia. Mol Med Rep 13: 1211-1219, 2016.
57. Tekin D, Dursun AD and Xi L: Hypoxia-inducible factor 1 (HIF-1) and cardioprotection. Acta Pharmacol Sin 31: 1085-1094, 2010.
58. Correia de Sousa M, Gjorgjieva M, Dolicka D, Sobolewski C and Foti M: Deciphering miRNAs' action through miRNA editing. Int J Mol Sci 20: 6249, 2019.
59. Sheng Z, Lu W, Zuo Z, Wang D, Zuo P, Yao Y and Ma G: MicroRNA-7b attenuates ischemia/reperfusion-induced H9C2 cardiomyocyte apoptosis via the hypoxia-inducible factor-1/p-p38 pathway. J Cell Biochem 120: 9947-9955, 2019.
60. Liu Y, Zou J, Liu X and Zhang Q: MicroRNA-138 attenuates myocardial ischemia reperfusion injury through inhibiting mitochondria-mediated apoptosis by targeting HIF1-α. Exp Ther Med 18: 3325-3332, 2019.

61. Serocki M, Bartoszewska S, Janaszak-Jasiecka A, Ochocka RJ, Collawn JF and Bartoszewski R: miRNAs regulate the HIF switch during hypoxia: A novel therapeutic target. Angiogenesis 21: 183-202, 2018.
62. Wu L, Chen Y, Chen Y, Yang W, Han Y, Lu L, Yang K and Cao J: Effect of HIF-1α/miR-10b-5p/PTEN on hypoxia-induced cardiomyocyte apoptosis. J Am Heart Assoc 8: e011948, 2019.
63. Wu K, Hu M, Chen Z, Xiang F, Chen G, Yan W, Peng Q and Chen X: Asiatic acid enhances survival of human AC16 cardiomyocytes under hypoxia by upregulating miR-1290. IUBMB Life 69: 660-667, 2017.
64. Bavelloni A, Ramazzotti G, Poli A, Piazzi M, Focaccia E, Blalock W and Faenza I: MiRNA-210: A current overview. Anticancer Res 37: 6511-6521, 2017.
65. Long B, Li N, Xu XX, Li XX, Xu XJ, Guo D, Zhang D, Wu ZH and Zhang SY: Long noncoding RNA FTX regulates cardiomyocyte apoptosis by targeting miR-29b-1-5p and Bcl2l2. Biochem Biophys Res Commun 495: 312-318, 2018.
66. Kopp F and Mendell JT: Functional classification and experimental dissection of long noncoding RNAs. Cell 172: 393-407, 2018.
67. Jiang X and Ning Q: The emerging roles of long noncoding RNAs in common cardiovascular diseases. Hypertens Res 38: 375-379, 2015.
68. Ong SB, Katwadi K, Kwek XY, Ismail NI, Chinda K, Ong SG and Hausenloy DJ: Non-coding RNAs as therapeutic targets for preventing myocardial ischemia-reperfusion injury. Expert Opin Ther Targets 22: 247-261, 2018.
69. Ren L, Chen S, Liu W, Hou P, Sun W and Yan H: Downregulation of long non-coding RNA nuclear enriched abundant transcript 1 promotes cell proliferation and inhibits cell apoptosis by targeting miR-193a in myocardial ischemia/reperfusion injury. BMC Cardiovasc Disord 19: 192, 2019.
70. Li X, Luo S, Zhang J, Yuan Y, Jiang W, Zhu H, Ding X, Zhan L, Wu H, Xie Y, *et al*: lncRNA H19 alleviated myocardial I/RI via suppressing miR-877-3p/Bcl-2-mediated mitochondrial apoptosis. Mol Ther Nucleic Acids 17: 297-309, 2019.
71. Yang F, Zhang H, Mei Y and Wu M: Reciprocal regulation of HIF-1α and lincRNA-p21 modulates the Warburg effect. Mol Cell 53: 88-100, 2014.
72. Yue X, Wang R, Li W, Wang C, Lu H and Zhang J: Research progress of long chain non-coding RNA H19 in anoxic environment mechanism. Zhong Nan Da Xue Xue Bao Yi Xue Ban 43: 1151-1158, 2018 (In Chinese).
73. Xue X and Luo L: LncRNA HIF1A-AS1 contributes to ventricular remodeling after myocardial ischemia/reperfusion injury by adsorption of microRNA-204 to regulating SOCS2 expression. Cell Cycle 18: 2465-2480, 2019.
74. Liu XW, Lu MK, Zhong HT, Wang LH and Fu YP: *Panax notoginseng* saponins attenuate myocardial ischemia-reperfusion injury through the HIF-1α/BNIP3 pathway of autophagy. J Cardiovasc Pharmacol 73: 92-99, 2019.
75. Shen K, Ji L, Gong C, Ma Y, Yang L, Fan Y, Hou M and Wang Z: Notoginsenoside Ft1 promotes angiogenesis via HIF-1α mediated VEGF secretion and the regulation of PI3K/AKT and Raf/MEK/ERK signaling pathways. Biochem Pharmacol 84: 784-792, 2012.
76. Huang X, Zuo L, Lv Y, Chen C, Yang Y, Xin H, Li Y and Qian Y: Asiatic acid attenuates myocardial ischemia/reperfusion injury via Akt/GSK-3β/HIF-1α signaling in rat H9c2 cardiomyocytes. Molecules 21: 1248, 2016.
77. Veloso CD, Belew GD, Ferreira LL, Grilo LF, Jones JG, Portincasa P, Sardão VA and Oliveira PJ: A mitochondrial approach to cardiovascular risk and disease. Curr Pharm Des 25: 3175-3194, 2019.
78. Guo H, Zheng M, Jiao YB and Zheng H: Paclitaxel enhances the protective effect of myocardial ischemia preconditioning on ischemia/reperfusion injury in aged rat. Zhonghua Xin Xue Guan Bing Za Zhi 46: 719-724, 2018 (In Chinese).
79. Cai Z, Zhong H, Bosch-Marce M, Fox-Talbot K, Wang L, Wei C, Trush MA and Semenza GL: Complete loss of ischaemic preconditioning-induced cardioprotection in mice with partial deficiency of HIF-1 alpha. Cardiovasc Res 77: 463-470, 2008.
80. Jia P, Wu X, Dai Y, Teng J, Fang Y, Hu J, Zou J, Liang M and Ding X: MicroRNA-21 is required for local and remote ischemic preconditioning in multiple organ protection against sepsis. Crit Care Med 45: e703-e710, 2017.
81. Yu X, Ge L, Niu L, Lian X, Ma H and Pang L: The dual role of inducible nitric oxide synthase in myocardial ischemia/reperfusion injury: Friend or foe? Oxid Med Cell Longev 2018: 8364848, 2018.
82. Cai Z, Luo W, Zhan H and Semenza GL: Hypoxia-inducible factor 1 is required for remote ischemic preconditioning of the heart. Proc Natl Acad Sci USA 110: 17462-17467, 2013.
83. Chen H, Jing XY, Shen YJ, Wang TL, Ou C, Lu SF, Cai Y, Li Q, Chen X, Ding YJ, *et al*: Stat5-dependent cardioprotection in late remote ischaemia preconditioning. Cardiovasc Res 114: 679-689, 2018.
84. Wan DY, Zhang Z and Yang HH: Cardioprotective effect of miR-214 in myocardial ischemic postconditioning by down-regulation of hypoxia-inducible factor 1, alpha subunit inhibitor. Cell Mol Biol (Noisy-le-grand) 61: 1-6, 2015.
85. Wang C, Zuo B and Wu X: The role of macrophage migration inhibitory factor in remote ischemic postconditioning. Can J Cardiol 35: 501-510, 2019.
86. Davidson SM, Ferdinandy P, Andreadou I, Bøtker HE, Heusch G, Ibáñez B, Ovize M, Schulz R, Yellon DM, Hausenloy DJ, *et al*: Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. J Am Coll Cardiol 73: 89-99, 2019.
87. Li D, Ni H, Rui Q, Gao R and Chen G: Mst1: Function and mechanism in brain and myocardial ischemia reperfusion injury. Curr Neuropharmacol 16: 1358-1364, 2018.
88. Wang S, Shao X, Li X, Su X, Huo Y and Yang C: HIF-1α may provide only short-term protection against ischemia-reperfusion injury in Sprague-Dawley myocardial cultures. Mol Clin Oncol 4: 579-583, 2016.
89. Chen C, Hu Q, Yan J, Yang X, Shi X, Lei J, Chen L, Huang H, Han J, Zhang JH and Zhou C: Early inhibition of HIF-1alpha with small interfering RNA reduces ischemic-reperfused brain injury in rats. Neurobiol Dis 33: 509-517, 2009.