Diabetes mellitus (DM) displays a high morbidity. The diabetic heart is susceptible to myocardial ischemia/reperfusion (MI/R) injury. Impaired activation of prosurvival pathways, endoplasmic reticulum (ER) stress, increased basal oxidative state, and decreased antioxidant defense and autophagy may render diabetic hearts more vulnerable to MI/R injury. Oxidative stress and mTOR signaling crucially regulate cardiometabolism, affecting MI/R injury under diabetes. Producing reactive oxygen species (ROS) and reactive nitrogen species (RNS), uncoupling nitric oxide synthase (NOS), and disturbing the mitochondrial quality control may be three major mechanisms of oxidative stress. mTOR signaling presents both cardioprotective and cardiotoxic effects on the diabetic heart, which interplays with oxidative stress directly or indirectly. Antihyperglycemic agent metformin and newly found free radicals scavengers, Sirt1 and CTRP9, may serve as promising pharmacological therapeutic targets. In this review, we will focus on the role of oxidative stress and mTOR signaling in the pathophysiology of MI/R injury in diabetes and discuss potential mechanisms and their interactions in an effort to provide some evidence for cardiometabolic targeted therapies for ischemic heart disease (IHD).

### 1. Introduction

Diabetes mellitus (DM) is a major risk factor for ischemic heart disease (IHD) [1]. The alteration of glucose metabolism leads to cardiac structural and functional perturbations, including left ventricular (LV) dysfunction, cardiac hypertrophy, and myocardial interstitial fibrosis. A number of diabetic subjects suffer from the impairments of diastolic dysfunction in an early stage without overt cardiovascular symptoms [2–4]. Cardiac hypertrophy is originally a compensatory response to pathological overload stress. However, the persistent DM-induced hypertrophy ultimately becomes maladaptive since it evolves into cardiac dysfunction, and finally develops into heart failure [5–7]. Hyperglycemia directly increases cardiac fibroblast and vascular smooth muscle cell proliferation and is associated with endothelial dysfunction, resulting in microvascular injury and hemodynamic alteration, which contribute to the vulnerability of tissue ischemia injury [8, 9]. Myocardial salvage after reperfusion may be limited by deleterious changes in the microcirculation of ischemic tissue [10]. All these pathophysiologic changes in the diabetic heart lead to a susceptibility to ischemia/reperfusion (I/R) injury [9, 11]. Consequences of increased cellular apoptosis and inflammation are present in the diabetic heart subjected to I/R injury [12–14]. It is truly different from the normotensive mechanisms since metabolic abnormalities and alteration of oxidative stress and autophagy. Among all these factors, oxidative stress and the mammalian target of rapamycin (mTOR) signaling are two critical ones [15, 16].

Oxidative stress is defined as an imbalance between free radicals production and destruction, which leads to multiple negative effects on cellular metabolism. mTOR kinase is also necessary for normal regulation of cardiac structure and cardiometabolic homeostasis. It promotes mitochondrial function in response to insulin resistance and affects cardiac energy deprivation and ischemia [17, 18]. Both of them participate in the pathogenesis and progression of myocardial ischemia/reperfusion (MI/R) injury under diabetes, acting as key regulators of cardiometabolism and cardiac function. However, the relationship between oxidative stress...
and mTOR signaling is complicated, since mTOR not only modulates oxidative stress but is also affected by reactive oxygen species (ROS) activation. In this review, we will focus on the role of oxidative stress and mTOR signaling in the pathophysiology of I/R injury in the diabetic heart and highlight their current interactions in an effort to provide some evidence for the potential cardiometabolic targeted therapies for IHD.

2. The Vulnerability of Diabetic Heart Subjected to MI/R Injury

DM severely damages cardiac energy homeostasis, leading to the cardiac dysfunction. It is well recognized that populations associated with DM were more likely to develop IHD and their long-term outcome is worsened [19]. Importantly, physical or pharmacologic ischemic preconditioning (IPC) and ischemic postconditioning (I-post) actions are ineffective under diabetic conditions [20–22], suggesting that the diabetic heart may be resistant to common cardioprotections.

2.1. Impaired Activation of Prosurvival Pathways. In the diabetic heart, the alteration of reperfusion injury salvage kinase (RISK) signaling significantly suppressed the cardioprotective effects of IPC [23, 24]. Studies demonstrated that glycogen synthase kinase-3β (GSK-3β) was activated by insulin resistance, thus inhibiting the prosurvival pathway of the phosphoinositol-3 kinase- (PI3k-) Akt signaling and the Janus-activated kinase- (Jak-) transcription 3 (STAT3) signaling, finally blunting the cardioprotective effects of I-post [25, 26]. Moreover, our previous study proved that adiponectin (APN) resistance existed in the diabetic cardiomyocytes and impaired APN’s cardioprotection against MI/R injury [27]. APN resistance led to the dysfunctional APN-AMP-activated protein kinase (AMPK) axis and blocked the AMPK-independent antiperoxide/antinitration pathway, increasing the vulnerability of diabetic cardiomyocytes to I/R injury [27, 28].

2.2. Endoplasmic Reticulum (ER) Stress. Disturbed cardiometabolic homeostasis facilitates ER stress. The unfolded protein response (UPR) was proved to be involved in the pathogenesis of DM [29, 30]. Miki et al. demonstrated that DM-induced ER stress augmentation enhanced the mitochondrial permeability transition pore (mPTP) opening and increased mitochondrial calcium overload via inhibition of extracellular regulated MAP kinase (ERK) 1/2-GSK-3β pathway [31]. In contrast, suppression of ER stress could reduce myocardial infarction (MI) size in high fat diet- (HFD-) induced type 2 diabetes mellitus (T2DM) [32]. Our recent study found that preconditioning of C1q/TNF-related protein (C1R) 9, a newly identified homologous of APN, protected the diabetic heart against I/R injury by reducing ER stress and inflammatory response [33].

2.3. Increased Basal Oxidative State and Impaired Antioxidant Signaling. Hyperglycemia enhances oxidative stress, promotes profibrogenic genes expression, and aggravates MI/R injury [34, 35]. ROS accumulation not only results from overproduction of free radicals, but also may be a consequence of decreased free radicals scavenger systems, including superoxide dismutase (Cu/Zn-SOD and Mn-SOD), catalase (CAT), and glutathione peroxidase (GPx) [36]. Cardiac expression of GPx levels is reduced in the diabetic apolipoprotein E-deficient mice [37]. Meanwhile, attempts to attenuate I/R injury using enzymatic and nonenzymatic antioxidants have not been universally successful in DM [38, 39].

2.4. Autophagy and mTOR Signaling. Autophagy is a cellular degradation pathway that crucially mediates cardiometabolism. It has been demonstrated that autophagy was required for IPC via mTOR signaling and Parkin-dependent pathway [40, 41]. However, mitochondrial biogenesis is impaired in the diabetic heart, following the alteration of autophagic activity. Hyperglycemia largely inhibited cardiac autophagosome and autolysosome formation by modulating mTOR-ULK1 signaling [42]. It deteriorated the cardioprotection of remote IPC (rIPC) because of the increase in nitrative stress and inhibition of autophagy via activation of mTOR signaling [43, 44].

3. The Role of Oxidative Stress in MI/R Injury under Diabetes

Oxidative stress is regarded as an imbalance between the generation and elimination of free radicals due to increased ROS and/or inadequate antioxidant defenses [45]. It develops directly or indirectly from hyperglycemia, hyperlipidemia, and insulin resistance under DM [15, 46] and in turn, disturbs metabolic hemostasis and impairs cardiac function. When available in appropriate amounts, free radicals act as signal transduction molecules while in large excess, they lead to DNA degeneration, lipid oxidation and membrane protein degeneration. However, in the diabetic heart, insulin resistance increases cardiomyocytes fatty acid oxidation together with a reduction of prostacyclin synthesis and endothelial nitric oxide (eNOS) synthase activity [47]. These changes lead to generation of ROS and reactive nitrogen species (RNS), endothelium dysfunction, formation of advanced glaciacion end products, and alteration of the mitochondrial quality control, all of which contribute to the deleterious MI/R injury under diabetes [48]. Thus, DM-induced oxidative stress can be a primary component that initiates the onset and progression of cardiac dysfunction in MI/R injury (Figure 1).

3.1. ROS and RNS Production. ROS are a group of short-lived, low-molecular-weight compounds derived from reactions oxygen undergoes, including superoxide (O2−), hydroxyl (OH·), hydrogen peroxide (H2O2), and hypochlorous acid (HOC). The generation of ROS in the heart is few under physiologic conditions. O2− leaksages from mitochondrial electron transport chains (ETC) and soon be catalyzed into less cytotoxic H2O2 by SOD catalyzes, then finally be converted into water and molecular oxygen by either CAT or GPx system [45]. However, the homeostasis of cardiac oxidative state would be broken under DM since the generation of O2− increased markedly. The accumulated
**Figure 1: DM-induced higher basal oxidative state plays a master role in the progression of cardiometabolic disorders and negatively affects the MI/R injury.** In this state, ROS and RNS accumulate dramatically. They initiate the reaction of \( \cdot OH \) in parallel with the ONOO\(^-\)/ONOO\(^{2-}\) generation, which becomes strong cytotoxic oxidant and causes oxidative damage and nitration. These then lead to endothelium dysfunction, formation of advanced glycation end products, and alteration of the mitochondrial quality control, all contributing to the deleterious MI/R injury in diabetic hearts.

\( \cdot OH \) is highly diffusible and damages cardiomyocytes [49]. \( H_2O_2 \) is more likely converted to \( \cdot OH \) rather than scavenged by CAT or GPx [50]. Moreover, hyperglycemia increases cardiac free fatty acid (FFA) levels, which extensively leads to myocardial contractile dysfunction and tissue damage in ischemia-reperfused rat hearts [54].

Diabetic myocardial RNS production is also greatly increased, including radicals nitric oxide (\( \cdot NO \)) and nitrogen dioxide (\( \cdot NO_2^\cdot \)). The rapid reaction of superoxide with nitric oxide (NO) forms a highly reactive intermediate, peroxynitrite (ONOO\(^-\)), under MI/R injury. With increased intracellular acidification, ONOO\(^-\) becomes more protonated to form peroxynitrous acid (ONOOH), which then rapidly turns into nitrogen dioxide (NO\(_2^\cdot\)) and \( \cdot OH \). The ONOO\(^-\)/ONOOH becomes strong cytotoxic oxidant and causes oxidative damage and nitration, which contributes in parallel with the reaction of \( \cdot OH \) generation during MI/R [45].

### 3.2. Uncoupled NOS.

Diabetic mice exhibited increased risk of aggravated MI/R injury primarily because of impaired NO bioavailability. ONOO\(^-\) may uncouple eNOS via oxidation of tetrahydrobiopterin (BH4), thus leads to further superoxide generation and an enhanced NO depletion [55]. However, reduced availability of BH4 was identified in diabetic rat vessels and endothelial cells. DM-induce NADPH increase further predisposes the heart to ROS uncoupling and ONOO\(^-\) generation [56]. Maalouf et al. demonstrated that S-glutathionylation uncoupled eNOS and subsequently impaired endothelium-dependent vasodilation under oxidative stress [57]. Moreover, inducible NOS (iNOS) is activated in DM by inflammatory mediators, which makes iNOS uncoupling a predominant contributor for oxidative/nitrosative stress in diabetic myocardium [58].

### 3.3. Disturbing the Mitochondrial Quality Control.

Mitochondria are the major sites of ROS production (0.2% to 2% of total oxygen taken by cells). These ROS can be scavenged by mitochondrial quality control to keep the mitochondria functional [59]. However, in the diabetic heart, mitochondrial quality control is damaged together with impaired mitochondrial respiratory capacity, leading to a dramatic accumulation of ROS [15]. Importantly, increased mitochondrial \( H_2O_2 \) emission then damages DNA, proteins, and lipid in membrane components and finally results in mitochondrial dysfunction [60]. The myocardium of db/db mice exhibited increased mitochondrial \( H_2O_2 \) generation, and overproduction of mitochondrial ROS occurring in conjunction with augmented electron delivery from increased fatty acid oxidation [51]. Taken together, these studies suggest that mitochondrial quality control regulates cellular oxidative stress, while, if damaged, oxidative stress in turn might affect mitochondrial dysfunction under DM.

### 4. The Dual Role of mTOR Signaling in MI/R Injury under Diabetes

mTOR is a 289kDa serine/threonine kinase that crucially mediates energy metabolism [61]. It has two distinct multiprotein complexes, mTORC1 (mTORC1) and mTOR complex 2 (mTORC2) [62–64]. mTORC1 regulates cellular homeostasis, stress responses, energy metabolism and autophagy by relying on the regulatory associated protein of mTOR (Raptor). In contrast, mTORC2 treats rapamycin-insensitive companion of mTOR (Rictor) as the component rather than Raptor and controls cell growth, survival, migration, and cell cycle progression [65]. mTOR kinase is necessary for normal regulation of cardiac structure and cardiometabolism. It also takes part in the maintenance of normal microvascular barrier function and endothelial permeability. However, the role of mTOR signaling in MI/R injury is still controversial. Researchers have found both cardioprotective and cardiotoxic effects of mTOR signaling when using its inhibitor-rapamycin or transgenic animals [66]. Besides, there is a complicated interplay between mTOR signaling and oxidative stress (Table 1).

#### 4.1. Cardiotoxic Effects of mTOR Signaling

Chronic increase of mTORC1 activity in T2DM causes insulin resistance, which contributes to hyperinsulinemia and hyperglycemia...
| Effect of mTOR | Study | Animal model | Interventions | Outcomes |
|---------------|-------|--------------|---------------|----------|
| Cardioprotective | Glazer et al. [67] | Transgenic mice | Overexpression of cardiac mTOR | Overexpression of cardiac mTOR reduced mortality in the acute phase and preserved cardiac function in the chronic phase after transient ischemia in vivo |
| Cardioprotective | Land and Tee [68] | Transgenic mice | Rapamycin (5 mg/kg i.v.) 10 min before I/R | mTOR-Tg mice performed better cardiac function recovery and had less of the necrotic markers CK and LDH subjected to I/R injury in high fat diet-induced obesity |
| Cardioprotective | Park et al. [69] | Diabetic mice induced by STZ | Rapamycin (5 mg/kg i.v.) immediately after MI with a short 2-day follow-up treatment to inhibit both mTORC1 and mTORC2 | Lin28a overexpression increased p-mTOR and p-p70s6k expression in myocardium exposed to I/R injury in diabetic mice while inhibition of mTOR reduced Lin28a cardioprotective effects |
| Cardioprotective | Schenkel et al. [70] | C57BL/6 mice | Torin1 (i.p.) immediately after MI with a short 2-day follow-up treatment to inhibit both mTORC1 and mTORC2 | Inhibition of both mTORC1 and mTORC2 with Torin1 led to increased cardiomyocyte apoptosis and tissue damage after MI. Predominant mTORC1 signaling by suppression of mTORC2 similarly increased cardiomyocyte apoptosis and tissue damage after myocardial infarction. In comparison, preferentially shifting toward mTORC2 signaling by inhibition of mTORC1 with PRAS40 led to decreased cardiomyocyte damage after MI |
| Cardioprotective | Tanguy et al. [50] | Neonatal rat ventricular cardiomyocytes | Rapamycin: 50 nM Adenovirus overexpressing mTOR | Inhibition of mTOR by rapamycin antagonized high glucose-induced inhibition of autophagy and enhanced cardiomyocyte death, while adenovirus-mediated overexpression of mTOR was sufficient to block autophagic flux regardless of glucose concentrations |
| Cardioprotective | Rajapakse et al. [71] | Human umbilical vein endothelial cells (HUVECs) | Rapamycin: 25 nM | mTOR activation enhances the activity of HIF1α by inhibiting proteolytic degradation, resulting in elevated VEGF expression |
| Cardioprotective | Chong et al. [72] | Human endothelial cells | Rapamycin: 5–10 ng/mL | Loss of mTOR blocks endothelial proliferation and angiogenesis as well as the proliferation of endothelial progenitor cells ex vivo |
| Cardiotoxic | Yao et al. [73] | HUVEC knockout cells | Rapamycin (2 mg/kg, i.p.) | Rapamycin reversed APN deficiency-induced drop of fat oxidation in high fat diet feeding |
| Cardiotoxic | Si et al. [74] | Transgenic mice | Conditional mTOR knockout mice | Inhibition of mTORC1 reduced endoplasmic reticulum stress, thereby reducing cardiomyocytes death |
| Cardiotoxic | Lemaitre et al. [75] | CD-1 mice | Rapamycin (0.25 mg/kg, i.p.) | Inhibition of mTOR by rapamycin before ischemia reduced I/R-induced myocardial infarction via activating the JAK2 signal transducer and activator of transcription 3 (STAT3) signaling pathway |
| Cardiotoxic | Fourcade et al. [76] | Transgenic mice | Cardiac-specific knockout Raptor to inhibit mTORC1 in vivo | In cardiac mTORC1 disrupted mice, fatty acid oxidation is significantly decreased, whereas glucose oxidation is increased subject to transverse aortic constriction (TAC) |
| Cardiotoxic | Maiese et al. [77] | Male WKY rats and HUVECs | Recombinant adenoviral (rAd) expressing short hairpin RNA (shRNA), S6K1 to inhibit mTORC1 | Inhibition of mTORC1/S6K1 signaling protected endothelial dysfunction related to eNOS uncoupling in vivo and in vitro |
| Cardiotoxic | Wang et al. [78] | AMPKα2 knockout mice | Metformin (100 mg/kg/day, gavage) for 3 weeks | Administration of metformin was effective in attenuating TAC-induced LV remodeling in both wild-type and AMPKα2 knockout mice and reduced p-mTOR at Ser2448 and its downstream target p-p70S6K at Thr389 |
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Pathway [90]. Inhibition of mTOR increased Akt phosphorylation in mTOR overexpressed mice than WT mice under HFD conditions [91]. Our previous studies also found that hypertension-induced mTOR activation altered cardiac morphology, function, and autophagy, which could be rescued by cardiac-specific overexpression of metallothionein [84, 85]. Importantly, activation of mTORC1 other than mTOR2 signaling affects cardiac metabolism and the susceptibility to ischemia injury [67]. A patient-level meta-analysis of randomized trials showed that selective activation of mTORC2 with concurrent inhibition of mTORC1 decreased cardiomyocytes apoptosis and tissue damage after MI [86]. It seems that different complex of mTOR performs different cardiac functions. Another cardiotoxic mTOR effect is altering STAT3 signaling pathway in the diabetic heart. Das et al. found that inhibition of mTOR by rapamycin (0.25 mg/kg, i.p.) before ischemia reduced I/R-induced MI in CD-1 mice via activating the JAK2-STAT3 signaling [87]. This was further proved in cardiac-specific STAT3-deficient mice [88].

4.2. Cardioprotections of mTOR Signaling. There are four major mTOR-related cardioprotective pathways: (1) insulin-mediated PI3K/Akt/mTOR signaling pathway; (2) GSK-3β inhibition signaling pathway; (3) mTOR-dependent angiogenesis signaling pathway; (4) mTORC2 activation signaling pathway. Cardiac PI3K/Akt causes insulin-stimulated glucose uptake and induces acute mTOR activation, thus improving cardiomyocytes survival and function [73]. Studies found that the PI3K/Akt/mTOR signaling pathway provided efficient cardioprotection against I/R injury induced by insulin [74]. Aoyagi et al. further observed that cardiac-specific transgenic mice overexpressing mTOR suppressed I/R-induced inflammation and necrosis, inhibited cardiac fibrosis in adverse LV remodeling in diet-induced obese mice [89]. They demonstrated that Akt phosphorylation was higher in mTOR overexpressed mice than WT mice under HFD conditions and it was unlikely that mTOR's cardioprotective effects were mediated through autophagic activity. Zhang et al. also demonstrated that Lin28a overexpression protected against MI/R injury in diabetic mice through the insulin-PI3K-mTOR pathway [90].

mTOR's cardioprotection required the inhibition of GSK-3β to reduce the reperfusion injury through mTORCI hyperactivation [85]. During periods of I-post, mTOR prevents cardiomyocytes apoptosis via mTOR-dependent GSK-3β inhibition mechanisms. mTORCI regulates mPTP opening and promotes mitochondrial biogenesis, which may favor cardiac recovery after MI/R and promote the upregulation of antioxidant genes via the activation of proliferator-activated receptor γ coactivator-1α (PGC-1α) [85, 91, 92].

The altered lipid metabolism induced by insulin resistance results in a propensity for microvascular barrier dysfunction, accelerated atherosclerosis, increased vessel wall reactivity, and plaque complications. Angiogenesis is an important component of cardioprotection against I/R injury, which has been proved to be mechanically via mTOR-dependent pathway. Inhibition of mTOR signaling by rapamycin (2 μM) for 1h leads to subsequent impaired angiogenesis in aortic endothelial cells [75]. Loss of mTOR activity by rapamycin (5–10 ng/mL) also blocks endothelial proliferation and angiogenesis [93] as well as the proliferation of endothelial progenitor cells ex vivo [94]. Hypoxia activates the mTOR pathway to promote angiogenesis and cell proliferation [93, 95]. mTOR activation enhances the activity of HIF1α by inhibiting proteolytic degradation, resulting in elevated VEGF expression. This effect is reversible by rapamycin (25 nM for human umbilical vein endothelial cells and 50 nM for HEK293 cells) [68, 69].

Study found that the cardioprotective effects mediated by mTOR overexpression were partly dependent on mTORC2 activation, which was beneficial to cardiomyocytes survival against I/R injury as well as chronic ischemic remodeling [96]. Considering that mTORC2 is rapamycin-insensitive, it is reasonable that using rapamycin to inhibit mTORC1 activity also presents cardioprotective actions against MI/R injury [97]. However, there was still little understanding of the complexity of mTORC2's regulation and its roles in cardiac functions.

4.3. Interactions between Oxidative Stress and mTOR Signaling. Cardiac mTOR is considered as an important regulator of oxidative stress by promoting mitochondrial biogenesis and oxidative metabolism through Ying-Yang 1 (YY1)-PGC-1α pathway [92]. Meanwhile, mTOR modulates autophagy, increases mitochondrial clearance and protects cardiomyocytes from oxidative stress-induced toxicity [72, 98] through the activation of protein kinase B (PKB) [99]. In contrast, other studies found that in cardiac mTOR disrupted mice, fatty acid oxidation is significantly decreased, whereas glucose oxidation is increased [100]. mTOR regulates oxidative stress-induced endothelium dysfunction. Inhibition of mTORCI either with rapamycin or by S6K1 silencing recouples eNOS function, improves NO production, and inhibits O2·− generation in the rat aortas [71]. mTOR also modulates cardiac fibrosis in the models of post-MI remodeling and cardiac hypertrophy [70, 101, 102] while treatment with rapamycin reduced ROS production in the myofibroblasts.

On the other hand, oxidative stress regulates mTORCI ordinarily. ROS production contributes to the inhibition of GSK-3β and mTOR signaling [85]. Alternative origins of ROS, such as NADPH oxidase, may as well provoke mTOR activation and subsequent impair autophagy [76]. An intriguing link between peroxisomes, oxidative stress and autophagy has been recently described. Peroxisomal ROS has been shown to suppress mTORCI activity, in models of the tuberous sclerosis complex signaling node TSC1 and TSC2.
proteins [77, 103]. In contrast, Vigneron et al. found that, in the isolated-perfused mouse heart, IPC protected against I/R injury via inhibition of GSK-3β and a constant opening of mitoKATP with ROS generation to activate the mTOR pathway and induce cardioprotection [104].

5. Potential Cardiometabolic Target against Diabetic MI/R Injury

Although animal studies have found potential regulator aiming at oxidative stress or mTOR signaling under experimental diabetic conditions, clinical studies are still disappointing. Thus, new therapeutic targets as well as efficient cardioprotections against DM-induced MI/R injury are urgently needed.

5.1. Metformin. It is well recognized that metformin could reduce cardiovascular end points of T2DM independently from its glucose-lowering effects. Administration of metformin significantly attenuates I/R injury via relieving ER stress [105] and activating of AMPK-ENOS prosurvival pathway in both nondiabetic and diabetic mice [105, 106]. However, further research demonstrated that metformin effecttively attenuated LV hypertrophy and dysfunction by activating mTOR, p70S6K (Thr389), and S6 phosphorylation in both wild-type and AMPKα2 KO mice, suggesting that metformin attenuated myocardial mTOR signaling independently of AMPKα2 activation [107]. Metformin reduces ROS generation and ameliorates oxidative stress-induced apoptosis and inflammation in cardiomyocytes [108] and endothelial cells [109]. It also protects against I/R-induced myocardial fibrosis by inhibiting fibrotic factors, including TGF-β1, TNF-α and basic fibroblast growth factor (bFGF) in the circulation and the myocardium [110, 111]. As a routine oral agent for T2DM, metformin might be a potential pharmacological therapeutic target to protect against MI/R injury under diabetes on the regulation of cardiac oxidative stress and mTOR signaling.

5.2. Sirtuin 1 (Sirt1). Sirt1 is a member of Sirtuins family [77]. It controls cellular processes and maintains metabolic homeostasis by reducing apoptosis, attenuating inflammation, and modulating oxidative stress [112, 113]. It is a critical regulator in DM-induced MI/R injury. Sirt1-mediated PGC-1α activation could directly respond to H2O2-induced oxidative stress on the regulation of glutathione GPx1, CAT, and Mn-SOD [114]. Overexpression of Sirt1 inhibited oxidative stress and reduced MI/R injury via modulating eNOS activity under diabetic condition [113]. There is a crosstalk between AMPK, Sirt1 and mTOR signaling in the regulation of oxidative stress and cardiomyocytes autophagy [115–117]. Sirt1 deacetylates FoxO3a while mTORC1 can inhibit FoxO-mediated transcription of antioxidant gene targets, including the antioxidants Mn-SOD and catalase [116]. Meanwhile, Sirt1 positively regulates transcription of Rictor, activating the mTORC2 signaling by triggering a cascade of Akt and FoxO phosphorylation. Sirt1 deficiency mice performed increased ROS production and impaired mTORC2 signaling, leading to insulin resistance that could be largely reversed with antioxidant treatment [78]. Considering its specific functions in modulating oxidative stress, mTOR signaling, and mitochondrial dysfunction perturbed in the diabetic heart, Sirt1 may be a promising novel therapeutic target for MI/R injury under DM.

5.3. CTRP9. CTRP9 is a newly found APN paralog. It protects against obesity and T2DM through anti-inflammation and antiapoptotic actions. Increasing the circulating CTRP9 level is a beneficial action against HFD-induced obesity and glucose intolerance [118], whereas CTRP9-deficiency mice performed exacerbated insulin resistance [119]. Importantly, CTRP9 performs cardioprotective effects via inhibition of oxidative stress. Kambara et al. demonstrated that administration of exogenous CTRP9 inhibited oxidative stress, attenuated cardiomyocytes apoptosis, and suppressed inflammatory reactions in the ischemic heart [120, 121]. Su et al. observed the same results in the HFD-induced T2DM mice, implicating that differing from APN, there is no CTRP9 resistance in DM [122]. Our recent finding proved that CTRP9 protected the diabetic heart against I/R injury by reducing ER stress and inflammatory response [33]. Interestingly, compared to general pharmacologic antioxidants, the amount of cardiac endogenous CTRP9 is abundant, much higher than its expression in adipocytes and circulation, suggesting that CTRP9 may be a novel cardiokine. These findings indicate that CTRP9 may also be a potential therapeutic target for diabetic cardiac complications.

6. Conclusions

It is well established that DM aggravates MI/R injury and diabetic IHD patients experience worse clinical outcomes. Oxidative stress and mTOR signaling are master mediators of cardiometabolism and MI/R injury. ROS and RNS accumulation induces cardiomyocytes damage by direct oxidation of proteins, reactive lipid peroxidation products, and interaction with DNA. Uncoupling NOS tigers oxidation/nitration reaction and disturbing the mitochondrial quality control causes mitochondrial dysfunction. These may be mechanisms of oxidative stress impairing the diabetic heart.

When turning to mTOR signaling, it is still controversial to clearly understand the role of mTOR signaling in MI/R injury under DM since both cardioprotective and cardiotoxic effects were observed in vivo and in vitro. The conflicted outcomes could be explained by the following. (1) There is different duration of rapamycin treatment [123]. Study demonstrated that inhibition of mTORC1 before ischemia reduced the size of MI while rapamycin was not cardioprotective if administered before the reperfusion phase [87]. Moreover, different duration of rapamycin treatment contributes to the alteration of metabolic homeostasis. Houde et al. found that administration of rapamycin for two weeks could enhance the insulin level, leading to a glucose intolerance and insulin resistance in mice. However, more than six weeks treatment could improve insulin sensitivity [124]. (2) There is different phosphorylation site of mTORC1. mTORC1 predominately phosphorylated the specific site encompassing 4E-BPI (T37) and (T46) that are rapamycin
resistant. However, mTORC1 could phosphorylated S6K1 (T389), which is rapamycin sensitive under conditions. (3) There are degrees of mTOR activation in the regulation of autophagy. Yu et al. demonstrated that mTOR signaling was inhibited during autophagy initially, but reactivated with prolonged autophagy. The progress was autophagy-dependent and required the degradation of autolysosomal products. The enhanced mTOR activity in reverse attenuated autophagy [125]. (4) There are different cardiac functions of mTORC1 and mTORC2. mTORC1 presents both beneficial and detrimental effects on MI/R injury while mTORC2 show mostly cardio-protective actions as its cellular survival functions [96, 97]. (5) There are inescapable defects of loss-of-function animal models. Conventional ablation of mTOR in mice results in embryonic death [126–128] while cardiac-specific mTOR knockout mouse also shows fatal, dilated cardiomyopathy [64]. Other deletions of mTOR downstream molecules including Raptor and S6K1 may partially inhibit mTOR signaling and also be detrimental since not only the maladaptive but also the physiological functions of the kinase are ablated.

The interplay between oxidative stress and mTOR signaling is complicated, since mTOR not only modulates oxidative stress but also is affected by oxidative stress activation [129]. However, it is unlikely that these fully explain what occurs in the diabetic heart, considering its complicated pathophysiological conditions. Further studies using appropriate in vivo models of DM are needed (Figure 2).

No therapeutic strategy has yet been demonstrated clinically effective against cardiac injury in diabetic population. Antihyperglycemic agent metformin and newly found free
radicals scavengers, Sirt1 and CTRP9, may serve as promising pharmacological cardiometabolic targeted therapeutic genes.

**Competing Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**

[1] D. Mozaffarian, E. J. Benjamin, A. S. Go et al., “Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association,” Circulation, vol. 133, no. 4, pp. 447–454, 2016.

[2] A. Zoroufian, T. Razmi, M. Taghavi-Shavazi, M. Lotfi-Tokalany, and A. Jalali, “Evaluation of subclinical left ventricular dysfunc- tion in diabetic patients: longitudinal strain velocities and left ventricular dyssynchrony by two-dimensional speckle tracking echocardiography study,” Echocardiography, vol. 31, no. 4, pp. 456–463, 2014.

[3] N. Hamdani, A.-S. Hervent, L. Vandekerckhove et al., “Left ventricular diastolic dysfunction and myocardial stiffness in diabetic mice is attenuated by inhibition of dipeptidyl peptidase 4,” Cardiovascular Research, vol. 104, no. 3, pp. 423–431, 2014.

[4] A. M. Shah, S. H. Shin, M. Takeuchi et al., “Left ventricular sys- tolic and diastolic function, remodelling, and clinical outcomes among patients with diabetes following myocardial infarction and the influence of direct renin inhibition with aliskiren,” European Journal of Heart Failure, vol. 14, no. 2, pp. 185–192, 2012.

[5] N. Frey and E. N. Olson, “Cardiac hypertrophy: the good, the bad, and the ugly,” Annual Review of Physiology, vol. 65, pp. 45–79, 2003.

[6] J. D. Molkentin and G. W. Dorn II, “Cytoplasmic signaling pathways that regulate cardiac hypertrophy,” Annual Review of Physiology, vol. 63, no. 3, pp. 391–426, 2001.

[7] N. G. Frangogiannis, “Matricellular proteins in cardiac adaptation and disease,” Physiological Reviews, vol. 92, no. 2, pp. 635–688, 2012.

[8] R. E. Gilbert, “Endothelial loss and repair in the vascular complications of diabetes—mechanisms and therapeutic implications,” Circulation Journal, vol. 77, no. 4, pp. 849–856, 2013.

[9] B. M. Everett, M. M. Brooks, H. E. A. Vlachos, B. R. Chaitman, R. L. Frye, and D. L. Bhatt, “Tropomin and cardiac events in stable ischemic heart disease and diabetes,” The New England Journal of Medicine, vol. 373, no. 7, pp. 610–620, 2015.

[10] C. Emanuelli, A. Caporali, N. Krankel, B. Cristofaro, S. Van Linthout, and P. Madeddu, “Type-2 diabetic Lepr(db/db) mice show a defective microvascular phenotype under basal conditions and an impaired response to angiogenesis gene therapy in the setting of limb ischemia,” Frontiers in Bioscience, vol. 12, pp. 2003–2012, 2007.

[11] M. A. Pfeffer, B. Claggett, R. Diaz et al., “Lixisenatide in patients with type 2 diabetes and acute coronary syndrome,” The New England Journal of Medicine, vol. 373, no. 23, pp. 2247–2257, 2015.

[12] H. Suzuki, Y. Kayama, M. Sakamoto et al., “Arachidonate 12/15-lipoxygenase-induced inflammation and oxidative stress are involved in the development of diabetic cardiomyopathy,” Diabetes, vol. 64, no. 2, pp. 618–630, 2015.

[13] K. A. Connelly, D. J. Kelly, Y. Zhang et al., “Functional, structural and molecular aspects of diastolic heart failure in the diabetic (mRen-2)27 rat,” Cardiovascular Research, vol. 76, no. 2, pp. 280–291, 2007.

[14] M. Rajesh, P. Mukhopadhyay, S. Btkai et al., “Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflamma- tory and cell death signaling pathways in diabetic cardiomyopathy,” Journal of the American College of Cardiology, vol. 56, no. 25, pp. 2115–2125, 2010.

[15] E. J. Anderson, A. P. Kypson, E. Rodriguez, C. A. Anderson, E. J. Lehr, and P. D. Neuf, “substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart,” Journal of the American College of Cardiology, vol. 54, no. 20, pp. 1891–1898, 2009.

[16] E. Braunwald, “Markers in heart failure,” The New England Journal of Medicine, vol. 358, no. 20, pp. 2148–2159, 2008.

[17] V. Parra, H. E. Verdejo, M. Iglewsks et al., “Insulin stimulates mitochondrial fusion and function in cardiomyocytes via the Akt-mTOR-N Raf-B-Opa-1 signaling pathway,” Diabetes, vol. 63, no. 1, pp. 75–88, 2014.

[18] Y. Matsu, H. Takagi, X. Qu et al., “Distinct roles of autophagy in the heart during ischemia and reperfusion: roles of AMP-activated protein kinase and beclin 1 in mediating autophagy,” Circulation Research, vol. 100, no. 6, pp. 914–922, 2007.

[19] Q. M. Nguyen, S. R. Sinivasan, J.-H. Xu, W. Chen, and G. S. Berenson, “Changes in risk variables of metabolic syndrome since childhood in pre-diabetic and type 2 diabetic subjects. The Bogalusa Heart Study,” Diabetes Care, vol. 31, no. 10, pp. 2044–2049, 2008.

[20] T. Miki, T. Itoh, D. Sunaga, and T. Miura, “Effects of diabetes on myocardial infarct size and cardioprotection by preconditioning and postconditioning,” Cardiovascular Diabetes, vol. II, article 67, 2012.

[21] B. Dregner, I. A. Ostrovskyi, M. Barak, Y. Nechamia-Arbel, E. Ziv, and J. H. Axelrod, “Diabetes blockade of sevoflurane post- conditioning is not restored by insulin in the rat heart: phosphorylated signal transducer and activator of transcription 3- and phosphatidylinositol 3-kinase-mediated inhibition,” Anesthesiology—The Journal of the American Society of Anesthesiologists, vol. 114, no. 6, pp. 1364–1372, 2011.

[22] P. Ferdinandy, D. J. Hausenloy, G. Heusch, G. F. Baxter, and R. Schulz, “Interaction of risk factors, comorbidities, and comedications with ischemia/reperfusion injury and cardio- protection by preconditioning, postconditioning, and remote conditioning,” Pharmacological reviews, vol. 66, no. 4, pp. 1142–1174, 2014.

[23] D. J. Hausenloy, S. Lecour, and D. M. Yellon, “Reperfusion injury salvage kinase and survivor activating factor enhancement (SAFE) pathway against reperfusion injury: two sides of the same coin,” Antioxidants & Redox Signaling, vol. 14, no. 5, pp. 893–907, 2011.

[24] N. Ghaboura, S. Tamareille, P.-H. Ducluzeau et al., “Diabetes mellitus abrogates erythropoietin-induced cardioprotec- tion against ischemic-reperfusion injury by alteration of the RISK/GSK-3β signaling,” Basic Research in Cardiology, vol. 106, no. 1, pp. 147–162, 2011.

[25] S. Lecour, “Activation of the protective Survivor Activating Factor Enhancement (SAFE) pathway against reperfusion injury: does it go beyond the RISK pathway?” Journal of Molecular and Cellular Cardiology, vol. 47, no. 1, pp. 32–40, 2009.

[26] C. Zhuo, Y. Wang, X. Wang, Y. Wang, and Y. Chen, “Cardioprotection by ischemic postconditioning is abolished in
depressed rats: role of Akt and signal transducer and activator of transcription-3,” Molecular and Cellular Biochemistry, vol. 346, no. 1-2, pp. 39–47, 2011.

[27] W. Yi, Y. Sun, E. Gao et al., “Reduced cardioprotective action of adiponectin in high-fat diet–induced type II diabetic mice and its underlying mechanisms,” Antioxidants & Redox Signaling, vol. 15, no. 7, pp. 1779–1788, 2011.

[28] Y. Wang, E. Gao, L. Tao et al., “AMP-activated protein kinase deficiency enhances myocardial ischemia/reperfusion injury but has minimal effect on the antioxidant/antinitrative protection of adiponectin,” Circulation, vol. 119, no. 6, pp. 835–844, 2009.

[29] D. L. Eizirik, A. K. Cardozo, and M. Cnop, “The role for endoplasmic reticulum stress in diabetic cardiomyopathy,” Biochimica et Biophysica Acta—Molecular Basis of Disease, vol. 1852, no. 2, pp. 209–218, 2015.

[30] T. Miki, T. Miura, H. Hotta et al., “Endoplasmic reticulum stress in diabetic hearts abolishes erythropoietin-induced myocardial protection by impairment of phospho–glycogen synthase kinase-3β–mediated suppression of myocardial permeability transition,” Diabetes, vol. 58, no. 12, pp. 2863–2872, 2009.

[31] L. A. Barr, Y. Shimizu, J. P. Lambert, C. K. Nicholson, and J. W. Calvert, “Hydrogen sulfide attenuates high fat diet–induced cardiac dysfunction via the suppression of endoplasmic reticulum stress,” Nitric Oxide, vol. 46, pp. 145–156, 2015.

[32] S. Bai, L. Cheng, Y. Yang et al., “Cig/TFN-related protein 9 protects diabetic rat heart against ischemia reperfusion injury; role of endoplasmic reticulum stress,” Oxidative Medicine and Cellular Longevity, vol. 2016, Article ID 902025, 14 pages, 2016.

[33] M. Aragno, R. Mastrocola, G. Allotti et al., “Oxidative stress triggers cardiac fibrosis in the heart of diabetic rats,” Endocrinology, vol. 149, no. 1, pp. 380–388, 2008.

[34] H. Su, L. Ji, W. Xing et al., “Acute hyperglycaemia enhances oxidative stress and aggravates myocardial ischaemia/reperfusion injury: role of thio-oxidant-interacting protein,” Journal of Cellular and Molecular Medicine, vol. 17, no. 1, pp. 181–191, 2013.

[35] M. H. Ghattas and D. M. Abo-Elmatty, “Association of polymorphic markers of the catalase and superoxide dismutase genes with type 2 diabetes mellitus,” DNA and Cell Biology, vol. 31, no. 11, pp. 1598–1603, 2012.

[36] P. Lewis, N. Stefanovic, J. Pete et al., “Lack of the antioxidant enzyme glutathione peroxidase-1 accelerates atherosclerosis in diabetic apolipoprotein E–deficient mice,” Circulation, vol. 115, no. 16, pp. 2178–2187, 2007.

[37] R. Luan, S. Liu, T. Yin et al., “High glucose sensitizes adult cardiomyocytes to ischaemia/reperfusion injury through nitrosative thio-oxidant inactivation,” Cardiovascular Research, vol. 83, no. 2, pp. 294–302, 2009.

[38] V. Kain, S. Kumar, and S. L. Sitasawad, “Azelnidipine prevents cardiac dysfunction in streptozotocin–diabetic rats by reducing intracellular calcium accumulation, oxidative stress and apoptosis,” Cardiovascular Diabetology, vol. 10, article no. 97, 2011.

[39] C. Huang, A. M. Andres, E. P. Ratliff, G. Hernandez, P. Lee, and R. A. Gottlieb, “Preconditioning involves selective mitophagy mediated by parkin and p62/SQSTM1,” PLoS ONE, vol. 6, no. 6, Article ID e20975, 2011.
rat hearts by increasing oxidative modifications of these proteins," Journal of Molecular and Cellular Cardiology, vol. 49, no. 1, pp. 58–69, 2010.

[56] C.-A. Chen, T.-Y. Wang, S. Varadaraj et al., "S-glutathionylation un couples eNOS and regulates its cellular and vascular function," Nature, vol. 468, no. 7327, pp. 1115–1118, 2010.

[57] R. M. Maalouf, A. A. Eid, Y. C. Gorin et al., "Nox4-driven reactive oxygen species mediate cardiomyocyte injury in early type 1 diabetes," American Journal of Physiology—Cell Physiology, vol. 302, no. 3, pp. C597–C604, 2012.

[58] T. Okazaki, H. Otani, T. Shimazu et al., "Reversal of inducible nitric oxide synthase uncoupling unmasks tolerance to ischemia/reperfusion injury in the diabetic rat heart," Journal of Molecular and Cellular Cardiology, vol. 50, no. 3, pp. 534–544, 2011.

[59] G. Ashrafi and T. L. Schwarz, "The pathways of mitophagy for quality control and clearance of mitochondria," Cell Death & Differentiation, vol. 20, no. 1, pp. 31–42, 2013.

[60] M. P. Murphy, "Induction of mitochondrial ROS production by electrophilic lipids: a new pathway of redox signaling?" American Journal of Physiology—Heart and Circulatory Physiology, vol. 290, no. 5, pp. H1754–H1755, 2006.

[61] S. Wullschleger, R. Loewith, and M. N. Hall, "TOR signaling in growth and metabolism," Cell, vol. 124, no. 3, pp. 471–484, 2006.

[62] S. C. Johnson, P. S. Rabinovitch, and M. Kaeberlein, "MTOR is a key modulator of ageing and age-related disease," Nature, vol. 493, no. 7432, pp. 338–345, 2013.

[63] M. Laplante and D. M. Sabatini, "Regulation of mTORC1 and its impact on gene expression at a glance," Journal of Cell Science, vol. 126, no. 8, pp. 1713–1719, 2013.

[64] D. Zhang, R. Contu, M. V. G. Latronico et al., "mTORC1 regulates cardiac function and myocyte survival through 4E-BP inhibition in mice," Journal of Clinical Investigation, vol. 120, no. 10, p. 3735, 2010.

[65] M. Laplante and D. M. Sabatini, "mTORC1 signaling in growth control and disease," Cell, vol. 149, no. 2, pp. 274–293, 2012.

[66] T. Aoyagi, Y. Kusakari, C.-Y. Xiao et al., "Cardiac mTORC1 protects the heart against ischemia-reperfusion injury," American Journal of Physiology—Heart and Circulatory Physiology, vol. 303, no. 1, pp. H75–H85, 2012.

[67] H. P. Glazer, R. M. Osipow, R. T. Clements, F. W. Sellke, and C. Bianchi, "Hypercholesterolemia is associated with hyperactive cardiac mTORC1 and mTORC2 signaling," Cell Cycle, vol. 8, no. 11, pp. 1738–1746, 2009.

[68] S. C. Land and A. R. Tee, "Hypoxia-inducible factor 1α is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif," Journal of Biological Chemistry, vol. 282, no. 28, pp. 20534–20543, 2007.

[69] J.-W. Park, W.-H. Kim, S.-H. Shin et al., "Visfatin exerts angiogenic effects on human umbilical vein endothelial cells through the mTOR signaling pathway," Biochimica et Biophysica Acta—Molecular Cell Research, vol. 1813, no. 5, pp. 763–771, 2011.

[70] P. C. Schenkel, A. M. V. Tavares, R. O. Fernandes et al., "Time course of hydrogen peroxide thioredoxin balance and its influence on the intracellular signalling in myocardial infarction," Experimental Physiology, vol. 97, no. 6, pp. 741–749, 2012.

[71] A. G. Rajapakse, G. Yepuri, J. M. Carvas et al., "Hyperactive S6K1 mediates oxidative stress and endothelial dysfunction in aging: inhibition by resveratrol," PLoS ONE, vol. 6, no. 4, Article ID e19237, 2011.

[72] Z. Z. Chong, Y. C. Shang, and K. Maiiese, "Cardiovascular disease and mTOR signaling," Trends in Cardiovascular Medicine, vol. 21, no. 5, pp. 151–155, 2011.

[73] H. Yao, X. Han, and X. Han, "The cardioprotection of the insulin-mediated PI3K/Akt/mTOR signaling pathway," American Journal of Cardiovascular Drugs, vol. 14, no. 6, pp. 433–442, 2014.

[74] R. Si, L. Tao, H. F. Zhang et al., "Survivin: a novel player in insulin cardioprotection against myocardial ischemia/reperfusion injury," Journal of Molecular and Cellular Cardiology, vol. 50, no. 1, pp. 16–24, 2011.

[75] V. Lemaître, A. J. Dabo, and J. D’Armiento, "Cigarette smoke components induce matrix metalloproteinase-1 in aortic endothelial cells through inhibition of mTOR signaling," Toxicological Sciences, vol. 123, no. 2, pp. 542–549, 2011.

[76] S. Fourcade, I. Ferrer, and A. Pujol, "Oxidative stress, mitochondrial and proteostasis malfunction in adrenoleukodystrophy: a paradigm for axonal degeneration," Free Radical Biology and Medicine, vol. 88, pp. 18–29, 2015.

[77] K. Maiiese, Z. Z. Chong, Y. C. Shang, and S. Wang, "Translating cell survival and cell longevity into treatment strategies with SIRT1," Romanian Journal of Morphology and Embryology, vol. 52, no. 4, pp. 1173–1185, 2011.

[78] R.-H. Wang, H.-S. Kim, C. Xiao, X. Xu, O. Gavrilova, and C.-X. Deng, "Hepatic Sirt1 deficiency in mice impairs mTORc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance," The Journal of Clinical Investigation, vol. 121, no. 11, pp. 4477–4490, 2011.

[79] S. C. Ranieri, S. Fusco, E. Panieri et al., "Mammalian lifespan determinant p66shc mediates obesity-induced insulin resistance," Proceedings of the National Academy of Sciences of the United States of America, vol. 107, no. 30, pp. 13420–13425, 2010.

[80] J. C. Drake, S. E. Alway, J. M. Hollander, and D. L. Williamson, "AICAR treatment for 14 days normalizes obesity-induced dysregulation of TORC1 signaling and translational capacity in fasted skeletal muscle," American Journal of Physiology—Regulatory Integrative and Comparative Physiology, vol. 299, no. 6, pp. R1546–R1554, 2010.

[81] S. Turdi, M. R. Kandadi, J. Zhao, A. F. Huff, M. Du, and J. Ren, "Deficiency in AMP-activated protein kinase exaggerates high fat diet-induced cardiac hypertrophy and contractile dysfunction," Journal of Molecular and Cellular Cardiology, vol. 50, no. 4, pp. 712–722, 2011.

[82] R. Guo, Y. Zhang, S. Turdi, and J. Ren, "Adiponectin knockout accentuates high fat diet-induced obesity and cardiac dysfunction: role of autophagy," Biochimica et Biophysica Acta - Molecular Basis of Disease, vol. 1832, no. 8, pp. 1136–1148, 2013.

[83] S. Ciarretta, P. Zhai, D. Shao et al., "Rheb is a critical regulator of autophagy during myocardial ischemia: pathophysiological implications in obesity and metabolic syndrome," Circulation, vol. 125, no. 9, pp. 1134–1146, 2012.

[84] L. Yang, J.-Y. Gao, J. Ma et al., "Cardiac-specific overexpression of malathion in mice attenuates myocardial remodeling and contractile dysfunction in 1-NAME-induced experimental hypertension: role of autophagy regulation," Toxicology Letters, vol. 237, no. 2, pp. 121–132, 2015.

[85] C. H. Jung, C. B. Jun, S.-H. Ro et al., "ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery," Molecular Biology of the Cell, vol. 20, no. 7, pp. 1992–2003, 2009.

[86] A. De Waha, A. Dibra, S. Kufner et al., "Long-term outcome after sirolimus-eluting stents versus bare metal stents in patients with coronary artery disease," Journal of Clinical Investigation, vol. 120, no. 11, pp. 4477–4490, 2011.

[87] S. Fourcade, I. Ferrer, and A. Pujol, "Oxidative stress, mitochondrial and proteostasis malfunction in adrenoleukodystrophy: a paradigm for axonal degeneration," Free Radical Biology and Medicine, vol. 88, pp. 18–29, 2015.
with Diabetes mellitus: a patient-level meta-analysis of randomized trials,” *Clinical Research in Cardiology*, vol. 100, no. 7, pp. 561–570, 2011.

[87] A. Das, F. N. Salloum, D. Durrant, R. Ockaili, and R. C. Kukreja, “Rapamycin protects against myocardial ischemia–reperfusion injury through JAK2–STAT3 signaling pathway,” *Journal of Molecular and Cellular Cardiology*, vol. 53, no. 6, pp. 858–869, 2012.

[88] A. Das, F. N. Salloum, S. M. Filipponi et al., “Inhibition of mammalian target of rapamycin protects against reperfusion injury in diabetic heart through STAT3 signaling.” *Basic Research in Cardiology*, vol. 110, no. 3, 2015.

[89] T. Aoyagi, J. K. Higa, H. Aoyagi, N. Yorichika, B. K. Shimada, and T. Matsui, “Cardiac mTOR rescues the detrimental effects of diet-induced obesity in the heart after ischemia–reperfusion,” *American Journal of Physiology—Heart and Circulatory Physiology*, vol. 308, no. 12, pp. H1530–H1539, 2015.

[90] M. Zhang, D. Sun, S. Li et al., “Lin28a protects against cardiac ischemia/reperfusion injury in diabetic mice through the insulin–PI3K–mTOR pathway,” *Journal of Cellular and Molecular Medicine*, vol. 19, no. 6, pp. 1174–1182, 2015.

[91] Z. Lu, X. Xu, X. Hu et al., “PGC-1α regulates expression of myocardial mitochondrial antioxidants and myocardial oxidative stress after chronic systolic overload,” *Antioxidants & Redox Signaling*, vol. 13, no. 7, pp. 1011–1022, 2010.

[92] J. T. Cunningham, J. T. Rodgers, D. H. Arlow, F. Vazquez, V. K. Mootha, and P. Puigserver, “mTOR controls mitochondrial oxidative function through a YY1-PGC-1α complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS,” *Nature Cell Biology*, vol. 110, no. 3, 2015.

[93] F. Vigneron, P. Dos Santos, S. Lemoine et al., “GSK-3β at the crossroads in the signalling of heart preconditioning: implication of mTOR and Wnt pathways,” *Cardiovascular Research*, vol. 90, no. 1, pp. 49–56, 2011.

[94] S. Sen, B. K. Kundra, H. C. Wu et al., “Glucose regulation of load-induced mTOR signaling and ER stress in mammalian heart,” *Journal of the American Heart Association*, vol. 2, no. 3, Article ID e004796, 2013.

[95] J. W. Calvert, S. Gundewar, S. Jha et al., “Acute metformin therapy confers cardioprotection against myocardial infarction via AMPK-eNOS-mediated signalling,” *Diabetes*, vol. 57, no. 3, pp. 696–705, 2008.

[96] X. Xu, Z. Lu, J. Fassett et al., “Metformin protects against systolic overload-induced heart failure independent of AMP-activated protein kinase a2.” *Hypertension*, vol. 63, no. 4, pp. 723–728, 2014.

[97] M. Hu, P. Ye, H. Liao, M. Chen, and F. Yang, “Metformin protects H9C2 cardiomyocytes from high-glucose and hypoxia/injury via inhibition of reactive oxygen species generation and inflammatory responses: role of AMPK and JNK,” *Journal of Diabetes Research*, vol. 2016, Article ID 296954, 9 pages, 2016.

[98] D. Kukidome, T. Nishikawa, K. Sonoda et al., “Activation of AMP-activated protein kinase reduces hyperglycemia-induced mitochondrial reactive oxygen species production and promotes mitochondrial biogenesis in human umbilical vein endothelial cells,” *Diabetes*, vol. 55, no. 1, pp. 120–127, 2006.

[99] X.-F. Wang, J.-Y. Zhang, L. Li, X.-Y. Zhao, H.-L. Tao, and L. Zhang, “Metformin improves cardiac function in rats via activation of AMP-activated protein kinase,” *Clinical and Experimental Pharmacology and Physiology*, vol. 38, no. 2, pp. 94–101, 2011.

[100] E. P. Daskalopoulos, C. Dufey, L. Bertrand, C. Beauloye, and S. Horman, “AMPK in cardiac fibrosis and repair: actions beyond metabolic regulation,” *Journal of Molecular and Cellular Cardiology*, vol. 91, pp. 188–200, 2016.

[101] S.-I. Imai and L. Guarente, “NAD+ and sirtuins in aging and disease,” *Trends in Cell Biology*, vol. 24, no. 8, pp. 464–471, 2014.

[102] G. Donmez and L. Guarente, “Aging and disease: connections to sirtuins,” *Aging Cell*, vol. 9, no. 2, pp. 285–290, 2010.

[103] L. Zhong and R. Mostoslavsky, "Fine tuning our cellular factories: sirtuins in mitochondrial biology," *Cell Metabolism*, vol. 13, no. 6, pp. 621–626, 2011.

[104] S.-B. Wu, Y.-T. Wu, T.-P. Wu, and Y.-H. Wei, “Role of AMPK-mediated adaptive responses in human cells with mitochondrial dysfunction to oxidative stress,” *Biochimica et Biophysica Acta—General Subjects*, vol. 1840, no. 4, pp. 1331–1344, 2014.

[105] F. Hong, M. D. Larrea, C. Doughty, D. J. Kwiatkowski, R. Squilace, and J. M. Slingerland, “mTOR-raptor binds and activates SGK1 to regulate p27 phosphorylation,” *Molecular Cell*, vol. 30, no. 6, pp. 701–711, 2008.
[117] K. Maiese, “Targeting molecules to medicine with mTOR, autophagy and neurodegenerative disorders,” *British Journal of Clinical Pharmacology*, vol. 82, no. 5, pp. 1245–1266, 2016.

[118] J. M. Peterson, Z. Wei, M. M. Seldin, M. S. Byerly, S. Aja, and G. W. Wong, “CTRP9 transgenic mice are protected from diet-induced obesity and metabolic dysfunction,” *American Journal of Physiology—Regulatory Integrative and Comparative Physiology*, vol. 305, no. 5, pp. R522–R533, 2013.

[119] Z. Wei, X. Lei, P. S. Petersen, S. Aja, and G. W. Wong, “Targeted deletion of C1q/TNF-related protein 9 increases food intake, decreases insulin sensitivity, and promotes hepatic steatosis in mice,” *American Journal of Physiology—Endocrinology and Metabolism*, vol. 306, no. 7, pp. E779–E790, 2014.

[120] H. Su, Y. Yuan, X.-M. Wang et al., “Inhibition of CTRP9, a novel and cardiac-abundantly expressed cell survival molecule, by TNFα-initiated oxidative signaling contributes to exacerbated cardiac injury in diabetic mice,” *Basic Research in Cardiology*, vol. 108, no. 1, article no. 315, 2013.

[121] T. Kambara, R. Shibata, K. Ohashi et al., “C1q/tumor necrosis factor-related protein 9 protects against acute myocardial injury through an adiponectin receptor 1-AMPK-dependent mechanism,” *Molecular and Cellular Biology*, vol. 35, no. 12, pp. 2173–2185, 2015.

[122] T. Kambara, K. Ohashi, R. Shibata et al., “CTRP9 protein protects against myocardial injury following ischemia-reperfusion through AMP-activated protein kinase (AMPK)-dependent mechanism,” *Journal of Biological Chemistry*, vol. 287, no. 23, pp. 18965–18973, 2012.

[123] Y. Fang, R. Westbrook, C. Hill et al., “Duration of rapamycin treatment has differential effects on metabolism in mice,” *Cell Metabolism*, vol. 17, no. 3, pp. 456–462, 2013.

[124] V. P. Houde, S. Brülé, W. T. Festuccia et al., “Chronic rapamycin treatment causes glucose intolerance and hyperlipidemia by upregulating hepatic gluconeogenesis and impairing lipid deposition in adipose tissue,” *Diabetes*, vol. 59, no. 6, pp. 1338–1348, 2010.

[125] L. Yu, C. K. McPhee, L. Zheng et al., “Termination of autophagy and reformation of lysosomes regulated by mTOR,” *Nature*, vol. 465, no. 7300, pp. 942–946, 2010.

[126] Y.-G. Gangloff, M. Mueller, S. G. Dann et al., “Disruption of the mouse mTOR gene leads to early postimplantation lethality and prohibits embryonic stem cell development,” *Molecular and Cellular Biology*, vol. 24, no. 21, pp. 9508–9516, 2004.

[127] M. Murakami, T. Ichisaka, M. Maeda et al., “mTOR is essential for growth and proliferation in early mouse embryos and embryonic stem cells,” *Molecular and Cellular Biology*, vol. 24, no. 15, pp. 6710–6718, 2004.

[128] D. A. Guertin, D. M. Stevens, C. C. Thor en et al., “Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCa, but not S6K1,” *Developmental Cell*, vol. 11, no. 6, pp. 859–871, 2006.

[129] Y. Rong, C. K. McPhee, S. Deng et al., “Spinster is required for autophagic lysosome reformation and mTOR reactivation following starvation,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 19, pp. 7826–7831, 2011.