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Review

SIRT3-mediated cardiac remodeling/repair following myocardial infarction

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ABSTRACT

The recent investigations have extensively focused on the importance of sirtuins, as a highly conserved family of gene products, particularly SIRT3 in various biological and pathological processes. SIRT3, the mitochondrial NAD + -dependent deacetylase has been demonstrated to target a broad range of proteins involved in the oxidative stress, ischemia–reperfusion injury, mitochondrial metabolism homeostasis and cellular death. The critical function of SIRT3 in myocardial infarction (MI), which is one of the complex phenotype of coronary artery disease and a result of interaction between various genetic and environmental factors, as well as in cardiac repair and remodeling post-MI have attracted more attention in the recent years. Therefore, in this review, we will summarize important literature about the involvement of SIRT3 in cardiac remodeling/repair following MI and its potential underlying mechanisms.

1. Introduction

Myocardial infarction (MI), as one of the complex phenotype of coronary artery disease, is a result of interaction between various genetic and environmental factors [1,2]. MI is followed by the some important structural remodeling in cardiac muscle including an increased inflammatory response and generation of fibrous scar at the site of infarction. More importantly, in the non-infarcted sites of affected myocardium, vascular remodeling and interstitial fibrosis are also observed [3]. At the site of cardiomyocyte loss, fibrous scar plays critical role in the preserving structural integrity, hence cardiac recovery, which finally results in the impairment of myocardial tissue behavior. Also, in this process, various substances and proteins have been reported to act crucial functions in cardiac repair/remodeling, therefore, attracted substantial interest as pharmacological intervention [4]. Recently, sirtuins, as a plausible novel highly conserved family of gene products, have been attracted a considerable attention, through their moonlighting role in the various biological processes including oxidative-stress resistance, cell-cycle regulation, insulin secretion, mitochondrial energetics and inflammatory cardiomyopathy [5]. This family has seven members named SIRT1–7, and SIRT1 is the most well-known member of this family. In addition to high degree of structural similarity in all sirtuin proteins, some significant differences are reported in their C and N termini, which have increasing importance in the diverse biological behavior of proteins including, enzymatic activities, specific substrates, expression pattern and subcellular localization [6]. Among this gene family, loss of function of SIRT3 has been reported to be involved in the pathogenesis of cardiac hypertrophy and the transition into heart failure. Additionally, accumulating studies investigating gain of function of SIRT3, as well as activation of SIRT3 through treatment approaches, have demonstrated that signaling through this member of sirtuin family can ameliorate cardiac pathologies through various

Abbreviations: MI, myocardial infarction; HIF, hypoxia inducible factor-1α; SOD2, superoxide dismutase; FOXO3A, forkhead box O3a; OPA1, optic atrophy 1; MMPs, matrix metalloproteinases; TGF-β, transforming growth factor-β; PARP-1, poly (ADP ribose)- polymerase 1; VEGF, vascular endothelial growth factor; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; EPCs, endothelial progenitor cells

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mechanisms, therefore represent a promising therapeutic strategy for cardiac pathologies, particularly cardiac repair following MI [7]. In the present review, we will focus on the underlying mechanism of SIRT3 signaling, by which cardiac repair/ remodeling can be increased.

2. SIRT3: structure and molecular signaling

SIRT3, as an important member of sitruins family with recently discovered plenty of biological functions, is a soluble protein located at mitochondria and has considerably high expression levels in tissues enriched with mitochondria [7]. In addition, recent studies investigating the precise physiological and pathophysiological function of this protein, have been reported the crucial role of SIRT3 in cellular stress, oxidative stress response, fatty acids metabolism, energy metabolism, tumor suppression, and age-associated hearing loss [7]. In the normal myocardium, it is estimated that oxidative phosphorylation in mitochondria is responsible for the providing approximately 90% of ATP required for cardiac normal function. The key material source for this type of energy production is fatty acid beta oxidation [4]. The main enzymes with critical function in oxidative phosphorylation, hence mitochondrial energy metabolism are under direct regulation of SIRT3, which can modulate the enzymatic activity of various enzymes through deacetylation [8]. Reduction in SIRT3 levels is one of the main promoters of glycolysis pathway through two different mechanisms. First, when SIRT3 is absent, hexokinase II is activated because of highly acetylated state of peptidylprolyl isomerase D, and through phosphorylation of glucose, produced glucose-6-phosphate (G6P) [9]. Second mechanism is consisted of stabilization of transcription factor, hypoxia inducible factor-(HIF) 1α, through inducing enhancement in the reactive oxygen (ROS) production. The results of this pathway are regulation of glycolytic gene expression [10]. Deacetylation activity of SIRT3 also plays critical function in stimulation of β oxidation through modification and activation long-chain acyl-CoA dehydrogenase [11]. Acylglycerol kinase, medium chain-specific acyl-CoA dehydrogenase, and acyl-CoA synthetase short-chain family member 2 are also reported to be directly regulated by SIRT3 [12–14]. The later one is involved in the conversion of acetate to acetyl-CoA and its entrance to tricarboxylic acid cycle [13,14]. 3-hydroxy-3-methylglutaryl-CoA synthase 2 (ketone-body biosynthesis) [15], glutamate dehydrogenase 1 (amino acid metabolism) [16], ornithine transcarbamylase (urea cycle) [17], the ribosomal protein MRPL10 [18], electron transport chain complex I and II including [16], ATP synthase activity [19], are all deacetylated and hence activated by SIRT3. Another important function of SIRT3 is enhancing the ability of the mitochondria to deal effectively with ROS, and subsequent increased oxidative stress, cellular damage and death, which are closely associated with various cardiac pathologies such as coronary atherosclerosis [20–24], cardiac hypertrophy [25–27], hyperlipidemia [17,28], diabetes [29,30]. SIRT3 is also demonstrated to deacetylate and activate Mn superoxide dismutase (SOD2), the main superoxide radicals scavenger [31–33], hence decrease ROS production and protective response against oxidative stress-induced cellular damage. SIRT3- mediated decrease in the translocation of Forkhead box O3a (FOXO3A) from the nucleus into cytosol results in the robust transcription of SOD2 and other antioxidation [34]. In addition to these well-defined functions of SIRT3, some studies have focused on the effects of SIRT3 expression on the apoptosis and reported controversial results. However, what is evident is that SIRT3 is a potent inhibitor of cardiomyocyte apoptosis in various studies. This function of SIRT3 is indicated to be mediated by interesting pathways, such as deacetylation and activation of optic atrophy 1 (OPA1) [35,36], Ku70 [34], and cyclophilin D [26], as well as inhibition of the mitochondrial permeability [37].

3. Cardiac repair/remodeling following MI

Following MI and necrotic death of cardiomyocytes, cardiac repair/remodeling, which recruits some inflammatory responses make some important structural changes in both infarct and remote site [38]. Immediately after an infarction event in myocardium, matrix metalloproteinases (MMPs) are activated and begin to degradation of extracellular matrix (ECM) and coronary vasculature [39,40]. After one week, significant upregulation occurs in the expression levels of tissue inhibitors of MMPs (TIMPs), which results in the decrease in proteolytic activity of MMPs [41]. Following MI, inflammatory cells including neutrophils, which involved in the proteolytic digestion, and monocytes/macrophages, which are contributed in phagocytosis of the affected tissues, are recruited to MI site, and enter to infarcted tissue by signaling through chemoattractant cytokines and adhesion molecules, as well as MMP proteolytic activity, event that occur in different sites of body like ovulation, embryo implantation, tissue repair, and cancer [40,42–49]. Endothelial cells of the various kind of tissues and coronary vasculature are responsible for the expression of these factors [45,50]. The peak of this inflammatory reaction occurs approximately 1 and 2 weeks after a MI event, and is abolished by disappearance of inflammatory cells from MI site, which is a result of apoptosis of these cells within 3–4 weeks. Lost parachymal cells are replaced by fibrogenic component, which is triggered by the activation of transforming growth factor (TGF)-β1, as a main component of fibrogenesis [50]. After one week, collagen fibers are appeared in infarcted site and begin to assembly in the form of scar tissue at week 2, by transformed fibroblast-like cells, with exclusive morphological and phenotypic properties [51]. Myofibroblasts are fibroblast-like cells, which express α-smooth muscle actin [52] microfilaments and earn contraction ability, through signaling by macrophages-released TGF-β1 [53]. Rapidly proliferation and expression of type I and III fibrillar collagens by myofibroblasts are responsible for the generation of the contractile scar tissue in infarct site [54]. These cells are also involved in the production of renin, angiotensin-converting enzyme, angiotensin receptors, endothelin-1, and vasopressin, which play key functional role in the promotion of scar tissue contraction [55–57]. In addition to infarct site, interstitial fibroblasts develop fibrosis non-infarcted myocardium at week 3. However, myofibroblasts do not appear at unaffected sites [50].

4. SIRT3 in cardiac diseases

Accumulating number of previous studies has been reported that SIRT3 paly pivotal role in the pathogenesis of various cardiovascular diseases, including ischemic heart disease, cardiac hypertrophy and heart failure, diabetic cardiomyopathy and cardiac lipotoxicity, drug-induced cardiotoxicity, and particularly MI, which is the main discussing of present review [8,58,59]. From the developmental point of view, SIRT3 has reported to not be an important player, since SIRT deficient mice do not present significant abnormality in phenotype. However, after birth, SIRT3-/- mice are very sensitive to stress stimuli [27,60]. The most important reason for this finding is the critical function of this sitruin in the regulation of the activity of mitochondrial substrates such as several enzymes involved in the oxidative stress, electron transport and ATP production. In addition, downregulation of SIRT3 results in the significant enhancement in the risk of ischemia-reperfusion injury in adult hearts, as well as cardiac-derived cells [61,62]. It is also increasingly reported that SIRT3 play substantial roles in the vascular inflammation, the fact which potentiates the importance of SIRT3 in atherosclerosis. In chemical- induced model of vascular inflammation, it was reported that downregulation of SIRT3 resulted in the ROS production and hence increase in inflammation in endothelial cells [63]. However, the precise mechanism underlying the function of SIRT3 in atherosclerosis is not clearly understood, particularly the results of a recent study, which showed that SIRT3 deficiency did not exert any significant impact on the atherosclerotic plaque stability, and lesions progression, is an indicative of this fact [64]. In addition, an accumulating body of recent studies have been showed that cardiac hypertrophy, which causes myocardial cell death and fibrosis, and

consequent heart failure are strongly associated with downregulation of SIRT3 [25,26,65]. The ejection fraction was reported to be decreased after transverse aortic constriction in mice with SIRT3 deficiency. This is resulted in the development of cardiac hypertrophy and fibrosis [66,67]. Additionally, it was also observed that SIRT3 downregulation decreased oxygen consumption, respiratory capacity, palmitate and glucose oxidation, and ATP synthesis, which showed a shift form oxidative phosphorylation to glycolysis [67]. In animal model of heart failure, decrease in SIRT3 expression levels, and subsequent SIRT3 deacetylation activity give rise into the increase in the acetylated form of mitochondrial proteins [68]. Some studies introduce various mechanisms for the downmodulation of SIRT3 in heart failure, some important example of them include, downregulation of PGC- 1a [69]; upregulation of poly (ADP ribose)- polymerase 1 (PARP-1), a DNA repair enzyme, which competes with SIRT3 for NAD + [70]; increase in the expression levels of RIP140, which inhibits SIRT3 [71], and decrease in the nicotinamide mononucleotide adenylyltransferase 3 (NMNAT3) activity, a mitochondrial enzyme supplying NAD + for SIRT3 function [72,73]. Due to critical function of SIRT3 in the regulation of energy metabolism [12,74], and protection against oxidative stress [12,27], the reported deleterious effects of SIRT3 downregulation in cardiac hypertrophy is very rational.

4.1. SIRT3 in MI

Various pathological processes such as metabolic disturbances, disruption in the ultrastructure of cardiomyocytes, and cell death, are some important catastrophic consults of MI [75]. On the other hand, increasing number of previous studies have been showed the critical role of SIRT3 in the pathological events of ischemic and reperfusion injury, which result in the ischemia–reperfusion injury (I/R). Artery occlusion- mediated MI was reported to be accompanied with significant decrease in the expression levels of SIRT3 [76]. SIRT3 knockout in animal models makes them more susceptible to I/R, which was concluded from the larger infarction sizes in SIRT3 deficient mice [61]. Downregulation of SIRT3 also disrupted normal cardiac function in these animals. However, another study showed that SIRT3 deficiency did not affect MI sized or cardiac function [77]. Myocardial ischemia resulted in the disruption in the sufficient supply of oxygen and energy for myocardium is associated with overexpression of hypoxia-inducible factors (HIFs), particularly oxygen-labile α subunit, HIF-1α such that its expressions is one of the early and useful event take place in response to MI [78]. In acute MI, it was demonstrated that administration of HIF-1α can efficiently decrease infarction size and stimulate angiogenesis [79]. Of note, HIF-1α is a downstream target of SIRT3, as shown in tumor cells and fibroblasts. However, it has been documented that SIRT3 alters proline hydroxylation enzymatic activity, hence modified HIF-1α degradation, such that its stabilization is disrupted by SIRT3 overexpression in case of cancer investigations [80]. In MI, the importance of SIRT3 and HIF-1α interaction need more investigation. In addition to HIF-1α, an interaction between angiotensin II and SIRT3 was also reported in MI. Angiotensin system plays critical roles in ischemic injury [81]. Administration of angiotensin II resulted in the significant decrease in the expression levels of SIRT3 [82], and remarkably, inhibition of this system normalized SIRT3 level in MI and improved cardiac function [16,76,83]. Significant increase in ROS production [84], as well as enhancement in the intracellular calcium concentration [85,86], are among some critical mechanisms for development ad progression of reperfusion injury, which ultimately open mPTP, consequent mitochondrial swelling, activation of necrotic and apoptotic pathways and cell death [87,88]. SIRT3 deficiency in animal models resulted in mPTP opening, and mitochondrial leakage [67]. Cyclophilin D, a regulatory subunit of mPTP is involved in the sensitization of mitochondrial transition to calcium during reperfusion injury. Interestingly, SIRT3 directly targets and deacetylates cyclophilin D, hence delays opening of the mPTP [67,89]. This function of SIRT3 is contributed in the alleviation of reperfusion injury [89]. Taking together, all mentioned data suggest that SIRT3 can exert substantial impacts on the various substrates and signaling pathways contributed in the pathology of I/R injury and MI.

4.2. SIRT3 in cardiac repair/remodeling following MI

As mentioned above, the importance of SIRT3 in cardiovascular system is so high that deficiency or disruption in its signaling results in the development of various cardiac diseases. In addition to atherosclerosis, cardiac hypertrophy, I/R injury, and other cardiac diseases, SIRT3 knockout is also reported to lead to coronary microvascular dysfunction, as well as impairment in the cardiac repair/ remodeling following myocardial ischemia and MI. He et al. [90] evaluated the role of SIRT3 in cardiac remodeling post-MI. the author showed that angiogenic capacity was significantly decreased in endothelial cells isolated form SIRT3 deficient mice. In SIRT3 knockout mice, it was observed that hyperemic peak diastolic blood flow velocity and coronary flow reserve were reduced and capillary-pericytes were lost in the heart, all of which are indicative of coronary microvascular dysfunction in the case of SIRT3 downregulation. Exposure of these mice to myocardial ischemia resulted in the more severe cardiac dysfunction in comparison with wild type mice. It was also reported that upregulation of SIRT3 resulted in the improvement of cardiac function in post-MI mice. At molecular levels, SIRT3 deficiency is accompanied with decrease in the expression levels of angiopoietin-1, vascular endothelial growth factor (VEGF) and 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), as well as increase in apoptosis [90]. In another study using SIRT3 $-/-$ mice, the function of SIRT3 in the repair of myocardial contractile function following I/R and MI was evaluated and surprisingly showed that despite pre-existing defects in cardiac function and mitochondrial respiratory capacity in SIRT3 deficient mice, SIRT3 downregulation did not additionally impair cardiac function following IR or MI [77]. Wei et al. [91] performed another study on SIRT3 knockout mice infused by angiotensin II. It was reported that angiotensin II infusion resulted in the development of more severe microvascular dysfunction and hypoxia in cardiac tissues, as well as mitochondrial dysfunction and enhanced collagen I and collagen III expression, leading to cardiac fibrosis. Interestingly, all effects of angiotensin II on cardiac function were facilitated by SIRT3 dowregulation. Therefore, overexpression of SIRT3 restored cardiac function through various mechanisms such as enhancement in Pink/Parkin-mediated mitophagy, attenuation of mitochondrial ROS generation, restoring vessel sprouting and tube formation, and decrease in fibrosis [91]. In addition, Guo et al. [92] reported another mechanism for the protective effects of SIRT3 against angiotensin II induced cardiac fibrosis. They showed that SIRT3 attenuated cardiac fibrosis by suppressing myofibroblasts transdifferentiation via STAT3-NFATc2 pathway in SIRT3 $-/-$ mice [92]. The transcriptional co-factor receptor-interacting protein 140 (RIP140), which is a negative regulator of cardiac mitochondrial function and energy metabolic homeostasis, is reported to exert its deleterious effects such as hypertrophy on cardiomyocytes through suppression of SIRT3 function [71]. Therefore, SIRT3 is in the downstream of various signaling pathways, as well as multiple therapeutic agents used for improvement of cardiac remodeling post MI.

5. SIRT3: underlying mechanism for Apelin-mediated protection post-MI

Apelin, as an endogenous bioactive peptide, which act through binding to a specific receptor known as Apelin receptor or APJ receptor, has a widely distribution pattern in numerous tissues such as brain, heart, lung, kidney, liver, skin, limbs, retina, and adipose tissue [93]. Signaling through Apelin/APJ system is involved in the various important biological processes such as immunity, water homeostasis,

glucose metabolism, cell proliferation, angiogenesis blood pressure, and specifically, cardiac contractility [94–96]. Various isoforms of Apelin have been identified including Apelin-12, Apelin-13, Apelin-17 and Apelin-36, each of them has a definite function [52,97–99]. Apelin-12 and Apelin-17 have been reported to enhance myocardial contractility [100]. Accumulating studies have been demonstrated the critical protective function of Apelin/APJ system in MI, particularly promotion of angiogenesis [101]. In cardiac muscle of post-MI mice, Apelin-13 was demonstrated to increase angiogenesis through overexpression of jagged-1 and notch-3, as well as promotion of vascular endothelial progenitor cells mobilization into infarct sites [102]. Another study investigated the underlying mechanism of Apelin-13- mediated of progenitor cells homing and found that SDF-1α/CXCR-4 axis played important role in this process [103]. By recruitment of progenitor cells into MI site, Apelin-13 stimulates angiogenic events and improves cardiac recovery post-MI. activation of VEGF, overexpression of epidermal growth factor homology domains (Tie-2), phosphorylation of Akt/eNOS (P-Akt/eNOS), and activation of angiopoietin-1 (Ang-1)/Tie 2 signaling pathway are other important pathways by which, Apelin-13 increases angiogenesis and improves cardiac function post-MI [104,105]. In recent years, it is increasingly reported that Sirt3 is a critical factor for Apelin-induced angiogenesis in post-MI (Fig. 1). Li et al. [21] showed that injection of bone marrow cells (BMCs) overexpressing Apelin into myocardium of post-MI mice increased cardiac repair and recovery through upregulation of SIRT3. The author reported that myocardium treatment with Apelin-BMCs resulted in the significant increase in the expression levels of VEGF, angiotensin I, Tie-2, Notch3, Akt, as well as SIRT3, which all resulted in the increase in angiogenesis capacity. Notably, the therapeutic strategy led to decrease in ROS production, stress-induced apoptosis, and consequent attenuation of cardiac fibrosis. Interestingly, knockout of SIRT3 completely abolished the therapeutic effects of Apelin-BMCs in post-MI mice [21]. In another study investigating the direct role of SIRT3 in Apelin-mediated angiogenesis in MI mice model, Hou et al. [106] found that adenovirus-Apelin treatment resulted in overexpression of SIRT3, angiopoietins/Tie-2 and VEGF/VEGFR2, as well as enhancement in the myocardial vascular densities, but these alterations were not observed in Sirt3 knockout mice. Therefore, Apelin gene therapy promotes angiogenesis and increases cardiac functional recovery via upregulation of SIRT3 pathway [106]. In addition to angiogenesis promotion, the same authors in another study demonstrated that Apelin- mediated increase in autophagy is SIRT3 dependent [107]. Upregulation of Apelin resulted in the significant increase in SIRT3, as well as reduction in gp91phox, and NF-κb-p65 expression, and ROS production. More importantly, upregulation of Apelin further increased autophagy markers (LC3-II and beclin-1) expression in post-MI heart, which all abolished with SIRT3 knockdown [107].

6. SIRT3 and cardioprotective drugs

Growing body of investigations has been demonstrated that most of cardioprotective drugs exert their beneficial effects on myocardium through modulation of SIRT3 expression (Fig. 1). In this regard metformin, an effective therapeutic agent for type 2 diabetes, has reported to significantly decrease the cardiovascular events, such that exert cardiovascular protective effects. In a study by Sun et al. [108] the effects of metformin on cardiac function were evaluated in mice model of heart failure after MI. It has been indicated that metformin treatment improves the mitochondrial respiratory function and mitochondrial membrane potential. It should be mentioned that metformin resulted in the overexpression of Sirt3 and the activity of PGC-1a in myocardial tissue post-MI. Metformin-mediated increase in deacetylation activity of SIT3 significantly reduced the acetylation level of PGC-1a, mitigated the damage to mitochondrial membrane potential and improved the respiratory function of mitochondria and finally improving the cardiac function of mice [108]. In addition to metformin, a series of experiments was conducted that melatonin has also a favorable effect in ameliorating I/R injury. For example, in a study by Zhai et al. [109] mice were pre-treated with or without a selective SIRT3 inhibitor and then subjected to I/R operation. As a result, melatonin treatment improved post-ischemic cardiac contractile function, reduced infarct size, decreased lactate dehydrogenase release, diminished the apoptotic

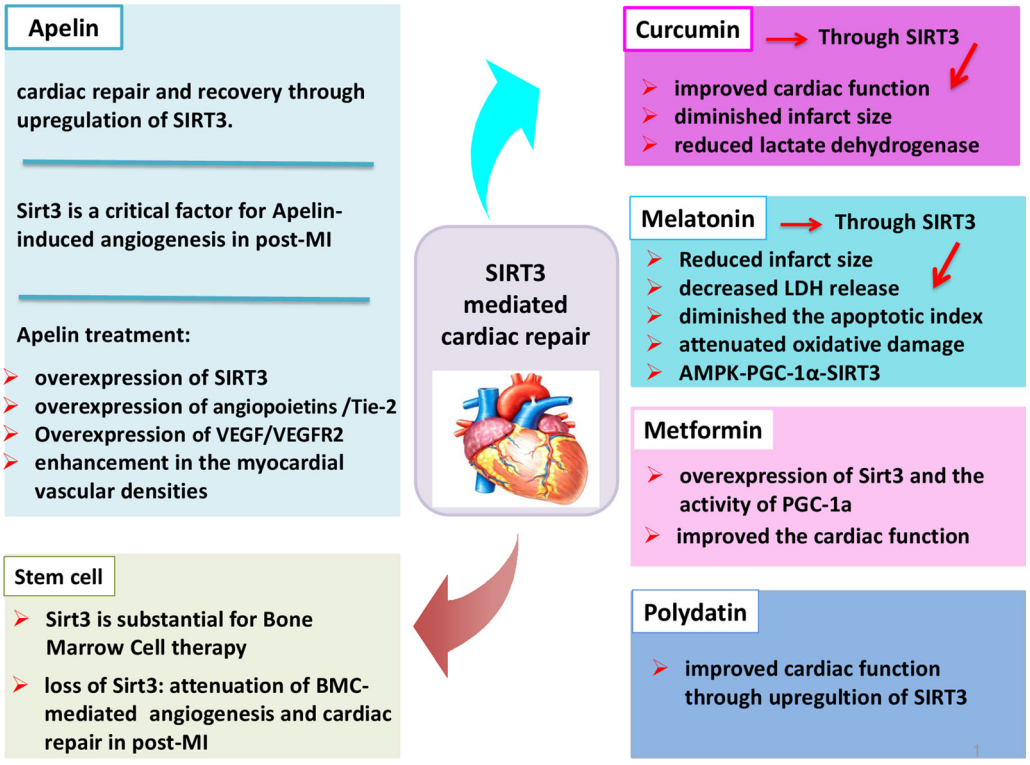

Fig. 1. Sirtuin3 mediated cardiac repair.

index and attenuated oxidative damage. Indeed, melatonin treatment reversed I/R induced decrease in SIRT3 expression and activity, and consequently reduced the acetylation of SOD2. More investigation demonstrated that SIRT3 inhibitor completely abolished the cardioprotective effects of melatonin, suggesting that SIRT3 have critical function in mediating the cardioprotective effects of melatonin. So, melatonin treatment attenuates MI injury by reducing oxidative stress and apoptosis via activating the SIRT3 signaling pathway [109]. In another study by Yu et al. [69] it was demonstrated that melatonin attenuate MI injury in type 1 diabetic rats by preserving mitochondrial function, which was achieved by decreasing mitochondrial oxidative stress and increasing its biogenesis, via AMPK-PGC-1α-SIRT3 signaling pathway. Additionally, SIRT3 siRNA inhibited the cytoprotective effect of melatonin without affecting p-AMPK/AMPK ratio and PGC-1α expression [69]. Polyphenols, natural products with potent anti-oxidative and anti-inflammatory effects, have also extensively studied in ameliorating MI injury. In this context, Wang et al. [110] investigated the effects of Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6 heptadi-ene-3,5-dione, diferuloylmethane), a polyphenol isolated from the rhizome of Curcuma longa (turmeric), on the cardiac function following MI. in vitro studies showed that Curcumin treatment of H9c2 cell significantly increased cell viability, and decreased cell apoptosis through overexpression of the anti-apoptotic protein Bcl-2, downregulation of the pro-apoptotic protein Bax and AcSOD2, as well as increase defense capacity against oxidative stress. Curcumin also activated SIRT3 expression and activity. Interestingly, in vivo model revealed that Curcumin significantly improved cardiac function, diminished infarct size, and reduced lactate dehydrogenase levels in isolated rat heart. Of note, Curcumin-induced protective effects were reversed by treatment with the SIRT3 inhibitor [110]. Polydatin, a monocrystalline and polyphenolic drug isolated from a traditional Chinese herb (*Polygonum cuspidatum*), was also reported to improve cardiac function through upregultion of SIRT3 [111]. Furthermore, losartan, an angiotensin receptor blockers commonly used for decreasing blood pressure, was reported to exert therapeutic effects against I/R by increasing ischemia-induced reduction in the expression levels of SIRT3 [76]. Another study provide evidence for beneficent role of SIRT3 was carried out by Zeng et al. [112] in which it has been reported that loss of SIRT3 give rise into attenuation of BMC-mediated angiogenesis as well as cardiac repair in post-MI infarction, hence suggested that in stem cell therapy in post MI, SIRT3 is an essential factor for cardioprotective effects of stem cell. Moreover, they revealed that loss of SIRT3 resulted in enhancement of ROS production and promotion of apoptosis in endothelial progenitor cells (EPCs), whilst overexpression of SIRT3 blunted apoptosis of these cells. In the light of these findings, they finally concluded that enhancement of SIRT3 in stem cell appear as a novel therapeutic factor for betterment of stem cell therapy in the case of ischemic heart disease.

7. Conclusion

SIRT3, as a potent mitochondrial deacetylase, targets a broad range of substrates that are involved in various biological processes such as, ATP production, oxidative stress and cellular death. An increasing number of recent studies indicated that SIRT3 have critical function in cardiovascular diseases including hypertrophic cardiomyopathy, myocardial infarction, I/R injury and heart failure. Based on beneficial effects on myocardial infarction and IR injury by treatment with metformin, melatonin, Curcumin and Polydatin, which increase the expression and/or activity of SIRT3, the development of specific SIRT3 activators could represent a novel therapeutic strategy by which cardiac function can be improved following myocardial function.

Conflicts of interest

The authors declare that there are no conflicts of interest and this research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

[1] B. Yousefi, Z. Faghfoori, N. Samadi, H. Karami, Y. Ahmadi, R. Badalzadeh, V. Shafiei-Irannejad, M. Majidinia, H. Ghavimi, M. Jabbarpour, The effects of Ramadan fasting on endothelial function in patients with cardiovascular diseases, Eur. J. Clin. Nutr. 68 (7) (2014) 835.

[2] H.R. Nejabati, A. Mihanfar, M. Pezeshkian, A. Fattahi, Z. latifi, N. Safaie, M. Valiloo, A.R. Jodati, M. Nouri, N1-methylnicotinamide (MNAM) as a guardian of cardiovascular system, J. Cell. Physiol. 233 (Oct. (10)) (2018) 6386–6394.

[3] H. Asadi, A.A. Abolfathi, R. Badalzadeh, M. Majidinia, A. Yaghoubi, M. Asadi, B. Yousefi, Effects of Ramadan fasting on serum amyloid a and protein carbonyl group levels in patients with cardiovascular diseases, J. Cardiovascular Thorac. Res. 7 (2) (2015) 55.

[4] W.C. Stanley, F.A. Recchia, G.D. Lopaschuk, Myocardial substrate metabolism in the normal and failing heart, Physiol. Rev. 85 (3) (2005) 1093–1129.

[5] N. Poulose, R. Raju, Sirtuin regulation in aging and injury, Biochimica et Biophysica Acta (BBA)-Mol. Basis Dis. 1852 (11) (2015) 2442–2455.

[6] A. Camins, F.X. Sureda, F. Junyent, E. Verdaguer, J. Folch, C. Pelegri, J. Vilaplana, C. Beas-Zarate, M. Pallàs, Sirtuin activators: designing molecules to extend life span, Biochimica et Biophysica Acta (BBA)-Gene Regul. Mech. 1799 (10) (2010) 740–749.

[7] D.-x. Hu, X.-b. Liu, W.-c. Song, J.-a. Wang, Roles of SIRT3 in heart failure: from bench to bedside, J. Zhejiang Univ.-SCIENCE B 17 (11) (2016) 821–830.

[8] W. Sun, C. Liu, Q. Chen, N. Liu, Y. Yan, B. Liu, SIRT3: A New Regulator of Cardiovascular Diseases, Oxidative Medicine and Cellular Longevity 2018, (2018).

[9] P.L. Pedersen, S. Mathupala, A. Rempel, J. Geschwind, Y.H. Ko, Mitochondrial bound type II hexokinase: a key player in the growth and survival of many cancers and an ideal prospect for therapeutic intervention, Biochimica et Biophysica Acta (BBA)-Bioenergetics 1555 (1–3) (2002) 14–20.

[10] L.W. Finley, A. Carracedo, J. Lee, A. Souza, A. Egia, J. Zhang, J. Teruya-Feldstein, P.I. Moreira, S.M. Cardoso, C.B. Clish, SIRT3 opposes reprogramming of cancer cell metabolism through HIF1α destabilization, Cancer Cell 19 (3) (2011) 416–428.

[11] M.D. Hirschey, T. Shimazu, E. Goetzman, E. Jing, B. Schwer, D.B. Lombard, C.A. Grueter, C. Harris, S. Biddinger, O.R. Ilkayeva, SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation, Nature 464 (7285) (2010) 121.

[12] W. Yang, K. Nagasawa, C. Münch, Y. Xu, K. Satterstrom, S. Jeong, S.D. Hayes, M.P. Jedrychowski, F.S. Vyas, E. Zaganjor, Mitochondrial sirtuin network reveals dynamic SIRT3-dependent deacetylation in response to membrane depolarization, Cell 167 (4) (2016) 985–1000 e21.

[13] B. Schwer, J. Bunkenborg, R.O. Verdin, J.S. Andersen, E. Verdin, Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA synthetase 2, Proc. Natl. Acad. Sci. 103 (27) (2006) 10224–10229.

[14] W.C. Hallows, S. Lee, J.M. Denu, Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases, Proc.Natl. Acad. Sci. 103 (27) (2006) 10230–10235.

[15] T. Shimazu, M.D. Hirschey, L. Hua, K.E. Dittenhafer-Reed, B. Schwer, D.B. Lombard, Y. Li, J. Bunkenborg, F.W. Alt, J.M. Denu, SIRT3 deacetylates mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 and regulates ketone body production, Cell Metab. 12 (6) (2010) 654–661.

[16] B.-H. Ahn, H.-S. Kim, S. Song, I.H. Lee, J. Liu, A. Vassilopoulos, C.-X. Deng, T. Finkel, A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis, Proc. Natl. Acad. Sci. 105 (38) (2008) 14447–14452.

[17] W.C. Hallows, W. Yu, B.C. Smith, M.K. Devires, J.J. Ellinger, S. Someya, M.R. Shortreed, T. Prolla, J.L. Markley, L.M. Smith, Sirt3 promotes the urea cycle and fatty acid oxidation during dietary restriction, Mol. Cell 41 (2) (2011) 139–149.

[18] Y. Yang, H. Cimen, M.-J. Han, T. Shi, J.-H. Deng, H. Koc, O.M. Palacios, L. Montier, Y. Bai, Q. Tong, NAD+-dependent deacetylase SIRT3 regulates mitochondrial protein synthesis by deacetylation of the ribosomal protein MRPL10, J. Biol. Chem. 285 (10) (2010) 7417–7429.

[19] L. Zhong, R. Mostoslavsky, Fine tuning our cellular factories: sirtuins in mitochondrial biology, Cell Metab. 13 (6) (2011) 621–626.

[20] C. Dong, D. Della-Morte, L. Wang, D. Cabral, A. Beecham, M.S. McClendon, C.C. Luca, S.H. Blanton, R.L. Sacco, T. Rundek, Association of the sirtuin and mitochondrial uncoupling protein genes with carotid plaque, PloS One 6 (11) (2011) e27157.

[21] L. Li, H. Zeng, X. Hou, X. He, J.-X. Chen, Myocardial injection of apelin-over-expressing bone marrow cells improves cardiac repair via upregulation of Sirt3 after myocardial infarction, PloS One 8 (9) (2013) e71041.

[22] M. Amani, A. Darbin, M. Pezeshkian, A. Afrasiabi, N. Safaie, A. Jodati, M. Darabi, M. Shaaker, Z. Latifi, A. Fattahi, The role of cholesterol-enriched diet and para-oxonase 1 inhibition in atherosclerosis progression, J. Cardiovasc. Thorac. Res. 9 (3) (2017) 133.

[23] O.M. Paytakhti, M. Pezeshkian, N. Safaie, M. Darabi, A. Fattahi, H. Bijanpour, M. Shaaker, A.R. Jodati, M. Nouri, Fatty acids composition of aorta and saphenous vein tissues in patients with coronary artery diseases, J. Cardiovasc. Thorac. Res. 9 (2) (2017) 78.

[24] J. Faisi, A. Fattahi, N. Raffel, I. Hoffmann, M.W. Beckmann, M. Schrauder, R. Dittrich, C. Löhberg, Effects of pomegranate seed oil and fermented juice polyphenols fraction in different solvents on copper-induced LDL oxidation, CyTA-J. Food 16 (1) (2018) 429–437.

[25] N.R. Sundaresan, M. Gupta, G. Kim, S.B. Rajamohan, A. Isbatan, M.P. Gupta, Sirt3

blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice, J. Clin. Invest. 119 (9) (2009) 2758–2771.
[26] A.V. Hafner, J. Dai, A.P. Gomes, C.-Y. Xiao, C.M. Palmeira, A. Rosenzweig, D.A. Sinclair, Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy, Aging (Albany NY) 2 (12) (2010) 914.
[27] V.B. Pillai, N.R. Sundaresan, M.P. Gupta, Regulation of Akt signaling by sirtuins: its implication in cardiac hypertrophy and aging, Circ. Res. 114 (2) (2014) 368–378.
[28] A. Giralt, E. Hondares, J.A. Villena, F. Ribas, J. Díaz-Delfín, M. Giralt, R. Iglesias, F. Villarroya, Peroxisome proliferator-activated receptor-γ coactivator-1α controls transcription of the Sirt3 gene, an essential component of the thermogenic brown adipocyte phenotype, J. Biol. Chem. 286 (19) (2011) 16958–16966.
[29] O.M. Palacios, J.J. Carmona, S. Michan, K.Y. Chen, Y. Manabe, J.L. Ward Iii, L.J. Goodyear, Q. Tong, Diet and exercise signals regulate SIRT3 and activate AMPK and PGC-1α in skeletal muscle, Aging (Albany NY) 1 (9) (2009) 771.
[30] M.D. Hirschey, T. Shimazu, E. Jing, C.A. Grueter, A.M. Collins, B. Aouizerat, A. Stančáková, E. Goetzman, M.M. Lam, B. Schwer, SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome, Mol. Cell 44 (2) (2011) 177–190.
[31] R.A. van de Ven, D. Santos, M.C. Haigis, Mitochondrial sirtuins and molecular mechanisms of aging, Trends Mol. Med. 23 (4) (2017) 320–331.
[32] R. Jahanban-Esfahlan, S. Mehrzadi, R.J. Reiter, K. Seidi, M. Majidinia, H.B. Baghi, N. Khatami, B. Yousefi, A. Sadeghpour, Melatonin in regulation of inflammatory pathways in rheumatoid arthritis and osteoarthritis: involvement of circadian clock genes, Br. J. Pharmacol. 175 (16) (2018) 3230–3238.
[33] B. Yousefi, N. Samadi, B. Baradaran, V. Rameshknia, V. Shafiei-Irannejad, M. Majidinia, N. Targhaze, N. Zarghami, Differential effects of peroxisome proliferator-activated receptor agonists on doxorubicin-resistant human myelogenous leukemia (K562/DOX) cells, Cell. Mol. Biol. (Noisy-le-Grand, France) 61 (8) (2015) 118–122.
[34] N.R. Sundaresan, S.A. Samant, V.B. Pillai, S.B. Rajamohan, M.P. Gupta, SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70, Mol. Cell. Biol. 28 (20) (2008) 6384–6401.
[35] A. Signorile, A. Santeramo, G. Tamma, T. Pellegrino, S. D'Oria, P. Lattanzio, D. De Rasmo, Mitochondrial cAMP prevents apoptosis modulating Sirt3 protein level and OPA1 processing in cardiac myoblast cells, Biochimica et Biophysica Acta (BBA)-Mol. Cell Res. 1864 (2) (2017) 355–366.
[36] S.A. Samant, H.J. Zhang, Z. Hong, V.B. Pillai, N.R. Sundaresan, D. Wolfgeher, S.L. Archer, D.C. Chan, M.P. Gupta, SIRT3 deacetylates and activates OPA1 to regulate mitochondrial dynamics during stress, Mol. Cell. Biol. 34 (5) (2014) 807–819.
[37] A. Cheng, Y. Yang, Y. Zhou, C. Maharana, D. Lu, W. Peng, Y. Liu, R. Wan, K. Marosi, M. Misiak, Mitochondrial SIRT3 mediates adaptive responses of neurons to exercise and metabolic and excitatory challenges, Cell Metab. 23 (1) (2016) 128–142.
[38] D.-Y. Nah, M.-Y. Rhee, The inflammatory response and cardiac repair after myocardial infarction, Korean Circ. J. 39 (10) (2009) 393–398.
[39] J.P. Cleutjens, J.C. Kandala, E. Guarda, R.V. Guntaka, K.T. Weber, Regulation of collagen degradation in the rat myocardium after infarction, J. Mol. Cell. Cardiol. 27 (6) (1995) 1281–1292.
[40] Z. Latifi, A. Fattahi, A. Ranjbaran, H.R. Nejabati, K. Imakawa, Potential roles of metalloproteinases of endometrium-derived exosomes in embryo-maternal cross-talk during implantation, J. Cell. Physiol. 233 (6) (2018) 4530–4545.
[41] Y. Sun, J.Q. Zhang, J. Zhang, S. Lamparter, Cardiac remodeling by fibrous tissue after infarction in rats, J. Lab. Clin. Med. 135 (4) (2000) 316–323.
[42] H. Hajipour, H.R. Nejabati, Z. Latifi, K. Hamdi, Z. Bahrami-asl, A. Fattahi, M. Nouri, Lymphocytes immunotherapy for preserving pregnancy: mechanisms and challenges, Am. J. Reprod. Immunol. (2018) e12853.
[43] Z. Latifi, A. Fattahi, K. Hamdi, A. Ghasemzadeh, P. Karimi, H.R. Nejabati, M.G. Novin, L. Roshangar, M. Nouri, Wnt signaling pathway in uterus of normal and seminal vesicle excised mated mice during pre-implantation window, Geburtshilfe Frauenheilkd. 78 (04) (2018) 412–422.
[44] H. Nejabati, A. Mota, L. Farzadi, M. Ghojazadeh, A. Fattahi, K. Hamdi, M. Nouri, Follicular fluid PlGF/sFlt-1 ratio and soluble receptor for advanced glycation end–products correlate with ovarian sensitivity index in women undergoing ART, J. Endocrinol. Invest. 40 (2) (2017) 207–215.
[45] H.R. Nejabati, Z. Latifi, T. Ghasemnejad, A. Fattahi, M. Nouri, Placental growth factor (PlGF) as an angiogenic/inflammatory switcher: lesson from early pregnancy losses, Gynecol. Endocrinol. 33 (9) (2017) 668–674.
[46] A. Fattahi, M. Darabi, L. Farzadi, A. Salmassi, Z. Latifi, A. Mehdizadeh, M. Shaaker, T. Ghasemnejad, L. Roshangar, M. Nouri, Effects of dietary omega-3 and-6 supplementations on phospholipid fatty acid composition in mice uterus during window of pre-implantation, Theriogenology 108 (2018) 97–102.
[47] M. Shahnazi, M. Mohammadi, G. Mohaddes, Z. Latifi, T. Ghasemnejad, M. Nouri, A. Fattahi, Dietary omega-3 and-6 fatty acids affect the expression of prostaglandin E2 synthesis enzymes and receptors in mice uteri during the window of pre-implantation, Biochem. Biophys. Res. Commun. (2018).
[48] M. Shahnazi, M. Nouri, G. Mohaddes, Z. Latifi, A. Fattahi, M. Mohammadi, Prostaglandin E pathway in uterine tissue during window of preimplantation in female mice mated with intact and seminal vesicle–excised male, Reprod. Sci. 25 (4) (2018) 550–558.
[49] A. Mihanfar, A. Fattahi, H.R. Nejabati, MicroRNA-mediated drug resistance in ovarian cancer, J. Cell. Physiol. (2017).
[50] Y. Sun, Myocardial repair/remodelling following infarction: roles of local factors, Cardiovasc. Res. 81 (3) (2008) 482–490.
[51] Y. Sun, J.P. Cleutjens, A.A. Diaz-Arias, K.T. Weber, Cardiac angiotensin converting enzyme and myocardial fibrosis in the rat, Cardiovasc. Res. 28 (9) (1994) 1423–1432.
[52] T.P. Kalantaripour, S. Esmaeili-Mahani, V. Sheibani, M. Asadi-Shekaari, H. Pasban-Aliabadi, Anticonvulsant and neuroprotective effects of apelin-13 on pentylenetetrazole-induced seizures in male rats, Biomed. Pharmacother. 84 (2016) 258–263.
[53] A. Desmoulière, A. Geinoz, F. Gabbiani, G. Gabbiani, Transforming growth factor-beta 1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing cultured fibroblasts, J. Cell. Biol. 122 (1) (1993) 103–111.
[54] Y. Sun, J.Q. Zhang, J. Zhang, F.J. Ramires, I.I. Angiotensin, Transforming growth factor-β1and repair in the infarcted heart, J. Mol. Cell. Cardiol. 30 (8) (1998) 1559–1569.
[55] T. Goto, F. Yanaga, I. Ohtsuki, Studies on the endothelin-1-induced contraction of rat granulation tissue pouch mediated by myofibroblasts, Biochimica et Biophysica Acta (BBA)-Mol. Cell Res. 1405 (1–3) (1998) 55–66.
[56] L.C. Katwa, S.E. Campbell, S.C. Tyagi, S.J. Lee, G.T. Cicila, K.T. Weber, Cultured myofibroblasts generate angiotensin peptidesde novo, J. Mol. Cell. Cardiol. 29 (5) (1997) 1375–1386.
[57] R. Passier, J. Smits, M. Verluyten, M. Daemen, Expression and localization of renin and angiotensinogen in rat heart after myocardial infarction, Am. J. Physiol.-Heart Circ. Physiol. 271 (3) (1996) H1040–H1048.
[58] K.G. Cheung, L.K. Cole, B. Xiang, K. Chen, X. Ma, Y. Myal, G.M. Hatch, Q. Tong, V.W. Dolinsky, Sirtuin-3 (SIRT3) protein attenuates doxorubicin-induced oxidative stress and improves mitochondrial respiration in H9c2 cardiomyocytes, J. Biol. Chem. 290 (17) (2015) 10981–10993.
[59] Q. Du, B. Zhu, Q. Zhai, B. Yu, Sirt3 attenuates doxorubicin-induced cardiac hypertrophy and mitochondrial dysfunction via suppression of Bnip3, Am. J. Trans. Res. 9 (7) (2017) 3360.
[60] V.B. Pillai, S. Bindu, W. Sharp, Y.H. Fang, G. Kim, M. Gupta, S. Samant, M.P. Gupta, Sirt3 protects mitochondrial DNA damage and blocks the development of doxorubicin-induced cardiomyopathy in mice, Am. J. Physiol.-Heart Circ. Physiol. 310 (8) (2016) H962–H972.
[61] G.A. Porter, W.R. Urciuoli, P.S. Brookes, S.M. Nadtochiy, SIRT3 deficiency exacerbates ischemia-reperfusion injury: implication for aged hearts, Am. J. Physiol.-Heart Circ. Physiol. 306 (12) (2014) H1602–H1609.
[62] R.M. Parodi-Rullán, X. Chapa-Dubocq, P.J. Rullán, S. Jang, S. Javadov, High sensitivity of SIRT3 deficient hearts to ischemia-reperfusion is associated with mitochondrial abnormalities, Front. Pharmacol. 8 (2017) 275.
[63] Ml. Chen, Xh. Zhu, L. Ran, Hd. Lang, L. Yi, Mt. Mi, Trimethylamine-N-oxide induces vascular inflammation by activating the NLRP3 inflammasome through the SIRT3-SOD2-mtROS signaling pathway, J. Am. Heart Assoc. 6 (9) (2017) e006347.
[64] S. Winnik, D.S. Gaul, F. Preitner, C. Lohmann, J. Weber, M.X. Miranda, Y. Liu, L.J. van Tits, J.M. Mateos, C.E. Brokopp, Deletion of Sirt3 does not affect atherosclerosis but accelerates weight gain and impairs rapid metabolic adaptation in LDL receptor knockout mice: implications for cardiovascular risk factor development, Basic Res. Cardiol. 109 (1) (2014) 399.
[65] N.R. Sundaresan, S. Bindu, V.B. Pillai, S. Samant, Y. Pan, J.-Y. Huang, M. Gupta, R.S. Nagalingam, D. Wolfgeher, E. Verdin, SIRT3 blocks aging-associated tissue fibrosis in mice by deacetylating and activating glycogen synthase kinase 3β, Mol. Cell. Biol. 36 (5) (2016) 678–692.
[66] V.B. Pillai, S. Samant, N.R. Sundaresan, H. Raghuraman, G. Kim, M.Y. Bonner, J.L. Arbiser, D.I. Walker, D.P. Jones, D. Gius, Honokiol blocks and reverses cardiac hypertrophy in mice by activating mitochondrial Sirt3, Nat. Commun. 6 (2015) 6656.
[67] C. Koentges, K. Pfeil, T. Schnick, S. Wiese, R. Dahlbock, M.C. Cimolai, M. Meyer-Steenbuck, K. Cenkerova, M.M. Hoffmann, C. Jaeger, SIRT3 deficiency impairs mitochondrial and contractile function in the heart, Basic Res. Cardiol. 110 (4) (2015) 36.
[68] J.M. Grillon, K.R. Johnson, K. Kotlo, R.S. Danziger, Non-histone lysine acetylated proteins in heart failure, Biochimica et Biophysica Acta (BBA)-Mol. Basis Dis. 1822 (4) (2012) 607–614.
[69] L. Yu, B. Gong, W. Duan, C. Fan, J. Zhang, Z. Li, X. Xue, Y. Xu, D. Meng, B. Li, Melatonin ameliorates myocardial ischemia/reperfusion injury in type 1 diabetic rats by preserving mitochondrial function: role of AMPK-PGC-1α-SIRT3 signaling, Sci. Rep. 7 (2017) 41337.
[70] H. Yang, T. Yang, J.A. Baur, E. Perez, T. Matsui, J.J. Carmona, D.W. Lamming, N.C. Souza-Pinto, V.A. Bohr, A. Rosenzweig, Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival, Cell 130 (6) (2007) 1095–1107.
[71] J. You, Z. Yue, S. Chen, Y. Chen, X. Lu, X. Zhang, P. Shen, J. Li, Q. Han, Z. Li, Receptor-interacting protein 140 represses sirtuin 3 to facilitate hypertrophy, mitochondrial dysfunction and energy metabolic dysfunction in cardiomyocytes, Acta Physiologica 220 (1) (2017) 58–71.
[72] Z. Yue, Y. Ma, J. You, Z. Li, Y. Ding, P. He, X. Lu, J. Jiang, S. Chen, P. Liu, NMNAT3 is involved in the protective effect of SIRT3 in Ang II-induced cardiac hypertrophy, Exp. Cell. Res. 347 (2) (2016) 261–273.
[73] X. Tang, X.-F. Chen, H.-Z. Chen, D.-P. Liu, Mitochondrial sirtuins in cardiometabolic diseases, Clin. Sci. 131 (16) (2017) 2063–2078.
[74] R. Paulin, P. Dromparis, G. Sutendra, V. Gurtu, S. Zervopoulos, L. Bowers, A. Haromy, L. Webster, S. Provencher, S. Bonnet, Sirtuin 3 deficiency is associated with inhibited mitochondrial function and pulmonary arterial hypertension in rodents and humans, Cell Metab. 20 (5) (2014) 827–839.
[75] R.M. Bell, D.M. Yellon, There is more to life than revascularization: therapeutic targeting of myocardial ischemia/reperfusion injury, Cardiovasc. Ther. 29 (6)

(2011).
[76] M.S. Klishadi, F. Zarei, S.H. Hejazian, A. Moradi, M. Hemati, F. Safari, Losartan protects the heart against ischemia reperfusion injury: sirtuin3 involvement, J. Pharm. Pharm. Sci. 18 (1) (2015) 112–123.
[77] C. Koentges, K. Pfeil, M. Meyer-Steenbuck, A. Lother, M.M. Hoffmann, K.E. Odening, L. Hein, C. Bode, H. Bugger, Preserved recovery of cardiac function following ischemia–reperfusion in mice lacking SIRT3, Can. J. Physiol. Pharmacol. 94 (1) (2015) 72–80.
[78] S.H. Lee, P.L. Wolf, R. Escudero, R. Deutsch, S.W. Jamieson, P.A. Thistlethwaite, Early expression of angiogenesis factors in acute myocardial ischemia and infarction, N. Engl. J. Med. 342 (9) (2000) 626–633.
[79] K.-G. Shyu, M.-T. Wang, B.-W. Wang, C.-C. Chang, J.-G. Leu, P. Kuan, H. Chang, Intramyocardial injection of naked DNA encoding HIF-1α/VP16 hybrid to enhance angiogenesis in an acute myocardial infarction model in the rat, Cardiovasc. Res. 54 (3) (2002) 576–583.
[80] P.T. Schumacker, SIRT3 controls cancer metabolic reprogramming by regulating ROS and HIF, Cancer Cell. 19 (3) (2011) 299–300.
[81] B. Yang, M. Phillips, P. Ambuehl, L. Shen, P. Mehta, J. Mehta, Increase in angiotensin II type 1 receptor expression immediately after ischemia-reperfusion in isolated rat hearts, Circulation 96 (3) (1997) 922–926.
[82] A. Benigni, D. Corna, C. Zoja, A. Sonzogni, R. Latini, M. Salio, S. Conti, D. Rottoli, L. Longaretti, P. Cassis, Disruption of the Ang II type 1 receptor promotes longevity in mice, J. Clin. Invest.n 119 (3) (2009) 524–530.
[83] R. Parodi-Rullan, G. Barreto-Torres, L. Ruiz, J. Casasnovas, S. Javadov, Direct renin inhibition exerts an anti-hypertrophic effect associated with improved mitochondrial function in post-infarction heart failure in diabetic rats, Cell. Physiol. Biochem. 29 (5-6) (2012) 841–850.
[84] R. Bolli, M.O. Jeroudi, B.S. Patel, C.M. DuBose, E.K. Lai, R. Roberts, P.B. McCay, Direct evidence that oxygen-derived free radicals contribute to postischemic myocardial dysfunction in the intact dog, Proc. Natl. Acad. Sci. 86 (12) (1989) 4695–4699.
[85] W.G. Nayler, Basic mechanisms involved in the protection of the ischaemic myocardium, Drugs 42 (2) (1991) 21–27.
[86] T. Kalogeris, C.P. Baines, M. Krenz, R.J. Korthuis, Cell biology of ischemia/reperfusion injury, International Review of Cell and Molecular Biology, Elsevier, 2012, pp. 229–317.
[87] D.J. Hausenloy, S.-B. Ong, D.M. Yellon, The mitochondrial permeability transition pore as a target for preconditioning and postconditioning, Basic Res. Cardiol. 104 (2) (2009) 189–202.
[88] D.R. Hunter, R.A. Haworth, The Ca2+-induced membrane transition in mitochondria: III. Transitional Ca2+ release, Arch. Biochem. Biophys. 195 (2) (1979) 468–477.
[89] T. Bochaton, C. Crola-Da-Silva, B. Pillot, C. Villedieu, L. Ferreras, M. Alam, H. Thibault, M. Strina, A. Gharib, M. Ovize, Inhibition of myocardial reperfusion injury by ischemic postconditioning requires sirtuin 3-mediated deacetylation of cyclophilin D, J. Mol. Cell. Cardiol. 84 (2015) 61–69.
[90] X. He, H. Zeng, J.-X. Chen, Ablation of SIRT3 causes coronary microvascular dysfunction and impairs cardiac recovery post myocardial ischemia, Int. J. Cardiol. 215 (2016) 349–357.
[91] T. Wei, G. Huang, J. Gao, C. Huang, M. Sun, J. Wu, J. Bu, W. Shen, Sirtuin 3 deficiency accelerates hypertensive cardiac remodeling by impairing angiogenesis, J. Am. Heart Assoc. 6 (8) (2017) e006114.
[92] X. Guo, F. Yan, J. Li, C. Zhang, P. Bu, SIRT3 attenuates AngII-induced cardiac fibrosis by inhibiting myofibroblasts transdifferentiation via STAT3-NFATc2 pathway, Am. J. Trans. Res. 9 (7) (2017) 3258.
[93] J.-C. Zhong, Z.-Z. Zhang, W. Wang, S.M. McKinnie, J.C. Vederas, G.Y. Oudit, Targeting the Apelin pathway as a novel therapeutic approach for cardiovascular diseases, Biochimica et Biophysica Acta (BBA)-Mol. Basis Dis. 1863 (8) (2017) 1942–1950.
[94] L. Li, L. Li, F. Xie, Z. Zhang, Y. Guo, G. Tang, D. Lv, Q. Lu, L. Chen, J. Li, Jagged-1/Notch3 signaling transduction pathway is involved in apelin-13-induced vascular smooth muscle cells proliferation, Acta Biochim. Biophys. Sin. 45 (10) (2013) 875–881.
[95] C. Liu, T. Su, F. Li, L. Li, X. Qin, W. Pan, F. Feng, F. Chen, D. Liao, L. Chen, PI3K/Akt signaling transduction pathway is involved in rat vascular smooth muscle cell proliferation induced by apelin-13, Acta Biochim. Biophys. Sin. 42 (6) (2010) 396–402.
[96] M.-q. Liu, Z. Chen, L.-x. Chen, Endoplasmic reticulum stress: a novel mechanism and therapeutic target for cardiovascular diseases, Acta Pharmacol. Sin. 37 (4) (2016) 425.
[97] A. Folino, P.G. Montarolo, M. Samaja, R. Rastaldo, Effects of apelin on the cardiovascular system, Heart Fail. Rev. 20 (4) (2015) 505–518.
[98] Y. Pelogeykina, G. Konovalova, O. Pisarenko, V. Lankin, Antioxidant action of Apelin-12 peptide and its structural analog in vitro, Bull. Exp. Biol. Med. 159 (5) (2015) 604–606.
[99] X.J. Zeng, L.K. Zhang, H.X. Wang, L.Q. Lu, L.Q. Ma, C.S. Tang, Apelin protects heart against ischemia/reperfusion injury in rat, Peptides 30 (6) (2009) 1144–1152.
[100] W. Wang, S.M. McKinnie, M. Farhan, M. Paul, T. McDonald, B. McLean, C. Llorens-Cortes, S. Hazra, A.G. Murray, J.C. Vederas, Angiotensin-converting enzyme 2 metabolizes and partially inactivates pyr-apelin-13 and apelin-17: physiological effects in the cardiovascular system, Hypertension 68 (2) (2016) 365–377.
[101] W. Wang, S.M. McKinnie, V.B. Patel, G. Haddad, Z. Wang, P. Zhabyeyev, S.K. Das, R. Basu, B. McLean, V. Kandalam, Loss of Apelin exacerbates myocardial infarction adverse remodeling and ischemia-reperfusion injury: therapeutic potential of synthetic Apelin analogues, J. Am. Heart Assoc. 2 (4) (2013) e000249.
[102] L.M. Yamaleyeva, H.A. Shaltout, J. Varagic, Apelin-13 in blood pressure regulation and cardiovascular disease, Curr. Opin. Nephrol. Hypertens. 25 (5) (2016) 396–403.
[103] L. Li, H. Zeng, J.-X. Chen, Apelin-13 increases myocardial progenitor cells and improves repair postmyocardial infarction, Am. J. Physiol-Heart Circ. Physiol. 303 (5) (2012) H605–H618.
[104] Y. Azizi, M. Faghihi, A. Imani, M. Roghani, A. Zekri, M.B. Mobasheri, T. Rastgar, M. Moghimian, Post-infarct treatment with [Pyr1] apelin-13 improves myocardial function by increasing neovascularization and overexpression of angiogenic growth factors in rats, Eur. J. Pharmacol. 761 (2015) 101–108.
[105] B.-H. Zhang, C.-X. Guo, H.-X. Wang, L.-Q. Lu, Y.-J. Wang, L.-K. Zhang, F.-H. Du, X.-J. Zeng, Cardioprotective effects of adipokine apelin on myocardial infarction, Heart Vessels 29 (5) (2014) 679–689.
[106] X. Hou, H. Zeng, X. He, J.X. Chen, SIRT3 is essential for Apelin-induced angiogenesis in post-myocardial infarction of diabetes, J. Cell. Mol. Med. 19 (1) (2015) 53–61.
[107] X. Hou, H. Zeng, Q.-H. Tuo, D.-F. Liao, J.-X. Chen, Apelin Gene therapy increases autophagy via activation of sirtuin 3 in diabetic heart, Diabetes Res. (Fairfax, Va.) 1 (4) (2015) 84.
[108] D. Sun, F. Yang, Metformin improves cardiac function in mice with heart failure after myocardial infarction by regulating mitochondrial energy metabolism, Biochem. Biophys. Res. Commun. 486 (2) (2017) 329–335.
[109] M. Zhai, B. Li, W. Duan, L. Jing, B. Zhang, M. Zhang, L. Yu, Z. Liu, B. Yu, K. Ren, Melatonin ameliorates myocardial ischemia reperfusion injury through SIRT3-dependent regulation of oxidative stress and apoptosis, J. Pineal Res. (2017).
[110] R. Wang, J. Zhang, M. Zhang, M. Zhai, S. Di, Q. Han, Y. Jia, M. Sun, H. Liang, Curcumin attenuates IR-induced myocardial injury by activating SIRT3, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 1150–1160.
[111] M. Zhang, Z. Zhao, M. Shen, Y. Zhang, J. Duan, Y. Guo, D. Zhang, J. Hu, J. Lin, W. Man, Polydatin protects cardiomyocytes against myocardial infarction injury by activating Sirt3, Biochimica et Biophysica Acta (BBA)-Mol. Basis Dis. 1863 (8) (2017) 1962–1972.
[112] H. Zeng, L. Li, J.-X. Chen, Loss of Sirt3 limits bone marrow cell-mediated angiogenesis and cardiac repair in post-myocardial infarction, PloS One 9 (9) (2014) e107011.