Review Article

Journal of Biomedicines

Remodeling and healing of the heart after myocardial infarction mediated by SIRT3.

Aynaz Mihanfar[a,b,1], Hamid Reza Nejabati[b,d,e,1], Amir Fattahif, Zeinab latifi[b,d],Yousef Faridvand[b], Masoud Pezeshkian[c], Ahmad Reza Jodatic, Naser Safaiec, Abbas Afrasiabic.

***Corresponding author**

A. Afrasiabi,
Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran..

Received Date : May 07, 2024
Accepted Date : May 09, 2024
Published Date : June 09, 2024

ABSTRACT

The significance of sirtuins, a highly conserved family of gene products, and specifically SIRT3 in a variety of physiologic and pathological processes has been the subject of numerous recent studies. It has been shown that a wide variety of proteins implicated in oxidative stress, ischemia-reperfusion injury, mitochondrial metabolism balance, and cellular death are targeted by SIRT3, the mitochondrial NAD+-dependent deacetylase. SIRT3's crucial role in myocardial infarction (MI), one of the intricate characteristics of coronary artery disease illness as a result of interactions between several genetic and environmental factors, as well as in the remodeling and repair of the heart after myocardial infarction, have garnered increased interest in the past few years. Consequently, we will discuss key research regarding SIRT3's role in myocardial remodeling/repair after MI and its potential in this review.

Keywords: Sirtuins,Myocardial infarction,Coronary artery disease,Cardiac remodeling/repair.

INTRODUCTION

One of the complicated phenotypes of coronary artery disease, myocardial infarction (MI), is caused by the interplay of several environmental and genetic variables [1,2]. Important structural modifications in the heart muscle, such as an augmented inflammatory response and the formation of fibrous scar at the infarction site, occur after myocardial infarction. More critically, vascular remodeling and interstitial fibrosis are also seen in the non-infarcted areas of the afflicted myocardium. [3] Fibrous scar at the location of cardiomyocyte loss is essential for maintaining structural integrity and, consequently, cardiac recovery, which ultimately leads to the deficiency of myocardial tissue behavior. Additionally, a number of chemicals and proteins have been shown to play significant roles in cardiac remodeling and repair during this phase, which has generated a lot of interest in pharmacological intervention. [4]. Sirtuins, a potentially new and highly conserved family of gene products, have garnered significant attention recently due to their dual roles in a number of biological processes, such as inflammatory cardiomyopathy, cell cycle regulation, insulin secretion, oxidative stress resistance, and mitochondrial energetics [5]. This household possesses There are seven members of this family, SIRT1–7, with SIRT1 being the most well-known. All sirtuin proteins share a high degree of structural similarity, but there are also some notable differences in their C and N termini that have been documented. These differences are becoming more significant in the variety of biological behaviors of proteins, such as enzymatic activities, specific substrates, expression patterns, and subcellular localization [6]. It has been suggested that SIRT3 loss of function within this gene family contributes to the pathophysiology of cardiac hypertrophy and the change from cardiac failure. Furthermore, a growing body of research examining SIRT3 function gain as well as treatment-induced SIRT3 activation methods, have shown that cardiac diseases can be improved by signaling through this sirtuin family member through a variety of mechanisms, in light of this, offer a potentially effective treatment approach for cardiac diseases, notably heart repair after MI [7]. We will concentrate on SIRT3's underlying mechanism in this review. signals, which can enhance cardiac remodeling and repair.

2. SIRT3: molecular signaling and its structure

SIRT3, a soluble protein found in mitochondria and a key member of the sitruins family with numerous biological activities recently revealed, is expressed at remarkably high levels in tissues that are rich in mitochondria [7]. Furthermore, it has been reported by recent investigations into the precise physiological and pathophysiological function of this protein that SIRT3 plays a critical role in the metabolism of fatty acids, energy metabolism, tumor suppression, oxidative stress response, cellular stress, and age-related hearing loss [7]. Within a typical heart, it is approximated that over 90% of the ATP needed for optimal heart function is produced by mitochondrial oxidative phosphorylation. The primary source

of information for Fatty acid beta oxidation is this process of energy production [4]. The primary enzymes involved in oxidative phosphorylation and, consequently, mitochondrial energy metabolism are directly regulated by SIRT3, which also has the ability to modify the enzymatic activity of other enzymes via deacetylation [8]. One of the primary drivers of the glycolysis route is a decrease in SIRT3 levels, which occurs via two distinct pathways. First, in the absence of SIRT3, the highly acetylated state of peptidylprolyl isomerase D activates hexokinase II, which then phosphorylates glucose to create glucose-6-phosphate (G6P) [9]. The second process involves activating hypoxia inducible factor (HIF) 1α to stabilize the transcription factor. an increase in the generation of reactive oxygen species (ROS). This pathway regulates the expression of genes involved in glycolysis [10]. The activation and modification of long-chain acyl-CoA dehydrogenase is achieved by the deacetylation activity of SIRT3, which is also essential for the stimulation of β oxidation [11].

It has also been demonstrated that SIRT3 directly regulates acylglycerol kinase, acyl-CoA synthetase short-chain family member 2, and medium chain-specific acyl-CoA dehydrogenase [12–14]. The latter is engaged in the tricarboxylic acid cycle's entrance and acetate's conversion to acetyl-CoA [13, 14]. The ribosomal protein MRPL10 [18], glutamate dehydrogenase 1 (amino acid metabolism) [16], ornithine transcarbamylase (urea cycle) [17], 3-hydroxy-3-methylglutaryl-CoA synthase 2 (ketone-body biosynthesis) [15], ATP synthase activity [19], and electron transport chain complex I and II including [16] are all deacetylated and hence activated by SIRT3. SIRT3 also plays a crucial role in improving the mitochondria's capacity to respond to reactive oxygen species (ROS), which can lead to elevated levels of oxidative stress, cellular damage, and death. These outcomes are strongly linked to a number of cardiac diseases, including diabetes [29,30], hyperlipidemia [17,28], cardiac hypertrophy [25–27], and coronary atherosclerosis [20–24]. Additionally, SIRT3 has been shown to deacetylate and activate Mn superoxide dismutase (SOD2), the primary scavenger of superoxide radicals [31–33], which reduces the formation of ROS and strengthens the body's defenses against oxidative stress-induced cellular damage. The robust transcription of SOD2 and other antioxidative enzymes is caused by the SIRT3-mediated reduction in the translocation of Forkhead box O3a (FOXO3A) from the nucleus into the cytoplasm [34]. Apart from these clearly established roles of SIRT3, some research has concentrated on how SIRT3 expression affects apoptosis. and revealed contentious outcomes. Nonetheless, a number of investigations have shown that SIRT3 is a strong inhibitor of cardiomyocyte death. This SIRT3 function is suggested to be mediated by intriguing mechanisms, including suppression of mitochondrial permeability [37], deacetylation and activation of optic atrophy 1 (OPA1) [35,36], Ku70 [34], and cyclophilin D [26].

3. Remodeling or repairing the heart after MI

Following MI and the necrotic death of cardiomyocytes, structural changes are made in both the infarct and the remote location of the heart by cardiac repair and remodeling, which triggers certain inflammatory responses [38]. Matrix metalloproteinases (MMPs) are activated immediately during a myocardial infarction event, leading to the breakdown of the extracellular matrix (ECM) and coronary vasculature [39, 40]. Significant increase of the expression levels happens after one week.

of tissue MMP inhibitors (TIMPs), which causes MMPs' proteolytic activity to decline [41]. After MI, inflammatory cells such as Neutrophils are involved in the process of proteolytic digestion, while macrophages and macrocytes aid in the phagocytosis of infected tissues. They are drawn to the MI site and penetrate infarcted tissue by means of adhesion molecules, chemoattractant cytokines, and MMP proteolytic activity. These events can take place in various bodily sites, such as ovulation, embryo implantation, tissue repair, and cancer [40, 42–49]. The expression of these factors is caused by endothelial cells found in the coronary arteries and other types of tissues [45,50].

About one to two weeks following a MI episode, this inflammatory reaction peaks and then subsides when the inflammatory cells from the MI site, which happens as a result of these cells dying off in 2-4 weeks. The stimulation of transforming growth causes fibrogenic component to replace lost parachymal cells.

factor (TGF)-β1 as a primary fibrogenesis component [50]. Collagen fibers first develop in the infarcted spot one week later. At week two, they start to assemble as scar tissue, thanks to fibroblast-like cells that have undergone morphological and phenotypic changes [51].

Myofibroblasts are cells that resemble fibroblasts and display α-smooth muscle actin [52], microfilaments, and the capacity to contract due to TGF-β1 secreted by macrophages [53]. The infarct site produces contractile scar tissue as a result of myofibroblasts' fast proliferation and production of type I and III fibrillar collagens [54]. Additionally, these cells produce renin, the enzyme that converts angiotensin to angiotensin, angiotensin receptors, endothelin-1, and vasopressin, all of which are essential for the development of scar tissue contraction [55–57]. Apart from the location of the infarct, interstitial In the third week, broblasts form a non-infarcted myocardium with fibrosis. Myofibroblasts, however, do not

show up at unaffected locations [50].

4. SIRT3 in heart conditions

A growing body of prior research has revealed that SIRT3 plays a critical role in the etiology of a number of cardiovascular disorders, including drug-induced cardiotoxicity, diabetic cardiomyopathy, cardiac lipotoxicity, ischemic heart disease, and heart failure [8,58,59]. In particular, MI is the primary topic of this review. According to reports, SIRT3 is not a significant participant from a developmental standpoint because SIRT is inadequate. Mice don't exhibit any notable phenotypic abnormalities.

SIRT3-/-mice, however, are extremely susceptible to stress stimuli after birth [27,60]. The primary cause of this discovery is the crucial role of this sitruin in controlling the activity of mitochondrial substrates, including a number of enzymes involved in the synthesis of ATP, electron transport, and oxidative stress. Furthermore, in adult hearts and cardiac-derived cells, downregulation of SIRT3 significantly increases the risk of ischemia-reperfusion injury [61,62]. Furthermore, there is growing evidence that SIRT3 contributes significantly to vascular inflammation, which heightens the protein's significance in atherosclerosis. In a chemically generated model of vascular inflammation, it was observed that the formation of ROS was caused by SIRT3 downregulation. and thus cause an increase in endothelial cell inflammation [63]. Nevertheless, the exact mechanism behind SIRT3's role in atherosclerosis remains unclear, especially in light of a recent study's findings that SIRT3 deficiency did not exert any discernible influence on the stability of atherosclerotic plaque and the propagation of lesions is a sign of this [64]. Furthermore, a growing number of recent investigations have demonstrated that cardiac hypertrophy, which results in the death and fibrosis of myocardial cells, and Consequently, downregulation of SIRT3 is closely linked to heart failure [25, 26, 65]. Mice with SIRT3 loss were observed to have a lower ejection percent following transverse aortic constriction. This is the development of heart fibrosis and hypertrophy [66,67]. Furthermore, it was noted that SIRT3 downregulation resulted in reduced respiratory capacity, ATP production, palmitate and glucose oxidation, and oxygen consumption, indicating a shift from oxidative phosphorylation to glycolysis [67]. The acetylated form of mitochondrial proteins increases in an animal model of heart failure due to a decrease in SIRT3 expression levels and subsequent SIRT3 deacetylation activity [68]. A downregulation of PGC-1a is one significant example of the several mechanisms for the downmodulation of SIRT3 in heart failure that have been introduced in some investigations [69];Reduced activity of the mitochondrial enzyme nicotinamide mononucleotide adenylyltransferase 3 (NMNAT3), which supplies NAD + for SIRT3, increased expression of RIP140, which inhibits SIRT3, and upregulation of poly (ADP ribose)-polymerase 1 (PARP-1), a DNA repair enzyme that competes with SIRT3 for NAD+ [70, 71].

Function of SIRT3 [72,73]. The documented negative consequences of SIRT3 downregulation in cardiac hypertrophy make perfect sense given the crucial role SIRT3 plays in the regulation of energy metabolism [12,74] and protection against oxidative stress [12,27].

4.1 SIRT3 in Michigan

Some significant catastrophic outcomes of MI include many pathological processes such metabolic abnormalities, change in the ultrastructure of cardiomyocytes, and cell death [75]. However, a growing body of prior research has demonstrated the crucial SIRT3's function in the pathogenic processes of reperfusion damage and ischemia, which lead to ischemia-reperfusion injury (I/R). SIRT3 expression levels were found to significantly decline in response to MI induced by artery blockage [76]. SIRT3 elimination increases their susceptibility to I/R in animal models, as evidenced by the higher infarction sizes observed in SIRT3 defective mice [61].

In these mice, downregulation of SIRT3 also interfered with normal heart function. Nevertheless, a different study found no correlation between SIRT3 deficiency and cardiac function or MI size [77]. The condition known as myocardial ischemia, which occurs when the myocardium does not receive enough oxygen or energy, is linked to the overexpression of hypoxia-inducible factors (HIFs), namely the oxygen-labile α subunit HIF-1α. This means that the expressions is one of the helpful and early reactions to MI that occurs [78]. It has been shown that HIF-1α treatment in acute MI can effectively reduce infarction size and promote angiogenesis [79].

Remarkably, SIRT3's downstream target HIF-1α has been demonstrated in fibroblasts and tumor cells. Nonetheless, it has been shown that SIRT3 alters proline hydroxylation enzyme activity, which modifies HIF-1α degradation. As a result, SIRT3 overexpression in cancer research disturbs HIF-1α stability [80]. The significance of the interaction between SIRT3 and HIF-1α in MI requires further research. Apart from HIF-1α, there has also been documentation of a connection between SIRT3 and angiotensin II in MI. Critical roles for the angiotensin system in ischemia damage [81]. Angiotensin II administration caused a notable reduction in SIRT3 expression levels [82], and it was remarkable that inhibiting this system restored SIRT3 levels in MI and enhanced cardiac function [16,76,83]. Notable rise in the generation of ROS [84], along with an improvement in the intracellular calcium concentration [85,86], are a few of the important factors

that lead to the development and progression of perfusion injury, which in turn causes mitochondrial enlargement, the activation of necrotic and apoptotic pathways, and cell death by opening the mitochondrial platelet potential [87,88]. In animal models, mPTP opening and mitochondrial leakage were caused by SIRT3 deficiency [67]. During reperfusion injury, cyclophilin D, a regulatory subunit of mPTP, plays a role in sensitizing mitochondrial transition to calcium. Remarkably, SIRT3 deacetylates and directly targets cyclophilin D, delaying the mPTP's opening [67,89]. The reduction of reperfusion injury is aided by SIRT3's function [89]. When combined, the data indicate that SIRT3 can have a significant impact on the different Substrates and signaling pathways had a role in MI and I/R damage pathogenesis.

4.2. SIRT3 in the remodeling and repair of the heart after MI

As was previously established, SIRT3 is so crucial to the cardiovascular system that deficiencies or abnormalities in its signaling cause a variety of heart disorders. SiRT3 deletion has been linked to coronary microvascular dysfunction, myocardial ischemia and MI-related impairment in cardiac remodeling and repair, and atherosclerosis, cardiac hypertrophy, I/R damage, and other cardiac disorders. He and colleagues' [90] assessment of SIRT3's function in cardiac remodeling after a MI. The author demonstrated that endothelial cells isolated from SIRT3-deficient mice had a markedly reduced angiogenic ability. It was noted that hyperemic peak diastolic blood flow velocity, coronary flow reserve, and the loss of capillary-pericytes in the heart occurred in SIRT3 knockout mice, all of which are signs of coronary microvascular dysfunction.

in the instance of downregulation of SIRT3. When compared to wild type mice, the animals that were exposed to myocardial ischemia had more severe cardiac dysfunction. Additionally, it was noted that in post-MI animals, SIRT3 overexpression led to an improvement in heart function. Reduced expression levels of angiopoietin-1, vascular endothelial growth factor (VEGF), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), and other molecules are observed in SIRT3 deficiency. rise in the death process [90]. In a different investigation, SIRT3−/− mice were used to assess the role of SIRT3 in the restoration of myocardial contractile function after myocardial infarction and myocardial infarction. Surprisingly, the results revealed that despite pre-existing cardiac After IR or MI, SIRT3 downregulation did not further affect heart function or mitochondrial respiratory capacity in SIRT3-deficient mice [77]. Another investigation using angiotensin II-infused SIRT3 knockout mice was conducted by Wei et al. [91]. Angiotensin II infusion was found to cause cardiac fibrosis by causing more severe microvascular dysfunction, hypoxia, mitochondrial dysfunction, and increased expression of collagen I and collagen III in the heart tissues. Remarkably, SIRT3 downregulation promoted all of angiotensin II's impacts on heart function. Thus, by enhancing Pink/Parkin-mediated mitophagy, reducing mitochondrial ROS production, reestablishing vessel sprouting and tube formation, and reducing fibrosis, SIRT3 overexpression restored cardiac function.

Furthermore, a different mechanism for SIRT3's protective benefits against angiotensin II-induced cardiac fibrosis was reported by Guo et al. [92]. It was demonstrated that in SIRT3−/− mice, SIRT3 reduced heart fibrosis by inhibiting myofibroblast transdifferentiation via the STAT3-NFATc2 pathway. [92]. It has been documented that the transcriptional co-factor receptor-interacting protein 140 (RIP140), a negative regulator of cardiac mitochondrial function and energy metabolic homeostasis, causes hypertrophy in cardiomyocytes by inhibiting SIRT3 function [71]. Consequently, SIRT3 is downstream of a number of signaling pathways and Several medicinal drugs are utilized to enhance heart remodeling following myocardial infarction.

5. SIRT3: the fundamental mechanism of Apelin-mediated post-MI protection

As an endogenous bioactive peptide, apelin acts by binding to the Apelin receptor, sometimes referred to as the APJ receptor. This receptor is widely distributed across several tissues, including the brain, heart, lung, kidney, liver, skin, limbs, retina, and adipose tissue [93].

Apelin/APJ system signaling is involved in several critical biological functions, including immunology, water homeostasis,blood pressure, angiogenesis, glucose metabolism, and, in particular, myocardial contractility [94–96]. Apelin has been found to have several isoforms, including Apelin-12, Apelin-13, Apelin-17, and Every one of Apelin-36 has a specific purpose [52,97–99]. It has been found that Apelin-12 and Apelin-17 improve cardiac contractility [100]. Apelin/APJ system plays a vital protective role in MI, especially in promoting angiogenesis, as evidenced by a growing body of research [101]. Apelin-13 was shown to enhance angiogenesis in the cardiac muscle of post-MI mice by overexpressing jagged-1 and notch-3 and by encouraging the recruitment of vascular endothelial progenitor cells into infarct areas [102]. Apelin-13-mediated progenitor cell homing was examined in another study, which discovered that the SDF-1α/CXCR-4 axis was crucial to the process [103]. through the enlistment of precursor cells Apelin-13 increases angiogenic events at the MI site and enhances heart healing after MI. stimulation of VEGF, phosphorylation of Akt/eNOS (P-Akt/eNOS), overexpression of Tie-2's homology domains, and activation of angiopoietin-1

(Ang-1)/Tie Other significant mechanisms via which Apelin-13 promotes angiogenesis and enhances cardiac function after MI include the 2 signaling pathway [104,105]. Apelin-induced angiogenesis in post-MI has been linked to Sirt3 in an increasing number of reports in recent years (Fig. 1). Li et al.'s study [21] demonstrated that by upregulating SIRT3, the injection of bone marrow cells (BMCs) overexpressing Apelin into the myocardium of post-MI mice boosted cardiac repair and recovery. The treatment of the myocardium with Apelin-BMCs, according to the author, significantly increased the expression levels of VEGF, angiotensin I, Tie-2, and Notch 3. SIRT3 and Akt both contributed to the rise in angiogenesis potential. Notably, the treatment plan reduced the generation of reactive oxygen species (ROS), apoptosis brought on by stress, and the resulting attenuation of cardiac fibrosis. Remarkably, total elimination of SIRT3 eliminated in post-MI mice the beneficial effects of Apelin-BMCs [21].

Hou et al. [106] discovered that adenovirus-Apelin treatment led to overexpression of SIRT3, angiopoietins/Tie-2 and VEGF/VEGFR2, as well as enhancement in the myocardial vascular densities. However, these alterations were not observed in Sirt3 knockout mice. This study examined the direct role of SIRT3 in Apelinmediated angiogenesis in MI mice model. Thus, through upregulating the SIRT3 pathway, Apelin gene therapy enhances heart functional recovery and stimulates angiogenesis [106]. Apart from the enhancement of angiogenesis, the same In a different investigation, the authors showed that the increase in autophagy mediated by Apelin is dependent on SIRT3 [107]. Significant increases in SIRT3, gp91phox, NF-κb-p65 expression, and ROS generation were all caused by Apelin upregulation. Significantly, Apelin overexpression raised autophagy markers even more.

SIRT3 knockdown eliminated the expression of (LC3-II and beclin-1) in the post-MI heart [107].

6. Cardioprotective medications and SIRT3

An increasing number of studies have shown that the majority of cardioprotective medications improve myocardial function by modifying SIRT3 expression (Fig. 1). Regarding this, it has been found that the type 2 diabetes treatment drug metformin considerably reduces cardiovascular events, hence exerting cardiovascular preventive benefits. A study conducted by Sun et al. [108] Mice used in a model of heart failure following MI were used to assess the impact of metformin on cardiac function. Evidence has suggested that metformin therapy enhances the potential of the mitochondrial membrane and mitochondrial respiratory activity. It should be noted that following a MI, metformin increased PGC-1a activity and Sirt3 overexpression in cardiac tissue. Mice's cardiac performance was ultimately improved by metformin-mediated increase in SIT3 deacetylation activity, which also considerably decreased the acetylation level of PGC-1a, alleviated damage to mitochondrial membrane potential, and enhanced mitochondrial respiratory function [108]. A number of studies have shown that melatonin, in addition to metformin, is beneficial in reducing I/R injury. For instance, Zhai et al.'s work [109] Prior to undergoing I/R surgery, mice were given a specific SIRT3 inhibitor or not. Melatonin therapy thereby enhanced post-ischemic heart contractile function, lowered the size of infarcts, decreased the production of lactate dehydrogenase, and decreased the apoptotic index and reduced the harm caused by oxidation. In fact, melatonin therapy reversed the reduction in SIRT3 expression and activity caused by I/R, which in turn decreased SOD2 acetylation. Further research revealed that the cardioprotective benefits of melatonin were entirely eliminated by SIRT3 inhibitors, indicating a crucial role for SIRT3.

in moderating melatonin's cardioprotective effects. Therefore, by decreasing oxidative stress and apoptosis through the activation of the SIRT3 signaling pathway, melatonin therapy attenuates MI injury [109]. Another work by Yu et al. [69] showed that melatonin attenuates MI injury in type 1 diabetic mice by maintaining mitochondrial function. This was accomplished by increasing the biogenesis of mitochondria and decreasing mitochondrial oxidative stress through the AMPK-PGC-1α-SIRT3 signaling pathway.

Furthermore, SIRT3 siRNA reduced melatonin's cytoprotective impact without changing the p-AMPK/AMPK ratio and Expression of PGC-1α [69]. Natural substances called polyphenols have been well-researched for their ability to reduce inflammation and oxidative stress in the aftermath of MI injuries. Wang et al. [110] examined the impacts of in this context After a myocardial infarction, curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6 heptadi-ene-3,5-dione, diferuloylmethane), a polyphenol, was extracted from the rhizome of Curcuma longa (turmeric). Curcumin treatment of H9c2 cells was demonstrated in vitro to significantly increase cell viability and decrease cell apoptosis by upregulating the pro-apoptotic proteins Bax and AcSOD2, downregulating the anti-apoptotic protein Bcl-2, and increasing defense capability against oxidative stress. SIRT3 expression and activity were likewise triggered by curcumin. Curcumin, it's interesting to note, dramatically enhanced heart function, decreased infarct size, and lowered lactate dehydrogenase levels in isolated rats, according to an in vivo model. heart. Notably, administration of the SIRT3 inhibitor abolished the protective benefits induced by curcumin [110]. A monocrystalline, polyphenolic medication called polydatin was extracted from a traditional Chinese herb called Polygonum.

cuspidatum), it was also noted that increasing SIRT3

might enhance heart function [111]. Moreover, it has been reported that losartan, an angiotensin receptor blocker that is frequently used to lower blood pressure, has therapeutic effects against I/R by enhancing the drop in SIRT3 expression levels brought on by ischemia [76]. Another study that supports SIRT3's beneficial role was conducted by Zeng et al. [112]. It found that SIRT3 loss results in a reduction of BMC-mediated angiogenesis and cardiac repair following myocardial infarction, which suggests that in post-MI stem cell therapy, SIRT3 plays a crucial role in the cardioprotective properties of stem cells.

Furthermore, they demonstrated that SIRT3 depletion increased ROS generation and encouraged death in endothelial progenitor cells.

cells (EPCs), whereas SIRT3 overexpression inhibited these cells' ability to undergo apoptosis. Based on these results, they ultimately came to the conclusion that increasing SIRT3 in stem cells may be a potential therapeutic approach to improve stem cell therapy for ischemic heart disease.

7. Conclusion

Strong mitochondrial deacetylase SIRT3 targets a wide variety of substrates involved in a number of biological processes, including cellular death, oxidative stress, and the synthesis of ATP. A growing body of recent research has demonstrated the crucial role SIRT3 plays in cardiovascular disorders, such as hypertrophic cardiomyopathy. heart failure, I/R damage, and myocardial infarction. Given that metformin, melatonin, curcumin, and polydatin therapy has positive effects on myocardial infarction and IR injury by increasing the expression and/or activity of SIRT3, the creation of particular SIRT3 activators may provide a potential therapeutic approach by which cardiac function can be enhanced after heart function.

conflicts of interest

The research did not receive any specific support from public, private, or not-for-profit funding bodies, and the authors state that they have no conflicts of interest.

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, 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-overexpressing 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 paraoxonase 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, CyTAJ. 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. 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.

34. 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.

35. 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.

36. 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 stressmediated cell death by deacetylation of Ku70, Mol. Cell. Biol. 28 (20) (2008) 6384–6401.

37. 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.