Chapter 8

Changes in the Expression and the Role of Sirtuin 3 in Cancer Cells and in Cardiovascular Health and Disease

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Abstract

Sirtuin 3, an NAD^+-dependent deacetylase, whose expression is considered a marker in life extension, is downregulated with age and in various diseases. Sirtuin 3 is predominantly localized to the mitochondria and considered a fidelity protein for the integrity and function of this organelle. Some studies report its localization in the nucleus to regulate the expression of stress response–related genes and that reduced expression of SIRT3 produces a cellular milieu permissive for human pathologies. Since the expression and activity of Sirtuin 3 are important for the regulation of antioxidant defense, metabolism, and apoptosis initiation, the expression of SIRT3 is also important in the context of age-associated illnesses. A variety of small molecules are being developed to modulate the expression or activity of Sirtuin 3 and are potentially a valuable strategy to change mitochondrial acetylome to treat several diseases. The AMPK-PGC1α-SIRT3 axis plays a critical role in preserving mitochondrial biogenesis and function. Here, we summarize how changes in Sirtuin 3 expression are regulated in cancer and dysfunctions in cardiovascular diseases. The potential therapeutic strategies by targeting Sirtuin 3 expression to improve mitochondrial function in cancer and cardiovascular diseases are summarized.

Keywords: sirtuin, SIRT3 expression, cancer, cardiovascular diseases, stress

1. Introduction

With the identification of sirtuins (SIRTs), acetylation/deacetylation of proteins has become evident as an essential and highly regulated posttranslational modification, especially for the majority of mitochondrial proteins [1]. Acetylation can regulate the activity of an enzyme, stability or subcellular localization of a protein, transcriptional activity, and DNA-protein interactions. Silent information regulator 2 (Sir2) is the founding member of sirtuins, which was characterized in yeast, *Saccharomyces cerevisiae*. Sir2 functions in silencing gene expression by histone deacetylation [2]. It has been proposed that overexpression of Sir2 leads to an

increase in life expectancy in yeast and other model organisms, such as *Caenorhabditis elegans* and Drosophila [3]. In these model organisms, the activity of Sir2 is stimulated by multiple physiological events and stress signals, including starvation, calorie restriction, osmotic stress, and heat shock [4, 5].

SIRT histone deacetylases differ from traditional class I and II histone deacetylases (HDACs) in two ways: first, the substrates of SIRTs are not limited to histones and they can target key enzymes or proteins in the cytoplasm and mitochondria in addition to histones in the nucleus [6]. Second, SIRTs require nicotinamide adenine dinucleotide (NAD^+) for their enzymatic activity. Their dependence on NAD^+ is important for the regulation of metabolism and links the activity of SIRTs to the energy status of the cells. This is important for a cell to respond to different stress factors with a suitable stress response to sustain homeostasis. For example, in starvation, calorie restriction, exercise, or a cellular genotoxicity, increased cellular NAD^+ levels can activate SIRTs. Like Sir2, activated and/or upregulated SIRTs deacetylate their numerous targets to create a proper cellular stress response.

In mammals, seven SIRT isoforms have been identified, which can be found in different subcellular compartments. SIRT1, SIRT6, and SIRT7 are localized to the nucleus; SIRT3, SIRT4, and SIRT5 are localized mainly in the mitochondria; and SIRT2 is mostly present in the cytoplasm, but it might translocate into the nucleus [7]. Mammalian SIRTs have been proposed to have numerous beneficial effects, such as increasing insulin secretion, ATP synthesis, and lipid mobilization; however, the mechanism of how these beneficial effects translate into life span extension is poorly understood. SIRT3 gene expression has been observed to be upregulated with high frequency in long-lived individuals [8, 9]. In these individuals, mutations in an enhancer region of the SIRT3 gene are believed to upregulate its expression, and high SIRT3 expression can be considered a marker for longevity.

Calorie restriction is defined as lowering dietary calorie intake without malnutrition and has been described to extend the life span of many organisms from yeast to mammals and decrease the occurrence of age-related diseases, such as cancer, cardiovascular diseases, neurodegenerative diseases, and diabetes [10, 11]. In both yeast and *C. elegans*, caloric restriction–induced longevity is reliant on the existence of Sir2 [4]. Parallel to studies on Sir2, subsequent studies suggested that beneficial effects of calorie restriction might be associated with the upregulation of SIRT expression. SIRT3 transcription was stimulated in hepatocytes and skeletal muscle of mice on calorie restricted–diet, while a long-term high-fat diet resulted in lowering SIRT3 expression and increasing mitochondrial protein acetylation [12, 13]. SIRT3 expression declines in individuals over 59 years of age [14, 15], which may contribute to the increased incidence of cardiovascular diseases and cancer in aging population. Studying SIRT3 in these diseases may provide important mechanistic connection between the mitochondrial function and age-associated disorders [16–20]. SIRT3 expression is important for mitochondrial biogenesis, regulation of metabolism, ATP synthesis, suppression of reactive oxygen species (ROS), stress responses, and cell signaling [15, 19, 21–23].

Investigators report that SIRT3 regulates the activity of the transcription factors, Forkhead box O 3a (FOXO3a), and nuclear factor κB (NF-κB) [24, 25]; however, regulation of SIRT3 transcription itself is not completely understood up-to-date. *SIRT3* gene is located in a bidirectional

arrangement with another gene, called *PSMD13*, in a phylogenetically conserved manner. The promoter of the two genes is separated by a 788-bp intergenic region. SIRT3 holds a rich GC content but lacks a TATA box. Human SIRT3 promoter has binding sites for activator protein (AP-1), NF-κB, ZF5 transcription factor, GATAs, and specificity protein 1 (SP1) [26]. There is evidence that peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) upregulates SIRT3 transcription, conveyed by an estrogen-related receptor (ERR)-binding element in the promoter of SIRT3 in mouse muscle cells and hepatocytes [27]. PGC-1α and ERRα display a synergic action on *SIRT3* promoter activity [27]. Furthermore, SIRT3 increases PGC1-α gene expression by activating AMPK signaling pathway and provides a positive feedback loop. Activation of AMPK signaling pathway leads to phosphorylation of cAMP response element-binding protein (CREB), which directly activates the PGC1-α promoter [28]. The positive feedback loop between SIRT3 and PGC1-α is important for mitochondrial biogenesis and activation of enzymes associated with the antioxidant system and regulation of metabolism [6, 27, 28]. In another study, bioinformatics analysis has been revealed that transcription factor binding motifs might be present in SIRT3 promoter. Nuclear respiratory factor 2 (NRF-2) transcription factor regulates mitochondrial genes, including antioxidant enzymes. NRF-2 has been reported to directly bind to the SIRT3 promoter and increase the expression of SIRT3 mRNA during nutrient stress [29].

2. Changes in Sirtuin 3 expression in carcinogenesis

Acetylation/deacetylation of specific lysine amino acids of proteins is a prevalent regulatory mechanism responsible for modulating signaling pathways, survival, apoptosis, and energy metabolism that takes part in important roles in cellular transformation [30]. SIRTs regulate various cellular activities, such as gene silencing, cellular proliferation, survival, apoptosis, stress response, and energy generation by protein deacetylation [31, 32].

SIRT3 is mostly localized in the mitochondria, and it deacetylates many critical metabolism-related proteins; decreases the levels of mitochondrial ROS; and ultimately regulates proliferation, differentiation, and survival in response to a stress stimulus [20, 33]. SIRT3 is considered a fidelity protein because it plays important roles in integrity and maintenance of mitochondrial function [6, 34, 35]. SIRT3 expression has been determined to be the highest in the heart, liver, brain, and brown adipose tissue where metabolic activity is relatively high [36]. Genetic deletion of SIRT3 in mouse has been reported not to produce any significant phenotypic abnormalities when the mouse is younger than 1 year old. SIRT3 knockout mice are viable, fertile, and metabolically active when these animals are still young. The difference between SIRT3-deficient mice and wild-type animals is that knockout mice express increased numbers of hyperacetylated proteins in their mitochondria, suggesting SIRT3 is the primary deacetylase in this organelle [37]. In normal conditions, SIRT3 gene deficiency does not produce any abnormalities; however, a different picture emerges when SIRT3 knockout mice get older than 12 months or encounter a stress stimulus. These mice might be prone to tumor formation, especially in the breast [38].

SIRT3-deficient mice older than 1 year old develop well-differentiated estrogen- and progesterone-positive mammary tumors [38]. This subtype of mammary tumors is more commonly observed in

women over 60 years old. In human estrogen- and progesterone-positive mammary tumor samples, SIRT3 expression is found to be reduced compared to noncancerous breast tissues [38]. The SIRT3 knockout mouse is suggested to be a convenient model to study this subtype of breast tumors. Additional studies on SIRT3-deficient mice revealed that ionizing radiation causes vacuolization in SIRT3 knockout mouse hepatocytes, suggesting SIRT3 protects hepatocytes against ionizing radiation–induced damage [38]. Moreover, SIRT3-deficient mice may develop age-related hearing loss [19]. SIRT3 expression is reduced in various tumors, and at least one allele of SIRT3 gene is deleted in about 40% of breast and ovarian tumors and 20% of all human cancer samples [38, 39]. SIRT3 expression is associated closely with cancer because it has essential regulatory roles in mitochondrial ROS scavenging, ATP synthesis, metabolism, and mitochondrial function [38].

Electron transport chain in mitochondria is the main source of the generation of ROS, such as superoxide. ROS homeostasis is strictly regulated in the cell, and while ROS play a part as secondary messengers at normal conditions, excessive ROS can damage cellular biomolecules and contribute to mitochondrial dysfunction and carcinogenesis [40]. SIRT3 has been shown to directly deacetylate and stimulate manganese superoxide dismutase (MnSOD) activity, which is the principle ROS scavenger in the mitochondria [20]. In addition, SIRT3 could induce expression of MnSOD, catalase, and isocitrate dehydrogenase (IDH2) by deacetylating FOXO3a transcription factor, triggering its translocation into the nucleus and transcription of these antioxidant enzymes [20, 25, 41, 42].

In the majority of tumors, pyruvate is preferentially transformed into lactate even in the existence of adequate oxygen. In this process, termed the Warburg effect, metabolism shifts in favor of glycolysis to increase the raw materials necessary for making new cancer cells [30, 43, 44]. In other words, glycolytic rate is increased in cancer cells. SIRT3 has been revealed to bring about degradation of HIF-1α, which results in suppression of the expression genes involved in glycolysis and angiogenesis [45]. SIRT3 displays this action indirectly through reductions in ROS level, which activates oxygen-dependent prolyl hydroxylases (PHD). In this regard, profilin1 (Pfn1) has been reported to have an anticancer feature in pancreatic cancer by upregulating SIRT3, which in turn results in degradation of HIF-1α and reduction in the expression of glycolytic genes [46]. Furthermore, SIRT3 has a second action to stimulate mitochondrial respiration by directly targeting electron transport chain and some metabolic enzymes, such as pyruvate dehydrogenase complex, and induce higher ATP production [22, 47–49].

Since SIRT3 takes part in mitochondrial ROS scavenging, regulation of metabolism, and mitochondrial function, it is not surprising that reduced expression of SIRT3 is highly associated with carcinogenesis [6, 30]. In addition, reduced SIRT3 expression is suggested to be a biomarker for breast cancer associated with poor prognosis [50, 51]. In addition to breast cancer, SIRT3 might play tumor suppressive roles in pancreatic cancer [52], hepatocellular carcinoma [53, 54], B cell lymphoma cells [55], and metastatic ovarian cancer [56]. In addition, kaempferol, a flavonoid, increases SIRT3 expression and its mitochondrial import; hence, it stimulates apoptosis in leukemia cell lines [57].

SIRT3 has also been reported to take part in an oncogenic function by promoting cancer initiation or progression depending on the tissue of origin and intracellular signal pathways

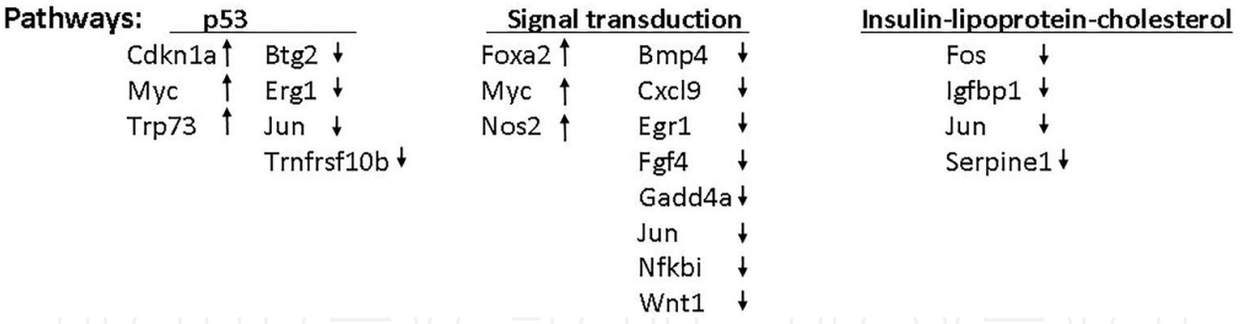

Figure 1. Changes in the expression of p53, signal transduction pathway, and insulin-lipoprotein-cholesterol genes in SIRT3-deficient livers compared to SIRT3 wild-type mouse based on [66].

[30]. Oncogenic properties of SIRT3 are attributed to its actions in stimulation of proliferation, resistance to oxidative stress, and suppression of apoptosis. SIRT3 could play an oncogenic role in a spectrum of cancers including oral squamous cell carcinoma [58], breast cancer [59], esophageal cancer [60], gastric cancer [61], colorectal cancer [62], and melanoma cell lines [63].

SIRT3 is predominantly located in the mitochondria; however, there are studies reporting its localization in the nucleus and having a function in regulating gene expression response to stress factors [64, 65]. We have previously shown that the loss of expression of SIRT3 in mouse liver and cultured mouse embryonic fibroblasts results in a cellular environment susceptible to carcinogenesis and cellular transformation [38, 66]. In the subsequent study, we investigated how SIRT3 alters the gene expression of cancer-related pathways in SIRT3 wild-type and SIRT3 knockout mouse hepatocytes. We studied how deficiency of SIRT3 expression might change the gene expression profile of various transcription factors and proteins linked to tumor formation in addition to genes associated with metabolism using a commercially available real-time polymerase chain reaction kit that screens gene expression profiling of diverse pathways [66]. We found upregulated expression of several genes having oncogenic properties including cyclin-dependent kinase inhibitor 1A P21 (Cdkn1a), myelocytomatosis oncogene (Myc), and nitric oxide synthase (NOS2) in SIRT3-deficient mouse liver. These genes are often overexpressed in human cancers, primarily in breast tumors. In contrast, several genes that were previously reported to be downregulated in human breast cancer containing B-cell translocation gene 2 (BTG2), early growth response 1 (EGR1), and Gadd4 had decreased expression with larger than 2-folds in the SIRT3-deficient hepatocytes [66]. The list of genes with larger than 2-folds in the cancer-associated pathways and genes associated with insulin-lipoprotein-cholesterol metabolism is presented in **Figure 1**.

3. Protective effects of SIRT3 in stress responses in the heart and changes in SIRT3 expression in cardiovascular diseases

The heart produces and uses more than 90% of its ATP from mitochondrial aerobic respiration in the cardiomyocytes, which have one of the highest mitochondrial density among all mammalian cells [67]. Mitochondria are critical in regulating oxidative stress signaling during cardiovascular

physiology and pathology by regulating cell death, ROS homeostasis, and ATP levels in cardiomyocytes. Heart failure might be caused by the imbalance in cardiac metabolism, oxidative stress, and opening of the mitochondrial permeability transition pore, which are important cellular contributors to myocardial ischemia/reperfusion (IR) injury and the development of cardiac hypertrophy [68–70]. Recent evidence demonstrated that the mitochondrial NAD^+-dependent enzyme, SIRT3, may regulate critical intracellular processes, such as oxidative stress, cell survival, and cellular metabolism for a healthy cardiac function [71].

In mammals, SIRT3 is one of seven NAD^+-dependent protein deacetylases or ADP-ribosyltransferases that regulates mitochondrial enzyme activity important in maintaining the integrity of the mitochondria and having a cardioprotective role [17, 72, 73]. Lanza et al. found that SIRT3 expression is downregulated with age, especially pronounced after 60 years old, and chronic endurance training causes elevation of SIRT3 expression along with beneficial health effects and potential lifespan-extending properties [74]. SIRT3, whose expression is rich in the heart, is the main deacetylase in the mitochondria and its absence produces hyperacetylation of numerous proteins in this organelle [75]. Increased acetylation of mitochondrial proteins, such as cyclophilin D, an important regulator of the permeability transition pore (mPTP), in the heart in response to IR injury has been reported [69, 76].

The changes in expression of SIRT3 are appealing to the study of cardiovascular diseases because of its presence mainly in the mitochondria, where a large part of the reactive oxygen species (ROS) is generated in the cardiomyocytes [77]. Overproduction of ROS in mitochondria has been linked to the development of cardiac hypertrophy [71]. High levels of cellular ROS damage biomolecules and accelerate the death of cardiomyocytes via apoptosis and necrosis [78–81]. Increased ROS was measured in cardiomyocytes isolated from hearts with hypertrophy induced by α-adrenergic agonists, namely angiotensin II, endothelin 1, norepinephrine, tumor necrosis factor, or cyclic mechanical stretch. Furthermore, induced hypertrophy could be repressed by the application of antioxidants [82–84]. ROS generation has been shown to activate diverse hypertrophic signal transduction pathways, including NF-κB, mitogen-activated protein kinase (MAPK), and protein kinase C (PKC) to stimulate hypertrophy [85–87]. SIRT3 mediates the mitochondrial ROS levels by inducing transcriptional expression of mitochondrial antioxidant enzymes by deacetylating FOXO3a transcription factor and its translocation into the nucleus [42]. In other words, SIRT3 has been well shown to participate in preventing hypertrophy by restricting ROS through activating MnSOD and catalase.

SIRT3 knockout mice are born without any significant abnormalities in their hearts; however, as they become 2 months of age, they display some indications of cardiac hypertrophic response and interstitial fibrosis, suggesting a protective role of SIRT3 against cardiac hypertrophy [42]. SIRT3 gene–removed mice have been reported to develop an accelerated age-related weakening in cardiac contractile function, which is characterized as an increase in end-diastolic volume, and are more prone to transaortic constriction-induced left ventricular hypertrophy [68, 88]. SIRT3 gene–removed mice can also display spontaneous pulmonary hypertension and have reduced oxygen consumption rate in their pulmonary artery smooth muscle cells [89]. In those knockout cells, the investigators pointed out that the expression of HIF1α, STAT3, and NFATc2 transcription factors increased, which might be responsible for the

development of this disease [89]. Knockdown of SIRT3 expression increases the vulnerability of both H9c2 cardiomyocytes and Langendorff preparations to simulate IR injury [18]. Moreover, IR injury is more pronounced in the aged hearts where SIRT3 expression is reduced, suggesting SIRT3 deficiency contributes to age-related loss of resistance to IR injury [18]. Consistently, exposure of SIRT3-deficient mouse hearts to global IR using a Langendorff-mode perfusion leads to significantly reduced postischemic recovery of cardiac function relative to wild-type mouse hearts due to both elevated mitochondrial ROS production and protein oxidation [90]. Expression of *SIRT3* is upregulated in response to stress and its overexpression has a protective role for cardiomyocytes from stress-mediated cell death by deacetylating Ku70 and preventing translocation of BAX to mitochondria [91]. Additionally, SIRT3 overexpression protects cardiomyocytes from oxidative stress by downregulating apoptosis regulator BAX and BCL-2 by inducing NF-κB transcription factor [24].

SIRT3 also has crucial roles in regulating metabolism of cardiovascular cells. SIRT3 improves mitochondrial oxidative phosphorylation for the production of ATP [47]. SIRT3 also regulates lipid metabolism by directly activating long-chain acyl CoA dehydrogenase (LCAD) enzyme activity, which diminishes lipid accumulation–induced cardiac hypertrophy [92]. In this regard, SIRT3 expression is downregulated in mice fed with high-fat diet; correspondingly, SIRT3 gene–removed mouse heart displays more noticeable hypertrophy [93]. Heart isolated from SIRT3-deficient mice shows impaired mitochondrial and cardiac contractile function accompanied by increased glycolysis and decreased palmitate oxidation and oxygen consumption [88]. Additionally, in SIRT3-deficient heart cells, 84 hyperacetylated mitochondrial proteins including enzymes for fatty acid metabolism, several subunits of electron transport chain, and enzymes involved in the Krebs cycle have been identified, proposing the importance of SIRT3 in maintaining a stable myocardial energy status [88].

Exogenous SIRT3 expression decreases mitochondrial ROS production and improves respiratory capacity in vitro [94, 95]. In recent years, increasing numbers of pharmacological agents to stimulate the expression or activity of SIRT3 to support a healthy cardiac function have been reported. Resveratrol, which is a general SIRT activator, is proposed to have a cardioprotective effect by decreasing the levels of mitochondrial ROS through upregulation of SIRT3 expression [96]. Resveratrol activates AMPK-PGC-1α, which activates the binding of ERRα to the SIRT3 promoter and increases SIRT3 mRNA transcription. Increased SIRT3 expression in the mitochondria in turn increases the deacetylation and activation of antioxidant enzymes, primarily MnSOD, and stimulates ATP synthesis to contribute to reduction in oxidative injury in endothelial cells [96]. In a recent study, it has been reported that adjudin, which is a lonidamine analog, upregulated the expression of SIRT3 and consequently protected cells against oxidative damage by eliminating ROS [97]. This agent might also have a cardioprotective potential.

In addition to resveratrol, other agents use the same signaling pathway to support cardioprotection. Melatonin has been reported to have an important cardioprotective action, which also uses AMPK-PGC-1α-SIRT3 signaling pathway. The investigators of the study reported that the protective effect of melatonin on diabetic myocardial IR injury is prevented by silencing SIRT3 expression [98].

Honokiol, which is a polyphenol derived from magnolia tree, lessens cardiac hypertrophy and fibrosis by activating SIRT3 and protects cardiomyocytes from doxorubicin-induced cell destruction and death by promoting mitochondrial fusion and limiting mitochondrial ROS levels and mtDNA damage [99, 100]. Adenovirus-mediated overexpression of SIRT3 might decrease pathogenesis of cardiovascular diseases by inhibition of Dox-induced cardiac hypertrophy and mitochondrial defects. Overexpression of the transcriptional cofactor receptor-interacting protein 140 (RIP140) increased cardiomyocyte hypertrophy and decreased ATP production along with mitochondrial dysfunction by decreasing the expression of SIRT3 in neonatal rat cardiomyocytes [101]. Repression of SIRT3 expression by RIP140 is dependent on ERRα [101]. A hexokinase inhibitor, 2-deoxy-d-glucose, administration significantly improves cardiac function and reduces myocardial apoptosis [102]. Zhen et al. pointed out that upregulation of SIRT3 expression along with SIRT1 by this agent might be important contributors to its protective action against septic cardiomyopathy [102]. Stimulation of SIRT3 expression improves the mitochondrial respiratory function and improves the cardiac function of mice. Metformin, which is a drug used for the treatment of diabetes, upregulates the expression of SIRT3 in about 8 weeks old mice with heart failure after myocardial infarction [103]. It was suggested that metformin-mediated SIRT3 upregulation and deacetylation of PGC-1α increase mitochondrial ATP production and mitochondrial oxygen consumption rates in the

SIRT3 stimulating potential cardioprotective agents	Upstream signaling of SIRT3	Direct or indirect SIRT3 substrates and targets	Potential effects of agents in cardiovascular system and cardiomyocytes	Associated references
Resveratrol	AMPK, PGC-1α, and ERRα	MnSOD, IDH2, GSH-Px, FOXO3a	Scavenges mtROS	[96]
Melatonin	AMPK and PGC1α	MnSOD, NRF1, TFAM, cytochrome c	Scavenges mtROS, stimulates mitochondrial biogenesis, and reduces apoptosis	[98]
Honokiol	N/A	MnSOD, OGG1, MFN1, OPA1, Ku70, BCL-2, BAX, NF-κB	Scavenges mtROS, reduces apoptosis, and enhances mitochondrial fusion	[24, 91, 100]
2-deoxy-d-glucose	N/A	BAX, BAK	Reduces apoptosis	[24, 102]
Metformin	N/A	PGC-1α	Stimulates mitochondrial ATP production and oxygen consumption rates	[103]
Adjudin	N/A	IDH2	Scavenges mtROS	[96, 97]
RIP140 (SIRT3 repressing TF)	ERRα	LCAD	Increases mtROS and lipid accumulation	[92, 101]

MnSOD: manganese superoxide dismutase; IDH2: isocitrate dehydrogenase; Forkhead box O 3a (FOXO3a); LCAD: long-chain acyl-CoA dehydrogenase; AMPK: AMP-activated protein kinase; GSH-Px: glutathione peroxidase; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ERRα: estrogen-related receptor alpha; NRF1: nuclear respiratory factor 1; TFAM: transcription factor A, mitochondrial; OGG1: 8-oxoguanine glycosylase; MFN-1: mitofusin-1; OPA1: dynamin-like 120 kDa protein; Ku70; ATP-dependent DNA helicase II, 70 kDa subunit; BCL-2: B-cell lymphoma 2; NF-κB: nuclear factor kappa-light-chain enhancer of activated B cells; TF: transcription factor.

Table 1. Various agents to stimulate the expression of SIRT3 and the cardioprotective actions of SIRT3.

mouse hearts of myocardial infarction and decrease the associated damage [103]. A summary of agents to stimulate the expression of SIRT3 to support a healthy cardiac function and the possible targets of SIRT3 is presented in **Table 1**.

4. Conclusions

Cardiovascular diseases and cancer are most common causes of age-associated death around the world. SIRT3 has been shown to have essential roles in aging, longevity, and stress response since reduced expression or loss of function of SIRT3 brings about an intracellular milieu permissive for age-related illnesses. The mechanisms of how SIRT3 protects cells against cancer formation or cardiovascular diseases are not well understood because of the fact that SIRT3 has several targets or interacting partners in diverse pathways. Beneficial possessions of SIRT3 on cancer and particularly on various cardiovascular diseases have been reported; however, translating the modulation of SIRT3 expression using small molecules for clinical benefit is in its initial stages. Identification of agents to target SIRT3 expression to improve mitochondrial function will harvest new therapeutic strategies in the treatment of cancer and cardiovascular diseases.

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