Review

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Advances in Understanding SIRT3's Relationship With Metabolic Diseases and Related Cardiovascular Complications

Hai Yu[1], Yi Luo[1], Ziyue Zhu[1], Tingting Yu[1], Jing Xu[1,*]

[1]School of Acupuncture and Tuina, Chengdu University of Traditional Chinese Medicine, 610000 Chengdu, Sichuan, China
*Correspondence: xujing@cdutcm.edu.cn (Jing Xu)

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In recent years, the incidence of metabolic diseases, such as obesity and diabetes, has steadily increased with continuous social development. These diseases substantially compromise individuals' quality of life and impose a significant socioeconomic burden. Furthermore, chronic metabolic dysregulation readily triggers various life-threatening cardiovascular complications. As the core of energy metabolism, mitochondria are closely associated with metabolic diseases and related cardiovascular complications. Sirtuin 3 (SIRT3), a mitochondrial deacetylase, regulates the majority of mitochondrial proteins through deacetylation modifications. This process enables it to be involved in various mitochondrial functions and modulate the pathological processes of metabolic diseases such as obesity and diabetes, as well as their cardiovascular complications. This review therefore focuses on SIRT3, summarizing the latest research on its relationship with metabolic diseases and related cardiovascular complications, with the aim of providing a reference for future studies.

Keywords: obesity; diabetes; SIRT3

Introduction

The rising incidence of metabolic diseases (e.g., obesity, diabetes) and their associated cardiovascular complications poses a serious threat to public health security [1,2]. These diseases not only significantly reduce patients' quality of life but also impose a heavy burden on healthcare systems. Epidemiological studies indicate that at least 603.7 million obese adults worldwide [3], while 463 million people are affected by diabetes [4]. These conditions frequently coexist, synergistically accelerating cardiovascular pathology, and are widely recognized as risk factors for cardiovascular disease onset and mortality [5,6]. Additionally, these diseases, which stem from prolonged imbalances in glucose and lipid metabolism, are intrinsically linked to mitochondria. As the central regulators of energy metabolism and oxidative stress, mitochondria play a crucial role in their pathogenesis [7]. Therefore, safeguarding mitochondrial homeostasis and preserving its normal function holds immense significance for metabolic disorders like obesity and diabetes.

Recent studies revealed that the mitochondrial deacetylase Silent Information Regulator 2 Type 3 (SIRT3) dynamically modifies over 80 mitochondrial proteins, directly regulating functions, including the mitochondrial tricarboxylic acid cycle, fatty acid oxidation, and antioxidant defense [8]. Moreover, it serves as a pivotal molecular hub linking metabolic diseases to cardiovascular complications [9]. In summary, SIRT3 plays a central protective role in metabolic-cardiovascular health, and its functional deficiency represents a critical link in disease cascade progression. Therefore, given this central role, SIRT3 forms the focus of this review, which synthesizes current knowledge on obesity, diabetes, and their associated cardiovascular complications, with the aim of providing a reference for future research.

Structure and Function of SIRT3

The silent information regulator (Sirtuins, SIRTs) family comprises a class of Nicotinamide Adenine Dinucleotide (NAD(+))-dependent protein deacetylases widely distributed in mammalian cells [10]. To date, seven distinct subtypes have been identified, each with a primary subcellular localization: *SIRT1*, *SIRT6*, and *SIRT7* are found in the nucleus; *SIRT2* is located in the cytoplasm; and *SIRT3*, *SIRT4*, and *SIRT5* are concentrated in the mitochondria [11,12]. These enzymes regulate various cellular processes through the deacetylation of target proteins. These enzymes extensively participate in various biological activities through deacetylation modifications of multiple substrates. Among them, *SIRT3* has been a focus of in-depth research in recent years. The human *SIRT3* gene is localized on chromosome 11p15.5 and is translated into a precursor protein containing 399 amino acids [13]. This precursor protein contains an N-terminal mitochondrial targeting se-

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quence (MTS) and a C-terminal catalytic domain. The MTS guides the *SIRT3* precursor across the mitochondrial membrane into the mitochondrial matrix under specific conditions. Upon entering the mitochondria, the MTS is cleaved and removed by mitochondrial proteases, ultimately yielding the mature SIRT3 protein composed of 242 amino acids with a relative molecular mass of approximately 28 kDa [14]. The mature SIRT3 structure comprises two catalytic domains of differing sizes, representing the conserved sequence typical of the sirtuin family. The larger domain features an inverted Rossmann fold for NAD(+) binding, while the smaller domain consists of helical structures and a zinc-binding sequence [15]. The interdomain cleft serves as the primary binding site for acetylated substrates. Mutations at these sites abolish the deacetylase's catalytic activity [16].

As the primary mitochondrial deacetylase, SIRT3's biological functions are closely linked to core mitochondrial physiology, regulating multiple critical processes, including energy metabolism, oxidative stress balance, and cell survival. In energy metabolism regulation, SIRT3 modifies key metabolic enzymes such as isocitrate dehydrogenase 2 (IDH2) [17], succinate dehydrogenase (SDH) [18], and long-chain acyl-CoA dehydrogenase (LCAD) [11], thereby promoting glucose and lipid metabolism. It also modulates oxidative phosphorylation by modifying Complex I, Complex II, and Complex V of the electron transport chain (ETC) [14]. Although mitochondria serve as the primary site for reactive oxygen species (ROS) production, excessive ROS accumulation leads to oxidative stress damage. SIRT3 expression increases with heightened oxidative stress, thereby promoting mitochondrial function by regulating antioxidant processes [19]. It enhances the activity of superoxide dismutase 2 (SOD2) through deacetylation, promoting the clearance of superoxide anions [20]. Concurrently, its deacetylation modification of manganese superoxide dismutase (MnSOD) enhances its capacity to scavenge excess ROS, thereby protecting cells from oxidative stress damage [21].

In summary, as a pivotal regulator of mitochondrial function, SIRT3 plays an irreplaceable role in maintaining cellular energy homeostasis and oxidative stress balance by integrating metabolic and stress signals. Elucidation of its molecular mechanisms provides potential therapeutic targets for the prevention and treatment of related diseases.

The Role of SIRT3 in Metabolic Diseases

Metabolic diseases typically involve a prolonged course, during which metabolic processes, such as glucose metabolism, fatty acid metabolism, and amino acid metabolism, gradually become imbalanced within the body. This process ultimately leads to the development of obesity, diabetes, liver disease, and kidney disease [11]. Mitochondria, as the core of energy metabolism, are responsible for maintaining cellular energy levels and are closely involved in physiological processes such as energy production, metabolism, apoptosis, and intracellular signaling [22]. The dysfunction of mitochondria is one of the key mechanisms underlying the onset of metabolic diseases [7]. As previously described, SIRT3 is a crucial mitochondrial deacetylase directly involved in the acetylation modification of over eighty mitochondrial proteins, which implies SIRT3 can regulate nearly all mitochondrial biological functions [23], and assist mitochondria in maintaining homeostasis. Consequently, as a key mitochondrial regulator, SIRT3 exerts a central effect on the development and progression of metabolic diseases.

SIRT3 and Obesity

Mammalian bodies contain two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT primarily stores excess energy in the form of triglycerides, while BAT converts stored energy into heat for thermoregulation. Under cold exposure or specific stimuli, the number of mitochondria in WAT significantly increases, transitioning WAT to BAT and releasing stored energy. Consequently, promoting BAT formation represents a major direction in current mechanism research for obesity treatment [24,25]. Research has revealed [26] that SIRT3 deficiency in endothelial cells leads to increased acetylation of fatty acid synthase (FASN), inducing caspase-1-mediated pyroptosis, thus disrupting normal fatty acid metabolism and adipocyte function, accelerating the conversion of BAT to WAT induced by a high-fat diet, and consequently contributing to obesity. This suggests SIRT3 plays a crucial role in adipose tissue conversion, and its underlying mechanisms have been extensively explored. Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) is a key regulator of mitochondrial biogenesis, driving mitochondrial DNA transcription and replication to promote mitochondrial formation [27]. Research indicates [28] that increased SIRT3 activity enhances PGC-1α function through deacetylation, thereby promoting mitochondrial biogenesis, inducing WAT browning, and significantly reducing body weight in mice. Notably, another study found that promoting PGC-1α also enhances SIRT3 activity [29] and improves obesity symptoms, as PGC-1α induces SIRT3 expression by coactivating Estrogen-Related Receptor α (ERRα) [30]. Thus, a positive feedback loop exists between SIRT3 and PGC-1α, providing insights for identifying therapeutic targets against obesity. Furthermore, SIRT3's role in protecting adipose tissue morphology and function to mitigate obesity is also associated with maintaining mitochondrial calcium homeostasis [31], reducing inflammatory interactions between adipocytes and macrophages [32], and enhancing oxidative metabolism [33].

SIRT3 and Diabetes

Impairment of pancreatic β-cell function and number is a key pathogenic factor in diabetes onset, often resulting from abnormal β-cell apoptosis or senescence under metabolic stress. In recent years, β-cell dedifferentiation has emerged as a novel contributor to β-cell exhaustion. This process involves mature β-cells losing their original structure and function under diabetic metabolic stress and gradually reverting to an undifferentiated state [34]. SIRT3 is a key regulator of cellular metabolism and survival [35] and is closely involved in the differentiation of multiple cell types [36,37]. Furthermore, research indicates that SIRT3 is one of the critical factors in fibroblast dedifferentiation [38]. Therefore, SIRT3 may participate in the β-cell dedifferentiation process. Nie *et al.* [39] found that downregulation of SIRT3 exacerbates the dedifferentiation of pancreatic β-cells. This effect may be linked to SIRT3 deficiency, which reduces Forkhead box O1 (FoxO1) deacetylation and subsequently impairs its transcriptional activity. Another study revealed that SIRT3 can prevent β-cell dedifferentiation by inhibiting the expression of both autocrine motility factor (Autotaxin, ATX) and lysophosphatidic acid (LPA) [40].

Given their limited antioxidant capacity, pancreatic β-cells are frequently susceptible to damage from excessive ROS. Thus, oxidative stress represents another critical factor in β-cell injury, beyond abnormal dedifferentiation. Clinical studies indicate that diabetes patients often exhibit excessive β-cell damage induced by oxidative stress [41]. As previously mentioned, SIRT3, acting as a pivotal regulator of mitochondrial function, effectively eliminates excess ROS through deacetylation modifications. Consequently, SIRT3 can modulate the onset and progression of diabetes based on its antioxidant capacity. Research indicates [42] that SIRT3 deficiency significantly elevates oxidative stress levels, activates the Jun N-terminal Kinase (JNK) signaling pathway, and induces severe β-cell damage. In contrast, increasing SIRT3 levels partially reverses oxidative stress-induced β-cell dysfunction. Furthermore, elevating SIRT3 expression enhances antioxidant enzyme activity (e.g., SOD2) and inhibits apoptosis-related proteins (e.g., cleaved Caspase-3, Bax), thereby mitigating excessive β-cell loss [43].

Although most studies indicate that SIRT3 deficiency is a critical factor in diabetes development, some research suggests that inhibiting SIRT3 expression may also alleviate diabetic symptoms. Researchers used berberine to suppress SIRT3 expression and found that the AMP-activated protein kinase (AMPK) pathway responsible for energy metabolism was activated, thereby promoting cellular glucose uptake and gluconeogenesis [44]. In contrast, Wu *et al.* [45] reported that promoting the AMPK/SIRT3-PGC-1α axis could also inhibit gluconeogenesis and enhance glucose metabolism and uptake. This apparent contradiction between the two studies may be due to the differences in the timing of their interventions during diabetes progression.

The Role of SIRT3 in Cardiovascular Complications of Metabolic Diseases

Metabolic diseases result from prolonged abnormalities in the body's energy metabolism, often adversely affecting various organs and tissues. Among these, damage to the heart is particularly prominent, leading to structural and functional impairments such as myocardial hypertrophy, myocardial ischemia, increased interstitial fibrosis, and cardiac remodeling [46]. Although intrinsically connected to metabolic diseases, SIRT3 has recently been shown to play a pivotal role in cardiac function. The heart ranks among the human body's tissues with the highest metabolic rates [47], necessitating a robust energy metabolism regulatory network. Heart relying almost exclusively on mitochondrial oxidative phosphorylation to fuel its continuous contractile function [48]. Therefore, maintaining mitochondrial integrity is paramount for cardiovascular health. As the primary deacetylase within mitochondria, SIRT3 is a master regulator of cardiac energy homeostasis, governing key enzymes involved in fatty acid oxidation, the Tricarboxylic Acid Cycle (TCA cycle), and electron transport chain activity [49]. Furthermore, SIRT3 orchestrates critical antioxidant defenses by activating enzymes like Mn-SOD, protecting cardiomyocytes from oxidative damage [50]. Given this central role, a decline in SIRT3 function directly compromises mitochondrial performance, leading to energy deficits and increased oxidative stress, hallmarks of cardiac pathology. Indeed, numerous studies have demonstrated that SIRT3 deficiency exacerbates pathological cardiac hypertrophy, accelerates the progression to heart failure, and worsens the outcomes of diabetic cardiomyopathy [50,51]. Consequently, the crucial role of SIRT3 extends beyond general metabolic diseases to the fundamental pathophysiology of related cardiovascular disorders.

In the following sections, we will systematically explore the protective roles of SIRT3 across a spectrum of major cardiovascular complications of metabolic diseases. Our discussion begins at the cellular and tissue levels, examining its impact on specific cardiomyopathies and cardiac hypertrophy as direct responses to metabolic stress. We will then broaden our focus to its influence on heart failure, a common endpoint for various cardiac insults. Subsequently, we will discuss SIRT3's crucial functions in the vasculature, focusing on its role in mitigating atherosclerosis and hypertension, which are major contributors of systemic cardiovascular deterioration.

SIRT3 and Endothelial Dysfunction/Atherosclerosis

In metabolic diseases, obesity and diabetes are key drivers of vascular injury. Both conditions can damage the vascular endothelium through abnormal adipokines, triggering chronic inflammation, insulin resistance, oxidative stress, and other factors that lead to endothelial dysfunction [52–54]. The disruption of the endothelial barrier and imbalance in vasomotor function further promote the progression of atherosclerosis [55], establishing a crucial pathological basis for the development of cardiovascular complications. Research has revealed [56] that SIRT3 deficiency leads to a significant reduction in nitric oxide (NO) levels within vascular endothelial cells (NO stimulates vasodilation and is used to monitor cardiovascular function), resulting in markedly diminished vasodilatory capacity. Regarding the underlying mechanisms, researchers appear to have focused their attention on oxidative stress. Hua *et al.* [57] demonstrated that activating SIRT3 significantly reduced oxidative stress levels and suppressed excessive ROS production, thereby improving the dilation function of thoracic aortic endothelial cells in diabetic mice. Conversely, SIRT3 activators had no these effects in SIRT3 knockout mice, further confirming SIRT3's critical role in protecting endothelial cell function under hyperglycemic conditions. Further elucidating the mechanism, Han *et al.* [58] examined the role of the SIRT3/AMPK pathway in mitigating oxidative stress responses and protecting against diabetes-induced endothelial cell damage.

Given that endothelial dysfunction marks the onset of atherosclerosis, SIRT3's protective effects on endothelial cells suggest that it may also alleviate atherosclerosis induced by metabolic diseases. A study involving 95 Type 2 Diabetes Mellitus (T2DM) patients revealed significantly lower serum SIRT3 levels in those with atherosclerosis compared to those without [59], suggesting SIRT3 may play a critical role in atherosclerotic progression. This mechanism may be related to SIRT3's ability to reduce endothelial cell apoptosis and oxidative stress [60].

SIRT3 and Cardiomyopathy

Cardiomyopathy represents an adaptive response involving structural remodeling when the heart faces sustained abnormal loads. Pathological cardiomyopathy often arises from metabolic disorders such as obesity and diabetes [61], a process closely linked to SIRT3. Research has shown [62] that a high-fat diet significantly reduces cardiac SIRT3 expression levels, leading to marked cardiac hypertrophy and decreased myocardial vascular density, thereby impairing cardiac structure and function. Activation of SIRT3, however, resulted in a noticeable return to normal left ventricular size and wall thickness in obese mice, alongside reduced oxidative stress in cardiac mitochondria and decreased myocardial cell apoptosis [63]. Further studies indicate that SIRT3's protective effects may be mediated primarily through two mechanisms. First, it can activate the AMPK pathway to promote autophagy initiation [64]. Second, it modulates the ROS-NF-κB-MCP-1 signaling pathway, which reduces cardiac inflammation and fibrosis, thereby preventing obesity-related cardiac remodeling [65]. Diabetic cardiomyopathy (DCM), a common cardiovascular complication of diabetes, ranks among the leading causes of mortality in diabetic patients [66]. Given the close association between DCM progression and impaired glucose metabolism [67], the SIRT3's mechanisms in this pathophysiological process were extensively explored, as detailed in Table 1 (Ref. [51,68–81]).

SIRT3 and Heart Failure

Heart failure is a disease caused by impaired cardiac pumping function, most commonly occurring when structural remodeling leads to severe damage in both diastolic and systolic function [82]. It often develops in the context of obesity, diabetes, and metabolic syndrome [83]. In cardiac biopsies of obese patients, researchers observed a 46% reduction in SIRT3 levels compared to healthy individuals. This decrease in SIRT3 was positively correlated with elevated levels of brain natriuretic peptide (BNP), a quantitative indicator of heart failure, suggesting that SIRT3 deficiency may be associated with the development of heart failure in obese patients. Subsequent animal studies validated that activating SIRT3 significantly alleviates ventricular dysfunction and slows heart failure progression [84]. Another study using a pulmonary artery model associated with metabolic syndrome found that SIRT3 activates the AMPK-GLUT4 (Glucose Transporter 4) signaling pathway to lower blood glucose levels and alleviate pulmonary artery failure [85].

SIRT3 and Myocardial Infarction/Ischemia-Reperfusion Injury

Myocardial infarction is a necrotic disease caused by acute myocardial ischemia and hypoxia resulting from acute coronary artery obstruction. It is commonly triggered by atherosclerotic plaque rupture, thrombus formation, and vascular blockage [86], posing severe threats to patient health. Conditions, such as obesity and diabetes, can exacerbate myocardial injury. Research has demonstrated [87] that SIRT3 activation promotes nuclear translocation and activation of FOXO3a, increasing expression of downstream antioxidant enzymes. This effectively clears ischemia-induced oxidative stress, protecting the myocardium of obese mice from injury. In diabetes-induced myocardial infarction, SIRT3 similarly reduces mortality following acute infarction by restoring myocardial cell redox homeostasis [88]. Notably, although timely reperfusion therapy after myocardial infarction is the optimal treatment, reperfusion itself may cause lethal cardiac injury—myocardial ischemia-reperfusion injury (MIRI) [89]—and diabetes may exacerbate this damage [90]. Research indicates that activating the AMPK-PGC1α-SIRT3 axis can reduce mitochondrial oxidative stress and enhance mitochondrial biogenesis, thereby improving MIRI in type 1 diabetes [91].

Table 1. Pathogenesis of diabetic cardiomyopathy.

Relevant channels	Cardiac structural and functional parameters	References
SIRT3/RKIP-TBK1-NF-κB	Improves cardiac function, alleviates metabolic disorders, reduces myocardial fibrosis, counteracts oxidative stress, inhibits cardiomyocyte apoptosis, and reduces cardiac inflammation.	[68]
SENP1/SIRT3	Ameliorates DCM, inhibits cardiomyocyte autophagy and cell death (ferroptosis and apoptosis), and restores mitochondrial stability.	[69]
Mst1/SIRT3	Attenuates adverse left ventricular remodeling and cardiac dysfunction, enhances autophagy, reduces apoptosis, alleviates mitochondrial dysfunction, and improves mitochondrial biogenesis.	[70]
AMPK-SIRT3	Improves cardiac function (reduces LVEDD, increases LVEF and FS), attenuates oxidative stress, and inhibits myocardial fibrosis, inflammation, and cardiomyocyte apoptosis.	[71]
apelin/SIRT3	Improves mitochondrial function, reduces myocardial fibrosis, inhibits apoptosis, improves cardiac function (increases LVEF and LVFS, decreases LVESD and LVEDD), and attenuates oxidative stress.	[72]
HOTAIR/FUS/SIRT3	Attenuates pyroptosis of diabetic cardiomyocytes and inhibits the inflammatory response.	[73]
Mst1/SIRT3/Parkin	Inhibition of Mst1 promotes mitophagy, clears damaged mitochondria, improves mitochondrial function, and ameliorates the DCM phenotype.	[74]
FAK/SIRT3/ROS	Promotes cardiomyocyte apoptosis, exacerbates oxidative stress, leads to cardiac dysfunction (reduced LVEF and FS), and causes cardiac hypertrophy.	[75]
FOXO3/Mst1/SIRT3/AMPK	Alleviates cardiac dysfunction (increases LVEF and LVFS, decreases LVEDD and LVESD), reduces myocardial injury and interstitial fibrosis, inhibits inflammation, promotes autophagy, and reduces cardiomyocyte apoptosis.	[76]
SIRT3-P53/TIGAR	Disrupts HIF-α signaling pathway, alters cardiomyocyte metabolism (decreases oxygen consumption rate, increases glycolysis).	[77]
CD38-NAD+/SIRT3/FOXO3a	Prevents DCM, improves cardiac function (increases LVEF and FS), and coordinately inhibits both pyroptosis and apoptosis.	[78]
SIRT3/NLRP3	Ameliorates cardiac dysfunction, hypertrophy, fibrosis, and injury; inhibits oxidative stress, inflammasome activation, and necroptosis.	[79]
PARP1-NAD+-SIRT3	Reverses cardiac remodeling, improves mitochondrial dysfunction, and counteracts oxidative stress.	[51]
periostin/NAP1L2/SIRT3	Induces cardiomyocyte hypertrophy, oxidative damage, and inflammation; impairs BCAA catabolism, leading to cardiac dysfunction and myocardial injury.	[80]
FGF21-Sirtuin 3	Attenuates cardiac dysfunction, reduces mitochondrial damage, increases mitochondrial enzyme activity, and maintains mitochondrial integrity.	[81]

Note: Key Pathway Summary: Comprehensive analysis of these studies reveals that Sirtuin 3 (SIRT3) and its associated signaling pathways play a central role in the pathophysiology of diabetic cardiomyopathy (DCM). As a critical mitochondrial deacetylase, SIRT3 activation is consistently linked to cardioprotective effects, effectively counteracting oxidative stress, ameliorating mitochondrial dysfunction, and inhibiting inflammation and various forms of cell death (including apoptosis, pyroptosis, and necroptosis). These actions collectively reduce myocardial fibrosis and hypertrophy, ultimately leading to improved cardiac function.

Several key upstream pathways converge on SIRT3. AMPK, a crucial energy sensor, is repeatedly identified as a primary upstream activator of SIRT3; exercise and various therapeutic compounds exert their protective effects through this axis. Conversely, Mst1 frequently acts as a SIRT3 inhibitor, and its overactivation exacerbates DCM pathology. Inhibiting Mst1 restores SIRT3 activity, promoting mitophagy and the clearance of damaged mitochondria. Furthermore, a complex regulatory network involving the lncRNA HOTAIR, periostin, and the CD38/NAD+ axis also fine-tunes SIRT3 activity. These findings collectively establish that maintaining or enhancing SIRT3 activity is a key therapeutic strategy for combating DCM, primarily by suppressing downstream cell death pathways that drive the disease's progression. AMPK, AMP-activated Protein Kinase; BCAA, Branched-Chain Amino Acid; DCM, Diabetic Cardiomyopathy; FAK, Focal Adhesion Kinase; FGF21, Fibroblast Growth Factor 21; FOXO3, Forkhead box O3; FS, Fractional Shortening; FUS, Fused in Sarcoma; HIF-α, Hypoxia-Inducible Factor-alpha; lncRNA, Long non-coding RNA; LVEDD, Left Ventricular End-Diastolic Dimension; LVESD, Left Ventricular End-Systolic Dimension; LVEF, Left Ventricular Ejection Fraction; Mst1, Mammalian Sterile 20-like Kinase 1; NAD+, Nicotinamide Adenine Dinucleotide; NAP1L2, Nucleosome Assembly Protein 1-Like 2; RKIP, Raf Kinase Inhibitor Protein; ROS, Reactive Oxygen Species; SENP1, Sentrin/SUMO-specific Protease 1; SIRT3, Sirtuin 3; TIGAR, TP53-Induced Glycolysis and Apoptosis Regulator.

SIRT3 and Arrhythmia

Atrial fibrillation is a common clinical tachyarrhythmia caused by chaotic electrical activity in the atria. It is characterized by the loss of regular atrial contractions, replaced by disorganized quivering, resulting in absolutely irregular ventricular rates. This condition severely impacts cardiac function and quality of life, making it a chronic disease of significant concern in the cardiovascular field. Currently, accumulating evidence identifies metabolic disorders, particularly obesity, as risk factors for the increasing incidence of atrial fibrillation [92]. Although the exploration of the mechanism linking SIRT3 to obesity-induced atrial fibrillation remains somewhat limited, studies have demonstrated that upregulating SIRT3 levels exerts a protective effect by improving insulin resistance, activating AMPK and Ak strain transforming (Akt) signaling pathways, and simultaneously inhibiting the HIF1α signaling pathway, thereby mitigating obesity-related atrial fibrillation [93].

Discussion

SIRT3 is unequivocally a master regulator of mitochondrial function, and this review has summarized its protective roles in metabolic diseases and their subsequent cardiovascular complications. However, a simple narrative of SIRT3 as a universal protector is insufficient and overlooks a growing body of contradictory evidence. The original discussion noted some discrepancies, such as the unexpected findings in the offspring of obese mice and the nuanced effects in specific tissues [94–96]. A deeper, more systematic analysis is needed to clarify these discrepancies and chart a path for future research.

Deconstructing the SIRT3 Paradox: Context is Key

The central challenge in the SIRT3 field is understanding why its manipulation yields conflicting results. The literature suggests that this paradox is not random but is governed by several key factors.

First, the specificity of tissue and cell-type is paramount. As noted in our review, SIRT3's impact on adipose tissue conversion is complex. The seemingly contradictory finding that SIRT3 knockout in adipocytes had minimal impact on whole-body metabolism [96] can be better understood in this light. Indeed, emerging evidence indicates that SIRT3 in the central nervous system is a crucial regulator of systemic metabolism. Through its role in maintaining mitochondrial integrity and function in key hypothalamic neurons, SIRT3 directly modulates both systemic energy homeostasis and peripheral metabolic processes [96–98]. This central regulatory function provides a compelling explanation for why targeting peripheral tissues alone may yield limited or unexpected results. Furthermore, recent studies reinforced that SIRT3's role in BAT is highly dependent on the cell type; its absence in endothelial cells, but not in adipocytes themselves, drives BAT "whitening" and metabolic dysfunction [32]. This collectively highlights that whole-tissue knockout studies may mask highly specific, critical functions within distinct cell populations.

Second, the nature and stage of the metabolic stress are critical determinants of SIRT3's function. Some studies revealed that SIRT3 inhibition counterintuitively appeared beneficial. This can be partially explained by the difference between acute and chronic stress. For example, while chronic SIRT3 activation is protective against long-term high-fat diet-induced damage, in the context of acute acetaminophen-induced liver toxicity, SIRT3 can paradoxically exacerbate injury by deacetylating and activating enzymes that contribute to toxic metabolite formation [99]. This suggests that SIRT3's role can shift from protective in chronic settings to potentially detrimental in certain acute injury models.

Third, functional redundancy and compensation within the Sirtuin family offer a robust explanation for many of the null-phenotype findings. The observation that SIRT3 knockout in obese female mice did not impair oocyte quality [95] was tentatively ascribed to compensation. This hypothesis is now strongly supported by evidence showing functional overlap and crosstalk between mitochondrial sirtuins (SIRT3, SIRT4, SIRT5) and even between mitochondrial and nuclear sirtuins (e.g., SIRT1). For example, in the heart of SIRT3 knockout mice, the SIRT1-PGC-1α pathway can be compensatorily upregulated to preserve cardiac function, demonstrating a clear inter-Sirtuin communication network [100]. This compensatory network can mask the true impact of losing SIRT3 alone, thereby requiring the use of double or triple knockout models to fully dissect its unique functions.

SIRT3 as a Therapeutic Target: Promise and Pitfalls

Given its central role in mitochondrial health, activating SIRT3 remains a highly attractive therapeutic strategy for metabolic and cardiovascular diseases. Natural activators, such as Honokiol, have shown remarkable promise in preclinical models, effectively mitigating pathological cardiac hypertrophy and protecting against doxorubicin-induced cardiotoxicity [101]. Recently, novel small-molecule SIRT3 activators have also been developed and validated. For instance, 3-(2-bromo-4-hydroxyphenyl)-7-hydroxy-2H-chromen-2-one (SZC-6) was demonstrated to directly bind to and activate SIRT3, attenuating cardiac hypertrophy and dysfunction in mice through the LKB1-AMPK pathway, a protective effect that is SIRT3-dependent [102]. Similarly, the activator 2-APQC was shown to alleviate cardiac hypertrophy and fibrosis by regulating mitochondrial homeostasis through multiple mechanisms, including the mTOR-p70S6K, JNK, and TGF-β/Smad3 pathways, as well as the SIRT3-PYCR1 (Pyrroline-5-Carboxylate Reductase 1) and AMPK-Parkin axes, also in a SIRT3-dependent manner [103]. These studies further underscore the therapeutic potential of targeting SIRT3 activation.

However, the path to clinical translation is fraught with challenges. Foremost among these is the issue of specificity. The high degree of structural homology among Sirtuin family members makes the development of highly specific SIRT3 activators difficult. Consequently, many existing compounds, including natural products like resveratrol, are known to affect multiple Sirtuins, leading to potential off-target effects that complicate the interpretation of results and pose safety risks [104,105].

Furthermore, the "double-edged sword" nature of SIRT3 in cancer presents a significant safety concern. While SIRT3 often acts as a tumor suppressor, in certain contexts, it can promote the survival of cancer cells and contribute to chemoresistance [106]. Therefore, any systemic, long-term SIRT3 activation therapy must be carefully evaluated for its potential to promote tumorigenesis, especially in high-risk populations.

Future Perspectives and Unanswered Questions

To advance the field, future research must transcend simplistic gain- or loss-of-function studies and embrace the complexity of SIRT3 biology. This entails moving beyond systemic models and prioritizing the development of tissue- and cell-type-specific modulators. Rather than systemic activation, designing strategies that can specifically boost SIRT3 activity in the heart, liver, or even specific neuronal populations could maximize therapeutic benefit while minimizing off-target risks. Second, we must unravel the complete SIRT3 "deacetylome" in different disease states. Using advanced proteomics, we need to identify the full spectrum of SIRT3 substrates in a context-dependent manner, which will reveal the most critical pathway in a given pathology, and could uncover novel, more "druggable" downstream targets. Finally, the interplay between SIRT3 and other mitochondrial quality control mechanisms, such as mitophagy and mitochondrial dynamics, warrants in-depth investigation. Understanding how SIRT3 activation or inhibition influences these interconnected processes is crucial for designing holistic therapies that truly restore mitochondrial homeostasis. Addressing these key questions will pave the way for translating the immense therapeutic promise of SIRT3 into clinical realities.

Conclusion

SIRT3 has emerged as a critical guardian of mitochondrial health and a central node in integrating metabolic status to cardiovascular function. This review has delineated its protective roles against key metabolic diseases, including obesity and diabetes, and traced its influence on a spectrum of subsequent cardiovascular complications, from cardiomyopathy and hypertrophy to heart failure and atherosclerosis. However, the functional landscape of SIRT3 is nuanced. Apparent contradictory findings in the literature underscore that its function is highly context-dependent, influenced by tissue specificity, the nature of the metabolic stress, and intricate compensatory networks within the Sirtuin family. Despite this complexity, the potent ability of SIRT3 to restore mitochondrial homeostasis solidifies its standing as a highly promising therapeutic target. Future research focused on developing specific, context-aware strategies to modulate SIRT3 activity holds the potential to unlock a new generation of therapies designed to combat the intertwined epidemics of metabolic and cardiovascular disease.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, HY and JX; methodology, HY; software, HY; validation, HY, JX, TTY and ZYZ; formal analysis, HY; investigation, HY; resources, JX; data curation, YL; writing—original draft preparation, HY and ZYZ; writing—critically review and editing, JX, YL and TTY; visualization, YL; supervision, JX; project administration, JX. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity are addressed.

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Conflict of Interest

The authors declare no conflict of interest.

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