Published in final edited form as:

J Mol Cell Cardiol. 2011 October ; 51(4): 614–618. doi:10.1016/j.yjmcc.2011.01.008.

Emerging roles of SIRT1 deacetylase in regulating cardiomyocyte survival and hypertrophy

Nagalingam R Sundaresan, Vinodkumar B. Pillai, and Mahesh P. Gupta*

Department of Surgery, Committee on Cellular and Molecular Physiology, University of Chicago, Chicago, IL., USA

Abstract

Calorie restriction is considered to be the best environmental intervention providing health benefits to mammals. The underlying mechanism of this intervention seems to be controlled by a group of NAD-dependent deacetylases, collectively called sirtuins. In mammals there are seven sirtuin analogues, SIRT1 to SIRT7. The founding member of this family, SIRT1 is shown to protect cardiomyocytes from apoptosis and age-dependent degeneration in a dose dependent manner—protecting cells at low doses but showing detrimental effects at high doses. Studies performed with over expression or knockdown of SIRT1 indicated that though it protects cells from oxidative stress and ischemia-reperfusion injury, it promotes hypertrophy of cardiomyocytes. Activation of endogenous SIRT1 by resveratrol also displayed pro-survival and pro-hypertrophic activity of SIRT1. In this article we review recent findings documenting the role of SIRT1 in regulating cardiac myocyte growth and survival under stress, and the proposed mechanism behind its cardio protective effects. We also briefly discuss two other sirtuin analogues which have been shown to have cardioprotective effects.

Introduction

Incidence of cardiovascular diseases is increasing at an alarming rate throughout the world. According to World Health Report 2010, Cardiovascular diseases (CVD) accounts for 17.1 million or 29% of global deaths a year. It is predicted that this number will rise to 23.6 million by 2030. (<http://www.who.int/mediacentre/factsheets/fs317/en/index.html>). In the United States heart failure is responsible for almost 1 million hospital admissions and 40,000 deaths annually. One major cause for this disturbing rise in CVD is our sedentary life style and recent change in dietary habits. Availability and consumption of high-calorie-high-fat diets increases the risk for atherosclerosis, diabetes, obesity, heart failure and other cardiovascular associated diseases. In contrast to this, calorie restriction is shown to extend life span by reducing ageing associated diseases, such as heart failure, renal dysfunction, neurodegenerative diseases, diabetes and cancer [1,2]. In the heart, modest calorie restriction improved cardiac contractile function, myocardial remodeling and prevented diastolic dysfunction [3]. Since calorie restriction is practically hard to follow in our day-to-day life, considerable research has been done to delineate the cell-signaling pathways involved in it, so that manipulation of implicated genes by its small molecule activators could mimic the

© 2010 Elsevier Ltd. All rights reserved.

*Corresponding author: Mahesh P. Gupta, Department of Surgery, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL., USA 60637, mgupta@surgery.bsd.uchicago.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

effects of calorie restriction. Though not free from controversies, several studies in this field suggest that a mammalian analog of yeast sir2 (silent information regulator 2), SIRT1 and its small molecular activator, resveratrol, can mimic the beneficial effects of calorie restriction [4-7]. Because aging is associated with reduced heart function and increased risk of cardiac diseases, studies evaluating the role of SIRT1 and resveratrol in preventing cardiovascular diseases have gained considerable attention and debate, hence are the focus of this review.

Expression and localization of SIRT1 in the heart

The mammalian genome encodes seven sirtuin isoforms SIRT1-SIRT7, which are ubiquitously expressed and possess a highly conserved deacetylase domain, first identified in the founding yeast Sir2 protein [8]. Sirtuins belongs to class-III group of HDACs, which, unlike other class of HDACs, need NAD for their deacetylation reaction. Because of their dependency on NAD, activity of sirtuins is highly sensitive to fluctuations in cellular NAD/NADH ratio. It has been shown that increased cellular NAD content elevates the enzymatic activity of sirtuins, whereas high NADH and nicotinamide levels do the opposite [9]. SIRT1 regulates a wide array of cellular processes that are crucial to cell survival, apoptosis, cell growth, cell senescence and metabolism, by deacetylating histones and a growing list of non-histone proteins [4].

SIRT1 is expressed in all mammalian cells and was originally identified as a nuclear protein [10]. However, recent studies showed that sub cellular localization of SIRT1 differs from cell to cell. While some cells showed nuclear localization of SIRT1, others expressed it either both in the nucleus and in the cytoplasm or in the cytoplasm alone. In the heart, nuclear and cytoplasmic localization of SIRT1 was found to be regulated developmentally and during stress of the heart [11]. In the mouse embryonic heart at E10.5 and E12.5 day of age, when four chambered heart appears, high level of SIRT1 was found in the nucleus of myocytes in both atria and ventricles. Expression of SIRT1 in the heart declines further with organogenesis. At E16.5 day SIRT1 levels in the heart were 21% of E12.5 day, and after birth they remain constant up to 27 months of age. In the adult heart of rodents, SIRT1 is localized mainly in the cytoplasm and moves to nucleus up on stress. Nuclear localization of SIRT1 in cardiomyocytes was inhibited by use of a PI3K inhibitor LY294002, which also blocked Akt activation, thus suggesting a possible role of PI3K/Akt mediated phosphorylation in the nuclear translocation of SIRT1 [12]. Likewise, JNK1-mediated phosphorylation of SIRT1 also promotes its importation into the nucleus [13]. This importation of SIRT1 to the nucleus was found to be essential for its cytoprotective effects against oxidative stress through activation of MnSOD [12], suggesting that phosphorylation mediated shuttling in and out of nucleus could be one mechanism by which SIRT1 activity is being regulated (Figure 1). This study also reported the presence of nuclear SIRT1 in different models of heart failure, including failing hearts of TO-2 hamsters, post myocardial infarction in rats and dilated cardiomyopathy in patients [12]. Because, the nuclear presence of SIRT1 is a feature of the fetal heart and SIRT1 localizes into nucleus under pathologic conditions, it is intriguing to think that nuclear translocation of SIRT1 could have a role in the activation of fetal gene program associated with the evolution of cardiac hypertrophy.

Gain of Function of SIRT1 in the heart

An Initial study carried out with over expression of SIRT1 in cardiomyocytes showed that it protects cells from death in response to serum starvation, but at the same time causes an overall increase in size of cardiomyocytes [14]. This study also showed that blocking of SIRT1 activity with inhibitors increased the propensity of cardiomyocytes to death, but prevented hypertrophy of myocytes in response to stress stimuli, thus implying that though cytoprotective, SIRT1 promotes cardiomyocyte growth under stress conditions. These

observations are supported by other reports where increased SIRT1 levels were found in hypertrophied and failing hearts [15,16]. Studies performed with cardiac-specific SIRT1 transgenic mouse model showed that SIRT1 exhibits hormesis; that is, depending on the magnitude of SIRT1 expression; it can be beneficial or harmful. A low to moderate expression of SIRT1 (2.5-7.5 fold over endogenous levels) was found to be protective against age dependent increase in cardiac hypertrophy, apoptosis, and cardiac dysfunction; whereas 12.5 fold over expression of SIRT1 induced dilatation, hypertrophy and cardiac failure [17]. A low level of SIRT1 over expression was also shown to reduce infarct size and improve cardiac functions in a mouse model of myocardial infarction [18]. These observations strengthen the perception that SIRT1 is pro-growth and pro-survival molecule for cardiomyocytes and hence its expression need to be tightly controlled to obtain its desirable effects.

Loss of Function of SIRT1 in the heart

SIRT1 homozygous knockout mice in an inbred genetic background exhibit severe developmental defects in the heart and they mostly die after birth [19,20]. However, SIRT1 knock-out mice developed on crossbred backgrounds are viable [19,21]. So far no studies have reported any cardiac phenotype in these mice. Similarly, cardiac-specific deletion of SIRT1 does not show any obvious phenotypes at basal conditions. These findings suggest that SIRT1 is dispensable for the survival of adult cardiomyocytes. However, these mice were more susceptible to cell death induced by ischemia/reperfusion injury [18]. Our unpublished data show that whole body SIRT1 knockout mice have smaller heart than their wild-type littermates, and are resistant to develop cardiac hypertrophy induced by hypertrophic agonists. These mice also show reduced activation of fetal gene program, lack of cardiomyocyte hypertrophy and impaired Akt-signaling following infusion of hypertrophic agonists, thus suggesting that SIRT1 is needed for the induction of cardiac hypertrophic program.

Resveratrol mediated activation of SIRT1 in the heart

The effect of endogenous SIRT1 activation achieved by resveratrol treatment has been also studied in different models of cardiac hypertrophy. Resveratrol treatment limits phenylephrine induced hypertrophic response of isolated cardiomyocyte cultures [22]. Resveratrol also reduced fatty lesions, cardiac muscle vacuolization, degeneration and inflammation in mice on a high calorie diet [23]. Pre-feeding of rats for 14 days with resveratrol showed protection of hearts from deleterious effects of pressure over load mediated cardiac hypertrophy [24]. Likewise, resveratrol feeding improved cardiac function in diabetic mice [25]. Further, oral administration of resveratrol to TO-2 hamsters suppressed fibrosis, preserved cardiac function, and significantly improved survival [12]. All these studies correlated the cardio-protective effects of resveratrol with its ability to activate SIRT1. Because resveratrol has many off target effects unrelated to SIRT1 and negatively regulates growth factors and pro-inflammatory cytokines [7,23], it remains to be tested whether cardioprotective effects of resveratrol are solely mediated by SIRT1 or they are product of combinations of alternative mechanisms. Nevertheless, based on the data available so far it appears that resveratrol treatment may be beneficial in the management of cardiac hypertrophy and cell death.

SIRT1 and angiogenesis

An adult heart is fully equipped to undergo hypertrophy in response to increased work load. During initial stages of stress this is an adaptive response, which provides a short term mechanism for decreasing ventricular wall stress and improving heart function. However, during prolonged intervals of stress this program becomes maladaptive, resulting in myocyte

cell death, fibrosis, ventricular dilation and transition to maladaptive cardiac hypertrophy, which is a precursor to heart failure. It has been shown that disruption of coordination between cardiac muscle growth and coronary angiogenesis invokes oxidative stress, which contributes to the progression of adaptive cardiac hypertrophy to pathological hypertrophy and eventually to heart failure [26]. SIRT1 has been identified as a critical regulator of sprouting angiogenesis during vascular growth [27]. Knockdown of SIRT1 resulted in near total loss of sprouting angiogenesis in vitro. Furthermore, endothelial cell specific SIRT1-knockout mice showed impaired ability to form new blood vessels in ischemic tissues, suggesting that increased activation of SIRT1 is needed to promote compensatory angiogenesis, and its reduced activity causes increased oxidative damage to the myocardium. Similarly, resveratrol pretreatment induced angiogenesis in a rat myocardial infarction model [28]. Contrary to this report, several other studies have demonstrated that resveratrol suppresses angiogenesis in tumor models and thus prevents tumor growth [29].

Apart from the role of SIRT1 in regulating angiogenesis, its activity is also critical for the maintenance of endothelial cell homeostasis. Endothelium covers the inner surface of the vascular system and its dysfunction is associated with increased cell permeability, apoptosis and inflammation leading to plaque formation [30]. Nitric oxide synthesized from endothelial cells promotes vasodilatation and provides atheroprotective effects. This endothelial nitric oxide is produced by endothelial nitric oxide synthase (eNOS), which is a target of SIRT1. SIRT1 deacetylates eNOS thereby stimulating eNOS activity and increasing endothelial nitric oxide (NO) synthesis; whereas inhibition of SIRT1 blocked endothelium-dependent vasodilatation and NO production [31]. Consequently, SIRT1 activation was associated with decreased atherosclerosis [32]. Additionally, several other studies have demonstrated that resveratrol activates eNOS and NO production conferring protection of heart from ischemia reperfusion injury [33]. Thus, besides regulating cardiomyocyte growth, SIRT1 activation also holds potential to maintain coordinated induction of coronary angiogenesis.

SIRT1 and signaling pathways

A wide range of stimuli can promote hypertrophic growth of the heart via a complex network of signaling mechanisms. There exist a considerable cross talk and redundancy in pathways that lead to maladaptive cardiac hypertrophy. One of the well documented targets of SIRT1 in cardiomyocytes is FOXO. FOXO is the mammalian homologue of Daf16 implicated in the SIRT1 mediated longevity of *C. elegans* [34]. In mammals there are four evolutionary conserved FOXO family members, FOXO1, FOXO3, FOXO4 and FOXO6. They control various cellular processes like cell cycle arrest, ROS production, DNA repair and apoptosis [35]. SIRT1 regulates FOXO activity either positively or negatively depending on the target gene or cell type [35]. SIRT1 deacetylates and activates FOXOs to synthesize anti-oxidants like MnSOD and catalase, thereby promoting cellular resistance against oxidative stress [36,37]. SIRT1 transgenic mice displayed retarded aging phenotype in the heart due to its ability to induce MnSOD and catalase expression through activation of FOXOs [17]. In the mouse myocardial infarction model, SIRT1 mediated upregulation of FOXO prevented cellular injury by activating pro-survival factors like thioredoxin-1 and Bcl-xL and suppressing the activity of pro-apoptotic molecules like Bax and cleaved caspase 3 [18]. Similarly, resveratrol-mediated activation of SIRT1 increased MnSOD levels in cardiomyocytes and suppressed fibrosis, preserved cardiac function and significantly improved survival of TO-2 hamsters [12]. In addition, there are several other studies which have proposed alternate mechanisms for SIRT1 mediated cardiac protection. These mechanisms are summarized in table 1. Our recent studies also suggest an intriguing connection between SIRT1 and Akt. We found that SIRT1 activates PI3K/Akt signaling to promote the cardiac hypertrophic response [38], and Akt inhibitors can prevent SIRT1-

mediated cardiac hypertrophy, thus suggesting that many of the cytoprotective and pro-growth effects of SIRT1 may be mediated through its ability to activate Akt signaling. All these studies suggest that SIRT1 is a central knot connecting a variety of mechanisms and pathways in the heart and hence a potential therapeutic target to manage cardiac growth and function.

Other sirtuin analogues implicated in regulation of cardiac hypertrophy

Two other sirtuins, SIRT3 and SIRT7, have been shown to be beneficial in resisting maladaptive transformations in the heart. SIRT3 was originally identified as a mitochondrial protein; however, recent studies from us and others have shown that it is also localized in the nucleus and cytoplasm [39-41]. SIRT3 levels were found to be highly sensitive to cardiac muscle growth. SIRT3 levels increased during initial stages of mild cardiac hypertrophy but were significantly decreased in severe form of cardiac hypertrophy [42]. Consequently, SIRT3 knock out mice, though looked normal at birth spontaneously developed cardiac hypertrophy at 8 weeks of age. These mice showed extreme hypertrophic response when challenged with hypertrophic agonists and displayed reduced activity of anti-oxidants MnSOD and catalase. On the other hand transgenic mice having cardiac-specific expression of SIRT3 effectively blocked agonist mediated cardiac hypertrophy. This SIRT3-mediated cardiac protection was mediated through activation of Foxo3a-dependent transcription of MnSOD and catalase, as well as by suppressing the ROS-mediated Ras activation and the downstream MAPK/ERK and PI3K/Akt signaling pathways [42]. Because cardiomyocyte hypertrophy is associated with reduced intracellular levels of NAD [43], in a later study we examined the role of exogenous NAD in agonist-induced hypertrophy in mice. Exogenous NAD treatment blocked the over-activation of Akt signaling and maintained the activity of anti-hypertrophic LKB1-AMPK signaling in the heart, which prevented subsequent over activation of mTOR [44]. In this study we also found that contrary to published cardio protective effects of SIRT1, the anti hypertrophic effects of NAD were mediated through activation of SIRT3 [44]. We also observed that in the heart, it was SIRT3 and not SIRT1, as reported in other tissues, which was able to deacetylate and activate LKB1, the upstream kinase of AMPK and thereby blocking over activation of Akt signaling during hypertrophy [44]. These studies suggest redundancy in SIRT1 targets and the obligatory role of SIRT3 in protecting the heart from developing maladaptive cardiac hypertrophy.

Comparatively less is known about other sirtuin analogue SIRT7 which is also implicated in protecting the heart from stress [45]. SIRT7 is the only mammalian sirtuin analogue that is associated with nucleoli and condensed chromosome [10]. It binds to RNA polymerase-I and activate ribosomal (r) RNA-encoding DNA (rDNA) transcription [46]. SIRT7 deficient mice showed increased inflammation and inflammatory cardiomyopathy, which was associated with increased pro-hypertrophic Akt signaling in the heart [45]. Similar to SIRT1, lack of SIRT7 also resulted in increased acetylation and activation of p53, and corollary, the primary cause of increased apoptosis observed in these hearts [45]. More work utilizing cardiac specific knockout and transgenic mice need to be performed to further understand the precise role of SIRT7 in the heart.

Future perspectives

Even though vast amount of literature is available regarding the role played by SIRT1 in the regulation of cellular functions, only a handful of studies addressed its effect on the heart. Myocardial Gene expression in the heart has been shown to be regulated in a circadian fashion [47]. SIRT1 is a core component of circadian clock signaling pathway. SIRT1 directly associates with CLOCK to get recruited to CLOCK/BMAL1 complex, where it deacetylates BAML1 and histone H3, thereby regulating the expression of several clock

genes [48,49]. Because cardiac specific SIRT1 transgenic mice studied, so far, utilized the α -MHC promoter which is sensitive to hypertrophic stimuli, the exact effect of SIRT1 in the heart is somewhat speculative. The role of SIRT1 in embryonic development and its negative role in skeletal muscle differentiation are well established [50], but its role in cardiomyocyte and cardiac fibroblast proliferation and differentiation is never studied. Several studies suggest the existence of cardiac stem cells, whose maintenance and regeneration is critical for maintaining cardiac homeostasis [51]. In this context it is valuable to study the role SIRT1 plays in growth and differentiation of these stem cells. Currently, activation of SIRT1 by transgene or by its small molecular activator resveratrol is ineffective in extending lifespan of mammals that were not subjected to stress, suggesting that the mechanisms underlying the beneficial effects of calorie restriction is not yet completely understood. During mild cardiac stress, along with SIRT1 other sirtuins such as SIRT3 and SIRT6 are also up regulated. However, it is not known whether these analogues coordinate with each other or they work independently to protect the heart from stress stimuli. Resveratrol remains the only small molecule activator of SIRT1 that is widely studied in the heart. SIRT1 activators more potent than resveratrol have been reported however, their effects in the heart have not been yet studied. Sirtuins are relatively newer class of molecules, which are emerging as key regulators of a variety of cellular functions. How sirtuins regulate cardiac growth and function is just beginning to be understood. With the present body of literature it appears that SIRT1 activation could be desirable in conditions where myocyte degeneration is primary cause of disease, however, one should keep in mind that SIRT1 is a pro-hypertrophic molecule. Undoubtedly, more work is needed to understand the role of SIRT1 and other sirtuins in cardiac cell biology before they could be taken as therapeutic targets valuable for translational medicine of heart failure.

Acknowledgments

This study was supported by NIH grants RO1 HL-77788 and HL-83423.

References

1. Ingram DK, Anson RM, de Cabo R, Mamczarz J, Zhu M, Mattison J, et al. Development of calorie restriction mimetics as a longevity strategy. *Ann N Y Acad Sci.* 2004; 1019:412–23. [PubMed: 15247056]
2. Sinclair DA. Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev.* 2005; 126:987–1002. [PubMed: 15893363]
3. Marzetti E, Wohlgemuth SE, Anton SD, Bernabei R, Carter CS, Leeuwenburgh C. Cellular mechanisms of cardioprotection by calorie restriction: state of the science and future perspectives. *Clin Geriatr Med.* 2009; 25:715–32. ix. [PubMed: 19944269]
4. Finkel T, Deng C-X, Mostoslavsky R. Recent progress in the biology and physiology of sirtuins. *Nature.* 2009; 460:587–91. [PubMed: 19641587]
5. Fontana L, Partridge L, Longo VD. Extending Healthy Life Span--From Yeast to Humans. *Science.* 2010; 328:321–6. [PubMed: 20395504]
6. Guarente L. Sirtuins in Aging and Disease. *Cold Spring Harbor Symposia on Quantitative Biology.* 2007; 72:483–8.
7. Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, et al. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab.* 2008; 8:157–68. [PubMed: 18599363]
8. Frye RA. Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. *Biochem Biophys Res Commun.* 2000; 273:793–8. [PubMed: 10873683]
9. Lin SJ, Ford E, Haigis M, Liszt G, Guarente L. Calorie restriction extends yeast life span by lowering the level of NADH. *Genes Dev.* 2004; 18:12–6. [PubMed: 14724176]

10. Michishita E, Park JY, Burneskis JM, Barrett JC, Horikawa I. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. *Mol Biol Cell*. 2005; 16:4623–35. [PubMed: 16079181]
11. Tanno M, Sakamoto J, Miura T, Shimamoto K, Horio Y. Nucleocytoplasmic shuttling of the NAD⁺-dependent histone deacetylase SIRT1. *J Biol Chem*. 2007; 282:6823–32. [PubMed: 17197703]
12. Tanno M, Kuno A, Yano T, Miura T, Hisahara S, Ishikawa S, et al. Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT1 promotes cell survival in chronic heart failure. *J Biol Chem*. 2010; 285:8375–82. [PubMed: 20089851]
13. Nasrin N, Kaushik VK, Fortier E, Wall D, Pearson KJ, de Cabo R, et al. JNK1 Phosphorylates SIRT1 and Promotes Its Enzymatic Activity. *PLoS ONE*. 2009; 4:e8414. [PubMed: 20027304]
14. Alcendor RR, Kirshenbaum LA, Imai S, Vatner SF, Sadoshima J. Silent information regulator 2alpha, a longevity factor and class III histone deacetylase, is an essential endogenous apoptosis inhibitor in cardiac myocytes. *Circ Res*. 2004; 95:971–80. [PubMed: 15486319]
15. Li L, Zhao L, Yi-Ming W, Yu YS, Xia CY, Duan JL, et al. Sirt1 hyperexpression in SHR heart related to left ventricular hypertrophy. *Can J Physiol Pharmacol*. 2009; 87:56–62. [PubMed: 19142216]
16. Vahtola E, Louhelainen M, Merasto S, Martonen E, Penttinen S, Aahos I, et al. Forkhead class O transcription factor 3a activation and Sirtuin1 overexpression in the hypertrophied myocardium of the diabetic Goto-Kakizaki rat. *J Hypertens*. 2008; 26:334–44. [PubMed: 18192848]
17. Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X, et al. Sirt1 regulates aging and resistance to oxidative stress in the heart. *Circ Res*. 2007; 100:1512–21. [PubMed: 17446436]
18. Hsu CP, Zhai P, Yamamoto T, Maejima Y, Matsushima S, Hariharan N, et al. Silent Information Regulator 1 Protects the Heart From Ischemia/Reperfusion. *Circulation*. 2010
19. McBurney MW, Yang X, Jardine K, Hixon M, Boekelheide K, Webb JR, et al. The mammalian SIR2alpha protein has a role in embryogenesis and gametogenesis. *Mol Cell Biol*. 2003; 23:38–54. [PubMed: 12482959]
20. Cheng HL, Mostoslavsky R, Saito S, Manis JP, Gu Y, Patel P, et al. Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice. *Proc Natl Acad Sci U S A*. 2003; 100:10794–9. [PubMed: 12960381]
21. Coussens M, Maresh JG, Yanagimachi R, Maeda G, Allsopp R. Sirt1 Deficiency Attenuates Spermatogenesis and Germ Cell Function. *PLoS ONE*. 2008; 3:e1571. [PubMed: 18270565]
22. Chan AY, Dolinsky VW, Soltys CL, Viollet B, Baksh S, Light PE, et al. Resveratrol inhibits cardiac hypertrophy via AMP-activated protein kinase and Akt. *J Biol Chem*. 2008; 283:24194–201. [PubMed: 18562309]
23. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006; 444:337–42. [PubMed: 17086191]
24. Juric D, Wojciechowski P, Das DK, Neticadan T. Prevention of concentric hypertrophy and diastolic impairment in aortic-banded rats treated with resveratrol. *Am J Physiol Heart Circ Physiol*. 2007; 292:H2138–43. [PubMed: 17488730]
25. Sulaiman M, Matta MJ, Sunderesan NR, Gupta MP, Periasamy M, Gupta M. Resveratrol, an activator of SIRT1, upregulates sarcoplasmic calcium ATPase and improves cardiac function in diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2010; 298:H833–43. [PubMed: 20008278]
26. Shiojima I, Sato K, Izumiya Y, Schiekofer S, Ito M, Liao R, et al. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. *J Clin Invest*. 2005; 115:2108–18. [PubMed: 16075055]
27. Potente M, Ghaeni L, Baldessari D, Mostoslavsky R, Rossig L, Dequiedt F, et al. SIRT1 controls endothelial angiogenic functions during vascular growth. *Genes Dev*. 2007; 21:2644–58. [PubMed: 17938244]
28. Fukuda S, Kaga S, Zhan L, Bagchi D, Das DK, Bertelli A, et al. Resveratrol ameliorates myocardial damage by inducing vascular endothelial growth factor-angiogenesis and tyrosine kinase receptor Flk-1. *Cell Biochem Biophys*. 2006; 44:43–9. [PubMed: 16456233]
29. Kraft TE, Parisotto D, Schempp C, Efferth T. Fighting cancer with red wine? Molecular mechanisms of resveratrol. *Crit Rev Food Sci Nutr*. 2009; 49:782–99. [PubMed: 20443159]

30. Goligorsky MS. Endothelial cell dysfunction: can't live with it, how to live without it. *AJP - Renal Physiology*. 2005; 288:F871–80. [PubMed: 15821252]
31. Mattagajasingh I, Kim CS, Naqvi A, Yamamori T, Hoffman TA, Jung SB, et al. SIRT1 promotes endothelium-dependent vascular relaxation by activating endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A*. 2007; 104:14855–60. [PubMed: 17785417]
32. Zhang, Q-j; Wang, Z.; Chen, H-z; Zhou, S.; Zheng, W.; Liu, G., et al. Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice. *Cardiovascular Research*. 2008; 80:191–9. [PubMed: 18689793]
33. Hung LM, Su MJ, Chen JK. Resveratrol protects myocardial ischemia-reperfusion injury through both NO-dependent and NO-independent mechanisms. *Free Radic Biol Med*. 2004; 36:774–81. [PubMed: 14990356]
34. Tissenbaum HA, Guarente L. Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*. *Nature*. 2001; 410:227–30. [PubMed: 11242085]
35. Giannakou ME, Partridge L. The interaction between FOXO and SIRT1: tipping the balance towards survival. *Trends Cell Biol*. 2004; 14:408–12. [PubMed: 15308206]
36. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer PL, Lin Y, et al. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*. 2004; 303:2011–5. [PubMed: 14976264]
37. Daitoku H, Hatta M, Matsuzaki H, Aratani S, Ohshima T, Miyagishi M, et al. Silent information regulator 2 potentiates Foxo1-mediated transcription through its deacetylase activity. *Proc Natl Acad Sci U S A*. 2004; 101:10042–7. [PubMed: 15220471]
38. Sundaresan N, Isbatan A, Samant S, Pillai V, PV R, Rajamohan S, et al. SIRT1, a stress responsive deacetylase is required for development of compensatory cardiac hypertrophy. *Circulation*. 2009; 119(Suppl 2):3603.
39. Scher MB, Vaquero A, Reinberg D. SirT3 is a nuclear NAD⁺-dependent histone deacetylase that translocates to the mitochondria upon cellular stress. *Genes Dev*. 2007; 21:920–8. [PubMed: 17437997]
40. Schwer B, North BJ, Frye RA, Ott M, Verdin E. The human silent information regulator (Sir)2 homologue hSIRT3 is a mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase. *J Cell Biol*. 2002; 158:647–57. [PubMed: 12186850]
41. Sundaresan NR, Samant SA, Pillai VB, Rajamohan SB, Gupta MP. SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70. *Mol Cell Biol*. 2008; 28:6384–401. [PubMed: 18710944]
42. Sundaresan NR, Gupta M, Kim G, Rajamohan SB, Isbatan A, Gupta MP. Sirt3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice. *J Clin Invest*. 2009; 119:2758–71. [PubMed: 19652361]
43. Pillai JB, Isbatan A, Imai S, Gupta MP. Poly(ADP-ribose) polymerase-1-dependent cardiac myocyte cell death during heart failure is mediated by NAD⁺ depletion and reduced Sir2alpha deacetylase activity. *J Biol Chem*. 2005; 280:43121–30. [PubMed: 16207712]
44. Pillai VB, Sundaresan NR, Kim G, Gupta M, Rajamohan SB, Pillai JB, et al. Exogenous NAD blocks cardiac hypertrophic response via activation of the SIRT3-LKB1-AMP-activated kinase pathway. *J Biol Chem*. 2010; 285:3133–44. [PubMed: 19940131]
45. Vakhrusheva O, Smolka C, Gajawada P, Kostin S, Boettger T, Kubin T, et al. Sirt7 Increases Stress Resistance of Cardiomyocytes and Prevents Apoptosis and Inflammatory Cardiomyopathy in Mice. *Circulation Research*. 2008; 102:703–10. [PubMed: 18239138]
46. Ford E, Voit R, Liszt G, Magin C, Grummt I, Guarente L. Mammalian Sir2 homolog SIRT7 is an activator of RNA polymerase I transcription. *Genes & Development*. 2006; 20:1075–80. [PubMed: 16618798]
47. Sole MJ, Martino TA. Diurnal physiology: core principles with application to the pathogenesis, diagnosis, prevention, and treatment of myocardial hypertrophy and failure. *J Appl Physiol*. 2009; 107:1318–27. [PubMed: 19556457]
48. Asher G, Gatfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, et al. SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell*. 2008; 134:317–28. [PubMed: 18662546]

49. Nakahata Y, Kaluzova M, Grimaldi B, Sahar S, Hirayama J, Chen D, et al. The NAD⁺-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell*. 2008; 134:329–40. [PubMed: 18662547]
50. Fulco M, Cen Y, Zhao P, Hoffman EP, McBurney MW, Sauve AA, et al. Glucose restriction inhibits skeletal myoblast differentiation by activating SIRT1 through AMPK-mediated regulation of Nampt. *Dev Cell*. 2008; 14:661–73. [PubMed: 18477450]
51. Leri A, Kajstura J, Anversa P. Cardiac stem cells and mechanisms of myocardial regeneration. *Physiol Rev*. 2005; 85:1373–416. [PubMed: 16183916]
52. Pillai JB, Chen M, Rajamohan SB, Samant S, Pillai VB, Gupta M, et al. Activation of SIRT1, a class III histone deacetylase, contributes to fructose feeding-mediated induction of the alpha-myosin heavy chain expression. *Am J Physiol Heart Circ Physiol*. 2008; 294:H1388–97. [PubMed: 18192211]
53. Hariharan N, Maejima Y, Nakae J, Paik J, Depinho RA, Sadoshima J. Deacetylation of FoxO by Sirt1 Plays an Essential Role in Mediating Starvation-Induced Autophagy in Cardiac Myocytes. *Circ Res*. 2010
54. Chen IY, Lypowy J, Pain J, Sayed D, Grinberg S, Alcendor RR, et al. Histone H2A.z is essential for cardiac myocyte hypertrophy but opposed by silent information regulator 2alpha. *J Biol Chem*. 2006; 281:19369–77. [PubMed: 16687393]
55. Rajamohan SB, Pillai VB, Gupta M, Sundaresan NR, Birukov KG, Samant S, et al. SIRT1 promotes cell survival under stress by deacetylation-dependent deactivation of poly(ADP-ribose) polymerase 1. *Mol Cell Biol*. 2009; 29:4116–29. [PubMed: 19470756]

Figure 1. Simplified scheme illustrating mechanism of cardio-protective effects of SIRT1

In the adult hearts SIRT1 localizes mostly in the cytoplasm [11]. During stress stimulation of cells, PI3K/Akt and JNK are activated, which promote nuclear importation of SIRT1, perhaps by phosphorylation [11,13]. In the nucleus SIRT1 activates transcription of Foxo-dependent anti-oxidant genes, MnSOD and catalase, leading to reduced cellular ROS (reactive oxygen species) levels and thus protecting cells from oxidative stress-mediated damage [12,17]. There is also evidence documenting that SIRT1 increases expression of α-MHC and SERCA2A, resulting in enhanced heart function [25,52].

Table 1

Mechanisms attributed to SIRT1 mediated cardio-protection

Model studied	SIRT1 Target	Effect on the heart and mechanism involved	Ref.
Cardiac specific SIRT1-TG mouse	FOXO1	Decreased cardiac aging due to increased FOXO1 activation causing increased transcription of MnSOD and catalase	[17]
Cardiac specific SIRT1 TG mouse	P53	Increased myocyte survival due to decreased P53 activity hence preventing apoptosis	[12]
Fructose feeding & Cardiac specific SIRT1 TG mouse	No direct target	Protection from cardiac hypertrophy by preventing myosin isoforms shift due to enhanced transcription of Alpha MHC	[53]
Resveratrol fed TO-2 hamsters	No direct target	Improved myocyte survival due to Increased transcriptional activity of MnSOD	[14]
Cardiac specific SIRT1 TG mouse	FOXO1	Reduced myocardial infraction due to FOXO1 activation causing increased expression of thioredoxin-1 and Bcl-xL	[52]
Cardiac specific SIRT1-KO mouse	FOXO1	Impaired autophagy and cardiac function due to reduced FOXO1 activation leading to reduced expression of Rab7	[25]
streptozotocin induced diabetic SIRT1-KO mouse	No direct target	Impaired contractile function due to reduced transcription of SERCA2A	[54]
In vitro cell culture	H2A.z	Prevented cardiac hypertrophy by increased H2A.z deacetylation leading to its ubiquitination mediated degradation	[18]
In vitro cell culture	PARP1	Improved myocyte survival due to decreased PARP1 activity by deacetylation	[43,55]