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Review Article

Sirtuins, oxidative stress and angiotensin-II mediated cardiac hypertrophy: evidence from animal studies

Paul J. Lijnen, John S. Prihadi

Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Sciences, Catholic University of Leuven (KULeuven), Leuven, Belgium

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Corresponding Author
Paul J Lijnen
Hypertension Unit,
Campus Gasthuisberg,
Herestraat 49 Box 702,
B-3000 Leuven, Belgium.
paul.lijnen@med.kuleuven.be

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Abstract
Angiotensin II-induced cardiac hypertrophy is associated with oxidative stress-dependent mitochondrial dysfunction. Sirtuins have recently emerged as important proteins contributing to stress resistance, cell growth, apoptosis, metabolism and aging. The involvement of sirtuins in the angiotensin II-stimulated production of reactive oxygen species and in the development of cardiac hypertrophy in animal studies will be discussed in this review article. Sirtuins play diverse roles in the cardiovascular system. This functional diversity is related to the existence of seven mammalian sirtuins and to the various molecular targets for its deacetylation and ADP ribosyltransfer reactions. In the heart SIRT-3 blocks the development of cardiac hypertrophy and protect cardiomyocytes from oxidative stress-mediated cell death. The antioxidant effect of SIRT-3 may play an important role in ameliorative hypertrophic agonist-induced cardiac hypertrophy. SIRT-3 is an endogenous negative regulator of cardiac hypertrophy by suppressing the cellular production of ROS. Undoubtedly, more research is needed to unravel the exact role of sirtuins in cardiac cell biology before they can be used as therapeutic targets valuable for translational medicine and heart failure. Whether the direct pharmacological modulation of sirtuins may confer greater benefit in cardiac diseases than the other antioxidant approaches, which shows disappointing results, is an intriguing concept.

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INTRODUCTION

The silence information regulator or sirtuin (SIRT) family of class III histone deacetylases are NAD^+-dependent deacetylases, while the class I and II histone deacetylases are Zn^{2+}-dependent [1]. Seven mammalian homologues designated as SIRT-1 through SIRT-7 are identified to date. These sirtuins are found in distinct subcellular compartments where they regulate specific biological functions [2].

Nuclear and cytosolic sirtuins

SIRT-1 and SIRT-2 are present both in the nucleus and in the cytoplasm. SIRT-1 deacetylates many non-histone proteins involved in cell survival, metabolism and stress response [3-8]. SIRT-2 is important for chromosomal stability during mitosis [9]. SIRT-6 is involved in the genomic stability, glucose homeostasis and inflammation [10-12]. SIRT-7 is found with nucleoli and condensed chromosomes [13-14].

Mitochondrial sirtuins

Three sirtuins namely SIRT-3, -4 and -5 are mitochondria enriched [15, 16]. SIRT-3 which is the most robust mitochondrial deacetylase [17], is referred to as a mitochondrial stress sensor. SIRT-3 which is transported from nuclei to mitochondria upon cellular stress and plays a role in mitochondrial functioning by deacetylating acetyl-CoA synthethase [18, 19].

SIRTUINS AND CARDIAC HYPERTROPHY

Angiotensin II (ANG II) has been considered as a potent stimulator of cardiac hypertrophy. Increased oxidative/nitrosative stress is a major component of the ANG II-mediated cell signaling contributing to cardiac hypertrophy. In mouse proximal tubular epithelial cells ANG II treatment lowers the expression levels of SIRT-3 and nicotinamide phosphoribosyltransferase (NAMPT), whose protein product increases

mitochondrial NAD^+, providing the co-substrate for SIRT-3. Candesartan, an ANG II type I receptor (AT_1R) blocker, inhibits this effect [20].

In rat vascular smooth muscle cells ANG II treatment increases SIRT-1 expression [21]. Miyazaki *et al* [22] reported that SIRT-1 inhibits the expression of AT_1R in smooth muscle cells. SIRT-1 counteracts ANG II-induced cardiomyocyte hypertrophy and reactive oxygen species (ROS)-dependent cell death [23].

Reactive oxygen species and sirtuins

Knockout of the AT_1R in mice increases life span by 26% and AT_1R knockouts have lower levels of cardiac fibrosis, hypertrophy and attenuated aortic damage [20]. They also have lower levels of oxidative stress and increased mitochondrial density compared to controls. Mitochondrial ROS are indeed reduced by 55% by the overexpression of SIRT-3 and by 84% by the co-expression of SIRT-3 and manganese superoxide dismutase (Mn-SOD), whereas overexpression of SIRT-3 in Mn-SOD knockout cells causes no significant mitochondrial ROS reduction, suggesting that SIRT-3 enhances the activity of Mn-SOD to scavenge mitochondrial ROS [24].

Overexpression of SIRT-3 in mouse embryonic fibroblasts (MEF's) reduces cellular ROS by 40%. However, reduction of cellular ROS mediated by SIRT-3 is blunted in Mn-SOD knockout MEF's, indicating that Mn-SOD is the major downstream mediator of SIRT-3 in reducing cellular ROS [25]. SIRT-3 has also been shown to decrease ROS production in brown adipocytes [26].

SIRT-3 deficient mice develop cardiac hypertrophy and interstitial fibrosis at 8 weeks of age; on the other hand transgenic mice overexpressing SIRT-3 in the heart effectively block agonist-mediated hypertrophy. Cardiomyocytes cultured from SIRT-3 deficient hearts show increased ROS levels suggesting that SIRT-3 prevents cardiac hypertrophy response by scavenging cellular ROS [27]. Cells lacking SIRT-3 also exhibit an increase in mitochondrial superoxide levels when exposed to ischemia reperfusion [28]. In mice, the level of SIRT-1 in the heart is significantly upregulated after 2 and 4 weeks of pressure overload and by paraquat injection, which induces oxidative stress [29].

Upon oxidative stress, SIRT-3 overexpression protects the cardiomyocytes against Bax-mediated apoptosis by deacetylating the substrate Ku70, promoting the binding of Ku70 to Bax, and hence blocking the Bax activation [30]. SIRT-3 also inhibits aging and makes the heart resistant to oxidative stress and heart failure. Mice lacking SIRT-3 develop severe age-related pathologies in the heart [31].

Mitochondrial antioxidant enzymes and sirtuins

The sirtuin family has been demonstrated to play an important role in the regulation of mitochondrial function and in the activation of antioxidant defenses.

Mn-SOD is acetylated at Lys68 and this acetylation decreases Mn-SOD activity. In HEK293T cells mitochondrial SIRT-3 binds to, deacetylates and activates Mn-SOD. Increase of ROS levels stimulate SIRT-3 transcription, leading to Mn-SOD deacetylation and activation. Mn-SOD mediated ROS reduction is synergistically increased by SIRT-3 overexpression, but is cancelled by SIRT-3 depletion. Both SIRT-3 transcript and protein levels are induced by the generation of mitochondrial ROS [24].

SIRT-3 deficiency and the associated mitochondrial protein hyperacetylation result in mitochondrial dysfunction [32]. In the SIRT-3 knockout mice, cardiac hypertrophy and the development of cardiac fibrosis are accelerated compared with SIRT-3-competent mice. In parallel, the absence of SIRT-3 results in the attenuation of antioxidant enzyme activities in response to the hypertrophic agents [33]. These data suggest that the antioxidant effects of SIRT-3 may play an important role in ameliorative hypertrophic agonist-induced cardiac hypertrophy [34]. This phenotype is also shown when pressure overload is directly induced by thoracic aortic constriction. The SIRT-3 knockout mice have a higher postoperative mortality from the banding studies compared with the wild-type mice and the knochout mice develop excessive age-associated hypertrophy and myocardial fibrosis [31].

Qiu *et al* [25] showed that calorie restriction lowers oxidative stress by SIRT-3-mediated Mn-SOD activation. SIRT-3 overexpression in mouse embryonic fibroblasts lowers ROS levels in a Mn-SOD dependent manner. They [25] further showed that SIRT-3 interacts with Mn-SOD and that SIRT-3-mediated deacetylation of Mn-SOD increases its activity which provided protection against oxidative stress. Tao *et al* [28] confirmed that SIRT-3 regulates Mn-SOD activity and subsequent protection against ionizing radiation.

SIRT-3 also interacts and deacetylases cyclophilin D, a key component of the mitochondrial permeability transition pore (mPTP), thereby inhibiting mPTP opening. This in turn reduces oxidative stress and eventually slows down cardiac aging. [35]. SIRT-3 acts thus as sensor of ROS that can lead to mitochondrial damage and activates specific cellular signaling pathway to counteract oxidative stress such as the expression of Mn-SOD antioxidant protein [36].

Taken together these data indicate that ROS levels are tightly controlled by SIRT-3 by increasing the activity of Mn-SOD [37]. In spontaneously hypertensive rats

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long-term histone deacetylase inhibition, independent of blood pressure response, reduces hypertrophic, proinflammatory and hypertensive responses by decreasing ROS and AT_1R expression in the heart, indicating the importance of uncontrolled histone deacetylase activity in hypertension [38].

In neonatal rat cardiomyocytes, SIRT-3 promotes nuclear localization of the Forkhead transcription factor FOXO3a, leading to enhanced transcription of the FOXO3a-dependent antioxidant gene Mn-SOD, thereby reducing cellular ROS levels [2, 27]. SIRT-1 also stimulates resistance to oxidative stress through FOXO in fibroblasts [39].

In adult rat cardiac fibroblasts we have reported that ANG II increases superoxide anion production and intracellular and mitochondrial formation of reactive oxygen species [40-43]. In rat vascular smooth muscle cells, FOXO3a interacts with the promoter of the Mn-SOD gene at a specific binding site [44]. The FOXO3a binding activity to the Mn-SOD and peroxiredoxin-3 (Prx-3) DNA is lower in nuclear extracts of ANG II-treated cardiac fibrtoblasts as compared to control fibroblasts [40, 44]. Upon phosphorylation of Akt (protein kinase B) by ANG II in cardiac fibroblasts we have shown that P-Akt is translocated from the cytosol to the nucleus and nuclear phosphorylation of FOXO3a by P-Akt leads to relocalization of FOXO3a form the nucleus to the cytosol, resulting in a decrease in its transcriptional activity and in the expression of the mitochondrial antioxidant enzymes Mn-SOD and Prx-3 [41, 45].

A schematic description of the ANG II-induced release of ROS and FOXO3a dependent Mn-SOD and Prx-3 expression in cardiac fibroblasts is given in figure 1.

Poly(ADP-ribose) polymerase-1 and sirtuins

Poly(ADP-ribose) polymerase-1 (PARP) is a 113 kDa multifunctional chromatin bound enzyme of the PARP family of proteins. PARP catalyzes the transfer of multiple ADP-ribose moieties from NAD^+ to the target proteins, through a process called poly-ADP-ribosylation, leading to depletion of cellular NAD^+ [46, 47].

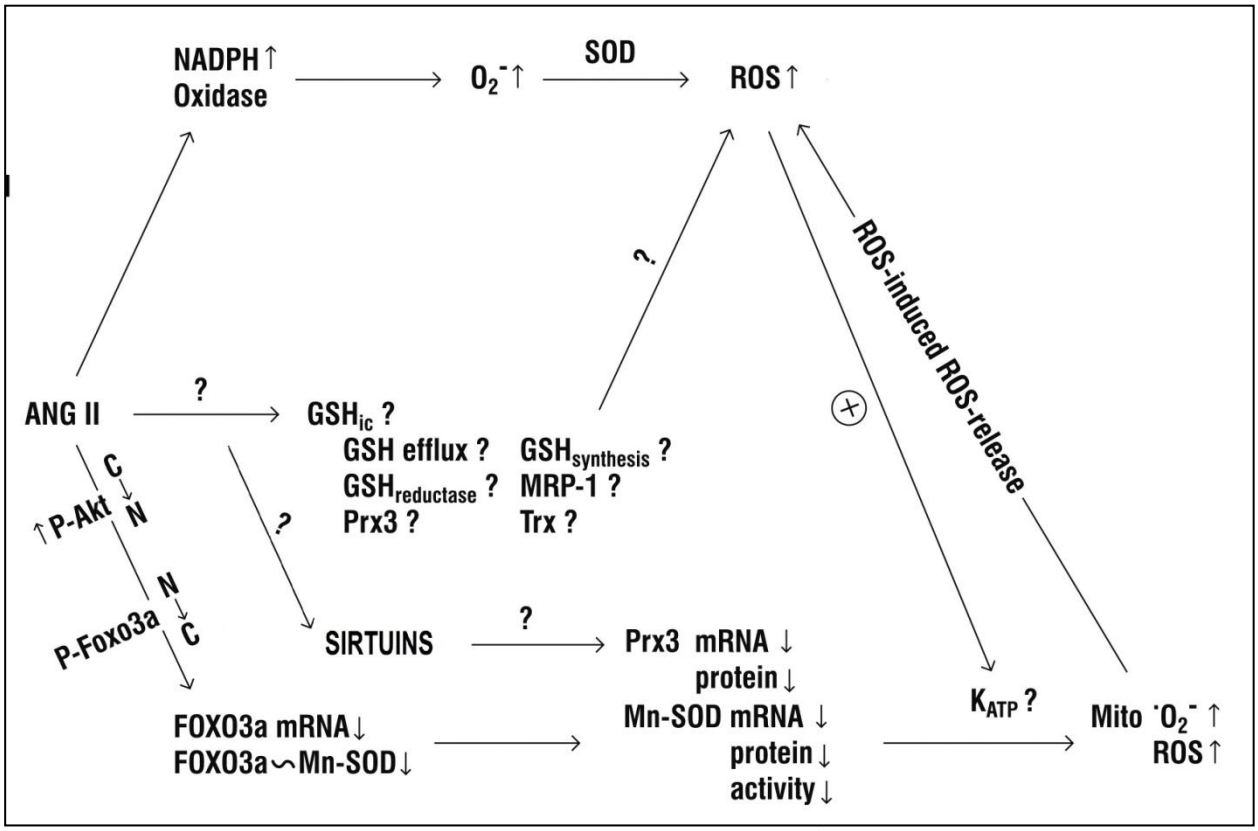

Figure 1. ANG II, through interaction with the AT_1R, stimulates NAD(P)H oxidase in cardiac fibroblasts leading to an enhanced intracellular and mitochondrial (Mito) production of superoxide anion ($O_2^{\bullet-}$) and ROS. Upon phosphorylation of Akt (protein kinase B) by ANG II in cardiac fibroblasts, P-Akt is translocated from the cytoplasm to the nucleus and nuclear phosphorylation of the Forkhead box class O transcription factor FOXO3a by P-Akt leads to relocalization of FOXO3a from the nucleus to the cytosol, resulting in a decrease in Mn-SOD and Prx-3 expression. The effect of ANG II on sirtuin expression, intracellular GSH system, mitochondrial ATP-sensitive potassium channels (K_{ATP}) in cardiac fibroblasts has to be further elucidated. [SOD, superoxide dismutase; C, cytosol; N, nucleus; GSH, glutathione; Prx3, peroxiredoxin 3; MRP-1, multidrug resistance related protein-1; Trx, thioredoxin; FOXO, Forkhead box class O; Akt, protein kinase B; ↑, increase; ?, not known in cardiac fibroblasts.]

PARP is activated during ANG II-induced cardiomyocyte hypertrophy and mice deficient in the PARP gene are protected from ANG II-mediated hypertrophy [48]. NAD^+ depletion, resulting from PARP overactivation, contributes to ANG II-mediated cardiac myocyte cell death [48]. This type of cell death is prevented by NAD^+ repletion, activation of the longevity factor SIRT-2α and by treatment with resveratrol [49]. Knocking down SIRT-2α levels by siRNA treatment eliminated the protective effect of resveratrol, thus indirectly indicating that PARP activation threatens cell survival by reducing the activity of NAD^+-dependent class III histone deacetylases or sirtuins [2, 48]. PARP is thus a downstream nuclear target of ANG II-induced signaling pathway, contributing to cardiac hypertrophy and failure. PARP inhibition may be a novel therapeutic approach for the management of heart failure.

Finally, in hamsters treated with resveratrol, nuclear SIRT-1 induces mitochondrial Mn-SOD, which reduces oxidative stress and participitates in cardiomyocyte protection [50]. By enhancing nuclear SIRT-1 that increases Mn-SOD levels, resveratrol suppresses myoblast death induced by ANG II [50]. SIRT-1 activators such as resveratrol could be novel therapeutic tools for the treatment of chronic heart failure. Indeed, in high-fat-diet-fed mice the synthetic SIRT-1 activator SRT1720 significantly reduces the number of ischemic foci in the heart and attenuates inflammatory gene expression in the heart [51].

CONCLUSIONS AND FUTURE PERSPECTIVES

Sirtuins play diverse roles in the cardiovascular system. This functional diversity is related to the existence of seven mammalian sirtuins and to the various molecular targets for its deacetylation and ADP ribosyltransfer reactions. In the heart SIRT-3 blocks the development of cardiac hypertrophy and protect cardiomyocytes from oxidative stress-mediated cell death. The antioxidant effect of SIRT-3 may play an important role in ameliorative hypertrophic agonist-induced cardiac hypertrophy. SIRT-3 is an endogenous negative regulator of cardiac hypertrophy by suppressing the cellular production of ROS. Undoubtedly, more research is needed to unravel the exact role of sirtuins in cardiac cell biology before they can be used as therapeutic targets valuable for translational medicine and heart failure. Whether the direct pharmacological modulation of sirtuins may confer greater benefit in cardiac diseases than the other antioxidant approaches, which shows disappointing results, is an intriguing concept.

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DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Haigis MC, Guarente LP. Mammalian sirtuins-emerging roles in physiology, aging and calorie restriction. Genes Dev 2006; 20:2913-21.
2. Pillai VB, Sundaresan NR, Jeevanandam V, Gupta MP Mitochondrial SIRT3 and heart disease. Cardiovasc Res 2010; 88:250-6.
3. Li X, Zhang S, Blander G, Tse JG, Krieger M, Guarente L. SIRT1 deacetylates and positively regulates the nuclear receptor LXR. Mol Cell 2007; 28:91-106.
4. Liu Y, Dentin R, Chen D, Hedrick S, Ravnskjaer K, Schenk S, Milne J, Meyers DJ, Yates J 3rd, Olefsky J, Guarente L, Montminy M. A fasting inducible switch modulates gluconeogenese via activator/coactivator exchange. Nature 2008; 456:269-73.
5. Motta MC, Divecha N, Lemieux M, Kamel C, Chen D, Gu W, Bultsma Y, McBurney M, Guarente L. Mammalian SIRT1 represses forkhead transcription factors. Cell 2004; 116:551-63.
6. Rodgers JT, Puigserver P. Fasting-dependent glucose and lipid metabolic response through hepatic sirtuin 1. Proc Natl Acad Sci USA 2007; 104:12861-6.
7. 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.
8. Vaziri H, Dessain SK, Ng Eaton E, Imai SI, Frye RA, Pandita TK, Guarente L, Weinberg RA. hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. Cell 2001; 107:149-59.
9. Inoue T, Hiratsuka M, Osaki M, Yamada H, Kishimoto I, Yamaguchi S, Nakano S, Katoh M, Ito H, Oshimura M. SIRT2, a tubulin deacetylase, acts to block the entry to chromosome condensation in response to mitotic stress. Oncogene 2007; 26:945-57.
10. Kawahara TL, Michishita E, Adler AS, Damian M, Berber E, Lin M, McCord RA, Ongaigui KC, Boxer LD, Chang HY, Chua KF. SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell 2009; 136:62-74.
11. Lombard DB. Sirtuins at the breaking point: SIRT6 in DNA repair. Aging (Albany NY) 2009; 1:12-6.
12. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry RE, Vadysirisack DD, Guimaraes A, Marinelli B, Wikstrom JD, Nir T, Cish CB, Vaitheesvaran B, Iliopoulos O, Kurland I, Dor Y, Weissleder R, Shirihai OS, Ellisen LW, Espinosa JM, Mostoslavsky R. The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1alpha. Cell 2010; 140:280-93.

 DOI 10.5455/oams.260412.rv.003

13. 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 Dev 2006; 20:1075-80.

14. Michishita E, Park JY, Burmeskis JM, Barrett JC, Horikawa I. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. Mol Biol Cell 2005; 16:4623-35.

15. Schwer B, Verdin E. Conserved metabolic regulatory functions of sirtuins. Cell Metab 2008; 7:104-12.

16. Huang JY, Hirschey MD, Shimazu T, Ho L, Verdin E. Mitochondrial sirtuins. Biochim Biophys Acta 2010; 1804:1645-51.

17. Lombard DB, Alt FW, Cheng HL, Bunkenborg J, Streeper RS, Mostoslavsky R, Kim J, Yancopoulos G, Valenzuela D, Murphy A, Yang Y, Chen Y, Hirschey MD, Bronson RT, Haigis M, Guarente LP, Farese RV Jr, Weissman S, Verdin E, Schwer B. Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. Mol Cell Biol 2007; 27:8807-14.

18. Hallows WC, Lee S, Denu JM. Sirtuinsdeacetylate and activate mammalian acetyl CoA synthetases. Proc Natl Acad Sci USA 2006; 103:10230-5.

19. Schwer B, Bunkenborg J, Verdin RO, Andersen JS, Verdin E. Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA-synthetase 2. Proc Natl Acad Sci USA 2006; 103:10224-9.

20. Benigni A, Corna D, Zoja C, Sonzogni A, Latini R, Salio M, Conti S, Rottoli D, Longaretti L, Cassis P, Morigi M, Coffman TM, Remuzzi G. Disruption of the Ang II type 1 receptor promotes longevity in mice. J Clin Invest 2009; 119: 524-30.

21. Li L, Gao P, Zhang H, Chen H, Zheng W, Lv X, Xu T, Wei Y, Liu D, Liang C. SIRT1 inhibits angiotensin II-induced vascular smooth muscle cell hypertrophy. Acta Biochim Biophys Sin 2011; 43:103-9.

22. Miyazaki R, Ichiki T, Hashimoto T, Inanaga K, Imayama I, Sadoshima J, Sunagawa K. SIRT1, a longevity gene, downregulates angiotensin II type 1 receptor expression in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 2008; 28:1263-9.

23. Vinciguerra M, Santini MP, Claycomb WC, Ladurner AG, Rosenthal N. Local IGF-1 isoform protects cardiomyocytes from hypertrophic and oxidative stresses via SIRT1 activity. Aging (Albany NY) 2010; 2:43-62.

24. Chen Y, Zhang J, Lin Y, Lei Q, Guan KL, Zhao S, Xiong Y. Tumour suppressor SIRT3 deacetylates and activates manganese superoxide dismutase to scavenge ROS. EMBO Reports 2011; 12:534-41.

25. Qiu X, Brown K, Hirschey MD, Verdin E, Chen D. Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. Cell Metab 2010; 12:662-7.

26. Shi T, Wang F, Stieren E, Tong Q. SIRT3, a mitochondrial sirtuindeacetylase, regulates mitochondrial function and thermogenesis in brown adipocytes. J Biol Chem. 2005; 280:13560-7.

27. Pillai VB, Sundaresan NR, Kim G, Gupta M, Rajamohan SB, Pillai JB, Samant S, Ravindra PV, Isbatan A, Gupta MP. Exogenous NAD blocks cardiac hypertrophic response via activation of the SIRT3-LKB1-AMP-activated kinase pathway. J Biol Chem 2010; 285:3133-44.

28. Tao R, Coleman MC, Pennington JD, Ozden O, Park SH, Jiang H, Kim HS, Flynn CR, Hill S, Hayes McDonald W, Olivier AK, Spitz DR, Gius D. Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates Mn-SOD activity in response to stress. Mol Cell 2010; 40:893-904.

29. Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X, Tian B, Wagner T, Vatner SF, Sadoshima J. Sirt1 regulates aging and resistance to oxidative stress in the heart. Circ Res 2007; 100:1512-21.

30. Sundaresan NR, Samant SA, Pillai VB, Rajamohan SB, Gupta MP. SIRT 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.

31. Hafner AV, Dai J, Gomes AP, Xiao CY, Palmeira CM, Rosenzweig A, Sinclair DA. Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. Aging (Albany NY) 2010; 2:914-23.

32. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stancakova A, Goetzman E, Lam MM, Schwer B, Stevens RD, Muehlbauer MJ, Kakar S, Bass NM, Kuusisto J, Laakso M, Alt FW, Newgard CB, Farese RV Jr, Kahn CR, Verdin E SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell 2011; 44:177-90.

33. 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.

34. Sack NN. Emerging characterization of the role of SIRT3-mediated mitochondrial protein deacetylation in the heart. Amer J Physiol 2011; 301:H2191-7.

35. Sadoshima J. Sirt3 targets mPTP and prevents aging in the heart. Aging (Albany NY) 2011; 3:12-3.

36. Jacobs KM, Pennington JD, Bisht KS, Aykin-Burns N, Kim HS, Mishra M, Sun L, Nguyen P, Ahn BH, Leclerc J, Deng CX, Spitz DR, Gius D SIRT3 interacts with the daf-16 homolog FOXO3a in the mitochondria, as well as increases Foxo3a dependent gene expression. Int J Biol Sci 2008; 4:291-9.

37. Webster BR, Lu Z, Sack MN, Scott I The role of sirtuins in modulating redox stressors. Free Radic Biol Med 2012; 52:281-90.

38. Cardinale JP, Sriramula S, Pariaut R, Guggilam A, Mariappan N, Elks CM, Francis J. HDAC inhibition attenuates inflammatory, hypertrophic and hypertensive responses in spontaneously hypertensive rats. Hypertension 2010; 56:437-44.

39. Brunet A, Sweeney LB, Sturgill JF, Chua KF, Greer Pl, Lin Y, Tran H, Ross SE, Mostoslavsky R, Cohen HY, Hu LS, Cheng HL, Jedrychowski MP, Gygi SP, Sinclair DA, Alt FW, Greenberg ME. Stress-dependent regulation of FOXO transcription factors by the Sirt1 deacetylase. Science 2004; 303: 2011-5.

40. Lijnen P, Papparella I, Petrov V, Semplicini A, Fagard R. Angiotensin II-stimulated collagen production in cardiac fibroblasts is mediated by reactive oxygen species. J Hypertens 2006; 24:757-66.

41. Lijnen P, van Pelt JF, Fagard R. Downregulation of manganese superoxide dismutase by angiotensin Ii in cardiac fibroblasts of rats: Association with oxidative stress in myocardium. Amer J Hypertens 2010; 23:1128-35.

42. Lijnen PJ, Prihadi JS, van Pelt JF, Fagard RH. Modulation of reactive oxygen species and collagen synthesis by angiotensin II in cardiac fibroblasts. Open Hypertens J 2011; 4:1-17.

43. Lijnen P, Petrov V, van Pelt J, Fagard R. Inhibition of superoxide dismutase induces collagen production in cardiac fibroblasts. Amer J Hypertens 2008; 21:1129-36.

44. Li M, Chiu JF, Mossman BT, Fukagawa NK. Down-regulation of manganese superoxide dismutase through phosphorylation of FOXO3a by Akt in explanted vascular smooth muscle cells from old rats. J Biol Chem 2006; 281:40429-39.

45. Lijnen P, Piccart Y, Coenen T, Maharani T, Finahari N, van Pelt J, Prihadi JS. Downmodulation of peroxiredoxin-3 expression by angiotensin II in cardiac fibroblasts through phosphorylation of FOXO3a by Akt. Oxid Antioxid Med Sci 2012; 1:25-33.

46. Burkle A Physiology and pathophysiology of poly-ADP-ribosylation. Bioassay 2001; 23:795-806.

47. Jagtap P, Szabo C. Poly(ADP-ribose)polymerase and the therapeutic effect of its inhibition. Nat Rev Drug Discov 2005; 4:421-40.

48. Pillai JB, Gupta M, Rajamohan SB, Lang R, Raman J, Gupta MP. Poly(ADP-ribose)polymerase-1-deficient mice are protected from angiotensin II-induced cardiac hypertrophy. Amer J Physiol 2006; 291:H1545-53.

49. Blander G, Guarente I. The Sir2 family of protein deacetylases. Ann Rev Biochem 2004; 73:417-35.

50. Tanno M, Kuno A, Yano T, Miura T, Hisahara S, Ishikawa S, Shimamoto K, Horio Y. 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.

51. Minor RK, Baur JA, Gomes AP, Ward TM, Csiszar A, Mercken EM, Abdelmohsen K, Shin YK, Canto C, Scheibye-Knudsen M, Krawczyk M, Irusta PM, Martin-Montalvo A, Hubbard BP, Zhang Y, Lehrmann E, White AA, Price NL, Swindell WR, Pearson KJ, Becker KG, Bohr VA, Gorospe M, Egan JM, Talan MI, Auwerx J, Westphal CH, Ellis JL, Ungvari Z, Vlasuk GP, Elliott PJ, Sinclair DA, de Cabo R. Srt1720 improves survival and healthspan of obese mice. Sci Rep 2011; 1:1-10.

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