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Hypertension and Mitochondrial Oxidative Stress Revisited: Sirtuin 3, the Improved "Antioxidant"

Francis J. Miller Jr.

Department of Medicine, Duke University and Veterans Affairs Medical Center, Durham, NC

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Despite approximately one in three adults having elevated blood pressure, at least 90% will have no identifiable cause. The availability and routine use of multiple classes of anti-hypertensives, often in a single patient, highlight the complexity and challenges of treating this disorder. A better understanding of the cellular mechanisms responsible for increased blood pressure may allow for more directed and effective treatment. An interesting observation in arteries from animal models and humans is the association of mitochondrial oxidative stress with hypertension. The treatment of mice with mitochondria-targeted antioxidants reduced blood pressure in both angiotensin II and deoxycorticosterone acetate (DOCA)-salt models of hypertension.[1] The efficacy of a subcellular targeted therapy in two different models of hypertension suggests the possibility of a common mitochondrial mechanism of the disease.

Even so, it is difficult not to be skeptical of experimental data from animals that touts the ability of an antioxidant to prevent disease. The sweeping failure of antioxidants in clinical trials of primary and secondary prevention of cardiovascular events was discouraging and compelled a reassessment of the role of oxidative stress in cardiovascular disease.[2] There are several potential explanations for this failure, but the results motivated the research community to identify the mechanisms of oxidant production as potential therapies. In this issue of Circulation Research, Dikalova et al. report that restoring depleted sirtuin 3 (SIRT3) levels in hypertensive mice normalized vascular superoxide levels, decreased blood pressure, and prevented endothelial dysfunction, vascular hypertrophy, and inflammation.[3] These findings identify SIRT3 as a promising therapeutic target in the treatment of vascular disease.

The sirtuins are a highly conserved family of nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases, whose potential contributions to cardiovascular disease have been recognized for less than ten years. The seven mammalian sirtuins can be grouped based on

Address for correspondence: Francis J. Miller, Jr., 203 Research Drive, MSRB1, Room 390, Durham, NC 27705, Francis.miller@duke.edu.

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None.

their primary subcellular localization; nuclear (SIRT1, SIRT6, and SIRT7), cytosolic (SIRT2), and mitochondrial (SIRT3, SIRT4, SIRT5).[4] All sirtuins have an NAD^+ binding domain and are sensitive to changes in the NAD^+/NADH ratio. Increased NAD^+ levels during times of energy demand, such as fasting and exercise, activate the extranuclear sirtuins to regulate several metabolic pathways. The sirtuins were thought to primarily catalyze lysine deacetylation, but recent studies reveal a broader range of post-translational activities, including removal of lipid modifications and adenosine diphosphate (ADP)-ribosylation. SIRT3 is the only sirtuin whose increased expression is associated with human longevity.[5] In human population studies, increased Sirt3 levels due to a polymorphism in the promoter region were linked to extended lifespan, whereas a different polymorphism that caused the decreased activity of Sirt3 was associated with metabolic syndrome.

SIRT3 physically interacts with mitochondrial superoxide dismutase (SOD2) and increases the activity of the enzyme by the deacetylation of two critical lysine residues. A loss of Sirt3 results in the hyperacetylation SOD2 and subsequent increase in mitochondrial superoxide levels. Several risk factors of cardiovascular disease, including tobacco smoking and hypertension, are associated with a decrease in vascular SIRT3 levels and SOD2 hyperacetylation.[6] Dikalove et al. report that arterioles from the mediastinal fat of hypertensive patients undergoing cardiac surgery have a 40% decrease in Sirt3 levels and 3-fold increases in SOD2 acetylation as compared with normotensive subjects. To determine the importance of SIRT3 in vascular dysfunction, they subjected SIRT3 knockout and overexpression mice to angiotensin II and DOCA-salt models of hypertension. Having previously shown that SIRT3 depletion exacerbated hypertension and endothelial dysfunction, they now demonstrate that the overexpression of SIRT3 normalized vascular superoxide levels, endothelial-dependent vasodilation, and improved blood pressure in both models of hypertension.[3, 7]

The infiltration of T lymphocytes and macrophages into the kidney contributes to hypertension. SIRT3 deficiency increased inflammatory cell infiltration, and Sirt3 overexpression reduced renal inflammatory cells as compared with wild-type mice. The infusion of angiotensin II increased medial hypertrophy of the aorta in wild-type mice, and SIRT3 deficiency increased, whereas SIRT3 overexpression decreased aortic wall thickness. Changes in SIRT3 expression also modified vascular inflammatory responses to angiotensin II with the overexpression of SIRT3 markedly attenuating adhesion molecule and monocyte chemoattractant protein-1 expression. This activation of inflammatory signaling is likely to be mediated by the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, which was recently shown to be activated by a decrease in SIRT3 and an increase in mitochondrial superoxide.[8] Vascular inflammation is crucial to many age-related cardiovascular diseases and it will be interesting to determine whether increasing SIRT3 levels has a protective effect in these conditions. Currently, there is conflicting evidence regarding the role of SIRT3 in atherosclerotic vascular dysfunction based on studies in hypercholesterolemic mice.

The myriad of protective effects provided by increased SIRT3, including endothelial function, smooth muscle cell hypertrophy, vascular permeability and inflammation, and inflammatory cell infiltration into the kidney, highlight a limitation in the study by Dikalova,

that is, the use of a global transgenic mouse model. Additional studies with cell-specific Sirt3 overexpression are warranted to define the specific role of endothelial Sirt3. It is tempting to attribute the SIRT3-dependent improvement in blood pressure to the associated reduction in vascular mitochondrial superoxide. However, Case et al. found that it was an increase in mitochondrial superoxide in the subfornical organ of the brain, and not in peripheral organs, that sensitized mice to angiotensin II-dependent hypertension.[9] Similarly, spontaneous hypertensive rats have decreased SOD2 expression and increased mitochondrial superoxide levels in the rostral ventrolateral medulla, and the overexpression of SOD2 to this region lowers blood pressure.[10] Based on these observations, the overexpression of SIRT3 in the brain, occurring in the global transgenic mice used by Dikalova, may contribute to the observed reduction in blood pressure.

It is also important to note that recent studies have implicated other sirtuins in the development of hypertension. SIRT1 decreased the expression of the angiotensin-1 receptor in smooth muscle cells and increased endothelial nitric oxide synthase activity.[11] In addition, the loss of endothelial SIRT6 increased blood pressure whereas the overexpression of SIRT6 prevented angiotensin II and DOCA-salt hypertension in mice by inducing expression of GATA-binding protein 5.[12] A role for these two nuclear sirtuins in modifying gene expression pathways involved in hypertension is not surprising but also a testament of the complexity of the disease.

Dikalova et al. provide direct evidence that increasing SIRT3 protects from the development of hypertension and vascular dysfunction. Additional studies are necessary to understand why SIRT3 levels decrease in age-related diseases, including hypertension, and the molecular mechanism by which mitochondrial superoxide alters cellular function to increase blood pressure. Meanwhile, the involvement of SIRT3 in diverse diseases has prompted researchers and pharmaceutical companies to develop SIRT3 activators. Many polyphenols modulate sirtuin activity. For example, honokiol, a natural biphenolic compound derived from the bark of magnolia trees and used in traditional Asian medicine, directly binds and activates Sirt3. Long-term administration of honokiol to spontaneously hypertensive rats decreased blood pressure and vascular hypertrophy.[13] Strategies to increase SIRT3 activity may prove to be more effective than antioxidants in decreasing oxidant stress and preventing cardiovascular disease.

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References

1. Dikalova AE, Bikineyeva AT, Budzyn K, Nazarewicz RR, McCann L, Lewis W, Harrison DG, and Dikalov SI. Therapeutic targeting of mitochondrial superoxide in hypertension. Circulation Research. 2010;107:106–116. [PubMed: 20448215]
2. Witztum JL and Steinberg D. The oxidative modification hypothesis of atherosclerosis: does it hold for humans? Trends in Cardiovascular Medicine. 2001;11:93–102. [PubMed: 11686009]

3. Dikalova AE, Pandey AK, Xiao L, Arslanbaeva L, Sidorova T, Lopez MG, Billings FT IV, Verdin E, Auwerx J, and Harrison DG. Mitochondrial Deacetylase Sirt3 Reduces Vascular Dysfunction and Hypertension While Sirt3 Depletion in Essential Hypertension Is Linked to Vascular Inflammation and Oxidative Stress. Circulation Research. 2020.

4. Elkhwanky MS and Hakkola J. Extranuclear Sirtuins and Metabolic Stress. Antioxid Redox Signal. 2018;28:662–676. [PubMed: 28707980]

5. Pillai VB, Sundaresan NR, Jeevanandam V, and Gupta MP. Mitochondrial SIRT3 and heart disease. Cardiovasc Res. 2010;88:250–6. [PubMed: 20685942]

6. Dikalov S, Itani H, Richmond B, Arslanbaeva L, Vergeade A, Rahman SJ, Boutaud O, Blackwell T, Massion PP and Harrison DG. Tobacco smoking induces cardiovascular mitochondrial oxidative stress, promotes endothelial dysfunction, and enhances hypertension. American Journal of Physiology-Heart and Circulatory Physiology. 2019;316:H639–H646. [PubMed: 30608177]

7. Dikalova AE, Itani HA, Nazarewicz RR, McMaster WG, Flynn CR, Uzhachenko R, Fessel JP, Gamboa JL, Harrison DG and Dikalov SI. Sirt3 impairment and SOD2 hyperacetylation in vascular oxidative stress and hypertension. Circulation Research. 2017;121:564–574. [PubMed: 28684630]

8. Chen MI, Zhu Xh, Ran L, Lang Hd, Yi L and Mi Mt. Trimethylamine-N-oxide induces vascular inflammation by activating the NLRP3 inflammasome through the SIRT3-SOD2-mtROS signaling pathway. Journal of the American Heart Association. 2017;6:e006347. [PubMed: 28871042]

9. Case AJ, Tian J and Zimmerman MC. Increased mitochondrial superoxide in the brain, but not periphery, sensitizes mice to angiotensin II-mediated hypertension. Redox Biol. 2017;11:82–90. [PubMed: 27889641]

10. Chan SH, Tai MH, Li CY and Chan JY. Reduction in molecular synthesis or enzyme activity of superoxide dismutases and catalase contributes to oxidative stress and neurogenic hypertension in spontaneously hypertensive rats. Free Radic Biol Med. 2006;40:2028–39. [PubMed: 16716903]

11. Miyazaki R, Ichiki T, Hashimoto T, Inanaga K, Imayama I, Sadoshima J and 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. [PubMed: 18420994]

12. Guo J, Wang Z, Wu J, Liu M, Li M, Sun Y, Huang W, Li Y, Zhang Y and Tang W. Endothelial SIRT6 is vital to prevent hypertension and associated cardiorenal injury through targeting Nkx3. 2-GATA5 signaling. Circulation Research. 2019;124:1448–1461. [PubMed: 30894089]

13. Zhang G-S, Wang R-J, Zhang H-N, Zhang G-P, Luo M-S and Luo J-D. Effects of chronic treatment with honokiol in spontaneously hypertensive rats. Biological and Pharmaceutical Bulletin. 2010;33:427–431. [PubMed: 20190404]