



Mitochondrial deacetylase Sirt3 in vascular dysfunction and hypertension

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Purpose of review

Hypertension is a multifactorial disorder involving perturbations of the vasculature, the kidney, and the central nervous system. Hypertension represents a major risk factor for stroke, myocardial infarction, and heart failure. Despite treatment with multiple drugs, 37% of hypertensive patients remain hypertensive, likely due to the mechanisms contributing to blood pressure elevation that are not affected by current treatments. This review focuses on recently described novel role of mitochondrial deacetylase Sirt3 in vascular dysfunction and hypertension.

Recent findings

In the past several years, we have shown that the mitochondria are dysfunctional in hypertension; however, the role of mitochondria in the pathogenesis of hypertension remains elusive. We recently showed that patients with essential hypertension have decreased levels of the mitochondrial deacetylase Sirt3 leading to hyperacetylation of mitochondrial proteins. There is likely a causative role. Indeed, genetic deletion of Sirt3 in mice promotes vascular dysfunction and hypertension. Sirt3 depletion promotes endothelial dysfunction, increases smooth muscle cell hypertrophy, instigates vascular inflammation, and induces age-dependent hypertension.

Summary

Sirt3 is critical for vascular cell homeostasis, however, multiple risk factors impair Sirt3 leading to mitochondrial dysfunction and vascular dysregulation which contribute to hypertension and end-organ injury. Targeting Sirt3 may represent novel therapeutic approach to improve treatment of vascular dysfunction and reduce hypertension.

Keywords

metabolism, mitochondria, oxidative stress, Sirt3

INTRODUCTION

Despite significant progress in the treatment of hypertension, it represents a significant health burden worldwide. Based on the recent guidelines, nearly half of adult population has hypertension and 37% of hypertensive patients remain hypertensive even though treated with multiple drugs [1]. Hypertension is linked to vascular dysfunction which contributes to end-organ-damage in this disease. There is an urgent need for new therapies to improve the treatment of vascular dysfunction and hypertension. Targeting molecular mechanisms that are not affected by current medications can be beneficial for treatment of hypertension. Metabolic disorders and oxidative stress contribute to pathogenesis of vascular dysfunction and hypertension. Meanwhile, common antioxidants like ascorbate and vitamin E are ineffective in hypertension. Furthermore, current strategies to improve the

systemic hypercholesterolemia and hyperglycemia does not address the cellular metabolic dysregulations. Mitochondria plays a critical role in regulation of cellular metabolism and oxidative stress; however, the role of mitochondria in hypertension is still obscure. It is important to note that mitochondria are not just an 'ATP cow' [2]. Mitochondria perform

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KEY POINTS

- Hypertension is associated with reduced expression and diminished activity of mitochondrial deacetylase Sirt3 resulting in hyperacetylation of mitochondrial proteins.
- Cardiovascular disease risk factors, such as aging, smoking, inflammation, and metabolic conditions causes Sirt3 impairment which contributes to development of vascular dysfunction and hypertension.
- Future clinical studies must be directed to determine the therapeutic potential for targeting Sirt3 in vascular dysfunction, essential hypertension, and hypertensive end-organ-damage using novel Sirt3 agonists and mitochondria-targeted strategies.

wide range of physiological metabolic and synthetic reactions, they regulate genome expression, cellular metabolic processes, cell homeostasis and cell death [3]. In the past decade, the role of mitochondrial dysfunction has been recognized as a contributing factor in cardiovascular pathological conditions [4,5¹¹], however, specific mitochondrial defects in hypertension are not characterized. Our group discovered that hypertension is associated with impairment of mitochondrial deacetylase Sirt3 (silent mating type information regulation 2 homolog 3). Sirt3 is critical in regulation of metabolic and antioxidant functions such as fatty acid β -oxidation and superoxide dismutase activity [6,7]. Unfortunately, the role of Sirt3 has been largely ignored. In this paper, we will discuss the Sirt3 alterations in vascular dysfunction and hypertension and discuss the therapeutic potential of mitochondria-targeted treatments in hypertension.

PHYSIOLOGICAL ROLE OF MITOCHONDRIAL DEACETYLASE SIRT3

The human Sirt3 protein deacetylase is expressed in the nuclei as 37 kDa precursor and transported into mitochondrial matrix where it is exclusively residing following truncation to 29 kDa protein [8]. Acetylation of protein lysine residues is a predominant posttranslational modification of mitochondrial proteins affecting enzymatic activity, stability, and complex formation because it changes the positively charged lysine residue to uncharged bulky lipophilic state. Sirt3 acts as a sensor of energy and redox metabolism because it requires NAD⁺ (nicotinamide adenine dinucleotide) and is regulated by Acetyl-CoA abundance [9]. Sirt3 mediated deacetylation is critical for regulation of Krebs cycle, fatty acid β -oxidation, superoxide dismutase 2

(SOD2), and mitochondrial electron transfer chain. Diet and nutrient availability dramatically affect Sirt3 levels and activity, for example, chronic high fat diet reduces Sirt3 expression, whereas calorie restriction increases Sirt3 levels [10]. Overall, Sirt3 function plays an important role in cellular homeostasis by regulation of mitochondrial metabolic pathways, activity of the antioxidant enzymes, and diminishing cellular inflammation [11,12].

IMPAIRMENT OF SIRT3 IN PATHOLOGICAL CONDITIONS

Clinical studies have shown that cardiovascular disease risk factors reduce Sirt3 level and Sirt3 declines with age [13], paralleling the increased incidence of cardiovascular disease and hypertension [14]. We have recently shown that patients with essential hypertension have decreased levels of the mitochondrial deacetylase Sirt3 leading to hyperacetylation of mitochondrial proteins [15]. There is likely a causative role. Indeed, genetic deletion of Sirt3 in mice increases vascular hypertrophy, promotes endothelial dysfunction, and increases hypertension while increased Sirt3 expression reduces vascular dysfunction and attenuates hypertension [16¹¹].

Longevity, risk factors and Sirt3 expression

Variable number tandem repeats in enhancer is associated with increased Sirt3 expression and human longevity, [17] whereas metabolic conditions, sedentary lifestyle, aging, smoking, and activation of renin-angiotensin II pathway reduce Sirt3 levels [13]. The role of Sirt3 in longevity is also supported by the reduced live span in the Sirt3 knockout mice and that increased Sirt3 expression reduces markers of cell-senescence and diminishes age-dependent cellular alterations [18]. These data suggest a potential role of Sirt3 decline in the age-associated vascular dysfunction and hypertension.

Sirt3 inactivation

Clinical studies show that cardiovascular disease risk factors are associated with reduced Sirt3 level [13] and activity [19]; however, specific mechanisms of Sirt3 impairment in human conditions have not been defined. Our human and animal studies showed 30% reduction in Sirt3 level and three-fold decrease in Sirt3 activity in hypertension implicating both reduced Sirt3 expression and Sirt3 inactivation in Sirt3 impairment [15,16¹¹]. There are several mechanisms which can reduce Sirt3 activity. First, NAD⁺ depletion inhibits activity of NAD⁺-dependent Sirt3 which can be rescued by

supplementation with NAD⁺ precursor nicotinamide riboside [20]. Indeed, animal and clinical studies showed potential benefits of nicotinamide riboside supplementation [21]. Second, Sirt3 is inactivated by S-glutathionylation of cysteine residue in the catalytic region while scavenging of mitochondrial H₂O₂ in mCAT mice diminishes Sirt3 S-glutathionylation and reduces hypertension [15]. Third, oxidative stress leads to formation of highly reactive and cytotoxic lipid oxidation products, isolevuglandins (isoLGs), which covalently adduct to proteins and inhibit Sirt3 activity [22]. To test the pathological role of mitochondrial isolevuglandins we developed mitochondria-targeted scavenger of isoLGs, mito2HOBA. It was found that mito2HOBA reduces protein-isolevuglandins adducts, improves deacetylation of mitochondrial proteins, improves mitochondrial and endothelial functions, and reduces hypertension [23^{***}]. We propose that metabolic conditions downregulate Sirt3 activity due to decrease in NAD⁺ and increase in Acetyl-CoA while oxidative stress causes redox inactivation of Sirt3. Therefore, Sirt3 inactivation may represent a new convergent mechanism underlying the interplay of major cardiovascular risk factors (Fig. 1).

Oxidative stress and Sirt3 impairment

Hypertension is associated with oxidative stress and inactivation of key antioxidant enzyme SOD2 due to reduced Sirt3 activity and SOD2 acetylation [15]. This results in imbalance between mitochondrial superoxide

production and SOD2-mediated superoxide dismutation leading to increased superoxide levels and oxidative damage of mitochondria. We proposed that increased Sirt3 expression reduces SOD2 acetylation and prevents SOD2 inactivation. Indeed, Sirt3 overexpression in mice prevents SOD2 hyperacetylation and inhibits vascular oxidative stress. Furthermore, increased Sirt3 expression attenuates development of hypertension in angiotensin II and DOCA-salt models [16^{***}].

In recent studies, we proposed that oxidative stress can directly contribute to Sirt3 inactivation due to formation of harmful lipid peroxidation products, isolevuglandins, in mitochondria. We discovered 250% increase in mitochondrial isolevuglandins in arterioles isolated from patients with essential hypertension [23^{***}]. Interestingly, scavenger of mitochondrial isolevuglandins, mito2HOBA, protects Sirt3 activity, improves SOD2 deacetylation and inhibits endothelial oxidative stress. We propose a feed-forward cycle between Sirt3 inactivation and mitochondrial isolevuglandins, and mito2HOBA breaks this cycle, improves vascular function, and reduces hypertension (Fig. 2).

Metabolic dysfunction – oxidative stress crosstalk

Patients with metabolic disorders are at greater risk for endothelial dysfunction and hypertension [24,25], and metabolic alterations are critical in the pathogenesis of cardiovascular disease. Mitochondria play a key role in the cellular metabolism; however, specific role

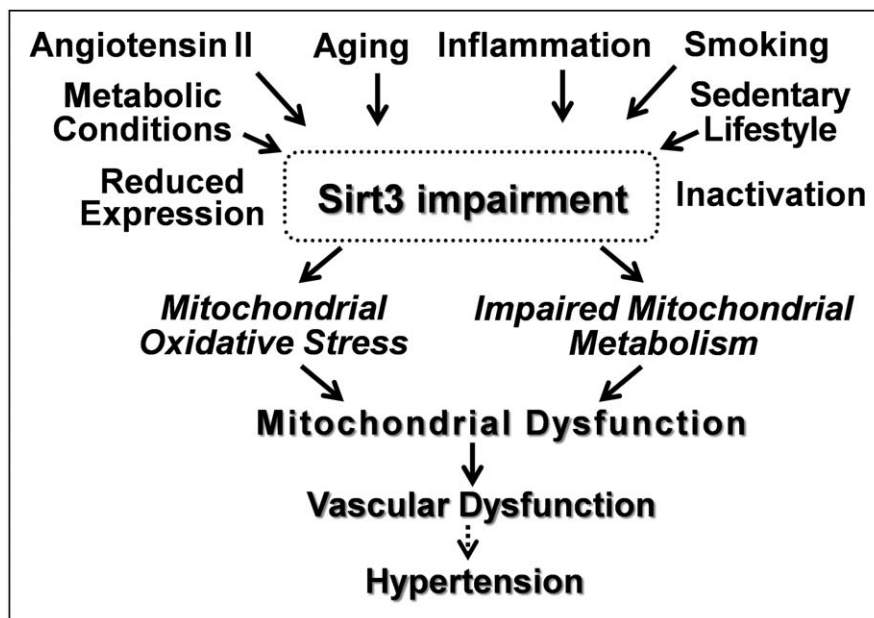


FIGURE 1. Multiple risk factors for hypertension, such as aging, metabolic conditions, smoking, and sedentary lifestyle reduce Sirt3 expression and activity which contributes to vascular dysfunction and hypertension.

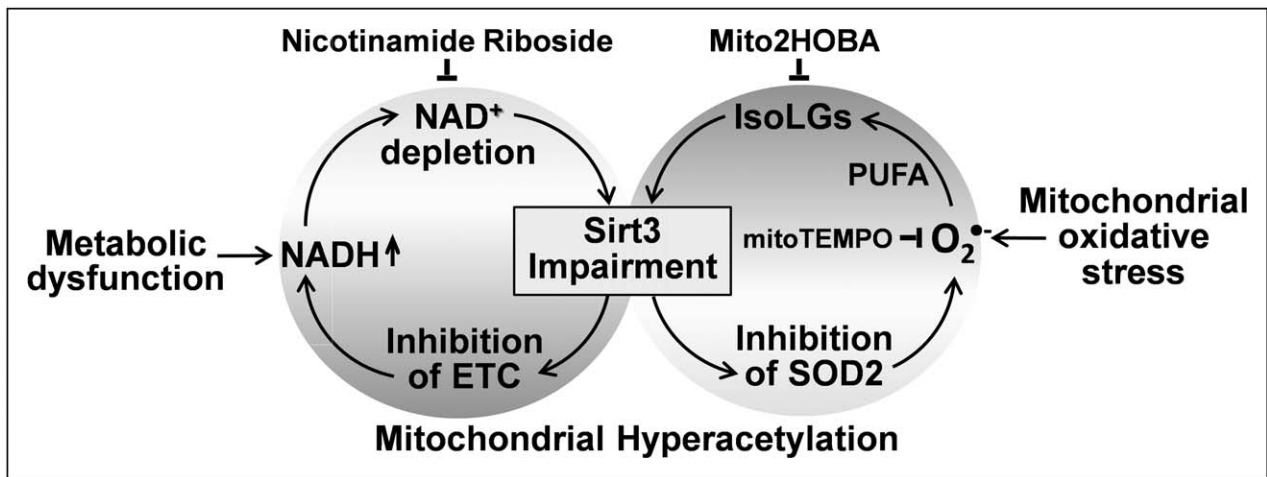


FIGURE 2. Crosstalk between metabolic dysfunction and mitochondrial oxidative stress contributes to end-organ dysfunction and hypertension.

of impaired mitochondrial metabolism in endothelial dysfunction is still elusive. Sirt3 is essential for mitochondrial fatty acid β -oxidation and mitochondrial electron transfer because Sirt3 activates long-chain acyl coenzyme A dehydrogenase, complexes I and V by deacetylation of specific lysine residues [26]. Oxidative stress promotes metabolic dysregulation, whereas metabolic conditions increase the production of reactive oxygen species [27,28]. This results in crosstalk between metabolic disorders and oxidative stress [29]. Sirt3 is one of the key nodes regulating both cellular metabolism and oxidative stress; therefore, targeting Sirt3 can break this viscous cycle and improve vascular function (Fig. 2).

Sirt3 depletion and inflammation

Activation of immune cells, increased production of inflammatory cytokines, and stimulation of

proinflammatory pathways in nonimmune cells have been recognized as critical drivers of hypertension and vascular dysfunction [30]. Interestingly, Sirt3 depletion promotes vascular inflammation while increased Sirt3 expression and activity inhibits expression of inflammatory markers and reduces inflammatory cytokine levels [12,16]. It has been proposed that targeting modifiable risk factors to improve Sirt3 activity by calorie restrictions, exercise, and smoking cessation can reduce vascular inflammation.

TARGETING SIRT3 IN HYPERTENSION

The studies described above support the pathogenic role of Sirt3 impairment in vascular dysfunction and hypertension suggesting therapeutic potential of targeting Sirt3 in these pathological conditions (Fig. 3). Several clinical and preclinical studies support this idea.

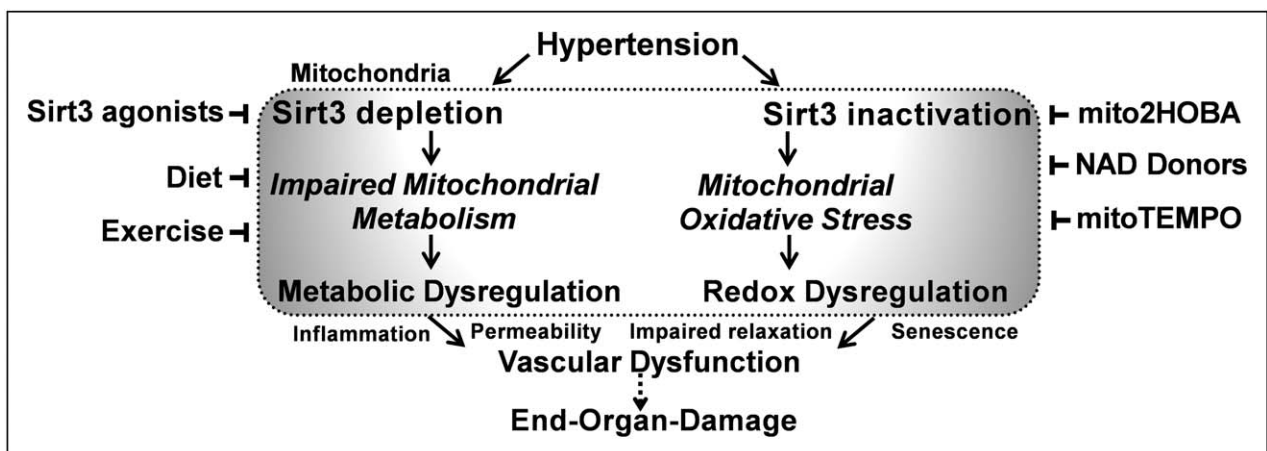


FIGURE 3. Targeting Sirt3 in hypertension. Hypertension is associated with reduced Sirt3 expression and Sirt3 inhibition. This can be improved by Sirt3 agonists diet and exercise increasing Sirt3 protein levels, whereas mito2HOBA, NAD donors, and mitoTEMPO can attenuate Sirt3 inactivation and inhibit the mitochondrial oxidative stress.

NAD⁺ donors

There are several NAD⁺ donors tested, including niacin, nicotinamide mononucleotide, nicotinamide riboside which can increase the Sirtuins activity; however, the results are widely varying [31[■]], and we need a better understanding of the therapeutic role of NAD⁺ precursors in human diseases.

Calorie restriction and Sirt3 expression

Calorie restriction is known for antiaging, anti-inflammatory, renoprotection, and antihypertensive effects which are linked to Sirt1 and Sirt3 upregulation and Sirt3 depletion voids protective effect of calorie restriction [32,33].

Sirt3 agonists inducing Sirt3 expression

Several polyphenols including natural compound honokiol and its derivative hexafluoro honokiol are able to increase Sirt3 expression and activity [34]. Chronic treatment of spontaneously hypertensive rats with honokiol decreases blood pressure and vascular hypertrophy [35].

CONCLUSION

There is a clear evidence for Sirt3 impairment in cardiovascular disease and hypertension. Sirt3 may represent a novel target in these pathological conditions. Animal studies support the pathophysiological role of Sirt3 dysfunction; however, therapeutic potential for Sirt3 targeting requires further preclinical and clinical studies using Sirt3 agonists, NAD⁺ donors and other approaches.

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Conflicts of interest

S.D. is an author on a patent application 'Mitochondria-Targeted Isoketal/Isolevuglandin Scavengers', International Application No. PCT/US2020/015197, filed January 27, 2020.

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