

Mitochondria - hypertension relationship, a novel ground for crossing the therapy frontier

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Abstract

Mitochondria are viewed nowadays not only as the powerhouse of the cells, but also as a key contributor in signaling regulation of intracellular homeostasis and survival. The role of mitochondria in hypertension is a novel, hot topic. Although the mechanistic involved is only partly deciphered by now, attempts for exploitation of the results in clinical trials are ongoing, aiming alleviation of the hypertension-associated end organ dysfunctions. Here, we briefly examine the progress so far on: (i) the mutations in mitochondrial transfer RNA genes, as risk factors in maternally inherited essential hypertension, (ii) the distinctive mitochondrial traits associated with hypertension (mitochondrial-related oxidative stress, hyperacetylation, and Sirtuin 3 deficiency), and (iii) the state of art on mitochondria-targeted therapies in hypertension. The above topics point not only to the current trends of basic research on mitochondria - hypertension correlation, but also to novel conducts in hypertension prevention and therapy.

Keywords: mtDNA, mttRNA, point mutations, mitochondrial dysfunction, SOD2, hyperacetylation, Sirt3

Introduction

The nowadays concept of personalized medicine has been anticipated in 1903 by Sir William Osler (Canadian physician, 1849 -1919, “The Father of Modern Medicine”); in his own words “the good physician treats the disease; the great physician treats the patient who has the disease” [1]. Since then, the quest for identification of the key inducer mechanisms of a disease, and for the right conduit for its alleviation still challenges the scientists.

Taking hypertension as an example, this multifactorial disorder implies a variety of inductors (genetic, environmental, anatomical, adaptive neural, endocrine, humoral, and hemodynamic factors) that contribute to the renal, cardiac, and vascular damages [2]. Interestingly, more than 90% of the hypertensive patients are currently diagnosed with “essential hypertension” (EH), or hypertension with undetermined causes [3]. The EH develops mostly under the influence of genetic factors and is maternally inherited [4]. It evolves with contribution of vascular mechanisms (endothelial dysfunction and reduced endothelial nitric oxide production) [5-7], the renin-angiotensin-aldosterone system (RAAS), metabolic syndrome, and a disturbed basal sympathetic tone [8]. Mitochondrial dysfunction is a

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newly recognized attribute of EH. It is associated with: (i) reduced electron transport chain activity and ATP generation, (ii) overproduction of reactive oxygen species (ROS), such as the harmful superoxide anions and hydroxyl radicals (that do not diffuse across membranes) and the hydrogen peroxide (a freely diffusible molecule), and (iii) the impaired mitochondrial dynamics. Recently, the investigation of the mitochondrial genome uncovered several molecular mechanisms underlying EH. Here we provide a survey on the followings: (i) the mutations in mitochondrial (mt) – transfer RNA (tRNA) genes, inherited risk factors in EH, (ii) the distinctive mitochondrial traits associated with hypertension, i.e. mitochondrial oxidative stress, mitochondria hyperacetylation, and Sirtuin 3 (Sirt3) deficiency, and (iii) the mitochondria-targeted therapies in hypertension.

(i) The mutations in mitochondrial (mt) – transfer RNA (tRNA) genes, inherited risk factors in EH

The genome of the mammalian mtDNA consists in 37 genes: 22 tRNAs, 2 rRNAs (12S and 16S rRNA), and 13 mRNAs encoding the proteins of the electron transport chain. As mitochondria contain less repair and protection systems, compared to the nucleus, the mtDNA is susceptible to mutations (nucleotide modifications). The most vulnerable to mutations are the 22 tRNAs, a modification acknowledged as one of the molecular bases of EH. Representative mt-tRNA mutations and the corresponding consequences are the followings [3, 9]:

- (a) the tRNAMet A4435G point mutation, that reduces with ~40-50% the tRNAMet level, alters the tRNAMet structure, impairs mt-tRNA metabolism, decreases ATP synthesis and mitochondrial membrane potential, and increases ROS generation. Thus, installment of mitochondrial dysfunction appears to be the ultimate contributor to EH in families carrying the A4435G mutation [10],
- (b) the tRNAMet and tRNAGln A4401G mutations conduct to defective processing and deficiency of tRNAMet transcription, associated with reduced mitochondrial oxygen consumption rate; the mutation is conserved for generations in the maternal lineage of Han Chinese families with EH,

- (c) the tRNAIle A4263G mutation is linked to diminished mitochondrial protein translation, increased ROS levels, and mitochondrial dysfunction,
- (d) the tRNAIle T4291C mutation, involves substitution of cytidine for uridine, impairs ribosomal binding, being correlated with metabolic defects,
- (e) the tRNAIle A4295G mutation conducts to a decrease in complex III protein levels, and to reduced mitochondrial respiratory chain functions,
- (f) tRNAMet 4467 C>A (cytosine to adenine) mutation contributes to oxidative stress and mitochondrial biogenesis dysfunction, both involved in maternally inherited EH [11],
- (g) tRNA Ala 5587T>C (thymine to cytosine) and tRNALeu(CUN) 12280A>G (adenine to guanine) mutations may lead to the failure of tRNAs metabolism, mitochondrial protein synthesis defects, and mitochondrial dysfunctions that are responsible for hypertension [12].

The mechanistic behind mt tRNA mutations is a novel issue to be considered in clinical manifestations of EH. Now, one can safely conclude that the maternally inherited EH involves mutations in mt tRNA that cause/aggravate mitochondrial dysfunction underlined by reduced ATP generation and increased ROS levels, launching the mitochondrial-mediated cell death pathways [3, 9].

(ii) The distinctive mitochondrial traits associated with hypertension

Hypertension is associated with oxidative stress, and mitochondria-derived ROS are important contributors to the renal and cardiovascular-related oxidative damages [13]. Mitochondria possess an own enzyme equipment that keeps ROS production under control. When the antioxidant capacity is exceeded, the oxidative stress is installed. The potent antioxidant melatonin is synthesized locally and is also taken up by mitochondria; it scavenges the toxic free radicals and regulates also the renin-angiotensin system [14]. The efficiency of antioxidants is proven by the fact that targeting mitochondrial oxidative stress has anti-hypertensive potential. Among the antioxidants with therapeutic potential we quote the superoxide dismutase (SOD) mimetics, which reduce also the blood pressure [15] and the targeting of mitochondrial Cyclophilin D, a source of toxic superoxide anions [16]. Furthermore, during post-translational modifications

of antioxidant SOD2 the positively charged lysine residues within the highly conserved catalytic center (in positions 68 and 122) are subjected to hyperacetylation. This reaction induces SOD2 conformational changes, steric hindrance, and the loss of electrostatic guidance for the superoxide anions within the active center. Nowadays, hyperacetylation is considered a prognostic factor in hypertension [17]. A close related partner of SOD2 is the NAD⁺-dependent deacetylase Sirt3; its reduced expression and redox inactivation leads to SOD2 downregulation and contributes to the pathogenesis of hypertension [18].

The alterations of mitochondrial dynamics in white adipose tissue were reported as contributors to the development and maintenance of hypertension-related to obesity [19].

Previous reports emphasized that the dynamic shape changes of mitochondria contributes to bioenergetics capacity preservation and mtDNA homeostasis [20, 21]. These roles are accomplished by three essential processes:

- (i) the “fusion” of dysfunctional mitochondria with “healthy” ones, with participation of specific molecules: mitofusin1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 (OPA-1) [22],
- (ii) the opposite “fission”(fragmentation) process that removes the malfunctional part, with involvement of dynamin-related protein 1 (Drp 1) and mitochondrial fission 1 protein (Fis1) [23], and
- (iii) the final autophagic degradation of mitochondria, known as mitophagy. Recently, a correlation was reported between mitochondrial dysfunction in endothelial progenitor cells (EPCs) and capillary rarefaction observed in hypertension; the mechanism consists in the deficient CXCR4/JAK2/SIRT5 signaling pathway, and indicates the potential of late EPCs mitochondria as a target for correction of the lower angiogenic ability in hypertension [24].

Interestingly, mtDNA appears in urine, and their elevated copy numbers in hypertensive patients indicate mitochondrial injury associated with renal dysfunction [25]; it is suggested that the mitoprotective drug elamipretide reduces the urinary mtDNA copy numbers at percutaneous transluminal angioplasty, improving blood pressure and the kidney functional outcomes [26].

(iii) The mitochondria-targeted therapies in hypertension.

Over recent years, the mitochondria targeting emerged as a promising strategy for mitigation of hypertension-related end-organ damages. A valuable approach is the use of mitochondria-targeted antioxidants. Examples are:

- (i) mitoTEMPO, that attenuates endothelial dysfunction (characterized by oxidative stress, reduced nitric oxide generation, and impeded vasorelaxation) and reduces blood pressure,
- (ii) mitoEbselen, that diminishes vascular oxidative stress and significantly reduces blood pressure,
- (iii) Ubiquinone, that improves oxidative phosphorylation and reduces “electron leakage” in mitochondria [15],
- (iv) the use of cardiolipin-protective compound Bendavia (Stealth BioTherapeutics), that protects the structure of mitochondrial cristae and promotes oxidative phosphorylation; it is well tolerated as assessed by Multiple Phase 1 and phase 2 clinical trials [15].

What is at the horizon in translation of mitochondria-targeted antioxidants from the bench to the bedside of hypertensive patients? One can emphasize the future exploitation of SOD2 mimetics [27], of Sirt3 agonists [17], and of melatonin that generates protective effects by both antioxidant and mitochondrial-related anti-inflammatory traits [28]. The ongoing studies are focused on understanding the mechanisms that govern the relationship between the decline in CXCR4 signaling (in late EPCs), mitochondrial dysfunction, and impaired angiogenic capacity of EPCs [24]. Moreover, mitochondrial hyperacetylation requires in-depth studies on the role of acetyl-CoA-binding protein acetyltransferase [29], and on the still unclear mechanism of mitochondrial biogenesis dysfunction associated with the tRNAMet C4467A mutation [11].

From the data reported so far, it is obvious that further experimental studies and clinical trials are needed to confirm the efficacy and safety of mitochondrial targeting; however, both basic researchers and clinicians should be aware that the mitochondria-targeted compounds may encompass also non-mitochondrial effects, that contribute to attenuation of hypertension-related dysfunctions [30].

Conclusion

The deciphering of mitochondria-hypertension relationship provides solid grounds for therapeutic exploitation. The topic is challenging, and the ongoing research is directed towards identification of mitochondria-targeted compounds with higher therapeutic efficiency in prevention /alleviation of hypertension.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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