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Invited Review

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Mitochondria revisited: Hypertension-related alterations and perspectives for therapy

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Abstract

Systemic hypertension increases heart workload, expose luminal vascular endothelium to shear stress, and alters cardiomyocytes structure and function. To fulfill cellular energetic demands, mitochondria generate ATP through the electron transport chain located on the inner mitochondrial membrane. This chain generates also reactive oxygen species (functioning as secondary messengers in signal transduction and metabolism) and imbalances the redox signaling, as key intracellular mechanisms implicated in hypertension onset and progression. The current overview presents and discusses novel issues in hypertension-related mitochondrial dysfunction focusing on: (i) cardiomyocytes, and emphasizing the decline in mitochondrial biogenesis, the energetics deficiency regulated by the dynamic processes of fusion and fission, the ROS overproduction, and the augmented mitochondrial degradation by mitophagy, and on (ii) arterial smooth muscle cells mitochondrial defects. The review is concluded by outstanding research themes compulsory for filling the gaps on mitochondria-targeted strategies in hypertension.

Keywords: cardiomyocytes, arterial smooth muscle cells, fusion, fission, "kissing", mitophagy

Introduction

Systemic hypertension (HT) is an important risk factor for cardiovascular disease, including acute myocardial infarction and stroke. As HT prevalence continues to increase worldwide, both basic and clinical research of the last decade describe key findings on underlying mechanisms. At present, HT is viewed as a multifactorial disease with genetic, environmental, anatomical, adaptive neural, endocrine, humoral, and hemodynamic causes having "oxidative stress" as a common denominator [1]. The latter implies an imbalance between the systemic manifestation of reactive oxygen species (ROS) and the cells ability to counteract the reactive intermediates or to repair their damages. Mitochondria are the main source of cellular ROS although their pathophysiological roles in HT are still incompletely understood [2]. The common opinion is that mitochondria have a core position in cellular homeostasis by their function as essential powerhouses of cells. Mitochondria utilize nutrients to generate ATP via the electron transport chain coupled with oxidative phosphorylation, *supporting cells survival* and normal function

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[3]. An example are mitochondrial cardiomyocytes that supply ATP for fulfilling the energetically demanding function of the heart [4]. The novel uncovered roles of mitochondria are related to control of cellular functions and metabolism, by several mechanisms: (i) contribution to maintenance of calcium homeostasis, (ii) intervention in cell signaling (via ROS) and modulation of redox signaling, (iii) generation of nitric oxide (NO) by mitochondrial nitric oxide synthase (NOS), (iv) interaction with other cellular organelles, nucleus included, (v) release of mitochondrial constituents (proteins, lipids, mitochondrial DNA, mtDNA) that can function as signaling molecules; these are known as "mitochondrial damage-associated molecular patterns"(DAMPs) considered to be potential biomarkers [5 - 8].

It is obvious that pathological defects in mitochondrial function, known as "mitochondrial dysfunction" are connected to reduced levels of generated ATP, to excessive ROS production, and diminished antioxidant defense. The latest data demonstrate that cardiac mitochondria cope with energetic deficiency by changing morphology through fission and fusion processes in an attempt to maintain their functionality [9]. Thus, mitochondrial energetic potential and morphology appear as both causal and resultant to excess ROS generation [4]. The overproduction of ROS irreversibly damages the cellular molecules and promote the intrinsic apoptotic pathway conducting to *mitochondria-related cell death* [10]. Among the pathologies associated with "mitochondrial dysfunction", the review is focused on systemic HT, as portal and pulmonary HT deserve distinct approaches. The following part examines the novel data on HT-related "mitochondrial dysfunction" in cardiomyocytes and resistance arteries smooth muscle cells.

Mitochondrial modifications in the hypertensive heart

There are several modifications of cardiomyocytes mitochondria in HT, such as the decline in biogenesis, reduced energetic efficiency, the overproduction of ROS, and the augmented degradation via mitophagy.

(i) **The decline of mitochondrial biogenesis** results from the inability of cardiomyocytes to support the increasing energy demand under pressure-overload conditions. Briefly, mitochondria biogenesis develops in response to energetic deficits, and is characterized by increase in cells mitochondrial mass [11, 12]. At molecular level, the mitochondrial biogenesis process is regulated by specific coactivators and transcription factors that control expression of components of the nuclear and mitochondrial genome. In this context, we quote peroxisome proliferator-activated receptor β/δ (PPAR β/δ), transcription factor peroxisome proliferator-activated receptor co-activator 1 α (PGC-1α, a known target gene of PPAR β/δ), Sirtuins, and AMP-activated protein kinase (AMPK) signaling cascades [13, 14]. To promote mitochondrial biogenesis, several pharmacological strategies exist, such as the use of bezafibrate to activate PPAR-PGC-1α axis, of quercetin or resveratrol as Sirt1 agonists, and of resveratrol to activate AMPK [14]. Recently, activation of cardiac AMPK was recognized as essential for accelerating ATP generation and repair of cardiomyocyte's function, ensuing protection of myocardium against cardiac dysfunction and apoptosis [15]. Another promoter of mitochondrial biogenesis is the prolonged laminar shear stress associated with aerobic exercise [16]. The alleviation of biogenesis decline is expected to increase the mitochondrial mass, oxidative metabolism and bioenergetics capacity under pressure-overload conditions.

(ii) **The deficient mitochondrial energetics**, i.e. the deficiency in ATP synthesis conducting to impaired heart contractility. The ATP deficit results from the complex interplay between mitochondrial ATP synthase and induction of the permeability transition pore (PTP), an inner membrane channel and key effector of cell death. Reports indicate that dimers of the ATP synthase form PTP [17, 18]. The malfunctioning cardiomyocyte mitochondria cope with energetic deficiency by *fusion* with "healthy" organelles, resulting in formation of elongated structures (Figure 1a) that survive under a lower energy outcome; moreover, normal mitochondria that locally display a modified membrane potential or the dysfunctional elongated organelles are subjected to *fragmentation (fission)* followed by removal of the dysfunctional part by autophagic degradation (mitophagy), while the "healthy" part of the organelle is committed to new fusions [19]. The dynamic processes of fusion and fission engage the interfibrillar mitochondria packed between sarcomeres, while the subpopulations of mitochondria located subsarcolemmal (Figure 1b) and perinuclear are not subjected to such sequences. Another form of mitochondrial dynamics is the close contact "*the kissing*" of the outer membranes in adjacent mitochondria [20]; zones with high density of mitochondria are common in the heart, and the "kissing" between them allows local intermitochondria communication (Figure 1c). Mitochondrial abnormalities have been identified in experimental models of HT [21]. Thus, in the left ventricle of spontaneously hypertensive rats mitochon-

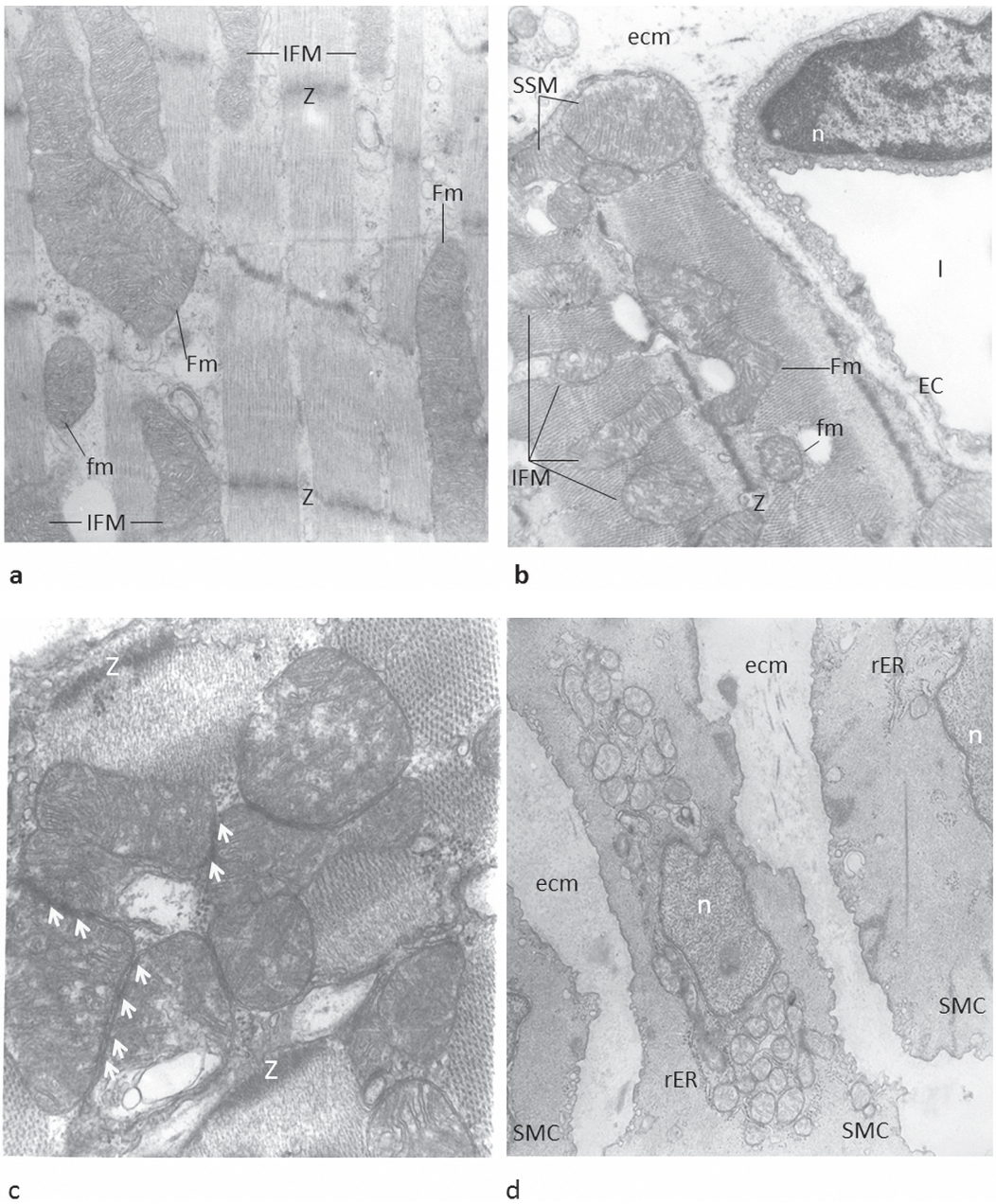

Figure 1. Representative transmission electron microscopy images of mitochondrial dysfunction in left ventricular cardiomyocytes (a, b, c) and resistance arteries smooth muscle cells (d). Note the partially damaged lamelliform structure of cristae in subsarcolemmal mitochondria (SSM)(a), the tubular structure of cristae in interfibrillar mitochondria (IFM), the fusion of the latter into elongated structures (Fm) and fragmentation into smaller mitochondria (fm)(a and b), the close contact ("kissing") of outer membranes of adjacent mitochondria, one apparently "healthy" and the other with partially destroyed cristae; their contacts appear at repeated sites (small arrows) and form communication zones between the two neighbors (c), the apparently swollen mitochondria, and their reduced cristae surface in a perinuclear zone of a smooth muscle cell (SMC) within the wall of a resistance artery (d). Abbreviations: Z: Z band, n: nucleus, rER: rough endoplasmic reticulum, ecm: extracellular matrix. Magnification: (a, b and d) x26,280; (c) x54,600.

drial dynamics is imbalanced, and is characterized by decreased levels of mitochondrial fission protein dynamin related protein-1(Drp1, localized to the outer mitochondrial membrane) and increased expression of fusion protein optic atrophy protein 1(OPA1, localized to the inner mitochondrial membrane), along with decreased SirT1/AMPK-PGC-1α signaling (involved in mitochondrial biogenesis) [22]. Among the strategies aiming energy recovery in HT, we quote activation of cardiac AMPK that accelerates ATP generation, attenuates ATP reduction, and protects the myocardium

against cardiac dysfunction and apoptosis [15], and the control of glutathionylation reactions mediated by glutaredoxin-2 (Grx2) [23]. Taken together, the novel results support the opinion that in cardiomyocytes, the impairment in energy generation is regulated, at least in part, by dynamic processes such as mitochondrial fusion, fission, and "kissing".

(iii) **The overproduction of mitochondrial ROS**. In human HT, excess generation of mitochondrial ROS, the exacerbated response to ROS, and the reduced efficiency of endogenous mitochondrial protective antioxidant defense mechanisms are issues under in depth scrutiny at present [1, 24, 25]. The common perception is that oxidative stress amplifies blood pressure elevation in the presence of pro-hypertensive factors (such as salty diet, activation of renin-angiotensin system, RAS) causing HT-related target-organ damage [26]. Moreover, there is a genetic link between mitochondrial proteins and HT. Thus, polymorphisms in cytochrome c gene (a subunit of complex IV) and in OPA-1 and mitofusin-2 (Mfn-2) genes are correlated with blood pressure [27–29]. The ROS cause an increased number of mtDNA deletions; in turn, damaged mtDNA codes for mutated polypeptides including those responsible for loss of the integrity of the respiratory chain, aggravating oxidative stress and damaging both nuclear and mtDNA [30]. Among the adaptive mechanisms induced in HT in response to increased production of mitochondrial ROS, we quote: (i) overexpression of major scavengers of mitochondrial $O_2^{\bullet -}$ and H_2O_2, such as superoxide dismutases 2 (SOD2) and glutathione peroxidase, (ii) increased expression of antioxidant enzymes (such those involved in glutathione synthesis), by induction of redox sensitive transcription factor NF-E2-related factor 2 (NRF2), (iii) attenuation of AngII-induced cytoplasmic and mitochondrial $O_2^{\bullet -}$ production, by mitochondrial reverse electron transfer inhibition with malonate, malate, or rotenone, (iv) inhibition of Nox, by NAPDH-oxidase inhibitor apocynin, (v) in vivo treatment of mice with mitochondrial targeted antioxidant, mitoTEMPO, and (vi) stimulation of mitochondrial uncoupling protein 2 (UCP2) [1, 31 - 33]. Interestingly, according to the new concept of "mitochondrial hormesis" or "mitohormesis" low levels of ROS induce an adaptive response, improving systemic defense mechanisms [34]. The above achievements demonstrate the advancement in our understanding since the earlier hypothesis according to which mitochondrial dysfunction *may be* involved in the development of systemic HT [29].

(iv) **The augmented mitochondrial degradation**. The last step in mitochondrial turnover is their degradation by autophagy (mitophagy), considered the hottest topic in mitochondrial biology [35]. Specifically, the damaged mitochondria resulting from the fission process are sequestered within autophagosomes and degraded after fusion with the lysosomal compartment. Mitophagy is a novel uncovered process of central role in cellular metabolism, as sustained by the following achievements: (i) it ensures cellular bioenergetics capacity and cellular homeostasis, by balancing biogenesis process, (ii) preserves a healthy population of mitochondria, by removal of damaged ones, (iii) promotes mitochondrial biogenesis under basal conditions, and (iv) it is a player in mitochondrial "quality control", involving transcriptional activation of nuclear genes during mitochondrial-nuclear communication via mitochondrial unfolded protein response (UPRMT) [5, 36 – 39]. In hypertensive hearts, mitophagy is enhanced in obesity and renovascular HT, and dysfunctional mitochondria are mentioned as contributors to this pathology [40 - 42]. At present, research is focused on procedures/compounds that maintain structural integrity of mitochondria [16]. In this context valsartan (an angiotensin II receptor blocker) appears as a therapeutic option ameliorating myocardial autophagy and mitophagy [40].

Mitochondrial modifications in the arterial smooth muscle cells

HT causes changes in the structure and function of the large and small resistance arteries. Besides inducing endothelial dysfunction, HT modifies vascular smooth muscle cells (VSMCs) phenotype. Recent results demonstrate that mitochondrial dysfunction is implicated in the regulatory control of VSMCs phenotype [43]. Figure 1d illustrates the conversion of the SMCs contractile phenotype into a secretory one in mesenteric resistance arteries; the switch of phenotype is assessed by the presence of rough endoplasmic reticulum, the site of protein synthesis. Mitochondrial dysfunction is illustrated by the occurrence of less electron dense mitochondria of rather small size, by reduced cristae density/mitochondrion, and by altered morphology of cristae organization. The small size mitochondria could be the result of a fission process involved in cells migration [44], as VSMCs express the mitochondrial fission protein DRP1; literature data assess that in VSMCs DRP1 is regulated by resistin, an adipocyte-specific hormone and an important link between obesity, insulin resistance and diabetes [45]. VSMCs express also Mfn-2, a mitochondrial outer membrane fusion protein that causes mitochondria assemble into

tubular networks and their attachment to the endoplasmic reticulum [46]. The reduced cristae density/mitochondrion, and the altered morphology of cristae organization entail impeded oxidative phosphorylation associated with reduced bioenergetics capacity; at present it is estimated that VSMCs mitochondrial respiration is an incompletely deciphered subject [47]. In metabolic syndrome, accumulation of synthetic and proliferating VSMCs was associated with augmented expression of miR-21 and with coronary collateral growth [48]. Additionally, in diabetes VSMCs dysfunction is characterized by mitochondrial membrane hyperpolarization, impaired mPTP opening, and alterations in the balance of fission and fusion processes; the final results are enhanced VSMCs migration and impaired vasoreactivity [49]. The latter is particularly important for hypertensive resistance arteries, that expose to the blood flow a more constricted vascular wall.

Outstanding questions on mitochondria-targeted strategies in HT

The starting point in less understood HT- mitochondria interaction is the fact that the latter possess both a functional renin-angiotensin system (RAS) and vitamin D receptors, and HT has an increasing prevalence at old age people [1, 2]. In this context, investigation of the interaction between mitochondria-targeted antioxidants and inhibitors of the RAS system appears as necessary [1]. There are *several topics under intense investigation*, such as: (i) the mitochondria-associated membranes (MAMs) that entails the physical connection between mitochondria and endoplasmic reticulum, a site for the intracellular signaling [50], (ii) the mitophagy, (iii) the mitochondria delivery (by nanotechnology-based carriers)[51], (iv) the contribution of inflammation-induced mitochondrial dysfunction to intracellular signaling [52], and (v) the activation of the innate immune system via Toll-like receptor 9 (TLR9) in HT [53]. Moreover, a complex of factors, such as aberrant signal transduction, augmented ROS generation, impaired response to ROS, and decreased antioxidant reserve contribute to increased oxidative stress, inflammation, and autoimmune vascular dysfunction in human HT [24, 54].

At the horizon, the rapidly advancing field of mitochondrial pharmacology has great potential for clinical application [55]. The *novel therapeutic strategies* should address the following biological relevant open issues: (i) the quality control function of mitochondria (by mitochondria mass regulation and bioenergetics capacity maintenance) [56], (ii) the regulation of mitochondrial fission, with the intent to decrease VSMCs migration and limit intimal hyperplasia [57], (iii) the protection against mtDNA damage, aiming improvement in mitochondrial function [58], (iv) the use of mitochondria specific therapies (such the antioxidant MitoTEMPO, a superoxide and alkyl scavenger [31], and (v) the adequate analytical methods to accurately assess oxidative stress in the clinic [26].

Taken together, the above results illustrate the endeavors in understanding the correlation between mitochondrial dysfunction and HT, point towards the present gaps, and direct towards the potential strategies to ameliorate the dysfunctional condition.

Conflict of interests

The author confirm that there are no conflicts of interest.

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