Mitochondria: A Pathogenic Paradigm in Hypertensive Renal Disease
Alfonso Eirin, Amir Lerman, Lilach O. Lerman

Mitochondria were first described in 1840 as bioblasts, elementary organisms responsible for vital cellular functions, but were subsequently named mitochondria, from the Greek names mitos (thread) and chondros (granule), which describes their appearance during spermatogenesis.1 Their discovery generated substantial interest given their structure resembling bacteria, which led in subsequent years to important scientific discoveries positioning mitochondria as the energy powerhouse of the cell.

The unique architecture of mitochondria, consisting of 2 membranes (outer and inner) and compartments (intermembrane space and matrix), is crucial for their vital functions. Mitochondria serve not only as primary sources of cellular energy, but also modulate several cellular processes, including oxidative phosphorylation, calcium homeostasis, thermogenesis, oxygen sensing, proliferation, and apoptosis.2 Therefore, mitochondrial injury and dysfunction might be implicated in the pathogenesis of several diseases.

Hypertension accounts for nearly 30% of patients reaching end-stage renal disease.3 Renal injury secondary to hypertension or to ischemia associated with renovascular hypertension (distal to renal artery stenosis) may have significant and detrimental effect on health outcomes. Studies have highlighted several deleterious pathways, including inflammation, oxidative stress, and fibrosis that are activated in the hypertensive kidney, eliciting functional decline.4,5 However, the precise molecular mechanisms responsible for renal injury have not been fully elucidated.

Over the past few years, increasing evidence has established the experimental foundations linking mitochondrial alterations to hypertensive renal injury (Table). Mitochondriopathies, abnormalities of energy metabolism secondary to sporadic or inherited mutations in nuclear or mitochondrial DNA (mtDNA) genes, may contribute to the development and progression of hypertension and its complications. In addition, several studies have reported mitochondrial damage and dysfunction consequent to hypertensive renal disease.

Importantly, hypertensive-induced renal injury is characterized by activation of several deleterious pathways, including oxidative stress, renin–angiotensin–aldosterone system (RAAS), renal remodeling, and apoptosis, all of which may compromise mitochondrial integrity and function. In addition, although not a direct consequence of hypertension, post-stenotic kidneys of renovascular hypertensive subjects are exposed to similar noxious insults and renal hypoperfusion, which may lead to mitochondrial structural abnormalities and decreased energy production. The goal of this review is to summarize the current understanding of the effect of mitochondrial injury and dysfunction on the pathogenesis of hypertension and ischemic nephropathy. Furthermore, we shall briefly discuss the effects of antihypertensive therapy, as well as novel strategies targeted to mitochondria, on hypertension-related renal mitochondrial disease.

Mitochondrial Injury as a Primary Cause of Hypertension

The mitochondrial genome, passed on along the maternal line, codes for merely 13 functional mitochondrial proteins, 22 transfer (t)RNA, and 2 ribosomal RNA.16 Unlike nuclear genes, mtDNA is continually exposed to reactive oxygen species (ROS) and lacks histones, introns, and efficient DNA repair systems. Therefore, mtDNA is more vulnerable to mutations than nuclear DNA.

Few studies have suggested a causal role of mtDNA mutations in maternally inherited hypertension.17,18 For example, mutational analysis of mtDNA from a large Chinese family with maternally transmitted hypertension identified a novel homoplasmic 4263A>G mutation located at the processing site for the tRNA(Ile) 5′-end precursor, suggesting that this pathogenic mtDNA mutation causes a genetic predisposition to essential hypertension.17 Similarly, mitochondrial genome of individuals with hypertension shows a homoplasmic mutation substituting cytidine for uridine immediately 5′ to the mitochondrial tRNA(Ile) anticodon.18

Mutations in the mitochondrial genome can also contribute to the pathogenesis of left ventricular hypertrophy and stroke. Mutations in several tRNA genes have been associated with hypertrophic cardiomyopathy,19 whereas cytochrome-b mutations have been implicated in cardiomyopathy associated with neuropathy, ataxia, retinitis pigmentosa, and gastrointestinal

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dysmotility. Hypertrophic cardiomyopathy in Leigh’s syndrome results from mutations in the mitochondrial ATPase-6 gene. Likewise, reduced expression of the mitochondrial protein frataxin causes Friedreich’s ataxia, a rare disease characterized by neurodegeneration and heart disorders, including hypertrophic cardiomyopathy. Finally, a mutation in the mtND1, a gene that encodes NADPH dehydrogenase proteins, causes mitochondrial encephalomyopathy, lactic acidosis with mitochondrial dysfunction and their cause/effect relationship.

**Renal Mitochondrial Damage Secondary to Hypertension**

Hypertension is commonly associated with mechanical stretch, increased production of ROS, extracellular matrix turnover, and fibrosis, which in turn alter the structure and function of all cellular organelles, including the mitochondria (Figure S1A in the online-only Data Supplement). Furthermore, activation of the RAAS in some models of hypertension may contribute to activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, aggravating ROS production and mitochondrial oxidative damage.

**Increased Oxidative Stress**

Hypertension may stimulate the RAAS, followed by angiotensin (Ang)-II–mediated activation of NAD(P)H-oxidase in vascular smooth muscle cells. After p47 phosphorylation, cytosolic subunits assemble and translocate to the membrane, forming superoxide anion. In addition to RAAS activation, hypertension-induced mechanical stretch on resident renal cells leads to oxidative stress by upregulating the expression of NAD(P)H-oxidase, increasing ROS production.

In turn, increased levels of cytosolic ROS produce damage of mitochondrial proteins, nucleic acids, and lipids, stimulating a forward-feeding loop of mitochondrial ROS generation and aggravated cell damage. ROS-induced oxidation of electron-transport chain complexes in the inner mitochondrial membrane impairs mitochondrial respiration and adenine triphosphate (ATP) production. Moreover, ROS induces mutations in mtDNA, which alter the coding instructions for mitochondrial proteins, including electron-transport chain-complex-IV and ATPase synthase subunits, decreasing electron-transport chain activity and ATP synthesis.

ROS-induced impairment in mitochondrial bioenergetics has been demonstrated in several models of experimental hypertension (Table). For example, decreased membrane potential and increased ROS production have been observed in glomerular and tubulointerstitial cells from spontaneously hypertensive rats. Similarly, mitochondria in the medullary thick ascending limb in Dahl salt-sensitive rats exhibit lower rates of oxygen utilization, underscoring their role in hypertension. Importantly, in rat kidney mitochondria, low respiration rates are associated with augmented mitochondrial release of hydrogen peroxide to the cytosol, creating a vicious cycle that aggravates oxidative damage.

Cytosolic ROS also cause peroxidation of cardiolipin, a phospholipid exclusively found in the inner mitochondrial membrane, where it sustains its structure and function.
Importantly, peroxidation of cardiolipin triggers formation of the mitochondrial permeability transition pore (mPTP), a voltage-dependent anion channel that allows passage of small molecules from the matrix to the cytoplasm. Opening of the mPTP favors release of mitochondrial ROS and cytochrome-c, eventuating in induction of the caspase-3 and -9 apoptotic pathway and cellular death.

Under normal conditions, mitochondrial superoxide dismutase-1 and -2 detoxify superoxide (\(O_2^-\)) into hydrogen peroxide, acting as an antioxidant defense. High-salt diet in mitochondrial superoxide dismutase-deficient mice elevates arterial pressure and urinary albumin excretion and upregulates NADPH oxidase, suggesting an important role of mitochondrial ROS in development of renal injury secondary to hypertension. Importantly, ROS-induced disruption of mitochondrial membranes impairs activity of mitochondrial superoxide dismutase-1 and -2, producing an imbalance in oxidant/antioxidant mechanisms. Therefore, supplementation with antioxidants might attenuate renal hypertensive injury. Indeed, several experimental studies suggest that supplementation of vitamin E and C decreases oxidative stress and ameliorates renal dysfunction in hypertensive rats. However, clinical trials do not support antioxidant supplementation for a protective effect on cardiovascular disease, possibly because of their paradoxical pro-oxidant effects in subjects with unperturbed redox status. In agreement, we have previously shown that chronic supplementation with antioxidant vitamins increases oxidative stress in the normal pig kidney. Alternatively, negative results of clinical trials might be secondary to the lack of protective effects of these compounds on mitochondria. Although antioxidants scavenge harmful ROS, they do not necessarily attenuate mitochondrial ROS production, resulting in incomplete antioxidant protection.

**The RAAS**

Recently, Abadir et al identified functional components of the RAAS in human mitochondria, specifically Ang-II type-2 receptor in the inner mitochondrial membrane in cardiac myocytes, renal tubular cells, and brain neurons. Furthermore, its activation modulates mitochondrial respiration, membrane potential, and ROS generation, suggesting that direct effects of Ang-II on the mitochondria may regulate hypertensive cellular injury. Additionally, Ang-II type-1 receptor activation stimulates vascular ROS formation via NADPH oxidase, which may promote local mitochondrial ROS production (Figure S1A). In agreement, studies in cultured human aortic endothelial cells and mouse models demonstrated that Ang-II induces mitochondrial superoxide production by Nox-2.

**Renal Remodeling**

Regardless of its origin, fibrosis is the final common pathway that perturbs renal structure and function. Strong evidence indicates that matrix metalloproteinases, implicated in Ang-II–induced hypertension, damage the mitochondria by disturbing mtDNA integrity and opening the mPTP, activating the apoptotic cascade. Conversely, mitochondria might also be involved in the progression of renal fibrosis. We and others have shown that mitochondrial protection in hypertension attenuates tissue injury and fibrosis, suggesting that mitochondrial dysfunction secondary to hypertension may contribute to progressive renal fibrosis and dysfunction.

Renal mitochondrial damage and dysfunction may be exacerbated by coexisting cardiovascular risk factors, including smoking, diabetes mellitus, aging, and hypercholesterolemia. Mitochondrial damage is implicated in podocyte injury, an early event in diabetic nephropathy associated with rapid disease progression, and age-related mitochondrial dysfunction in rats is commonly accompanied by ultrastructural alterations and mtDNA mutations. Similarly, free cholesterol loading of macrophages in vitro instigates mitochondrial dysfunction and apoptosis. Interaction among these risk factors and with hypertension may therefore aggravate renal mitochondrial injury.

**Apoptosis**

Apoptosis, or programmed cell death, is an essential process in the progression to renal disease, which can be activated by extrinsic and intrinsic pathways. Extrinsic apoptosis is initiated by extracellular signals, which promote caspase-8 activation, and in turn caspase-3. Intrinsic apoptosis is a mitochondria-dependent pathway activated in response to intracellular damage, characterized by mitochondrial membrane permeabilization and release of cytochrome-c to the cytoplasm, triggering caspase-3 activation.

Accumulating evidence suggests a primary role of intrinsic apoptotic pathways in renal cell loss secondary to hypertension. Ang-II induces apoptosis in cultured rat renal proximal tubular cells via both Ang-II type-1 and Ang-II type-2 receptors, generation of profibrotic mediators, and activation of caspase-3. Similarly, kidneys from hypertensive Dahl/Rapp salt-sensitive rats display increased apoptosis, associated with augmented cytochrome-c release, caspase-3 and -9 activation, and severe renal injury, underscoring a role of mitochondria-dependent apoptosis in the pathogenesis of hypertensive nephrosclerosis. Elucidation of mechanisms linking hypertension and renal mitochondrial injury may be relevant to develop targeted interventions to preserve the hypertensive kidney.

**Mitochondrial Injury in Renovascular Hypertension**

Renovascular hypertension activates different pathological mechanisms responsible for stenotic and contralateral kidney injury. Unilateral renal artery stenosis is characterized by atrophy of the stenotic kidney and compensatory hyperplasia and hypertrophy of the contralateral kidney, which might also contribute to the pathogenesis of renovascular disease. Poststenotic kidney mitochondria are exposed to noxious insults that resemble, but are often more severe than those induced by hypertension, including RAAS activation, oxidative stress, and fibrosis, leading to structural abnormalities and decreased energy production. In addition, coexisting renal hyperperfusion compromises cellular bioenergetics, as mitochondria are susceptible to ischemia. Contrarily, the contralateral kidney mitochondria are exposed to hypertensive injury.

**Stenotic Kidney**

Experimental evidence demonstrates impaired mitochondrial homeostasis in the post-stenotic kidney (Table). Mitochondria are dynamic organelles that continuously regulate their...
content to adapt to insults or the metabolic milieu. Therefore, imbalance between mitochondrial proliferation and degradation results in cellular degeneration and stimulation of cell death pathways. We have previously demonstrated that renal mitochondrial biogenesis, the process by which new mitochondria are formed, is impaired in post-stenotic pig kidneys, associated with augmented apoptosis, oxidative stress, tubular injury, and fibrosis. Furthermore, decreased cardiolipin content associated with increased renal fibrosis (Figure S1B) implicates cardiolipin peroxidation and loss in post-stenotic renal injury. Similarly, mitophagy, which targets mitochondria for degradation via autophagy, is upregulated in the clipped rat kidney, associated with renal necrosis and fibrosis. Taken together, these observations implicate dysregulated mitochondrial homeostasis as central pathogenic mechanisms in renovascular disease.

Mitochondrial injury may also result from abrupt reperfusion of an ischemic kidney, which induces calcium overload, ROS generation, and apoptosis. Ischemia reduces electron-transport chain activity, making mitochondria vulnerable to ischemia-reperfusion injury (IRI). During reperfusion, ROS peroxide cardiolipin, triggering mPTP formation, whereas increased intracellular calcium concentration induces cardiolipin peroxidation by directly stimulating cytochrome-c peroxidase activity. Furthermore, elevated calcium evokes outer mitochondrial membrane permeabilization, favoring release of cytochrome-c and other apoptosis-inducing factors.

In rats with IRI, progressive deterioration of mitochondrial structure and function is associated with renal inflammation, oxidative stress, apoptosis, and dysfunction, which can be attenuated by preventing mPTP opening. Likewise, inhibition of intrinsic apoptosis prevents tissue injury in swine IRI, implicating apoptosis in acute kidney injury after ischemia. Indeed, IRI in cadaveric kidney transplants correlates with mitochondria-dependent apoptosis.

In the post-stenotic kidney, apoptosis contributes to vascular loss, partly by promoting inflammation and tissue injury. Oxidative stress is a main contributor to microvascular remodeling and loss in the stenotic kidney, which leads to progressive injury and dysfunction, associated with poorer outcomes revascularization. Therefore, strategies aimed to protect mitochondria might preserve the post-stenotic microvessels and function. In line with this notion, we have recently found in swine that renovascular disease increased renal oxidative stress and apoptotic signals associated with functional deterioration, which were attenuated by mitochondrial protection. Better understanding of the involvement of mitochondria in the pathogenesis of renovascular hypertension will produce the means to design novel therapies oriented to protect the stenotic kidney.

Non-Stenotic Kidney

The role of mitochondrial damage in the hypertensive contralateral kidney injury is less clear. We have previously shown in swine renovascular disease a mild but significant increase in oxidative stress, apoptosis, and fibrosis in the contralateral kidney, which were, however, unaffected by mitochondrial protection, arguing against major involvement of the mitochondria in the contralateral kidney injury. However, hypertension-induced mitochondrial injury in the contralateral kidney could have been undetectable or attenuated because of the short duration and modest increase in blood pressure and the use of relatively young animals. Moreover, comorbid conditions, including essential hypertension or atherosclerosis, can aggravate mitochondrial dysfunction in the non-stenotic kidney. Further studies are needed to rule out the involvement of mitochondrial dysfunction in the pathogenesis of contralateral kidney injury in human renovascular disease.

Management of Hypertensive Mitochondrial Disease

Antihypertensive Drugs

Treatment with angiotensin-converting enzyme inhibitors or Ang-II receptor blockers confers remarkable benefits in attenuating hypertension and preventing its complications. Furthermore, RAAS blockade preserves mitochondria in experimental hypertension by increasing antioxidant defenses and preventing oxidative stress. In swine renovascular hypertension, valsartan treatment preserves stenotic kidney perfusion and decreases oxidative stress more efficiently than conventional triple therapy and attenuates myocardial remodeling and mitochondrial damage.

In spontaneous hypertensive rats, treatment with losartan and the calcium channel blocker amlodipine similarly reduces blood pressure, yet only losartan prevents mitochondrial dysfunction and attenuates structural and functional changes in the kidney. Contrarily, captopril aggravates cardiac and kidney mitochondrial energy deficiency, possibly because of a direct effect on mitochondrial membrane fluidity and ATPase activity. Clearly, additional studies are needed to assess the potential effect of RAAS blockade on mitochondria in hypertension.

Mitochondria as a Therapeutic Target

In recent years, drug discovery efforts have focused on designing compounds capable of exerting antioxidant and protective effects on mitochondria. For example, formoterol, a potent inducer of mitochondrial biogenesis, restores mitochondrial and kidney function, attenuates tubular injury, and reduces necrosis in mice when administered after IRI, but also reduces cardiac relaxation, mitochondrial protein synthesis, and oxidative capacity, limiting its clinical application. In rats with IRI, preconditioning with cyclosporine, a potent mPTP inhibitor, restores mitochondrial superoxide dismutase activity and decreased renal fibrosis, but increased blood pressure and nephrotoxicity restrict its use in hypertensive patients. Similarly, conjugated triphenyl-phosphonium-ion to coenzyme-Q restores mitochondrial respiration and decreases mitophagy and apoptosis in cultured endothelial cells subjected to lipid peroxidation, but its efficacy to concentrate in mitochondria is membrane potential-dependent, which limits its applicability.

More recently, Bendavia, a novel tetrapeptide that prevents cardiolipin peroxidation and loss, was found to reduce apoptosis and necrosis in rats with IRI. Additionally, we have found that daily subcutaneous injections of Bendavia decreased tissue damage in the swine stenotic kidney. Bendavia also normalized renal function and improved oxygenation. Furthermore, in renal artery endothelial cells subjected to lipid peroxidation and mitochondrial dysfunction, restoration of cardiolipin content with Bendavia preserves mitochondrial structure (Figure S1B).
SIC). These results illustrate the potential of mitochondrial protection to preserve renal function.

To date, few clinical trials have tested the efficacy of mitochondria-targeted compounds. In a small pilot trial, cyclosporine administration during percutaneous coronary intervention decreased infarct size76; an ongoing clinical trial is evaluating whether intravenous Bendavia in conjunction with coronary revascularization can reduce myocardial infarction size among patients with acute ST-segment elevation myocardial infarction.78 Furthermore, an ongoing randomized placebo controlled clinical trial is assessing the efficacy of intravenous Bendavia on renal function in patients with renovascular hypertension undergoing renal revascularization (NCT01755858). Results from these studies will help elucidate the role of mitochondria in the pathogenesis of hypertension-related renal disease. Further studies are also needed to test the efficacy of chronic subcutaneous administration of Bendavia in humans.

Revascularization

Renal revascularization was a popular intervention in renovascular disease till clinical trials failed to identify benefits beyond medical therapy.77 In swine renovascular hypertension, renal revascularization fails to attenuate stenotic kidney injury, despite a fall in arterial pressure.79 However, infusion of adjunct Bendavia during renal revascularization attenuates damage and restores function in the post-stenotic kidney.11 Notably, Bendavia confers similar protection in experimental reperfusion injury in mouse kidneys exposed to various forms of hypertension. The precise mechanisms involved in the pathogenesis of hypertension-induced mitochondrial injury are incompletely understood, but ROS-induced peroxidation of cardiolipin and mPTP opening are often observed. However, a cause–effect relationship between mitochondrial injury and hypertension remains to be established. Elucidation of this relationship would likely have important therapeutic implications for protecting renal mitochondria as a target or culprit in hypertension. Novel mitochondrial-targeted drugs have shown promise in experimental and clinical research is needed to confirm their importance models of IRI and hypertension. Nevertheless, further experimental and clinical research is needed to confirm their reno-protective properties in human subjects. The rapidly increasing understanding of the pathophysiological implications of mitochondria and the development of mitochondria-targeted therapies may offer novel treatment paradigms for hypertensive and renovascular nephropathy.

Conclusions and Perspectives

The prevalence of hypertensive renal disease continues increasing, warranting development of adequate therapies to target underlying mechanisms. Experimental studies have illustrated mitochondrial abnormalities and dysfunction in kidneys exposed to various forms of hypertension. The precise mechanisms involved in the pathogenesis of hypertension-induced mitochondrial injury are incompletely understood, but ROS-induced peroxidation of cardiolipin and mPTP opening are often observed. However, a cause–effect relationship between mitochondrial injury and hypertension remains to be established. Elucidation of this relationship would likely have important therapeutic implications for protecting renal mitochondria as a target or culprit in hypertension. Novel mitochondrial-targeted drugs have shown promise in experimental models of IRI and hypertension. Nevertheless, further experimental and clinical research is needed to confirm their reno-protective properties in human subjects. The rapidly increasing understanding of the pathophysiological implications of mitochondria and the development of mitochondria-targeted therapies may offer novel treatment paradigms for hypertensive and renovascular nephropathy.

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Disclosures

A. Lerman and L.O. Lerman serve on the Advisory Board for Stealth Biotherapeutics.

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Mitochondria: a pathogenic paradigm in hypertensive renal disease

Short title: Mitochondria in hypertension

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**Figure S1.** A: Interplay of mechanisms by which hypertension produces renal mitochondrial damage. Mechanical stretch secondary to elevated blood pressure activates the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and thereby formation of reactive oxygen species (ROS), which cause mitochondrial structural and functional damage. The renin-angiotensin-aldosterone system (RAAS) and its major effector angiotensin (Ang)-II can also activate the NAD(P)H oxidase complex. Furthermore, Ang-II receptor expressed in the inner mitochondrial membrane modulates local ROS generation. Both mechanical stretch and extracellular matrix turnover may directly impair the mitochondria by facilitating the opening of the mitochondrial permeability transition pore (mPTP) leading to oxidative damage and apoptosis. B: Staining for cardiolipin (top) and trichrome (bottom) showing decreased post-stenotic kidney cardiolipin content and increased fibrosis in pigs with renovascular hypertension. Red: nonyl-acridine-orange, Green: cytokeratin, Blue: nuclei. C: Transmission electron microscopy of renal artery endothelial cells (RAEC) and RAEC incubated with Bendavia, tert-butyl-hydroperoxide (tBHP) that induces mitochondrial damage, or tBHP+Bendavia. Treatment with Bendavia preserved mitochondrial structure. mPTP: mitochondrial permeability transition pore, ETC: electron-transport chain, AT2R: Ang-II type-2 receptor, mtDNA: mitochondrial DNA.