HHS Public Access

Author manuscript

Handb Exp Pharmacol. Author manuscript; available in PMC 2017 August 12.

Published in final edited form as:

Handb Exp Pharmacol. 2017 ; 240: 229–250. doi:10.1007/164_2016_6.

The Emerging Role of Mitochondrial Targeting in Kidney Disease

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Abstract

Renal disease affects millions of people worldwide, imposing an enormous financial burden for health-care systems. Recent evidence suggests that mitochondria play an important role in the pathogenesis of different forms of renal disease, including genetic defects, acute kidney injury, chronic kidney disease, aging, renal tumors, and transplant nephropathy. Renal mitochondrial abnormalities and dysfunction affect several cellular pathways, leading to increased oxidative stress, apoptosis, microvascular loss, and fibrosis, all of which compromise renal function. Over recent years, compounds that specifically target mitochondria have emerged as promising therapeutic options for patients with renal disease. Although the most compelling evidence is based on preclinical studies, several compounds are currently being tested in clinical trials. This chapter provides an overview of the involvement of mitochondrial dysfunction in renal disease and summarizes the current knowledge on mitochondria-targeted strategies to attenuate renal disease.

Keywords

ATP; Cardiolipin; Kidney; Mitochondria

1 Introduction

Renal disease encompasses acute or chronic conditions that damage the kidneys and reduce their function. It remains an increasing public health issue that affects a significant proportion of the world's population and is associated with tremendous medical costs (Jha et al. 2013). Furthermore, its short-term and long-term complications increase cardiovascular and all-cause morbidity and mortality rates. For example, acute kidney injury (AKI),

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characterized by a rapid loss of renal function, may result in fluid overload, electrolyte abnormalities, and coagulopathy, which might contribute to multi-organ failure. Likewise, gradual loss of kidney function, known as chronic kidney disease (CKD), is associated with grave complications, including cardiovascular disease, anemia, mineral and bone disorders, and cognitive decline. Moreover, congenital and inherited disorders, tumors, and aging may compromise kidney function and adversely impact several organ systems. Ultimately, all these conditions can progress toward end-stage renal disease (ESRD), requiring costly and renal replacement therapy. Alas, adequate strategies to prevent progressive renal dysfunction are in dire need.

The kidney receives 20% of the cardiac output and utilizes 10% of body oxygen consumption to accomplish its primary function, regulating the body fluid composition through filtering and reabsorbing materials. This process occurs at the level of the nephron, the functional unit of the kidney, by both energy-dependent and independent mechanisms. The most energy demanding process of the kidney is reabsorption of solutes, which occurs both passively and actively by the renal tubular cells, which consume adenosine triphosphate (ATP) generated exclusively by aerobic metabolism. Congruently, tubular cells are rich in mitochondria, and mitochondrial injury and dysfunction bear harmful consequences on multiple renal cell functions.

Accordingly, increasing evidence indicates that mitochondrial damage and dysfunction in renal disease (Fig. 1) may contribute to the multiple underlying pathological processes (Che et al. 2014). Acute or chronic insults might compromise mitochondrial structure, evoking mitochondrial DNA (mtDNA) damage, decreased matrix density, and/or impaired outer and inner membrane integrity. Furthermore, renal disease has been associated with changes in mitochondrial homeostasis, the molecular control of mitochondrial formation (biogenesis), morphology (fusion/fission), and degradation (mitophagy). Finally, mitochondrial abnormalities and impaired homeostasis lead to bioenergetic dysfunction (reduced ATP generation and calcium signaling), triggering oxidative stress and apoptosis. Therefore, over the past few years, mitochondria have emerged as novel therapeutic targets in renal diseases. Small molecules that specifically concentrate within mitochondria include mitochondrial permeability transition pore (mPTP) inhibitors, antioxidants, biogenesis activators, fission inhibitors, gene therapy, and cardiolipin protection (Tabara et al. 2014). The efficacy of these compounds has been tested in several in vitro and in vivo experimental studies, as well as in few clinical trials. In this chapter, we evaluated and summarized evidence implicating mitochondrial dysfunction in the pathogenesis of renal disease, with particular attention to studies testing the potential of promising mitochondria-targeted therapies for ameliorating renal injury and dysfunction.

2 Evidence of Mitochondrial Injury in Renal Disease

2.1 Mitochondrial Genetic Defects

Mitochondrial cytopathies (MCs) encompass a group of disorders characterized by mitochondrial or nuclear DNA mutations in genes encoding for mitochondrial proteins. MCs can affect any organ, but have predilection for those dependent upon mitochondrial energy supply (Finsterer 2004). Mutations resulting in MCs could be either inherited (primary MCs)

or imposed by exogenous factors (secondary MCs), such as drugs or increased oxidative stress. In the kidney, MCs commonly manifest as glomerular disease, tubular dysfunction, renal cysts, or neoplasia.

A point mutation in the mitochondrial tRNAleu (UUR) at position 3243 (A3243G) has been associated with focal and segmental glomerulosclerosis (FSGS) (Dinour et al. 2004), an important cause of nephrotic syndrome in children and adolescents that frequently progresses to ESRD. This mutation causes mitochondrial myopathy, encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, as well as maternally inherited diabetes and deafness. Renal biopsies of patients with MELAS-associated FSGS reveal numerous abnormal mitochondria in tubular cells and podocytes, associated with severe effacement of foot processes (Gucer et al. 2005), implicating mitochondrial alterations in the pathogenesis of FSGS.

MCs have been also linked to renal tubular dysfunction, which mainly manifest as Bartter-like or Fanconi syndromes. The most common tubular defect associated with MCs is Toni-Debré-Fanconi syndrome, a rare disorder characterized by impaired tubular reabsorption. Mutations and large mtDNA deletions have been reported in patients with this syndrome (Lee et al. 2012), associated with mitochondrial respiratory complex defects and giant atypical mitochondria (Au et al. 2007). Kearns–Sayre syndrome, an MC caused by deletions of mtDNA and characterized by isolated involvement of the muscles controlling eyelid movement, may present with renal involvement resembling Barter syndrome (Emma et al. 2006). Patients with Barter syndrome suffer from electrolyte abnormalities due to mutations in ion transporters, which impair the ability to reabsorb potassium. Renal biopsies of patients with Kearns–Sayre and Bartter-like syndrome show ultrastructural changes in mitochondria in the thick ascending loop of Henle, associated with impaired cytochrome-c oxidase (COX) activity and fibrosis (Goto et al. 1990), implicating mitochondrial structural and functional impairment in the pathogenesis of tubular derangements.

Bilateral enlarged cystic kidneys have been also documented in patients with mitochondrial cytopathies including mutations of the mitochondrial tRNA genes (Guery et al. 2003). Furthermore, glomerulocystic kidneys have been reported in association with Leigh disease, a MC caused by mutations in the Surfeit locus protein-1 gene and COX assembly factors (Lake et al. 2015).

Lastly, MCs might coexist with renal tumors. Rare cases of patients with MELAS associated with renal cell carcinoma (RCC) have been previously reported. Mutations of components of the mitochondrial oxidative phosphorylation complex have been described in benign and malignant renal tumors (Housley et al. 2010; Ricketts et al. 2008). Furthermore, a high mutational rate of the mtDNA has been observed in benign renal tumors (Gasparre et al. 2008) and tumors arising in ESRD (Nagy et al. 2003), implicating MCs in renal tumorigenesis.

2.2 AKI

AKI has increased in incidence over the last decades and is currently responsible for 2% of hospitalized patients in the USA. AKI may result from prerenal (hypoperfusion), renal

(intrinsic damage), or post-renal (urinary tract/venous obstruction) causes that trigger a rapid decline in GFR, associated with tubular necrosis, vascular changes, and interstitial inflammation. Evidence suggests that mitochondrial damage is associated with important events in the pathogenesis of several etiologies of AKI, including toxic, ischemic, septic, and hypertensive injury.

Toxic Injury—Several studies have documented mitochondrial structural and functional changes in kidneys exposed to exogenous drugs or toxins. Cyclosporine (Yuan et al. 2005) and cisplatin (Zsengeller et al. 2012) nephrotoxicity is characterized by decreased mitochondrial mass, disruption of cristae, and extensive mitochondrial swelling, as shown in murine studies. Similarly, kidney mtDNA depletion and ultrastructural mitochondrial abnormalities were reported in human immunodeficiency virus-infected patients treated with antiretroviral therapy (Cote et al. 2006).

Renal mitochondrial structural abnormalities are often associated with impaired bioenergetics. Cisplatin-induced renal mitochondrial injury in mice is accompanied by reduced nicotinamide adenine dinucleotide dehydrogenase (NADH) and COX activity, indicating impaired mitochondrial function (Mukhopadhyay et al. 2012). Likewise, mtDNA depletion and loss of mitochondrial mass are associated with decreased COX efficiency in patients treated with the antiretroviral drug tenofovir (Lopez et al. 2006).

Nephrotoxic drugs can also compromise mitochondrial homeostasis. Renal mitochondrial biogenesis is suppressed in folic acid-induced AKI, disclosed by decreased expression of its master regulator, peroxisome proliferator gamma coactivator 1α (PGC-1α) (Stallons et al. 2014). In addition, expression of dynamin-related protein (DRP)-1, which mediates outer mitochondrial membrane fission, is markedly upregulated in mice kidneys with glycerol-induced AKI, suggesting mitochondrial fragmentation (Funk and Schnellmann 2012). Moreover, expression of the autophagic marker microtubule-associated protein 1A-/1B-light chain 3 (LC3) is elevated in these animals, implying mitochondrial degradation.

Drug-induced changes in mitochondrial structure, function, and homeostasis may promote apoptosis. In rodent models of cisplatin-induced nephrotoxicity, mitochondrial outer membrane permeabilization triggers mitochondrial fragmentation, cytochrome-c release, and apoptosis (Brooks et al. 2009). Renal tubular epithelial cells of rats exposed to the organic compound ethylbenzene show damaged mitochondria with vacuolar structure, associated with increased numbers of apoptotic cells, and upregulated expression of the apoptogenic factor cytochrome-c, suggesting mitochondria-mediated renal tubular cell apoptosis (Zhang et al. 2010).

Obstructive Injury—Obstruction in the urinary tract below the kidneys is a frequent problem, but accounts for only 5–10% of AKI. Tubular atrophy and nephron loss due to unilateral ureteral obstruction in rodents is associated with increased mitochondrial hydrogen peroxide production, autophagy, and apoptosis (Xu et al. 2013). These changes were confirmed by in vitro studies in renal tubular cells exposed to oxalate, a major component of kidney stones, demonstrating that obstructive AKI induce parallel autophagy and mitochondrial dysfunction-mediated apoptosis (Cao et al. 2004).

Septic Injury—Sepsis is a frequent cause of AKI in critically ill patients. Mitochondrial damage is thought to play an important role in the pathogenesis of septic AKI (Parikh et al. 2015). For example, *Staphylococcus aureus*-induced sepsis damages renal mDNA in the mouse kidney, leading to induction of the nuclear program of mitochondrial biogenesis (Bartz et al. 2014). Similarly, administration of lipopolysaccharide in mice increases renal tubular cytochrome-c release into the cytosol and active caspase-3 expression, implying mitochondria-dependent apoptosis (Stoyanoff et al. 2014). Renal tubular cells from septic mice show mitochondrial ultrastructural changes and reduced expression of COX (Choi et al. 2013), which may contribute to renal tubular cell apoptosis and AKI in sepsis.

Ischemic Injury—An abrupt interruption or decrease in renal oxygen supply and ischemia–reperfusion injury (IRI) are the most common causes of AKI and kidney allograft dysfunction. Several studies suggest that mitochondrial damage plays a pivotal role in ischemic AKI, contributing to renal dysfunction. Mitochondria respiratory capacity is significantly reduced in rats with uncontrolled hemorrhagic shock (Li et al. 2012b), associated with increased mitochondrial reactive oxygen species (ROS) and lipid peroxidation (Wang et al. 2015a).

Renal IRI in rats is characterized by rounded, swollen renal tubular cell mitochondria with disrupted cristae membranes and release of matrix materials into the cytosol (Szeto et al. 2011). Mitochondrial respiration and ATP production decreases, whereas oxidative stress increases, suggesting mitochondrial structural and functional decline. Autophagy and mitophagy are activated in both in vivo and in vitro models of renal IRI (Ishihara et al. 2013). We have shown in swine renovascular disease that ongoing post-stenotic inflammatory and pro-fibrotic injury that renal revascularization fails to reverse is associated with impaired renal mitochondrial biogenesis, apoptosis, and oxidative stress, implicating mitochondrial homeostasis in the pathogenesis of renal IRI (Eirin et al. 2012). Finally, IRI in kidney transplants has been associated with increased renal tubular expression of proapoptotic molecules and diffuse cytosolic distribution of cytochrome-c, suggesting activation of mitochondria-dependent apoptosis (Castaneda et al. 2003).

2.3 CKD

The prevalence of CKD is estimated to be 8–16% worldwide and is associated with catastrophic health expenditures. Importantly, many uremic conditions are associated with changes in mitochondrial structure and dysfunction.

Diabetic Nephropathy—Diabetic kidney disease is the leading cause of CKD, accounting for 42% of patients on ESRD. Importantly, severity of CKD predicts all-cause mortality in type-1 and type-2 diabetes mellitus. Studies have suggested that mitochondrial abnormalities and dysfunction might favor the development and progression of diabetic nephropathy.

Apoptotic tubular cells and dysmorphic mitochondria were observed in the kidneys of diabetic mice, associated with decreased mtDNA content and altered mitochondrial function (Sun et al. 2008). COX-III activity is significantly decreased and contributes to oxidant production in diabetic renal mitochondria (Munusamy et al. 2009). In agreement, diabetic mice show decreased renal mitochondrial ATP production and excess generation of

superoxide (Tan et al. 2010), a ROS with the ability of exacerbating renal mitochondrial dysfunction in hyperglycemic rats (Munusamy and MacMillan-Crow 2009). In line with this finding, studies in two murine models of type-1 and type-2 diabetes showed that glucose-induced mitochondrial ROS production initiates podocyte apoptosis in vitro and in vivo (Susztak et al. 2006). Moreover, polymorphisms in the mitochondrial antioxidant superoxide dismutase (SOD)-2 are associated with progressive renal functional decline in patients with type-1 diabetes (Mohammedi et al. 2014), suggesting that mitochondrial oxidative stress constitutes a major pathway resulting in diabetic renal injury.

Mitochondrial homeostasis seems to play an important role in diabetic nephropathy. Overexpression of the fusion marker mitofusin-2 attenuates pathological changes in the kidneys of diabetic rats (Tang et al. 2012). Likewise, renal expression of PGC-1α is downregulated in patients with both diabetes and CKD. Urine metabolome in patients with diabetic kidney disease reveals metabolites linked to mitochondrial metabolism and reduced mitochondrial content of urinary exosomes, suggesting suppression of mitochondrial activity in diabetic kidney disease (Sharma et al. 2013).

Hypertensive Injury—Experimental studies directly implicate mitochondrial injury in the development and progression of renal hypertension (Eirin et al. 2015). In kidneys from spontaneously hypertensive rats, mitochondrial membrane potential, nitric oxide synthase, COX activity, and mitochondrial uncoupling protein-2-content were reduced, suggesting that hypertension occurs in concurrence with a decline of kidney mitochondrial function (de Cavanagh et al. 2006). Furthermore, expression of SOD-2 is blunted in hypertensive rats, and its deficiency is associated with activation of intrarenal inflammatory and ROS-generating pathways (Jin and Vaziri 2014). Finally, a proteomic analysis of mitochondria isolated from medullary thick ascending limb cells identified seven differentially expressed proteins between hypertensive and control rats involved in mitochondrial metabolism and oxygen utilization (Zheleznova et al. 2012). These observations highlight the critical role of renal mitochondrial injury in the pathogenesis of hypertensive CKD, although it remains unknown whether mitochondrial abnormalities are primary or secondary to hypertension.

Ischemic Injury—Chronic underperfusion of the renal parenchyma secondary to renal artery stenosis (RAS) is an important cause of CKD in the elderly population and has been linked to mitochondrial structural alterations and dysfunction. In the rat RAS model, necrotic death of tubular epithelial cells in the clipped kidneys is dependent on upregulation and mitochondrial translocation of the pro-mitophagy protein BCL2/adenovirus E1B 19 kDa protein-interacting protein-3, associated with impaired mitochondrial biogenesis, mass, and mtDNA copy number (Fedorova et al. 2013). Furthermore, in swine atherosclerotic RAS, the post-stenotic kidney exhibits loss of cardiolipin, a phospholipid exclusively distributed in the inner mitochondrial membrane that regulates mitochondrial structure and function (Klingenberg 2009), associated with apoptosis, oxidative stress, microvascular loss, fibrosis, and renal dysfunction (Eirin et al. 2014). Taken together, these studies implicate mitochondrial structural and functional alterations in the pathogenesis of ischemic CKD.

Glomerulonephritis—Chronic glomerulonephritis accounts for approximately 10% of all causes of CKD. Accumulation of abnormal-shaped mitochondria are commonly found in

podocytes, distal tubules, and collecting ducts of patients with genetically proven mitochondrial disease and secondary FSGS (Kobayashi et al. 2010). Mutation of pro-autophagic genes in mice during nephrogenesis causes podocyte and tubular cell mitochondrial abnormalities that precede the appearance of FSGS (Kawakami et al. 2015), suggesting that impaired autophagic mitochondrial turnover is sufficient to recapitulate the characteristic features of FSGS in mice.

Polycystic Kidney Disease (PKD)—Comparative proteomics analysis implicates mitochondria in autosomal recessive PKD, a genetic disorder characterized by cyst development. Abnormally expressed proteins in PKD include proteins involved in biological processes related to signal transduction, cell cycle regulation, and electron transport, which play key roles in the pathogenesis of PKD (Li et al. 2012a). Notably, 13 of these proteins, including SOD-2, COX subunit Va, and peroxiredoxin-3, are localized in mitochondria, implying that mitochondrial dysfunction partly contributes to renal injury in PKD.

2.4 Renal Tumors

Tumors can originate from different renal cell types, and their incidence has increased in the last two decades. Mitochondrial damage has been suggested to be causally linked to benign renal tumors and RCCs (Hervouet and Godinot 2006; Hervouet et al. 2007). A recent clinical trial indicates that low mitochondrial DNA copy number in peripheral blood leukocytes is associated with significantly increased risk of clear cell RCC (Melkonian et al. 2015). Furthermore, decreased renal tumor expression of cytochrome-c and human 8-oxoguanine DNA glycosylase-1, a DNA repair protein located in the mitochondria, has been reported, implicating mitochondrial loss and defective DNA repair in tumor development or progression (Mukunyadzi et al. 2003). Mitochondrial dysfunction in patients with RCC correlates with oxidative phosphorylation complexes content and ATPase activity rather than to the mtDNA content, suggesting that decreased mitochondrial capacity primarily favors tumor invasiveness (Simonnet et al. 2002). Contrarily, the number of enzymes involved in mitochondrial energy metabolism is reduced in RCC, but does correlate with tumor grade, metastasis, or proliferative activity, implying that low renal mitochondrial activity is an early event in RCC formation (Meierhofer et al. 2004).

Renal oncocytoma is a rare and almost invariably benign tumor. Interestingly, renal oncocytomas show mitochondria with piled lamellar cristae, whereas chromophobe RCCs exhibit mitochondria with tubulovesicular cristae (Barcena et al. 2010). Despite increased COX activity, complex-I activity is decreased in renal oncocytomas (Simonnet et al. 2003), associated with increased number of mitochondrial vacuoles, suggesting increased mitophagy (Koller et al. 2000).

2.5 Aging

Aging is associated with gradual loss of function in the kidney, accompanied by mesangial expansion, glomerulosclerosis, and interstitial fibrosis. Aged rats show aging-associated ultrastructural changes in kidney mitochondria, disclosed by ill-defined cristae and reduced density, associated with increased mitochondrial hydrogen peroxide production and impaired respiratory control, antioxidant activity, and uncoupling protein-2 levels (de

Cavanagh et al. 2003). Furthermore, reduction of age-associated renal damage in mice chronically treated with angiotensin-converting enzyme inhibitors is accompanied by increased number of mitochondria in the proximal tubules (Ferder et al. 2002), implicating mitochondria in the pathogenesis of age-related kidney disease.

Importantly, mitochondria regulate permanent cell growth, modulating cellular senescence, leading to a state of irreversible growth arrest (Ziegler et al. 2015). In line with this notion, oxidative stress and cell senescence promote tubular cell apoptosis and mitochondrial dysfunction in vitro, impairing the kidney's regenerative potential (Small et al. 2012). In old rats, increased expression of markers of senescence, such as p16 and senescence-associated-galactosidase, is accompanied by decreased expression of autophagosome and mitophagy markers (Cui et al. 2013). Interestingly, these changes are exacerbated in animals fed with a high-calorie diet, but ameliorated in those with calorie restriction, suggesting that diet modulates mitochondrial degradation and recycling that occur in the aging kidney. In aged diabetic rats, oxidative stress promotes mitochondrial oxidative dysfunction, reflected as increased lipid peroxidation and decreased glutathione activity (Perez-Gallardo et al. 2014). Notably, nonsteroid anti-inflammatory drugs do not aggravate aging-induced injury (Rocha-Rodrigues et al. 2013).

2.6 Chronic Allograft Injury

Chronic allograft nephropathy, characterized by a slow decline in renal function more than three months posttransplant, remains one of the most common causes of ESRD. Several immunological risk factors for chronic allograft dysfunction have been suggested, yet non-immunological mediators of this progressive injury largely remain unknown. A recent study that analyzed gene expression microarray of kidney transplant biopsies taken one year after transplantation revealed a unique molecular signature of impaired mitochondrial function, characterized by inadequate mitochondrial energy generation, biogenesis, and antioxidant response (Zepeda-Orozco et al. 2015). These observations support development of mitochondria-targeted treatments to slow the progression of chronic allograft dysfunction.

3 Renal Mitochondrial Targeting

In recent years, several mitochondria-targeted strategies have been designed to prevent or attenuate renal disease (Fig. 2). Although their efficacy in human renal disease needs to be explored, several studies demonstrated their ability to attenuate renal injury in experimental animal models.

3.1 Genetic Therapy

Neutralizing deleterious mtDNA alterations using targeted mitochondrial RNA import is a novel and promising therapy for rescuing mitochondrial function in patients with MCs. Mitochondrial defects in cytoplasmic hybrid (cybrid) cells derived from patients with myoclonic epilepsy with ragged red fibers (MERRF) and MELAS can be partially rescued by targeted import of allotopically encoded wild-type tRNAs, an approach that specifically targets mRNA to the mitochondrial outer membrane (Wang et al. 2012). Notably, functional defects in mitochondrial RNA (mtRNA) translation and cell respiration were reversed in

MERRF and MELAS cybrids cells. Similarly, mitochondrial targeting of recombinant tRNAs bearing the identity elements for human mitochondrial leucyl-tRNA synthetase rescues the phenotype caused by MELAS mutation in cultured transmitochondrial cybrid cells (Karicheva et al. 2011), whereas yeast tRNALys derivatives expressed in human immortalized cells and primary fibroblasts rescue mitochondrial functions in cultured cells from patients with the MERRF syndrome, underscoring the potential of these transcript engineering approaches to confer mitoprotection and mitigate renal injury in patients with MCs.

3.2 Biogenesis Activators

Synthesis and assembly of new mitochondria involve multiple coordinated processes tightly regulated by PGC-1α. Silent mating-type information regulation 2 homolog (SIRT)-1 is a NAD-dependent deacetylase that positively regulates PGC-1α activity and restores renal expression of PGC-1α, mitochondrial mass, ATP levels, and renal function in rats with ischemia–reperfusion injury (Funk and Schnellmann 2013; Khader et al. 2014). In line with this, treatment with the SIRT-1 activator resveratrol protects mice against aldosterone-induced podocyte injury by upregulating PGC-1α (Yuan et al. 2012). Resveratrol supplementation following hemorrhagic shock in rats also restores mitochondrial respiratory capacity and decreases mitochondrial ROS production and lipid peroxidation (Wang et al. 2015a), underscoring SIRT-1/PGC-1α axis activation as therapeutic approach.

Agonists for the β2-adrenoceptors induce mitochondrial biogenesis in both the renal proximal tubular cells and cardiomyocytes, disclosed by increased mtDNA copy numbers, oxygen consumption rate, and mRNA levels of PGC-1α and multiple genes involved in mitochondrial regulation (Wills et al. 2012). Moreover, the β2-adrenergic receptor agonist formoterol in mice with IRI-induced AKI restores renal function, rescues renal tubules from injury, and diminishes necrosis (Jesinkey et al. 2014). However, long-acting β2-adrenoceptor agonists, including formoterol, impair cardiac relaxation, mitochondrial protein synthesis, and oxidative capacity, limiting its clinical translation (Leger et al. 2011).

3.3 Mitochondrial Antioxidants

Mitochondrial ROS has been implicated in the pathogenesis of several types of renal disease, which often results from an imbalance between mitochondrial ROS production and antioxidant defenses. Thus, compounds that specifically target mitochondria may confer greater protection against renal injury due to increased mitochondrial ROS generation than untargeted cellular antioxidants such as vitamin E or N-acetylcysteine.

Several triphenylalkylphosphonium cation (TPP+)-conjugated antioxidants have been designed to reduce mitochondrial ROS. These positively charged compounds can cross the mitochondria-phospholipid bilayer and concentrate in their matrix in a membrane potential-dependent manner, where they exert potent antioxidant properties by sequestering ROS. Conjugating TPP+ to lipophilic antioxidants such as coenzyme-Q (MitoQ) attenuates renal dysfunction due to several types of AKI and CKD. For example, administration of MitoQ prior to bilateral renal ischemia in mice decreases mitochondrial oxidative damage and renal dysfunction (Dare et al. 2015). Furthermore, addition of MitoQ to cold storage solution

(during kidney transplantation) preserves mitochondrial function by decreasing oxidative stress and tubular damage in isolated rat and porcine kidneys (Parajuli et al. 2012). In a genetic model of type-1 diabetes, increased proteinuria and tubulointerstitial fibrosis were also attenuated by MitoQ (Chacko et al. 2010). Importantly, MitoQ has been shown to be safe for patients with Parkinson's disease (NCT00329056), fatty liver disease (NCT01167088), and hepatitis C (NCT00433108), encouraging future clinical studies in renal disease.

MitoTEMPO, a piperidine nitroxide conjugated to a TPP+ (Sims et al. 2014), scavenges ROS in the mitochondria, reverses renal mitochondrial dysfunction, and attenuates sepsis-induced AKI in mice (Patil et al. 2014). Treatment with either MitoTEMPO or conjugated TPP+ with α-tocopherol (MitoE) improves mitochondrial respiration and reduces oxidative stress and inflammation in septic rats kidneys (Lowes et al. 2013), whereas TPP+ conjugation with the SOD mimetic nitroxide (MitoCP) prevents mitochondrial damage and renal injury in mice with cisplatin-induced nephropathy (Mukhopadhyay et al. 2012).

In addition to TPP+-conjugated drugs, several antioxidants have been successfully delivered into renal mitochondria. Mitochondria-targeted antioxidants of the SkQ group such as plastoquinonyl-decyl-triphenylphosphonium (SkQ1) and plastoquinonyl decylrhodamine 19 (SkQR1) are positively charged compounds that prevent IRI-induced AKI (Plotnikov et al. 2012) and ameliorate gentamicin-induced damage of rat kidney (Jankauskas et al. 2012). Likewise, specific mitochondrially targeted heme oxygenase (HO)-1 protects against hypoxia-dependent renal epithelial cell death and loss of mitochondrial membrane potential (Bolisetty et al. 2013). HO-1 is a potent cytosolic antioxidant enzyme that translocates to the mitochondrion under conditions of oxidative stress and modulates their biogenesis (Piantadosi and Suliman 2012). Taken together, these results suggest that mitochondrially targeted antioxidants represent a novel approach to prevent or attenuate several forms of kidney injury.

3.4 mPTP Inhibitors

Opening of the mPTP, a channel formed in the inner membrane of the mitochondria in response to certain pathological conditions, plays a central role in several forms of AKI. Indeed, mPTP inhibitors have been shown to ameliorate renal IRI and shock-induced AKI.

In addition to its well-known immunosuppressive properties, cyclosporine-A (CSA) is a potent inhibitor of the mPTP, which acts by interacting with cyclophilin D, an essential structural component of the pore that regulates its calcium and ROS-mediated activation (Kim et al. 2014). In small clinical trials in patients with myocardial infarction undergoing reperfusion, CSA showed ability to reduce infarct size (Piot et al. 2008), but a recent randomized clinical trial failed to confirm its efficacy to improve clinical outcomes (Cung et al. 2015). Currently, two more clinical trials are testing safety and effectiveness of CSA in cardiac arrest (NCT01595958) and severe traumatic brain injury (NCT01825044). CSA improves renal function, histopathological damage, and antioxidant enzyme status in rats with renal IRI (Singh et al. 2005) and preserves rat kidneys subjected to traumatic hemorrhagic shock (Lei et al. 2015). Yet, high-dose CSA would shift mitochondrial dynamics toward fission (de Arriba et al. 2013); decrease activity of the mitochondrial Krebs

cycle, oxidative phosphorylation, and electron transfer (Puigmule et al. 2009); and result in nephrotoxicity, limiting their use in patients with renal disease (Issa et al. 2013).

Targeting glycogen synthase kinase (GSK) 3β, a ubiquitous serine–threonine protein kinase that phosphorylates cyclophilin D and promotes mPTP opening, has also shown promising therapeutic potential for preventing toxic AKI. The GSK3β inhibitor 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (TDZD-8) confers protection against podocyte injury in a murine model of adriamycin-induced AKI (Wang et al. 2015b). Likewise, TDZD-8 diminishes mitochondrial permeability transition, improves acute kidney dysfunction, and ameliorates tubular injury in mice with nonsteroidal anti-inflammatory drug-induced AKI (Bao et al. 2012), suggesting GSK3β inhibition as adjunct therapy in drug-induced AKI.

3.5 Cardiolipin Protection

Peroxidation and loss of cardiolipin has been shown to play a crucial role in the pathogenesis of several forms of AKI and CKD, leading to discovery and development of cardiolipin-targeted compounds. Szeto–Schiller (SS)-31 is a tetrapeptide that concentrates in the mitochondria and selectively binds to cardiolipin, preventing its peroxidation and loss, as well as the transformation of cytochrome-c into a peroxidase (Birk et al. 2013; Szeto 2014).

Administration of SS-31 in rats before onset of ischemia and at the onset of reperfusion prevents mitochondria swelling and protects cristae membranes in endothelial and tubular cells four weeks after bilateral renal ischemia, associated with increased number of peritubular capillaries and cortical arterioles and decreased interstitial inflammation and fibrosis (Liu et al. 2014). In rats, SS-31 reduces oxidative stress and inflammation, preventing AKI caused by warm IRI (Szeto et al. 2011) and unilateral ureteral obstruction (Mizuguchi et al. 2008). SS-31 pretreatment also serves a protective role against hypoxia-/reoxygenation-induced apoptosis of human renal tubular epithelial cells, partly by suppression of p66Shc (Zhao et al. 2013), a gene that encodes for an adaptor protein that regulates oxidative stress and apoptosis. Moreover, intraperitoneal injections of SS-31 in rats alleviate contrast-induced AKI, primarily due to an antioxidant action (Duan et al. 2013).

Similarly, in swine atherosclerotic RAS systemic infusion of SS-31 during renal revascularization promotes renal mitochondrial biogenesis and ameliorates renal injury four weeks later (Eirin et al. 2012). Furthermore, chronic subcutaneous injections of SS-31 attenuate swine stenotic-kidney microvascular loss and injury and improves renal oxygenation, hemodynamics, and function (Eiin et al. 2014), demonstrating the efficacy of cardiolipin-targeted therapies for preserving the ischemic kidney in chronic experimental renovascular disease. SS-31 has demonstrated to be safe in several clinical trials (NCT01754818, NCT01513200, NCT01518985, NCT01115920, NCT01786915), and its efficacy is currently being tested in patients with renovascular disease undergoing renal revascularization (NCT01755858). Outcomes of this study will advance our understanding of the role of cardiolipin in renal disease as well as the efficacy of mitochondria-targeted therapies.

3.6 Fission Inhibitors

Mitochondrial fission is governed by dynamin-related protein (DRP)-1, a GTPase protein localized in the perinuclear region. Once recruited from the cytosol to the mitochondrion, DRP-1 interacts with mitochondrial fission-1 protein to induce outer mitochondrial membrane constriction and fragmentation (Qi et al. 2013). Furthermore, activation of DRP-1 triggers mitochondrial depolarization and subsequent mitophagy (Twig and Shirihai 2011). Therefore, targeting DRP-1 might be beneficial in the treatment of diseases associated with altered mitochondrial fission.

Dynasore is a cell-permeable small molecule that inhibits the GTP hydrolysis of DRP-1, interferes with endocytic functions, and inhibits cell spreading and migration (Macia et al. 2006), but its efficacy in preserving renal mitochondria has yet to be tested. Unlike dynasore, mitochondrial division inhibitor (Mdivi)-1 selectively inhibits DRP-1 activity by blocking its assembly, acting through the GTPase domain (Cassidy-Stone et al. 2008). Although treatment of porcine preimplantation embryos and fibroblast cells with mdivi-1 reduces mitochondrial membrane potential and blastocyst cell number, increasing ROS and apoptosis (Yeon et al. 2015), its delivery in vivo inhibits mPTP opening and protects cardiomyocytes exposed to renal (Sumida et al. 2015) and cardiac (Ong et al. 2010) IRI. Furthermore, intraperitoneal injections of mdiv-1 prevent mitochondrial fragmentation and tubular cell apoptosis in murine AKI (Tang et al. 2013). Nevertheless, no studies have addressed their renoprotective properties in humans.

4 Conclusions and Perspectives

Studies in various animal models have implicated mitochondrial damage in the pathogenesis of genetic defects, acute kidney injury, chronic kidney disease, aging, and renal tumors. Kidney mitochondrial injury may manifest as ultrastructural abnormalities, changes in homeostasis, dysfunction, and loss. These result in decreased cellular energy production, increased oxidative stress, and apoptosis, triggering microvascular loss, inflammation, fibrosis, and renal failure. Notwith-standing the evidence supporting mitochondrial damage in the pathogenesis of different types of renal disease, a cause–effect relationship remains to be established.

Mitochondrial targeting has been demonstrated as a potential intervention to preserve mitochondrial structure and function and ameliorate kidney injury in several animal models of renal disease. Although these compounds concentrate at the level of mitochondria, it is difficult to rule out non-mitochondrial effects that could have been partly responsible for attenuating renal injury and dysfunction. Some of these compounds such as SS-31 and MitoQ are being evaluated in humans for various therapeutic indications (see ClinicalTrials.gov). Yet, further in vivo animal studies and clinical trials are needed to confirm the efficacy and safety of mitochondrial targeting.

Acknowledgments

Sources of Funding This work was supported by the NIH grants DK73608, DK102325, DK106427, and HL-123160 and the Mayo Clinic Center for Regenerative Medicine.

Disclosures Drs. A. Lerman and L.O. Lerman: Advisory Board, Stealth Biotherapeutics.

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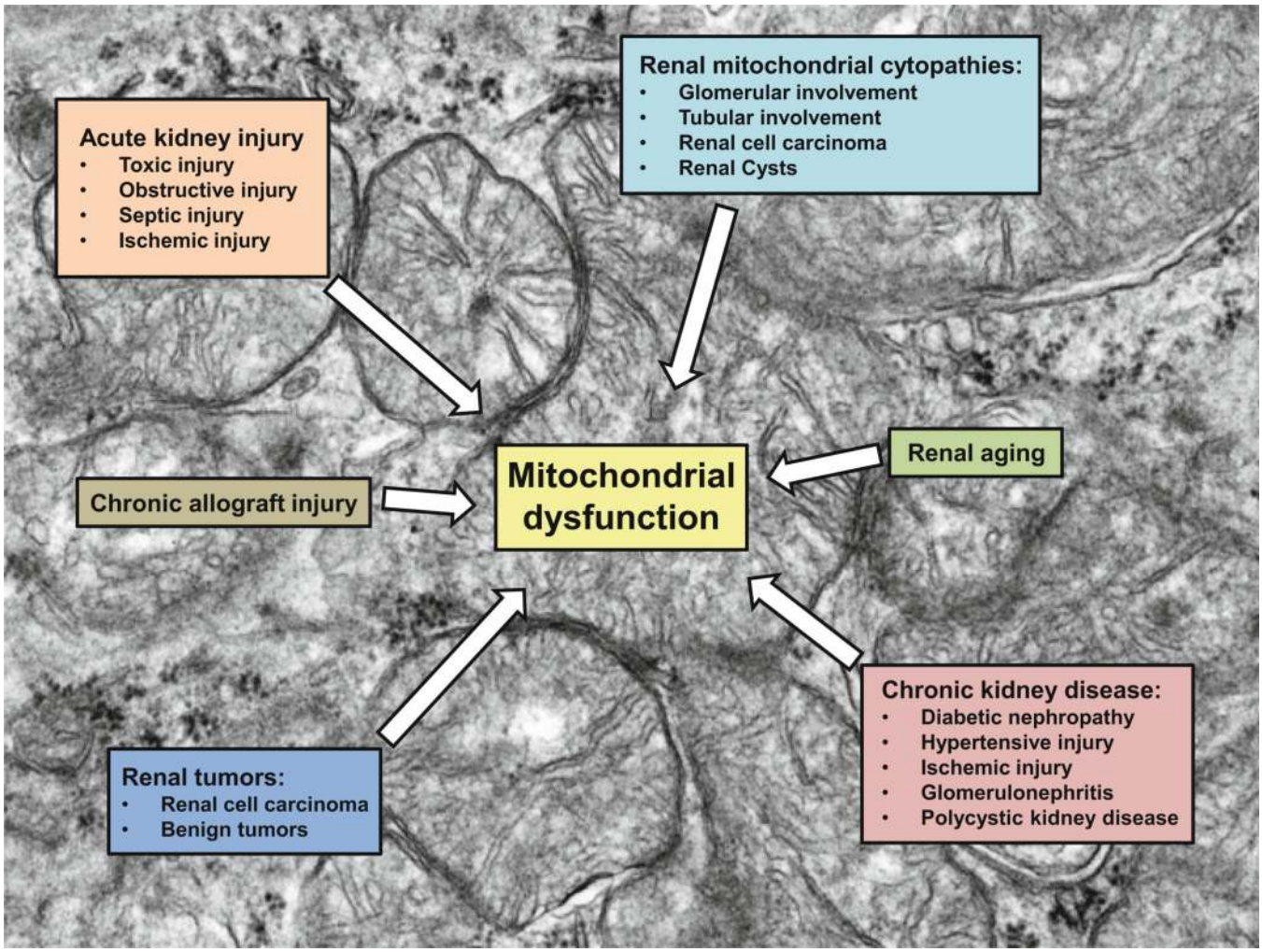

Fig. 1.

Representative transmission electron microscopy showing swollen mitochondria with loss of cristae and matrix in swine renovascular disease. Mitochondrial damage and dysfunction have been implicated in several renal conditions

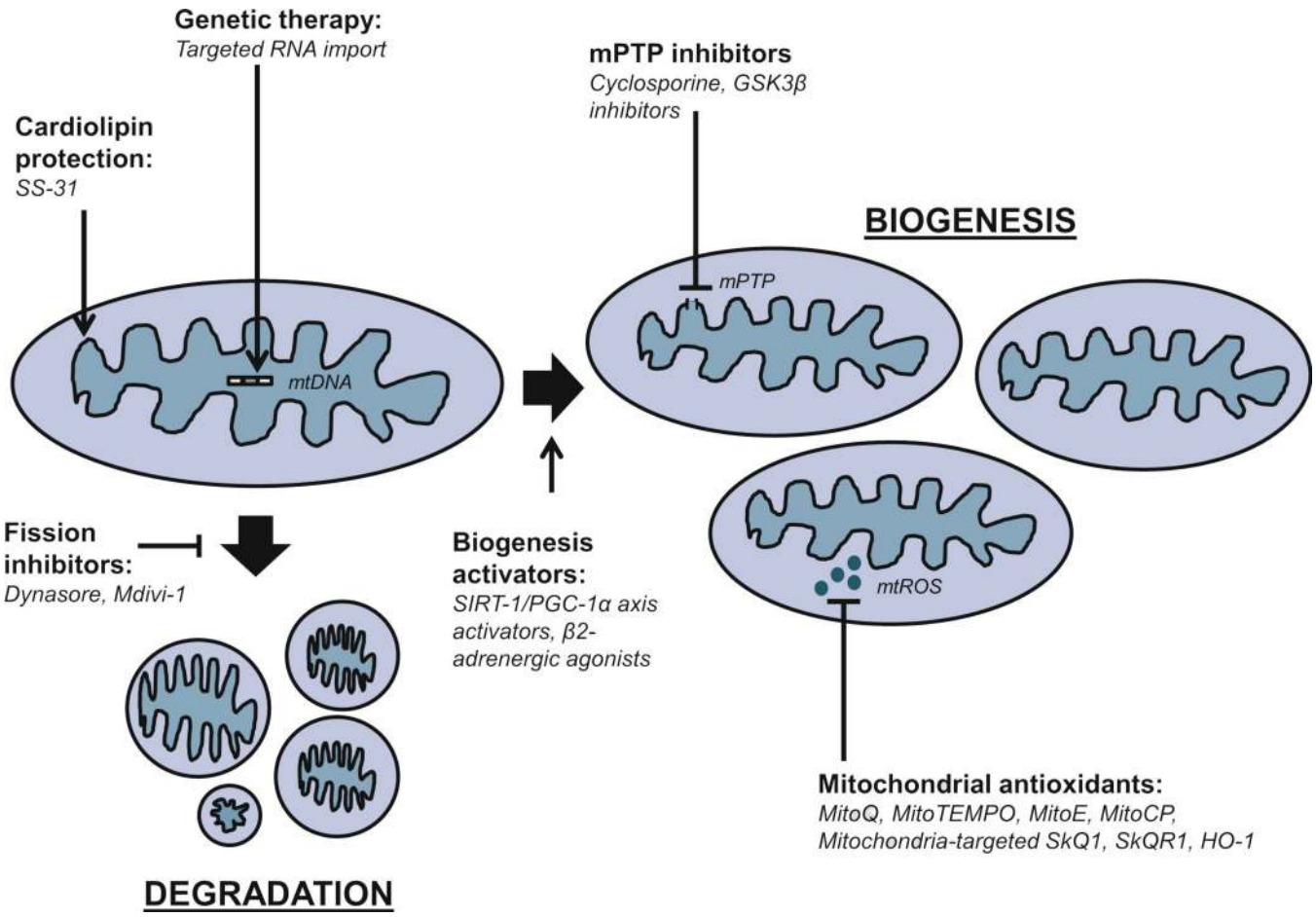

Fig. 2.

Schematic of experimental therapeutic interventions that may ameliorate renal mitochondrial (mt) injury and dysfunction. *mPTP* mt permeability transition pore, *SS* Szeto–Schiller peptide, *PGC* peroxisome proliferator-activated receptor gamma coactivator, *GSK* glycogen synthase kinase, *Mdivi1* mt division inhibitor, *Mito* mitochondrial targeted, *Q* coenzyme-Q, *TEMPO* piperidine nitroxide, *E* α-tocopherol, *CP* nitroxide, *SkQ1* plastoquinonyl-decyl-triphenylphosphonium, *SkQR1* plastoquinonyl decylrhodamine 19, *HO* heme oxygenase