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From Physiology to Pathology: The Role of Mitochondria in Acute Kidney Injuries and Chronic Kidney Diseases

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Abstract
Background: Renal diseases remain an increasing public health issue affecting millions of people. The kidney is a highly energetic organ that is rich in mitochondria. Numerous studies have demonstrated the important role of mitochondria in maintaining normal kidney function and in the pathogenesis of various renal diseases, including acute kidney injuries (AKIs) and chronic kidney diseases (CKDs). ***Summary:*** Under physiological conditions, fine-tuning mitochondrial energy balance, mitochondrial dynamics (fission and fusion processes), mitophagy, and biogenesis maintain mitochondrial fitness. While under AKI and CKD conditions, disruption of mitochondrial energy metabolism leads to increased oxidative stress. In addition, mitochondrial dynamics shift to excessive mitochondrial fission, mitochondrial autophagy is impaired, and mitochondrial biogenesis is also compromised. These mitochondrial injuries regulate renal cellular functions either directly or indirectly. Mitochondria-targeted approaches, containing genetic (microRNAs) and pharmaceutical methods (mitochondria-targeting antioxidants, mitochondrial permeability pore inhibitors, mitochondrial fission inhibitors, and biogenesis activators), are emerging as important therapeutic strategies for AKIs and CKDs. ***Key Messages:*** Mitochondria play a critical role in the pathogenesis of AKIs and CKDs. This review provides an updated overview of mitochondrial homeostasis under physiological conditions and the involvement of mitochondrial dysfunction in renal diseases. Finally, we summarize the current status of mitochondria-targeted strategies in attenuating renal diseases.

Introduction

Acute kidney injuries (AKIs) and chronic kidney diseases (CKDs) have become a global concern, affecting millions of people worldwide, and are associated with increased morbidity and mortality and tremendous medical costs [1, 2]. However, currently, there is no effective clinical treatment for renal diseases.

The kidney is a highly energetic organ that is rich in mitochondria, especially in tubular cells [3]. Increasing evidence indicates that mitochondrial dysfunction

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contributes to the pathogenesis of AKIs, including ischemia, nephrotoxicity, and sepsis injury, and CKDs, including diabetic nephropathy, glomerulonephritis, tubulointerstitial fibrosis, aging-associated renal injury, and polycystic kidney disease (PKD). Acute or chronic insults might damage the mitochondria, characterized by decrease in mitochondrial DNA (mtDNA), increase in reactive oxygen species (ROS), and reduction of ATP generation, thus triggering oxidative stress and cell injury. Moreover, kidney diseases are associated with disrupted mitochondrial homeostasis, the molecular control of mitochondrial formation (biogenesis), mitochondrial dynamics (fusion/fission), mitochondrial degradation (protease/mitophagy), and biogenesis [4]. Therefore, this review first discusses mitochondrial homeostasis under physiological conditions and then indicates the involvement of mitochondrial dysfunction in renal diseases. Finally, we summarize mitochondrial-targeting therapeutic agents for the treatment of AKIs and CKDs.

Mitochondrial Homeostasis

The homeostasis state of the mitochondria is closely regulated by fine-tuning the mitochondrial energy balance, fission and fusion processes (mitochondrial dynamics), degradation of damaged mitochondrial components (mitophagy), and the synthesis of new components (biogenesis).

Mitochondrial Energy Metabolism and Mitochondrial ROS

Mitochondria are the main site for energy production in living organisms. The tricarboxylic acid cycle uses acetyl-CoA derived from carbohydrates, fatty acids, and amino acids to generate the reducing agents NADH and FADH2. These two molecules then act as electron donors in the electron transport chain (ETC)/oxidative phosphorylation (OXPHOS) to produce ATP. Under physiological conditions, the transferal of an electron from complexes Ⅰ to Ⅴ and the leakage of its minor portion from complexes Ⅰ and Ⅲ cause a reduction in O_2, thereby forming highly reactive metabolites of O_2, including the superoxide anion (O2•−), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH). These mitochondrial ROS (mtROS) function as essential second messengers to activate target proteins [5]. However, in pathological processes, such as ischemic reperfusion injury, complex Ⅰ undergoes reverse electron transfer, resulting in a dramatic increase in the production of superoxide in the mitochondria. These toxic mtROS are released into the matrix and may contribute predominantly to oxidative stress [6].

Mitochondrial Dynamics: Fusion/Fission

Mitochondria constantly change their shape and size through fusion and fission processes, collectively known as mitochondrial dynamics, in response to metabolic and signaling cues in the cell environment [7]. During mitochondrial fission, a mitochondrion divides into two daughter organelles, while during mitochondrial fusion, two mitochondria organelles merge into one larger mitochondrion. Mitochondrial outer membrane fusion is mainly mediated by two dynamin-related GTPases, mitofusin 1 (MFN1) and mitofusin 2 (MFN2). Crystal structure studies have revealed that MFN1 and MFN2 can interact as homo- or heterodimers to mediate mitochondrial fusion [8, 9]. In contrast, inner membrane fusion is mediated by another dynamin-related GTPase optic atrophy 1 [10]. Dynamin-related protein 1 (Drp1), the main mediator of mitochondrial fission, is phosphorylated and recruited to the outer mitochondrial membrane and hydrolyzes GTP to partition the mitochondria [11, 12]. Other four proteins, fission protein 1 (Fis1) [13], mitochondrial fission factor [14], and the mitochondrial elongation factors 1 and 2, function as adapters during the fission process [15, 16]. The shift from mitochondrial dynamics homeostasis to excessive mitochondrial fission during cell injury is demonstrated below.

Mitochondrial Biogenesis and Mitophagy

Mitophagy is the selective degradation of damaged mitochondria, which prevents cell death from mitochondrial oxidative stress and proapoptotic signaling. Currently, two main mitophagy mechanisms have been proposed, including ubiquitin-dependent and non-ubiquitin-dependent mechanisms. The ubiquitin-independent mechanism is regulated by mitophagy receptors that localize on mitochondrial outer membrane, such as FUN14 domain containing 1 (FUNDC1), BCL2, and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3)/BNIP3-like protein (NIX), and the ubiquitin-dependent pathway is mediated by the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1)/Parkin signaling system [17–22]. PINK1, the main regulator of mitophagy, translocates to damaged mitochondria and activates Parkin E3-ubiquitin ligase, which in turn gets protein ubiquitinated, a marker of autophagy machinery recruitment [23]. Usually, mitophagy is activated by adverse conditions, such as hypoxia, nutrient deprivation, or DNA damage. In contrast, mitochondrial biogenesis occurs to generate newly synthesized organelles to replace damaged

mitochondria. Mitochondrial biogenesis requires coordination of the nuclear and mitochondrial genomes [24]. Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) plays a pivotal role in activating nuclear transcription factors, including nuclear respiratory factor NRF1, NRF2, PPARα, estrogen-related receptor α, and yin-yang 1 [25–29]. NRF1 and NRF2 further stimulate the expression of mitochondrial transcription factor A, mitochondrial transcription factor B1, and mitochondrial transcription factor B2 [30]. Therefore, by acting on these transcription factors, PGC-1α can drive virtually all aspects of mitochondrial biogenesis, including mtDNA replication and transcription, fatty acid oxidation (FAO), respiratory chain activation, and ROS detoxification [31].

Mitochondria and AKIs

It is well recognized that mitochondrial dysfunction is an initiator and contributor to renal tubular dysfunction in AKIs. This section summarizes an update on the pathophysiological significance of mitochondria in AKIs evoked by ischemia-reperfusion (I/R), drug toxicity, and sepsis.

I/R Injury

AKI through I/R results from a temporary cessation of blood flow followed by the restoration of circulation. The I/R injury depresses mitochondrial respiration and ATP production, increases the production of ROS, and decreases the mitochondrial transmembrane potential. Moreover, impaired energy metabolism, characterized by impaired FAO and enhanced glycolysis, was reported to be a hallmark of renal I/R injury [32–35].

In addition, the mitochondrial dynamics shift to the fission process in I/R-induced kidney injury. The fission mediator Drp1 is phosphorylated and translocated to the mitochondria upon tubular cell injury and involves in the constriction and cleavage of mitochondria, which further leads to mitochondrial outer membrane fission [36–38]. Drp1 ablation and mitochondrial fission inhibitor Mdivi-1 were proven protective against I/R injury-induced kidney damage and promoted kidney recovery [11, 39]. In a recently published paper, Qin et al. [40] reported that renal uncoupling protein 2 could protect against I/R-induced AKI by limiting mitochondrial fission and improving mitochondrial dynamics balance. In contrast, another study showed that microRNA-214 (miR-214) repressed Mfn2, and induced mitochondrial fission, thus promoting renal tubular cell apoptosis and aggravating ischemic AKI [41]. More detailed studies showed that tumor necrosis factor superfamily member LIGHT (homologous to lymphotoxins, inducible expression, competes with herpesvirus glycoprotein D for herpesvirus entry mediator, a receptor expressed on T lymphocytes), mammalian STE20-like kinase 1 (Mst1), and adaptor protein Numb also participate in I/R-AKI pathogenesis by modulating Drp1 phosphorylation [36, 38, 42].

Mitophagy is activated in I/R-induced AKI. Tang et al. [19, 43] proved that in the ischemic AKI model, activating the PINK1-Parkin pathway and BNIP3 can both improve mitochondrial quality and protect renal function. Interestingly, one study also showed that activation of FUNDC1-dependent mitophagy conferred renoprotection in ischemic AKI possibly via suppression of the Drp1-mediated mitochondrial fission [21]. The mitochondrial biogenesis regulator PGC-1α and its target transcription factors are suppressed in ischemic AKI [44]. PGC-1α knockout mice suffered worse renal function and tubular injury after I/R injury, whereas tubule-specific PGC-1α overexpressing transgenic mice exhibited less severe AKI and quicker restoration of renal function after injury, demonstrating a renal protective effect of PGC-1α in an I/R-injured kidney [45]. Clinical data also suggested that higher PGC-1α expression is associated with faster and more complete recovery from delayed renal graft function after renal transplantation [46].

Drug Toxicity Injury

Drugs commonly associated with acute renal injury are antibiotics, such as vancomycin and aminoglycosides, chemotherapeutic agents, such as cisplatin and methotrexate, and contrast agents. Overdosage of acetaminophen (APAP) can also cause acute renal injury. Recent studies have demonstrated mitochondrial structural and functional changes in kidney injuries induced by cisplatin, APAP, aminoglycoside, and contrast agents [47–50]. Consistent with other studies, our findings have shown that cisplatin-induced mitochondrial injury is characterized by impaired energy metabolism and increased ROS production, dysregulated mitochondrial dynamics, and altered mitophagy [42, 43, 48, 51–55]. As with I/R-induced AKI, cisplatin-induced AKI is also accompanied with FAO disruption and inducing FAO improves cisplatin-induced AKI [56, 57]. The role of glycolysis in drug-induced AKI remains less understood, with two studies reporting that inhibition of pyruvate kinase M2 (PKM2) (which catalyzes the final step in glycolysis) and PFKFB3 (a key regulator of cellular glycolytic metabolism) functions to protect cisplatin nephrotoxicity in mice

[33, 58], while other studies indicated that glycolysis intermediates, such as pyruvate and fructose 1,6-bisphosphate, functioned to ameliorate cisplatin-induced AKI [59, 60]. In addition, sirtuin 3 (SIRT3), a NAD-dependent protein deacetylase, displayed a therapeutic role in maintaining mitochondrial function [61]. The underlying mechanisms may be associated with an increase in mitochondrial fusion via recruitment of Drp1 and mitochondrial fission factor to the mitochondrial outer membrane [62], and in mitochondrial biogenesis by activating PGC-1α [63].

In the clinic, excessive APAP and aminoglycoside can also cause acute renal injury. Our previous study found that inhibiting mitochondrial complex I with rotenone could blunt mitochondrial oxidative stress and inflammation to protect kidneys against APAP-induced injury [47]. Studies in animal models have shown that gentamicin induced the generation of ROS, increased NADPH oxidase activity, and mitochondrial oxidation in the kidneys [49, 64]. In addition, loss of mitochondrial COX activity in proximal tubules was observed in patients treated with the antiretroviral drug tenofovir disoproxil fumarate [65]. Contrast-induced AKI (CI-AKI) is the third common cause of AKI in hospitalized patients, which is mainly caused by an iodine contrast agent used for diagnostic imaging [66]. Increased mtROS and activated mitophagy are dominantly observed in CI-AKI. Studies have shown that protective agents with antioxidant activity and mitophagy-activating effect show protective effects in CI-AKI [22, 50].

Septic Injury

Mitochondrial dysfunction is also an important pathogenic factor in septic AKI. Because the renal vulnerability to the septic milieu primarily arises from the associated shock and hypoperfusion, many pathological features of mitochondrial dysfunction in septic AKI are common with I/R-induced AKI [67]. A decrease in ATP production and mitochondrial dysfunction is also documented in septic-associated AKI resulting from loss of mitochondrial respiratory proteins in proximal tubules, and mitochondrial-targeted antioxidants were reported to attenuate septic renal injury [68]. In addition, the expression of PGC-1α was suppressed in the tubular cells of septic AKI models, and PGC-1α knockout mice exhibited exacerbation of increases in BUN and serum creatinine in these models [69]. Mitophagy is activated in the early stage of sepsis, which facilitates damaged mitochondria clearance and accelerates cell recovery. Inducing mitophagy improved the mitochondrial and renal functions in experimental septic AKI models [70–73].

Apart from shock and hypoperfusion, sepsis is characterized by excessive immune reactions caused by a bacterial infection [74]. One elegant research showed that in response to sepsis, mtDNA was released into the systemic circulation in the early phase of septic AKI, which activates a systematic inflammatory response via the TLR9 pathway, showing an interplay between mitochondrial injury and immune responses in sepsis-associated AKI [75].

Mitochondria Dysfunction in CKDs

CKD is a growing epidemic affecting 9–10% of the population worldwide [76]. This section summarizes the mitochondria in CKD, including diabetic kidney disease (DKD), glomerulonephritis, aging-associated CKD, autosomal dominant PKD (ADPKD), and renal tubulointerstitial disease.

Diabetic Kidney Disease

DKD is a major cause of end-stage renal disease worldwide with limited therapeutic options. Time-course study in diabetic rats indicated that changes in kidney mitochondrial bioenergetics and dynamics precede the development of albuminuria and renal histological changes [77], indicating that early stabilization of the mitochondria may prevent the progress of DKD.

Increased glycolysis and overactivation of coupled ETC and OXPHO occur in DKD. In early DKD, metabolic fuel sources are altered by chronic hyperglycemia. Increase of glycolysis occurs in early DKD and excessive glucose fluxes to the Krebs cycle and subsequently causes overactivation of coupled ETC and OXPHO [78, 79]. Excess electrons leak from ETC and donate superabundant electrons to produce ROS. In addition, changes in metabolic fuel sources in diabetes and continuous ATP demand lead to an increase in oxygen consumption, which contributes to renal hypoxia [80]. Indeed, several studies published by King's group have reported that elevated PKM2 in podocytes, a glycolysis metabolism enzyme, increased glucose flux and protected mitochondrial function, thus alleviating the progression of diabetic glomerular pathology [78, 81, 82]. A recent study highlighted the antiapoptotic potential of PKM2 by upregulating mitochondrial fusion protein Mfn1 [83].

Moreover, mitochondrial fission is the predominating mitochondrial feature in the kidney throughout the DKD and is associated with the extent of renal damage in DKD models and human diabetic kidneys [84]. Under hyperglycemia conditions, Drp1 is phosphorylated and

translocated from the cytosol to the outer membrane of the mitochondria by Rho-associated coiled-coil-containing protein kinase 1 and A-kinase anchoring protein, thus facilitating fission in podocytes and endothelial cells [85, 86]. Drp1 is induced by RCAN1.4 overexpression, and mitochondrial fission is also stimulated in mesangial cells [87]. Inhibition of Drp1 by pharmaceutical or genetic methods protects against the development of DKD in rodent models [88, 89].

In the diabetic kidney, the autophagy machinery is also disrupted. From in vitro experiments to in vivo and clinical studies, emerging evidences have suggested the defective tubular cell mitophagy under diabetic condition [90–94]. Hyperglycemia-induced tumor necrosis factor alpha-induced protein 8-like 1 (TNFAIP8L1/TIPE1) and FoxO1/putative kinase 1 (PINK1)/Parkin pathways were separately reported to be involved in the downregulation of tubular mitophagy in diabetic nephropathy [91, 94]. Although mitophagy in DKD is a relatively new research area, several researches have shown a decline in mitochondrial biogenesis in both DKD rodent models and DKD patients [95–97]. Reduction in PGC-1α accounted for the decreased mitochondrial biogenesis and has been implicated in the development of DKD and renal fibrosis [98]. Additionally, an updated research showed the potential of activating mitophagy and mitochondrial biogenesis in preventing renal diabetic pathological changes through PINK1/Parkin pathway and Nrf2/SIRT1/PGC-1α axis [99]. All these results pose a possibility that manipulation of signal molecules increasing mitochondrial biogenesis may show renoprotective effects. The G protein-coupled bile acid receptor TGR5 activation has been reported to induce mitochondrial biogenesis and inhibits kidney disease in obesity and diabetes [100]; the activation of mitochondrial glycerol 3-phosphate dehydrogenase induces mitochondrial biogenesis and prevents podocyte injury and proteinuria in DKD [101]; klotho induces adenosine monophosphate-activated protein kinase (AMPK)-PGC-1α-mediated mitochondrial biogenesis and ameliorates DKD [102]. Thus, facilitating mitophagy and mitochondrial biogenesis may function to maintain mitochondrial dynamics and prevent DKD progression [103].

Glomerulonephritis

Investigators have observed the overexpression of HIF-1α, upregulation of pentose phosphate pathway, and downregulation of tricarboxylic acid cycle, glutaminolysis, and FAO in patients with nephrotic syndrome, antineutrophil cytoplasmic antibody-associated vasculitis, and systemic lupus erythematosus. Activation of the pentose phosphate pathway was tightly linked to intrarenal macrophage infiltration, cytokine production, and reduced kidney function [104]. Another study reported that the blockage of branched-chain aminotransferase 1 inhibited the catabolism of branched-chain amino acids, which retarded, oxygen consumption and glycolysis in macrophages and attenuated the severity of crescentic glomerulonephritis in rats [105]. In light of this, the modulation of glucose metabolism may offer novel immune-modulatory therapeutic approaches in glomerulonephritis.

In addition to defects in energy metabolism, deregulation of mitochondrial dynamics also plays an important role in driving the pathogenesis of glomerulonephritis. Wei et al. [106] found the overproduction of mitochondrial fission proteins Drp1, phospho-Drp1 (Ser 616), and Fis1 in children with membranous nephropathy. Also, mitochondrial fission proteins were also involved in podocyte injury in vitro and ADR-induced glomerulonephritis [107, 108]. These studies demonstrated that mitochondrial dynamics might be disturbed in glomerulonephritis.

Deficiency in mitophagy also leads to mitochondrial dysfunction and glomerulonephritis. In an earlier study, Kawakami and collages reported that mutation of critical autophagy genes ATG5 or ATG7 in mice kidney epithelium played an important role in the progression of nephropathy. Most objects with ATG5 or ATG7 mutation developed slight podocyte and tubular dysfunctions within 2 months, then progressed to glomerular and tubular changes resembling human focal segmental glomerulosclerosis by 4 months, and finally died from kidney failure after 5 months [109]. A recent study found that autophagy was also activated in lupus nephritis, especially in the podocytes [110]. In these types of glomerulonephritis, increasing autophagy is cytoprotective against mitochondrial dysfunction and kidney injury. Similarly, mitochondrial biogenesis was downregulated in rodent models and patients with glomerulonephritis; therefore, inducing mitochondrial biogenesis may also enhance podocyte recovery from glomerular injury [111, 112].

Not only podocyte and tubular epithelial cells, but also endothelial cells play and important role in glomerulonephritis. Daehn et al. [113] demonstrated that in ADR-induced glomerulosclerosis, podocytes released endothelin-1 (EDN1), which mediated mitochondrial oxidative stress and dysfunction in adjacent endothelial cells via paracrine EDN1 receptor type A activation. Inhibition of EDN1 receptor type A or scavenging of mtROS prevented podocyte loss, albuminuria, glomerulosclerosis, and renal failure efficiently. Thus, endothelial

dysfunction in turn promoted podocyte apoptosis, showing reciprocal crosstalk between the podocytes and endothelial cells in glomerulosclerosis.

Aging-Associated CKD

Mitochondrial dysfunction has been proposed to underlie age-related kidney pathologies, such as glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. Lower levels of antioxidant enzymes, denatured respiratory chain complexes, mtDNA, and mitochondrial mass have been observed in aged kidney under physiological conditions [114, 115]. Meanwhile, Lee et al. [116] found that the depletion of isocitrate dehydrogenase 2, a major enzyme responsible for generating mitochondrial NADPH, destroyed redox balance and accelerated renal dysfunction in aged mice. Another group reported that the knockout of cytochrome P450-2E1, a well-established source of ROS production, alleviated mitochondrial nitroxidative stress and prevented aging-related kidney injury [117]. Mitochondrial dysfunction in the proximal tubular epithelial cells also leads to decreases in vascular endothelial growth factor secretion and impaired angiogenesis, which in turn leads to renal injury in the aging kidney [118]. More importantly, these age-related renal pathological changes could be mitigated by mitochondrial protection [119–121].

Autosomal Dominant PKD

PKD is a severe inherited nephropathy characterized by cysts in the kidney and the progressive development of end-stage renal disease. Mutations of two polycystin genes, PKD1 and PKD2, which encode polycystin 1 and polycystin 2, are the most common causes of ADPKD [122], whereas the molecular mechanisms remain largely unclear. Early in 2012, an unbiased proteomic analysis suggested that mitochondria were involved in ADPKD [123]. Reciprocally, increased mitochondrial abnormity, including reduced mitochondrial mass, altered structure, and fragmentation, was present in renal tubular epithelial cell-specific PKD1 knockout mice [124].

Studies have focused on alterations in cell metabolism in ADPKD. Increased glycolysis, defective fatty acid β-oxidation, and altered mitochondrial function are observed in vitro and in ADPKD animal models and kidney tissues of ADPKD patients [122, 125, 126]. Kuo et al. [127] reported that mutation of PKD2 might contribute to the increased oxidative metabolism and aberrant cell proliferation of kidney cysts in ADPKD. Another interesting study showed that a C-terminal cleavage product of plasma cell glycoprotein 1 could translocate to the mitochondria matrix and that expression of this functional protein increased mitochondria elongation and promoted mitochondrial function in PKD1 knockout cells and *Drosophila melanogaster*. Moreover, Hajarnis et al. [128] demonstrated that an miR-17-mediated inhibition of OXPHOS added to the metabolism disturbance feature of PKD. Genetic and pharmacological methods used to rectify mitochondrial metabolism disturbance slowed cyst proliferation, reduced cyst size, and improved renal function [128–130].

Renal Tubulointerstitial Disease

Renal tubulointerstitial fibrosis is the common process that occurs in virtually every type of CKD and a final common pathway to end-stage renal failure [131]. Emerging evidence has proven that mitochondria play a role in renal tubulointerstitial fibrosis. The direct evidence is that homoplasmy mutations in mtDNA which encodes mitochondria tRNAPhe (m.616T > C and m.547A > T) cause inherited tubulointerstitial kidney disease [132–134]. Mitochondrial injury, characterized by the mitochondrial genome released from dying cells, is considered a biomarker to better identify chronic renal injury in hypertensive patients [135].

Various cell types, such as tubular epithelial cells, interstitial fibroblasts, endothelial cells, and inflammatory cells, are known to contribute to tubulointerstitial fibrosis progression; mitochondrial dysfunction was reported to account for the pathologic changes in these cells. Numerous studies have reported that adjusting mitochondrial metabolism quality [136] in tubular epithelial cells suppresses epithelial to mesenchymal transition-like phenotype and attenuates tubulointerstitial fibrosis in experimental models [136–139]. In renal fibroblasts, the activation of Drp1 mediated mitochondrial fission and promoted cell activation and fibrogenesis [140]. In endothelial cells, two groups separately reported that inhibition of arginase-2 and latent transforming growth factor beta-binding protein 4 reduces renal fibrosis by maintaining mitochondrial function [141, 142].

New Mitochondria-Targeted Therapeutics

The critical role of mitochondrial dysfunction as a mechanism underlying all kidney diseases has been emphasized above. Here, we discuss several mitochondria-targeted approaches that have recently been developed, including genome editing in the mitochondria, some compounds specifically targeting the mitochondria, and activators promoting mitochondrial biogenesis (Fig. 1).

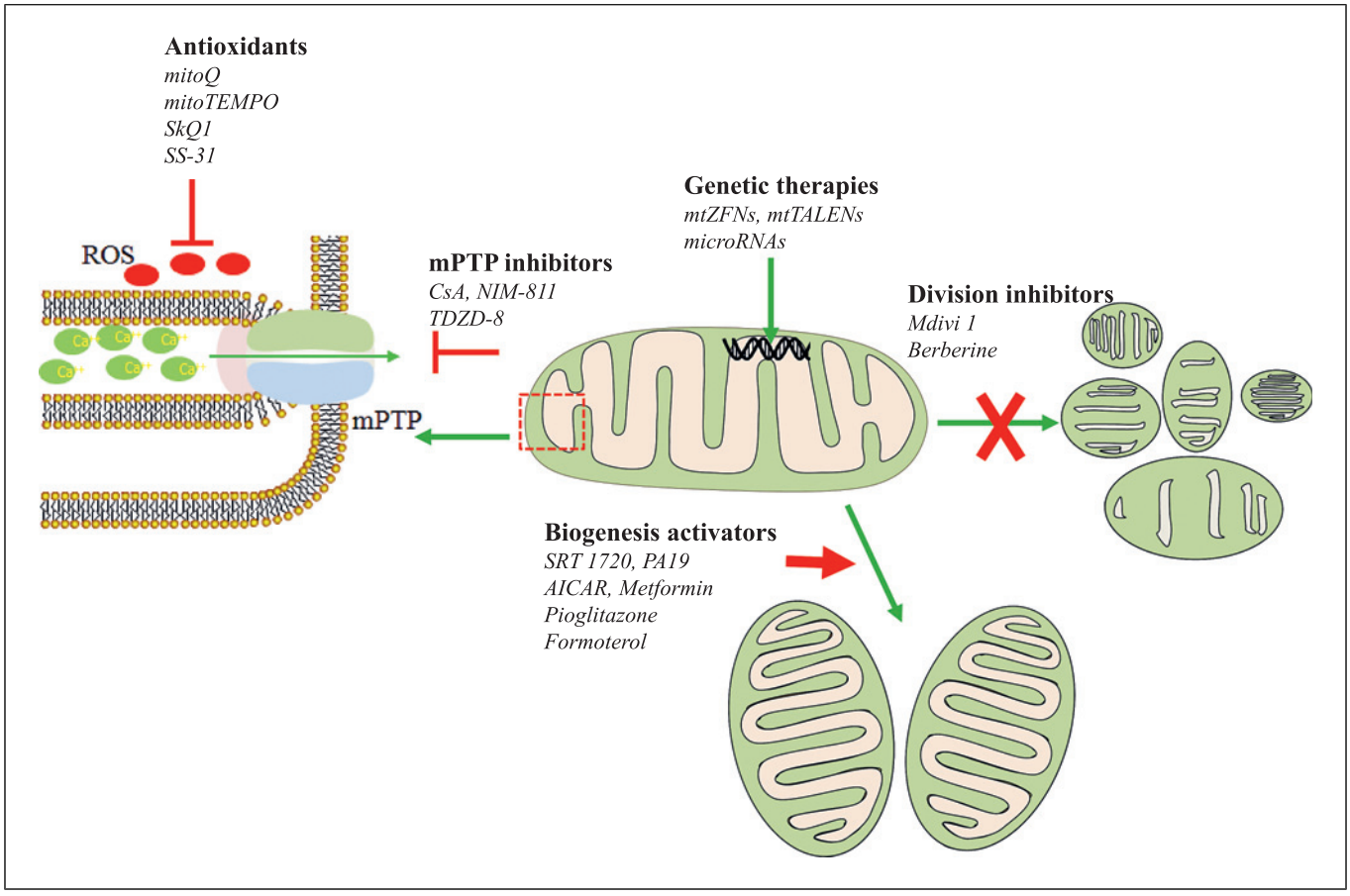

Fig. 1. Mitochondria-targeted therapeutics. Genetic therapies targeting mtDNA mutations are promising and open the way for the first treatment of mitochondrial diseases with kidney involvement. Mimics or inhibitors of miRNAs and pharmacological agents, including mitochondria-targeting antioxidants, mPTP inhibitors, mitochondrial fission inhibitors, and biogenesis activators, have shown potential in maintaining mitochondrial fitness and kidney protection. AICAR, 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside; CsA, cyclosporine-A; mPTP, mitochondrial permeability transition pore; NIM-811, N-methyl-4-isoleucine cyclosporine; TDZD-8, 4-benzyl-2-methyl-1, 2,4-thiadiazolidine-3, 5-dione.

Genetic Therapies

Given the heterogeneous penetrance, presentation, and prognosis of mitochondrial diseases, nephropathy induced by mtDNA mutations is currently incurable and mitochondria-targeted genetic therapies are still very limited in kidney disease. Genome editing in the mitochondria would be the hope of curing complex clinical disorders. Gammage et al. [143] used a programable nuclease therapy approach, mitochondrially targeted zinc finger nucleases delivered by an adeno-associated virus, to successfully induce specific elimination of mutant mtDNA (m.5024C > T in mitochondrial tRNAAla) across the heart in mice, causing a reversion of molecular and biochemical phenotypes. Similarly, Bacman et al. [144] showed that the mitochondrial-targeted TALENS could reduce the mutant mtDNA load in the muscle and heart in mice with a heteroplasmic mtDNA mutation. These remarkable findings could open the way for the first treatment of mitochondrial diseases with kidney involvement.

In addition to directly editing mitochondrial genes, microRNAs (miRNAs) may indirectly regulate the expression of mitochondrial genes through their binding with target transcripts. Recently, some nuclear-encoded miRNAs have been reported to translocate to the mitochondria (mitomiRs) and modulate mitochondrial genome encoding in several diseases [145–147]. Our previous studies demonstrated a pathogenic role of miR-214 and miR-709 in CKD and AKI models by targeting mitochondrial genes [148, 149], suggesting the potential for mitomiRs to serve as a therapeutic target for kidney diseases. In contrast, other miRNAs may play protective

roles in the kidney. For example, in ischemic AKI, miR-668 was induced and functioned to repress mitochondrial protein 18 kDa and preserve mitochondrial dynamics for renal tubular cell survival and kidney protection [150]. Fierro-Fernández et al. [151] found that miR-9-5p offered protection from renal fibrosis in the mouse model of unilateral ureteral obstruction (UUO) by modulating PGC-1α. Thus, identifying the specific role of each miRNA and its corresponding targets may help improve the treatment of patients with AKI and CKD.

Pharmacological Agents

Mitochondria-Targeting Antioxidants

Several triphenyl alkyl phosphonium cation (TPP+)-conjugated antioxidants, such as mitoQ, mitoTEMPO, mitoE, and mitoCP, have shown benefits in several types of renal diseases. These compounds can cross the outer and inner mitochondrial membranes and accumulate in the mitochondrial matrix in a membrane potential-dependent manner. MitoQ is an antioxidant that conjugates TPP+ with lipophilic antioxidants (coenzyme-Q) and has been shown to be hundreds of times more effective than regular CoQ10 supplements. Administration of mitoQ before unilateral renal ischemia in rats [152] or bilateral renal ischemia in mice decreased mitochondrial oxidative damage and kidney IR injury [153]. MitoQ administered to graft kidneys during cold storage shows the potential in improving outcomes after transplantation [154]. MitoQ administration also dramatically reversed type 1 diabetes mouse kidney tubular injury via Nrf2/PINK1-mediated mitophagy and downregulate the oxidative stress level in tubular cells [92]. In an angiotensin II-induced kidney injury model, mitoQ exerts a protective effect on podocytes by maintaining mitochondrial fitness [155]. Furthermore, in a mice model of ADPKD, increased mtROS, oxidative damage, and cyst epithelial cell proliferation were also attenuated by mitoQ [156]. Owing to its promising protective effects in animal studies, mitoQ trials are now being conducted for several human diseases and are a novel therapeutic option for improving vascular function and reducing the risk of age-related cardiovascular diseases (NCT0259702, NCT04851288) [157, 158]. However, the effect of mitoQ on AKI and CKD remains to be tested clinically.

MitoTEMPO is a piperidine nitroxide conjugated to a TPP+, and it is thought to scavenge oxygen radicals in the mitochondria [159]. MitoTEMPO reduces renal dysfunction and systemic inflammation in experimental sepsis in mice [160]. MitoTEMPO reduced systemic inflammation levels, relieved renal oxidative stress, and ameliorated renal dysfunction in fecal peritonitis [68] and LPS-induced sepsis models [160, 161]. Wen et al. [162] found that mitochondrial dysfunction and NLRP3 inflammation activation were markedly inhibited by mitoTEMPO treatment in I/R-triggered kidney injury. In vitro, treatment with mitoTEMPO has also shown potential in preventing oxalate-induced injury in NRK-52E cells by inhibiting mitochondrial dysfunction and modulating oxidative stress [163]. A clinical study reported that infusion of mitoTEMPO significantly increased the plateau phase cutaneous vascular conductance, improving CKD-related vascular dysfunction in patients [164]. Moreover, mitoTEMPO ameliorated podocyte depletion and albuminuria, and improved glomerular histopathology in DKD [165]. Similar to the function of mitoQ and mitoTEMPO, mitoE (conjugated TPP+ with α-tocopherol) and mitoCP (conjugated TPP+ with the SOD mimetic nitroxide) can also prevent mitochondrial damage and renal injury in mice [166, 167].

Except for the TPP+-conjugated antioxidants, cationic plastoquinone derivatives SkQs (including SkQ1 and SkQR1) have also shown pronounced protective effects in kidney ischemia [168]. One report found that SkQ1 treatment delayed the appearance of traits of aging, including ameliorated kidney pathologies, in mtDNA mutator (PolgAmut/PolgAmut) mice [169]. Overall, these results suggest that mitochondria-targeted antioxidants provide a new method for the treatment and prevention of kidney diseases.

The tetrapeptide D-Arg-dimethyl Tyr-Lys-Phe-NH2 (SS-31, also named MTP-131 or elamipretide) is another type of mitochondria-targeted ROS scavenger. SS-31 selectively interacts with cardiolipin on the inner mitochondrial membrane and protects its electron-carrying function by preventing cardiolipin from converting cytochrome c into a peroxidase, which further promotes OXPHOS [170]. In LPS, ischemia, and cisplatin-induced AKI [171, 172] or renal damage induced by diabetes [173, 174] and a high-fat diet [175], SS-31 administration has beneficial effects on reducing mitochondrial oxidative stress and preventing tubular or podocyte injury. In rats, SS-31 intervention ameliorated UUO or 5/6 nephrectomy (5/6 Nx)-induced interstitial fibrosis by scavenging mtROS [176, 177]. Furthermore, in the kidneys of mice with advanced age, administering a short course of SS-31 could prevent and/or partially reverse changes in the glomerular architecture [119]. A phase IIa clinical trial in patients with atherosclerotic renal artery stenosis showed that adjunctive SS-31 during percutaneous transluminal renal angioplasty and stenting could attenuate post-procedural hypoxia, increase renal blood flow, and improve renal function [178]. Moreover, SS-31 administration in PKD1 knockout mice during pregnancy and lactation ameliorated the

progression of kidney disease in both mothers and their affected offspring without teratogenic or harmful effects observed [130]. Currently, SS-31 is enrolled in phase 1 and phase IIa clinical trials in kidney disease (NCT02436447, NCT01755858) and gained great attention.

Mitochondrial Permeability Transition Pore Inhibitors

Mitochondrial membrane depolarization, which is induced by the opening of the mitochondrial permeability transition pore (mPTP) in the mitochondrial membrane, can significantly interrupt ETC and then lead to decreased energy production, increased ROS production, and cell death. Cyclosporine-A (CsA) is a well-known immunosuppressant interacting with cyclophilin A and is clinically used in the treatment of graft rejection and autoimmune diseases, including kidney disease [179]. In addition, CsA is also known as an mPTP inhibitor, which can bind to cyclophilin D of the mPTP and inhibit mPTP opening [180]. Lemonine et al. [181] found that delivery of CsA protected the kidney from I/R injury, but the dose and timing of the injection were crucial to ensure the efficacy of treatment [182]. Moreover, demonstrated by increased tubulointerstitial fibrosis, inflammation, and podocyte damage, CsA is intrinsically nephrotoxic [183]. N-methyl-4-isoleucine cyclosporine (NIM-811) is a derivative of CsA and selectively inhibits cyclophilin D, but not cyclophilin A. Therefore, NIM-811 is non-immunosuppressive and potentially reduces rhabdomyolysis and impairment of the kidney after lower limb I/R injury [184]. However, the pharmacological inhibitor of cyclophilin D did not rescue mitochondrial function and kidney injury in db/db diabetic mice [185].

Recently, glycogen synthase kinase (GSK) 3β, a ubiquitous serine/threonine protein kinase, has been reported to phosphorylate cyclophilin D and promote mPTP opening. The GSK3β inhibitor 4-benzyl-2-methyl-1, 2,4-thiadiazolidine-3, 5-dione (TDZD-8) prominently ameliorated proteinuria and glomerular sclerosis in a murine model of ADR-induced podocytopathy by desensitizing mitochondrial permeability transition, concomitant with diminished oxidative stress and improved mitochondrial function [186]. In addition, Bao et al. [187] showed the blockade of GSK3β by lithium or TDZD-8 protected podocytes from LPS or ADR-induced injury. Moreover, Su et al. [188] found that TDZD-8 could reduce oxidative stress injury, ultimately reducing I/R injury during kidney transplantation. These results suggest that GSK3β inhibition might serve as a novel therapeutic therapy for treating renal diseases and the mechanism is partially mediated by mPTP inhibiting.

Mitochondrial Fission Inhibitors

A pharmacological inhibitor of Drp1, Mdivi1, which could inhibit Drp1 assembly and GTPase activity, has been demonstrated to blunt mitochondrial fission and rescue key pathologic features of DKD in mice or glomerular mesangial cells [189, 190]. Moreover, administration of Mdivi-1 decreased mitochondrial fragmentation and renal tubular cell apoptosis in rhabdomyolysis-induced AKI mice [191], as well as in an acute cardiorenal syndrome mouse model [192] and sepsis-induced organ dysfunction, including heart, kidney, and liver [193]. Similarly, Mdivi-1 attenuated fibroblast accumulation and interstitial fibrosis in UUO mice [140]. A recent study showed that a type of isoquinoline alkaloid present in Chinese herbal medicines, berberine, could inhibit Drp1 and protect glomerular podocytes in DN [88]. These data suggest that mitochondrial fragmentation by division machinery may be a new therapeutic target in AKI and CKD, while more studies need to confirm their renoprotective properties in humans.

Biogenesis Activators

Several recent studies have confirmed the protective role of PGC-1α, the key mitochondrial biogenesis regulator, in various kidney diseases [194, 195], thus making it a pharmacologic target for kidney diseases. AMPK could promote the expression of PGC-1α, thus enhancing mitochondrial biogenesis and the cellular response to energetic challenges [196]. 5-Aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) and metformin are reported AMPK activators. Morigi et al. [196] reported that in mice with cisplatin-induced AKI, AICAR could ameliorate tubular damage and improve renal function; consistent with this, PGC-1α was robustly enhanced at the same time. AICAR and metformin effectively attenuated albuminuria and renal histopathology in the kidneys of diabetic mice by increasing PGC-1α activity [197]. Metformin also inhibits the NLRP3 inflammasome and retards renal fibrosis via PGC-1α activating in adenine-fed and UUO mice. In addition, AMPK activators play a protective role in several kidney diseases through other pathways, such as suppressing mTOR and phosphorylation of acetyl-CoA carboxylase [198].

SIRT1, an NAD+-dependent deacetylase, also positively activates PGC-1α and regulates ATP generation and mitochondrial adaptive response to stress in several renal diseases [199]. Consistently, treatment with resveratrol, a SIRT1 activator, ameliorated podocyte damage in diabetic mice [200] or high-glucose treatment [201]. Resveratrol administration ameliorated oxidative stress and mitochondrial dysfunction in aging-related progressive renal injury

[120], sepsis-induced AKI [202], and 5/6 Nx damage [203]. A more specific SIRT1 activator, SRT1720, showed potential in ameliorating cisplatin-induced AKI in mice, inhibiting renal tubular cell epithelial to mesenchymal transition in db/db mice, attenuating renal fibrosis in UUO mice, and preventing anti-Thy 1.1 mesangial proliferative glomerulonephritis in rats [204–207]. A novel resveratrol analog PA19 also showed a protective effect in obesity-induced cardiac and renal injury [208]. A small clinical trial found that 500 mg of resveratrol supplementation for 4 weeks had no effect on Nrf2 and NF-κB expression in peripheral blood mononuclear cells of nondialyzed CKD patients [209]. Additional studies are needed to explore the effects of SIRT1 activators on CKD patients.

Other Pharmacological Agents

PPAR-γ agonists, including rosiglitazone, pioglitazone, and troglitazone, are traditional medicines for type 2 diabetes mellitus. Our previous studies showed that rosiglitazone attenuated podocyte damage and proteinuria by improving mitochondrial function [210, 211]. Recently, pioglitazone was reported to activate PGC-1α and mitigate chronic kidney injury in the 5/6 Nx rat model [212], the DN model [213], and patients with obesity-related glomerulopathy [213]. However, Small et al. [214] found that PPAR-γ agonists promoted mitochondrial destabilization and proximal tubular epithelial cell apoptosis under H_2O_2 treatment. Clinical trials of rosiglitazone in focal segmental glomerulosclerosis are currently underway [215]. The role of PPAR-γ agonists in the human kidney remains to be further studied.

β2-adrenergic receptor (β2-AR) belongs to the G protein-coupled receptor superfamily. Formoterol is currently reported to be a β2-AR agonist, which could stimulate PGC-1α expression and mitochondrial biogenesis [216]. Jesinkey et al. [217] observed that formoterol injection after I/R restored mitochondrial and renal functions and rescued tubular injury via the upregulation of mitochondrial protein. A recent study demonstrated that regulation of renal mitochondrial homeostasis by proximal tubule β2-AR was the mechanism by which formoterol accelerated the recovery of renal function after I/R-induced AKI [218]. Activating PGC-1α-dependent mitochondrial biogenesis, formoterol was also reported to restore glomerular function in mice after acute nephrotoxic serum nephritis or chronic ADR-induced glomerulopathy [111]. Thus, β2-ARs could serve as novel therapeutic targets, and formoterol may serve as a therapeutic compound for treating AKI and CKD.

Conclusion

Growing evidence suggests that mitochondria play a critical role in the pathogenesis of various renal diseases. The altered mitochondrial metabolic state, mitochondrial dynamics, mitophagy, and biogenesis are the primary aspects involved. In this review, we discussed in detail the relationship between mitochondrial dysfunction and AKI and CKD pathogenesis and summarized new therapeutic strategies targeting mitochondria dysfunction. More efforts are needed to explore the relatively unexplored area and to clarify the effectiveness of the therapeutic strategies clinically.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

A.Z., M.W., and M.B. contributed to the conception and design of the study. M.W., M.B., and L.Z. organized and wrote the first draft of the manuscript. M.M. and X.X. wrote sections of the manuscript. A.Z. contributed to manuscript revision. All authors read and approved the submitted version.

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