HHS Public Access

Author manuscript

Clin Sci (Lond). Author manuscript; available in PMC 2023 March 16.

Published in final edited form as:

Clin Sci (Lond). 2022 March 18; 136(5): 345–360. doi:10.1042/CS20210512.

Renal mitochondrial injury in the pathogenesis of CKD: mtDNA and mitomiRs

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Abstract

Chronic kidney disease (CKD) is a public health concern that affects over 200 million people worldwide and is associated with a tremendous economic burden. Therefore, deciphering the mechanisms underpinning CKD is crucial to deaccelerate its progression towards end-stage renal disease. Renal tubular cells are populated with a high number of mitochondria, which produce cellular energy and modulate several important cellular processes, including generation of reactive oxygen species, calcium homeostasis, proliferation, and apoptosis. Over the past few years, increasing evidence has implicated renal mitochondrial damage in the pathogenesis of common etiologies of CKD, such as diabetes, hypertension, metabolic syndrome, chronic renal ischemia, and polycystic kidney disease. However, most compelling evidence is based on preclinical studies because renal biopsies are not routinely performed in many patients with CKD. Previous studies have shown that urinary mitochondrial DNA (mtDNA) copy numbers may serve as non-invasive biomarkers of renal mitochondrial dysfunction. Emerging data also suggest that CKD is associated with altered expression of mitochondria-related microRNAs (mitomiRs), which localize in mitochondria and regulate the expression of mtDNA and nuclear-encoded mitochondrial genes. This review summarizes relevant evidence regarding the involvement of renal mitochondrial injury and dysfunction in frequent forms of CKD. We further provide an overview of non-invasive biomarkers and potential mechanisms of renal mitochondrial damage, especially focusing on mtDNA and mitomiRs.

Keywords

Chronic kidney disease; Metabolic syndrome; Polycystic Kidney Disease; Mitochondria; microRNA; mtDNA

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Conflict of Interest

None.

Introduction

Chronic kidney disease (CKD) is increasingly recognized as a major public health problem worldwide that affects more than 15% of Americans and over 200 million people across the globe[1]. CKD, historically termed chronic renal failure (CRF), refers to the slow and irreversible deterioration of kidney function over time, and is commonly associated with adverse renal and cardiovascular outcomes and premature death. Renal impairment in CKD may gradually progress to end-stage renal disease (ESRD), the final and permanent stage of CKD, requiring renal replacement therapy. Although many patients can access to treatment with kidney transplant or dialysis, marked differences remain in the availability of treatment for ESRD according to race, ethnicity, and socioeconomic status[2].

The National Kidney Foundation defined CKD as either kidney damage or a decline in glomerular filtration rate (GFR) to less than 60 mL/min/1.73 m^2 for at least 3 months[3]. The Kidney Disease Outcomes Quality Initiative (KDOQI) subsequently established guidelines to classify CKD as G1-G5, based on the levels of kidney function and/or evidence of renal parenchymal damage[3]. The etiology of CKD varies globally, but the top 2 leading causes are diabetes and hypertension, which account for up to two-thirds of the cases[4]. Metabolic syndrome (MetS), which refers to the co-occurrence of obesity, hypertension, insulin resistance, and hyperlipidemia, is a strong and independent risk factor for CKD associated with increased risk of ESRD[5, 6]. Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of CKD and the fourth leading cause of renal failure in adults worldwide[7]. Other common primary diseases causing CKD include glomerulonephritis, chronic tubulointerstitial nephritis, other inherited kidney disorders, infections, obstructive uropathy, plasma cell dyscrasias, and neoplasms[8].

The prevalence of CKD has been increasing over recent years and is projected to increase to 17% by 2030[4]. This growing prevalence imposes a tremendous economic burden worldwide. In the US, annual costs associated with ESRD and CKD exceed $30 and $50 billion dollars, respectively, consuming more than 20% of the total annual budget[9]. Likewise, the burden of CKD per million of the population with diabetes in the UK is expected to rise to £11.4 billion by 2025[10], whereas the high costs of dialysis and kidney transplantation in Latin America warrants cost-effective forms of renal replacement therapy[11].

Beyond the economic impact, CKD is independently associated with serious complications. Patients with CKD have increased cardiovascular risk manifesting as heart failure with reduced or preserved ejection fraction[12], which might be present in more than 50% of patients with CKD[13]. Similarly, CKD might be associated with mineral bone disease, anemia, acidosis, hyperphosphatemia, hyperkalemia, and all-cause mortality[14–17]. A worldwide cohort study revealed that CKD resulted in 1.2 million deaths and was responsible for 1.4 million of all cardiovascular disease deaths in 2017[18]. What is more, deaths associated with CKD are predicted to increase further over the next decade[4]. Therefore, deciphering the mechanisms underpinning chronic renal injury in CKD is crucial to deaccelerate its progression towards ESRD and death.

The kidney is equipped with a very high number of mitochondria[19], which not only produce cellular energy, but also modulate several important cellular processes, including redox status, calcium homeostasis, proliferation, and programmed cell death[20]. Accumulating experimental evidence suggest that several forms of CKD are associated with important mitochondrial structural and functional abnormalities in different renal cell types[21–23]. However, most data were originated from preclinical studies because renal biopsies are not routinely performed in many patients with CKD, underscoring the need to identify surrogate markers of mitochondrial injury. Likewise, the primary mechanisms implicated in CKD-induced renal mitochondrial damage remain to be clarified.

Over the last couple of years, several studies in patients with several forms of CKD have shown that damaged or dying renal cells may release fragments of their mitochondrial genome into the urine, and urinary mitochondrial DNA (mtDNA) copy numbers may serve as non-invasive biomarkers of renal mitochondrial injury and dysfunction[24–26]. More recently, studies revealed that CKD is associated with altered expression of mitochondria-related microRNAs (mitomiRs)[27, 28], a group of miRNAs that localize in mitochondria and regulate the expression of mtDNA and nuclear-encoded mitochondrial genes[29]. This review summarizes current knowledge of the contribution of renal mitochondrial injury and dysfunction in the pathogenesis of common forms of CKD. In particular, we discuss the role of mtDNA as non-invasive biomarkers of renal mitochondrial injury and mitomiRs as potential mediators of renal mitochondrial damage in CKD.

Renal mitochondrial damage in CKD

Mitochondrial density varies greatly among different organs and cell types. In the kidney, renal tubular cells, responsible for active transport of solutes, contain high numbers of mitochondria[19], whereas these organelles occupy only a small fraction of the cytoplasmic volume of endothelial cells[30]. Mitochondria are characterized by two lipid bilayers, the outer membrane, freely permeable to small molecules, and the inner membrane permeable only to oxygen, carbon dioxide, and water. This double-membrane structure generates two major compartments, the intermembrane space, which houses only 5% of the mitochondrial proteome, and the matrix, which contains mtDNA and the enzymes of the tricarboxylic acid (TCA) cycle[20], a series of reactions that produce NADH and FADH2 and provide metabolites for several biosynthetic processes[31]. To maximize energy production, numerous folds (cristae) of the inner membrane project towards the matrix, increasing its total surface area. These cristae contain the electron transport chain (ETC) system that generates ATP by shuttling electrons from NADH and FADH2 to molecular oxygen.

Although the primary function of mitochondria is the production of cellular energy by oxidative phosphorylation, these organelles are also key regulators of essential cell processes, such as proliferation, survival, and calcium homeostasis[32]. Mitochondria play a central role in intrinsic apoptosis. Release of cytochrome-c and second mitochondria-derived activator of caspase from mitochondria to the cytosol activates the caspase pathway, initiating apoptosis[33]. In addition, mitochondria represent an important cellular source of reactive oxygen species (ROS). Mitochondrial superoxide is primarily generated due to leakage of electrons at complex-I and complex-III at the electron transport

chain[34]. However, major mitochondrial antioxidant systems, such as manganese superoxide dismutase (SOD-2), peroxiredoxin, and thioredoxin reductase may counterbalance ROS production, modulating the cellular redox state[35]. Importantly, mitochondrial ROS impact on multiple cellular signalling pathways, including the nuclear factor (NF)-κB, the mitogen-activated protein kinase, and the phosphoinositide-3-kinase-Akt pathways, ultimately coordinating cell homeostasis, fate, and function[36].

An increasing body of evidence suggest that mitochondrial structural damage and dysfunction might be implicated in the pathogenesis of common forms of CKD, including diabetes[37] and hypertension[38]. Exposure of mouse podocytes to high glucose results in apoptosis and NADPH superoxide generation both *in vitro* and *in vivo*[39] (Figure 1). NADPH oxidase (NOX)-4-derived ROS inactivates mitochondrial respiratory chain complex I[40] and promotes extracellular matrix accumulation in mesangial cells[41, 42]. However, the apoptotic effect of glucose is prevented by inhibitors of the mitochondrial respiratory chain and NADPH oxidases[43], underscoring the role of mitochondria in glucose-induced podocyte damage. Likewise, spontaneously hypertensive rats exhibit renal mitochondrial structural abnormalities (swelling, enlargement, less defined cristae), impaired bioenergetics[44], and reduced expression of uncoupling protein (UCP)-2[45], a mitochondrial anion carrier protein that uncouples oxygen consumption from ATP synthesis[46]. A high salt diet in SOD-2-deficient mice is associated with intrarenal inflammation and increased production of ROS[47]. Furthermore, proteomic analysis of hypertensive rat renal tubular cells identified several differentially expressed mitochondrial proteins implicated in glucose metabolism and oxygen utilization[48], suggesting that renal mitochondrial damage might be implicated in the pathogenesis of hypertensive CKD.

Similarly, in MetS, nutrient surplus supplies excessive amounts of electrons to the respiratory chain, favoring superoxide formation and mitochondrial dysfunction[49] (Figure 2). MetS is also associated with increased systemic markers of lipid oxidation, such as oxidized low-density lipoprotein (Ox-LDL), which trigger mitochondrial superoxide production and promote SOD-2 protein degradation, contributing to cell apoptosis[50]. Studies in mouse models of MetS have shown that renal alterations in energy metabolism and lower tissue ATP levels are associated with decrease kidney mitochondrial density and increase oxidative stress[21]. High fat diet in mice induces mitochondrial structural damage and apoptosis in different renal cell types, including tubular cells, podocytes, and endothelial cells[51]. Intracellular lipid accumulation not only favors oxidative stress, but also uncouples oxidative phosphorylation, inhibiting ATP production[52]. In line with this, we found that renal mitochondrial structural damage and dysfunction in swine MetS are associated with renal lipid peroxidation and oxidative stress, reflected in increased expression of Ox-LDL[53]. This particle obtained from circulating LDL can damage the inner mitochondrial membrane phospholipid cardiolipin, which plays a central role in preserving mitochondrial structure and function[54]. Indeed, in obese mouse[51] and pigs[53] restoration of cardiolipin preserved mitochondrial bioenergetics and attenuated renal damage, supporting an important role for renal mitochondrial injury and dysfunction in experimental MetS.

Renal mitochondrial abnormalities have been also described in murine models of PKD, as well as in human PKD tubular epithelial cells[55–57]. Comparative proteomic analysis

of human cystic kidney tissue and histological and functional studies in mouse and human PKD cells as well as animal models of PKD suggest that mitochondrial injury and dysfunction may contribute to the development and progression of the disease[58–61]. Polycystin-1 deficiency is associated with changes in the expression of mitochondria-endoplasmic reticulum associated membranes and impaired mitochondrial calcium uptake[62]. Renal expression of peroxisome proliferator-activated receptor γ coactivator (PGC-1α), the master regulator of mitochondrial biogenesis was decreased in both mouse and rat models of ADPKD and correlated inversely with the levels of oxidative stress[63] (Figure 3). In agreement, we found that PCK rats have increased NOX-4-induced oxidative stress and mitochondrial abnormalities predominantly in cyst-lining tubular cells and renal endothelial cells, which correlate with endothelial dysfunction and worsening of renal disease[23]. Expression of the mitochondrial SOD-2 is downregulated in cpk mice ([64] and patients with ADPKD[65], creating a vicious cycle of excessive ROS generation and impaired antioxidant defenses that aggravates mitochondrial damage. Treatment with mitochondria-specific antioxidants reduce intracellular superoxide levels and ameliorate cyst epithelial cell proliferation stress[63], linking renal mitochondrial injury and dysfunction to disease progression in experimental ADPKD. Yet, additional studies are needed to define the exact role of these organelles in energy metabolism in this prevalent form of CKD.

Mitochondrial structural and functional alterations may also play a pivotal role in chronic renal ischemia. The clipped kidneys of the Goldblatt's 2 kidney 1 clip (2K1C) rat animal model of RVD is characterized by impaired mitochondrial biogenesis and increased mitophagy[66] (Figure 4), a form of macroautophagy that selectively degrades damaged mitochondria[67]. Importantly, RVD-induced renal mitochondrial damage was associated with renal oxidative stress, fibrosis, and necrotic death, which were prevented by inhibition of the pro-death protein BCL2 Interacting Protein 3. Surgically induced RVD in swine is also associated with post-stenotic kidney mitochondrial structural damage and impaired biogenesis, associated with oxidative stress, microvascular loss, fibrosis, and renal dysfunction[68]. Interestingly, restoration of mitochondrial cardiolipin preserved mitochondrial damage and improved renal function, implicating mitochondrial injury in renal deterioration in chronic experimental RVD. The mechanisms by which renal ischemia and hypertension contribute to renal mitochondrial damage are multifactorial. Activation of the NADPH oxidase complex in response to mechanical stretch favors ROS generation and alter mitochondrial structure[69]. Extracellular matrix turnover may also compromise the integrity of mitochondrial membranes and mtDNA, increasing mitochondrial permeability[70]. Furthermore, activation of angiotensin-II receptors in the inner mitochondrial membrane may compromise mitochondrial respiration and membrane potential, promoting local ROS generation[71, 72].

Importantly, the coexistence of MetS and CKD may synergistically aggravate mitochondrial structural damage and dysfunction. We have recently shown in swine that the concurrence of MetS and RVD amplify renal tubular mitochondrial damage (Figure 5) and impair energy production in the poststenotic kidney, leading to greater renal fibrosis[22]. Notably, both MetS and CKD can also induce mitochondrial damage in endogenous repair cells, such as mesenchymal stem cells[28, 73] and scattered tubular-like cells (STCs)[27, 74], a dedifferentiated phenotype that can be adopted by surviving tubular epithelial cells to repair neighboring

injured renal tubular cells[75]. Taken together, these studies implicate renal mitochondrial damage in the pathogenesis of CKD, and position mitochondria as a potential therapeutic target. Nevertheless, additional studies are needed to establish a cause-effect relationship and test the safety and efficacy of mitoprotective drugs in patients with CKD.

Urinary mtDNA – non-invasive biomarkers of renal injury, mitochondria dysfunction, or decreased mitochondria content

Mitochondrial DNA (mtDNA) is a very small circular (16,500 base pairs) double-stranded DNA caged within the double mitochondrial membrane. It contains very few introns and only 37 genes encoding for 13 proteins, 22 transfer-RNA, and 2 ribosomal-RNA, which are critically important to sustain energy production and modulate several mitochondrial functions. Indeed, mtDNA damage has been linked to impaired cellular bioenergetics, proliferation, and increased apoptosis[76]. Unlike nuclear DNA, mtDNA is inherited maternally, and is located near the primary sites of generation of ROS, which can induce oxidative damage such as DNA strand breaks, base modification or removal, and cross linking[77]. Fragments of mtDNA may escape from the matrix to the cytosol and then outside the cell, and may be ultimately released into the systemic circulation[78]. In renal cells, disruption of mitochondrial integrity may result in release of mtDNA genes into the urine, which may serve as surrogate markers of renal mitochondrial injury and dysfunction. On the other hand, a decrease in urinary or circulating mtDNA copy number, which is proportional to the cell mtDNA content, has been associated with mitochondrial dysfunction in several diseases and could serve as a surrogate marker of mitochondrial integrity and function[79–82].

Previous studies in patients with acute kidney injury (AKI) have shown that elevated urinary mtDNA copy numbers correlate with mitochondrial dysfunction and renal injury. Urinary mtDNA levels are significantly elevated in patients with severe sepsis-induced AKI, and positively correlated with plasma creatinine, urinary neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule (KIM)-1, and inversely with the estimated GFR (eGFR)[83]. Likewise, urinary mtDNA copy number is associated with progression of renal dysfunction in patients with AKI after cardiac surgery[84], could identify newly developed AKI, and predict renal replacement therapy or hospital mortality in surgical intensive care unit patients[85].

Similarly, studies in patients with different forms of CKD suggest that urinary copies of mtDNA genes, such as cytochrome-c oxidase-3 (COX3) and NADH dehydrogenase subunit-1 (ND1) may serve as novel markers of mitochondrial stress and damage (Table 1). We have previously shown that urinary mtDNA copy number is elevated in patients with essential hypertension and renovascular RVD and correlate with markers of renal injury (NGAL and KIM-1) and dysfunction (serum creatinine and eGFR)[86]. Treatment with renal revascularization leads to an acute rise in urinary mtDNA levels in RVD patients, likely reflecting renal ischemia-reperfusion injury-induced mitochondrial damage[25]. Importantly, urinary mtDNA levels vary as a function of serum creatinine and eGFR 3 months after medical therapy and renal revascularization, implicating mitochondrial injury in kidney damage in human hypertensive CKD.

Urinary levels of ND1 and COX3 are also elevated in patients with IgA nephropathy[87] and minor glomerular abnormalities[88], correlate positively with changes in proteinuria, but inversely with changes in eGFR. Glomerular hyperfiltration in obese African American essential hypertensive patients is also associated with elevated urinary levels of COX3 and ND1, suggesting that mitochondrial injury may aggravate renal damage and contribute to hypertension-related morbidity and mortality rates in this population[26]. In agreement, studies in patients with biopsy-proven diabetic nephropathy observed that urinary supernatant mtDNA levels correlate inversely with eGFR and positively with interstitial fibrosis[89]. Urinary copy numbers of ND1 and COX3 genes are also higher in patients with obesity compared to healthy volunteers and further increased in those with coexisting type-2 diabetes[24]. Interestingly, bariatric surgery reduced urinary mtDNA copy numbers 6 months later, underscoring the potential of this intervention to ameliorate renal mitochondrial damage in obesity and diabetes.

In individuals with glomerular diseases, mtDNA is highly filtered by the kidney. Thus, increased systemic mtDNA levels are often associated with higher urinary levels. Circulating mitochondrial DNA is extremely high in untreated patients with anti-neutrophil cytoplasmic antibody-associated vasculitis[90], and their urinary levels increase with the severity of kidney injury and neutrophil infiltration in pathology[91]. In contrast, we found discrepancies between circulating and urinary mtDNA levels in hypertensive patients. Although urinary levels of COX3 and ND1 were elevated in essential hypertensive and RVD patients, their plasma levels were comparable to healthy volunteers and remained unaltered 3 months after medical therapy or revascularization, suggesting primarily renal production[25, 86]. Similarly, urinary (but not plasma) mtDNA levels were further elevated in obese African American hypertensive patients[26]. Yet, serum COX-3 copy numbers have been reported to be higher in obese patients with or without diabetes compared to controls[24].

Contrarily, the urine exosomes of patients with diabetic nephropathy demonstrate decreased mtDNA levels, associated with reduced mitochondrial metabolites and low renal mitochondrial protein compared to healthy controls[92]. Along the same lines, impaired renal mitochondrial biogenesis is associated with reduced mtDNA copy number in the kidney tissue of mice and rats with PKD[63]. Nevertheless, studies suggest that the role of urinary mtDNA level may be limited in certain etiologies of CKD. A prospective study of 102 non-diabetic CKD patients followed for 48 months found that urinary mtDNA levels have no significant association with the rate of renal function decline, but correlate with baseline renal function, proteinuria, and the severity of glomerulosclerosis and tubulointerstitial fibrosis[93]. Although higher mtDNA copy number in peripheral blood has been associated with the lower prevalence of microalbuminuria[79], studies in patients with diabetic nephropathy reported a significant inverse correlation between urinary supernatant and intra-renal mtDNA levels, implying that intra-renal mitochondrial loss may result in increased urinary mtDNA levels[89].

Most studies assessed mtDNA levels by quantitative real-time PCR (qPCR), but genotyping microarray probe intensities and DNA sequencing read counts, such as whole genome and whole exome sequence may be more accurate and reliable methods for detecting mtDNA levels[94]. Analysis of somatic mtDNA mutations may also assist in developing

early detection and monitoring strategies for patients with renal urothelial cell carcinoma[95]. Collectively, these observations suggest that although urinary mtDNA levels might serve as surrogate markers of permanent renal damage, they should be interpreted with caution in several etiologies of CKD. No doubt future large prospective cohort studies are needed to explore the exact role of urinary and plasma mtDNA in renal mitochondrial damage in the development and progression of CKD.

Mechanisms of renal mitochondrial injury - mitomiRs

Notwithstanding the evidence implicating mitochondrial injury in the pathogenesis of CKD, the precise mechanisms responsible for CKD-induced renal mitochondrial damage are incompletely understood. Deciphering these mechanisms is fundamental to develop novel therapies to preserve renal mitochondrial morphology and function and decrease the progression towards ESRD.

Several studies in humans and animal models have postulated miRNAs as master regulators of renal gene expression implicated in the pathogenesis of AKI and CKD[96, 97]. These small (19–23 nucleotides), endogenous, single-stranded noncoding RNAs regulate expression of protein-coding genes by repressing mRNA translation or promoting its degradation[98]. There are currently over 2,000 human miRNAs known. MiRNA biosynthesis encompases several enzymatic steps in both the nucleus and cytoplasm[99, 100] (Figure 6). MiRNA genes are transcribed in the nucleus by the RNA polymerase II (Pol II) which produces primary miRNAs (pri-miRNAs), which are then modified by the RNAse III class enzyme, Drosha, to form precursor-miRNAs (pre-miRNAs)[101]. Pre-miRNAs are then exported from the nucleus to the cytoplasm by exportin 5 (EXP5) and subsequently processed to produce mature miRNAs[102]. Although most mature miRNAs are present in the cytosol, studies have revealed the presence of few miRNAs, known as ‘mitomiRs’, in the mitochondrion[29, 103, 104].

mitomiRs can either bind to and repress mRNA expression in the cytoplasm or being imported into mitochondria to target mtDNA genes or induce post-transcriptional repression of nuclear-encoded mitochondrial genes on the mitochondrial surface[105]. The later are imported by the polynucleotide phosphorylase (PNPase) situated in the inner mitochondrial membrane and intermembrane space[106]. PNPase interacts with the RNA-induced silencing complex protein Argonaute 2 (Ago2) to shuttle mitomiRs from the cytosol into the mitochondrion. Therefore, expression and localization of PNPase and Ago2 modulate mitochondrial translocation of mitomiRs, ultimately regulating mitochondrial gene expression and function.

Recent studies suggest that regulation of mitochondrial function by mitomiRs could contribute to renal disease progression in CKD (Table 2). Studies in mice with unilateral ureteral obstruction have shown that the mitomiR miR-30e, which targets UCP2, has an important role in mediating transforming growth factor (TGF)-β1-induced epithelial-mesenchymal transition and kidney fibrosis[107]. Importantly, this mitomiR can also target the translocase of inner mitochondrial membrane-22 (TIMM22) and the mitochondrial inner membrane organizing system-1 (MINOS1), which maintains crista junctions, inner membrane architecture, and formation of contact sites to the outer membrane. Other studies

have shown that upregulation of miR-21 in tubular epithelial cells in response to TGF-β promotes progression of renal fibrosis in established obstructive nephropathy[108]. This mitomiR modulates mitochondrial-mediated apoptosis by altering the BAX/BCL2 ratio and mitochondrial fission, which in turn alter mitochondrial membrane potential, cytochrome-c release, and caspase activity[109].

Similarly, miR-27a promotes renal tubulointerstitial fibrosis via suppressing peroxisome proliferator-activated receptor pathway in streptozotocin-induced diabetic rats[110]. In addition, miR-29, which targets the mitochondrial Apoptosis Regulator, BCL2 Family Member (MCL1), modulates the production of collagen IV in proximal tubular cells exposed to high glucose[111]. MCL1 is a critical modulator of the mitochondrial fusion and fission machinery[112]. Therefore, miR-29 may represent a mechanism for regulating mitochondrial dynamics and intracellular matrix components in proximal tubular cells during the progression of diabetic nephropathy.

The mitomiR miR-17 is induced in kidney cysts of mouse and human ADPKD, and its genetic deletion inhibits cyst proliferation and disease progression in several ADPKD mouse models irrespective of the mutated gene (Pkd1 or Pkd2)[60]. These observations have important clinical implications as miR-17 inhibition also suppresses proliferation and growth of primary ADPKD cysts cultures derived from human donors. Mechanistic studies revealed that the deleterious effect of mitomiR miR-17 was in part mediated by inhibition of mitochondrial fatty acid oxidation and oxidative phosphorylation through direct repression of peroxisome proliferator-activated receptor-(PPAR)-α, one of the top downregulated genes in human ADPKD[113]. Therefore, miRNA-based approaches that specifically target this mitomiR may provide hope for therapies to attenuate disease progression in ADPKD.

Intriguing insights into the contribution of mitomiRs to renal mitochondrial damage may be gleaned from studies assessing cellular senescence, a state of stable and irreversible cell cycle arrest that plays an important role in the pathogenesis of different forms of renal damage, including CKD[114]. Senescent cells contain dysfunctional mitochondria, which play a major role in the promotion of the senescence-associated secretory phenotype[115]. Recent studies suggest that mitomiRs may influence the energetic, oxidative, and Inflammatory status of senescent cells by translocating to mitochondria and targeting numerous mRNAs encoding for proteins implicated in vital mitochondrial functions[116]. Studies in rats have shown that miR-335 and miR-34a contribute to renal aging by inhibiting intracellular pathways such as those involving the mitochondrial antioxidative enzymes SOD-2 and thioredoxin reductase-2[117]. Our group has recently shown that experimental RVD may induce senescence in endogenous STCs and impair their in vivo reparative capacity[118]. Moreover, we found that swine RVD-STCs exhibited increased expression of the mitomiRs miR-15a, miR-181a, miR-196a, and miR-296-3p, which targeted and reduced the expression of several mtDNA genes implicated in oxidative phosphorylation, such as the complex I genes ND2, ND4, ND4L, and ND5, and the complex V gene ATP6[27].

Similar findings can be noted in pig MSCs exposed a high fat and high fructose diet for 16 weeks, a model that develops many features of clinical MetS[119]. We found that expression of several mitomiRs (miR-15a, miR-137, and miR-181c) was higher in

MetS-MSCs compared to Lean-MSCs, which modulate expression of genes encoding for mitochondrial proteins primarily implicated in energy pathways and mitochondrial dynamics[28]. Interestingly mitochondrial fusion and ATP production were impaired in MetS-MSCs compared to their lean counterparts, suggesting that MetS-induced post-transcriptional regulation of mitochondrial genes might have accounted for mitochondrial damage in MSCs. Likewise, increased expression of the mitomiRs miR-196a and miR-296-5p in MetS-MSCs interfered with mitochondrial protein import and impaired mitochondrial homeostasis and energy production, highlighting the important role of mitomiRs in mitochondrial damage in this endogenous repair mechanism[120].

mitomiRs have been also implicated in the pathogenesis of glomerulopathies, including focal segmental glomerulosclerosis (FSGS) and membranous nephropathy. For example, miR-196a, which targets the mitochondrial fission protein mitochondrial elongation factor-1 (MIEF1), is elevated in the urine of patients with FSGS[121], whereas miR-15a, which targets the transcription factor A mitochondrial (TFAM) that promotes mitochondrial DNA replication and repair, is upregulated in peripheral blood lymphocyte cells from patients with membranous nephropathy[122]. Collectively, these observations suggest that dysregulation of mitomiRs capable of compromising critical functions of mitochondria might be implicated in the pathogenesis of several forms of CKD. However, further mechanistic studies using miRNA mimics and antagomiRs are needed to establish a cause-effect relationship between mitomiRs and renal mitochondrial damage in CKD.

Summary and future perspectives

There is considerable evidence suggesting that dysfunctional mitochondria may be implicated in the development and progression of renal damage in common causes of CKD. While the effect of mitochondrial dysfunction in the pathogenesis of CKD has been studied extensively, most compelling evidence were generated in preclinical studies as renal biopsies are not routinely performed in many patients with CKD. Although great progress was made in understanding the role of urinary mtDNA as non-invasive markers of renal mitochondrial damage, contradicting findings emphasize the need of additional studies to elucidate the biological mechanisms and exact role of mtDNA in the pathogenesis of CKD. miRNA localizing in mitochondria (mitomiRs) may contribute to CKD-induced mitochondrial damage by post-transcriptional regulation of mtDNA and nuclear-encoded gene expression related to mitochondrial functions. It is therefore hopeful that continued studies on the precise mechanism of mitomiRs in mitochondrial injury will advance our understanding of their role in renal damage and contribute to develop novel therapeutic strategies for patients with chronic renal injury.

Acknowledgments

This work was supported by the NIH grants: DK129240, DK104273, DK118391, DK128017, GM104357, HL095638, the PKD Foundation (PKDF243G20a), and Regenerative Medicine Minnesota (RMM 091620 DS 004).

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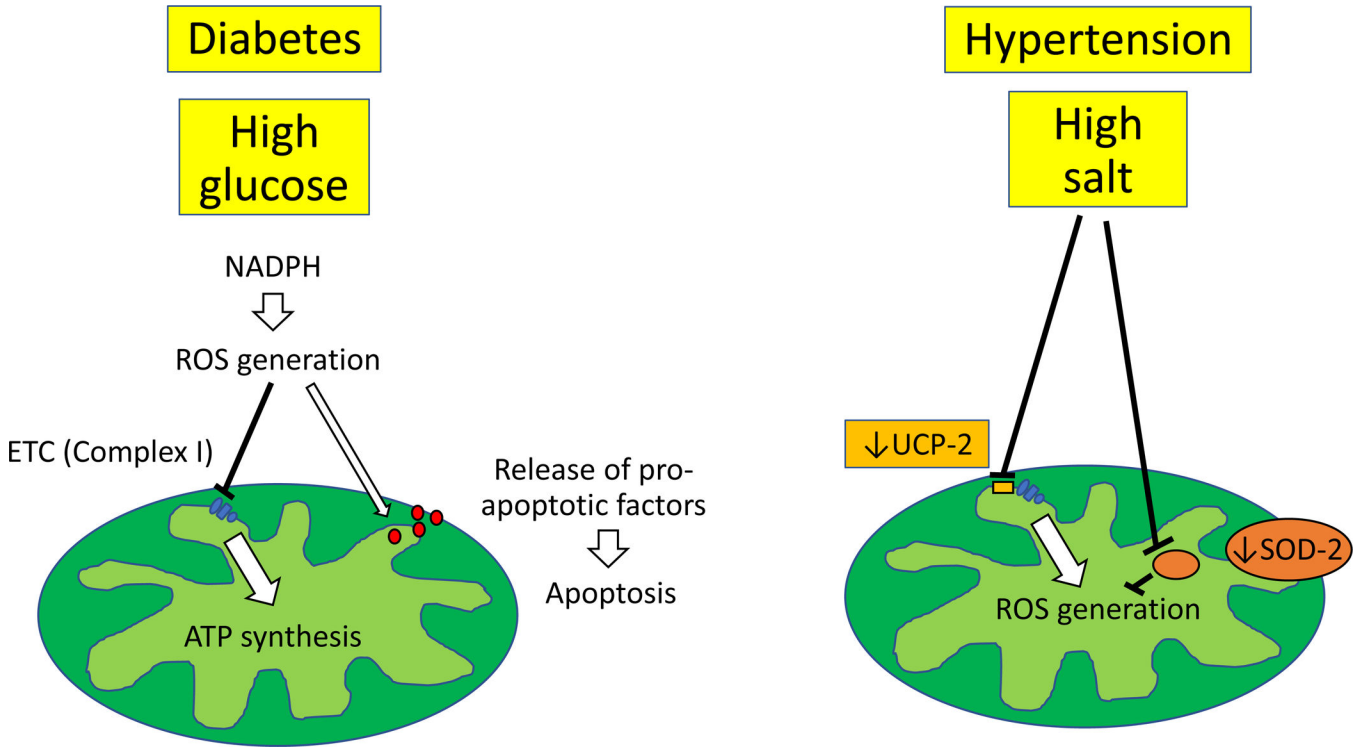

Figure. 1. Potential mechanisms of renal mitochondrial damage in hypertensive and diabetic CKD.

Exposure of podocytes to high glucose results in apoptosis and NADPH superoxide generation. This in turn inactivates mitochondrial respiratory chain complex I and favors release of pro-apoptotic factors, contributing to impaired bioenergetics and apoptosis. A high salt diet induces structural mitochondrial abnormalities and impaired bioenergetics, associated with reduced expression of uncoupling protein-2 and increased production of ROS.

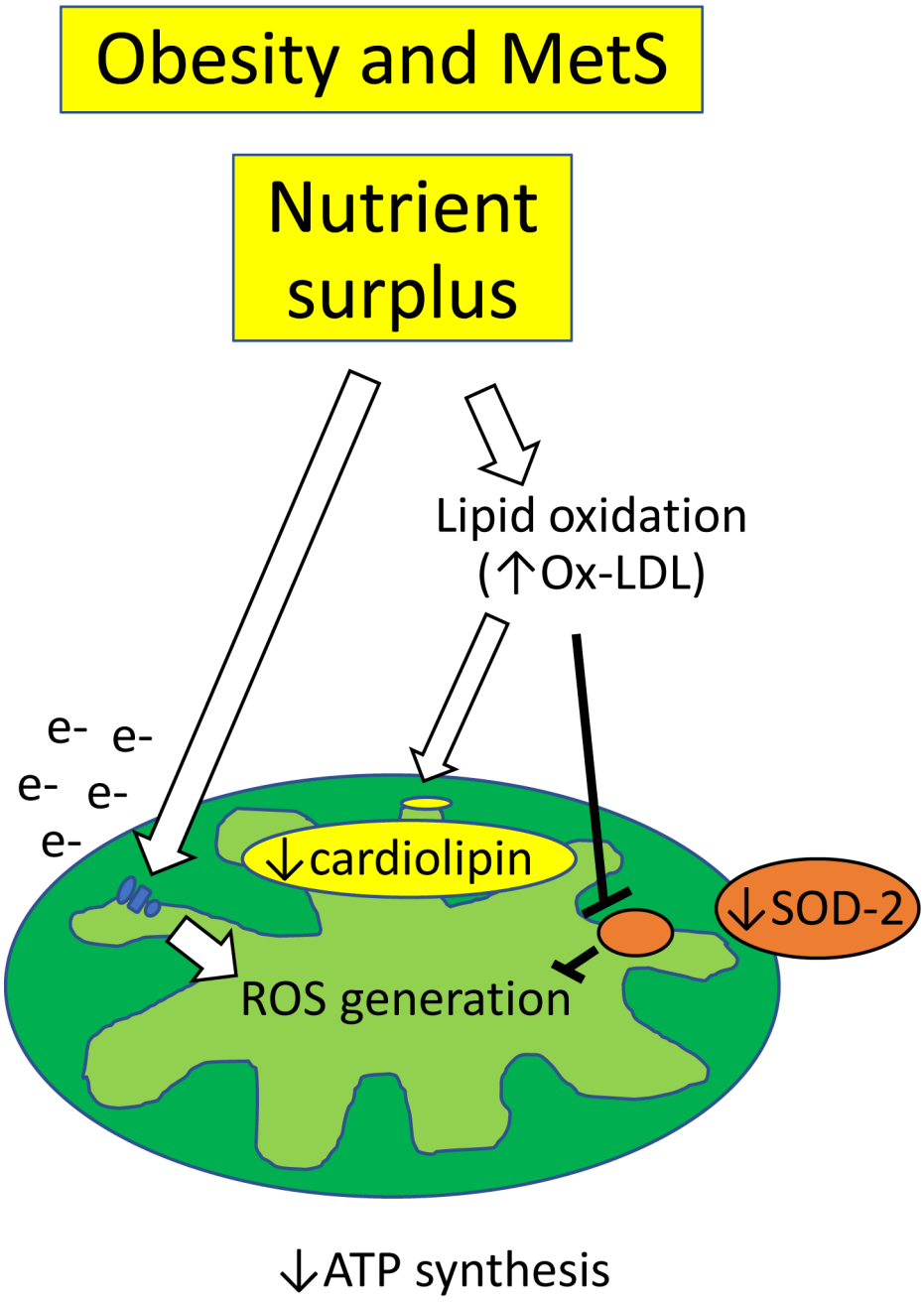

Figure 2. Mechanisms of renal mitochondrial damage in obesity and MetS.

Nutrient surplus supplies excessive amounts of electrons to the respiratory chain, favoring superoxide formation. Increased lipid oxidation, such as oxidized low-density lipoprotein (Ox-LDL), triggers mitochondrial superoxide production by promoting SOD-2 protein degradation. Ox-LDL can also damage cardiolipin, leading to excessive ROS formation and impaired bioenergetics.

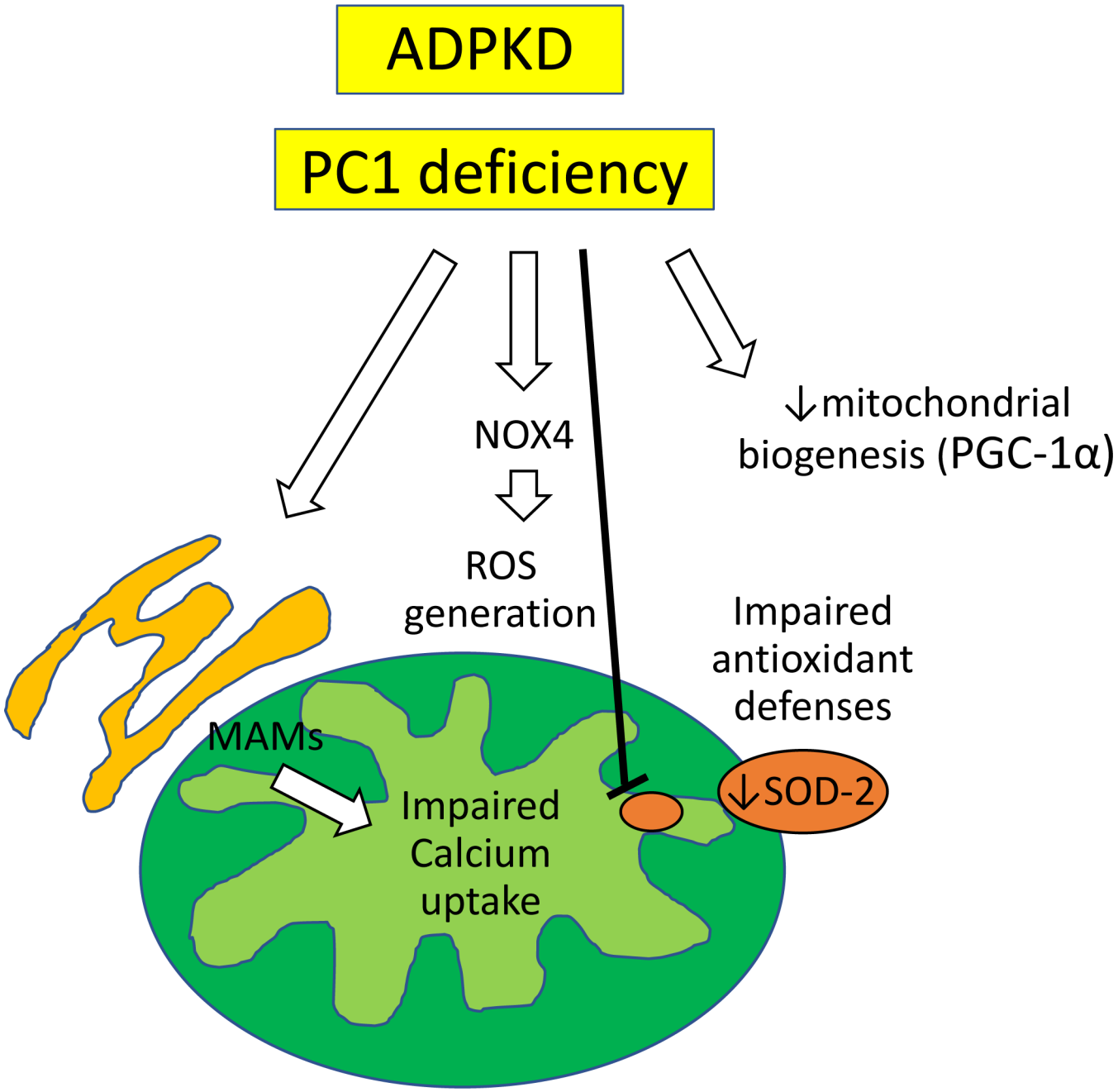

Figure 3. Mitochondria-mediated mechanisms of disease progression in ADPKD.
In ADPKD, polycystin-1 deficiency is associated with changes in the expression of mitochondria-associated endoplasmic reticulum membranes (MAMs) and impaired mitochondrial calcium uptake. Peroxisome proliferator-activated receptor γ coactivator (PGC-1α) expression, the main regulator of mitochondrial biogenesis is also suppressed. Expression of NOX-4 increases, whereas expression of SOD-2 decreases, creating a vicious cycle of excessive ROS generation and impaired antioxidant defenses that aggravates mitochondrial damage.

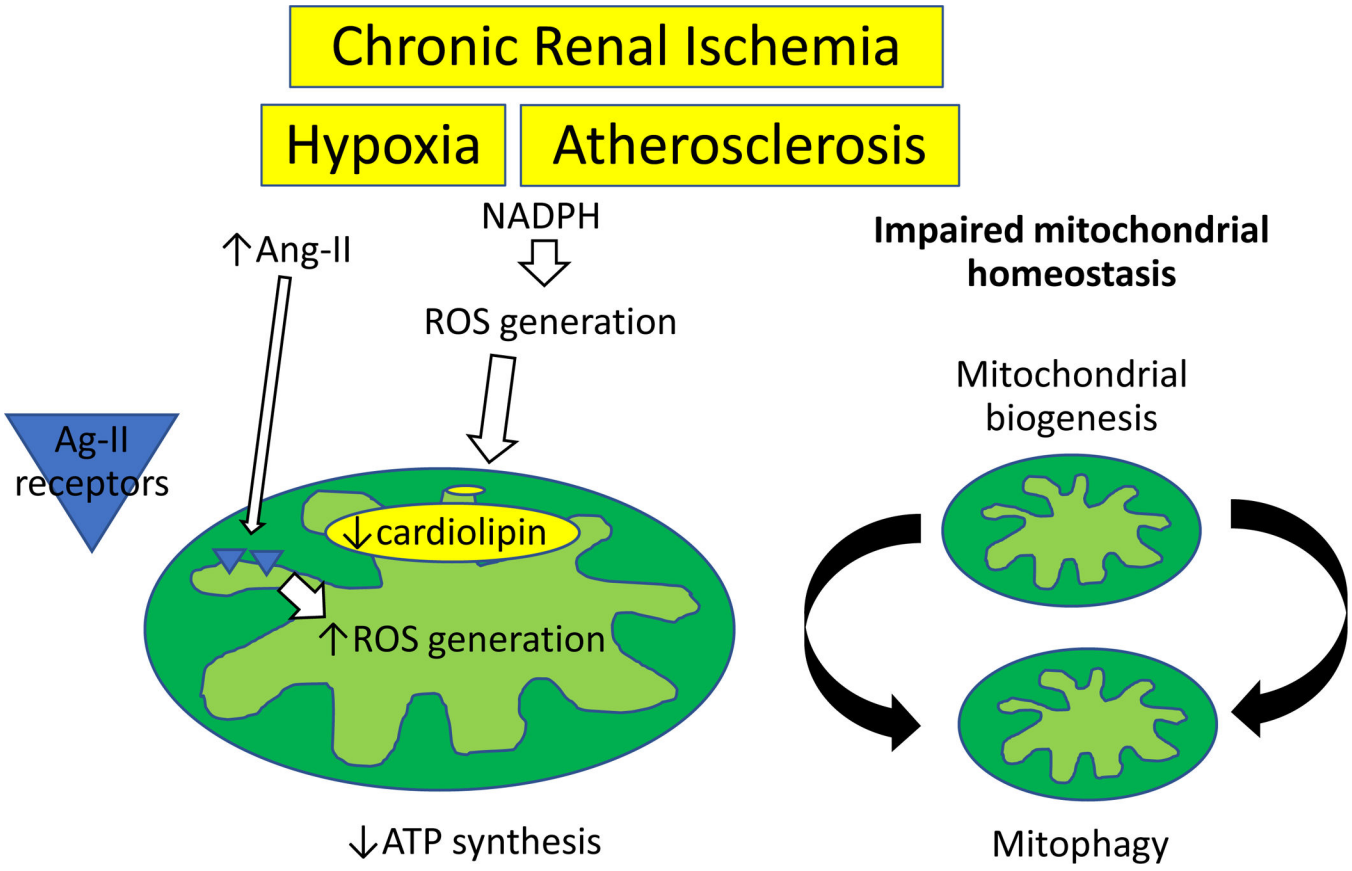

Figure 4. Mitochondrial structural and functional alterations in chronic renal ischemia.
Experimental RVD alters renal mitochondrial biogenesis and mitophagy and decreases cardiolipin content. Activation of the NADPH oxidase complex in response to mechanical stretch favors ROS generation, whereas activation of angiotensin (Ang)-II receptors in the inner mitochondrial membrane may compromise mitochondrial respiration and promote local ROS generation.

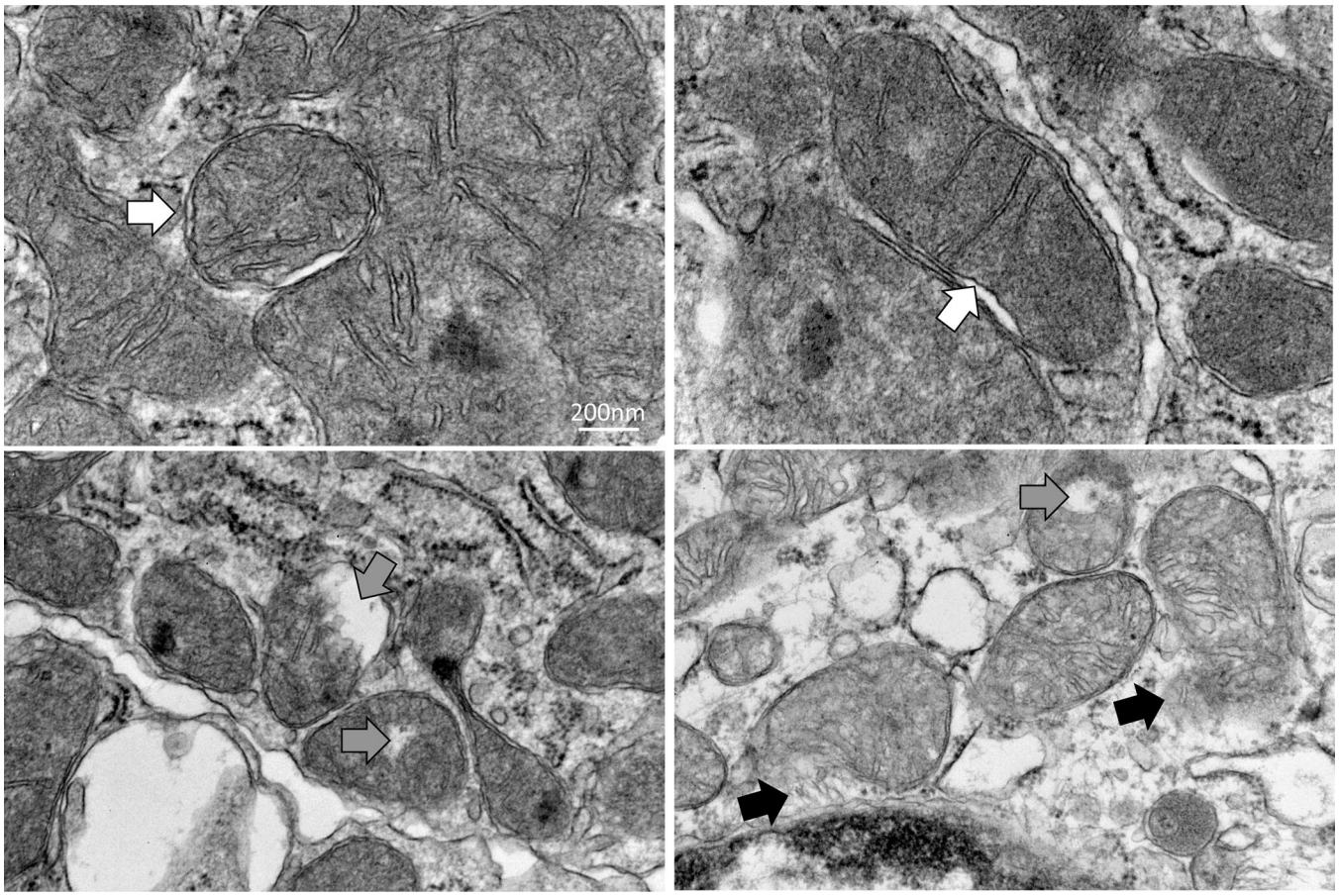

Figure. 5. Experimental MetS and CKD induce renal tubular cell mitochondrial injury.
Representative transmission electron microscopic images of renal tubular cell mitochondrial from MetS+CKD pigs showing mitochondrial swelling and decreased cristae membranes (white arrows). Disruption of the outer mitochondrial membrane favors entry of water to the organelle (grey arrows) and release of matrix content to the cytosol (black arrows).

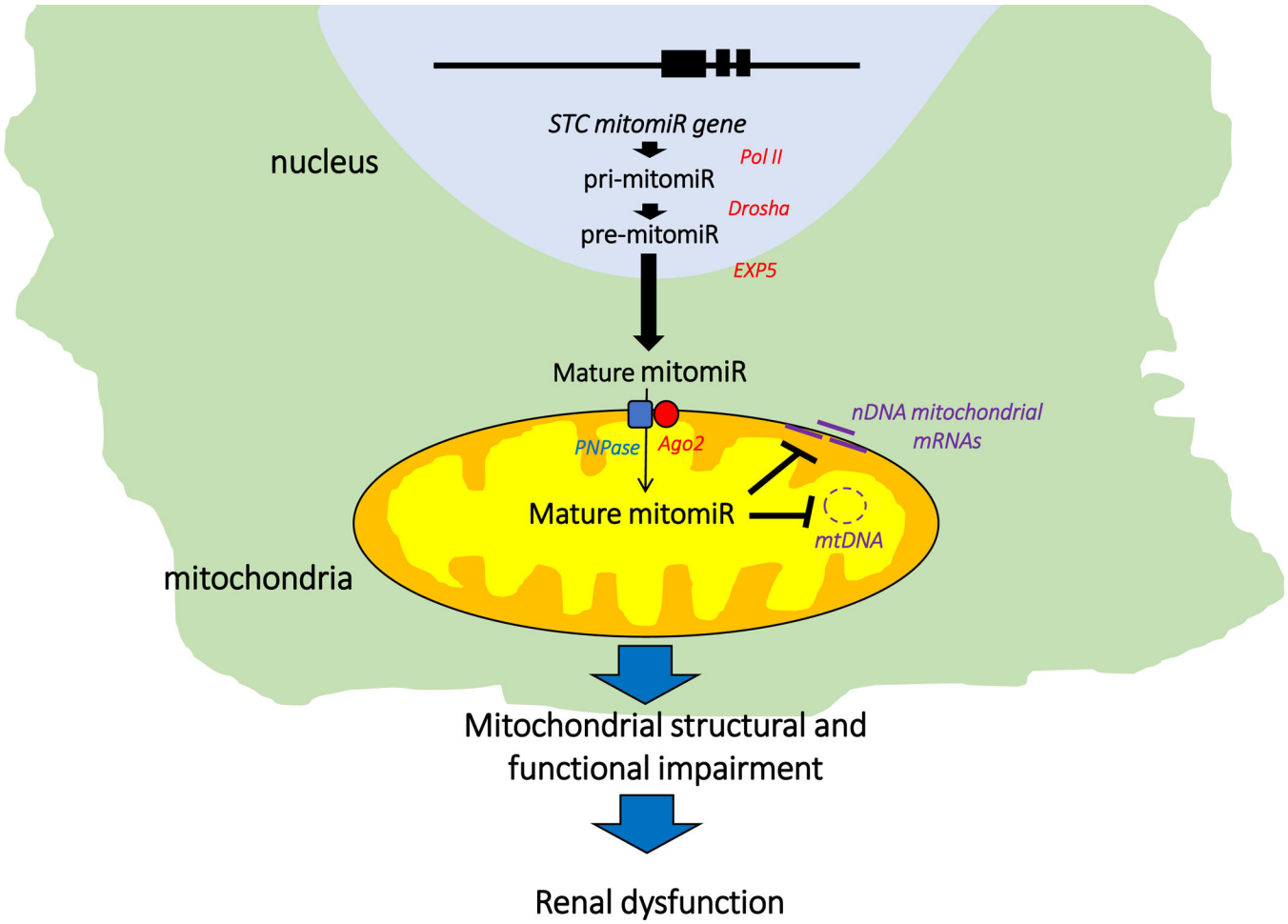

Figure. 6. mitomiR biosynthesis.

mitomiRs are transcribed in the nucleus by the RNA polymerase II (Pol II) which produces primary miRNAs (pri-mitomiRs), which are then modified by the RNAse III class enzyme, Drosha, to form precursor-miRNAs (pre-mitomiRs). Pre-mitomiRs are exported to the cytoplasm by exportin 5 (EXP5) and subsequently processed to produce mature mitomiRs, which will be subsequently imported into the organelle by the polynucleotide phosphorylase (PNPase) and RNA-induced silencing complex protein Argonaute 2 (Ago2) to target mtDNA genes or induce post-transcriptional repression of nuclear-encoded mitochondrial genes on the mitochondrial surface.

Table 1.

Studies reporting changes in urinary mtDNA levels in patients with different etiologies of CKD

Condition	Main Findings	References
Essential hypertension / RVD	• Elevated urinary copies of COX3 and ND1 • mtDNA correlates with markers of renal injury and dysfunction	• Eirin A, et al[86]
RVD revascularization	• Revascularization leads to an acute rise in urinary mtDNA levels • mtDNA levels correlate with renal function 3 months after therapy	• Eirin A, et al[25]
IgA nephropathy / Minor glomerular abnormalities	• Elevated urinary copies of COX3 and ND1 • mtDNA correlates positively with changes in proteinuria, but inversely with changes in eGFR	• Yu BC, et al[87, 88]
Diabetic nephropathy	• Urinary supernatant mtDNA level correlates inversely with eGFR and positively with interstitial fibrosis	• Wei, et al[89]
Obesity / Bariatric surgery	• Elevated urinary copies of COX3 and ND1 • Bariatric surgery reduces urinary mtDNA copy numbers 6 months later	• Seo M, et al[24]
ANCA-associated Vasculitis	• Increase urinary and plasma mtDNA levels that correlate with the severity of kidney injury	• Wu SJ, et al[91]
Obesity / Hypertension	• Elevated urinary copies of COX3 and ND1 • mtDNA correlates with renal hyperfiltration	• Eirin A, et al[26]
Diabetic nephropathy	• Decreased mtDNA levels in urine exosomes	• Sharma K, et al[92]
Non-diabetic CKD	• Urinary mtDNA levels correlate with baseline renal function, proteinuria, and the severity of glomerulosclerosis and tubulointerstitial fibrosis	• Wei PZ, et al[93]

mtDNA: mitochondrial DNA; CKD: Chronic kidney disease; RVD: renovascular disease; COX3: cytochrome-c oxidase-3, ND1: NADH dehydrogenase subunit-1; eGFR: estimated glomerular filtration rate; ANCA: anti-neutrophil cytoplasmic antibody

Table 2.

mitomiRs commonly implicated in CKD

mitomiR	Disease/Model	Main mitochondrial target genes	References
miR-30e	• Unilateral ureteral obstruction	• UCP2, UCP3, MINOS1, GOT2, TIMM22	• Jiang L, et al[107]
miR-21	• Obstructive nephropathy	• BAX, BCL2, MRPL49, MRPL45, CMC1	• Zhong X, et al[108]
miR-27a	• Diabetic nephropathy	• ATPAF1, TIMM10, CLPP, ATP5G3, SLC25A25, TOMM40L, GPD2, MICU3, MRPS14, SLC25A16	• Hou X, et al[110]
miR-29	• Diabetic nephropathy	• MCL1, CPS1, GPAM, GRPEL2, ATP5G3, CLPX, DIABLO, SLC25A22, TSFM, MIEF1, SLC25A29	• Du B, et al[111]
miR-17	• ADPKD	• PPARA, GPD2, TIMM8B, CLUH, MALSU1	• Hajarnis S, et al[60]
miR-335, miR-34a	• Aging	• SOD2, TXNRD2, PTPMT1, TACO1, ATP5S, MRPL3, MRPL52	• Bai Xy, et al[117]
miR-15a, miR-181a, miR-196a, miR-296-3p	• RVD	• ND2, ND4, ND4L, ND5, ATP6, GLS2, TCAIM, SLC25A22, SLC25A37, UCP2, AIFM1, MINOS1, MTFR1L, CLUH, TOMM20, MALSU1, SLC25A37, SLC25A4, GOT2, GPD2, SLC25A24, SLC25A25, TSFM, MCUR1, CMPK2, CLUH, TFAM, IARS2, GRPEL2, MARS2, MIEF1, SLC25A22, MRRF	• Farahani RA, et al[27]
miR-15a, miR-137, miR-181c, miR-196a miR-296-5p	• MetS	• SLC25A5, ATPAF1, MPC1, GPD2, AIFM2, GPAM, GLS2, TCAIM, SLC25A22, SLC25A37, UCP2, AIFM1, MINOS1, MTFR1L, CLUH, TOMM20, MALSU1, GRPEL2, MARS2, MIEF1, SLC25A22, MRRF, TSFM, SLC25A23	• Farahani RA, et al[28], Aghajani Nargesi A, et al[120]
miR-196a	• FSGS	• MIEF1, GRPEL2, MARS2, MIEF1, SLC25A22, MRRF	• Zhang W, et al[121]
miR-15a	• Membranous nephropathy	• TFAM, GLS2, TCAIM, SLC25A22, SLC25A37, UCP2, AIFM1, MINOS1, MTFR1L, CLUH, TOMM20, MALSU1	• Chen W, et al[122]

ADPKD: Autosomal dominant polycystic kidney disease; RVD: Renovascular disease; MetS: Metabolic syndrome; FSGS: Focal segmental glomerulosclerosis.