HHS Public Access

Author manuscript

Nat Rev Nephrol. Author manuscript; available in PMC 2017 June 13.

Published in final edited form as:

Nat Rev Nephrol. 2016 May ; 12(5): 267–280. doi:10.1038/nrneph.2015.214.

Mitochondrial dysfunction in inherited renal disease and acute kidney injury

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Abstract

Mitochondria are increasingly recognized as key players in genetic and acquired renal diseases. Most mitochondrial cytopathies that cause renal symptoms are characterized by tubular defects, but glomerular, tubulointerstitial and cystic diseases have also been described. For example, defects in coenzyme Q_{10} (CoQ_{10}) biosynthesis and the mitochondrial DNA 3243 A>G mutation are important causes of focal segmental glomerulosclerosis in children and in adults, respectively. Although they sometimes present with isolated renal findings, mitochondrial diseases are frequently associated with symptoms related to central nervous system and neuromuscular involvement. They can result from mutations in nuclear genes that are inherited according to classic Mendelian rules or from mutations in mitochondrial DNA, which are transmitted according to more complex rules of mitochondrial genetics. Diagnosis of mitochondrial disorders involves clinical characterization of patients in combination with biochemical and genetic analyses. In particular, prompt diagnosis of CoQ_{10} biosynthesis defects is imperative because of their potentially reversible nature. In acute kidney injury (AKI), mitochondrial dysfunction contributes to the physiopathology of tissue injury, whereas mitochondrial biogenesis has an important role in the recovery of renal function. Potential therapies that target mitochondrial dysfunction or promote mitochondrial regeneration are being developed to limit renal damage during AKI and promote repair of injured tissue.

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Author contributions

All authors researched the data, made a substantial contribution to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

Mitochondria are key organelles that have an essential role in the life and death of cells. They derive from ancient Gram-negative bacteria similar to *Rickettsia prowazekii*, which began an endosymbiotic process with progenitors of eukaryotic cells more than 2 billion years ago[1]. Mitochondria have retained the structure of these bacteria; they have a highly permeable outer membrane and an inner membrane that is impermeable to most solutes and has several introflexions, named cristae[2]. Most importantly, mitochondria contain their own mitochondrial (mt)DNA, which is a relic of the ancestral endosymbiont genome and resembles prokaryotic DNA. The mitochondrial genome is composed of a single double-stranded circular loop that lacks introns, is not organized into chromatin and uses a different genetic code from that of eukaryotic cells[3]. mtDNA is present in multiple copies per mitochondrion, and transmission of mtDNA-linked traits does not follow classical Mendelian rules[4] (TABLE 1). mtDNA encodes 37 genes, including 13 structural subunits of the mitochondrial respiratory chain. Proteins encoded by mtDNA represent only a small fraction of the total mitochondrial proteome; the majority of mitochondrial proteins are synthesized in the cytosol and imported into mitochondria via specialized systems[5].

The most important function of mitochondria is the generation of ATP through oxidative phosphorylation. They are also the site of essential metabolic pathways (including pyrimidine and haem biosynthesis as well as specific reactions of the urea cycle and the β-oxidation pathway) and they have key roles in thermogenesis, calcium homeostasis and control of the intrinsic apoptotic pathway[6]. Mitochondria are highly dynamic organelles; a complex mechanism of fusion and fission processes regulates the remodeling of cristae, which are essential for cytochrome c release and for the initiation of apoptosis[7]. They also have an essential role in tissue injury and repair processes, and have been implicated in various types of renal disorders, both inherited and acquired. In this Review we discuss the main types of mitochondrial cytopathies that can result in renal disease as well as the role of mitochondrial dysfunction in acute kidney injury (AKI).

The mitochondrial respiratory chain

The mitochondrial respiratory chain is comprised of five enzymatic complexes and two electron carriers: coenzyme Q_{10} (CoQ_{10}) and cytochrome c. Complexes I, II, III and IV transfer electrons from high-energy compounds generated by the reactions of the Krebs cycle (that is, NADH and $FADH_2$), to molecular oxygen, and utilize the energy produced by these reactions to transfer protons from the mitochondrial matrix to the intermembrane space. These processes create an electrochemical gradient that is used by ATP synthase (also known as complex V) to synthesize ATP (FIG. 1). The respiratory chain complexes I, III and IV assemble to form super-complexes, which optimize electron flow and minimize the formation of reactive oxygen species (ROS)[8]. With the exception of complex II, which contains only nuclear (n) DNA-encoded subunits, the respiratory chain complexes are comprised of both mtDNA-encoded and nDNA-encoded subunits. Biogenesis of the respiratory chain also requires a large set of ancillary genes, which are encoded by nDNA. These assembly factors are necessary to import and direct structural subunits to the mitochondrial inner membrane, to stabilize assembly intermediates, and to synthesize and insert prosthetic groups into the holo-enzymes[9]. A large number of other nuclear gene products are required for the replication and maintenance of the mitochondrial genome,

transcription and processing of mitochondrial RNA species, and synthesis of mitochondrial proteins[10] (FIG. 2).

Key points

- Healthy mitochondria are essential for normal kidney function; mitochondrial cytopathies can result in renal disease and mitochondrial damage has a role in the pathophysiology of acute kidney injury (AKI)
- Although mitochondrial diseases are characterized by maternal inheritance, many mitochondrial disorders are caused by mutations in nuclear genes and are inherited according to classic Mendelian rules
- Most mitochondrial diseases with kidney involvement cause tubular defects; however, mutations in the coenzyme Q10 (CoQ_{10}) biosynthesis pathway and the mtDNA 3243 A>G mutation primarily cause glomerular disease
- Diagnosis of genetic mitochondrial disorders increasingly relies on new sequencing techniques, but thorough biochemical and clinical characterization of patients is essential to guide these analyses
- In AKI, mitochondrial dysfunction occurs primarily in the proximal tubule and participates in the physiopathology of tissue damage; mitochondrial biogenesis represents a crucial step in the recovery phase
- Potential therapies that target mitochondrial dynamics, mitophagy and/or mitochondrial biogenesis might limit renal damage during AKI and promote recovery of kidney function

The electron carrier CoQ_{10} is a small lipophilic molecule comprising a quinone group and an isoprene tail. In the respiratory chain, coenzyme Q shuttles electrons from complexes I and II to complex III. CoQ_{10} is also a key antioxidant, a modulator of apoptosis, and a cofactor for several other dehydrogenases. Biosynthesis of CoQ_{10} requires at least 13 proteins (encoded by nuclear *COQ* genes)[11], which are assembled into a multi-enzyme complex localized in the mitochondrial matrix[12]. Cytochrome c is synthesized in the cytosol, imported by a non-canonical mechanism into the mitochondrial intermembrane space and covalently bound to a haem group by holocytochrome c-type synthase.[13] The main role of cytochrome c is the transfer of electrons from complex III to complex IV of the respiratory chain, but this small protein is also an essential component of the intrinsic apoptotic pathway.

Genetic mitochondrial defects

Mitochondrial dysfunction is a common finding in many pathological conditions and might be the direct consequence of a specific genetic defect or the result of a variety of environmental noxae. Although in principle, the term ‘mitochondrial disorder’ should be used to indicate any defect affecting mitochondrial enzymes or structural proteins, in clinical practice this term is generally used to indicate defects that directly or indirectly affect mitochondrial oxidative phosphorylation[14]. Genetic diseases involving oxidative

phosphorylation can be caused by defects in mtDNA (with maternal inheritance or through *de novo* mutations) or in nDNA (associated with classic Mendelian genetics; TABLE 2). A third group of disorders includes mtDNA anomalies that are secondary to defects in nuclear genes controlling mtDNA maintenance[10]. Even if these disorders are associated with abnormalities in mtDNA, they are transmitted as autosomal dominant or recessive diseases[10]. Disease-causing mutations that result in defects in oxidative phosphorylation have been reported in >100 genes[15]. Although each individual defect is rare, the overall prevalence of mitochondrial disorders in the general population is probably greater than 1 in 5,000 (REF. 16).

In general, mtDNA mutations are heteroplasmic, whereas polymorphisms are homoplasmic (that is, they affect all mitochondrial genomes in an individual). A few examples of homoplasmic mutations also exist, such as the three common mutations that are associated with Leber hereditary optic neuropathy[17] and the mtDNA 1555A>G mutation in the 12S rRNA gene, which causes deafness after exposure to aminoglycosides[18]. These mutations usually have a fairly mild phenotype with selective tissue involvement (either the optic nerve or the cochlea) and their expression is modulated by specific mtDNA haplogroups, nuclear background and epigenetic factors[18].

As complete disruption of oxidative phosphorylation is not compatible with life, residual activity is always present, either because mutations are hypomorphic[19] or redundancy in the system enables a minimal number of functional complexes to be assembled. In the case of mtDNA, heteroplasmy ensures that a small amount of wild-type mitochondrial genome is always expressed, enabling the synthesis of a minimal amount of functional respiratory chain complexes to sustain extra-uterine life. Notably, cells with high turnover (such as haematopoietic cell precursors) express lower levels of mutated mtDNA than those with low turnover (such as skeletal muscle and possibly renal cells) as a result of the natural selection of cells with higher percentages of wild-type mtDNA, which replicate more efficiently[20]. Renal disease has been reported in patients with genetic defects involving assembly factors, CoQ_{10} biosynthesis, mtDNA translation and mtDNA maintenance (TABLE 3).

Clinical features of mitochondrial diseases

In general, defects in oxidative phosphorylation produce two major effects: a reduction in ATP production and an increase in ROS production. A direct relationship between the magnitudes of these effects is not always present; for example, mild CoQ_{10} deficiency can result in a substantial increase in ROS production without significantly impairing ATP production, whereas severe CoQ_{10} deficiency causes an important bioenergetic defect without a substantial increase in ROS production[21]. Defects in electron carriers also affect apoptosis because cytochrome c and CoQ_{10} have important roles in this process. CoQ_{10} is a modulator of the mitochondrial permeability transition pore and acts as an antiapoptotic factor, whereas mutations in cytochrome c cause deregulation of apoptosis, which is more clinically relevant than the associated bioenergetic defect[21–23].

Not surprisingly, the tissues that are most severely affected by defects in oxidative phosphorylation are those that are most reliant on aerobic metabolism for ATP production,

such as the central nervous system and skeletal muscle. The majority of mitochondrial disorders, therefore, present with some degree of encephalomyopathy[10]. However, given the ubiquitous distribution of mitochondria, virtually all tissues and organs might be affected by mitochondrial diseases (TABLE 4).

In the kidneys, mitochondrial disorders can result in various forms of tubulopathies, tubulointerstitial nephritis, cystic renal disease or glomerular disease, most commonly focal segmental glomerulosclerosis (FSGS)[20]. Renal symptoms are rarely isolated and commonly form part of a multisystemic disorder. Exceptions include some mtDNA mutations and some cases of CoQ_{10} deficiency in which renal dysfunction might be the only clinical manifestation at presentation[24]. In general, the coexistence of neuromuscular symptoms and renal defects should raise suspicion of a mitochondrial defect[25]. Some symptoms, such as sensorineural deafness or cardiomyopathy, might remain subclinical and require systematic testing. Specific skin and hair lesions have also been described[26]. The first symptoms of mitochondrial defects develop within the first weeks of life in approximately one-third of patients; more than 80% of patients are symptomatic by the age of 2 years[27].

Renal tubular disorders

After the brain, the kidneys have the highest oxygen consumption per dry weight of tissue, owing to the intense reabsorption and excretion processes that occur in the renal tubules, particularly in cells of the proximal tubule, distal convoluted tubule and connecting segments, which are very rich in mitochondria. Most of the chemical gradients necessary to reabsorb and excrete solutes from the crude glomerular filtrate arise from the basolateral Na-K ATPase. In intact kidneys, approximately 1 mmol of oxygen is estimated to be required for the reabsorption of 20–30 mEq of sodium[28,29]. In addition to glucose, the kidney oxidizes fatty acids and amino acids to meet this constant metabolic demand.

Unsurprisingly, many mitochondrial disorders are characterized by various degrees of tubular dysfunction. The most severe form of tubulopathy is complete Fanconi syndrome with low-molecular-weight proteinuria, reflecting global dysfunction of the proximal epithelial cells, which can be associated with more distal tubular defects[20,27,30–36]. Fanconi syndrome has also been reported in children with specific mitochondrial syndromes, including Kearns-Sayre syndrome, Pearson syndrome, Leigh encephalopathy and CoQ_{10} deficiency[20,27,30,31,37–46]. More frequently, patients present with partial defects, including isolated renal tubular acidosis (RTA), aminoaciduria, glycosuria or a combination of the above[20,27,45,47–51]. In some children, a Bartter-like phenotype has been reported[52,53]. Some patients might also present with isolated hypermagnesuria[20]. Tubular defects are frequently not recognized because their clinical manifestations are often mild or overshadowed by more severe neurological symptoms. In a systematic study of 42 patients with mitochondrial disorders, half had renal tubular dysfunction, but only eight had overt disease, suggesting that the prevalence of renal involvement in mitochondrial cytopathies is underestimated[51].

Mutations involving both nuclear and mitochondrial genes have been described to cause tubular defects. In general, consistent phenotypes that link mutations in a given gene to a specific tubular defect have not been identified[20]. Some mutations do, however, tend to be

characterized more frequently by certain renal phenotypes; for example, mutations in *BCS1L*, *UQCC2* or *FBXL4*, which are involved in oxidative phosphorylation, frequently cause proximal renal tubular acidosis[47,48]. A homozygous p.Ser78Gly mutation in *BCS1L* produces a specific clinical phenotype called GRACILE syndrome, which is characterized by intrauterine growth retardation, fulminant lactic acidosis, aminoaciduria and liver haemosiderosis, and is usually fatal in the neonatal period[54]. This syndrome is found almost exclusively in Finnish patients.

To date, two distinct familial mitochondrial tubular disorders have been identified. Mutations in the mitochondrial isoleucine tRNA gene ($tRNA^{Ile}$ or *MT-TI*) that involve a critical nucleotide for codon–anticodon recognition have been associated with mitochondrial hypomagnesaemia in a large white kindred[55]. Symptoms segregated in the family following a maternal dominance modality and included at least one of the following: hypomagnesaemia, hypercholesterolaemia or hypertension. Serum Mg^{2+} levels were low in half of the family members in the maternal lineage and were associated with increased urinary Mg^{2+} excretion and decreased urinary Ca^{2+} excretion, suggesting a specific defect of the distal convoluted tubule[55]. The mechanisms that underlie Mg^{2+} losses in these patients are not fully understood; however, cells of the distal convoluted tubule have very high energy consumption[56] and Mg^{2+} reabsorption in this segment requires ATP-dependent Na^{+} reabsorption[55,57–59]. In many cell models blocking oxidative phosphorylation impacts transcellular Na transport.

A second large family with autosomal dominant Fanconi syndrome characterized by prominent renal bicarbonate and phosphate losses was found to carry mutations in *EHHADH*[60]. The encoded protein, peroxisomal bifunctional enzyme, is involved in fatty acid oxidation and is primarily expressed in peroxisomes along the terminal segments of the proximal tubule. The mutation that segregates with disease in this family causes mistargeting of the protein to mitochondria, resulting in impaired mitochondrial oxidative phosphorylation with a dominant-negative effect. The latter finding is further substantiated by the absence of Fanconi syndrome in *Ehhadh*-knockout mice[60].

Glomerular diseases

Podocytes are highly differentiated cells with limited replicative capacity. They are a major component of the glomerular filtration barrier, support the other capillary components in counteracting endocapillary pressure, synthesize major cytoskeletal proteins and extracellular matrix components, and have several immunological roles[61]. To maintain all of these functions, podocytes are particularly dependent on energy and are rich in mitochondria. Impairment of oxidative phosphorylation in podocytes results in excessive generation of ROS and in functional and structural alterations, resulting in disruption of the glomerular filtration barrier, proteinuria and ultimately the development of glomerular sclerotic lesions[62,63]. Podocyte mitochondrial dysfunctions can be acquired, such as in diabetic nephropathy[64] and other chronic renal conditions[65,66], or caused by genetic defects in mtDNA or nDNA. In addition to sporadic cases of glomerulopathies secondary to mutations in genes that encode mitochondrial proteins[20], two major glomerular diseases have been identified: mitochondrial cytopathies secondary to genetic defects in the CoQ_{10}

biosynthesis pathway and those that are caused by the mtDNA 3243 A>G mutation in the $tRNA^{Leu(UUR)}$ gene.

CoQ_{10} biosynthesis defects

Glomerular involvement in these disorders can be isolated or occur as part of a multisystemic disease with a variable age of onset. In most cases, renal involvement is characterized by steroid-resistant proteinuria or nephrotic syndrome with or without haematuria, which usually progresses to chronic renal failure, and FSGS lesions in renal biopsy samples. High numbers of abnormal mitochondria in the cytoplasm of podocytes might sometimes be visible on electron microscopy (FIG. 3).

Diseases resulting from defects in CoQ_{10} biosynthesis are receiving increasing attention as a growing number of potentially treatable defects are recognized. These diseases are characterized by broad molecular and clinical heterogeneity, which is related to the large number of enzymes involved in CoQ_{10} biosynthesis and the possibility of redundancy in different organs. The clinical relevance of this group of mitochondrial cytopathies is related to their response to oral supplementation with CoQ_{10} (REFS 67–69), a treatment that is unparalleled in other mitochondrial diseases. Early diagnosis of affected patients might prevent the development of irreversible neurological lesions and reverse the renal phenotype[67].

Genetic defects that affect CoQ_{10} synthesis result in mitochondrial dysfunction and excessive production of ROS, which damage and ultimately cause apoptosis of podocytes. Interestingly, patients with idiopathic FSGS can have partial CoQ_{10} deficiencies that might affect their podocyte biology and participate in the development of FSGS lesions[70]. To date, mutations in nine genes involved in the synthesis of CoQ_{10} have been shown to cause primary CoQ_{10} deficiency (*PDSS1, PDSS2, COQ2, COQ4, COQ6, COQ7, ADCK3, ADCK4* and *COQ9*). Mutations in these genes produce a heterogeneous clinical picture, ranging from fatal multisystem disease to isolated steroid resistant nephrotic syndrome (SRNS) or encephalopathy[24]. Mutations in *COQ2* (REF. 71), *PDSS2* (REF. 72), *COQ6* (REF. 68), *ADCK4* (REF. 69) and *PDSS1* (REF. 73) have been associated with glomerular involvement.

COQ2—The first genetic defect that was identified in patients with primary CoQ_{10} deficiency was a mutation in *COQ2*, which encodes 4-hydroxybenzoate-polyprenyl transferase, the enzyme that catalyses the second step in the mitochondrial CoQ_{10} biosynthetic pathway[71]. To date, *COQ2* mutations have been reported in 15 children from 10 unrelated families; 11 of these patients had glomerular involvement[74–78]. SRNS usually developed within the first year of life or in the neonatal period, and often represented the first symptom of the disease, with or without neurologic symptoms. However, not all patients with *COQ2* mutations develop renal lesions[79] and some show renal involvement later in the course of their disease[78]. Various histologic lesions have been reported; in most cases the renal histology showed FSGS, including one case of collapsing glomerulopathy, but crescentic glomerulonephritis or mild mesangial proliferation have also been reported[75]. On electron microscopy, podocytes appear swollen and packed with abnormal

mitochondria[75] (FIG. 3). The nephrotic syndrome is characterized by a rapid decline in renal function that does not recur after kidney transplantation. Prompt treatment with high doses of CoQ_{10} (30 mg/kg) has been shown to halt the progression of the disease, substantially improve proteinuria and reverse the clinical manifestations related to nephrotic syndrome[67].

PDSS1 and PDSS2—*PDSS2* encodes a subunit of the enzyme required for synthesis of the decaprenyl tail of CoQ_{10}. In humans, the active form of this enzyme forms a heterotetramer comprising two PDSS1 and two PDSS2 units. To date, *PDSS2* mutations have been identified in four patients with glomerular mitochondrial cytopathies associated with CoQ_{10} deficiency from two unrelated families[72,80]. The first family, with three affected siblings, was originally described in 2006 (REF. 81). All three children presented with progressive encephalopathy and SRNS; two children underwent successful renal transplantation at the ages of 8 years and 9 years, whereas the third child died at 8 years of age as a consequence of rapid neurological deterioration. Treatment with oral CoQ_{10} (5 mg/kg per day) improved the neurologic symptoms in the surviving children over 3 years of follow-up. In the second family, the patient presented at 3 months of age with seizures and hypotonia. He subsequently developed cortical blindness and nephrotic syndrome and died at 8 months of age because of severe refractory focal status epilepticus[72]. His brain MRI was compatible with Leigh syndrome. From 3 months of age, this child was treated with oral CoQ_{10} (50 mg per day) with no apparent clinical improvement. The reasons for this lack of response are unclear, but the treatment might have been started too late, when neurological and renal lesions could no longer regress. Two patients with *PDSS1* mutations have also been described: the first showed no renal abnormalities[82] whereas the second presented with nephrotic syndrome[73].

A mouse model (*kd/kd*) harbouring a spontaneous homozygous missense mutation in *Pdss2* recapitulates the human renal phenotype and does not show major extra-renal defects[83]. In this model, CoQ_{10} supplementation is effective in preventing the onset of renal disease[84]. Interestingly, treatment with the antioxidant and hypolipidemic compound probucol is also effective in preventing renal lesions in these mice[85]. Whether this beneficial effect is related to the antioxidant properties of probucol or whether the drug stimulates CoQ_9 biosynthesis in these animals is unclear. No clinical data on probucol are available, but other antioxidants, such as idebenone (a soluble analogue of CoQ_{10}) do not rescue defects that result in a reduction in the activity of complex II+III[86] and seem to be ineffective at ameliorating symptoms in animal models[80]. The role of ROS in the pathogenesis of glomerulopathy in the *kd/kd* mouse model is supported by the observation that CoQ_9 deficiency is ubiquitous in these animals, but a significant increase in ROS production is present only in the kidneys, where tissue damage occurs[87].

COQ6—*COQ6* encodes a mono-oxygenase, which catalyses the C5 hydroxylation step of the quinone ring. Mutations in this gene have been described in 11 patients from five families[68]. All of the affected children presented with SRNS and sensorineural deafness, generally at older ages than those reported for patients with *COQ2* mutations. Proteinuria was diagnosed between 0.2 years and 6 years of age (median 1.2 years) and renal function deteriorated rapidly to reach end-stage renal disease (ESRD) between 0.4 years and 9 years

of age (median 1.7 years). Five children died at a median age of 5 years. The most frequent renal histological picture (seen in seven patients) was FSGS; diffuse mesangial sclerosis was diagnosed in one biopsy sample. Facial dysmorphism and neurological impairment, including seizures, white matter abnormalities and ataxia, were also reported[68]. Notably the uniformity of the phenotype, and in particular the renal involvement, could reflect selection bias as all of the patients were identified from a SRNS cohort. A yeast complementation study that tested all of the mutated *COQ6* alleles reported to date, showed that the defect could be rescued by vanillic acid or 2,4-dihydroxybensoic acid (DHB)[19]. These nontoxic analogues of the ring precursor of CoQ_{10} are able to bypass the enzymatic defect. DHB has also been shown to be effective in fibroblasts from patients with *COQ7* mutations[88].

ADCK4—*ADCK4* is the human orthologue of the yeast *COQ8* gene (L. Salviati, unpublished data), which encodes an atypical kinase involved in the regulation of CoQ_{10} biosynthesis. In yeast, overexpression of *ADCK4* stabilizes the CoQ multienzyme biosynthetic complex, even in the absence of any of its components[89]. Mutations in *ADCK4* account for the highest number of patients with renal disease secondary to CoQ_{10} biosynthesis defects reported to date: 38 patients from 18 families have been retrospectively described[69,90]. These patients typically presented with proteinuria and SRNS and most had a renal histological picture of FSGS, including a small number of patients with a collapsing variant. Extrarenal symptoms were present in a minority of patients, differed between affected patients and included mild neurologic disturbances and a single case of dilated cardiomyopathy. A patient who was treated with oral CoQ_{10} showed partial remission[90]. Compared with other CoQ_{10} biosynthesis defects, mutations in *ADCK4* seem to result in a less severe clinical entity, with a more prominent renal phenotype, higher age at onset of SRNS (usually 10–20 years), slower progression to ESRD and good patient survival owing to the lack of extrarenal manifestations.

The relatively mild phenotype observed in patients with *ADCK4* defects is probably related to the fact that the encoded enzyme has a modulatory function without catalytic activity, enabling residual CoQ_{10} synthesis even in the complete absence of this protein. In animal models *ADCK4* knockout caused reduced podocyte motility *in vitro*, which could be reversed by adding CoQ_{10} to the culture medium[69]. In mice null mutations in other *COQ* genes prevent CoQ_{10} biosynthesis and are not compatible with life[11]. Mutations in *ADCK3*, a paralogue of *ADCK4*, also causes CoQ_{10} deficiency, but the resulting phenotype is completely different from that of *ADCK4* mutations and includes cerebellar ataxia and encephalopathy without renal disease[91,92]. The functional relationship between these two genes requires further study.

Other mutations—Other genetic defects of CoQ_{10} biosynthesis, such as mutations in *COQ4, COQ9* and *COQ7*, have not been linked to glomerular disease. Moreover, a patient with a *COQ9* mutation had a tubulopathy without apparent glomerular involvement[44]. The reasons for this phenotypic discrepancy are unclear, but different degrees of destabilization of the CoQ_{10} biosynthetic complex by individual mutations might explain some of the variability[93].

mtDNA 3243 A>G mutation

The mtDNA 3243 A>G mutation in the $tRNA^{Leu(UUR)}$ gene is one of the most common mtDNA point mutations. This mutation was initially described in patients with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, a progressive neurodegenerative disorder that usually presents in children or young adults[94]. Approximately 80% of patients with MELAS syndrome harbour the mtDNA 3243 A>G mutation[95], but other causative mtDNA mutations have also been reported[43]. The phenotypic expression of the mtDNA 3243 A>G mutation can be highly variable and causes a wide range of clinical manifestations, including muscle weakness, exercise intolerance, failure to thrive, developmental delay, progressive encephalopathy, migraine, stroke-like episodes, peripheral neuropathy and visual complaints due to ophthalmoplegia. Some patients present with myoclonic epilepsy with ragged red fibres (MERRF) syndrome or maternally inherited diabetes and deafness (MIDD).

Renal involvement is not very common in patients with MELAS syndrome. However, several patients with the mtDNA 3243 A>G mutation have developed proteinuria and renal failure, usually in association with other symptoms (such as diabetes and/or sensorineural hearing loss), but also as an isolated finding, at least at disease onset. The renal disease generally corresponds to a glomerulopathy with proteinuria, which is below the nephrotic range in two-thirds of patients. From the histological standpoint, most patients have FSGS lesions, but three cases of tubulointerstitial nephritis have also been described[20]. Approximately 80% of patients with renal involvement have some degree of deafness, so might be misdiagnosed with Alport syndrome. Overall, patients with the mtDNA 3243 A>G mutation seems to have less overt haematuria than those with Alport syndrome, and their renal biopsy samples do not show the typical ultrastructural findings of this disease. The absence of these features should always raise suspicion of the mitochondrial $tRNA^{Leu}$ mutation. To date more than 30 patients with MELAS syndrome and renal involvement have been described in detail; approximately two-third of these patients were female and their age at diagnosis ranged from 14 years to 50 years[20,96]. The majority of patients were diagnosed with renal disease in their second or third decade of life and chronic kidney disease was present in half of these cases. Moderate neurologic symptoms were also present in the majority of patients.

A large-scale proteomic analysis of urine samples from adult patients with mitochondrial diseases showed that 75 of 117 participants carried the mtDNA 3243 A>G mutation[97]. Nearly half of the patients with this mutation had albuminuria and/or low-molecular-weight proteinuria, indicating that mtDNA 3243 A>G probably represents the most common mitochondrial disorder with renal involvement. Approximately half of the patients with this disorder presented with MIDD, whereas most of the remaining patients presented with MELAS or MERRF syndromes[97].

Diagnosis of oxidative phosphorylation defects

Analysis of lactate levels

The diagnosis of defects in oxidative phosphorylation is a complex task that requires a combination of approaches[10]. As a functional respiratory chain is required for the oxidation of lactate (the final product of glycolysis) to carbon dioxide and water, the presence of increased lactate levels in serum or cerebrospinal fluid is an important finding. Such analyses can be integrated with magnetic resonance spectroscopy, which enables estimation of lactate levels in the brain[98]. These levels often fluctuate, however, and might be normal even in the presence of severe defects in oxidative phosphorylation[99]. The lactate-to-pyruvate ratio helps distinguish between oxidative phosphorylation disorders and other defects such as pyruvate dehydrogenase deficiency. Analysis of urinary organic acids might detect lactic aciduria and other abnormalities, such as dicarboxylic aciduria, which is a frequent, albeit nonspecific finding in patients with defects in oxidative phosphorylation[24]. Patients with mitochondrial renal disease often do not have constant hyperlactacidemia but might have elevated urinary lactate excretion. In addition, levels of fibroblast growth factor 21 are increased in patients who have mitochondrial disorders with significant muscle involvement[100].

Neuroimaging

Neuroimaging often provides important clues to aid diagnosis. Focal lesions in deep grey matter structures, such as the putamen and basal ganglia, are among the most common findings, especially in paediatric patients[101,102]. Leigh syndrome, which is characterized by focal, bilateral, symmetric lesions involving basal ganglia and the periaqueductal grey matter, represents the effects of severe deficiencies in energy production in the central nervous system in infancy[103]. Older patients might present with stroke-like lesions in non-vascular territories, especially in the parieto-occipital region. These lesions are typical of MELAS syndrome[101], but are also seen in other defects, including CoQ_{10} deficiencies[74]. Less-specific findings include cortical and cerebellar atrophy, as well as various white matter abnormalities.

Analysis of biopsy samples

Muscle biopsy is still considered the gold standard for diagnosis of oxidative phosphorylation defects[10]. Morphological analyses coupled with histochemical staining enables the detection of COX-deficient fibres and mitochondrial proliferation[104]. A uniform pattern points to a nDNA defect, whereas a mosaic distribution (owing to heteroplasmy) is suggestive of a mtDNA abnormality, which can occur as a result of a mutation in mtDNA or as a secondary effect of a mutation in a nuclear mtDNA maintenance gene. Oil-Red staining might detect lipid accumulation, which is often observed in CoQ_{10} deficiencies[105].

Spectrophotometric measurements of enzymatic activities might distinguish between defects involving individual complexes and combined deficiencies. Analysis of the combined activity of complexes II and III, which require CoQ_{10} to shuttle electrons to complex III (FIG. 1), provides an indirect but reliable assessment of CoQ_{10} levels[89]. Finally, CoQ_{10} concentrations in muscle specimens can be measured using HPLC. Standardized analysis

protocols for this technique have been developed and validated[106,107]. Similar analyses can be performed in cultured primary skin fibroblasts; however, some defects are not expressed in these cells. Cultured fibroblasts also enable functional studies.

In theory, CoQ_{10} analyses performed on muscle specimens can also be carried out on renal tissue[75]. Histochemical analyses of renal cortex samples might provide similar information to analyses of muscle specimens[20]; however, spectrophotometric analyses are more problematic because a surgical biopsy is necessary to obtain a large enough sample.

Next-generation sequencing

Next-generation sequencing approaches are revolutionizing the molecular diagnosis of mitochondrial disorders. The entire mtDNA can now be sequenced rapidly at low cost[108]. In patients with renal involvement, urinary sediment cells could be the optimal material for DNA extraction[109]. Likewise, in cases of nuclear defects, large gene panels or the entire exome can now be analysed[19]. In the past few years, numerous defects have been characterized at the molecular level using these techniques. Nonetheless, detailed phenotypic characterization of patients remains necessary to restrict the data analysis, which is time consuming and complicated.

Screening for CoQ_{10} deficiency—As timely diagnosis is crucial for the success of therapy, the possibility of CoQ_{10} deficiency should always be considered in patients with SRNS, particularly infants. No pathognomonic clinical features exist, but SRNS in association with neuromuscular symptoms or deafness should raise the suspicion of CoQ_{10} deficiency. Many patients, however, present with SRNS without extrarenal involvement at diagnosis. Moreover, although patients usually present in infancy or early childhood, onset of symptoms might occur later in life. The optimal diagnostic strategy for CoQ_{10} deficiency is still debated[110]. Traditional approaches require time and invasive procedures; such delay is not of critical importance in most disorders of oxidative phosphorylation, but might have dramatic consequences in the case of CoQ_{10} deficiencies. In principle, all individuals with isolated SRNS should be screened for CoQ_{10} deficiency, but performing a skin or muscle biopsy is not always possible. With new technological advances and cost reductions, screening using next-generation sequencing and specific gene panels is becoming a valuable diagnostic approach. Even if only 1% of patients with SRNS have CoQ_{10} deficiency[111], the benefits of preventing ESRD and probably also neurological deterioration in these patients outweighs the cost of genetic screening, which is routinely performed in most cases. Systematic electron microscopy of renal biopsy samples could also enable rapid identification of many patients, as abnormal mitochondrial proliferation in podocytes is frequently observed[75].

Mitochondrial dysfunction in acute kidney injury

As the renal tubules represent one of the most metabolically active epithelia in the human body, it is unsurprising that AKI — whether septic, ischaemic, or toxic in origin — involves early pathological changes in the mitochondria of the tubular epithelium[112,113]. These changes include decreased mitochondrial abundance, swelling of individual organelles, and disruption of the otherwise tightly stacked cristae. The proximal tubule is a primary site for

mitochondrial disruption in AKI, but changes in the thick ascending limb and distal tubules have also been reported[114]. Evidence for mitochondrial involvement in human AKI was shown in early electron microscopy studies of specimens from patients who had died from septic shock[115]. Subsequent autopsy studies following sepsis and sequential biopsy studies during controlled renal ischaemia (for example, for nephrectomy) revealed similar lesions in mitochondria[116,117].

Mitochondrial dysfunction in AKI typically accompanies ultrastructural pathology. For example, experimental cisplatin nephrotoxicity induces a decrease in the activity and expression of cytochrome c oxidase in the proximal tubule, but not in the distal nephron segments. This finding is consistent with the clinical observation that proximal tubular manifestations dominate the presentation of platinum-induced renal injury[118]. Comparison of a toxic form of AKI, glycerol-induced rhabdomyolysis, with post-ischaemic AKI showed that both conditions result in widespread loss of mitochondrial respiratory proteins from proximal tubules[119], whereas experimental sepsis leads to a profound decrease in the expression and activity of multiple enzymatic components of the mitochondrial electron transport chain.[112]

Injured mitochondria not only deprive the cell of ATP, but are an important source of molecules that amplify injury, precipitate cell death and induce inflammation (FIG. 4). ROS released from damaged mitochondria contribute to the oxidative stress widely reported in AKI. Structural disruption of mitochondria also releases cytochrome c, a trigger of apoptosis, as well as mtDNA, which can serve as a proinflammatory danger signal[120]. A highly orchestrated process of mitochondrial biogenesis, replication, and clearance via macroautophagy enables healthy cells to avoid the dangers of mitochondrial injury. Conversely, growing evidence indicates that mitochondria might be a compelling therapeutic target in multiple forms of AKI.

Fatty acids

Although comprehensive discussion of mitochondrial energy metabolism in AKI is beyond the scope of this Review, the roles of fatty acids and ROS need to be highlighted. Fatty acids are the most efficient source of mitochondrial ATP generation, but their intracellular accumulation can result in lipotoxicity. During ischaemia, a mismatch develops between ongoing hydrolysis of membrane phospholipids and reduced clearance of these fatty acids via re-esterification and mitochondrial fatty acid oxidation. This imbalance leads to the accumulation of non-esterified fatty acids (NEFAs), which can act as detergents that weaken the membrane structure, culminating in apoptosis. Biochemical interventions to reduce NEFAs (for example, by applying citric acid cycle substrates) protect freshly isolated proximal tubules from hypoxia–reoxygenation injury and restore normal ATP production[121–123]. In transgenic mice that overexpress the transcription factor peroxisome proliferator-activated receptor-α, protection against ischaemic AKI is associated with restoration of normal fatty acid metabolism[124]. Finally, the sequestration of noxious fatty acids into the storage form of triglycerides might be an endogenous adaptive response to injury. Triglyceride accumulation in cortical and medullary segments of nephrons seems to

be a hallmark of diverse renal injuries, ranging from acute obstruction to experimental sepsis and ischaemia–reperfusion injury (IRI)[125,126].

Reactive oxygen species

During normal mitochondrial metabolism, a large concentration gradient of hydrogen ions across the inner mitochondrial membrane provides the energy for the phosphorylation of ADP to ATP. When components of the electron transport chain are downregulated, disassembled, spatially displaced or altered, the movement of electrons can become dysregulated, resulting in the generation of excess ROS. Mitochondria seem to be a major source of excess ROS during acute cellular injury as a result of inflammation or ischaemic stress. Although ROS have vital signalling roles in healthy cells, excess levels can lead to catalytic free-radical damage to all classes of macromolecules. Generic antioxidants might have limited therapeutic potential in AKI, but two different classes of mitochondria-targeted antioxidants seem promising in preclinical models. One class of such molecules, an example of which is MitoQ, covalently links the antioxidant ubiquinone to a lipophilic cation that 'locks' the compound into mitochondria[127,128]. Another therapeutic strategy involves linking the antioxidant chemical to a peptide that provides mitochondrial targeting, for example a Szeto-Schiller peptide[129]. Experiments using mitochondria-targeted antioxidants have confirmed that mitochondria are an important source of ROS during various types of renal injury and shown that reduction of mitochondria-derived ROS can ameliorate AKI[130,131]. These molecules are currently being examined in clinical settings of excess mitochondrial ROS generation, such as IRI.

Mitochondrial dynamics

Ischaemic and toxic forms of AKI are characterized by marked mitochondrial fragmentation. The fragmented mitochondria are potential sources of ROS, cytochrome c, mitochondrial DNA and other potentially injurious molecules. Inhibition of mitochondrial fission by genetically or pharmacologically blocking dynam-in-related protein 1 (Drp1) has been shown to protect cultured renal tubular cells from stress-induced apoptosis and attenuate AKI following ischaemia–reperfusion or cisplatin exposure[113]. Experimental pigment nephropathy can also be ameliorated by Drp1 inhibition[132]. Although complementary experiments with gain-of-function mutations remain to be performed, these findings suggest that altered mitochondrial dynamics are a key feature of AKI and a potential therapeutic target. Consistent with this hypothesis, experimental evidence suggests that the NAD-dependent protein deacetylase sirtuin 3 might attenuate cisplatin-induced mitochondrial fragmentation and protect against experimental AKI[133].

Mitophagy

Safe disposal of fragmented mitochondria via mitophagy might protect stressed cells from death and ameliorate AKI. Renal IRI has been shown to induce mitophagy in renal tubules[134], and mice that lack the autophagy regulator Atg7 show increased sensitivity to cisplatin nephrotoxicity[135]. Drugs that induce mitophagy, such as rapamycin, merit further exploration as therapeutic strategies to enhance the clearance of injury-propagating fragmented mitochondria and accelerate recovery after AKI.

Mitochondrial biogenesis

To maintain a steady pool of mitochondria, losses to mitophagy must be replenished by the expansion of mitochondrial mass. An array of nuclear transcription factors and co-activators are involved in mitochondrial biogenesis. The best studied co-activator is peroxisome proliferator-activated receptor-γ co-activator 1-α (PGC-1-α), which is highly expressed in the most metabolically active organs, including the heart, kidney, brains, skeletal muscle and liver[136]. In the kidney PGC-1-α expression reflects the relative distribution of mitochondria; the highest expression is in the cortex, followed by the tubules with much lower levels in the glomerulus[112]. In ischaemic and septic AKI, an initial decrease in PGC-1-α expression is followed by a return to normal levels as organ function recovers, suggesting a role of this co-activator in AKI recovery[112,119]. Consistent with this hypothesis, specific knockout of *Ppargc1a*, which encodes PGC-1-α, from the proximal tubule blunted renal recovery following experimental sepsis[112]. Signals from innate inflammatory pathways might result in downregulation of PGC-1-α during infection[137,138].

Data from gain-of-function experiments also suggest that targeting mitochondrial biogenesis might attenuate renal injury and/or accelerate recovery from AKI. In cultured proximal tubular cells, induction of PGC-1-α after (but not before) oxidant exposure accelerated recovery of mitochondrial function[139]. To identify pharmacological stimulators of mitochondrial biogenesis, Jesinkey *et al.* screened a large library of small molecules in model cellular systems. One such compound, the β-adrenergic agonist formoterol, stimulated mitochondrial biogenesis, reduced necrosis and improved kidney function in mice that had been subjected to renal IRI[140]. Further studies are required to determine whether PGC-1-α is required for formoterol-dependent renoprotection, and to delineate the underlying mechanisms. However, these findings are promising because they suggest the translational utility of unbiased cell-based drug screens targeting mitochondrial processes to identify agents that might aid recovery from established AKI.

Conclusions

Healthy mitochondria are essential for normal renal health and mutations that directly or indirectly impair mitochondrial function or assembly can cause renal disease. The genetics of mitochondrial disorders is complex and can follow various patterns of inheritance. Although most patients with renal disease resulting from a mitochondrial disorder have a tubulopathy, two well-defined glomerular diseases in patients with mitochondrial cytopathies have been described: FSGS resulting from defects in the CoQ_{10} biosynthesis pathway and FSGS secondary to the mtDNA 3243 A>G mutation. These latter diseases are particularly important because defects in CoQ_{10} biosynthesis might be rescued by oral CoQ_{10} supplementation and renal diseases caused by the mtDNA 3243 A>G mutation are transmitted following a maternal pattern of inheritance and associated with extrarenal symptoms that need to be monitored.

In most cases, however, mitochondrial damage is acquired. Injury to tubular mitochondria represents an early event during AKI. As injured mitochondria release multiple noxious factors, the cellular processes that occur upstream and downstream of this event are of substantial interest. Research into the effects of targeting mitochondrial dynamics,

mitophagy and biogenesis has yielded consistent and exciting results that suggest the potential of manipulating these processes to ameliorate AKI. New approaches developed to treat acquired mitochondrial damage might also be potentially beneficial in some genetic mitochondrial disorders. Other alternative strategies, such as pronuclear transfer — a technique for mitochondrial replacement — might also represent potentially valuable approaches in some diseases, but ethical considerations need to be addressed before such techniques can be adopted in clinical practice[141].

Acknowledgments

Mitochondrial studies in S.M.P.'s laboratory are supported by R01-DK0950972. Studies in L.S.'s laboratory are supported by Telethon grants 14187 and 13222.

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Biographies

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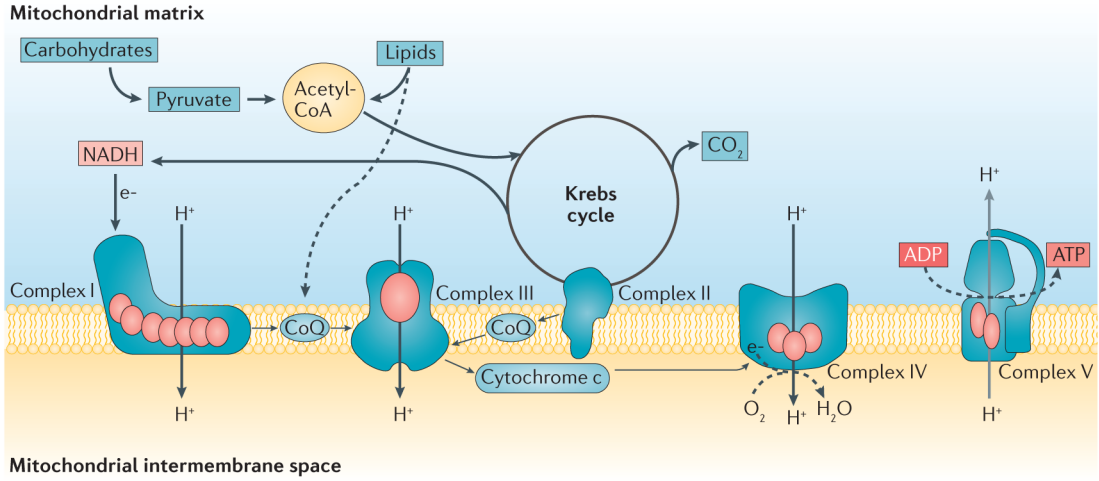

Figure 1. Mitochondrial energy metabolism and the respiratory chain

Acetyl-coenzyme A (Acetyl-CoA) is the terminal product of carbohydrate and lipid metabolism, and is oxidized through the reactions of the Krebs cycle to produce CO_2. The high energy electrons (e^-) produced by these reactions enter the respiratory chain and eventually reduce molecular oxygen (0_2) to form water (H_20). The energy released by this process is used to pump protons (H^+) across the mitochondrial inner membrane and generate the electrochemical gradient that enables complex V to synthesize ATP. The red ovals represent mitochondrial DNA-encoded subunits of the respiratory chain complexes. CoQ, coenzyme Q.

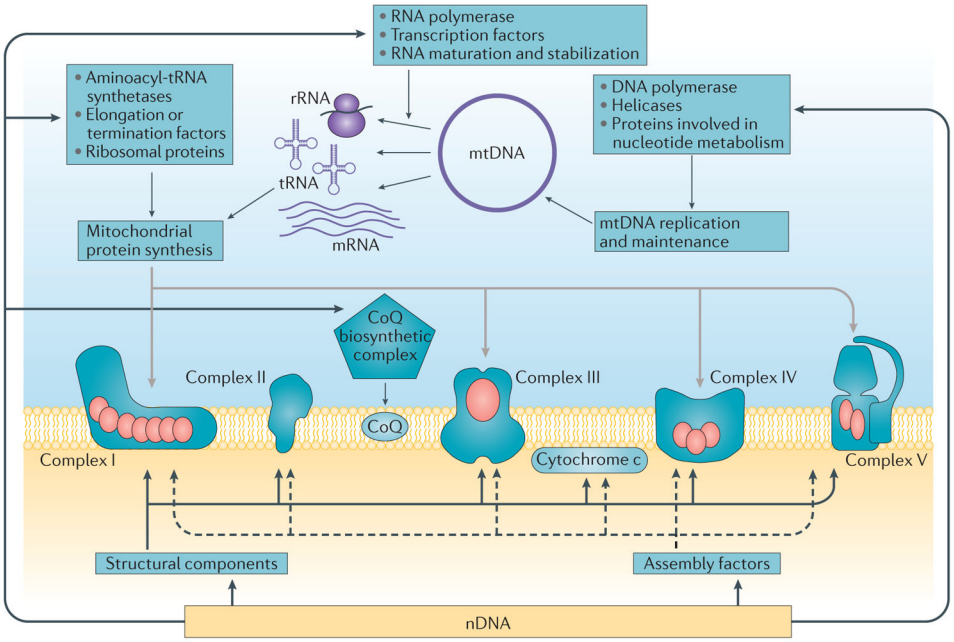

Figure 2. Interplay of mitochondrial and nuclear genes in the biogenesis of the respiratory chain

Mitochondrial (mt) DNA encodes 13 structural subunits of the respiratory chain complexes (red ovals) as well as two ribosomal (r)RNAs and 22 transfer (t)RNAs that are required for mitochondrial protein synthesis. Nuclear (n)DNA encodes all the other structural subunits of the respiratory chain complexes, cytochrome c, assembly factors, the enzymes required for coenzyme Q (CoQ) biosynthesis and proteins involved in mtDNA replication and maintenance and in mitochondrial protein synthesis.

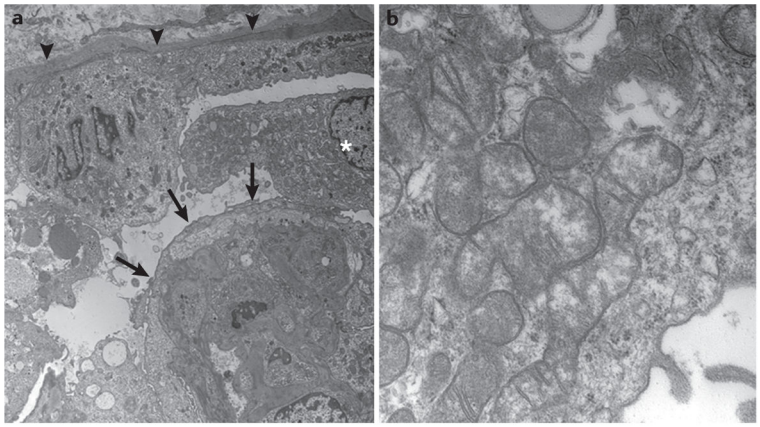

Figure 3. Electron microscopy images of a renal biopsy sample obtained from a patient with a *COQ2* mutation

a | The parietal epithelium of the Bowman capsule (arrowheads) appears healthy and contains a normal number of mitochondria. By contrast, the urinary space is occupied by swollen podocytes (asterisk) that show extensive foot-process fusion (arrows). **b** | Enlarged view of a podocyte showing the cytoplasm packed with mitochondria, several of which are dysmorphic.

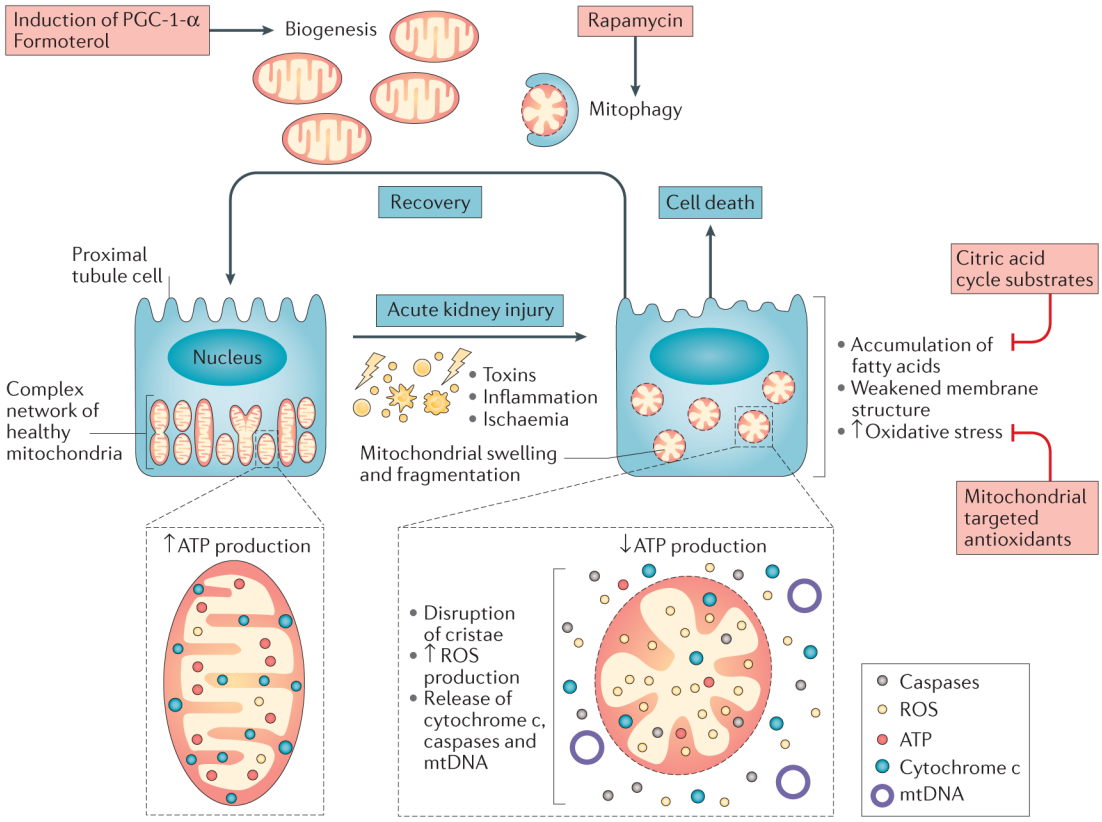

Figure 4. Mitochondrial injury and recovery during acute kidney injury (AKI)

Tubular epithelial cells in the proximal tubule and outer medulla are heavily invested with mitochondria in order to generate the ATP necessary for solute transport. Diverse aetiologies of AKI injure the mitochondria, leading to organellar swelling and fragmentation. Injured mitochondria, in turn, release an array of proinflammatory and injurious molecules, such as reactive oxygen species (ROS), which, if unchecked, promote cell death. Experimental findings suggest that recovery from AKI might require the clearance of injured mitochondria through mitophagy and the replenishment of mitochondrial mass through mitochondrial biogenesis, a process mediated by the transcriptional co-activator peroxisome proliferator-activated receptor-γ co-activator 1-α (PGC-1-α). Examples of potential preventive and therapeutic strategies are highlighted in pink boxes. mtDNA, mitochondrial DNA.

Table 1

Characteristics of mitochondrial genetics

Characteristic	Description
Maternal inheritance	Both genders might be affected by mtDNA mutations, but only females transmit mutations to their children
Heteroplasmy	Wild type and mutant mtDNA molecules can coexist in different proportions within cells of the same tissue or in different tissues of the same individual
Threshold effect	A mutation must affect a critical proportion (usually >70%) of the total mtDNA molecules within a cell or tissue to cause a biochemical effect resulting in a clinical phenotype
Random drift	Mutant and wild type mtDNA molecules segregate randomly in daughter cells during each cell division

mtDNA, mitochondrial DNA.

Table 2

Genetic defects that impair mitochondrial function

Defect	Description and examples
mtDNA	
Mitochondrial protein synthesis	Point mutations or gross rearrangements in mtDNA usually impair mitochondrial protein synthesis as a whole, resulting in combined defects of several respiratory chain complexes[10]; complex II is spared, as only nuclear genes encode this complex Many point mutations affect genes that encode tRNAs or rRNAs The most frequent gross rearrangement is the recurrent 4,977 base pair 'common' deletion[142] The renal phenotype is usually tubulopathy; glomerular defects are associated with the mtDNA 3243 A>G mutation
Structural subunits	Mutations in mtDNA-encoded structural subunits usually cause defects in individual respiratory chain complexes
nDNA	
Assembly factors	Assembly factors are not part of the respiratory chain, but are necessary for its biogenesis; mutations in genes that encode assembly factors are usually referred to as 'indirect hits' Some assembly factors are required for specific steps in the biogenesis of individual complexes (for example *COX10* encodes a farnesyltransferase that is involved in the biosynthesis of the heme group of complex IV[143]), whereas others have shared functions and their mutations consequently affect multiple complexes, often including complex II (for example, mutations in *LYRM4*, which is required for the synthesis of iron–sulphur clusters, impair the activities of complexes I, II and III[144])
Electron carriers	Mutations in genes that are required for CoQ_{10} biosynthesis cause primary CoQ_{10} deficiency Secondary CoQ_{10} deficiency is associated with mutations in nDNA genes that are not directly involved in CoQ_{10} biosynthesis, such as *APTX* and *ETFDH*, as well as with several mtDNA defects[89]; therefore, a reduction in CoQ_{10} levels does not necessarily indicate a mutation in a *COQ* gene Secondary forms of CoQ_{10} deficiency are probably much more frequent than primary forms Mutations in cytochrome c are transmitted as autosomal dominant traits and associated with familial thrombocytopenia; the disease pathogenesis results from deregulation of apoptosis rather than the bioenergetic defect
Mitochondrial dynamics	The most common defects in genes that control mitochondrial dynamics involve the profusion proteins OPA1 and mitofusin-2 In addition to promoting mitochondrial fusion, OPA1 is essential for the control of cristae remodelling and the formation of supercomplexes[145], which increase the efficiency of oxidative phosphorylation Mitofusin-2 tethers mitochondria to the endoplasmic reticulum; this process is probably important for calcium metabolism[146]
Mitochondrial protein synthesis	Genes that are involved in mitochondrial protein synthesis include those that encode aminoacyl–tRNA synthases, mitochondrial ribosomal proteins, elongation factors, proteins that are involved in the maturation of mRNAs and tRNAs, and other components of the translation machinery[10] Mutations in these genes typically result in combined defects that spare complex II
mtDNA maintenance	Mutations in genes that encode proteins involved in mtDNA replication or nucleotide metabolism cause secondary mtDNA defects, including depletion (reduction in copy number), multiple deletions (resulting in the tissue-specific presence of mtDNA species with various types of gross deletions) and specific point mutations[147] Defects in mtDNA maintenance are usually associated with combined deficiencies Some defects alter the lipid milieu of the mitochondrial inner membrane and indirectly impair oxidative phosphorylation[15]; for example, *TAZ* mutations result in in Barth syndrome, which is characterized by abnormal cardiolipin metabolism OPA1 and mitofusin-2 are also required for mtDNA maintenance and their deficiencies cause mtDNA depletion by unclear mechanisms[145]
Structural subunits	Nuclear gene defects might directly involve structural subunits of individual complexes, most commonly complex I

CoQ_{10}, coenzyme Q_{10}; mRNA, messenger RNA; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; OPA1, optic atrophy 1 (also known as dynamin-like 120 kDa protein, mitochondrial); tRNA, transfer RNA.

Table 3

Nuclear gene defects that affect respiratory chain biogenesis

Category	Gene	Renal phenotype	Refs
Structural subunits	None yet described	NA	NA
Electron carriers (including CoQ biosynthesis)	*PDSS1*	SRNS	73
	PDSS2	SRNS	72
	COQ2	SRNS	71
	COQ6	SRNS	68
	ADCK4	SRNS	69
	COQ9	Tubulopathy	44
Assembly factors	*COX10*	Tubulopathy	148
	SURF1	Tubulopathy *	149
	BCS1L	Tubulopathy	150
	UQCC2	Tubulopathy	151
	TMEM70	Tubulopathy *	152
mtDNA translation	*MRPS22*	Tubulopathy	153
	YARS2	Tubulopathy	154
	SARS2	Tubulopathy	155
mtDNA maintenance	*RRM2B*	Tubulopathy	156
	TWINKLE	Tubulopathy	157
	MPV17	Tubulopathy	158
	SUCLA2	Tubulopathy *	159
	DGUOK	Tubulopathy *	160
Lipid milieu	None yet described	NA	NA
Mitochondrial dynamics	None yet described	NA	NA

CoQ, coenzyme Q; mtDNA, mitochondrial DNA; NA, not applicable; SRNS, steroid-resistant nephrotic syndrome.

* Occasional manifestation.

Table 4

Mitochondrial disorders: non renal effects

Organ or system	Common manifestation
Endocrine system	Diabetes mellitus
	Hypoparathyroidism
Gastrointestinal tract	Intestinal dysmotility
	Pseudo-obstruction
	Malabsorption
Heart	Hypertrophic (rarely dilated) cardiomyopathy
	Conduction defects
Hematologic system	Sideroblastic anaemia
	Thrombocytopenia
	Neutropenia
Liver	Liver failure
Nervous system	Psychomotor retardation and/or regression
	Dementia
	Seizures
	Myoclonus
	Migrane
	Ataxia
	Spasticity
	Dystonia
	Stroke-like episodes
	Leukoencephalopathy
	Peripheral neuropathy
Sensory system	Deafness
	Blindness
	Optic nerve atrophy
	Retinitis pigmentosa
	Cataracts
	Progressive external ophthalmoplegia
Skeletal muscles	Muscle weakness
	Exercise intolerance
	Myoglobinuria