The Not So ‘Mighty Chondrion’: Emergence of Renal Diseases due to Mitochondrial Dysfunction

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Abstract

Mitochondria are intracellular organelles with a variety of vital functions, including the provision of energy in the form of adenosine 5'-triphosphate. Increasingly, we are becoming more aware of the importance of mitochondrial dysfunction in a number of common medical conditions. In this review and overview, we focus on the growing evidence that mitochondrial dysfunction is involved in either the etiology or underlying pathophysiology of a broad spectrum of renal diseases, including acute renal injury due to ischemia-reperfusion injury, renal Fanconi syndrome, and glomerular disorders such as focal segmental glomerulosclerosis. In addition, mitochondrial dysfunction may also contribute to the growing burden of chronic kidney disease seen in our aging population, which is still largely unexplained. Unfortunately, at present, our ability to diagnose and treat renal disorders related to mitochondrial dysfunction is limited, and further work in this field is needed.

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Introduction

Recognition of the importance of mitochondria in clinical medicine is increasing rapidly. Not only is the list of common diseases linked to mitochondrial dysfunction lengthening – including diabetes mellitus, neurodegeneration, cardiac ischemia-reperfusion injury (IR), and septic shock –, mitochondria are also believed to play a key role in the process of aging. Furthermore, current thinking is that the acquisition of mitochondria by eukaryotes may have been the critical step necessary for complex organisms like ourselves to evolve from prokaryotes [1]. Therefore, it is not surprising that disorders of these vital intracellular organelles can affect renal function, and in this article, we draw together the evidence for a link between disordered mitochondrial function and renal disease.

Mitochondria in the kidney are vulnerable to insults like hypoxia in ischemic acute renal injury (ARI) or toxins filtered from blood. The kidney consumes a large amount of energy supplied as adenosine 5'-triphosphate (ATP) from mitochondria which drives directly, and indirectly, the reabsorption of large quantities of fluid and solutes across the renal tubular epithelium; any disruption in this supply is likely to cause renal dysfunction.

Fig. 1. Metabolic symbiosis. Mitochondria are believed to have evolved from aerobic bacteria that fused with an anaerobic species, creating a new organism with a significant metabolic advantage.

However, a reduced supply of ATP may not be the only mechanism by which mitochondria can affect the renal function. The challenge is for us to elucidate the exact role(s) of the mitochondria in renal cell function and thereby in renal disease. Current means of diagnosis and treatment are inadequate, and a better understanding of mitochondrial pathophysiology, especially in the setting of renal disease, should lead to improvements in both.

Mitochondrial Biology

Mitochondria are intracellular organelles that exist inside all human cells, except erythrocytes. They are believed to be the ultimate example of symbiosis, having been (perhaps) independent prokaryotic (bacterial) cells capable of using oxygen (generating 36 molecules of ATP per glucose) which fused with primitive eukaryotic cells lacking mitochondria or other bacterial cells dependent for their energy on fermentation (generating 2 molecules of ATP per glucose); indeed, these two organisms may have coexisted and functioned independently, yet interdependently, before eventually combining to form a single cell-like organism (fig. 1).

The role of mitochondria in cells was previously thought to be exclusively energy provision via oxidative phosphorylation and the production of ATP (fig. 2). However, more recent evidence suggests that mitochondria

may have many other 'metabolic' functions, including intracellular calcium homeostasis, free radical generation and elimination, cellular proliferation, and regulation of cell death by apoptosis [2].

As our understanding of the role of mitochondria in cell function increases, so does our knowledge of mitochondrial genetics. Mitochondria contain their own DNA (mtDNA) inherited maternally¹ and encoding 13 or 14 proteins involved in the respiratory chain (fig. 2), two rRNA subunits, and 22 tRNA molecules necessary for protein synthesis. However, the majority of mitochondrial proteins are encoded by *nuclear* (chromosomal), rather than mitochondrial, DNA – of the mitochondrion's approximately 3,000 proteins, only around 37 are encoded by mtDNA. This increases the chances of a mitochondrial disorder being inherited as a Mendelian trait: autosomal dominant, recessive, or X-linked. The mutation rate in mtDNA is about ten times higher than in nuclear DNA (due to a higher rate of replication and a lack of protection from histones and DNA repair mechanisms) which results in variation in mitochondria within the same species. Moreover, DNA mutations affecting mitochondria tend to exhibit tissue specificity, depending, for example, on energy requirements [3]. Each mitochondri-

¹ According to some recent reports, paternal inheritance of mtDNA can occur, challenging the established view of exclusive maternal inheritance.

Fig. 2. Mitochondrion: respiratory chain complexes I–V. The components of the respiratory chain are situated in the inner mitochondrial membrane (IMM). Fuels are oxidized in the citric acid cycle, and electrons are passed, via donors, to complex I (by NADH) and complex II (by FADH₂). The electrons are then moved along the chain, releasing energy that is utilized to pump protons into the intermembrane space. Protons then pass back down the concentration gradient, through complex V, and the energy released is coupled to the generation of ATP. OMM = Outer mitochondrial membrane; TCA = tricarboxylic acid.

on carries several copies of the mitochondrial genome (2–10), and each cell has a large and varied number of mitochondria; some copies may carry mtDNA mutations and others not. This is known as *heteroplasmy* and can vary from cell to cell – in *homoplasmy*, all copies of mtDNA in a cell are similarly affected. With heteroplasmy, a ‘threshold level’ may need to be reached before cellular and tissue functions are impaired sufficiently to cause clinical disease. Furthermore, there is variation in the nature of the nuclear-encoded proteins in the mitochondria of different cells which will also confer tissue specificity, when mutations arise. Mitochondria may also have different roles in different cells: for example, in eosinophils, mitochondria are net consumers of ATP and are likely to have functions other than energy supply, such as regulation of cell death by apoptosis [4]. The kidney may be particularly sensitive to mitochondrial damage, because it is the major excretory route, via filtration and secretion, for *xenobiotics*, some of which may be mitochondrial toxins.

Hereditary Mitochondrial Cytopathy

Because of the complexities outlined above, mitochondrial disorders can be very difficult to recognize, both phenotypically and genotypically. The subject of mitochondrial cytopathy has been covered extensively in the more

recent neurology and pediatric literature, including pediatric nephrology [5], and it is not our intention to cover this in any detail, but to focus on renal disease in adults.

In children, a number of renal diseases, including renal Fanconi syndrome (FS), nephrotic syndrome, tubulointerstitial disease, a Bartter-like syndrome, and renal tubular acidosis, have all been reported in hereditary mitochondrial disorders. Most of these children have presented at an early age, and their renal disease has been part of a multisystem disorder. In contrast to the many different mtDNA mutations found in pediatric nephrology, in adult patients, only one point mutation has been linked to renal disease: the A3243G mutation of the tRNA(Leu) gene. This is the same mutation that causes MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome) and some cases of diabetes with deafness, indicating how heterogeneous mitochondrial disease can be. In a case series of 9 patients with this mutation and renal disease, focal segmental glomerulosclerosis (FSGS) was the most common pathology found. However, even in this select group, the phenotype varied enormously, from tubulointerstitial disease to polycystic kidney disease [6]. This mutation may be more common than is appreciated – one study of diabetic patients on hemodialysis reported a prevalence of 5.9% [7]. The potential role of mitochondrial dysfunction in the pathogenesis of glomerular disease is discussed below (see Glomerular Disorders).

Ischemia-Reperfusion Injury

Ischemic prerenal injury is the commonest cause of ARI, and in spite of the numerous therapies tried (such as volume replacement, dopamine, furosemide, natriuretic peptide) and aimed at restoring renal perfusion and tubular function, morbidity and mortality in this condition remain high [8]. One possible explanation for the failure of these treatments to alter outcomes is the phenomenon of IR, in which cells that have survived an initial ischemic insult suffer further damage following (warm) reperfusion. IR has been studied extensively in cardiac myocytes and neurons, and mitochondria seem to play a central role.

Work on IR in cardiac myocytes has shown that ischemia leads to a decrease in intracellular ATP, as expected. Interestingly, under these circumstances mitochondria become significant net consumers of ATP, using it to pump protons out of the mitochondrion in order to maintain the inner membrane potential [9] – highlighting the importance of maintaining the proton gradient for cellular function. Eventually, with prolonged ischemia and no reperfusion, the cell dies by necrosis. However, reperfusion itself is toxic to myocytes and can lead to cell death by apoptosis. Suggested mechanisms include the generation of reactive oxygen species (ROS) and changes in the mitochondrial calcium concentration [10]. More recently, nitric oxide generation has been implicated [11].

The final common pathway appears to involve the insertion of a large and nonselective multiunit ion channel in the mitochondrial inner membrane, called the *mitochondrial permeability transition pore* (mPTP). This causes a rapid depolarization of the mitochondrial membrane with release of proapoptotic factors, such as *cytochrome c*, which results in a cascade of events ending in apoptotic cell death [12]. Cytochrome *c* has been detected in the urine of mice with experimental ARI, and this could prove to be a useful human marker of tubular cell mitochondrial dysfunction [13].

Attention has focused on potential therapeutic interventions in IR. In myocytes, the phenomenon of ‘ischemic preconditioning’ is protective against IR [14]. This is achieved by exposing cells to short and nonlethal episodes of ischemia which confers protection against the effects of more prolonged IR. Experimental work has suggested that this is mediated by the activity of a mitochondrial potassium (KATP) channel and that blockers of these channels, like glibenclamide, can reduce the beneficial effect of ischemic preconditioning [15]. Recently, ex-

posure of renal tubular cells to glibenclamide has been shown to cause a dose-dependent reduction in mitochondrial function [16].

Inhibitors of mPTP have also been shown to be protective in IR. One of these inhibitors is the immunosuppressive drug cyclosporin A which binds to the cyclophilin domain of mPTP. Cyclosporin A has now been used in experimental models of IR in the kidney, where it has also been found to be protective [17]. Perhaps donated kidneys should be exposed to cyclosporin A before transplantation, to reduce IR, as well as after transplantation to prevent rejection. This work highlights the fact that cyclosporin A has wide-ranging intracellular actions that account for its side effects and nephrotoxicity. Indeed, rats exposed to cyclosporin A develop abnormal-looking mitochondria [18].

Another drug in common use in nephrology and now linked to IR protection is erythropoietin (Epo). Used widely to treat renal anemia, Epo is known to work by inhibiting apoptosis in erythrocyte precursors. It has emerged recently that, in addition to working as a conventional hormone, Epo can also act in a localized and paracrine fashion and that it is released from various tissues in conditions of metabolic stress, such as IR. Experimental models suggest that when given exogenously, Epo is protective against IR in brain, heart, and kidney [19]. As well as reducing levels of inflammation, Epo appears to inhibit apoptosis in tissues exposed to IR by acting on multiple signaling pathways to either increase the levels of antiapoptotic factors or decrease the levels of proapoptotic factors – reducing the likelihood of mitochondrial activation of programmed cell death [20]. Therapeutic trials are required to determine whether these experimental findings apply in clinical practice.

In cadaveric renal transplantation, kidneys are subjected to cold ischemia, and experimental work on renal cell lines suggests that cold storage is toxic to the mitochondria, even in the absence of ischemia. Apoptosis occurs on rewarming, and the addition of antioxidants can limit this [21]. Since cell death from cold ischemia and subsequent warm reperfusion may account for poorer outcomes in cadaveric as compared with living-donor transplantation [22], strategies to protect mitochondrial integrity and prevent apoptosis would seem to be advantageous. A more specific inhibitor of mPTP (than cyclosporin A) is now available (sanglifehrin) that is protective in IR in myocytes [23], but it has not been tried so far in renal tubular cells.

Renal FS and Proximal Tubulopathy

The proximal tubule is responsible for the reabsorption of solutes and low-molecular-weight proteins (LMWPs) from the glomerular filtrate. Bicarbonate, phosphate, glucose, and amino acid transport across the apical membrane of proximal tubular cells is coupled to sodium transport which is driven by the sodium gradient established by the basolateral ATP-dependent sodium pump. The reabsorption of LMWPs, such as vitamins and hormones, occurs via receptor-mediated endocytosis. FS is characterized by a failure of the proximal tubular cells to reabsorb LMWPs and solutes. The causes of FS are many, and the mechanism(s) by which they can cause an almost global failure of proximal tubular transport function is unclear. A possible mechanism could involve abnormal regulation of the transport processes at the apical membrane, due to impaired cellular metabolism and energy supply linked to mitochondrial dysfunction. In addition to several pediatric case reports linking mitochondrial disease and FS, a screening study of 42 children with a variety of hereditary mitochondrial mutations found that 5 had evidence of FS and a further 13 had a subclinical proximal tubulopathy [24].

Experimental models of diseases caused by inborn errors of metabolism, and associated with FS, have suggested links to mitochondrial dysfunction. In *cystinosis*, the commonest cause of FS in children, excess cystine accumulates intracellularly in lysosomes. Experimentally, exposing rat proximal tubular cells to cystine causes a decrease in solute reabsorption. This is associated with a fall in ATP levels and oxygen consumption, and more detailed analysis suggests inhibition of complex I (see figure 2) in the mitochondrial respiratory chain [25]. More recent work on primary cultures of human proximal tubular cells derived from urine has demonstrated that although mitochondria in cystinosis appear to function normally under baseline conditions, the levels of the important intracellular antioxidant agent glutathione are reduced. Therefore, the cells are vulnerable to oxidative stress and show significantly impaired mitochondrial function and ATP production when exposed to hypoxia [26].

In *tyrosinemia*, succinylacetone accumulates and has been shown to inhibit the proximal tubular cell phosphate transport in vitro. This is associated with reduced ATP levels in the cell and mitochondrial oxygen consumption, probably (as in cystinosis) by inhibition of complex I of the respiratory chain [27].

Acquired FS can occur in the setting of myelomas and is rarely the presenting feature. Biopsy specimens of patients with myeloma and FS have been reported to show abnormalities of mitochondrial morphology on electron microscopy, and rats exposed to nephrotoxic light chains also show histological evidence of mitochondrial damage [28]. Indeed, a number of toxins and drugs cause mitochondrial injury and FS (see Drug-Related Tubulopathy).

Alcohol is known to be toxic to mitochondria, possibly via ROS formation [29]. In a screening study of alcoholic patients, without evidence of liver cirrhosis, there was evidence of proximal tubulopathy detected by tubular proteinuria [30]. This abnormality was found to improve with abstinence; the patients maintained a normal glomerular filtration rate throughout the study. Various heavy metals are also known to be toxic to the proximal tubules and to cause FS. In a rat model, exposure of renal tubular cells to cadmium causes FS, and this is associated with mtDNA deletion and impaired mitochondrial function, with reduced ATP content [31].

Experimentally, applying inhibitors of oxidative phosphorylation to proximal tubular cells causes a decrease in ATP levels and inhibition of sodium-coupled phosphate and glucose transport, analogous to FS [32]. Metabolic inhibitors can also affect the amino acid transport [33]. However, a decrease in ATP levels may not be the only way in which mitochondrial dysfunction can cause FS. In another experimental model of FS, produced by the toxin maleate, the levels of the antioxidant glutathione are low in proximal tubular cells, making them vulnerable to damage by ROS; the associated transport defects and glutathione levels are improved by glycine, another antioxidant [34]. As already mentioned, reabsorption of proteins in the renal proximal tubule is by endocytosis, a process that can be sensitive to changes in intracellular Ca^{2+} levels [35], which may in turn be controlled by mitochondria.

Primary biliary cirrhosis is a liver disease associated with antimitochondrial antibodies, and 2 patients with this disorder have now been reported with FS. Interestingly, antibodies isolated from 1 of these patients were able to inhibit mitochondrial enzymes in vitro, providing a potential explanation for the proximal tubular dysfunction [36]. In addition, bile salts themselves are thought to be toxic to the renal tubule by stimulating generation of ROS by mitochondria [37].

One issue that is still unclear is why the proximal tubule seems particularly sensitive to mitochondrial injury and its consequences. An obvious answer is that its trans-

Table 1. Drugs known to be toxic to mitochondria and associated with renal FS

Drug	Usage	Mechanism of toxicity
NRTIs	antiretroviral	inhibition of DNA polymerase (gamma), leading to mtDNA depletion
Aminoglycosides	antibacterial	inhibition of oxidative phosphorylation in vitro and/or ROS production
Sodium valproate	anticonvulsant	unknown; causes swollen mitochondria on electron microscopic examination of kidneys in mouse models
Ifosfamide	chemotherapy	inhibition of complex II of the respiratory chain in vitro; MtDNA depletion in vivo
Cisplatin	chemotherapy	initiation of apoptosis via translocation of proapoptotic factors from cytosol into mitochondria, with subsequent activation of caspases
Suramin	antiparasitic, chemotherapy	reduced activity of complex IV of the respiratory chain

port activity requires high levels of energy in the form of ATP. However, the highest density of mitochondria in the nephron is found in the medullary thick ascending limb of Henle's loop [38]. This has a more precarious oxygen supply than the proximal convoluted tubule, and although a Bartter-like syndrome in mitochondrial disease has been reported [39], it is very unusual. However, differences could be due to variations in dependence on oxidative phosphorylation versus anaerobic glycolysis for energy supply, making some tubular segments more vulnerable than others to mitochondrial dysfunction [40]. It may be that the specialized functions of the proximal tubule, like the uptake of LMWPs by endocytosis, are more sensitive to the other consequences of mitochondrial dysfunction and not just to ATP depletion.

Drug-Related Tubulopathy

A number of drugs have been reported to cause FS (see table 1), including aminoglycosides, sodium valproate, ifosfamide, suramin, and, more recently, the antiretrovirals [41] – all are thought to cause mitochondrial dysfunction. In the case of valproate, mice exposed to the drug develop FS and swollen mitochondria on electron microscopy [42]. Experiments in a rat model suggest that aminoglycosides like gentamicin can inhibit oxidative phosphorylation in renal tubular cells and reduce the levels of ATP [43]. Interestingly, in these studies, mitochon-

dria exposed to gentamicin looked normal in spite of their impaired function, indicating that the mitochondrial morphology may not be a sensitive guide to mitochondrial function. Other studies with gentamicin have suggested that the generation of ROS from tubular mitochondria is crucial in the development of tubular damage and can be ameliorated by ROS scavengers [44]. Non-steroidal anti-inflammatory drugs are known to be harmful to the renal tubule; in vitro evidence suggests that this could also be due to mitochondrial toxicity and ROS generation, which may have direct effects on the tubular transport of glucose [45].

HIV infection per se is known to be toxic to renal tubular and glomerular epithelial cells, causing apoptosis [46]. In addition, some of the nucleoside reverse transcriptase inhibitors (NRTIs) used to treat HIV infection, such as didanosine, can cause FS [47], which has been linked to mitochondrial toxicity. NRTIs inhibit DNA polymerase (gamma) which is required for mtDNA replication, leading to a reduction in mtDNA [48]. Tenofovir is one of the newer NRTIs and is effective against more resistant strains of HIV. Initially, tenofovir was thought not to be nephrotoxic; however, a number of case reports of FS in patients taking tenofovir have now been published [49]. Tenofovir has also been associated with nephrogenic diabetes insipidus [50] and acute tubular necrosis [51]. There is now evidence that tenofovir's toxicity may be due to mitochondrial dysfunction – renal biopsy specimens from patients on tenofovir only show ultrastruc-

tural mitochondrial abnormalities, while specimens from patients taking tenofovir in combination with didanosine show reduced levels of mtDNA [52]. This combination of drugs has also been shown to impair mitochondrial function in leukocytes [53]. Clearly, given the increasing use of antiretroviral drugs, HIV specialists and nephrologists need to be made aware of the potential adverse effects of these drugs on the kidney.

Ifosfamide is a cytotoxic agent used to treat cancers in children. It has been shown to cause FS as an early and late side effect [54] – studies done in platelets from patients exposed to the drug have shown it to be toxic to mitochondria, causing depletion of mtDNA and reduced respiratory chain activity [55]. Suramin is a drug with anticancer and antiparasite actions. It can also cause FS, and muscle biopsy specimens from affected patients revealed abnormal-looking mitochondria on electron microscopy. Furthermore, biochemical tests on the respiratory chain in muscle mitochondria confirmed a reduced activity of complex IV of the respiratory chain (see figure 2), again consistent with mitochondrial toxicity [56].

Glomerular Disorders

It is becoming increasingly clear that abnormalities of glomerular podocyte function are involved in the etiology of glomerular pathology. In the case of FSGS, mutations in podocyte proteins like podocin are believed to underlie some familial forms [57]. Children with mitochondrial cytopathies have also been reported to develop FSGS, and biopsy specimens in these cases show abnormalities of podocyte mitochondria on electron microscopy, with normal-looking mitochondria in the renal tubules [58]. These findings have led to the speculation that the cellular location of mutated mitochondria in the kidney determines the pattern of nephropathy that occurs (glomerular vs. tubular).

Although mitochondria-related glomerular disease is considered to be less common than renal tubular disease (attributed to differences in energy requirements), steroid-resistant primary FSGS due to a mitochondrial cytopathy has been reported in an adult patient [59]. This raises the possibility that other examples of a primary glomerulopathy could be due to an unrecognized mitochondrial cytopathy, and such a diagnosis should always be considered, particularly in cases that do not respond to steroids, or if there is a family history or evidence of other organ involvement, like diabetes or deafness. In a rat model of FSGS, puromycin aminonucleoside nephro-

sis (PAN), the levels of mtDNA and mitochondrial encoded proteins within podocytes were found to be low, perhaps as a result of oxidative damage, adding further support for a role of mitochondrial dysfunction in glomerular disease [60]. In mouse models of type II diabetes, the earliest detected renal pathology is also FSGS, associated with podocyte loss by apoptosis. Evidence points to glucose-induced oxidative stress mediated by mitochondria-dependent pathways [61]. Therefore, as well as having a role in the development of diabetes mellitus, mitochondrial dysfunction may also be involved in the pathogenesis of diabetic nephropathy.

Chronic Kidney Disease

Hypertension is one of the most important causes of chronic kidney disease and its progression. Hypertension leads to glomerular and tubulointerstitial damage which can be slowed by drugs that inhibit the actions of angiotensin II, like losartan. These drugs reduce glomerular injury by decreasing the intraglomerular pressure, but how they slow progression of tubulointerstitial disease, the major determinant of renal prognosis in chronic kidney disease, is less clear. What is now emerging from studies in hypertensive rat models is that the benefit of inhibiting angiotensin II is not only from reducing blood pressure and proteinuria, but also from mitochondrial protection and a decrease in the levels of oxidative stress in renal tubular cells [62]. Chronic kidney disease progression may also be related to chronic hypoxia [63] – angiotensin II antagonists augment the renal cortical microvascular pO_2 which might explain their protective effect to reduce oxidative stress [64].

Chronic kidney disease is predominantly a disease of the elderly [65]. Like all organs, the kidney shows a steady deterioration in function with age. As described earlier, mtDNA is more vulnerable to mutations accumulating over time, leading to impaired mitochondrial function, and this has been linked to the process of aging. Animal studies have shown evidence of increased levels of ROS and abnormal mtDNA in renal tissue with age [66], and this provides a possible explanation for the high prevalence of chronic kidney disease in the elderly.

Mitochondrial dysfunction may also be an important cause of unexplained chronic kidney disease in younger patients. A recent mouse model of mitochondrial pathology has been created using a known mutation of mitochondrial DNA. Although these mice develop extrarenal

dysfunction, the cause of death at around 6 months is renal failure, and the histology of the kidneys shows segmental glomerular sclerosis with dilation of the tubules [67]. One of the difficulties in diagnosing mitochondrial disease, which has been recognized in pediatric nephrology, is that commonly used markers of mitochondrial dysfunction, like blood lactate concentration or lactate:pyruvate ratio, are relatively insensitive and may not be altered (even after exercise), perhaps because of excess urinary losses of lactate, if the renal tubular function is affected [5].

Renal Stone Disease

Oxalate is a major common component of renal calculi and is known to be toxic to renal tubular cells. Oxalate crystals precipitate in the kidney in ethylene glycol poisoning and are thought to cause tubular damage in this uncommon form of self-poisoning, causing ARI. Evidence from in vitro studies suggests that oxalate toxicity is mediated by impairment of mitochondrial function and increased production of ROS [68], indicating yet another role for mitochondria in kidney disease.

Diagnosis and Treatment of Mitochondrial Dysfunction

Although our understanding of the role of mitochondrial dysfunction in the etiology and pathogenesis of renal diseases is increasing, we are still limited in our ability to diagnose and treat these disorders. Diagnosis is hampered by a lack of available tools to readily detect and identify mitochondrial dysfunction. In the absence of neurological manifestations, clues can come from the presence of other organ dysfunction (such as deafness, diabetes, cardiac abnormalities, and isolated hypomagnesemia) or the abnormal appearance of mitochondria on muscle or renal biopsies. However, proving mitochondrial dysfunction is much more difficult.

Mitochondrial function tests (including respiratory chain enzyme activities) can be performed on fresh renal tissue, but this is not widely available, and it requires a high index of suspicion for the diagnosis. Tissue can also be obtained from more accessible sources, like peripheral leukocytes and muscle; however, due to the tissue specificity of mitochondrial disease, some cases can still be missed. As mentioned, a blood lactate level, which is often used as a screening test for mitochondrial dysfunction,

can be normal in renal disease. Moreover, even if mitochondrial function tests are carried out, they may be normal under basal conditions and abnormalities evident only under 'stress' [26].

In hereditary mitochondrial disease, a positive family history is an important diagnostic clue, but is not always easy to recognize. Genotyping of mtDNA for point mutations with polymerase chain reaction can be done, but the yield from this is limited by the range of mutations routinely screened for; moreover, mutations affecting mitochondrial proteins encoded by nuclear genes will not be detected. Deletions or large-scale rearrangements of mtDNA are more commonly acquired than inherited, but can be screened for by Southern blotting.

Future treatment of renal disease due to mitochondrial dysfunction is likely to focus on protection of mitochondrial integrity using blockers of mitochondrial membrane depolarization (such as cyclosporin A), inhibitors of apoptosis, and ROS scavengers, which are all potential therapeutic options. Successful renal transplantation has been carried out in cases of inherited mitochondrial disease; however, patients develop complications like diabetes and strokes at a relatively early stage after transplantation [6]. Experimental mouse models of mitochondrial disease indicate that gene therapy might be an option in the future, at least in reducing the risk of passing on mutations to offspring [69].

Conclusions

In this brief overview of mitochondrial function and dysfunction, we have considered aspects of nephrology, in which mitochondrial disease may play a role. Much has been learnt from studying mitochondria in other organs which is relevant to nephrology. Strategies to protect and preserve mitochondrial function could be of therapeutic benefit in important conditions like ischemic ARI, chronic kidney disease, and FS. Nephrologists need to be aware of the potential adverse effects on the kidney of drugs toxic to mitochondria, including newer agents used to treat HIV infection and some anticancer therapies.

The incidence of mitochondrial disease in nephrology is probably underestimated, particularly in cases of unexplained chronic kidney disease and in primary glomerular and tubular disorders. Mitochondria are now known to have multiple functions other than energy supply, and they are likely to prove important in many idiopathic dis-

eases, including in nephrology. Unfortunately, we still do not have reliable and straightforward tests to diagnose mitochondrial dysfunction, and until these become readily available, we must rely on a high index of clinical suspicion.

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