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Mitochondrial Dysfunction in Kidney Tubulopathies

Charlotte A. Hoogstraten, Joost G. Hoenderop, and Jeroen H.F. de Baaij

Department of Medical Biosciences, Radboud University Medical Center, Nijmegen, The Netherlands; email: Jeroen.deBaaij@radboudumc.nl

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Abstract

Mitochondria play a key role in kidney physiology and pathology. They produce ATP to fuel energy-demanding water and solute reabsorption processes along the nephron. Moreover, mitochondria contribute to cellular health by the regulation of autophagy, (oxidative) stress responses, and apoptosis. Mitochondrial abundance is particularly high in cortical segments, including proximal and distal convoluted tubules. Dysfunction of the mitochondria has been described for tubulopathies such as Fanconi, Gitelman, and Bartter-like syndromes and renal tubular acidosis. In addition, mitochondrial cytopathies often affect renal (tubular) tissues, such as in Kearns-Sayre and Leigh syndromes. Nevertheless, the mechanisms by which mitochondrial dysfunction results in renal tubular diseases are only scarcely being explored. This review provides an overview of mitochondrial dysfunction in the development and progression of kidney tubulopathies. Furthermore, it emphasizes the need for further mechanistic investigations to identify links between mitochondrial function and renal electrolyte reabsorption.

INTRODUCTION

Mitochondrial DNA (mtDNA): the circular genome that is present in multiple copies in mitochondria and contains information for organelle function

Tubulopathy: disease affecting a tubular segment of the nephron, often representing complex conditions with nonspecific symptoms

Oxidative phosphorylation (OXPHOS): the generation of ATP from ADP in mitochondria using energy obtained by electron transport under aerobic conditions

Reactive oxygen species (ROS): naturally occurring derivatives of oxygen that may lead to molecular damage when formation is elevated

The kidney has one of the highest energy demands in our body, which is required for the reabsorption of water and electrolytes. In particular, the cortical segments of the nephron have a high mitochondrial density, taking advantage of the high oxygen availability (1–3). Mitochondria function as a central hub in renal cell metabolism and signaling; they generate and facilitate stress responses and regulate cellular life, stress, and death pathways (2, 4, 5). Consequently, defects in mitochondrial biogenesis, dynamics, and mitophagy and mutations in nuclear or mitochondrial DNA (mtDNA) often result in kidney disease. Dysfunctional mitochondria cause reduced adenosine triphosphate (ATP) production, inflammation, and/or renal epithelial cell death (6, 7).

A role for mitochondria in the pathogenesis of common kidney diseases, such as acute kidney injury (AKI), diabetic nephropathy, and chronic kidney disease (CKD), has comprehensively been described and reviewed (8–15). Tubulointerstitial nephropathy and glomerular disease are commonly observed in primary mitochondrial diseases (16). In recent years, an increasing number of studies have established mitochondrial defects as the central cause of renal tubulopathies (17–20). Conversely, mitochondrial dysfunction contributes to disturbed water and electrolyte reabsorption in renal tubulopathies with a nonmitochondrial (primary) cause. In this review, we therefore provide an overview of the physiological role of mitochondria in renal function. Additionally, we evaluate mitochondrial dysfunction in the development and progression of kidney tubulopathies, including diseases of the proximal tubule (PT), thick ascending limb (TAL), distal convoluted tubule (DCT), and collecting duct (CD).

MITOCHONDRIA IN HEALTH AND RENAL DISEASE

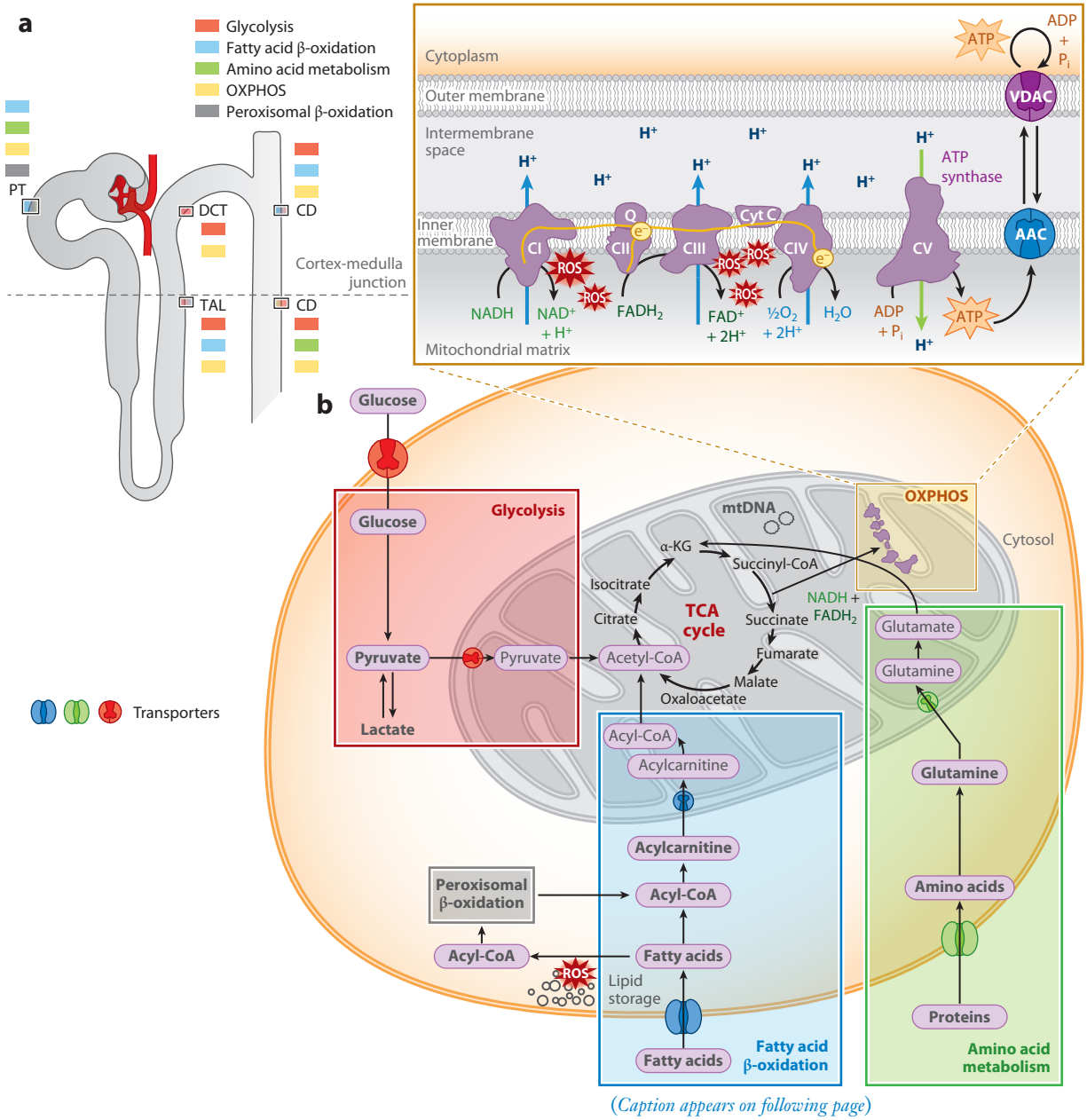
Mitochondria in Cellular Metabolism

Mitochondria are key contributors to cellular metabolism, essential for life and death pathways. Their canonical function is the generation of ATP in a highly efficient and oxygen-dependent way (4, 5, 21, 22). Mitochondria facilitate central metabolic pathways, including the tricarboxylic acid (TCA) or Krebs cycle and oxidative phosphorylation (OXPHOS) (23). Briefly, the glycolytic product pyruvate crosses, in the presence of oxygen, the outer mitochondrial membrane (OMM) and feeds the TCA cycle, which leads to the generation of energized nucleotides and accumulation of the reduced coenzyme nicotinamide adenine dinucleotide (NADH) in the mitochondrial matrix (5). Via redox reactions, NADH is catalyzed by the respiratory multisubunit complexes I–IV and the diffusible cytochrome C and coenzyme Q10 embedded in the inner mitochondrial membrane (IMM). The OXPHOS complexes I–IV function as electron shuttles in the electron transport chain, creating a proton (H^+) gradient over the IMM toward the intermembrane space. Subsequently, this electron gradient is used by complex V (F_1F_0-ATP synthase) activity to convert adenosine diphosphate (ADP) into ATP (5). The generated ATP molecules are transported to the cytosol using ADP/ATP carriers to increase intracellular ATP stores (24). Next to generating ATP from glucose, mitochondria coordinate many other biosynthetic and catabolic pathways. These include fatty acid β-oxidation; heme biosynthesis; steroid-, keto- and gluconeogenesis; and amino acid metabolism (5). Also, mitochondria play a role in cell proliferation and differentiation, Ca^{2+} signaling and storage, regulation of intracellular pH, generation of reactive oxygen species (ROS), initiation and propagation of immune responses, and programmed cell death (5, 25–31).

Energy Requirements Along the Renal Tubule

Renal tubules contain among the most energy-consuming cells, mostly to sustain the activity of ATP-dependent pumps (e.g., Na^+-K^+-ATPase). In the kidney, approximately 40–70% of the

oxygen consumption is required to fuel Na^+-K^+-ATPase and drive the reabsorption and secretion of water, solutes, and waste products (2, 3, 32). As the segments of the nephron have their own function, the energy demands and the mechanism by which ATP is produced change along the nephron (3, 33, 34) (**Figure 1**). Cortical segments are characterized by a high mitochondrial content (2, 35). In particular, those cell types that reabsorb significant amounts of filtered solutes and water are reflected by the large numbers of ATP-consuming transporters and a high mitochondrial density (36). Fatty acids are the preferred fuel source for highly metabolic cells, including those



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Overview of metabolic pathways in each nephron segment. Colored boxes of tubular cell types (*a*) indicate the main pathways used for energy metabolism (*colored boxes*, panel *b*) in each nephron segment. In glycolysis (*red*), glucose is converted into cytosolic pyruvate through multiple intermediate steps. Pyruvate is transported into mitochondria via the mitochondrial pyruvate carrier and is converted into CoA, which enters the TCA cycle. In fatty acid β-oxidation (*blue*), fatty acids are activated to acyl-CoA in the cytosol. At the OMM, acyl-CoA is converted into acylcarnitine via transesterification and shuttled across the IMM through the carnitine-acylcarnitine translocase. In the mitochondrial matrix, acylcarnitine is reconverted into acyl-CoA and, through a series of cyclic processes (β-oxidation), converted into acetyl-CoA. Very-long-chain fatty acids are oxidized by peroxisomes (*gray*), and products are transported into mitochondria for further oxidation and subsequent ATP production via the OXPHOS system. An alternative to fatty acid oxidation is the amino acid metabolism of glutamine (*green*). Glutamine transfers into mitochondria via the glutamine transporter (SLC1A5), followed by conversion into glutamate and α-KG, which fuels the TCA cycle. Energy-rich ATP, NADH, and $FADH_2$ are produced, and electrons of NADH and $FADH_2$ enter the OXPHOS system to generate ATP. The OXPHOS system (*insert*) is embedded in the IMM, consisting of the electron transport chain (CI–CIV) and CV (F_0F_1-ATPase), which converts ADP into ATP. CI, CIII, and CIV generate a H^+ gradient over the IMM toward the intermembrane space, and the electron flow is shown by a yellow line. ATP is released in the intermembrane space and cytosol via AAC and VDAC, respectively. ADP translocates from the cytosol into the mitochondrial matrix via VDAC and AAC. Abbreviations: α-KG, alpha-ketoglutarate; AAC, ADP/ATP carrier; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CD, collecting duct; CI–CV, mitochondrial protein complexes I–V; CoA, acetyl-coenzyme A; Cyt C, cytochrome C; DCT, distal convoluted tubule; $FAD^+/FADH_2$, flavin adenine dinucleotide oxidized/reduced; IMM, inner mitochondrial membrane; mtDNA, mitochondrial DNA; NAD^+/NADH, nicotinamide adenine dinucleotide oxidized/reduced; OMM, outer mitochondrial membrane; OXPHOS, oxidative phosphorylation; PT, proximal tubule; Q, coenzyme Q; ROS, reactive oxygen species; TAL, thick ascending limb of Henle's loop; TCA, tricarboxylic acid; VDAC, voltage-dependent anion channel.

of the PT, as fatty acid oxidation (FAO) provides higher levels of ATP (106 units) per molecule than does the oxidation of glucose, which generates 36 ATP units (37–39). Changes in oxygen levels mainly impact the PT, due to the high oxygen consumption in this segment (40, 41). Fatty acyl-coenzyme A synthetase and the carnitine shuttle embedded in the IMM are required for fatty acid degradation into acetyl coenzyme A, which enters the TCA cycle (5, 42). Other sources that may be used include lactate, glutamine, and ketone bodies (2, 43, 44). In contrast, the utilization of glucose as an energy source is limited to the more distal nephron segments, including the TAL, DCT, and CD (2, 43, 44). The expression levels of glycolytic enzymes such as pyruvate kinase and hexokinase are high in these segments, indicating that the metabolism of glucose into pyruvate drives the TCA cycle and subsequent ATP generation through the OXPHOS system (36, 44). Alternatively, pyruvate may be metabolized into lactate, resulting in a net yield of two ATP units (45). An extensive overview of major metabolic pathways in the kidney was previously described by Tian & Liang (43).

Oxidative Stress and Consequences for Development of Tubulopathies

While the OXPHOS system enables the generation of large amounts of ATP through the electron transport chain to sustain renal cell metabolism and health, it is concurrently a major source of incomplete oxygen reduction (e.g., ROS formation) in the mitochondrion. Most of the ROS is generated at the level of complexes I and III (3, 5, 46). ROS is normally produced as a byproduct of respiration and is an important physiological mediator in intracellular signaling pathways and developmental processes, including tissue regeneration and transcriptional regulation via epigenetic processes (5, 47–49). In renal physiology, ROS has been shown to regulate solute reabsorption, particularly in the TAL and CD (50–52). However, whether the described effects of ROS molecules on tubular function are the result of mitochondrial oxidative stress or whether they originate from ROS as a byproduct of cytosolic oxidase/reductase activity remains unknown. Therefore, the source of ROS-induced effects and the exact role for mitochondria in inducing tubular defects require further exploration. Excessive ROS levels may lead to protein oxidation and changes in the mitochondrial membrane permeability and induce (mitochondrial) DNA mutations, apoptotic cell death, and aging (53–56). Hence, a balance between ROS production and scavenging is critical for

maintaining mitochondrial function. In the kidney, mitochondrial ROS has been associated with disturbed FAO, which results in ATP depletion, accumulation of lipids, and inflammation. Tubular inflammation caused by overproduction of ROS has, for example, been described for the progression of diabetic kidney disease (DKD) (57, 58). Although oxidative stress has been described as a major regulator of ion channels and transporters (50), its role in renal tubulopathies remains elusive. Moreover, future studies should discriminate between a cytosolic and mitochondrial origin of ROS and their effects on ion reabsorption.

Mitochondrial Dynamics in Tubular (Patho)Physiology

Mitochondrial morphology (e.g., length, shape, size, and number) is highly dynamic, which enables the adequate coordination of mitochondrial metabolism in response to cellular demands (7, 59–61). Elongated, filamentous organellar networks result from the fusion of two separate mitochondria and are associated with increased production and distribution of ATP throughout the cell (7, 62, 63). Cells that undergo intra- or extracellularly induced stress adapt by mitochondrial fission or fragmentation (61). This latter dynamic event is required for the induction of mitophagy, a process in which damaged or dysfunctional mitochondria are directed to lysosomal degradation (59, 64). Loss of functional organelle induces mitochondrial biogenesis (mitogenesis) to maintain cellular homeostasis and regeneration, mediated by upregulation of the transcription factor PGC1α (65). The interplay of biogenesis, fission, fusion, and mitophagy has a fundamental role in renal tubule function, as a disbalance has previously been linked to mitochondrial dysfunction in renal PT cells in in vitro and in vivo models of DKD (66). Moreover, pharmacological therapies that stimulate mitochondrial biogenesis have already been successful in reducing blood pressure in several clinical trials (67–70). This may suggest that renal ion transport requires balanced mitochondrial dynamics. However, direct effects of mitochondrial dynamics on renal tubular function have not been extensively evaluated.

Mitochondrial DNA in Tubular (Dys)Function

The unique origin of mitochondria as cellular organelles is reflected in their extraordinary genetic characteristics, including their own mitochondrial circular genome, which encodes for 13 proteins involved in OXPHOS, 22 transfer RNAs (tRNAs), and 2 ribosomal RNAs (rRNAs) that are required for translation of mitochondrial proteins (71, 72). mtDNA mutations in the *MT-TK*, *MT-TL1*, and *MT-ND5* genes are causative for Fanconi syndrome (73–76) (**Table 1**). Homoplasmic (>95%) mutations in mitochondrial tRNAs for Ile and Phe (*MT-TI* and *MT-TL*) result in hypomagnesemia, a characteristic primary defect in the DCT; Gitelman-like syndrome; and mitochondrial dysfunction through inhibition of OXPHOS complexes (17, 77–79). In addition, mitochondria are distinguished from other organelles by the tremendous amount of mtDNA copies, compared to just two existing copies in nuclear DNA (nDNA). Heteroplasmic mutations, not affecting all mtDNA copies, induce phenotypic effects when the mutation load is above a certain threshold. Although heteroplasmy may explain differences in clinical and tissue-specific manifestations (80, 81), renal tubulopathies are mostly associated with near-homoplasmic (>95%) mutations (17, 82). mtDNA deletions are also common in renal tubulopathies, with more than 30 cases reported to date (**Table 2**). Although the exact deletion varies from patient to patient, the deleted region often includes the mitochondrial rRNA subunits and the *MT-ND1* and *MT-ND2* genes. Additional genetic causes of mitochondrial cytopathies may include mutations in the nDNA (83, 84) (**Table 1**). Most mitochondrial proteins are encoded by nDNA, and several of these are posttranslationally imported into mitochondria to function in the regulation and maintenance of the mitochondrial genome (85). Consequently, genes involved in mitochondrial translation or mitochondrial function may also result in renal tubulopathies due to mitochondrial defects.

Fanconi syndrome: a global inherited or acquired defect in the proximal tubule leading to malabsorption of electrolytes

Gitelman syndrome: a distal convoluted tubule disorder, often due to autosomal recessive Na^+, Cl^- cotransporter mutations and characterized by hypokalemia, hypomagnesemia, and low urinary calcium excretion

Heteroplasmy: presence of wild-type and mutant mitochondrial DNA within a cell; the percentage of mitochondrial DNA containing mutations may range between 1% and 99%

Table 1 Mitochondrial cytopathies resulting from mtDNA and nDNA mutations

Gene	Mutation	Mitochondrial OXPHOS complex defect	Renal function	Tubulopathy	Other clinical features	Reference(s)
mtDNA mutations						
MT-TF	m.591C>T	IV ↓	↓	Gitelman	NA	17
MT-TF	m.616T>C	NR	↓/↔	Gitelman	NA	17
MT-TF	m.643A>G	IV ↓	↓	Gitelman	NA	17
MT-TI	m.4291T>C	IV ↓	↔	Gitelman	NA	17
MT-TK	m.8344A>G	I ↓ + IV ↓	↔	Fanconi ± SIADH	MERRF	74, 75
MT-TL1	m.3243A>G	IV ↓	NR	Fanconi	MELAS	76
MT-ND5	m.13513G>A	I ↓	NR	Fanconi ± SIADH	LS	73
nDNA mutations						
BCS1L	Multiple	III ↓	↔/↓	Fanconi	GRACILE	19, 120, 121
C10orf2	c.1183T>C	↔	↔	Fanconi	Neurodegeneration	122
COQ9	c.730C>T	II ↓ + III ↓	↔	Fanconi	NA	119
COX10	Multiple	IV ↓	NR	Fanconi?	LS	237, 238
MRPS22	c.509G>A	I ↓ III ↓ IV ↓	NR	Unspecified	Cardiomyopathy	239
NDUFAF2	c.114C>G	I ↓ III ↓	NR	Fanconi	LS	125
RRM2B	c.850 C>T	I ↓ III ↓ IV ↓	NR	Fanconi	Neurodegeneration	123
SARS2	c.1169A>G	NA	↓	Gitelman	HUPRA	20, 183
TARS2	Multiple	I ↓ III ↓ IV ↓	↔	Bartter	Encephalomyopathy	240
TMEM70	c.317–2A>G	NR	NR	Fanconi	Encephalocardiomyopathy	126
SUCLA2	c.534+1G>A	NR	NR	Fanconi	LS	124
SUCLG1	c.40A>T	NR	NR	Fanconi?	Hepatoencephalomyopathy	241
SURF1	Multiple	IV ↓	↔	Fanconi	LS	127
UQCC2	c.214–3C>G	III ↓	↔	Fanconi	Growth retardation	128

↓ indicates a reduction in OXPHOS complex activity or renal function in patients with the mutation versus healthy controls, and ↔ indicates no change in OXPHOS complex activity or renal function in patients with the mutation versus healthy controls. Abbreviations: GRACILE, growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death; HUPRA, hyperuricemia-pulmonary hypertension-renal failure-alkalosis syndrome; KSS, Kearns-Sayre syndrome; LS, Leigh syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; mtDNA, mitochondrial DNA; NA, not applicable; nDNA, nuclear DNA; NR, not reported (not evaluated in the patients carrying the mutation); OXPHOS, oxidative phosphorylation; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Electrolytes in Mitochondrial Physiology

Many micronutrients required for human physiology are found in mitochondria and are expected to function in metabolism, since deficiencies have been associated with increased ROS production, redox imbalance, and mitochondrial decay. In addition, supplementation was shown to contribute to mitochondrial health and vitality (86–89). The interest in electrolyte homeostasis in

Table 2 Mitochondrial cytopathies caused by mtDNA deletions

Number of cases	Mitochondrial OXPHOS complex defect	Renal function	Tubulopathy	Other clinical features	References
20+	Multiple	↔/↓	Fanconi	KSS, Pearson	114–118
4	↔?	↔	Bartter	KSS	129, 181, 182, 234
2	I ↓ + IV ↓	↔	Gitelman	KSS	235, 236

A ↓ indicates a reduction in OXPHOS complex activity or renal function in patients with the mutation versus healthy controls, and ↔ indicates no change in OXPHOS complex activity or renal function in patients with the mutation versus healthy controls. Abbreviations: KSS, Kearns-Sayre syndrome; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation.

mitochondria has grown in recent years as several reviews have explored electrolyte regulation in the mitochondrion, including sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), and more (87, 89–92). Na^+, for example, maintains mitochondrial volume, membrane polarization, and Ca^{2+} and H^+ levels (87, 93, 94), while K^+ is also involved in regulating levels of oxidative stress (87, 95–97). Moreover, many proteins such as mitochondrial pyruvate kinase require binding to monovalent cations, including K^+, for optimal function (87, 98). Ca^{2+} and Mg^{2+} are essential in mitochondrial physiology as many enzymes and proteins located inside mitochondria (TCA enzymes such as isocitrate dehydrogenase) require these ions for their activity (99). Ca^{2+} has important roles in many homeostatic processes as it stimulates ATP production, alters mitochondrial dynamics, regulates energetics, and triggers apoptosis when levels are persistently high via activation of the mitochondrial permeability transition pore (100, 101). Similarly, Mg^{2+} has a prominent function in mitochondrial physiology. Bound to ATP, it acts as a cofactor for or regulator of enzymes or proteins such as oxoglutarate dehydrogenase, pyruvate kinase, hexokinase, and subunits of OXPHOS. In addition, Mg^{2+} is important for structural balance and charge neutralization when bound to membranes, proteins, or other molecules. A major part of cellular Mg^{2+} locates to mitochondria for its function. Mg^{2+} deficiencies are therefore expected to result in oxidative stress, ATP depletion, disruption of mitochondrial membrane potential, and overall mitochondrial dysfunction (87, 102, 103). Thus, precise regulation of these and other electrolyte levels is key for maintaining mitochondrial and, consequently, renal cellular function.

MITOCHONDRIAL FUNCTION IN THE PROXIMAL TUBULE

Energy Metabolism

The PT is responsible for 60–70% of the tubular reabsorption of Na^+, K^+, and chloride (Cl^-) and solely responsible for reabsorption of glucose, amino acids, and small proteins (104). Consequently, the PT has a high energy demand to facilitate these transport processes. Although paracellular transport accounts for a significant part of the ion transport, approximately 25% of the ion transport and all of the glucose transport is transcellular secondary active transport, dependent on the activity of the Na^+-K^+-ATPase (104).

In healthy conditions, β-oxidation of fatty acids by peroxisomes and mitochondria provides the main energy source of the high-energy-requiring PT cells (105–109). Glycolysis barely contributes to ATP production under physiological conditions, as rate-limiting enzymes of glycolysis are poorly expressed in the PT (44). The use of fatty acids as an energy source has multiple advantages: (*a*) Energy metabolism does not interfere with glucose reabsorption in the PT,

(*b*) glucose remains available for medullary tubular segments that face low oxygen availability, and (*c*) it even allows for the generation of glucose by gluconeogenesis. Especially in fasting conditions, renal gluconeogenesis is essential for the maintenance of systemic glucose homeostasis. It has been estimated that the kidney is responsible for 40% of endogenous glucose production during the postprandial period (110). An alternative energy source for PT cells is glutamine, which also provides the basis for gluconeogenesis and ammoniagenesis in the PT (111, 112).

Autophagy: a cellular process of degrading dysfunctional or redundant molecules, proteins, and organelles via lysosome-dependent pathways

The energy metabolism in PT cells undergoes significant reprogramming under pathological conditions. Mitochondrial dysfunction in the PT is therefore a key factor in the progression of DKD and AKI. The roles of mitochondria in DKD and AKI have been reviewed elsewhere (8, 9).

Proximal Tubular Dysfunction in Mitochondrial Cytopathies

Mitochondrial cytopathies are characterized by genetic heterogeneity as well as variability in the clinical presentations (113). Fanconi syndrome is a common feature of mitochondrial dysfunction (**Table 1**) and is a widely known inherited or acquired defect of the PT, preventing the absorption of electrolytes and other substances that are normally reabsorbed by this nephron segment. Consequently, Fanconi patients present with proteinuria, hypophosphatemia, glycosuria, and renal tubular acidosis. A recent screening of renal biopsies of patients with mitochondrial cytopathies demonstrated dysmorphic mitochondria in approximately 35% of the tubular cells (82). Although this report did not specify the exact cell type, renal biopsies are taken from the cortex, which largely represents PT cells. Mitochondrial cytopathies comprise genetic defects in mtDNA and nDNA. Fanconi syndrome has been linked to more than 10 genes on both the mtDNA and nDNA (19, 73–76, 114–128) (**Table 1**). However, a clear genotype-phenotype correlation between the Fanconi phenotype and certain genes or mutations has not been established to date. A Fanconi phenotype is repeatedly reported in mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome, but this may just reflect the high prevalence of this disorder compared to other mitochondrial cytopathies (82). A recent screening of 81 patients only identified a Fanconi phenotype in 10% of the cases (82). PT dysfunction is relatively common in mtDNA deletions associated with Kearns-Sayre syndrome (KSS) and Pearson's marrow-pancreas syndrome (115–118, 129). Although the exact mtDNA deletion varies among patients, the deleted region often includes the mitochondrial rRNAs and the MT-ND1 and MT-ND2 subunits of OXPHOS complex I (115–118, 129). To date, the penetrance of Fanconi syndrome in this population and the mechanistic and functional consequences on PT function have never been systematically investigated.

It is tempting to speculate that ATP deficiency is the underlying molecular cause of Fanconi syndrome. Reduced ATP production would inevitably result in low Na^+-K^+-ATPase activity and, consequently, reduced transcellular transport processes of glucose, amino acids, and electrolytes. However, other mechanisms, such as oxidative stress or disturbed autophagy, cannot be excluded. Further elucidation of these mechanisms may be important to understand the low penetrance of Fanconi syndrome in mitochondrial cytopathies and identify targets for treatment.

Mitochondrial Dysfunction in Proximal Tubulopathies

Mitochondrial dysfunction is a common consequence of impaired lysosomal function, observed in nephropathic cystinosis or Dent's disease. In cystinosis, rare inherited mutations in the *CTNS* gene result in impaired cystine transport out of the lysosome (130, 131). Dent's disease is caused by mutations in the *CLCN5* gene and is characterized by impaired lysosomal acidification due to defects in Cl^- transport into the endosomes and lysosomes (132, 133). Patients with nephropathic cystinosis or Dent's disease present with a Fanconi syndrome phenotype consisting of polyuria, glycosuria, phosphaturia, and proteinuria (134).

In these PT disorders, the lysosomal proteolysis is disturbed, resulting in defects in catabolic degradation of proteins and organelles. As a consequence, the PT cells cannot perform autophagy for degradation of macromolecules in cases of energy stress. In renal PT epithelial cells of patients with nephropathic cystinosis, increased levels of autophagosomes were detected, accompanied by higher microtubule-associated protein light chain 3 II (LC3-II) over LC3-I expression, which is indicative of defective autophagy (135). The autophagy-lysosome pathway is of particular importance for the breakdown of dysfunctional mitochondria. Indeed, morphologically abnormal mitochondria have been detected in cystinosis (135). Consequently, the damaged mitochondria will remain in the PT cells, resulting in oxidative stress, reduced ATP levels, and impaired epithelial barrier and transport function (136) (**Figure 2**). Oxidative stress has also been observed in *Ctns*$^{-/-}$ mouse models, and disease progression could be delayed by antioxidant therapy (137). Several groups have demonstrated that cystinotic cells contain lower ATP levels (135, 138, 139), which may be explained by reduced complex I and V activities and a disturbed mitochondrial membrane potential (138). It should be noted, however, that complex I–V function was normal in fibroblasts from patients with nephropathic cystinosis, suggesting that these defects predominantly occur in the kidney (139). Other mitochondrial defects in cystinosis include impaired fission-fusion and lower cyclic AMP (cAMP) levels, resulting in adjusted organelle shape and number in cells and defective cytoplasm-mitochondrion cross talk, respectively (138, 140). Treatment with cysteamine or bicalutamide-cysteamine improves these mitochondrial defects (138, 141). The mitochondrial involvement in Dent's disease has been less studied. However, as oxidative stress is increased in a mouse model of Dent's disease (142), defects in autophagy and mitochondrial breakdown similar to cystinosis can be anticipated (143).

MITOCHONDRIAL FUNCTION IN THE THICK ASCENDING LIMB

Energy Metabolism

The TAL is responsible for 25% of the Na^+, K^+, and Cl^- reabsorption mostly via the Na^+-K^+-Cl^--cotransporter 2 (NKCC2) (144). As this transport is largely transcellular, the energy requirement of TAL cells is almost similar to that of PT cells (104). However, the mitochondrial density and the delivery of oxygen in the TAL is significantly lower than in the PT. Consequently, the TAL cells depend on glucose in addition to fatty acids as their preferred energy source (105–107). In particular, in the medullary TAL, a region with low oxygen supply, anaerobic glycolysis has been reported based on single-cell RNA sequencing and studies in isolated tubules (105, 145).

Loop of Henle Dysfunction in Mitochondrial Cytopathies

In mitochondrial cytopathies, disturbed ion reabsorption in the TAL is scarce. In a case of mitochondriopathy with sensorineural blindness of unknown genetic origin, signs of Bartter syndrome such as hypokalemic metabolic alkalosis and volume depletion were reported (146). However, this patient may also have diminished DCT function, as the presence of severe hypomagnesemia in this patient points toward Gitelman syndrome rather than Bartter syndrome (146). Notably, combined TAL/DCT phenotypes with mixed features of Bartter and Gitelman syndrome are observed in patients with loss-of-function mutations in chloride voltage-gated channel Kb (*CLCNKB*) and Ras-related GTP binding D (*RRAGD*) (147, 148).

The low prevalence of TAL dysfunction in mitochondrial cytopathies may be explained by the lower number of mitochondria in this segment compared to the PT and DCT. Nevertheless, in an animal model of obstructive nephropathy, inhibition of mitochondrial complex-1 prevented the downregulation of NKCC2, suggesting that mitochondrial function can regulate NKCC2 (149). Indeed, it has been repeatedly demonstrated that oxidative stress stimulates NKCC2

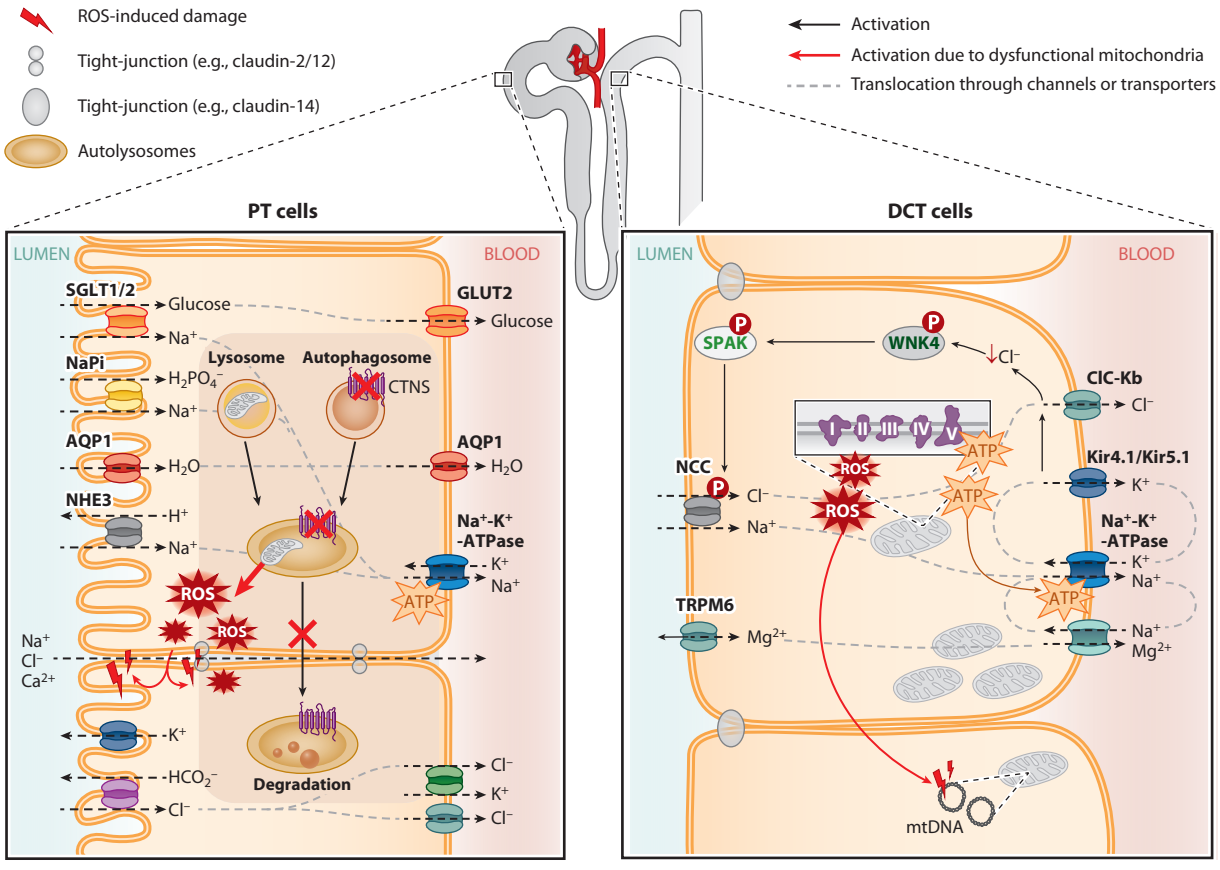


Figure 2

Schematic overview of dysfunctional mitochondria and consequent effects in a PT (*left*) and DCT (*right*). In the PT and, in particular, nephropathic cystinotic PT cells, inherited mutations in the *CTNS* gene impair cystine transport out of lysosomes, resulting in disturbed lysosomal proteolysis and defects in catabolic degradation of proteins and organelles. As a consequence, dysfunctional mitochondria are not degraded and remain in PT cells, resulting in oxidative stress, reduced ATP levels, and impairments in the epithelial barrier and potentially the transport function of glucose, water, and electrolytes. In the DCT, ATP generated by mitochondria is required for Na^+-K^+-ATPase activity. Extracellular K^+ determines basolateral K^+ efflux via Kir4.1/Kir5.1 channels. When K^+ is low, the basolateral membrane is hyperpolarized, leading to Cl^- efflux via ClC-Kb. Low-Cl^--induced WNK4 and SPAK, in turn, phosphorylate and activate the NCC. Dysfunctional mitochondria disturb this pathway and thus NCC activity, as hyperpolarization of the basolateral membrane depends on Na^+-K^+-ATPase activity fueled by mitochondrial ATP. Abbreviations: AQP1, aquaporin 1; ATP, adenosine triphosphate; ClC-Kb, voltage-gated Cl^- channel Kb; CTNS, cystinosin; DCT, distal convoluted tubule; GLUT2, glucose transporter; Kir, inward rectifier-type K^+ channel; mtDNA, mitochondrial DNA; NaPi, Na^+, phosphate cotransporter; NCC, Na^+, Cl^- cotransporter; NHE3, Na^+, H^+ exchanger; OSR1, oxidative stress–responsive kinase; PT, proximal tubule; ROS, reactive oxygen species; SGLT1/2, Na^+, glucose cotransporter; SPAK, Ste20-like proline-alanine-rich kinase; TRPM6, transient receptor potential melastatin type 6; WNK4, with-no-lysine 4 kinase.

phosphorylation to maintain volume and ion homeostasis in a mechanism dependent on Ste20-like proline-alanine-rich kinase (SPAK) and oxidative stress–responsive 1 (OSR1) kinase (150, 151).

Mitochondrial Dysfunction in Thick Ascending Limb Tubulopathies

Little is known about the role of mitochondria in other TAL disorders. In autosomal-dominant tubulointerstitial kidney disease due to mutations in uromodulin (ADTKD-UMOD), TAL cells

showed a decreased number of mitochondria and mitochondrial proteins (152). In this study, the LKB1-AMPK pathway was activated, indicating low intracellular ATP levels and reduced energy availability (152). Whether these mitochondrial defects are only secondary to tubulointerstitial fibrosis or whether they contribute to the development and progression of ADTKD-UMOD remains to be examined.

MITOCHONDRIAL FUNCTION IN THE DISTAL CONVOLUTED TUBULE

Energy Metabolism

The DCT regulates the active transcellular reabsorption of approximately 5–10% of the filtered load of Na^+, Ca^{2+}, Cl^-, and Mg^{2+} (153–155). DCT cells quickly respond to the demands of the body in a highly regulated manner. The ability to extensively amplify their basolateral cell membrane simultaneously increases the transport capacity via the expression of Na^+-K^+-ATPase. The DCT is known for having the highest Na^+-K^+-ATPase activity of any nephron segment (156). These transport processes are energy demanding, and mitochondria are abundantly present in these cells (157). While the PT mainly oxidizes fatty acids to fuel cellular function and has a significant role in the production of glucose, cells of the DCT utilize glucose as metabolic fuel, which is reflected by high glycolytic enzyme expression of hexokinase, pyruvate kinase, and phosphofructokinase (44, 158). Studies using multiphoton imaging indeed revealed a reduced oxidative state of mitochondria in the DCT compared to PT in rat based on several observations: (*a*) Mitochondria in the distal part of the nephron better maintain the higher membrane potential upon inhibition of oxidative respiration, (*b*) there are reduced levels of ROS, and (*c*) there is lower expression of the endogenous inhibitor of mitochondrial ATPase (IF1) (34).

In the DCT, Na^+ and Cl^- are reabsorbed via the apically expressed thiazide-sensitive Na^+, Cl^- cotransporter (NCC) (159). The activity of NCC is determined by its phosphorylation state and regulated by a complex regulatory mechanism, termed the K^+ switch (160). In short, the extracellular K^+ concentration determined the basolateral K^+ efflux via inward rectifier-type K^+ (Kir)4.1/Kir5.1 channels. In low K^+ conditions, the membrane is hyperpolarized, resulting in basolateral Cl^- efflux via the voltage-gated Cl^- channel Kb (ClC-Kb). This mechanism relieves the Cl^--dependent autophosphorylation of with-no-lysine (WNK). SPAK is considered the dominant kinase that phosphorylates NCC in response to WNK activation (161). This pathway is dependent on mitochondrial function on multiple levels. First, the hyperpolarization of the basolateral membrane requires activity of the Na^+-K^+-ATPase for increased levels of Na^+ transport. Since Na^+-K^+-ATPase is fueled by mitochondrial ATP, a high density of mitochondria is necessary to sustain its activity. The DCT transports 5–10% of the filtered ion load in a 500-μm length of tubule, compared to 66% of filtered load transport in 5 mm of PT; therefore, each DCT cell transports approximately 50% more Na^+ per cell. Considering the low Na^+ in DCT tubular fluid, Na^+ reabsorption is more costly as it must be transported against a steeper gradient (162). Second, NCC, OSR1, and Kir4.1/Kir5.1 are activated by oxidative stress pathways, explaining why oxidative stress is associated with hypertension. This may be of particular relevance in the context of renin-angiotensin-aldosterone system (RAAS) activation, since angiotensin II induces mitochondrial ROS production (163), thereby stimulating Kir4.1/Kir5.1, OSR1, and NCC activity.

Ten percent of the filtered Mg^{2+} load is reabsorbed in the DCT via transient receptor potential melastatin type 6 (TRPM6) divalent cation channels (164, 165). TRPM6 activity is highly regulated by cAMP, epidermal growth factor (EGF), insulin, and pH (166–168). Basolateral Mg^{2+} extrusion is Na^+ dependent, with cyclin M2 (CNNM2) and/or solute carrier family 41 member 3

(SLC41A3) as putative transporters (169, 170). As such, transcellular Mg^{2+} reabsorption is a secondary active process depending on the Na^+ gradient set by the Na^+-K^+-ATPase, and it is thus dependent on mitochondrial activity. Moreover, oxidative stress inhibits TRPM6 expression and activity (171, 172). Renal Mg^{2+} reabsorption is significantly impaired in type 2 diabetes, resulting in renal Mg^{2+} wasting and hypomagnesemia (173, 174). Although the exact mechanisms are unknown, animal studies using high-fat and low-Mg^{2+} diets have demonstrated impaired tubular metabolism and phospholipid deposition (175, 176). As mitochondrial dysfunction is a hallmark of type 2 diabetes, it would be of interest to know whether mitochondrial dysfunction in the DCT can explain the renal Mg^{2+} wasting.

In conclusion, ion reabsorption in the DCT is dependent on mitochondrial function and the prevention of oxidative stress. This may explain why drugs that target mitochondrial biogenesis have been associated with antihypertensive effects (67–70).

Distal Convoluted Tubule Dysfunction in Mitochondrial Cytopathies

Mitochondrial cytopathies are widely known for their heterogeneity. Multisystem disorders are common and affect renal tubules, such as KSS or Leigh syndrome (LS) (177–179). OXPHOS complex I–V activity measurements indicate that the Gitelman phenotype is associated with disturbed activity of complexes I and IV (**Table 1**). Indeed, complex IV inhibition with K^+ cyanide was demonstrated to reduce NCC activity (17). Moreover, mitochondria-derived oxidative stress–induced activation of the renin-angiotensin system has been reported to relate to increased NCC activity and thus regulation of DCT-specific NaCl reabsorption in albuminuria (50, 180). Mutations and large deletions in genes encoded by mtDNA (**Tables 1** and **2**) have been described to induce distal tubulopathies, such as Gitelman and Bartter syndrome (17, 181, 182). Specifically, mitochondrial tRNAs MT-TI and MT-TF and tRNA synthetases SARS2 and TARS cause DCT dysfunction, resulting in a clinical presentation of hypomagnesemia, hypokalemia, and hypocalciuria (20, 77, 183). The high mitochondrial density in the DCT, required to sustain ATP-dependent electrolyte transport, may explain this DCT-specific mtDNA genotype-phenotype relationship, but the connection is speculative. Although these mutations affect genes involved in mitochondrial translation, mitochondrial protein synthesis has never been examined. One patient with Gitelman syndrome features was additionally diagnosed with adrenocortical hormone (ACTH) deficiency, demonstrating the phenotypic variability of mitochondrial cytopathies (184).

Hypomagnesemia is a common renal manifestation of mitochondrial cytopathies (77, 185) and is often observed with hypoparathyroidism (177, 186–188), as Mg^{2+} affects the release of parathyroid hormone (PTH), resulting in low plasma Ca^{2+} and high levels of phosphate and a KSS-related phenotype, for example, renal tubular acidosis. Often, the variability of symptoms increases the complexity of collectively differentiating mitochondrial cytopathies from renal tubulopathies or other syndromes.

Mitochondrial Dysfunction in Distal Convoluted Tubule Tubulopathies

Gitelman syndrome is caused by mutations in *SLC12A3*, encoding NCC (159). Studies in $NCC^{-/-}$ mice have demonstrated a reduced number of mitochondria in the DCT (189). As renal biopsies are not commonly taken, it is unclear whether this finding translates to humans. However, animal studies indicate that the mitochondrial density is closely linked to the energy requirement of the DCT, showing changes in mitochondrial density and oxygen consumption rate in response to dietary Na^+ availability and diuretics (190–192).

Pathogenic variants in Cl^- channel ClC-Kb, K^+ channels Kir4.1/Kir5.1 (*KCNJ10/KCNJ16*), and Na^+-K^+-transporting ATPase subunits (*ATP1A1/FXYD2*) and their transcriptional regulator

sPCBD1/HNF1B result in a Gitelman-like phenotype (193–201). However, mitochondrial dysfunction in these syndromes has never been systematically investigated and requires further studies.

Mitochondrial cytopathy: a heterogeneous group of inherited or acquired mutations in mitochondrial DNA or nuclear DNA that encode proteins required for mitochondrial function

MITOCHONDRIAL FUNCTION IN THE COLLECTING DUCT

Energy Metabolism

The CD consists of principal cells (PCs) and intercalated cells (ICs). The PCs express aquaporin 2 (AQP2) for vasopressin-mediated water reabsorption and the epithelial Na^+ channel (ENaC) and renal outer medullary potassium channel (ROMK) for aldosterone-regulated Na^+ reabsorption and K^+ secretion. Water and electrolyte transport in the PCs is ultimately dependent on the Na^+/K^+-ATPase. By contrast, the alpha ICs secrete H^+ via the apical membrane–localized H^+ and H^+/ATPases (202). Beta ICs secrete HCO_3^- via the apical localized Cl^-/HCO_3^- exchanger pendrin (203). Acid-base transport in ICs is driven by H^+/ATPase activity rather than the Na^+/K^+-ATPase (204). The CD mainly uses glucose as an energy source, especially in the inner medulla. Consequently, the expression of glycolytic enzymes is high (2, 44). However, compared to the PCs, expression of mitochondrial enzymes in ICs is higher, which is also reflected in the higher mitochondrial density in ICs (205–210). Nevertheless, mitochondria in those cells have low ATP synthase (OXPHOS complex V) expression, and in contrast, high anaerobic glycolytic capacity and lactate production and high expression of glucose transporters, which seems key for apical V-ATPase-mediated acidification of urine (3, 211–214). Given these observations, the exact nature of mitochondrial metabolism in ICs remains poorly understood.

Mitochondria regulate tubular Na^+ transport in the CD via ENaC (215, 216). In addition to that, ENaC activity and corresponding Na^+ transport are widely described as being (partially) ROS regulated via RAAS (50, 217–219). Dysfunctional mitochondria (e.g., overproduction of ROS) may therefore lead to disturbed RAAS-mediated regulation of ENaC.

Collecting Duct Dysfunction in Mitochondrial Cytopathies

To date, little is known about CD dysfunction in mitochondrial cytopathies. The high anaerobic capacity of this part of the nephron may contribute to ATP maintenance in response to inhibition of aerobic metabolism, and as such, this segment may be less susceptible to mitochondrial dysfunction compared to other parts of the nephron (106). Indeed, evaluation of OXPHOS respiratory capacity in a renal biopsy of a case of Bartter-like syndrome in a child with KSS revealed that different sections of the nephron varied in OXPHOS activity without affecting the CD (182). In contrast, a recent case reported the presence of granular swollen epithelial cells, previously reported as specific to a mitochondrial cytopathy, in the medullary CD epithelium of an individual with maternally inherited diabetes and deafness, a mitochondrial disorder caused by a m.3243A>G mutation and characterized by hearing impairment and type 2 diabetes mellitus (220). However, the case also presented with progressed renal damage (CKD), suggesting that the CD abnormality was a secondary effect.

Another described CD disorder is the syndrome of inappropriate antidiuretic hormone secretion, which is characterized and caused by a vasopressin-induced translocation of AQP2 channels to the CD plasma membrane, leading to increased water permeability (221). A case of LS with a m.13513G>A mutation in the ND5 subunit of OXPHOS complex I was reported and presented with hyponatremia as a result of Na^+ loss and inappropriate vasopressin secretion in addition to cardiomyopathy (73). Interestingly, an additional case of LS and inappropriate vasopressin secretion was described and genetically explained by a m.8344A>G mutation, more frequently

observed in mitochondrial myoclonic epilepsy with ragged-red fibers syndrome (74). Whether the phenotype is directly related to specific mitochondrial mutations remains to be elucidated.

Mitochondrial Dysfunction in Collecting Duct Tubulopathies

Nephrogenic diabetes insipidus (NDI) due to mutations in *AQP2* or arginine vasopressin receptor 2 is characterized by polyuria, polydipsia, and low urine osmolarity (222, 223). Early pathological reports demonstrate dysmorphic mitochondria along the kidney tubule, suggestive of mitochondrial dysfunction (224). Although a major role of mitochondria in the pathogenesis of NDI has never been demonstrated, damaged mitochondria and impaired autophagy were detected in a mouse model of hypokalemic NDI (225). Comparable disturbances in autophagy were reported in response to hypercalcemia (226), similar to cystinosis in the PT, and impaired mitophagy may thus be a feature of NDI.

Mutations in ENaC are known to induce Liddle's syndrome, characterized by hypertension, hyperkalemic metabolic alkalosis, hyporeninemia, and reduced aldosterone secretion (227). Nevertheless, no mitochondrial effects associated with Liddle's have been reported yet.

PERSPECTIVES

Defects in mitochondrial function are increasingly linked to renal tubulopathies. PT defects, with Fanconi syndrome in particular, seem to be the most frequent tubulopathies with mitochondrial cytopathy (193, 228), although Bartter-like and Gitelman-like syndromes and renal tubular acidosis have also been reported (229). A study in children with mitochondrial disease identified that almost half of the cases suffered from proximal tubulopathy, indicating that this renal manifestation is significantly underrated in multisystem mitochondrial cytopathies (228). The frequently observed PT defects and mitochondrial dysfunction may, although speculative, be explained by the limited anaerobic glycolytic capacity and accompanying dependency on aerobic metabolic activity for ATP production in the proximal part of the nephron (2, 230). Furthermore, specialized functions of the PT, such as receptor-mediated endocytosis, may increase vulnerability to mitochondrial disease (231). The mechanisms by which mitochondrial function impairs PT physiology are poorly described, as most experimental work has been executed in the context of DKD or AKI.

Some mitochondrial cytopathies present with electrolyte disorders, reminiscent of Bartter or Gitelman syndrome, which suggests the involvement of remaining tubular segments, including TAL and DCT, respectively. However, knowledge of these specific segments of the nephron in the context of disturbed mitochondrial function is limited, despite the high mitochondrial density in these cell types. Therefore, future research on disease mechanisms with particular focus on these segments is invaluable in order to understand disease onset and progression and improve current treatment possibilities.

In patients with mitochondrial cytopathies, renal symptoms may be subclinical or overshadowed by extrarenal symptoms, as previously described (228). Measurements of tubular function in patients suffering from mitochondrial disorders would thereby provide an important addition to the clinical workup of patients (228). Moreover, mitochondrial genetic and functional screening is often performed in nonrenal tissues such as blood or muscle. The heterogeneity and lack of convincing biomarkers hamper diagnosis. Conventional detection of serum lactate, especially in the context of renal disease, can result in normal levels due to increased loss in the urine, as described for Fanconi syndrome (232). Studying mitochondrial function in patient-derived kidney cells, such as urine-derived epithelial cells or kidney organoid models (193, 233), would provide an important step forward to elucidate the mechanisms of mitochondrial dysfunction in the kidney.

Although we advocate for the inclusion of mtDNA in the genetic screening of patients with hereditary tubulopathies, the clinical value of mitochondrial activity measurements in less clear. Mitochondrial dysfunction can be the primary cause of renal tubulopathies; however, it can also be secondary to another cause, for example, metabolic disease or drugs. Consequently, the interpretation of mitochondrial testing for diagnostic purposes can be challenging. Nevertheless, much remains to be learned, and further mitochondrial investigations are essential to identify the pathophysiological mechanisms of and links between mitochondrial cytopathies and renal tubulopathies.

FUTURE ISSUES

1. What is the prevalence of kidney tubulopathies in primary mitochondrial disorders?
2. Does reduced adenosine triphosphate production explain proximal tubule and distal convoluted tubule dysfunction caused by mitochondrial DNA mutations and deletions?
3. Oxidative stress regulates ion channels and transporter activity, but to what extent does it contribute to mitochondrial reactive oxygen species activity and specifically to ion reabsorption in renal tubules?
4. Can genotype-phenotype relationships be identified for specific mitochondrial gene mutations/deletions and renal tubulopathies?
5. Why do defects in genes associated with mitochondrial translation result in a Gitelman-like phenotype?
6. Are mitochondrial function and mitochondrial dynamics therapeutic targets for renal tubulopathies?

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