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From Rare Disorders of Kidney Tubules to Acute Renal Injury: Progress and Prospective

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Keywords
Rare tubulointerstitial diseases · Acute kidney injury · Mitochondrial disorder

Abstract
Background: Acute kidney injury (AKI) is a severe condition marked by rapid renal function deterioration and elevated mortality, with traditional biomarkers lacking sensitivity and specificity. Rare tubulointerstitial diseases encompass a spectrum of disorders, primarily including monogenic diseases, immune-related conditions, and drug-induced tubulointerstitial diseases. The clinical manifestations vary from electrolyte and acid-base imbalances to kidney function insufficiency, which is associated with AKI in up to 20% of cases. Evidence indicated that rare tubulointerstitial diseases might provide new conceptual insights and perspectives for novel biomarkers and potential therapeutic strategies for AKI. ***Summary:*** Autosomal dominant tubulointerstitial kidney disease (ADTKD) and Fanconi syndrome (FS) are rare tubulointerstitial diseases. In ADTKD, UMOD and REN are closely related to AKI by affecting oxidative stress and tubuloglomerular feedback, which provide potential new biomarkers for AKI. Both rare tubulointerstitial diseases and AKI share etiologies and treatment responses. From the mechanism standpoint, rare tubulointerstitial diseases and AKI involve tubular transporter injury, initially manifesting as tubular dysfunction in tubulointerstitial disorder and progressing to AKI because of the programmed cell death with apoptosis, pyroptosis, or necroptosis of proximal tubule cells. Additionally, mitochondrial dysfunction has been identified as a common mechanism in both tubulointerstitial diseases and AKI induced by drugs, pSS, or monoclonal diseases. In the end, both AKI and FS patients and animal models responded well to the therapy of the primary diseases. ***Key Messages:*** In this review, we describe an overview of ADTKD and FS to identify their associations with AKI. Mitochondrial dysfunction contributes to rare tubulointerstitial diseases and AKI, which might provide a potential therapeutic target.

Introduction

Acute kidney injury (AKI) is a critical condition characterized by rapid renal function decline associated with increased mortality rates, longer in-hospital stays,

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and higher medical costs. The mortality rate ranges from 10% to 20% for hospitalized patients and 44.7–53% for ICU patients [1], caused by various factors such as sepsis, trauma, cardiac surgery, nephrotoxic drugs, and underlying chronic kidney disease. However, traditional biomarkers such as serum creatinine, blood urea nitrogen, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1 (KIM-1) are limited in terms of sensitivity and specificity due to factors like age, gender, muscle mass, and hydration status, which presents a challenge for the development of effective treatments for AKI [2]. Experiences from bedside and animal studies indicated the intensive correction between AKI and tubular dysfunction, injury, or programmed death. It pushed us to learn more about tubular and interstitial pathophysiological mechanisms, while the precise medicine from rare genetic tubule disease opened this window.

Rare tubulointerstitial diseases mainly result from mutations in genes encoding transporter proteins in the renal tubule, which primarily affect electrolyte homeostasis and acid-base balance, leading to hypokalemia, hypomagnesemia, renal glucosuria, and renal tubular acidosis (RTA), with three categories according to the location of the affected transporters, including the proximal tubule, thick ascending limb (TAL), distal convoluted tubule (DCT), and collecting duct. Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a newly recognized group of rare diseases with progressive renal dysfunction. Regarding the pathological types of AKI, approximately 20% patients present as acute tubular/tubulointerstitial nephropathy-associated AKI (ATIN-AKI), with more severe stages of AKI [3]. Therefore, in-depth knowledge of rare tubulointerstitial diseases provides new conceptual and perspective clues for novel biomarkers and potential therapeutic strategies for AKI.

In this review, we focus on the current knowledge regarding the associations between AKI and rare tubulointerstitial kidney disease to identify the mitochondrial mechanism for potential biomarkers and therapeutic targets of AKI.

ADTKDs and AKI

ADTKD is a rare kidney disease characterized by mild urinary concentrating defect and progressive tubulointerstitial renal damage associated with inflammatory cell infiltrate and interstitial fibrosis without glomerular lesions, leading to end-stage renal disease (ESRD). ADTKD is a monogenic kidney disease with mutations in different genes, including UMOD, MUC1, REN, HNF1B, and SEC61A1. Table 1 shows the characteristics of ADTKD reported recently. Among these genes, ADTKD-UMOD and ADTKD-REN are closely associated and provide potential biomarkers for AKI.

ADTKD-UMOD and AKI

ADTKD-UMOD is the most frequent form of ADTKD caused by missense mutations in the UMOD gene, resulting in the retention and accumulation of abnormal uromodulin protein within the endoplasmic reticulum (ER), initiating ER stress and the unfolded protein response, leading to inflammation and cell death ultimately [14]. This accumulation not only induces defective autophagy, protein homeostasis, and mitochondrial dysfunction in TAL cells [15] but also disrupts the trafficking of the mutant protein to the plasma membrane and its secretion into the culture medium [16], contributing to significantly decreased urinary uromodulin in ADTKD-UMOD patients. Individuals with ADTKD-UMOD develop tubulointerstitial fibrosis with inflammatory cell infiltration and tubular dilation, characterized as urinary concentrating defects, a slow and progressive increase in serum creatinine, and eventually progressing to ESRD. Hyperuricemia and gout are present in more than 50% of patients in their teenage and typically precede the onset of chronic kidney disease and AKI in a few patients [17].

The gene UMOD encodes uromodulin (well known as Tamm-Horsfall glycoprotein), the most abundant protein in normal human urine. Uromodulin is exclusively produced by epithelial cells in the TAL and DCT of the nephron, with a daily secretion of 50–150 mg in urine [18], approximately 1,000 times higher than in serum [19]. Uromodulin is a glycoprotein comprising four epidermal growth factor-like domains, a cysteine-rich domain of unclear function (D8C), and a bipartite elastase-resistant C-terminal Zona Pellucida (ZP) domain [20]. The cryo-electron microscopy structure of uromodulin appears as a filamentous core responsible for bacterial aggregation and preventing adherence to the urinary tract, thereby exerting a protective role against urinary tract infections [21, 22]. Uromodulin expression is positively correlated with solute carrier family 12 member 1 (NKCC2), solute carrier family 12 member 3 (NCC), and renal outer medullary potassium channel (ROMK) transporters in the TAL and DCT segments [23]. In UMOD knockout mice, the activity of NKCC2 was decreased, resulting in urinary concentrating defects under water deprivation [24]. Furthermore, studies in the population have confirmed the association between

Table 1. Autosomal dominant tubulointerstitial kidney disease affected proteins and acute renal injury

	Affected gene	Protein	Effect of protein on AKI	Possible pathophysiology
ADTKD-UMOD	UMOD	Uromodulin	Protective	Uromodulin inhibits the chemokine signal and reduces damage to neighboring proximal tubule cells during AKI [4] Uromodulin determines renal mononuclear phagocytes (MPCs) abundance and polarization to M2 healing type macrophages during AKI [5]
ADTKD-MUC1	MUC1	Mucin 1	Protective	Mucin 1 enhances HIF-1 and β-catenin protective pathway [6, 7] Mucin 1 mitigates the renal inflammatory response to TLR4 activation and reduces M1-type macrophages [8]
ADTKD-HNF1B	HNF1B	Hepatocyte nuclear factor 1β	Unclear	HNF1β may ameliorate cisplatin-induced AKI by regulating the NF-κB signaling pathway [9] Inhibition of HNF1β leads to mitochondrial disorders Resulting in a lower production of reactive oxygen species which gives a protective phenotype to epithelial cells [10] Precluding further adaptation to ATP depletion following AKI [11]
ADTKD-REN	REN	Preprorenin	Unclear	Inhibition of renin ameliorated ischemia-reperfusion (I/R) induced renal injury through decreasing nitric oxide and AT-2 levels [12]
ADTKD-SEC61A1	SEC61A1	α1 subunit of SEC61	Unclear	SEC61 mutation alters post-translational modifications, folding, and sorting of various secretory and transmembrane proteins (including uromodulin, mucin 1, and renin) [13]

ADTKD, autosomal dominant tubulointerstitial kidney disease; AKI, acute kidney injury.

UMOD gene SNPs and hypertension risk [25, 26]. Our previous study based on Mendelian randomization has corroborated that elevated levels of urinary and serum uromodulin may be harmful to hypertension, serving as a causal risk factor for hypertension [27], potentially mediated by the estimated glomerular filtration rate (eGFR) [28].

Experiments from patients and animal studies proved the predictive value of urine UMOD in assessing the morbidity of AKI. Our previous study confirmed a negative correlation between uUMOD and AKI, particularly in pediatric and surgical patients [29]. Additionally, another study has confirmed the crucial role of circulating uromodulin in regulating systemic oxidative stress by inhibiting transient receptor potential cation channel, subfamily M, member 2 (TRPM2) activity in IRI-induced AKI [30]. Given the insufficient research on uromodulin and AKI, further investigations are needed to elucidate the underlying mechanisms and determine the potential value of uUMOD as a predictor of AKI.

Given the current acknowledgment of rare diseases lacking extensive cohort studies, it is insufficient to rely on a few case reports to ascertain the incidence of AKI in ADTKD-UMOD and ADTKD-REN. Hence, we would like to share a case from our hospital involving a 32-year-old female patient diagnosed with ADTKD-UMOD. This patient experienced an acute exacerbation of chronic interstitial nephritis, attributed to a COVID-19 infection. These findings imply that individuals with ADTKD may exhibit heightened vulnerability and sensitivity to external insults, thus warranting increased attention from clinicians.

ADTKD-REN and AKI

ADTKD-REN is a rare disease resulting from lower renin levels and an accumulation of mutated renin protein deposited in the ER and Golgi, which impairs the secretion of renin and prorenin by juxtaglomerular cells [31]. The low renin levels induced a decrease in eGFR associated with tubuloglomerular feedback (TGF). The clinical manifestations are childhood-onset anemia, hyperuricemia, gout, mild hypertension, hyperkalemia, and renal function insufficiency [32].

The gene REN encodes preprorenin, a precursor of prorenin and renin synthesized and secreted by the

juxtaglomerular cells, a specialized vascular smooth muscle cells in the afferent arterioles. The renin-angiotension-aldosterone system plays various roles in nephrogenesis, blood pressure control, erythropoiesis production, and TGF regulation. The macula densa-based TGF is a critical regulator of eGFR, which relies on adenosine 5′-triphosphate (ATP) and adenosine. Upon detection of an increase in sodium chloride concentration in the tubule fluid, the macula densa stimulates ATP hydrolysis to adenosine, leading to the contraction of afferent arterioles and reduced renin secretion by juxtaglomerular cells, resulting in dilation of efferent arterioles and a subsequent reduction in GFR [33]. It constitutes a crucial pathophysiological mechanism underlying drug-induced AKI, including renin-angiotensin system inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and cyclosporine, leading to the hemodynamic disorder of glomeruli.

Our previous studies have indicated the crosstalk between the renin-controlled angiotensin II (AngII) and the second messenger cAMP of TGF, which plays a critical role in the poor renal function of individuals with AKI [34]. Furthermore, a recent study also demonstrated a synergistic effect between the fibroblast growth factor 2 (FGF2)-FGF binding protein 1 (FGFBP1) axis and AngII in inducing vasoconstriction in both the kidney and cerebral vessels during AKI [35]. It revealed the potential regulatory crosstalk between the cAMP-adenosine and FGF2-FGFBP1 signaling pathways to control renin-dependent TGF in afferent arterioles. The detailed mechanism underlying this phenomenon warrants further investigation.

Fanconi Syndrome and AKI

Fanconi syndrome (FS) is a collection of inherited and acquired proximal convoluted tubule (PCT) alterations that impair PCT reabsorption, characterized by normoglycemic glycosuria, hyperphosphaturia, hypophosphatemia, aminoaciduria, hypouricemia, and proximal RTA [36] (Table 2; Table 3). PCT is responsible for about 65% of the filtration load and is crucial in regulating homeostasis [37]. As shown in Figure 1, there are a variety of substances reabsorbed by Na^+-H^+ exchanger (NHE3), Na^+/phosphate cotransporter (NaPi), Na^+/glucose cotransporter (SGLT2 or SGLT1), Na^+/amino acid cotransporters at the apical membrane, glucose transporters (GLUT1 and GLUT2), and Na^+-K^+-ATPase pump located at the basolateral side [38]. The function of the transporters is also regulated by different mechanisms, for example, the Na^+-H^+ exchanger regulatory factor 1 (NHERF-1) [39] and angiotensin II [40]-mediated modulation of NHE3 activity.

Immune-Related FS: Co-Occurrence with AKI

Both inherited and acquired FS share common pathogenic mechanisms and the response to primary disease therapies, including transporter or mitochondrial disorder by drug-induced nephrotoxicity, monoclonal gammopathies, autoimmune diseases, and heavy metal exposure (Fig. 2). Monoclonal immunoglobulin (Ig) light chain associated FS (LC-FS) was secondary to multiple myeloma [49], leukemia [50], lymphoma [51], and other monoclonal light chain deposition diseases [52–54], with the accumulation of Ig light chains in the renal tubules resulting in faulty endocytosis and proteolysis processes, reabsorption dysfunction of PCT cells, and even decreased eGFR. As a rare disease, LC-FS was reported in less than 200 cases with different degrees of proximal tubular (PT) lesions and impaired renal function, accompanied by AKI in 20% of patients [49, 55, 56]. Our previous study included 26 Chinese LC-FS patients with mild renal function impairment and varying degrees of PTC dysfunction [53]. The causes of monoclonal gammopathy-induced AKI are often multifactorial, involving pre-renal hypovolemia, proliferative glomerulonephritis with monoclonal Ig deposits, acute tubular necrosis, and hypercalcemia [57]. The chemotherapy has been confirmed to improve both GFR and tubular functions [49, 52], potentially related to the hematological response [53].

Sjogren's syndrome (pSS) is the most common autoimmune cause of FS, with 10–42% PT dysfunction in pSS-renal patients [58]. In our 25 FS patients with pSS (pSS-FS), young-onset pSS-FS patients had a higher prevalence of positive anti-SSB antibody and hypocomplementemia, with more severe hypokalemia and better eGFR levels [59]. Consistent with other inherited FS, decreased expression of megalin and cubilin in our pSS-FS patients contributes to underlying PT reabsorption defect, possibly due to Th17 infiltration and ectopic germinal center formation [60]. On the other hand, pSS-FS is also associated with the presence of positive antimitochondrial antibodies [61]. AKI in pSS (pSS-AKI) is not common but has higher incidence rates of deep venous thrombosis, septic shock, and pulmonary edema [62]. In our previous data, 47.1% of pSS-FS patients showed significant renal function improvement (>30%) following glucocorticoid therapy, which is consistent with other studies in response to both eGFR [63, 64] and tubular functions [59].

Table 2. Inherited FS classification, inheritance information, and the extrarenal manifestation

	Classification	Inheritance	Gene	Protein	Extrarenal manifestation
PFS	FRST1	AD	GATM	Glycine amidinotransferase	
PFS	FRST2	AR	SLC34A1	Sodium-dependent phosphate transport protein 2A	Rickets
PFS	FRST3	AD	EHHADH	Enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase	
PFS	FRST4	AD	HNF4A	Hepatocyte nuclear factor 4 alpha	Maturity-onset of diabetes in the young
PFS	FRST5	AR	NDUFAF6	Ubiquinone oxidoreductase complex assembly factor 6	Pulmonary fibrosis
PFS	Mitochondrial DNA deletion		Mitochondrial DNA deletion		
PFS	Idiopathic FS	Unknown	Unknown		
FSSTHS	Cystinosis	AR	CTNS	Cystinosin	Cystine storage, developmental delay, hepatomegaly
FSSTHS	Tyrosinemia type I	AR	FAH	Fumarylacetoacetate hydrolase	Cystine storage, poor development, hepatomegaly, rickets
FSSTHS	Hereditary fructose intolerance	AR	ALDOB	Aldolase B	Hepatomegaly, vomiting, hypoglycemic ketosis
FSSTHS	Lowe syndrome	XLR	OCRL	Inositol polyphosphate-5-phosphatase	Cataracts, developmental delay
FSSTHS	Dent's disease	XLR	CLCN5	Voltage-gated chloride channel CLC-5	
FSSTHS	Lysinuric protein intolerance	AR	SLC7A7	Y (+) L-type transporter 1	
FSSTHS	Fanconi-Bickel syndrome	AR	SLC2A2	Glucose transporter 2	Hepatomegaly, dwarfism, hypoglycemic ketosis
FSSTHS	Alport syndrome	XLD/AR/AD/ autosomal two-gene			
FSSTHS	Galactosemia	AR	GALT	Galactose-1-phosphate uridylyl transferase	Hepatomegaly, encephalopathy, hypoglycemic ketosis, sepsis
FSSTHS	Wilson's disease	AR	ATP7B	ATPase copper transporting beta	Liver cirrhosis and neurological symptoms, Kayser-Fleischer rings
FSSTHS	Mitochondrial myopathies				

PFS, primary Fanconi syndrome; FSSTH, Fanconi syndrome secondary to hereditary disorders; FS, Fanconi syndrome; AR, autosomal recessive; AD, autosomal dominant; XLD, X-linked dominant; XLR, X-linked recessive.

Table 3. The mechanism, clinical manifestation, and medical recommendation of acquired FS

Classification	Example	Mechanism	Comorbid with AKI	Clinical manifestation	Medical recommendation
Anticancer agents [41]	Cisplatin	Renal accumulation of cisplatin inducing various intracellular stresses and stress response pathways	Yes	Decline in glomerular filtration rate	Renal function monitoring during cisplatin exposure
Anti-viral drugs [42]	Tenofovir disoproxil fumarate	Cellular accumulation through increased entry from the human organic anion transporters and decreased efflux into tubular lumen		Decline in eGFR, hypophosphataemia, increase in urine protein/Cr, renal insufficiency even if stable (eGFR < 60 mL/min) and tubular proteinuria	Renal monitoring during TDF exposure and cautions against prolonged TDF exposure in individuals with a low or declining eGFR
Antibiotics [43]	Aminoglycoside antibiotics	Direct proximal tubule cytotoxicity including disruption in protein synthesis and mitochondrial dysfunction	Yes	Hypomagnesemia and decreased concentrating ability	Appropriate hydration during antibiotic usage
Anticonvulsants [44, 45]	Sodium valproate	Decrease renal blood flow and increase free radical toxicity		Increased N-acetyl-β-d-glucosaminidase level and serum creatinine levels	L-cysteine has renal protective effect
Salicylates [46]	5-aminosalicylic acid	Inhibit the synthesis of intra-renal prostaglandins and the pentose phosphate shunt		Indolent, severe, chronic, and progressive interstitial nephritis	Tight monitoring
Tyrosine kinase inhibitors [47]	Pazopanib	Inhibit tyrosine phosphorylation of nephrin and cause cytoskeleton alteration and apoptosis		Proteinuria and hypertension	Monitor renal function for appropriate Drug interruption and dosage tapering
Multiple myeloma [48]		Incomplete catabolism of the light chains	Yes	Hypokalemia, hypophosphatemia, proximal RTA, hypouricemia, normoglycemic glycosuria, and aminoaciduria	Avoiding using lenalidomide

eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate; Cr, creatinine.

Drug-Induced FS: Similar Mechanisms of AKI

The drug-induced PCT dysfunction is frequent and characterized by tubular transporter defects, mitochondrial disorder, and programmed cell death. The clinical manifestations varied depending on the medication, presenting as AKI or FS. For instance, tenofovir-induced renal injury is mainly associated with urinary abnormalities that resemble FS. In contrast, cisplatin typically induces AKI, although some cases may involve both [65]. There are several mechanisms of drug-induced acute tubular injury. First, PCT cells take up drugs through the blood via basolateral transporters (cisplatin and tenofovir) and from the filtrate via apical endocytosis (aminoglycosides). Subsequently, the drugs accumulate within lysosomes or PCT cells, producing harmful substances such as reactive oxygen species and tumor necrosis

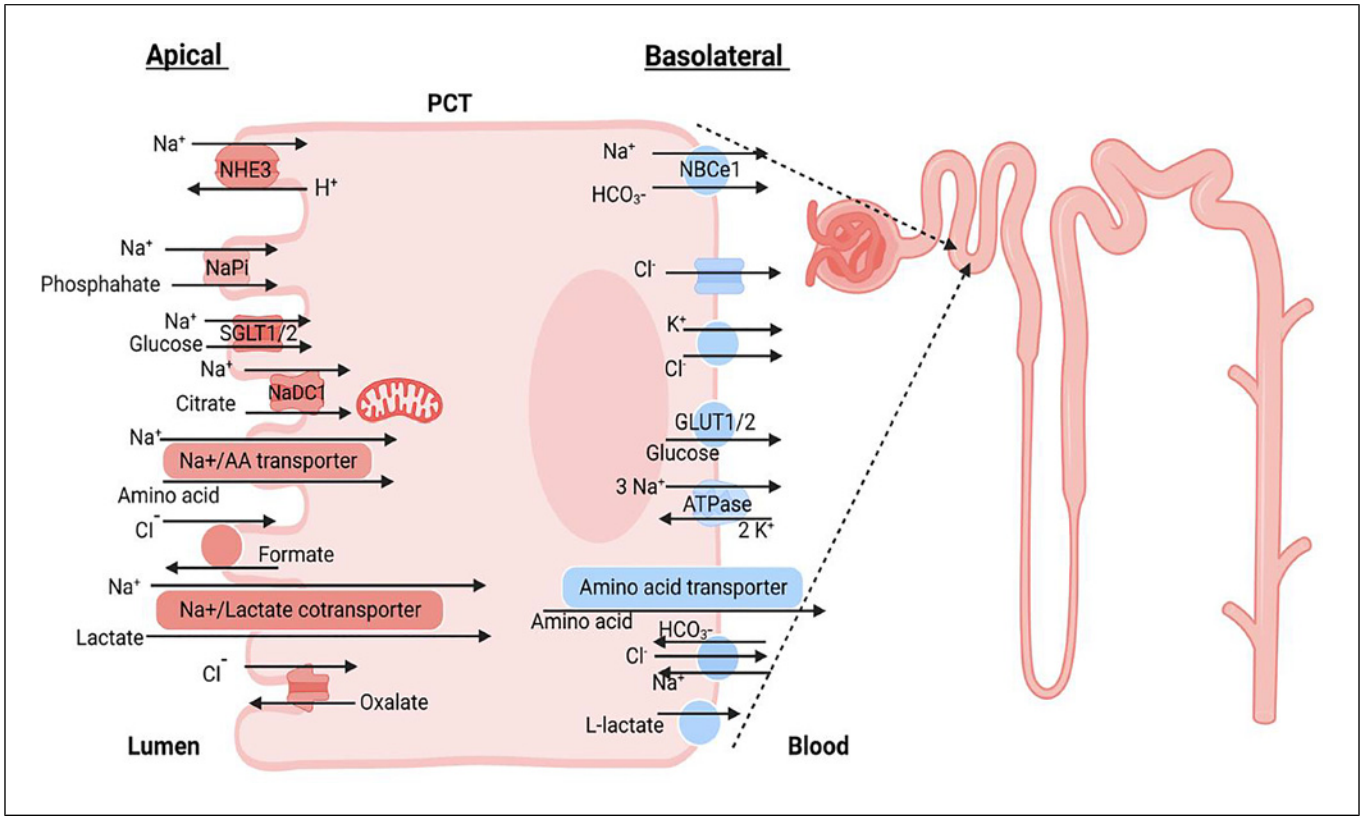

Fig. 1. Transporters in the PCT. The electrochemical gradient for passive entry of Na^+ and other solutes via these transporters established by the basolateral Na^+-K^+-ATPase in PCT mediates the Na^+ extrusion from the cytosol to the blood. NHE3 mediates the extrusion of H^+ and reabsorption of Na^+. Phosphate, glucose, amino acids, and lactate are reabsorbed into PCT via NaPi, SGLT1/2, Na^+/amino acid, and Na^+/lactate cotransporters. Citrate is reabsorbed via NaDC-1 and is then transported to the mitochondria for energy production. Cl^- can be reabsorbed through Cl^-/oxalate and Cl^-/formate exchangers and enter the blood via Cl^- channel, K^+-Cl^- cotransport, and Na^+-$2HCO3^-$/Cl^- exchanger. $HCO3^-$ is generated from glutamine in the cytosol and enters the bloodstream via the NBCe1. PCT, proximal convoluted tubule; NHE3, Na^+-H^+ exchanger; NaPi, Na^+/phosphate cotransporter; SGLT2, Na^+/glucose cotransporter 2; SGLT1, Na^+/glucose cotransporter 1; GLUT2, glucose transporter 2; GLUT1, glucose transporter 1; NaDC-1, Na^+/dicarboxylate cotransporter 1; NBCe1, Na^+/$HCO3^-$ cotransporter; ATPase, Na^+-K^+-ATPase.

factor-alpha (TNF-α). Finally, mitochondrial damage could result in cell apoptosis or necrosis [66].

The megalin-cubulin pathway is another crucial mechanism for drug-induced PTC injury. Megalin, a glycosylated endocytic receptor, is expressed in the apical membrane of PCT cells for reabsorbing various peptides, proteins, and some drugs [67]. Yoshihisa Hori et al. demonstrated that blocking megalin with cilastatin can suppress nephrotoxicity caused by gentamicin, colistin, vancomycin, and cisplatin by competing with megalin-mediated drug reabsorption into PCT cells [68]. In contrast, a study revealed decreased expression of megalin and cubulin in tenofovir nephrotoxicity, which is associated with a poor renal prognosis [69]. The phenomenon is consistent with our previous study on patients with pSS-FS [60]. These findings suggest that megalin-cubulin may exert various roles in different drug-induced nephrotoxicity. Table 4 summarizes PTC injuries, with 60% of AKI cases attributed to COVID-19 infection, tenofovir and diclofenac administration, and hemolysis caused by left ventricular assist device.

Mitochondria Disorder in Rare Tubulointerstitial Diseases and AKI

Mitochondria play a vital role in the activity, function, and viability of eukaryotic cells and are implicated in genetic and acquired renal diseases. Mitochondrial cytopathies could cause renal symptoms with tubular dysfunctions, while mitochondrial dysfunction in the PCTs induces apoptosis and contributes to the

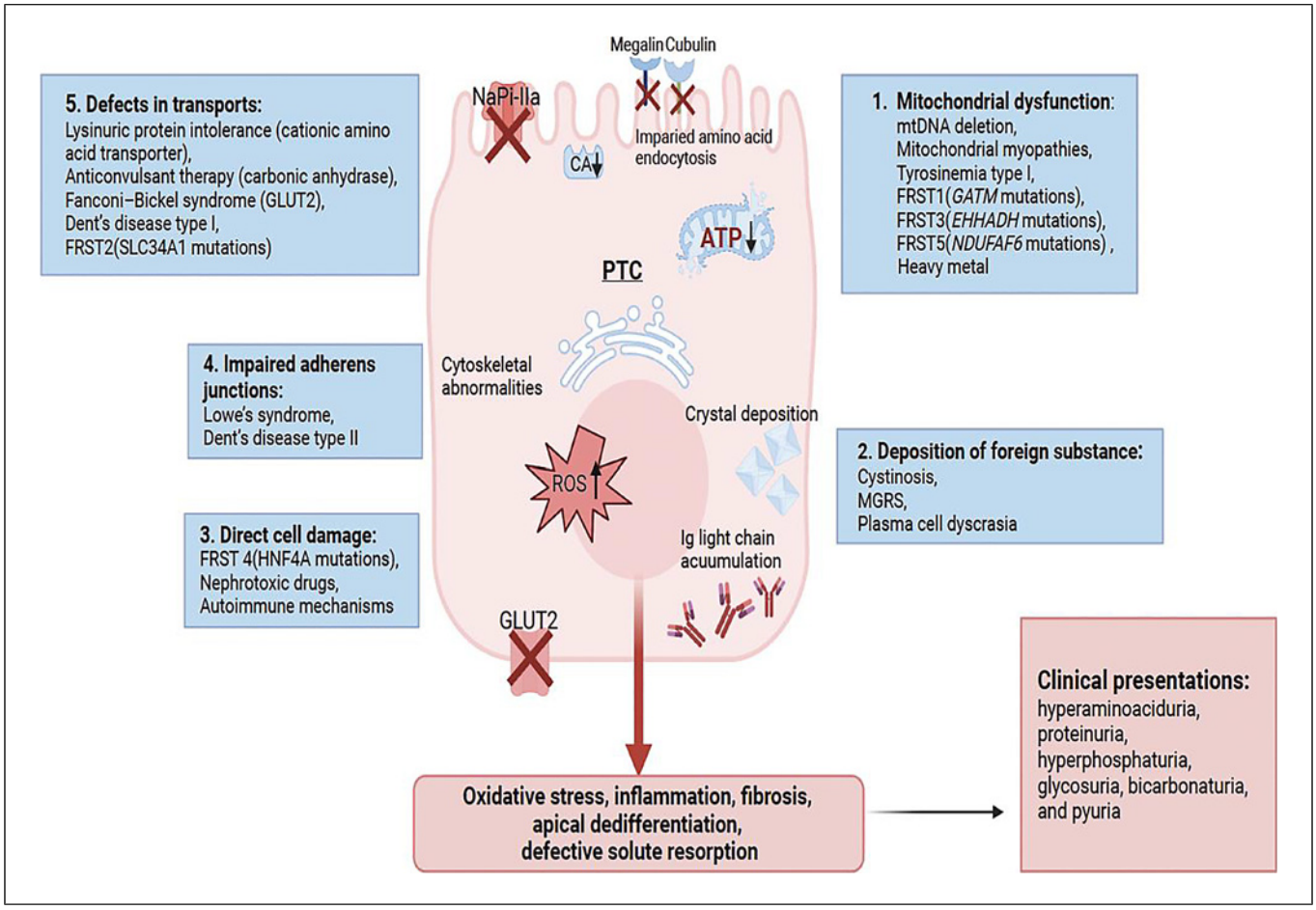

Fig. 2. The overall pathogenic mechanisms of FS. The etiologies of FS are primary and acquired mechanisms contributing to the dysfunction of PCT cells. The predominant mechanism is mitochondrial dysfunction secondary to mtDNA deletion, mitochondrial myopathies, tyrosinemia type 1, FRTS 1, 3, and 5, and heavy metal exposure, which impair the electron transport chain in mitochondria, resulting in reduced ATP production and accumulation of ROS. The second way is the deposition of Ig light chain or cystine crystal substances in MGRS and cystinosis, respectively. The other two mechanisms are direct cell damage or disruption of the cytoskeletal abnormality impairing the protein trafficking and adherens junctions by nephrotoxic drugs, autoimmune disease, FRST4, and an inherited disease (Lowe's syndrome, and Dent's disease). The last reason is the defective solute transports, especially the dysfunction of transporters resulting from FRST2 (NaPi), Fanconi-Bickel syndrome (GLUT2), lysinuric protein intolerance (cationic amino acid transporter), and Dent's disease type I (amino acid transported by megalin and cubulin). These mechanisms facilitate the increase in oxidative stress, inflammation, and fibrosis, ultimately leading to apical dedifferentiation and defective solute resorption. As a consequence, patients with FS may exhibit hyperaminoaciduria, proteinuria, hyperphosphaturia, glycosuria, bicarbonaturia, and pyuria. FS, Fanconi syndrome; mtDNA, mitochondrial DNA; FRTS, Fanconi reno tubular syndrome; ROS, reactive oxygen species; MGRS, monoclonal gammopathies of renal significance.

progression of AKI [73]. PCT are abundant in mitochondria, which provide sufficient energy for intensive reabsorption and excretion processes. Mitochondrial disorders have been implicated in the pathogenesis of ADTKD, specifically ADTKD-UMOD and ADTKD-REN. These conditions are characterized by mutations in specific genes that result in mitochondrial dysfunction within renal tubular cells [74]. Furthermore, mitochondrial dysfunction can manifest with varying degrees of tubular dysfunction, while complete FS is the most severe form [75]. Mutations in EHHADH (FRTS1), GATM (FRTS3), and NDUFAF6 (FRTS5) cause defects in mitochondrial structure and protein aggregation, inflammasome activation, and collagen accumulation, resulting in various degrees of FS and renal dysfunction [76–78]. The mutation genes categorized as electron carriers, mitochondrial DNA translation genes, and mitochondrial DNA maintenance-associated genes

Table 4. The epidemiology features of AKI in in patients with FS of different etiologies

Etiologies	Percentage of AKI	Mechanisms	Recovery rate
COVID-19 infection [70]	66.7% (n = 30)	Damage renal PT cells via ACE2 causing FS, followed by AKI	20% in HD treatment
Tenofovir and diclofenac administration [71]	61.9% (n = 21)	Reduction of renal blood flow and interstitial nephritis by diclofenac; prior CKD, AIDS, HCV infection and liver disease	Not available
Hemolysis induced by LVAD [72]	60.0% (n = 7)	Chronic PT functional alterations might impair kidney adaptability	Not available

COVID-19, coronavirus disease 2019; ACE2, angiotensin converting enzyme 2; HD, hemodialysis; FS, Fanconi syndrome; AKI, acute kidney injury; CKD, chronic kidney disease; AIDS, acquired immunodeficiency syndrome; HCV, hepatitis C virus; LVAD, left ventricular assist device.

contribute to different clinical presentations of disease. For example, the mutations of BCS1L, UQCC2, or FBXL4 affect oxidative phosphorylation, resulting in RTA with associated multi-organ involvement [73]. Drugs can enter PCT cells through brush borders or basolateral transporters, leading to direct damage to mitochondria [79].

The critical role of mitochondrial disorder in AKI had solid evidence, serving as an energy source for cells and regulating cell death. First, changes in mitochondrial structure are commonly observed in AKI, typically manifesting as swelling and the disappearance of intermitochondrial membrane cristae, which result from ATP depletion and membrane potential decrease [80]. Second, mitochondrial dynamics has been shown to be related to the progression of AKI. Proteins such as Drp1, Mfn, and Opa1 regulate mitochondrial fission and fusion, leading to mitochondrial fragmentation and cytochrome c release, ultimately inducing cell apoptosis during AKI [81]. Third, mitochondrial biogenesis benefits tubular repair following AKI. Peroxisomal proliferator-γ coactivator-1α (PGC-1α) is predominantly expressed in proximal tubules and enhances mitochondrial biogenesis through transcriptional coactivators such as nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF2) [82]. In mouse models of AKI, both PGC-1α and OXPHOS genes were inhibited proportionally to the severity of kidney injury but were restored during the recovery phase [83, 84]. Our previous study demonstrated that PGC-1α promotes mitochondrial biogenesis by translocating to the nucleus in FS and AKI models [85]. In general, the injury and repair process of AKI is accompanied by the disorder of mitochondrial structure, dynamics, and biogenesis, promoting the development of mitochondria-targeted compounds. Based on the mitochondrial-related mechanisms, there are four categories, including cardiolipin protectors, mitochondrial fragmentation inhibitors, mPTP mitochondrial oxidant inhibitors, and mitochondrial biogenesis-promoting compounds [86].

Mitochondrial dysfunction in both AKI and FS exhibits shared underlying mechanisms, such as impaired oxidative phosphorylation capacity, structure defects, mitochondrial biogenesis, dynamics, and mitophagy, suggesting that the discoveries regarding mitochondrial disorders in FS can provide valuable insights into AKI. The specific mechanisms involved in mitochondrial dysfunction in FS, including the role of mutated genes, hereditary disorders, and acquired etiologies, might also be associated with AKI. Additionally, identifying the common pathways and targets associated with mitochondrial dysfunction holds promise for developing novel therapeutic strategies in both FS and AKI.

ALDH2: A Potential Target for the Prevention of Mitochondrial Injury

Recently, we identified that aldehyde dehydrogenase 2 (ALDH2) might be a novel therapeutic target to prevent AKI progression by alleviating mitochondrial dysfunction [85]. ALDH2 is a crucial enzyme in the alcohol-metabolism process from acetaldehyde catalyzing into acetate, as a tetramer protein structure consists of four identical subunits with distinct domains, including catalytic, NAD+ coenzyme-binding, and oligomerization [87]. Glu487 plays a critical role in dimer and tetramer formation, and being substituted with Lys487 (ALDH2 Glu487Lys) leads to disorder of the α-helices and the destruction of NAD+ binding sites, resulting in a significant decrease in ALDH2 activity [88].

ALDH2 could modulate mitochondrial oxidative ATP production and reactive oxygen species (ROS) in various diseases, including myocardial [89], liver [90], and

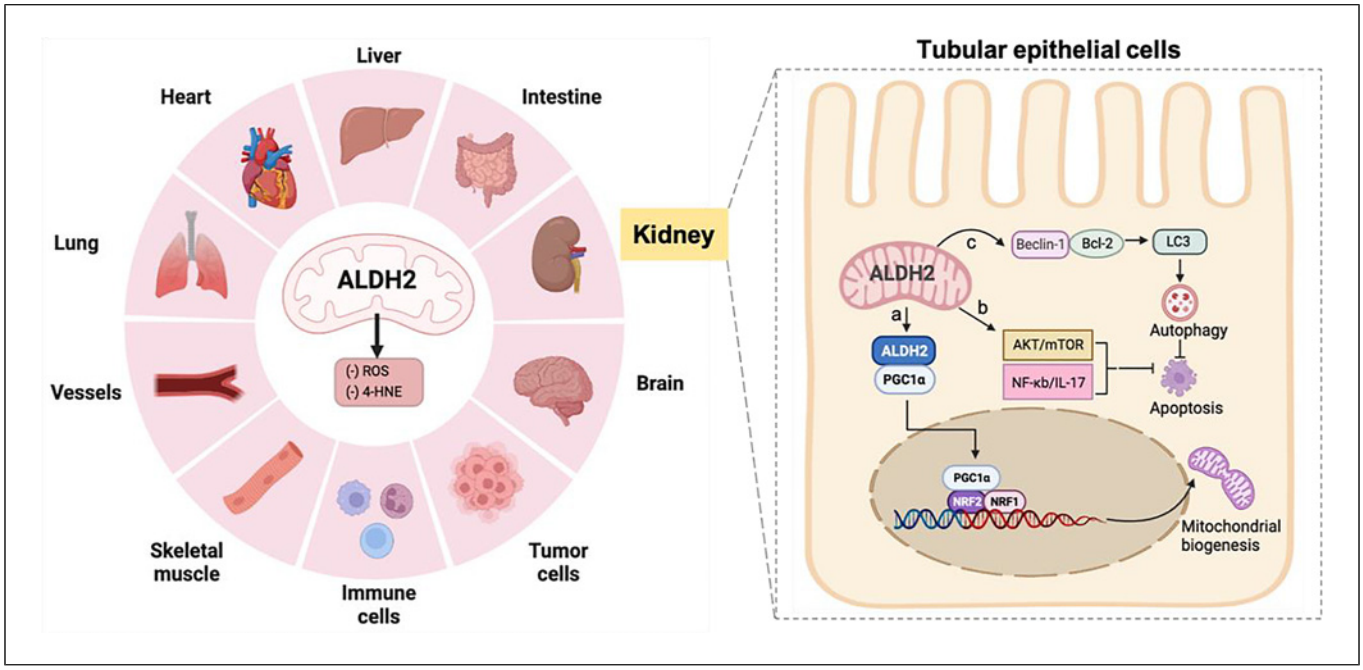

Fig. 3. ALDH2 exerts protective roles in various organs and cells by inhibiting ROS and 4-HNE. The main regulatory mechanism of ALDH2 in AKI. a: ALDH2 promotes mitochondrial biogenesis by interacting with PGC-1α. b: ALDH2 suppresses cell apoptosis by activating AKT/mTOR and NF-κb/IL-17 pathway. c: ALDH2 regulates autophagy by upregulating the Beclin/Bcl-2 pathway. ROS, reactive oxygen species; 4-HNE, 4-hydroxynonenal; PGC-1α, peroxisomal proliferator-γ coactivator-1α.

neurology diseases [91]. Recent evidence highlights the protective role of ALDH2 against AKI induced by IRI and sepsis via activation of the AKT-mTOR and MAPK pathways [92, 93]. Xu et al. [94] confirmed that ALDH2 upregulated Beclin-1 expression, promoted autophagy activation, and reduced apoptosis using murine models and human renal tubular epithelial cells exposed to iohexol. However, a contradictory result has been reported with continuous infusion of Alda-1 (an ALDH2 agonist) for 7 days, resulting in renal tubular injury and crystal deposition in an IRI model [95]. In our mouse models of FS and AKI established by maleic acid and cisplatin, Alda-1 alleviated renal tubular injury by restoring mitochondrial energy metabolism through its interaction with PGC-1α to facilitate nuclear translocation [85], which first indicated ALDH2 as a potential target molecule in rare tubulointerstitial diseases with similar mitochondria mechanisms. More research is needed to investigate the specific pathway and potential therapeutic value of ALDH2 in rare tubulointerstitial diseases. Figure 3 shows the role of ALDH2 in the kidney and other organs.

ALDH2 also potentially interacts with tubular transporters. Empagliflozin, an SGLT2 inhibitor, can mitigate ALDH2*2-induced endothelial cell dysfunction with the best docking pose with Alda-1 through the inhibition of Na^+/H^+ exchanger 1 (NHE-1) and activation of AKT kinase and endothelial NO synthase pathways [96]. While tubular transporters play a significant role in rare tubulointerstitial diseases, there is little research investigating the involvement of ALDH2 in these conditions. Therefore, further studies are necessary to understand the role of ALDH2 in rare tubulointerstitial diseases and explore its direct relationship with tubular transporters, including their structure, function, and potential interactions, which will provide valuable insights into the pathogenesis of rare tubulointerstitial diseases and may unveil new therapeutic possibilities.

Conclusion

In summary, rare tubulointerstitial diseases such as FS and ADTKD share common mechanisms with AKI and may offer potential diagnostic biomarkers or therapeutic targets. Activation of ALDH2 might be a promising target for preventing AKI and FS by repairing mitochondrial disorders.

Acknowledgments

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jiaying Li drafted the manuscript; Fangxing Hou, Ning Lv, and Ruohuan Zhao prepared the figures and tables; Lei Zhang, Cai Yue, and Min Nie revised the manuscript; and Limeng Chen designed the work and performed the final edits. Both authors approved the final version of the article and agreed to be accountable for all aspects of the work.

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