RENAL FAILURE
2025, VOL. 47, NO. 1, 2506812
https://doi.org/10.1080/0886022X.2025.2506812

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Mitochondrial dysfunction: the hidden catalyst in chronic kidney disease progression

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ABSTRACT

Chronic kidney disease (CKD) represents a global health epidemic, with approximately one-third of affected individuals ultimately necessitating renal replacement therapy or transplantation. The kidney, characterized by its exceptionally high energy demands, exhibits significant sensitivity to alterations in energy supply and mitochondrial function. In CKD, a compromised capacity for mitochondrial ATP synthesis has been documented. As research advances, the multifaceted roles of mitochondria, extending beyond their traditional functions in oxygen sensing and energy production, are increasingly acknowledged. Empirical studies have demonstrated a strong association between mitochondrial dysfunction and the pathogenesis of fibrosis and cellular apoptosis in CKD. Targeting mitochondrial dysfunction holds substantial therapeutic promise, with emerging insights into its epigenetic regulation in CKD, particularly involving non-coding RNAs and DNA methylation. This article presents a comprehensive review of contemporary research on mitochondrial dysfunction in relation to the onset and progression of CKD. It elucidates the associated molecular mechanisms across various renal cell types and proposes novel research avenues for CKD treatment.

HIGHLIGHTS OF THE STUDY

- **Comprehensive Analysis of Mitochondrial Biology in CKD**
- The study examines mitochondria's crucial roles in ATP production, signal transduction, and oxidative phosphorylation in CKD, highlighting their structural and functional impairments and their impact on disease progression.
- **Molecular Mechanisms of Mitochondrial Dysfunction Across CKD Cell Types**
- The paper explores the complex molecular mechanisms of mitochondrial dysfunction in various kidney cell types, revealing cell-specific processes that drive CKD progression.
- **Connection Between Mitochondrial Dysfunction and Different Types of Regulated Cell Death**
- The research investigates how mitochondrial dysfunction influences regulated cell death (RCD) pathways, such as apoptosis, ferroptosis, and mitophagy, contributing to kidney injury and fibrosis in CKD.
- **Targeting Mitochondrial Dysfunction for Novel CKD Therapies**
- The study suggests that addressing mitochondrial dysfunction could be a therapeutic approach to decelerate the progression of CKD. It explores possible strategies to enhance mitochondrial function and decrease kidney damage by adjusting RCD pathways.

ARTICLE HISTORY
Received 7 April 2025
Accepted 10 May 2025

KEYWORDS
Chronic kidney disease; mitochondrial dysfunction; cell death; mitophagy; oxidative stress

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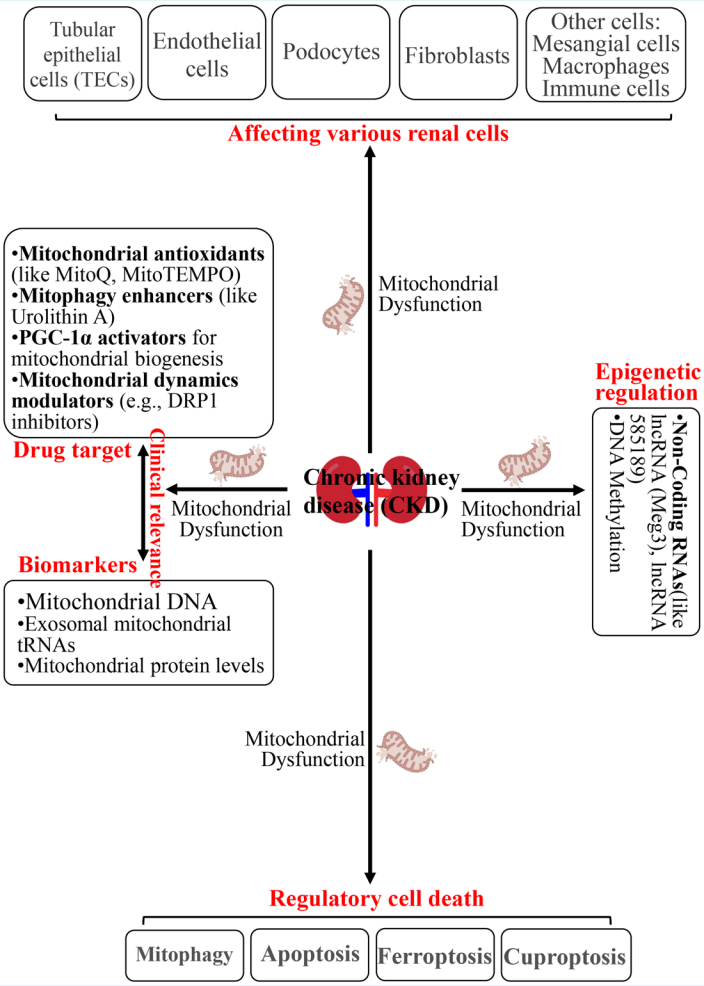
GRAPHICAL ABSTRACT



1. Introduction

Chronic kidney disease (CKD) is a global health problem with high morbidity and mortality [1–4]. The targeting of mitochondrial function is emerging as a viable strategy to delay the progression of CKD. Therefore, an understanding of mitochondrial biology and pathophysiological processes is crucial for the development of effective treatment options for CKD [5,6].

Mitochondrial quality control (MQC) regulates and maintains mitochondrial homeostasis by various processes, including biogenesis, mitochondrial fission, fusion, proteolysis, and mitophagy degradation [7–10]. Mitochondrial dysfunction and oxidative stress (OS) are the main causes of CKD, as renal cells are affected by mitochondrial damage, overproduction of reactive oxygen species (ROS), activation of apoptotic pathways, and defective mitophagy [5,11,12]. Mitochondrial dysfunction leads to increased ROS levels, which may arise from mitochondrial biogenesis, bioenergetics, kinetics, turnover, oxidative stress, ultrastructural abnormalities, increased susceptibility to apoptosis, and accumulation of damaged mitochondria. Our review provides a detailed overview of mitochondrial dysfunction in CKD, examining its effects on different kidney cell types. We uniquely address the interconnected roles of apoptosis, ferroptosis, mitophagy, and cuproptosis, and emphasize the often-overlooked epigenetic regulation of mitochondrial function, including non-coding RNAs and DNA methylation. Furthermore, we discuss therapeutic strategies targeting mitochondrial dysfunction, highlighting both their potential and the challenges of clinical application. This approach distinguishes our review from previous works [13–17].

2. Mitochondria biology and dysfunction in CKD

Mitochondria are bilayer membrane organelles that play a critical role in ATP synthesis, signal transduction, and partial oxidative phosphorylation through autonomous protein synthesis [18–20]. Studies have demonstrated the presence of impairments in mitochondrial structure and function in CKD [21]. Investigating the biological functions of mitochondria and their pathophysiological mechanisms can help elucidate potential pathological mechanisms and identify new therapeutic targets for CKD.

2.1. Mitochondrial quality control

Mitochondrial quality control is an endogenous protective mechanism that maintains mitochondrial homeostasis [22–24]. Dysregulation of this process can lead to disrupted cellular energy metabolism, inflammation, oxidative stress, and ultimately results in cell death, severe tissue damage, and organ failure [15,25].

2.1.1. Mitochondrial dynamics in CKD

Mitochondria maintain a dynamic structure by balancing fusion and fission to adapt to cellular energy and biological demands in a process known as mitochondrial dynamics [26]. Concurrently, mitophagy clears away aging or damaged mitochondria to maintain mitochondria quality [27]. These two processes are interconnected and contribute to mitochondrial homeostasis. Mitochondrial dynamics are regulated by fusion proteins such as MFN1, MFN2, OPA1, and fission proteins such as DRP1 and FIS1. Studies have indicated that an imbalance in fusion and fission proteins in CKD leads to mitochondrial fragmentation and worsens kidney damage [28–32]. In obstructive kidney disease mouse models, DRP1 knockouts and Mdivi-1, a small molecule inhibitor of DRP1, can alleviate kidney fibrosis [31]. In diabetic kidney disease (DKD) mouse models, Mdivi-1 can significantly reduce mitochondrial division [33]. Mitophagy includes parkin-dependent and parkin-independent pathways, and research has shown that the kidney has a higher rate of mitochondrial autophagy compared to other organs [34–36], playing a protective role in CKD [37–39]. Dysregulation of mitochondrial autophagy is associated with various chronic kidney diseases, such as DKD and FSGS (Focal Segmental Glomerulosclerosis) [27,40]. In DKD mouse models, the level of mitophagy decreases [41,42], resulting in excessive accumulation of damaged mitochondria and increased oxidative stress and inflammation [41,43].

2.1.2. Mitochondrial biogenesis in CKD

Mitochondrial biogenesis refers to the process of replacing damaged mitochondria with newly generated mitochondria, and is regulated by PPARs and PGC1-α [44]. In the early stages of diabetes, compensatory upregulation of PGC1-α can be observed [45]. However, in renal tissues of patients with DKD and other chronic kidney fibrosis, the expression of PGC1-α is significantly suppressed, which is associated with mitochondrial damage and decreased mitochondrial biogenesis [46–49]. Studies have shown that overexpression of PGC1-α in a TGF-β1-induced mouse model can restore abnormal fatty acid metabolism and ATP depletion by increasing mitochondrial abundance, improving renal pathological changes [50]. Post-translational modifications can also regulate the activity of PGC1-α. In a DKD mouse model, Sirt1-mediated deacetylation of PGC1-α can improve mitochondrial dysfunction and alleviate aldosterone-induced podocyte injury [51], reducing proteinuria and glomerular lesions [52]. However, overexpression of PGC1-α in podocytes in mice can also lead to glomerular collapse, suggesting a narrow therapeutic window for podocyte PGC1-α [53]. Mitochondrial dynamics and biogenes is summarized in Figure 1.

2.1.3. Mitochondrial protein quality control

Molecular chaperones are a class of proteins responsible for stabilizing, folding, and unfolding precursor proteins and facilitating their import into mitochondria [54,55]. Heat shock proteins (HSPs), as highly conserved proteins, play a key role as molecular chaperones in protein homeostasis. In a DKD rat model, upregulation and phosphorylation of HSP25, HSP27, HSP60, and HSP70 have been observed to exert a protective effect on the kidneys [56]. Furthermore, other work has suggested that the downregulation of HSP90 may mediate podocyte apoptosis, exacerbating kidney injury [57]. Additionally, molecular chaperones interact with mitochondrial proteases [58], the ubiquitin-proteasome system [59], and other components, to form the mitochondrial protein quality control system, which eliminates misfolded or aggregated proteins and clears dysfunctional mitochondria. However, the specific mechanisms of mitochondrial protein quality control in CKD are still unclear to date.

2.2. Mitochondrial energy metabolism

The kidneys require a large amount of ATP to maintain filtration, reabsorption, and secretion. Under physiological conditions, 90% of the energy necessary for kidney function comes from oxidative phosphorylation (OXPHOS) in mitochondria. Therefore, any factors that affect mitochondrial energy metabolism may have adverse effects on kidney function.

2.2.1. TCA cycle

The tricarboxylic acid (TCA) cycle, also known as the citric acid cycle, is a central hub of aerobic respiration and many metabolic pathways. The TCA cycle begins with the combination of acetyl-CoA, derived from the oxidation of fatty acids, ketone bodies, or amino acids, with oxaloacetate to form citrate. Citrate is then converted to α-ketoglutarate (AKG) through decarboxylation and isomerization reactions. AKG, with the action of NAD and FAD dehydrogenases, generates metabolic intermediates and reducing equivalents (such as NADH and FADH2) in the cycle. These reducing equivalents input electrons into the electron transport chain (ETC) and create an electrochemical gradient on the inner mitochondrial membrane (IMM) to drive the conversion of ADP to ATP through complex V, a process known as oxidative phosphorylation (OXPHOS). The four-carbon molecule, succinate, can be converted back to oxaloacetate and participate in a new cycle of the TCA [60].

In the state of CKD, the energy output of the TCA cycle can be influenced by multiple factors. First, kidney dysfunction may lead to the accumulation of metabolic byproducts, which can affect the normal operation of the TCA cycle and ATP production [61]. Urinary TCA metabolites have been reported as novel biomarkers for predicting CKD progression [62]. Second, oxygen serves as the final acceptor in the mitochondrial ETC. CKD patients may experience severe anemia, which restricts oxygen supply and consequently affects the normal progression of the TCA cycle. Furthermore, the metabolites of the TCA cycle and acetyl-CoA can also act as

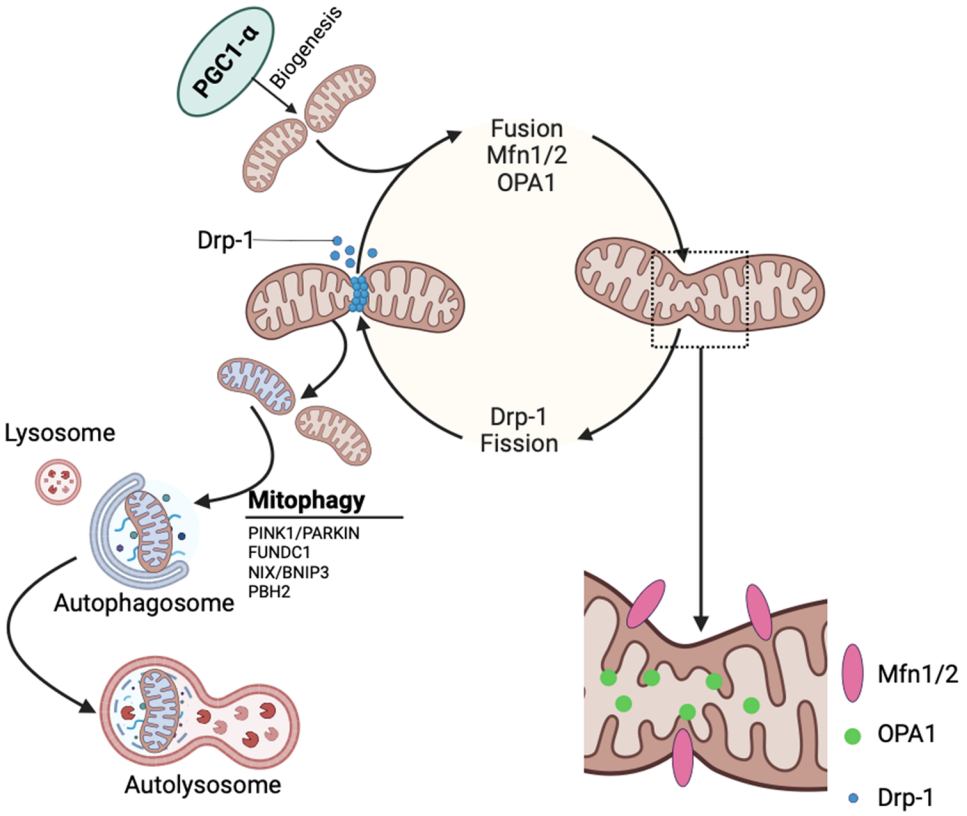


Figure 1. Mitochondrial dynamics and biogenesis. The biogenesis of mitochondria is regulated by PGC1-α. Mitochondrial fusion is mediated by Mfn1/2 and OPA1, with Mfn1/2 mediating OMM fusion and OPA1 mediating IMM fusion. Drp1 mediates mitochondrial fission. Mitophagy, the degradation of mitochondria, is facilitated by both PRKN-dependent pathways and PRKN-independent pathways involving FUNDC1, BNIP3/Nix, and PHB2. Mitochondria are targeted to autophagosomes for degradation through these pathways and eventually fuze with lysosomes to complete mitochondrial degradation. PGC1-α: the transcriptional coactivator peroxisome proliferator activated receptor gamma coactivator 1; Mfn1/2: mitofusin 1/2; OPA1: optic atrophy protein 1; Drp-1: dynamin-related protein 1; PINK1: PTEN-induced putative kinase 1; PARKIN: parkin RBR E3 ubiquitin-protein ligase; FUNDC1: FUN14 Domain Containing 1; NIX: BCL2/adenovirus E1B 19kDa interacting protein 3-like; BNIP3: BCL2 Interacting Protein 3; PHB2: prohibitin 2.

signaling molecules to drive various cellular functions. Studies have shown their involvement in the regulation of kidney function through pathways such as epigenetic modifications, antioxidant capacity, acid-base balance, and immune modulation, and their association with various pathological states, including CKD [63].

2.2.2. Oxphos

Oxidative phosphorylation is the main source of cellular energy, and the main reaction occurs on the inner mitochondrial membrane in the ETC. In the TCA cycle or fatty acid oxidation (FAO) process, NADH and FADH2 capture high-energy electrons and transport them to complex I and complex II on the ETC [64,65]. The electrons pass through complex I, complex II, and coenzyme Q (CoQ) and eventually reach complex IV, where they are transferred to molecular oxygen, generating water and releasing energy. During the operation of the ETC, the flow of electrons drives the pumping of protons into the inner mitochondrial membrane, creating a proton gradient that is utilized by complex V to synthesize ATP [66]. Under normal conditions, when electrons are transferred to molecular oxygen through the ETC, complex I and complex III produce low levels of reactive oxygen species (ROS). However, in the presence of mitochondrial dysfunction, the proton gradient across the IMM cannot be maintained, leading to increased oxidative stress. Low levels of ROS have physiological functions in promoting proliferation and survival, while high levels of ROS are pathological, causing mitochondrial dysfunction and cellular toxicity [67,68]. Specifically, high levels of ROS can cause mtDNA damage, negatively regulate ETC efficiency, reduce ATP synthesis, and impair the biological activity of proteins and lipids, leading to mitochondrial dysfunction [69]. Furthermore, high levels of ROS can trigger calcium overload, activate apoptosis by releasing cytochrome C [70], and ultimately contribute to the occurrence and progression of CKD.

2.2.3. FAO

FAO in mitochondria is the main source of ATP in the kidneys, and its dysfunction leads to ATP depletion and lipotoxicity, resulting in inflammation and fibrosis [71]. Previous research suggests that defects in fatty acid (FA) metabolism and lipotoxicity can be observed in various kidney diseases from an early stage [72].

Defects in FA synthesis, uptake, and oxidation play important roles in the occurrence and progression of CKD. In proximal tubular cells, FAs can be reabsorbed from the glomerular filtrate through membrane FA transport proteins (such as CD36 and FABP) or receptor-mediated endocytosis of FA-bound albumin [73,74]. Increased renal triglyceride synthesis has been observed in the unilateral ureteral obstruction (UUO) rat

model [75], and CD36-deficient mice have been shown to exhibit reduced fibrosis after UUO treatment [76].

Within the cytoplasm, FAs are activated to acyl-CoA by acyl-CoA synthetases and catalyzed by carnitine palmitoyltransferase-1 (CPT-1) on the outer mitochondrial membrane (OMM) to form acylcarnitine [73,77,78]. Acylcarnitine crosses the inner mitochondrial membrane (IMM) and is converted back to acyl-CoA by carnitine palmitoyltransferase-2 (CPT-2) and then undergoes further reactions in the mitochondrial matrix through β-oxidation to form acetyl-CoA for entry into the TCA cycle [77]. Studies have shown decreased expression of CPT1 in renal fibrosis patients and animal models [50], indicating impaired FAO [79]. Inhibition of CPT1 leads to lipid deposition, ATP depletion, and cell death in renal tubular epithelial cells in CKD mice [50]. Conversely, overexpression of CPT1 in tubules significantly improves FAO, restores mitochondrial homeostasis, and prevents further deterioration of renal fibrosis and dysfunction [79].

Metabolic changes are also crucial in exacerbating renal injury. The key regulatory factor PPARα is highly expressed in renal proximal tubular cells. Genetic deletion of PPARα in mice leads to increased lipid accumulation and exacerbates aging and DKD-related renal fibrosis [80]. PPARα agonists have been shown to reverse these effects in various kidney injury models [81,82].

2.3. Mitochondrial metal ion transport and homeostasis

Mitochondria contain various metal ions whichplay essential and indispensable roles in enzymatic reactions, ETC function, regulation of mitochondrial membrane potential, and other mitochondrial processes. Research has shown that imbalanced mitochondrial metal ion homeostasis may play a role in the pathogenesis of CKD.

2.3.1. Mitochondrial calcium metabolism

Ca^{2+} is one of the most common second messengers in cellular processes [83]. Changes in its concentration mediate nearly all cellular functions, such as proliferation, secretion, protein folding, and energy metabolism [84]. Mitochondria can regulate Ca^{2+} dynamics *via* uptake and storage. Ca^{2+} typically needs to pass through the highly permeable outer mitochondrial membrane (OMM) and the ion-impermeable inner mitochondrial membrane (IMM) to enter the mitochondrial interior. Calcium passage through the highly permeable OMM occurs *via* voltage-dependent anion channel protein 1 (VDAC1) [85,86]. Passage through the IMM, the rate-limiting step for mitochondrial Ca^{2+} uptake, requires the electrochemical gradient generated by OXPHOS [87]

Mitochondrial Ca^{2+} uptake is primarily mediated by the mitochondrial Ca^{2+} uniporter (MCU) complex [88]. The MCU complex, consisting of four protein subunits, includes the ion channel forming MCU, EMRE, and the regulatory proteins, MICU1 and MICU2, which control MCU activity [89]. Research has shown that the regulation of MCU activity by MICU1-MICU2 involves a gating mechanism: MICU1-MICU2 inhibits Ca^{2+} entry through MCU at low cytoplasmic Ca^{2+} concentrations during cell resting states and allows Ca^{2+} entry when cells are stimulated and Ca^{2+} concentration exceeds a threshold [90,91]. Excessive intracellular Ca^{2+} can precipitate with phosphate, affecting cellular substance and energy metabolism. Therefore, most of the Ca^{2+} in cells exists in a bound form within cellular organelles, with mitochondria being one of the important intracellular stores [92]. Mitochondria have limited Ca^{2+} capacity, and the formation of mitochondrial calcium phosphate precipitates allows mitochondria to function as important Ca^{2+} buffers, while maintaining [Ca^{2+}]. In the absence of effective efflux mechanisms, Ca^{2+} overload can occur, leading to cell death. MCU uptake is primarily balanced by efflux *via* the mitochondrial Na^{+}/Ca^{2+} exchanger (mNCX) and the mitochondrial H+/Ca2+ exchanger (mHCX) [93]. However, under stress, the efflux pathways are insufficient in preventing mitochondrial Ca^{2+} overload. Overload leads to increased production of reactive oxygen species (ROS) [94] and sustained opening of the mitochondrial permeability transition pore [95], resulting in the release of pro-apoptotic factors such as cytochrome C [70].

In CKD, changes in calcium homeostasis can be observed in various cells, including podocyteS. In a type 2 diabetes mouse model, administration of palmitic acid can induce mitochondrial ROS, activate phospholipase C, trigger abnormal endoplasmic reticulum calcium ion release, and ultimately damage podocytes [96]. In the UUO model, intracellular calcium levels increase alongside activation of calcium channel protein 1 (Orai1) during Ca^{2+} release. Knockdown of Orai1 through shRNA and inhibition of Orai1 *via* channel blocker SKF96365 can reduce fibrosis markers and alleviate renal tubulointerstitial injury in the UUO model [97].

2.3.2. Mitochondrial iron metabolism

Iron is an essential metal element for the development and maintenance of cell homeostasis. An indispensable component in the synthesis of iron-sulfur clusters and heme, iron also participates in redox reactions, shuttling between its oxidized form (Fe^{3+}) and reduced form (Fe^{2+}) [98]. In mitochondria, a sufficient quantity of iron is necessary to maintain its normal physiological functions. While iron deficiency can impair mitochondrial metabolism and respiratory activity, iron overload can promote the production of mitochondrial ROS and oxidative damage to mitochondrial proteins, lipids, and DNA, potentially leading to mitochondrial dysfunction and the development of various diseases [99,100].

In mitochondria, iron enters the intermembrane space through various proteins such as VDAC1 and DMT1 in the OMM [101], and is then transported across the IMM by mitoferrins (MFRNs) [102]. MFRN1 (SLC25A37) is highly expressed in red blood cells and is essential for heme synthesis and erythrocyte development [103]. MFRN2 (SLC25A28), on the other hand, is expressed in various non-erythroid tissues [103–105], but its specific role in mitochondrial iron homeostasis is still not clear [106,107]. In addition to iron import and utilization, mitochondria also need to export iron periodically in the form of heme, Fe-S clusters, and elemental iron [102]. Disruption of mitochondrial iron export leads to severe mitochondrial iron overload.

Disruptions in systemic iron balance, including iron overload and iron deficiency, can contribute to kidney damage. Iron-induced oxidative stress and mitochondrial dysfunction are believed to be involved in the progression of various kidney injury models [108,109]. In CKD patients, disturbances in iron homeostasis occur due to reduced iron intake and absorption, increased iron loss and storage, and decreased mobilization [110]. In the context of imbalanced iron metabolism, renal iron deposition and increased urinary iron concentration can worsen kidney injury [111,112]. Renal iron deposition may catalyze the formation of reactive oxygen species, disrupt mitochondrial oxidative metabolism, and ultimately lead to kidney damage. Several animal CKD models have shown that reducing iron intake or using iron chelators to lower renal iron exposure can delay CKD progression [113–117], although there is not yet sufficient evidence from human studies.

2.3.3. Mitochondrial copper metabolism

Copper is a transition metal element that exhibits both reducibility and oxidizability. It serves as a cofactor for enzymes involved in various physiological processes [118]. The redox state changes of copper ions in cells partly reflect and influence the cellular redox status and are closely related to mitochondrial function, oxidative stress, and programmed cell death.

In mitochondria, copper is one of the main components of complex IV (cytochrome C oxidase (CCO)). Cu^{1+} binds to the copper chaperone Cox17 in the intermembrane space of mitochondria and is then transported to Sco1 or Cox11, which deliver copper to the Cox1 or Cox2 subunits of cytochrome oxidase. While copper is essential for the function of cytochrome oxidase, the transporters and regulatory mechanisms of mitochondrial copper are still not fully understood.

Mitochondria serve as major reservoirs for copper and are the primary organelles for copper utilization inside cells [119]. In conditions of copper deficiency, cells prioritize mitochondrial copper homeostasis, indicating a crucial significance for mitochondrial copper [120]. Approximately 25% of the mitochondrial copper pool is utilized by CCO, which is the most important copper-containing enzyme in mitochondria. As the terminal enzyme of the mitochondrial respiratory chain, CCO catalyzes the transfer of electrons from reduced cytochrome C to molecular oxygen while pumping protons from the mitochondrial matrix into the intermembrane space, providing the driving force for mitochondrial ATP synthesis [121]. Therefore, alterations in copper levels can impair ETC function, lead to mitochondrial dysfunction, and exacerbate the progression of CKD. Studies have demonstrated that the overexpression of copper transporter 1 (CTR1), resulting in intracellular copper overload, can promote renal fibrosis, and that treatment with copper chelators can improve renal fibrosis [122]. Additionally, excess copper has been observed in fibrotic kidneys in both *in vitro* and *in vivo* CKD models and has been implicated in the disruption of complex IV activity, mitochondrial dysfunction, and apoptosis. COX17 plays an anti-fibrotic role in the kidney by alleviating mitochondrial copper overload and restoring complex IV activity [123].

2.4. Biosynthesis in mitochondria

With further research, mitochondria are no longer considered simple cell energy converters. Mitochondria also participate in other important cellular metabolic processes, such as the synthesis of heme, iron-sulfur clusters, lipids, and cytochromes, encompassing various crucial pathways responsible for cellular homeostasis.

2.4.1. Heme and Fe-S clusters synthesis

In mitochondria, iron is primarily involved in various functions through the formation of iron-sulfur (Fe-S) clusters and heme, both of which are integral components of the electron transport chain complexes involved in energy generation through oxidative phosphorylation. Fe-S clusters are assembled from trivalent iron within mitochondria and incorporated into Fe-S proteins in mitochondria and the cytoplasm through specific mechanisms [124]. They participate in physiological processes including ribosome regulation, biochemical reaction catalysis, protein translation, lipid synthesis, and regulation of cellular iron metabolism [111,125]. Heme, on the other hand, undergoes a complex biosynthetic process and is ultimately formed in the mitochondrial matrix [126]. It participates in the formation of hemoglobin and myoglobin, facilitating oxygen transport in red blood cells and muscles, respectively [127]. Additionally, heme is involved in promoting cytochrome P450 enzyme reactions, maintaining circadian rhythms, and signal transduction functions [128].

2.4.2. Lipogenesis

Lipogenesis is mediated by various enzymes in a precise and coordinated manner [129]. In the postprandial state, elevated blood glucose and insulin levels promote glucose uptake and glycolysis, resulting in the production of pyruvate, which enters the mitochondria as a substrate for the TCA cycle through the mitochondrial pyruvate carrier (MPC). In the TCA cycle, citrate is generated and exported from the mitochondria, then modified into malonyl-CoA and acetyl-CoA by ATP-citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC), respectively. Subsequently, fatty acid synthase (FASN) catalyzes a series of reactions, including Claisen condensation of malonyl-CoA with acetyl-CoA, ultimately yielding the key precursor, palmitic acid, for fatty acid synthesis. Other forms of lipids can be further synthesized through additional reaction pathways [130,131].

2.4.3. Cytochrome C biogenesis

Cytochrome C is an important component of the mitochondrial respiratory chain, located in the mitochondrial intermembrane space. It is synthesized from two inactive precursor molecules, apo-cytochrome C and ferrous heme. Cytochrome C is encoded by nuclear genes, translated on cytoplasmic ribosomes, and then transported into the

mitochondria, where it undergoes covalent modification and assembly with ferrous heme [132,133]. Due to its heme group, Cytochrome C can transfer electrons between respiratory complex III (cytochrome reductase) and IV (cytochrome oxidase). Lack of cytochrome C disrupts electron transport chain, resulting in ATP deficiency and cellular death [134]. In addition to its role in electron transfer, cytochrome C is closely associated with apoptosis [135]. The release of cytochrome C from mitochondria is necessary for caspase-mediated apoptosis [136]. Furthermore, upon release from mitochondria, cytochrome C can impact electron transfer in the respiratory chain, causing electron leakage from ETC and leading to excessive ROS generation, thereby inducing oxidative stress and apoptosis [137].

3. Molecular mechanism of mitochondrial dysfunction in different cells of CKD

Mitochondrial dysfunction is crucial in CKD, affecting various renal cells like tubular epithelial cells (TECs), endothelial cells, podocytes, and fibroblasts. Key factors like oxidative stress, altered mitochondrial dynamics, and impaired energy metabolism drive CKD progression. Understanding these processes can reveal new therapeutic targets to slow disease progression and improve outcomes.

3.1. Tubular epithelial cells

TECs are rich in mitochondria and are susceptible to hypoxia, drug-related toxicity, uremic toxins, metabolic disorders, senescence induced cell damage, and are the main targets of CKD [11,138,139]. The energy requirements for TECs are nearly entirely dependent on OXPHOS [15]. Post-translational modifications (PTMs) of mitochondrial proteins may alter mitochondrial function and biogenesis [140,141]. Phosphorylation and oxidation are most abundant in mitochondrial proteins under high glucose (HG) and may partially contribute to mitochondrial dysfunction of TECs [142–145]. While protein phosphorylation leads to an increase in intracellular ROS levels, apoptosis-inducing factor (AIF) restores mitochondrial homeostasis in TECs [146]. Mitochondrial DNA released from damaged TECs is considered a biomarker of mitochondrial dysfunction in CKD [11]. Angiotensin II (Ang II), lipopolysaccharide (LPS) and HG for TECs can promote the production of ROS in TECs, which interfere with mitochondrial OXPHOS and reduce cytochrome C functioning, leading to mitochondrial dysfunction [147–150]. PGC-1α, as a master regulator of mitochondrial biogenesis, is highly expressed in the medullary cortex and outer striae, where mitochondrial activity is relatively higher [151]. PGC-1a overexpression in TECs increases mitochondrial mass and serves a protective role in renal diseases in animal models [44,152,153]. Mitochondrial dynamics are involved in the progression of CKD, demonstrated by the significant impact of TEC DRP1 upregulation and MFN2 downregulation [154,155]. In summary, molecular regulation of mitochondrial biogenesis and dynamics in TECs play a key role in the progression of CKD.

3.2. Endothelial cells (ECs)

CKD is associated with mitochondrial dysfunction in renal cells, including ECs [156] and podocytes [157].Glomerular ECs are highly specialized cells with a nitrile bone and an intraluminal glycocalyx layer, and contribute to the completion of the glomerular filtration barrier [158–162].Mitochondrial dysfunction in glomerular ECs is associated with increased expression of glomerular endothelin-1 receptor type A (EDNRA) and increased circulating endothelin-1 (EDN1). The expression of EDNRA is associated with increasing mtROS, which causes mitochondrial dysfunction and mtDNA instability. Selective blockade of EDNRA or mitochondrial- targeted ROS scavenging can prevent mitochondrial OS in ECs. EDNRA, oxidized mtStress and oxidative mtDNA damage promote EC morphological damage [156]. Glomerular ECs also exhibit mitochondrial oxidative stress (mtStress) associated with endothelial dysfunction [163]. In diabetic mice with reduced glomerular mitochondrial function and increased mtDNA damage, accumulation of oxidized mtDNA is associated with OS and mitochondrial dysfunction [70]. Much research suggests that glomerular endothelial dysfunction and glycocalyx damage represent the initial steps in diabetic albuminuria [164,165]. EDNRA-induced mitochondrial dysfunction and OS have emerged as promising therapeutic strategies in kidney diseases [166]. EC damage mediated by the EDN1/EDNRA signaling pathway leads to apoptosis of podocytes., Therefore, glomerular ECs maintain mitochondrial dysfunction and oxidative mtDNA damage plays a key role in CKD development.

3.3. Podocytes

Podocytes, important components of the glomerular filtration barrier, may also be damaged by mitochondrial dysfunction. Podocyte loss is the earliest glomerular pathomorphological change and plays a key role in the progression of CKD [167–170]. The mitochondrial functions of podocytes are affected by mtRNAs, biosynthesis of coenzyme Q10, control of protein synthesis, mitochondrial fission, and mitophagy [11]. Deficiency of pyruvate kinase M2 (PKM2) in podocytes accelerates mitochondrial dysfunction, podocyte apoptosis, and glomerulopathy, which lead to the disturbance of various transcription and translation processes as well as ROS overproduction. Activation of PKM2 in podocytes can improve mitochondrial function through the TCA cycle, which improves mitochondrial dysfunction by increasing mitochondrial metabolism (including levels of PGC-1α, mitochondrial mass, etc.) [157,171–174]. PKM2 increases metabolic flux through glycolysis, and podocyte glycolytic activity may partially preserve mitochondrial function [175–177]. Otherwise, PKM2 can improve mitochondrial fusion by the enhancement of OPA1 [178]. ABCA1 deficiency leads to mitochondrial oxidative phosphorylation and mitochondrial dysfunction, which can lead to podocyte injury. HG and aldosterone induce increased ROS in mouse podocytes through the ROS/Nox4 system, resulting in mitochondrial dysfunction and increased apoptosis [179,180]. Therefore, ABCA1 may delay the development of CKD by improving mitochondrial function in podocytes.

3.4. Fibroblasts

Fibroblasts are derived from various sources, including peritubular capillary pericytes, interstitial fibroblasts, leukocytes, endothelial cells, and injured epithelial cells [6,181–183]. Interstitial fibroblast dysfunction is the key pathogenic process of CKD progression [152,184–188].The intramitochondrial signaling pathway regulates the phosphorylation of cytochrome oxidase (COX), which plays an important role in the regulation of mitochondrial function in fibroblasts [189]. Under hypoxic conditions, the cell's primary metabolic mode shifts from mitochondrial respiration to glycolysis [190]. During the development of renal fibrosis, the metabolism of myofibroblasts shifts from oxidative phosphorylation to glycolysis [191]. Mitochondrial fusion promotes mitochondrial oxidative phosphorylation and reduces glycolysis, whereas mitochondrial fission exacerbates glycolysis [192,193]. Abnormal mitochondrial morphology increases expression of glycolytic enzymes and proliferation of interstitial fibroblasts [194]. Drp1-mediated mitochondrial fission leads to increased glycolysis and fibroblast activation by TGF-β1 [31]. p-Drp1S616 promotes mitochondrial fission in fibroblasts and leads to renal fibrosis, but p-Drp1S637 inhibits its activity and causes mitochondrial elongation [31]. Traditional medicines improve mitochondrial dynamics, morphology and function by regulating Drp1-induced mitochondrial fission [195,196]. Therefore, the modulation of mitochondrial dynamics in fibroblasts may become a new therapeutic strategy against renal fibrosis.

3.5. Other cells

3.5.1. Mesangial cells

HG causes the accumulation of intracellular ROS (of which Nox may play a role), cytokines and advanced glycation end products (AGEs) in the mesangium, resulting in DKD [197]. Alleviating OS by reducing AGE-induced NF-κB stimulation, protein kinase C (PKC) activation, and antioxidant-induced (vitamin E and nitrophenone) TGFβ1 transcription in the mesangial cell may prevent the development of DKD [198,199].

3.5.2. Macrophages

Macrophages play an integral role in inflammation and progression of renal fibrosis [200]. Mitophagy plays a key role in preserving renal function by maintaining MQC and pathological states. PINK1/PRKN-mediated macrophage mitophagy is functionally impaired in CKD renal fibrosis, and the mitophagy regulator MFN2 and PINK1 downregulate PRKN in renal fibrosis, which promotes the accumulation of ECM, interstitial fibrosis, and transformation of M2 macrophages. Therefore, macrophage mitophagy can regulate the PINK1/MFN2/PRKN-mediated pathway to prevent renal fibrosis. Loss of this mitophagy pathway produces abnormal mitochondrial aggregation and increased mtROS production [201].

3.5.3. Immune cells

Innate immune cells, such as the regulatory T cells, are recruited in response to damage-associated molecular patterns released by necrotic cells in renal damage [202]. Regulatory T cells counteract pro-inflammatory responses through contact-dependent mechanisms and production of anti-inflammatory IL-10, thereby limiting excessive inflammation to promote repair processes. T cells are also thought to release anti- inflammatory cytokines and promote renal recovery [203]. Mitochondrial oxidative stress and damage underlie functional defects of regulatory T cells in autoimmunity [204]. The role of mitochondrial dysfunction in various renal cells of CKD is summarized in Table 1.

Overall, mitochondrial issues disrupt cellular balance and promote kidney damage in CKD. The crucial role of mitochondria in CKD is highlighted by the involvement of mitochondrial oxidative stress, changes in dynamics, and metabolic reprogramming in various cell types like TECs, ECs, podocytes, and fibroblasts. Grasping these mechanisms is crucial for creating targeted treatments that preserve mitochondrial function and decelerate the advancement of kidney fibrosis and failure.

4. Mitochondrial dysfunction in regulatory cell death in CKD

Mitochondria not only serve as the center for cellular energy metabolism but also regulate cell death through various mechanisms, thereby playing vital roles in organism development, internal homeostasis, and organ development. Regulated cell death (RCD) can be activated by various stimuli, including excessive production of reactive oxygen species (ROS), metabolic disturbances, and damage to energy generation. RCD is closely associated with various kidney diseases, and targeting RCD and its signaling pathways has shown promise in the prevention and treatment of CKD.

4.1. Mitophagy

Autophagy is a cellular recycling process that involves the degradation and recycling of damaged organelles and proteins, which is beneficial for maintaining renal physiological function and homeostasis [211]. Mitophagy, a type of autophagy specifically targeting dysfunctional mitochondria, is an important mechanism involved in multiple processes related to the pathogenesis of CKD [27]. It activates through PTEN-induced kinase 1 (PINK1)/Parkin pathway and receptor-mediated mitophagy to maintain mitochondrial quality control, thereby reducing local oxidative damage and inflammation and exerting a protective effect on the kidneys [37–39]. PARKIN-dependent mitophagy is the major autophagic pathway that recognizes and links polyubiquitinated substrates on the mitochondrial membrane through LC3 adaptors, guiding mitochondria into autophagosomes [212]. In contrast to LC3 adaptors that rely on ubiquitinated protein substrates on the mitochondrial membrane, mitophagy receptors can directly interact with LC3 to guide damaged mitochondria into autophagosomes. Known mitophagy receptors include NIX, BNIP3, FUNDC1, BCL2L13, FKBP8, PHB2, and cardiolipin [213].

Research has shown that high glucose (HG) can accelerate mitochondrial dysfunction and podocyte apoptosis by

Table 1. The roles of mitochondrial dysfunction in various renal cells of CKD.

Cells	Pathways	Factors	Model	Mechanisms	Effect	Reference
Tubular epithelial cells	Up-regulation of DRP1 and down-regulation of MFN2	AIF, OXPHOS, ROS; cyto c; mtDNA; Nox4; iNOS; $O2^-$; PI3K; Akt; GSK3; mtDNA; DRP1; MFN2	HG for HK2 cells; Ang II for HK2 cells; LPS for mProx; STZ for mice; IRI for mice	1. Mitochondrial protein phosphorylation and oxygen 2. Restored mitochondrial oxidative phosphorylation of OXPHOS 3. Increase mitochondrial mtDNA levels 4. Up-regulation of DRP1 and down-regulation of MFN2	Mitochondrial biodynamics and abnormal division and fusion of mitochondrial organisms	[15,44,140–155,205–209]
Endothelial cells	EDN1/EDNRA signaling pathway mediated endothelialcell injury	EDN1, EDNR, mtStress, mtROS, mtDNA	HG for murine glomerular endothelial cells (mGECs); HG for glomerular endothelial cells (GECs); STZ for mice	Increase mtStress, mitochondrial ROS, fragmentation, and mtDNA instability	Mitochondrial oxidative stress and mitochondrial oxidative mtDNA; Increased mitochondrial ROS	[156–166,210]
Podocytes	TCA,ABCA1,ROS/Nox4 pathway	PKM2;TCA; PGC-1α, MMPOPA1 ABCA1, ROS/ Nox4(PKM2); PGC-1α, MMP; OPA1; ROS/Nox4	HG for PKM2-knockdown podocytes; TEPP-46 for podocytes; HK2 cells; STZ for podocyte specific PKM2-KO mice (PPKM2-KO);TEPP-46 for mice	1. PKM2 activation to improve levels of mitochondrial metabolism and mitochondrial mass 2. Enhance OPA1 activity, induce mitochondrial fusion to improve mitochondrial dysfunction 3. ABCA1 deficiency leads to cardiolipin accumulation and mitochondrial oxidative phosphorylation changes *via* the ROS/Nox4 system	Mitochondrial biogenesis and mitochondrial kinetics, oxidative phosphorylation	[167–180]
Fibroblast cells	Drp1-mediated mitochondrial fission	Drp1; p-Drp1S616; H3K27; PGC-1a; PKA; COX4	UUO for mice; TGF-β for NRK-49F; A/I for rats; SSR or Fenofibrate for rats; Hypoxia for NRK-52E cells; SSR / glycolysis inhibitors for NRK-52E cells	1. Enhanced mitochondrial respiration and phosphorylation 2. Mitochondrial division leads to increased glycolysis and fibroblast activation 3. PGC-1α overexpression increases mitochondrial mass	Mitochondrial dynamic changes and biogenetic abnormalitie	[31,181–188,190–196]
Other cells Mesangial cells	Antioxidants, prevented AGE-dependent NF-κBactivation and normalized PKC activity and associated TGFβ1 transcription	Nox; AGE; NF-κB; PKC; TGFβ1	AGE-BSA and H_2O_2 for rat renal mesangial cells	Reduce AGE-induced NF-κB stimulation, PKC activation, and antioxidant effects on TGFβ1 transcription	Mitochondrial ROS accumulation	[197–199]
Macrophages	PRKN-mediated mitophagy pathway	PINK1; MFN2; PRKN	UUO for mice; TGF-β for THP-1–derived human macrophages	Regulate PINK1/MFN2/ PRKN-mediated mitophagy pathway	Abnormal mitophagy; Increased mtROS	[200,201]
Regulatory T cell	regulation of IL-10 expression	IL-10	IRI for mice; IL-10 for DN T cells	Release anti-inflammatory cytokines	Mitochondrial oxidative stress	[202,203]

DRP1: dynamin-related protein 1; MFN2: mitofusin 2; AIF: apoptosis-inducing factor; OXPHOS: oxidative phosphorylation; ROS: reactive oxygen species; PI3K: phosphoinositol 3-kinase; AKT: V-akt murine thymoma viral oncogene homolog; GSK3: glycogen synthase kinase-3; HG: high glucose; LPS: lipopolysaccharide; STZ: streptozotocin; IRI: ischaemia-reperfusion injury; EDN1: endothelin-1; EDNRA: endothelin-1 receptor type A; mtStress: mitochondrial oxidative stress; TCA: tricarboxylic acid; ABCA1: ATP-binding cassette transporter A1; NOX4: NADPH oxidase 4; PKM2: pyruvate kinase M2; AGE: advanced glycation end product; PKC: protein kinase C; PGC-1a: the transcriptional coactivator peroxisome proliferator activated receptor gamma coactivator 1; MMP, matrix metalloproteinases; PKA: protein kinase A; COX4: cytochrome C oxidase 4; UUO: unilateral ureteral obstruction; PRKN: parkin RBR E3 ubiquitin-protein ligase; PINK1: PTEN-induced putative kinase 1; IL-10: interleukin-10; OPA1: optic atrophy protein 1; NF-κB: nuclear factor-kappa B; SSR: severe steroid-resistant asthma; TEPP-46: a PKM2 agonis.

inhibiting mitochondrial autophagy [42,214]. Overexpression of FOXO1 in podocytes activates PINK1/Parkin-dependent mitophagy, degrades dysfunctional mitochondria, and alleviates podocyte injury [214]. In a mouse model of diabetic kidney disease (DKD), the expression of nuclear receptor subfamily 4 group A member 1 (NR4A1) was upregulated and suppressed PARKIN-mediated mitophagy. Knockout of NR4A1 restored PARKIN-mediated mitophagy, suppressed ROS production, improved mitochondrial function and ATP production, and alleviated the progression of DKD [215].

4.2. Apoptosis

Apoptosis is a non-inflammatory self-defense mechanism that helps the body eliminate damaged or abnormal cells to maintain tissue and organ homeostasis, with mitochondria playing a crucial role in this process. Apoptosis is mediated by two signaling pathways: the intrinsic mitochondrial pathway and the extrinsic death receptor pathway [216]. Dysregulation of these processes may contribute to the pathogenesis of various diseases, including CKD [217]. Under stress conditions such as calcium overload, DNA damage, and oxidative stress, the pro-apoptotic proteins of the Bcl-2 family are activated, leading to the activation and clustering of BAX and BAK in the outer mitochondrial membrane, resulting in the formation of pores that allow the release of apoptotic molecules, such as cytochrome c, into the cytoplasm. Cytochrome c then binds with the pro-apoptotic factor APAF-1 and dATP to form the apoptosome and gradually activate caspase-9 and caspase-3, eventually leading to apoptosis [218]. Genome-wide association studies on kidney function have identified Caspase-9 as a risk gene for kidney disease. Silencing Caspase-9 to alleviate apoptosis can protect mice from kidney injury and fibrosis [219].

4.3. Ferroptosis

Ferroptosis is an iron-dependent form of regulated cell death [220,221], characterized by intracellular iron overload and accumulation of reactive oxygen species (ROS), leading to lipid peroxidation. This process is regulated by the system χc-/GPX4/GSH signaling pathway. Overall, mitochondria may play multiple roles in ferroptosis, including iron metabolism, ROS generation, and lipid peroxidation, with a central aspect being the accumulation of cellular reactive oxygen species beyond the capacity of reduced glutathione (GSH) and the oxidative-reduction ability of phospholipid hydroperoxide glutathione peroxidase, which uses GSH as a substrate [222,223]. Ferroptosis is associated with various diseases and pathological conditions. It can serve as a tumor suppressive mechanism [224,225] but can also promote the development of various diseases when excessively activated [226–229].

Ferroptosis is closely related to the pathological and physiological mechanisms of CKD. Studies have found that the renal iron content is significantly increased in diabetic rats, and blood creatinine and urinary protein levels are positively correlated with kidney iron levels and iron proteins [230]. In STZ-induced diabetic mice, iron overload, reduced antioxidant capacity, accumulation of ROS, lipid peroxidation, and morphological changes in mitochondria indicative of ferroptosis can be detected in the kidneys [231]. UUO treatment can induce ferroptosis in renal tubular epithelial cells and promote secretion of fibrogenic factors [232]. Conversely, inhibiting ferroptosis can alleviate kidney damage in CKD. In TGF-β1-stimulated renal tubular epithelial cell injury, SLC7A11 and GPX4 expression is reduced, but ferroptosis inhibitor Ferrostatin-1 (Fer-1) can mitigate gene expression reduction [233]. In a 5/6 nephrectomy-induced CKD rat model, deferoxamine alleviates renal damage and fibrosis by regulating iron metabolism and the TGF-β1/Smad3 pathway [234]. These studies indicate the importance of ferroptosis in the progression of CKD, and signify that the targeting ferroptosis for therapy may prevent renal fibrosis in CKD patients and hold potential therapeutic prospects.

4.4. Cuproptosis

Cuproptosis is a novel form of copper-dependent cell death that may be associated with various cancer processes [235]. The mechanisms and specific forms of cuproptosis cell death have long been unclear, but recent research suggests that cuproptosis is an independent form of cell death. Excess copper directly binds to sulfhydrated proteins in the mitochondrial TCA cycle, leading to abnormal aggregation of sulfhydrated proteins and loss of iron-sulfur cluster proteins in the respiratory chain complex, causing protein toxicity stress response and ultimately resulting in cell death [236]. When disrupted, copper homeostasis or cuproptosis can promote the occurrence of a range of diseases, such as tumors, cardiovascular diseases, and obesity [236]. However, the role and regulatory mechanisms of cuproptosis in CKD are yet to be elucidated.

4.5. Interplay of mitophagy, apoptosis, ferroptosis and cuproptosis in CKD

There is complex crosstalk among different types of regulated cell death (RCD). These interactions are crucial for maintaining cellular health and regulating physiological processes.

Studies have shown that the Bcl-2 family of proteins plays a critical regulatory role between mitochondrial autophagy and apoptosis. The pro-apoptotic members (BAX and BAK), when stimulated or activated, undergo conformational changes and induce changes in the outer mitochondrial membrane permeability (MOMP), leading to the release of apoptotic factors. The anti-apoptotic members (such as Bcl-2 and Bcl-xL) bind to BAX/BAK and inhibit their activity, preventing MOMP and exerting anti-apoptotic effects. Additionally, Bcl-2/Bcl-xL can interact with mitochondrial autophagy regulatory proteins such as Beclin1 through BH3-only domains, which inhibit the Beclin1 activity and hinder autophagosome formation, thereby suppressing the initiation of mitochondrial autophagy. Caspases can cleave

Beclin1 protein when cells are subjected to stress stimuli, disrupting its autophagic activity [237,238]. Furthermore, the C-terminal fragment generated by Beclin1 cleavage can amplify mitochondria-mediated apoptosis [237]. The role of Bcl-2 family proteins in regulating autophagy and apoptosis in CKD has been widely studied [239–242]. In a high glucose-induced mouse podocyte (MPC5) model, treatment with wogonin (a flavonoid extracted from Scutellaria root) decreased the binding of Beclin1 to Bcl-2 and increased the binding of BAX with Bcl-2 to exhibit inhibitory effects on apoptosis. *In vivo* experiments showed that wogonin treatment significantly reduced proteinuria and inflammatory levels in a streptozotocin-induced type 1 diabetes mouse model, ultimately slowing down the progression of kidney dysfunction [243]. In addition to their roles in apoptosis and mitochondrial autophagy, Beclin1 can interact with SLC7A11 to inhibit system Xc- activity, induce lipid peroxidation, and aggravate ferroptosis [244]. However, the involvement of Beclin1 in autophagy may contribute to the clearance of harmful oxidative products and alleviate the severity of ferroptosis, and this dual regulation phenomenon may depend on environmental conditions or other molecular interactions.

P53 protein is an important tumor suppressor protein and is considered a guardian in cellular biology, playing a crucial role in various regulated cell death processes. P53 can activate transcription of BAX and APAF-1 [245,246] or interact with BAK at the mitochondrial level, inactivating the anti-apoptotic genes, BCL-2 and BCL-xL, to induce MOMP [247] and apoptosis. Accumulation of iron and lipid peroxidation are two major features of ferroptosis. Transferrin receptor 1 (TfR1) is responsible for cellular iron uptake and is considered one of the specific markers of ferroptosis [248]. P53 regulates TfR1 levels in a transcription-dependent manner and mediates iron overload [249]. Additionally, P53 can downregulate the expression of SLC7A11, leading to reduced glutathione (GSH) biosynthesis and eventually resulting in lipid peroxidation and ferroptosis [224,250]. As an important metabolic regulator, P53 can modulate copper homeostasis, enhance Fe-S cluster biogenesis, and coordinate the levels of the copper chelator GSH, leading researchers to speculate that P53 may play a regulatory role in cuproptosis [251]. Cross-talk among different types of cell death is summarized in Figure 2.

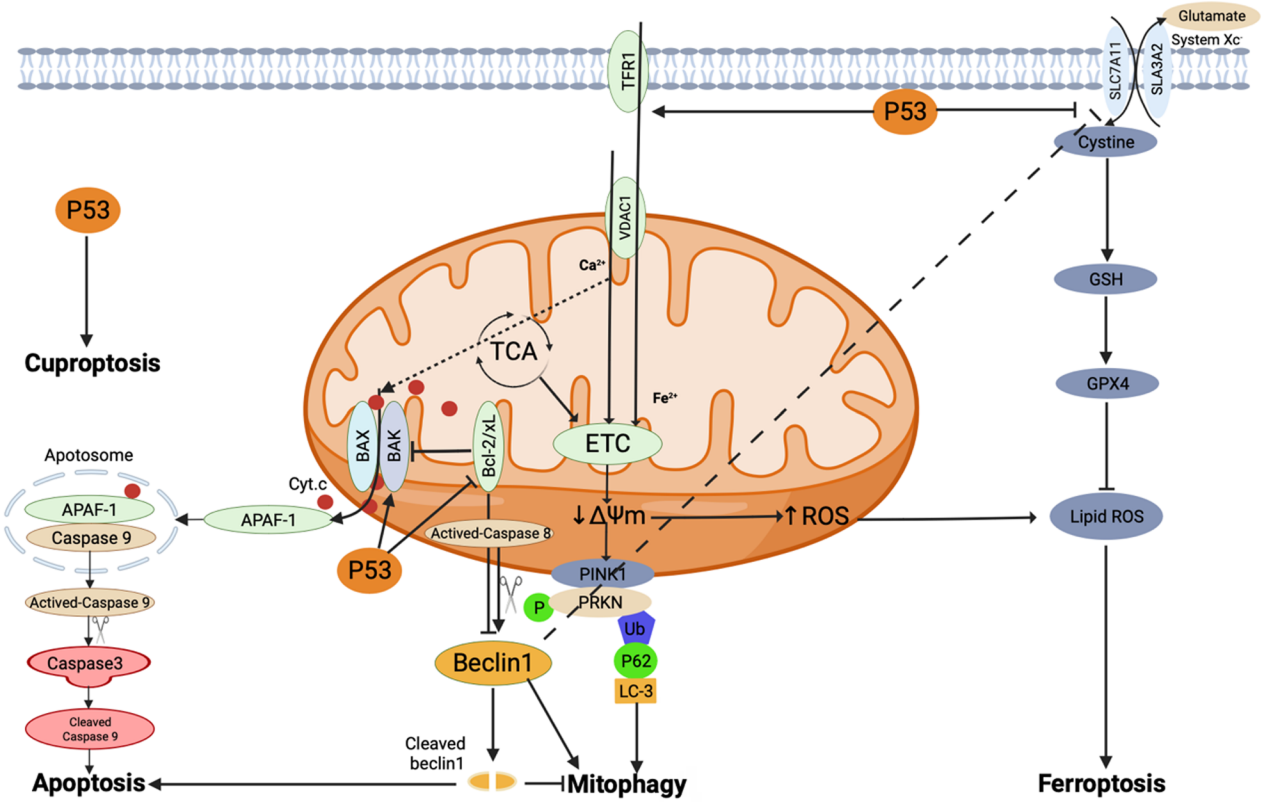


Figure 2. Cross-talk among different types of cell death. Stimulation or activation of the pro-apoptotic proteins BAX and BAK can induce changes in the permeability of the mitochondrial outer membrane, leading to the release of apoptotic factors and triggering cell apoptosis. The anti-apoptotic members Bcl-2 and Bcl-xL bind to BAX/BAK and inhibit their activity, preventing mitochondrial outer membrane permeabilization (MOMP) and exerting anti-apoptotic effects. Moreover, Bcl-2/Bcl-xL can interact with the BH3-only domain of mitochondrial autophagy regulatory proteins such as Beclin1, hindering the formation of autophagosomes and suppressing mitochondrial autophagy. Caspases can cleave the Beclin1 protein, impairing mitochondrial autophagy activity, and the C-terminal fragment generated by Beclin1 cleavage mediates apoptosis. Beclin1 can also interact with SLC7A11 to inhibit system Xc- activity, induce lipid peroxidation, and exacerbate ferroptosis. P53 can activate the transcription of BAX and APAF-1 or inhibit BAK to induce MOMP and subsequently promote cell apoptosis. TfR1 is responsible for cellular iron uptake, and P53 regulates TfR1 levels in a transcription-dependent manner, mediating iron overload. Furthermore, P53 can downregulate the expression of SLC7A11, leading to reduced glutathione (GSH) biosynthesis and ultimately resulting in lipid peroxidation and ferroptosis. Studies have shown that P53 may play an important regulatory role in cuproptosis. BAX: BCL-2-associated X protein; BAK: BCL2 antagonist/killer 1; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; MOMP: mitochondrial outer membrane permeabilization; BH3: Bcl-2 homology domain 3; SLC7A11: solute carrier family 7 member 11; APAF-1: apoptotic protease activating factor 1; TfR1: transferrin receptor 1; GSH: glutathione; P53: tumor protein 53; GSH: glutathione; GPX4: glutathione peroxidase 4; VDAC1: voltage-dependent anion channel 1; ETC: electron transport chain; TCA: tricarboxylic acid cycle; PINK1: PTEN-induced putative kinase 1; PRKN: parkin RBR E3 ubiquitin-protein ligase; P62: sequestosome-1 (SQSTM1); LC-3: microtubule-associated protein 1 light chain 3; Cyt.c: cytochrome C; ROS: reactive oxygen species.

5. Epigenetic regulation of mitochondrial dysfunction in CKD: roles of non-coding RNAs and DNA methylation

Recent studies [29,252,253] emphasize the role of epigenetic regulators, such as non-coding RNAs (ncRNAs) and DNA methylation, in mitochondrial function and CKD progression. ncRNAs, including microRNAs and long non-coding RNAs, influence mitochondrial dynamics, mitophagy, and oxidative stress, which are vital in CKD development. For instance, lncRNA (Meg3) [254] is elevated in podocytes of both DKD and diabetic mice, promoting mitochondrial fission and podocyte injury *via* Drp1. Besides, lncRNA 585189 [255] inhibits SIRT1 through hnRNP A1, impeding recovery from mitochondrial issues and podocyte damage. Thus, targeting lncRNA 585189 could be a promising approach for treating DKD by reversing mitochondrial dysfunction.

Additionally, DNA methylation affects mitochondrial gene expression and activity, influencing cellular stress responses [256]. In Type 1 diabetes, changes in methylation linked to mitochondrial function are connected to kidney disease [257]. Zhao et al. [258] found that mitochondria-targeted antioxidants like Mito-TEMPO can reverse the epigenetic suppression of NDRG2, suggesting that addressing ROS-induced hyper-methylation of the NDRG2 promoter could be an effective treatment for renal fibrosis. This approach highlights the potential of targeting epigenetic regulators to develop new therapies for CKD by improving mitochondrial function and reducing oxidative stress and fibrosis.

6. Clinical relevance and translational challenges

Researchers are exploring various drugs targeting mitochondrial pathways to treat CKD by addressing mitochondrial dysfunction. Mitochondrial-targeted antioxidants like MitoQ [38] and MitoTEMPO [259] are designed to neutralize ROS in mitochondria. In CKD, high metabolic demands in the kidneys cause excessive ROS, worsening renal damage. These antioxidants, linked to lipophilic cations, accumulate in renal cell mitochondria, reducing oxidative stress and protecting against renal dysfunction and fibrosis. Additionally, mitophagy enhancers like Urolithin A [261] are studied for their ability to clear damaged mitochondria, maintaining mitochondrial health and reducing cell injury. In CKD, impaired mitophagy leads to the buildup of dysfunctional mitochondria, further harming the kidneys. Drugs that boost mitochondrial biogenesis, like PGC-1α activator [260,261], are being explored to enhance new mitochondria production, potentially restoring energy in renal cells and reducing kidney damage. Additionally, modulators of mitochondrial dynamics, such as DRP1 inhibitors or MFN2 activators [262–265], aim to correct the imbalance between mitochondrial fission and fusion in CKD, potentially preventing kidney fibrosis and functional decline. Despite their promise, these therapies are still in early stages, with challenges like drug delivery, long-term safety, and patient variability needing resolution before widespread use.

To monitor mitochondrial dysfunction and therapeutic responses, several biomarkers have been suggested. Circulating mitochondrial DNA (mtDNA) and exosomal mitochondrial tRNAs and miRNAs are promising markers [256,266,267], as they indicate mitochondrial damage and is often elevated in CKD patients, signaling early damage and providing insights into renal cell damage and dysfunction. Mitochondrial protein levels, such as changes in mitochondrial inner membrane proteins, ATP synthase, and antioxidant enzymes, may also serve as markers of mitochondrial function [268,269]. While these biomarkers show promise in experimental studies, their clinical accuracy and reliability need further validation. Additionally, patient stratification is challenging [270,271], as CKD patients exhibit varying degrees of mitochondrial dysfunction. Identifying patients who will benefit from mitochondrial-targeted therapies is essential for effective treatment. Personalized patient stratification allows for more precise strategies. While biomarkers offer new treatment possibilities for CKD, further clinical studies are needed to confirm their diagnostic and therapeutic roles.

7. Conclusion

Mitochondria are integral to cells characterized by high energy demands. Recent studies have demonstrated that, beyond their role in ATP production, mitochondria significantly influence the pathophysiology of kidney diseases. While elucidating the mechanisms underlying mitochondrial dysfunction in various renal cell types is critical for the development of targeted therapeutic strategies, current research is constrained by several limitations. The majority of research concerning mitochondrial dysfunction in CKD is predominantly in the preliminary phases of fundamental experimentation and has yet to be translated into clinical practice. Furthermore, our comprehension of the precise mechanisms through which mitochondrial dysfunction contributes to cellular apoptosis and fibrosis is still inadequate. Consequently, targeted interventions aimed at rectifying mitochondrial dysfunction to decelerate the progression of CKD remain largely uninvestigated. Continued research is essential to elucidate the molecular pathways of mitochondrial involvement in CKD, thereby informing the development of novel therapeutic targets.

Acknowledgments

Jinhu Chen, and Qiuyuan Zhou drafted the manuscript. Lianjiu Su and Lihua Ni contributed to the conception and design of the study. All authors have read and agreed to the published version of the manuscript.

Author contributions

CRediT: **Jinhu Chen**: Formal analysis, Software, Writing – original draft; **Qiuyuan Zhou**: Writing – original draft; **Lianjiu Su**: Conceptualization, Software, Supervision; **Lihua Ni**: Conceptualization, Writing – original draft.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by grants from the National Natural Science Foundation of China [82200807], Hubei Natural Science Foundation Innovation Development Joint Fund [2025AFD383], Outstanding Young and Middle-aged Talents Training Program of Zhongnan Hospital of Wuhan University [ZNYQ2022007]. The Research Fund from Medical Sci-Tech Innovation Platform of Zhongnan Hospital, Wuhan University [ZNXKPY2022049].

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