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REVIEW ARTICLE

Mitochondrial dysfunction in acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) is a systemic clinical syndrome increasing morbidity and mortality worldwide in recent years. Renal tubular epithelial cells (TECs) death caused by mitochondrial dysfunction is one of the pathogeneses. The imbalance of mitochondrial quality control is the main cause of mitochondrial dysfunction. Mitochondrial quality control plays a crucial role in AKI. Mitochondrial quality control mechanisms are involved in regulating mitochondrial integrity and function, including antioxidant defense, mitochondrial quality control, mitochondrial DNA (mtDNA) repair, mitochondrial dynamics, mitophagy, and mitochondrial biogenesis. Currently, many studies have used mitochondrial dysfunction as a targeted therapeutic strategy for AKI. Therefore, this review aims to present the latest research advancements on mitochondrial dysfunction in AKI, providing a valuable reference and theoretical foundation for clinical prevention and treatment of this condition, ultimately enhancing patient prognosis.

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1. Introduction

Acute kidney injury (AKI) is a common and life-threatening clinical emergency characterized by a rapid deterioration of renal function [1]. It has a high incidence and mortality rate; approximately 13 million people suffer from AKI, and 1.7 million deaths occur each year [2]. The incidence of AKI among hospitalized patients in high-income countries is up to 20%, affecting approximately 50% and 25% of adult and pediatric patients in intensive care, respectively [3,4]. AKI is caused by nephrotoxic drugs, sepsis, rhabdomyolysis, urinary tract obstruction, and ischemia-reperfusion injury (IRI), among others [5]. There are no definite preventive or therapeutic measures for AKI, except for dialysis to relieve symptoms [6]. AKI is an important factor leading to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [7]. Approximately 30%–70% of patients with AKI develop CKD within one year with approximately 17% of cases progressing to ESRD [8]. Additionally, the 5-year rehospitalization rate is 32.4% with more than 2 million AKI-related deaths annually worldwide [9]. Mitochondria play a critical role in both the physiological functioning and pathological processes of the kidney [10]. They serve as a central hub in renal cell metabolism and signaling [11]. These organelles generate adenosine triphosphate (ATP) necessary to power energy-intensive reabsorption mechanisms of water and solutes across the nephron [12]. Most ATP generated during aerobic respiration is produced through the transfer of electrons to the electron transport chain (ETC) during oxidative phosphorylation. This process starts with glucose fueling the TCA cycle *via* glycolysis, transferring electrons to complexes I and II of the mitochondrial inner membrane ETC [13]. Electrons then move through the ETC to complex IV, where they combine with molecular oxygen. As electrons pass through complexes I, III, and IV, protons are pumped into the intermembrane space, facilitating the conversion of ADP to ATP by ATP synthase (complex V) [14]. Dysfunctional mitochondria cause a decrease in ATP production, inflammation, and/or renal epithelial cell death [12,15,16]. In addition to generating ATP from glucose, mitochondria coordinate numerous other biosynthetic and catabolic pathways. These include fatty acid β-oxidation, heme biosynthesis, steroidogenesis, ketogenesis, gluconeogenesis, and amino acid metabolism [17]. Presently, investigations into mitochondrial dysfunction in AKI predominantly rely on mouse and cell models in the realm of medical research. Several studies have shown that mitochondrial dysfunction influences the injury, repair, and progression of AKI [18–20]. Various mitochondrial quality control mechanisms are involved in regulating mitochondrial integrity and function to withstand stress and maintain the integrity and function of organelles, including antioxidant defense, protein quality control, mtDNA repair, mitochondrial dynamics (fusion and fission), mitophagy, and mitochondrial biogenesis [21]. Therefore, maintaining the integrity and function of the mitochondria is essential for cell homeostasis. In this review, we

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discuss the mechanisms and potential therapeutic approaches associated with mitochondrial dysfunction in the pathogenesis of AKI.

2. Renal energy metabolism

The kidney is one of the highest energy-consuming organs and requires a large amount of energy to actively maintain various metabolic, plasma hemodynamics, electrolyte and water homeostasis, nutrient reabsorption, and hormone secretion. The kidney exhibits the second highest mitochondrial content and oxygen consumption after the heart [22]. In the renal cortex, where there is abundant oxygen delivery and dense mitochondria, energy is created through aerobic metabolism with essentially no glycolysis. The renal cortex depends primarily on oxidation of fatty acids for Krebs cycle substrates. Almost all of ATP utilized by the renal tubules is dedicated to active reabsorption, and the production of ATP through oxidative phosphorylation adapts to meet the resorptive requirements of the tubules [23].

3. Mitochondrial dysfunction in renal tubule epithelial cells (TECs)

The development of AKI is influenced by a multitude of factors and encompasses a variety of cell types within renal tissue. Among these, the damage and subsequent death of renal TECs are recognized as the primary pathological mechanisms underlying AKI. As the primary component of the renal cortex, TECs are the main target cells of kidney injury due to their low tissue blood flow and oxygen supply, as well as the accumulation and concentration of various harmful substances in these cells [24,25]. Due to the high mitochondrial content of TECs, cellular injury can lead to changes in mitochondrial metabolism, the production of reactive oxygen species (ROS), an imbalance in calcium homeostasis, and cell apoptosis [26] (Figure 1). Cumulatively, mitochondrial defects in renal tubules contribute to epithelial atrophy, inflammation, or cell death, thereby driving the development of kidney diseases [11].

The highly dynamic nature of mitochondrial morphology, including changes in length, shape, size, and number, allows for the coordination of mitochondrial metabolism in response to cellular needs [27]. Various injurious stimuli, such as inflammatory cytokines, ischemia-reperfusion, drug, and toxins, can damage mitochondria [23]. This damage disrupts the normal vectorial pumping of protons across the inner mitochondrial membrane by enzymatic complexes in the ETC. Subsequent loss of membrane potential impairs selective permeability, leading to mitochondrial swelling. AKI leads to mitochondrial fragmentation, swelling, formation of vacuoles, and disappearance of mitochondrial cristae [28]. In certain animal models of AKI, we observed sepsis induced AKI(SI-AKI) or IRI-AKI may lead to a decrease in mitochondrial number and alterations in ultrastructure due to the depletion of ATP and a decrease in membrane potential [29,30]. SI-AKI is characterized by tubular cell death, interstitial inflammatory cell infiltration, and mitochondrial dysfunction [31]. Conspicuous pathological alterations over time, including severe vacuolar degeneration,

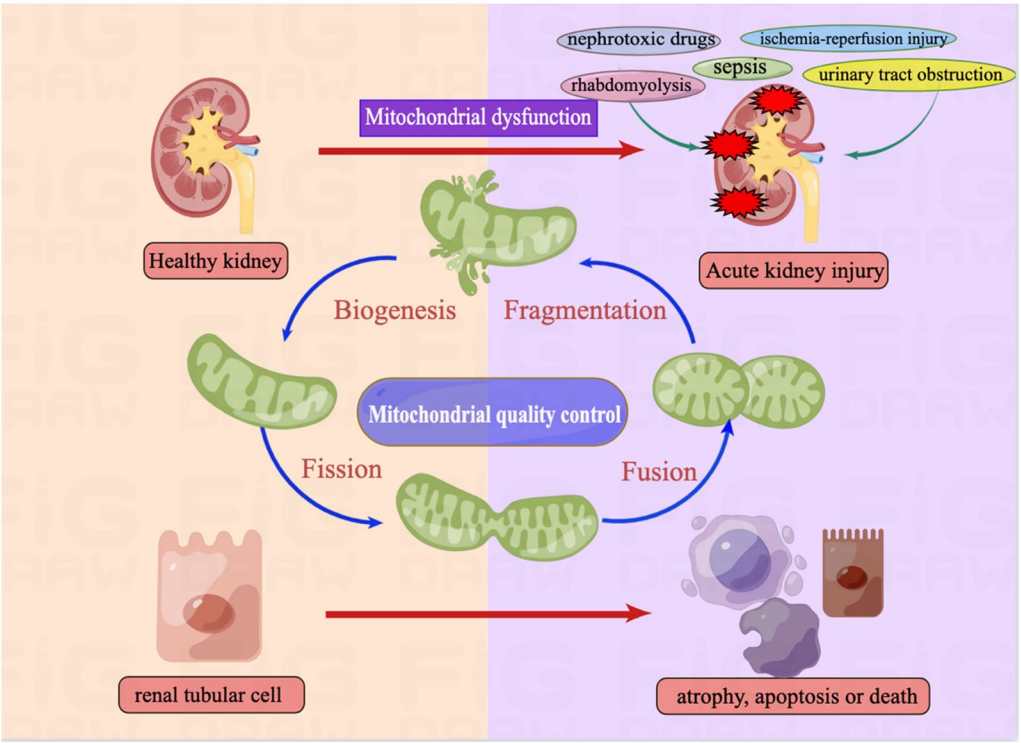

Figure 1. Mitochondrial dysfunction in AKI. After the kidney is damaged by various factors, under the involvement of a variety of mitochondrial quality control mechanisms, severe hypoxia, and acidosis of TECs lead to atrophy, necrosis, and apoptosis.

detachment of TECs and tubular lumen dilatation showed in lipopolysaccharide (LPS)-induced septic AKI mice [32]. In SI-AKI, there is an upregulation of autophagy and apoptosis [33]. In IRI-AKI, mitochondrial fragmentation, autophagy, and apoptosis are elevated [34,35]. Furthermore, prior investigations have documented that the pathogenesis of contrast induced AKI (CI-AKI) includes the cytotoxic impact of iodinated contrast media leading to oxidative stress, endothelial injury, and secretion of vasoconstrictors affecting the TECs. Finally, mitochondrial dynamics dysregulation has been documented in both an *in vivo* murine model of cisplatin-induced AKI (CisI-AKI) and an *in vitro* cellular model using HK-2 cells [36–39]. Additionally, in toxic AKI, there is an increase in both autophagy and mitochondrial fragmentation alongside a decrease in synthesis [40,41]. These results provide hope for patients with AKI by improving renal tubular mitochondrial dysfunction [42]

4. Mitochondrial energy metabolism and AKI

Mitochondria are highly dynamic and morphologically plastic organelles in cells, containing their unique DNA, and consisting of four components including the inner membrane (IMM), outer membrane (OMM), membrane gap (IMS), and matrix. Their roles in cellular respiration, production of ROS, and oxidative phosphorylation (OXPHOS) enable them to produce ATP for energy production [43]. Once mitochondria are damaged, not only are there morphological and functional changes, but also the accumulation of damaged mitochondria can result in several pathological changes, including the accumulation of by-products ROS, a decrease in mitochondrial membrane potential, and the translocation of apoptotic proteins [44]. Mitochondrial dysfunction precipitates a significant release of ROS, which in turn trigger apoptosis and proinflammatory pathways, exacerbating the injury [28,45]. Studies have shown that LPS-induced AKI is associated with hexokinase activation and increased glucose-6-phosphate dehydrogenase activity, which enhance pentose phosphate pathway activity [46–49]. Sepsis induces a metabolic shift driven by the mammalian target of rapamycin complex 1 (mTORC1)–induced stabilization of hypoxia-inducible factor–1α (HIF-1α) [46]. When ATP levels decrease, AMP-activated protein kinase (AMPK), an essential sensor of energy deficit states, becomes activated. AMPK activation facilitates mitochondrial biogenesis and mitophagy through the induction of peroxisome proliferator-activated receptor (PPAR) γ coactivator 1α (PGC-1α) [50]. Additionally, AMPK boosts glycolytic flux, fatty acid oxidation, and glucose transport [51]. During SI-AKI, modulating metabolism by reducing OXPHOS and mitochondrial ROS production, optimizing energy expenditure, and strengthening cellular defenses against oxidative damage helps stabilize energy balance through mitochondrial biogenesis and mitophagy. Furthermore, the impaired combustion of fuel in AKI results in the intracellular accumulation of fatty acids, which serve as the principal fuel for the renal cortex [52]. This accumulation may contribute to cellular dysfunction and death through lip toxicity, ultimately fostering fibrosis [53].

AKI leads to a reduction in local nicotinamide adenine dinucleotide (NAD+). NAD+, functioning as an electron carrier from glycolysis, the Krebs cycle, and β-oxidation to the ETC is indispensable for the efficient generation of ATP [54]. In the context of mitochondrial dysfunction, an overload of mitochondrial reactive oxygen species (mtROS) can cause significant alterations in the mitochondrial membrane. This can lead to a persistent and intense state of mitochondrial acidosis, which in turn triggers the influx of extracellular calcium ions (Ca2+) and results in cytoplasmic Ca2+ overload [55]. Ca2+ overload causes a range of harmful effects, including ATP depletion, degradation of cell membrane proteins and phospholipids, damage to mtDNA, heightened oxidative stress, and ultimately, the re-opening of the mitochondrial permeability transition pore (mPTP) by Ca2+ overload and mtROS [20]. The opening of MPTP can trigger changes in the osmotic pressure between IMM and OMM, which ultimately leads to further damage to mitochondrial structures and the onset of a vicious cycle. However, reducing mtROS production and inhibiting changes in mitochondrial permeability can help maintain the integrity of the mitochondrial membrane, improve mitochondrial morphology, and reduce the extent of kidney damage [18]. Before the clinical manifestation of AKI, the mitochondrial structure of ischemic human kidneys changes, indicating that changes in the mitochondrial structure might not appear after injury; instead, mitochondrial dysfunction might be the cause of kidney injury [56]. Additionally, mitochondrial dysfunction can exacerbate kidney injury. Damaged mitochondria impair cellular energy metabolism and become the main source of ROS, which mediate oxidative stress and disrupt the stability of mtDNA. They are released along with mtDNA as damage-associated molecular patterns (DAMPs) in the cytoplasm, where they activate inflammatory responses [57–59]. A study found that NADH: ubiquinone oxidoreductase core subunit V1 (NDUFV1) improved the integrity and function of mitochondria, leading to reduced oxidative stress and maintain mitochondrial homeostasis in IRI-AKI mice [60] (Table 1). Hence, improving

Table 1. Mitochondrial dysfunction in AKI.

Mitochondrial dysfunction type	Protective mechanism	Experimental model	References
Energy metabolism	1. ROS scavenger 2. Maintaining membrane potential 3. Decrease oxidative phosphorylation	IRI-AKI	[60]
Mitochondrial dynamics	4. Mitochondrial fusion and fission	IRI-AKI SI-AKI	[84–86] [32]
The antioxidant defense system	5. Preventing excessive ROS production 6. Maintaining optimal ATP production 7. Decrease elevated oxidative stress	IRI-AKI SI-AKI CisI-AKI CI-AKI	[57] [72,73] [70] [75] [76]
Mitochondrial biogenesis	8. Increasing ATP production 9. Promote mitochondrial biogenesis	IRI-AKI SI-AKI CisI-AKI	[97] [31,111] [39]

SI-AKI: sepsis-induced acute kidney injury; IRI-AKI: ischemia/reperfusion-induced acute kidney injury; CisI-AKI: cisplatin-induced acute kidney injury; CI-AKI: contrast-induced acute kidney injury.

mitochondrial function is a promising strategy for treating renal dysfunction.

5. Mitochondrial quality control and AKI

The mitochondrial quality control system comprises molecular and organelle quality control mechanisms. Mitochondria are the main source of cellular energy and the primary target of ROS in cells [61]. Thus, they are particularly vulnerable to damage under stressful conditions. Various quality control mechanisms in the mitochondria act at the molecular or subcellular level to alleviate stress and maintain the integrity and functions of organelles, including antioxidant defense, protein quality control, mtDNA repair, mitochondrial dynamics (fusion and fission), mitophagy, mitochondrial biogenesis mitochondrial DNA repair and protein quality control [11,62] (Figure 2). These quality control mechanisms facilitate the reduction of stress and maintenance of the steady state of mitochondrial structure and function [62]. Mounting evidence underscores the involvement of perturbations in mitochondrial quality control in the pathogenesis of AKI and incomplete or maladaptive renal repair [62]. In the kidneys, mitochondrial quality control is a prerequisite for maintaining mitochondrial function, energy production, and cellular function. However, mitochondrial dysfunction due to AKI caused by multiple factors can cause cell death and tissue damage, which can further promote kidney dysfunction, eventually leading to organ failure [63,64]. Several studies have shown that mitochondrial dysfunction greatly promotes the pathogenesis of AKI and adversely affects kidney repair after AKI [62,65,66]. Mitochondrial pathology can be detected in the kidney before the occurrence of renal injury and persists in the renal tubules that fail to recover after AKI. Disruption of mitochondrial homeostasis persisted for up to 144 h following glycerol injection or IRI-AKI in mice [40]. Also, pre-AKI and post-AKI mitochondrial protection (such as inhibiting mitochondrial fragmentation through genetic or pharmacological methods) can alleviate kidney injury and decrease the transition to CKD [67].

5.1. The antioxidant defense system in the mitochondria

The antioxidant defense system in the mitochondria helps in preventing excessive ROS production, maintaining optimal ATP production, and the proper functioning of the mitochondria. Mitochondria generate ATP through ETC. Although concentrations of ROS in cells act as signaling molecules, high concentrations of ROS can react rapidly with NO to form strong oxidants and nitrogenous compounds, causing damage to mitochondria and cells [68]. When ROS production exceeds the ROS removal ability of the antioxidant defense system of the cell, mitochondrial oxidative stress occurs, leading to the fragmentation of mtDNA, which results in mtDNA mutations in the next generation. The fragmentation

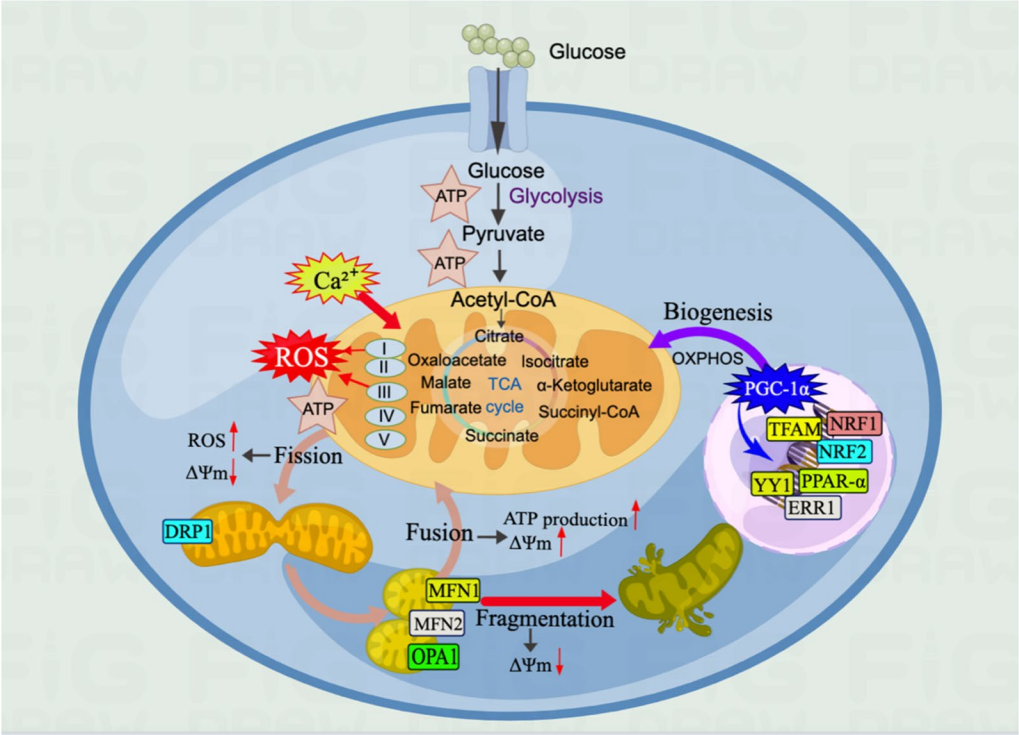

Figure 2. Mitochondrial quality control. Mitochondria quality control includes the biogenesis of mitochondrial structural proteins from nuclear DNA and dynamic remodeling of the mitochondrial network *via* fission and fusion to maintain an optimally functioning mass of mitochondria within the cell. PPAR-α: peroxisome proliferator-activated receptor alpha; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1 alpha; NRF1/2: nuclear respiratory factor 1/2; TFAM: mitochondrial transcription factor A; ERR1: estrogen-related receptor-1; OPA1: optic atrophy 1; MFN1/2: mitochondrial fusion protein 1/2; DRP1: dynamin-related protein-1; YY1: transcriptional repressor protein 1; ΔΨm: mitochondrial transmembrane potential; ROS, reactive oxygen species; OXPHOS: Oxidative phosphorylation.

of mtDNA reduces the efficiency of the ETC, decreases ATP production, and damages proteins and lipids [69]. In IRI-AKI, ROS promotes kidney damage by suppressing the maintenance of mtDNA mediated by mitochondrial transcription factor A (TFAM), leading to a decrease in mitochondrial energy metabolism and an increase in the release of cytokines [57]. Recent evidence has unequivocally demonstrated the protective role of transcription factor EB(TFEB) in mitochondrial function [70]. TFEB acts as a master regulator of the autophagy-lysosomal pathway, facilitating the removal of misfolded protein aggregates or damaged organelles. The TFEB pathway governs mitochondrial quality control through three primary mechanisms: mitophagy, mitochondrial biogenesis, and scavenging of ROS [71]. In CisI-AKI, TFEB decreased in a concentration-dependent manner in mouse kidney tissue and HK-2 cells treated with cisplatin. Knockdown of TFEB worsened cisplatin-induced kidney cell injury, which was partially improved by TFEB overexpression in HK-2 cells. TFEB knockdown also worsened cisplatin-induced damage to mitochondria *in vitro*, causing membrane potential depolarization, mitochondrial fragmentation, and swelling [70]. ROS can also release cytochrome C, triggering apoptosis and causing mitochondrial dysfunction [69]. During AKI and renal repair, the ability of TECs to remove ROS from the mitochondria is impaired, leading to the accumulation of ROS and inhibition of mitochondrial oxidative phosphorylation, which in turn decreases the activity of cytochrome C oxidase and causes mitochondrial dysfunction [62]. Furthermore, recent studies have shown RIPK3 exacerbates kidney tubular injury by inducing elevated oxidative stress and mitochondrial dysfunction and treatment with a mitochondria-targeted antioxidants (SkQR1) after SI-AKI improved the function of the kidneys in rats [72,73]. Also, considering that oxidative stress is also thought a main cause of CI-AKI. Electrons leaking from the ETC undergo reactions with oxygen resulting in the formation of superoxide anions, which can be subsequently converted to hydrogen peroxide by superoxide dismutase (SODs) [74]. Recent studies have shown delivery of recombinant sestrin2 ameliorates oxidative stress, mitochondrial damage, and renal dysfunction in CI-AKI [75]. Cisplatin's accumulation in the mitochondrial matrix can impact cytochrome c oxidase, resulting in a decrease or even depletion of intracellular ATP levels and an elevation in ROS [76]. Conversely, administration of a mitochondrial-specific SOD mimetic (GC4419) alleviated AKI triggered by a single cisplatin dose and kidney fibrosis induced by repeated cisplatin administrations [77]. Therefore, the balance between ROS production and clearance in the mitochondria is crucial for maintaining mitochondrial function and cell activity.

5.2. Mitochondrial dynamics and AKI

Mitochondria are highly dynamic organelles with a lifecycle that includes continuous remodeling through fission, fusion, and mitophagy, followed by intracellular disposal. Under physiological conditions, the balance between mitochondrial fusion and fission is maintained, and fission and fusion facilitate the exchange of substrates and metabolites in cells, producing subcellular organelles [78,79]. Many studies have shown that during AKI, fission occurs more often than fusion, leading to mitochondrial fragmentation. Mitochondrial fragmentation occurs before TECs apoptosis, and inhibiting mitochondrial fission can alleviate TECs death and kidney injury [80].

Dynamin-related protein 1 (Drp1), a pivotal regulator of mitochondrial fission, promptly translocate to mitochondria upon tubular cell injury onset [81]. Drp1, which is mainly found in the cytoplasm, translocate to the mitochondrial outer membrane upon activation by interacting with receptor proteins like mitochondrial fission factor (MFF), mitochondrial elongation factor 1 (Mid51), and mitochondrial fission 1 (Fis1), thereby carrying out its function [82,83]. Recent research findings suggest that Drp1 inhibitors can mitigate Drp1-mediated mitochondrial fragmentation by inhibiting the interaction between Drp1 and Fis1, thereby providing significant protective effects in mice kidney IRI and Bama miniature pig kidney IRI models [84]. Additionally, both siRNA-mediated knockdown of Drp1 and the expression of a dominant-negative Drp1 significantly mitigated mitochondrial fragmentation, cytochrome c release, caspase activation, and apoptosis, promote TECs repair and kidney recovery, and reduce kidney fibrosis [84–86]. Subsequent *in vivo* investigations demonstrated mitochondrial fragmentation in proximal tubular cells during renal IRI and cisplatin-induced nephrotoxicity in mice [35]. The stagnation of mitochondrial fusion also enhances mitochondrial fragmentation and TECs death in AKI. *In vitro* study reported that the loss of mitochondrial fusion protein 2 (MFN2), a key factor for mitochondrial OMM fusion, can promote Bax-mediated TECs injury and death through the mitochondrial pathway, which indicated that inhibiting mitochondrial fusion can also exacerbate TECs injury in AKI [87]. Recent research suggests that SIRT3 plays a protective role against AKI [88]. It is proposed that enhancing Sirt3 activity to improve mitochondrial dynamics holds promise as a therapeutic approach to improving outcomes in renal injury [41]. Sirt3 overexpression mitigated LPS-induced mitochondrial damage and apoptosis in TECs by enhancing OPA1-mediated mitochondrial fusion *via* the deacetylation of i-AAA protease (YME1L1), an upstream regulatory factor of OPA1 [32]. Overall, these findings suggest that the activation of fission and the stagnation of fusion can induce mitochondrial fragmentation, and thus, they are crucial for renal tubular injury repair in AKI.

5.3. Mitochondrial biogenesis and AKI

Abnormal mitochondrial biogenesis in TECs also occurs in AKI. Mitochondrial biogenesis involves the production of new mitochondria and the replication of mtDNA, which can increase ATP production to meet the growing energy demand. Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is a major regulator of mitochondrial biogenesis, and it is highly expressed in the proximal tubules [89]. PGC-1α serves as the master regulator of mitochondrial biogenesis, orchestrating the transcriptional processes that

result in augmented mitochondrial mass [18,90]. This family consists of three members: PGC-1α, PGC-1β, and PGC-1-related coactivator (PRC) [91]. The former two have close homology, and they are both involved in the regulation of mitochondrial physiological processes. PGC-1α can activate the expression of several nuclear genes, including TFAM, TFEB, nuclear respiratory factor 1 (NRF1), nuclear respiratory factor 2 (NRF2), peroxisome proliferator-activated receptor alpha (PPAR-α), estrogen-related receptor 1 (ERR1), and transcriptional repressor protein 1 (YY1) to promote mitochondrial biogenesis [92]. Therefore, it is anticipated that PGC-1α expression would rise in metabolically active tissues like the kidney [93]. However, PGC-1α levels significantly decline in kidney diseases, encompassing AK and CKD [18]. Notably, PGC-1α downregulation is consistently observed in experimental AKI models induced by conditions such as sepsis, IRI, cisplatin exposure, or folic acid administration [94–99]. This downregulation correlates with mitochondrial dysfunction and impaired mitochondrial biogenesis. Furthermore, NRF2 is a pivotal transcription factor involved in safeguarding against oxidative stress and modulating the inflammatory cascade [100]. The NRF2-mediated antioxidant response orchestrates the expression of genes encoding proteins, these proteins act either directly or indirectly to scavenge free radicals, thereby mitigating cellular oxidative stress [101]. Recent research indicates that Nrf2 may exert protective effects against inflammation beyond its antioxidant functions [102]. Nrf2 plays a crucial role in modulating the innate immune response by downregulating the expression of pro-inflammatory genes while enhancing anti-inflammatory signaling [103,104]. NRF2 deficiency exacerbates susceptibility to both ischemic and nephrotoxic AKI in mice, culminating in oxidative stress and consequent tissue injury [105,106]. TFAM and TFEB serves as a critical regulator of mitochondrial DNA transcription and replication [92]. TFEB enhances mitochondrial biogenesis by upregulating PGC-1α expression, which subsequently fosters TFEB expression [71]. Numerous mitochondrial genes harbor YY1 binding sites within their promoter regions, and this transcription factor has been identified to collaborate with PGC-1α in regulating their expression [107]. DNA-binding sites for ERR-α have been delineated in a considerable number of nuclear-encoded mitochondrial genes, encompassing those pivotal in oxidative phosphorylation, fatty acid oxidation, the TCA cycle, and regulators of mitochondrial dynamics such as fusion and fission. Moreover, the transcriptional coactivators PGC-1α and PGC-1β serve as potent activators of ERRs, stimulating the expression of mitochondrial genes [108]. Meanwhile, PGC-1α regulates the expression of intracellular mitochondrial antioxidant defense substances, which can elevate the levels of manganese superoxide dismutase (MnSOD, SOD2), cyclooxygenase-5, cyclooxygenase-3, uncoupling protein 2 (UCP-2), thioredoxin reductase 2 (TRXR2), and thioredoxin 2 (TRX), thereby protecting cells from damage caused by mitochondrial dysfunction. Many studies have shown that enhancing the expression of PGC-1α through mitochondrial biogenesis can decrease kidney injury and help in repairing AKI [109,110]. In folic acid-induced AKI(FA-AKI), the level of PGC-1α decreases with the severity of kidney injury but returns to normal during the kidney recovery period, indicating a negative association between PGC-1α expression in the renal tubules and the severity of AKI [95]. Furthermore, the expression of PGC-1α in the renal cortex of wild-type mice decreased during the development of IRI-AKI. PGC-1α knockout mice developed more severe AKI symptoms, decreased NAD and nicotinamide adenine dinucleotide (NAM) levels in TECs, accumulation of fatty acids in TECs, and failure to recover renal function [97]. In addition, the renal biopsy samples of AKI patients show a lower expression of PGC-1α compared to its expression in normal human kidney tissue [97]. These results suggest that the production of new mitochondria to replace damaged and degraded mitochondria during AKI can meet the increased metabolic and energy demands during the recovery phase of acute injury [91]. LPS induced decreased expression of PGC-1α and its downstream mitochondrial target genes in renal cortical cells of SI-AKI mice and decreased mitochondrial DNA content in the renal cortex [31,111]. Furthermore, a reduction in the level of PGC-1α, a transcription coactivator responsible for regulating mitochondrial biogenesis, was noted in the CisI-AKI mouse model, indicating impairment of mitochondrial biogenesis [39]. Pharmacological approaches to restore mitochondrial biogenesis have been developed and have shown effective improvement in ischemic kidney injury. For example, the β2-adrenergic receptor (β2AR) agonist Formoterol and the selective 5-HT1F receptor agonists LY344864 and LY334370 have been used [112,113]. These are feasible approaches to reducing damage due to AKI and promoting recovery.

5.4. Mitophagy and AKI

Some studies have suggested that mitophagy strongly influences the pathogenesis of AKI and is generally considered to be a defense mechanism under pathological conditions [114]. Mitophagy is a selective form of autophagy that can sequester and degrade surplus or damaged mitochondria through autophagosomes, thus eliminating ROS to promote the maintenance of cellular energy metabolism, inhibiting excessive activation of mitochondrial fission, regulating mitochondrial quality control, and maintaining cellular homeostasis [57,115,116]. In the initial stage of kidney injury, inducing mitochondrial engulfment by removing damaged mitochondria ensures quality control, which in turn can prevent the accumulation of ROS and the release of pro-apoptotic factors, ultimately reducing TECs injury and death [117]. The induction of mitophagy can also prevent damaged mitochondria from releasing mtDNA, which can help decrease immune activation and inflammation related to the pathogenesis of AKI. Two signaling pathways mediate mitophagy, including the mitophagy receptor pathway (consisting of BNIP3, BNIP3L/NIX, FUNDC1) and the PINK1/PARK2 (or PINK1/Parkin) pathway [118] (Figure 3). Mitophagy is induced through the receptor-mediated mitophagy pathway by recruiting mitophagy structural protein and microtubule-associated protein light chain and binding with the mitochondrial BNIP3L

membrane protein NIX and mitochondrial outer membrane domain-containing protein FUNDC1, which constitute the receptor-mediated mitophagy pathway [119–123]. Additionally, phosphatase and tensin homolog-induced putative kinase 1 (PINK1)-mediated mitophagy induced by the mitochondrial outer membrane protein homolog PINK1 is the most widely studied classic mitophagy pathway in research on age-related diseases. PINK1 is a mitochondrial serine/threonine kinase, and Parkin is an E3 ubiquitin ligase that depends on cytoplasmic protein-linking enzymes. Mitophagy is regulated through the PINK1/E3 ubiquitin ligase Parkinson's disease protein 2 (Parkin/PARK2) classic pathway *via* the activity of PINK1 and E3 ubiquitin ligase [124–129]. Damaged mitochondria and lysosomes fuze to form mitochondrial autolysosomes, which eliminate damaged mitochondria and prevent the excessive accumulation of ROS. Several recent studies have shown that mitophagy is activated by the action of IRI, cisplatin, and contrast agents. Mitophagy reduces mtROS, improves energy metabolism, attenuates inflammatory response, and maintains mitochondrial dynamic homeostasis, thus decreasing TECs death in AKI, improving organ function, and promoting injury repair (Table 2).

Mitophagy is triggered in TECs in ischemic AKI models, both *in vitro* and *in vivo* [130]. In mice, renal IRI triggers PINK1-PARK2-mediated mitophagy in TECs. Mice deficient in Pink1, Park2, or both exhibits exacerbated mitochondrial damage and heightened inflammatory cell infiltration in the context of renal IRI [124]. When mitochondria are damaged, PINK1 accumulates in the outer mitochondrial membrane, where it binds to the translocase of the outer mitochondrial membrane and becomes activated by autophosphorylation. Activated PINK1 then phosphorylates ubiquitin, leading to the recruitment of PRKN to the mitochondria and activation of its E3 ligase activity. This process ultimately ubiquitinates mitochondrial substrates and initiates mitophagy [115]. Additionally, BNIP3 overexpression ameliorates renal injury and enhances mitophagy in tubular HIF-1α-deficient mice subjected to IRI [123]. Furthermore, Ndrg2 deficiency may emerge as a promising therapeutic target for IRI injury by reducing oxidative stress, preserving mitochondrial homeostasis, and promoting PINK1/Parkin-mediated mitophagy activation in mice []. In SI-AKI, it was found that the impediment of Parkin recruitment to mitochondria hinders the initiation of mitophagy, leading to extensive apoptosis of TECs and exacerbating kidney damage [129,131]. The protective effects of mitophagy in sepsis-induced AKI can be attributed to a reduction in inflammation [132]. Liu et al. found that PINK1 deficiency improved cisplatin-induced AKI in rats, potentially through the inhibition of DNM1L-mediated mitochondrial fission and excessive mitophagy [133]. In CI-AKI models, both

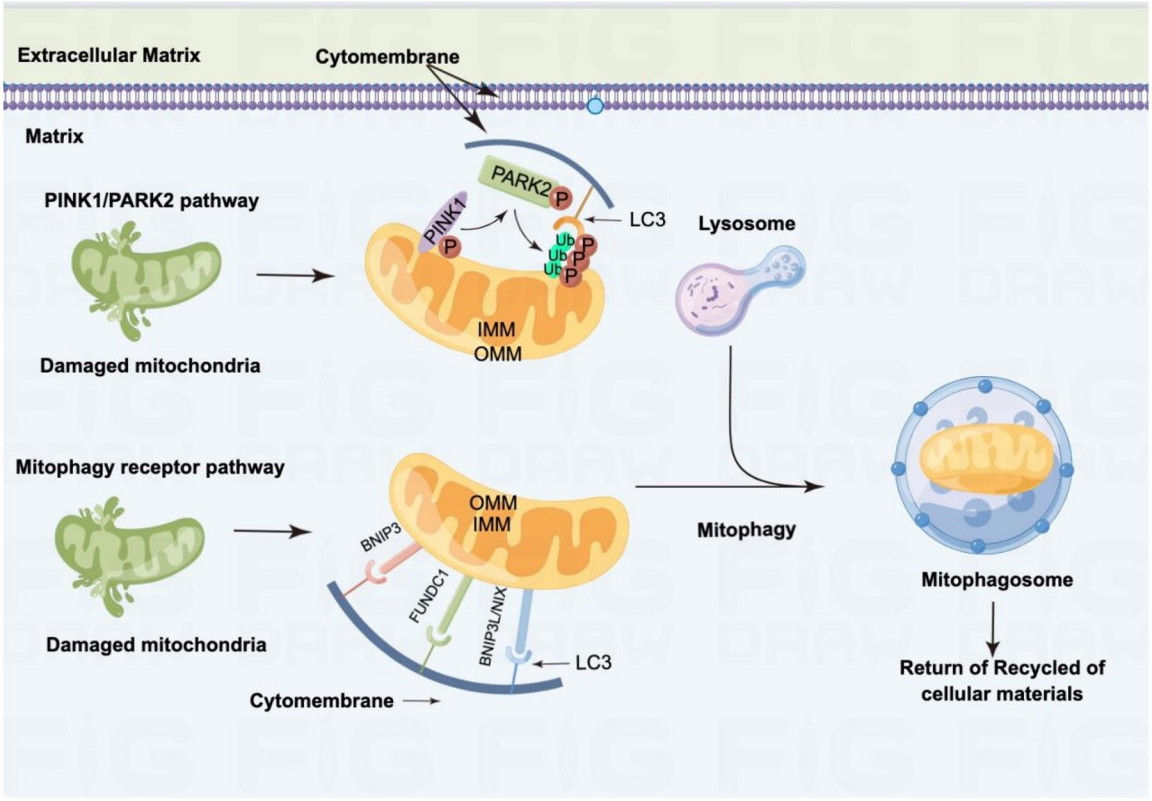

Figure 3. Molecular mechanisms of mitophagy. There are two major mechanisms for mitochondrial priming in mitophagy. In the PINK1/PARK2 pathway, mitochondrial damage or depolarization impairs the import of PINK1 into the mitochondria, resulting in the accumulation of PINK1 on OMM. Then, PINK1 recruits PINK2 from the cytosol and activates its E3 ligase activity *via* phosphorylation. Upon activation, PINK2 catalyzes the formation of poly-ubiquitin chains on OMM proteins. In the mitophagy receptor pathway, BNIP3、BNIP3L/NIX and FUNDC1 mitophagy receptors localize to the OMM and interact directly with LC3 to mediate mitochondrial elimination.PINK1: PTEN-induced putative kinase-1; parkin: Parkinson protein-2 E3 ubiquitin protein ligase; BNIP3: BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3; BNIP3L: BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3-like; nix: NIP3-like protein X; FUNDC1: FUN14 domain-containing 1; IMM: inner mitochondrial membrane; OMM: outer mitochondrial membrane; LC3: light chain 3.

Table 2. Activation mechanism and protective effect of mitophagy in AKI.

Mechanism	Experimental model	Protective effect against AKI	References
PINK1/PARK2 pathway	IRI-AKI	1. Removal of damaged mitochondria 2. Scavenging ROS 3. Reducing inflammatory response 4. Inhibiting apoptosis 5. Inhibiting mitochondrial depolarization 6. Modulate cell death	[124,125,128]
	CisI-AKI	7. Inhibiting apoptosis 8. Scavenging ROS 9. Inhibit mitochondrial depolarization	[126,156]
	SI-AKI	10. Inhibiting apoptosis 11. Mitochondrial quality control 12. Removal of damaged mitochondria	[127,129,131]
	CI-AKI	13. Reduction of mtROS production 14. Inhibition of NLRP3 inflammatory vesicle activation 15. Reduce mitochondrial damage	[58]
BNIP3 pathway	IRI-AKI	16. Removal of damaged mitochondria 17. Scavenging ROS 18. Reduce inflammatory response. 19. Inhibiting apoptosis	[119–122]
	CI-AKI	20. Inhibition of NLRP3 inflammatory vesicle activation 21. Inhibit apoptosis	[157]
FUNDC1 pathway	IRI-AKI	22. Inhibiting apoptosis 23. Mitochondrial quality control	[116]
BNIP3L/NIX pathway	IRI-AKI	24. Inhibiting apoptosis 25. Reduction of mtROS production	[123,158]

PINK1: PTEN-induced putative kinase-1; PNRK2: Parkinson protein-2 E3 ubiquitin protein ligase; BNIP3: BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3; BNIP3L: BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3-like; FUNDC1: FUN14 domain-containing 1; Drp1: power-related protein 1; SI-AKI: sepsis-induced acute kidney injury; IRI-AKI: ischemia/reperfusion-induced acute kidney injury; CisI-AKI: cisplatin-induced acute kidney injury; CI-AKI: contrast-induced acute kidney injury; mtROS: mitochondrial reactive oxygen species; NLRP3: NOD-like receptor family pyrin structural domain 3.

in vitro and *in vivo*, PINK1-PRKN-mediated mitophagy prevented apoptosis and tissue damage by lowering mitochondrial ROS levels and suppressing NLRP3 inflammasome activation [58]. However, knocking out the key factors of the mitophagy signaling pathway, i.e., PINK1, Parkin, or BNIP3, can increase mitochondrial damage, ROS production, and cell apoptosis in the mice renal tubules [134]. These findings suggest that the activation of TECs mitophagy might be a potential therapeutic strategy to alleviate renal tubular injury in AKI.

5.5. Mitochondrial protein quality control in AKI

Maintaining mitochondrial proteomic homeostasis is paramount for cellular health and bioenergetics [135]. The mitochondrial protein quality control system comprises chaperones catalyzing protein folding and ATP-dependent proteases responsible for removing unwanted and unrepaired proteins [62]. Proper protein import, targeting, folding into functional proteins, and their regulated turnover are indispensable for mitochondrial health and integrity. These molecular processes collectively constitute the mitochondrial protein quality control (MPQC) system [136]. When the system's capacity is overwhelmed by excessive amounts of unfolded or misfolded proteins, it triggers the mitochondrial unfolded protein response (UPRmt) [137]. A diminished capacity of mitochondrial protein quality control systems can lead to mitochondrial dysfunction, thereby contributing to the development of various diseases [138]. Additionally, signal transduction from mitochondria to the cell nucleus occurs through the SiRT3-FOXO3A axis [139,140]. Accumulation of misfolded proteins induces mitochondrial autophagy and antioxidant defense mechanisms to reduce oxidative stress within the mitochondria [141]. However, there is currently no literature definitively elucidating the functional relationship between mitochondrial protein quality control systems and AKI. Further research is warranted to explore this topic more comprehensively.

5.6. Mitochondrial DNA repair in AKI

Mitochondria are regulated by dual-genome control mechanisms, whereby mtDNA encodes a small portion of mitochondrial proteins, while over 99% of mitochondrial proteins are encoded by nuclear DNA (nDNA), synthesized in the cytoplasm, and subsequently translocated into the mitochondria [142–144]. Human mitochondrial DNA (mtDNA) is a double-stranded circular molecule comprising 16,569 base pairs with a molecular mass of 107 daltons [145]. It consists of two intertwined strands forming a double helical structure, including a heavy chain and a light chain. The heavy chain encodes 28 genes, while the light chain encodes 9 genes, totaling 37 genes. Among these, only 13 genes encode proteins crucial for mitochondrial energy production. Additionally, 7 genes encode proton pumps in the electron transport chain, which are responsible for receiving electrons from NADH [146]. With increasing age, mutations in mtDNA accumulate, resulting in a higher frequency of mutations in mtDNA compared to nDNA.The progressive accumulation of mtDNA mutations can lead to insufficient cellular energy production and oxidative stress, ultimately culminating in mitochondrial dysfunction [147]. Dysfunction in mtDNA repair

mechanisms compromises mitochondrial function, heightens susceptibility to cell death, and has been associated with human diseases including cognitive impairment, cardiac and skeletal myopathies, nephropathies, hepatopathies, and endocrinopathies [145].

The dynamic interplay between mitochondrial fission and fusion is crucial for maintaining the organization and integrity of mtDNA [148,149]. Inhibition of mitochondrial fission leads to the aggregation of mtDNA, resulting in mitochondrial deformation [150]. Additionally, the uneven distribution or defects in mtDNA can hinder oxidative phosphorylation in the mitochondrial respiratory chain [151]. Deficiencies in mitochondrial fusion can further impair and diminish mtDNA synthesis. Reduced expression of mitochondrial fusion proteins may result in increased levels of mutant mtDNA, indicating a potential role of mitochondrial fusion in mitigating the detrimental effects of defective mtDNA through dilution [152]. In a rat model of IRI, a significant presence of oxidized DNA was observed in the cytoplasm of renal tubular epithelial cells one hour after reperfusion [153]. Treatment with the ATP-sensitive potassium channel opener diazoxide effectively reduced oxidative mitochondrial DNA levels [154]. As it stands, treatment options for mtDNA repair remain limited. However, advancements in model organism research are progressively enhancing our comprehension of the pathophysiology underlying these conditions. This growing understanding is expected to catalyze the development of novel therapeutic drugs aimed at addressing mtDNA-related diseases in the future.

6. Mitochondrial targeting for AKI therapy

Mitochondrial dysfunction plays a crucial role in the development of various kidney diseases, highlighting the potential of mitochondria as therapeutic targets that require further investigation. Current research focuses on several key areas related to mitochondrial dysfunction in kidney diseases, including alterations in mitochondrial biogenesis, imbalances between fusion and fission processes leading to mitochondrial fragmentation, oxidative stress, release of cytochrome c and mitochondrial DNA resulting in apoptosis, mitophagy, and defects in energy metabolism [20,62].

Recently, numerous agents have emerged as potential therapeutic approaches in kidney pathology, targeting different mitochondrial processes. For example, in a mouse model of ischemic AKI, the lack of Drp1 inhibited mitochondrial fragmentation in TECs, or treatment with a mitochondria-targeted antioxidant (SS-31) promoted renal recovery and mitigated renal fibrosis [37]. Moreover, Mitoquinone (MitoQ), a mitochondria-targeted antioxidant known for its capacity to inhibit mitochondrial ROS production, exhibits a propensity to accumulate within cells, facilitated by the positive charge of the plasma membrane. Subsequently, it undergoes further enrichment within mitochondria, driven by the

Table 3. Therapeutic targeting of drugs for mitochondrial dysfunction in AKI.

Drug name	Drug type	Mechanism	Experimental model	References
SS-31	Cardiolipin protection	Binds cardiolipins Prevents their peroxidation Maintains mitochondrial membrane structure and potential	IRI-AKI SI-AKI CisI-AKI UUO CI-AKI	[159–162]
SS-20		1. Binds cardiolipins 2. Increases ATP 3. ROS scavenger	IRI-AKI	[163]
Mdivi-1	Fission inhibitor	Selectively inhibits Drp1 Induces mitochondria fusion Increases ATP production	IRI-AKI SI-AKI CisI-AKI UUO	[164]
SRT1720	Biogenesis activator	4. Activates Sirtuin1 5. Increase expression of PGC-1α	IRI-AKI UUO CisI-AKI	[165,166]
Resveratrol		Activates Sirtuin1 ROS scavenger	IRI-AKI	[167]
Formoterol		6. Increase PGC-1α synthesis	IRI-AKI	[168]
LY344864		7. Selectively activates 5-HT1F receptor	IRI-AKI	[169,170]
Thiazolidinediones		8. Increased PPAR-γ expression 9. Reduced oxidative stress	IRI-AKI	[62,171–173]
TDZD-8	mPTP inhibitor	Selectively inhibits GSK-3β Decreases MPT	IRI-AKI NSAID-AKI	[174,175]
MitoQ	Antioxidants	10. ROS scavenger 11. Maintain mitochondrial ΔΨm	CisI-AKI	[155]
SkQR1		12. Maintain mitochondrial ΔΨm	IRI-AKI	[176]
Curcumin		13. Weaken oxidant stress	IRI-AKI	[177]
Urolithin A	Enhancement of Mitophagy and Autophagy	14. Maintain mitochondrial ΔΨm 15. Restores ATP production	CisI-AKI	[178]

SS-20: Szeto–Schiller peptide 20; SS-31: Szeto–Schiller peptide 31; Mdivi-1: mitochondrial division inhibitor 1; IRI-AKI: ischemia/reperfusion-induced acute kidney injury; CisI-AKI: cisplatin-induced acute kidney injury; CI-AKI: contrast-induced acute kidney injury; NSAID-AKI: non-steroidal anti-inflammatory drug-induced acute kidney injury; UUO: unilateral ureteral obstruction; mPTP: mitochondrial permeability transition pore; SkQR1: 10-(6′-plastoquinonyl) decylrhodamine 19; TDZD-8: 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione; 5HT1F: 5-hydroxytryptamine receptor 1 F; GSK-3β:, glycogen synthase kinase 3β; MitoQ: mitochondrial coenzyme Q; ΔΨm: mitochondrial membrane potential.

positive charge of the mitochondrial membrane [155]. Li et al. discovered that the suppression of Drp1 phosphorylation, facilitated by mitochondrial division inhibitor-1 (Mdivi-1), markedly attenuates renal IRI-induced mitophagy in rats, while not impacting overall autophagy. Their findings further validated that diminished mitophagy exacerbates cellular apoptosis and exacerbates IRI-induced renal dysfunction [130]. These agents aim to restore mitochondrial function and mitigate the harmful effects of mitochondrial dysfunction on renal health. Currently, a variety of strategies are being employed to target mitochondria to enhance kidney function and improve kidney treatment. The agents utilized in these strategies can be categorized as biogenesis activators, fission inhibitors, antioxidants, mPTP inhibitors, and compounds that promote mitophagy and protect cardiolipin [67] (Table 3). Additionally, several clinical trials are currently underway investigating targeted treatments for AKI. These include a Phase I study evaluating MTP-131 in subjects with impaired kidney function(NCT02436447), a trial assessing an antioxidant's efficacy in reducing renal uremic toxins and oxidative stress in patients undergoing hemodialysis(NCT03946176), and a study investigating the use of the antioxidant coenzyme Q10 to mitigate acute kidney injury following cardiac surgery(NCT04445779, NCT01408680, NCT00908297, NCT00307996). Finally, curcumin, a natural polyphenol compound found in turmeric, has been studied for its potential antioxidant, anti-inflammatory, and nephroprotective properties [20]. A randomized controlled trial on the efficacy of curcumin in preventing CI-AKI following kidney transplant surgery (NCT04890704, NCT01225094, NCT01285375, NCT03935958).

7. Conclusion

In this review, we comprehensively explore the underlying mechanisms that precipitate mitochondrial dysfunction in AKI and succinctly introduce pertinent mitochondrial-targeted therapeutic drugs and ongoing clinical trials. The research findings suggest that preserving mitochondrial function holds promise for renal protection and mitigating the burden of AKI. AKI is frequently linked to significant necrosis and apoptosis in TECs, with mitochondrial dysfunction emerging as a central pathophysiological factor. However, the kidney is a heterogeneous organ comprising diverse cell types, with researchers primarily concentrating on tubular epithelial cells; hence, mitochondrial dysfunction in other cell types often remains largely uncharted.

Presently, although numerous therapeutic targets for AKI have been identified through research, and with advancements in human clinical trials assessing the efficacy and safety of mitochondrial-targeted therapy for AKI treatment, the clinical implementation of these targeted therapeutic drugs holds paramount importance in retarding the progression of AKI and enhancing the prognosis of AKI patients. In summary, despite the potential therapeutic benefits of mitochondrial-targeted drugs in AKI, their clinical utilization still encounters several challenges and unknown factors, including adaptation to different AKI subtypes, the side effects of targeted drugs, and the uncertainty surrounding treatment outcomes, necessitating further research to gain a deeper understanding of the pathophysiological role of mitochondria in AKI and additional clinical trials to tackle these issues.

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Authors contributions

Conceptualization, Heng Jin; validation, Songtao Shou; writing—original draft preparation, Congcong Yao; visualization, Keke Sun; supervision, Yan Zhang; project administration, Ziwei Li. All authors have read and agreed to the published version of the manuscript.

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