Kidney Diseases

Review Article

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Mitophagy Regulates Kidney Diseases

Xiaolu Fan[a] Linlin Wu[b] Fengqi Wang[a, c] Dong Liu[b] Xufeng Cen[a] Hongguang Xia[a, c]

[a]Research Center of Clinical Pharmacy of The First Affiliated Hospital and Liangzhu Laboratory, Zhejiang University School of Medicine, Hangzhou, China; [b]Hangzhou PhecdaMed Co., Ltd, Hangzhou, China; [c]Department of Biochemistry and Research Center of Clinical Pharmacy of The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

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Abstract
Background: Mitophagy is a crucial process involved in maintaining cellular homeostasis by selectively eliminating damaged or surplus mitochondria. As the kidney is an organ with a high dynamic metabolic rate and abundant mitochondria, it is particularly crucial to control mitochondrial quality through mitophagy. Dysregulation of mitophagy has been associated with various renal diseases, including acute and chronic kidney diseases, and therefore a better understanding of the links between mitophagy and these diseases may present new opportunities for therapeutic interventions. ***Summary:*** Mitophagy plays a pivotal role in the development of kidney diseases. Upregulation and downregulation of mitophagy have been observed in various kidney diseases, such as renal ischemia-reperfusion injury, contrast-induced acute kidney injury, diabetic nephropathy, kidney fibrosis, and several inherited renal diseases. A growing body of research has suggested that PINK1 and Parkin, the main mitophagy regulatory proteins, represent promising potential therapeutic targets for kidney diseases. In this review, we summarize the latest insights into how the progression of renal diseases can be mitigated through the regulation of mitophagy, while highlighting their performance in clinical trials. ***Key Message:*** This review comprehensively outlines the mechanisms of mitophagy and its role in numerous kidney diseases. While early research holds promise, most mitophagy-centered therapeutic approaches have yet to reach the clinical application stage.

Introduction

Mitochondria play a vital role in various cellular processes, including ATP production, lipid and heme biosynthesis, calcium homeostasis, and regulatory signaling pathways [1, 2]. However, when reactive oxygen species (ROS) are generated from the electron transport chain, mitochondria may face constant oxidative stress, leading to structural and functional failure [3]. Therefore, the quality control of mitochondria is crucial for maintaining cellular homeostasis and preventing the accumulation of dysfunctional organelles. Mitophagy, a selective form of autophagy, targets and engulfs damaged or surplus mitochondria through lysosomal degradation, ensuring the proper functioning of the organelles and overall cellular health [4, 5].

In the context of kidney diseases, such as acute kidney injury (AKI) and chronic kidney disease (CKD), abnormal

Xiaolu Fan and Linlin Wu: co-first authors.

karger@karger.com
www.karger.com/kdd

Correspondence to:
Dong Liu, dong.liu@phecdamed.com
Xufeng Cen, 0616502@zju.edu.cn
Hongguang Xia, hongguangxia@zju.edu.cn

mitophagy has been implicated in the development and progression of renal damage. Mitophagy plays a vital role in kidney diseases by maintaining mitochondrial quality control and preventing the accumulation of damaged mitochondria [6, 7]. In view of this, this review is aimed at summarizing the mechanisms involved in regulating mitophagy and its dysregulation in kidney diseases, paving the way for the development of novel therapeutic strategies to mitigate renal damage.

Mechanisms of Mitophagy

Mitophagy is a selective autophagic process responsible for the removal of damaged or dysfunctional mitochondria, thereby maintaining mitochondrial quality and function. This process is achieved through intracellular autophagic mechanisms, ensuring cellular homeostasis and health. The process of mitophagy can be divided into four main steps: recognition and tagging, engulfment, fusion, and degradation. Under stress conditions such as ROS stress, nutrient deprivation, and cellular aging, mitochondrial DNA (mtDNA) mutations gradually accumulate, leading to a decrease in mitochondrial membrane potential and depolarization damage. To maintain mitochondrial and cellular homeostasis and prevent damaged mitochondria from harming the cell, these damaged mitochondria are selectively encapsulated into autophagosomes and fused with lysosomes, a process known as mitophagy. In simple terms, mitophagy is a selective autophagic process that removes dysfunctional mitochondria from the cytoplasm to maintain mitochondrial integrity and cellular homeostasis. The mitophagy process can be characterized by four critical steps: recognition and tagging, engulfment, fusion, and degradation. Damaged mitochondria undergo permeability transition, leading to depolarization and loss of membrane potential, which activates mitophagy-related proteins. The damaged mitochondria are then encapsulated by autophagosomes, forming mitophagosomes. Mitophagosomes fuse with lysosomes to form mature mitophagolysosomes. Lysosomal hydrolases degrade the mitochondria, and the nutrients are recycled for reuse.

Mitophagy plays a crucial role in maintaining cellular homeostasis and disease prevention. Its pathophysiological significance includes maintaining mitochondrial quality by removing damaged mitochondria, reducing oxidative stress by decreasing the production of ROS, regulating apoptosis and cell survival by preventing the release of pro-apoptotic factors, and participating in cellular metabolism and adaptation by helping cells respond to different metabolic demands and environmental stresses. Understanding the process of mitophagy and its pathophysiological significance is crucial for revealing the mechanisms of many diseases and developing new therapeutic strategies (Table 1). Due to the essential role mitophagy plays in mitochondrial quality and quantity control, the mechanisms of it have been widely investigated (shown in Fig. 1).

Pink/Parkin-Driven Mitophagy

Pink1 (phosphatase and tensin homologue (PTEN)-induced putative kinase 1) and Parkin (Parkin RBRE3 ubiquitin protein ligase)-driven mitophagy is the most characterized pathway, and investigation of these two proteins has been further developed [1, 8]. This pathway regulates ubiquitin-dependent mitophagy and integrates various aspects of mitochondrial physiology, including mitochondrial dynamics, biogenesis, transport, and the recruitment of autophagic machinery, ensuring the elimination of defective organelles. Under normal conditions, PINK1, a serine/threonine-protein kinase, is imported into the mitochondria where it is translocated to the inner mitochondrial membrane. In the inner mitochondrial membrane, PINK1 is cleaved by mitochondrial proteases such as mitochondrial processing peptidase and presenilin-associated rhomboid-like protease (PARL) [9]. The cleaved form of PINK1 is subsequently degraded by the ubiquitin-proteasome system. Upon mitochondrial depolarization or the accumulation of misfolded mitochondrial proteins, PINK1 import is blocked, leading to its stabilization on the outer mitochondrial membrane (OMM). Stabilized PINK1 on the OMM undergoes auto-phosphorylation, activating its kinase activity. PINK1 phosphorylates ubiquitin (Ub) attached to OMM proteins and recruits cytosolic Parkin to the mitochondrial surface [10, 11]. Parkin, an E3 ubiquitin ligase, is then activated through phosphorylation by PINK1, which also phosphorylates ubiquitin. Activated Parkin ubiquitinates multiple OMM proteins, generating poly-Ub chains. These poly-Ub chains on OMM proteins are recognized by mitophagy receptors such as sequestosome-1 (p62/SQSTM1), nuclear dot protein 52 (NDP52), and optineurin (OPTN). These receptors interact with microtubule-associated protein 1 light chain 3 (LC3) via the LC3-interacting region (LIR) motif. Mitophagy receptors subsequently recruit autophagy initiation proteins, such as Unc-51-like kinase 1 (ULK1), to form autophagosomes, which engulf the damaged mitochondria, forming mitophagosomes.

Table 1. Summary of role of mitophagy in kidney diseases

Kidney diseases	Key molecules	Role	Mechanism
AKI			
Ischemia/ reperfusion (I/R)	FUNDC1	Deficiency results in excessive Drp1-dependent fission	Mitophagy induction through FUNDC1 helps protect against I/R-AKI by maintaining mitochondrial quality and reducing oxidative stress
	BNIP3	Protects against renal I/R injury	Promotes mitochondrial depolarization, ROS generation, and dissociation of the Bcl-2-Beclin 1 complex
	PINK1/Parkin	Maintains mitochondrial quality, protects tubular cells	Activation helps remove damaged mitochondria, reduces mitochondrial ROS production and subsequent cellular injury
	Drp1	Dual role in mitochondrial fission	Drp1 translocation triggers mitophagy, protecting against renal dysfunction. Excessive Drp1 activity can exacerbate kidney injury
Cisplatin-induced AKI	PINK1/Parkin	Protects against cisplatin-induced AKI	Enhances mitophagy, reducing oxidative stress and inflammation, protecting against kidney damage
	NIX (BNIP3L)	Contributing to mitophagy induction	Promotes mitochondrial depolarization and ROS generation, helping clear damaged mitochondria and mitigating kidney injury
	Drp1	Inhibition can ameliorate cisplatin-induced AKI	Reduces mitochondrial fragmentation, protecting against mitochondrial dysfunction and kidney injury
	SFP/NGN NFs	Protects against cisplatin-induced AKI	Reduces ROS accumulation, enhances antioxidant defenses, and promotes PINK1/ Parkin-mediated mitophagy
CI-AKI	PINK1/Parkin	Protects against CI-AKI	Activation reduces mitochondrial ROS production and inhibits NLRP3 inflammasome activation, mitigating renal injury
	BNIP3	Crucial for protecting against CI-AKI.	Transcriptional target of HIF-1 promotes mitophagy under hypoxic conditions, protecting against mitochondrial damage and renal injury
	HIF1A	Promotes mitophagy during hypoxia, protecting against CI-AKI	Enhances BNIP3 expression, increasing mitophagy and reducing mitochondrial damage and inflammation
	NLRP3 Inflammasome	Protects against CI-AKI	Inhibition enhances HIF1A and BNIP3-mediated mitophagy, reduces inflammation and mitochondrial damage
CKD			
DN	PINK1/Parkin	Essential in protecting against DN	Enhances mitophagy, reducing oxidative stress and improving renal function
	SIRT1	Regulates mitophagy through the PINK1/Parkin pathway	Promotes mitophagy, improving mitochondrial function and reducing oxidative stress
	AMPK	Promotes mitophagy and protects against DN	Phosphorylates ULK1, promoting mitophagy, regulates BNIP3 phosphorylation
	mTOR	Protects against DN	Inhibition enhances mitophagy, promotes the interaction between ULK1 and AMPK, reducing renal tubular cell injury
	Nrf2	Protects against DN	Enhances clearance of damaged mitochondria, reducing oxidative stress

Table 1 (continued)

Kidney diseases	Key molecules	Role	Mechanism
Kidney fibrosis	PINK1/Parkin	Crucial in preventing fibrosis	Promotes clearance of damaged mitochondria, reducing oxidative stress
	NIX (BNIP3L)	Protects against mitochondrial dysfunction and fibrosis	Induces mitophagy by promoting mitochondrial depolarization and ROS generation
	SIRT1	Against kidney fibrosis	Enhances mitophagy through the PINK1/Parkin pathway, improving mitochondrial function and reducing oxidative stress
	AMPK	Promotes mitophagy and protects against fibrosis	Phosphorylates ULK1, promoting mitophagy, regulates BNIP3 phosphorylation
	mTOR	Inhibition enhances mitophagy	Promotes the interaction between ULK1 and AMPK, reducing renal tubular cell injury
	Nrf2	Induces mitophagy and protects against fibrosis	Enhances clearance of damaged mitochondria, reducing oxidative stress
	Macrophages	Mitophagy mediated by PINK1/MFN2/Parkin pathway protects against fibrosis	MFN2 regulates mitophagy and mtROS production, preventing macrophage-derived fibrotic responses
RCC			
ccRCC	NR3C1	Inhibits proliferation, migration, and invasion in ccRCC	Activates ER stress and induces mitophagy through the ATF6-PINK1/BNIP3 pathway
	GPD1L	Correlates positively with RCC prognosis	Regulates mitophagy via the PINK1/Parkin pathway
pRCC	PINK1 and PARK2	Potential prognostic markers in pRCC	Involved in aggressive tumor behavior through mitophagy regulation
Inherited renal diseases			
Alport syndrome	Nrf2	Causes nephritis with sensorineural hearing loss due to genetic mutations in the type IV collagen alpha chain	Agents targeting mitochondrial quality, such as Nrf2, are under evaluation. Nrf2 upregulates mitophagy by targeting PINK1, enhancing mitochondrial quality control
ADPKD	PKD1 and PKD2	Leads to bilateral renal cysts and progressive kidney failure due to variants in PKD1 or PKD2	Impaired Nrf2 antioxidant pathway drives oxidative damage and disease progression. Mitophagy induction by Nrf2-PINK1 pathway is crucial for managing oxidative stress
FD	mTOR	An X-linked LSD affecting renal, cardiac, and nerve cells	Overactive mitophagy indicated by upregulated LC3-II levels and decreased mTOR activity. Lysosomes' involvement in mitophagy suggests a key role in FD pathophysiology

ccRCC, clear cell renal carcinoma; pRCC, papillary renal cell carcinoma; LSD, lysosomal storage disorder.

Mitophagosomes then fuse with lysosomes to form mature mitophagolysosomes, where lysosomal hydrolases degrade the mitochondria. The Pink1/Parkin pathway is finely regulated through a balance between ubiquitination and deubiquitination events. Deubiquitinating enzymes such as ubiquitin-specific peptidase 15 (USP15), USP30, and USP35 counteract mitophagy by removing ubiquitin chains from the mitochondrial surface, thus regulating energy homeostasis. Phosphorylated ubiquitin and poly-Ub chains generated by Parkin display diminished hydrolysis by these deubiquitinases, ensuring efficient mitophagy.

NIX-Driven Mitophagy

NIX (also known as BNIP3L) is a crucial receptor in mitophagy, regulated through both transcriptional and post-translational mechanisms. NIX expression significantly increases under hypoxic and iron depletion

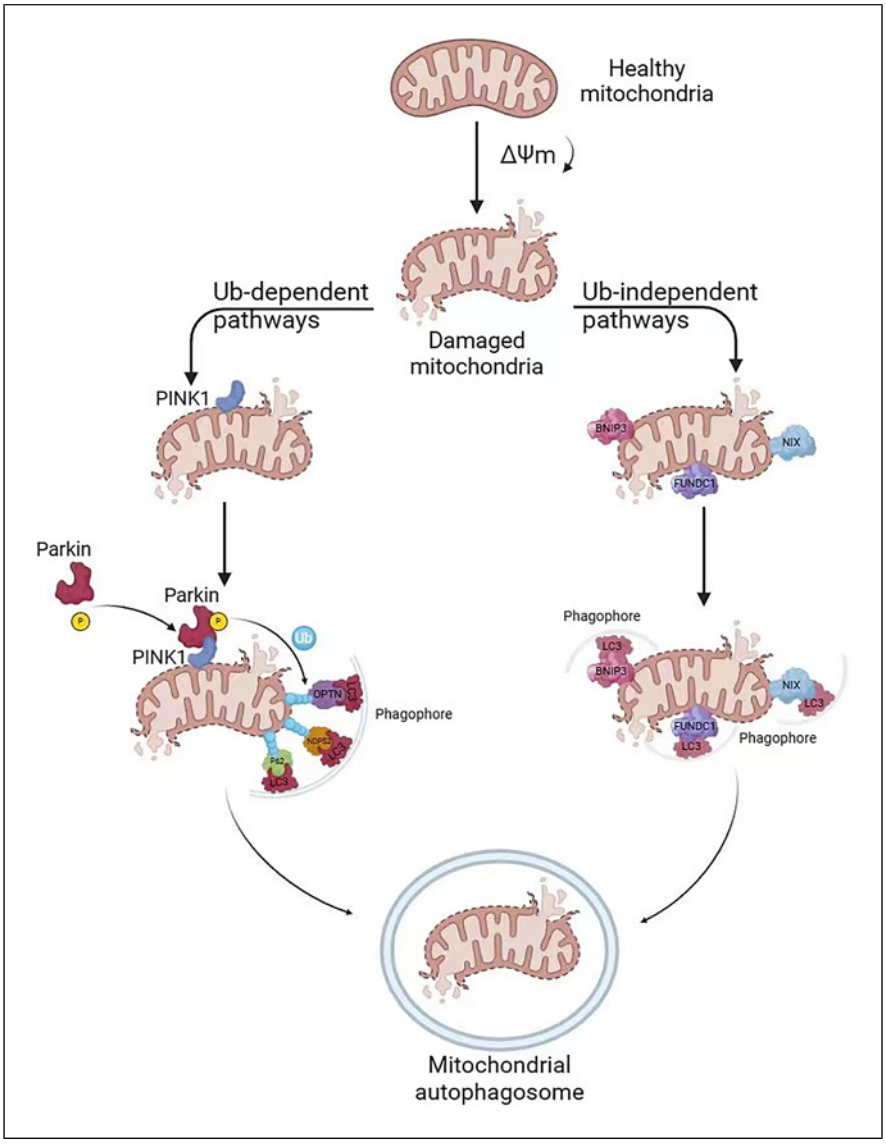

Fig. 1. Mechanisms of mitophagy. PINK1, PTEN-induced putative kinase1; Parkin, Parkin RBRE3 ubiquitin protein ligase; ΔΨm, mitochondrial membrane potential; Ub, ubiquitin; P, phosphorylation; NDP52, nuclear dot protein 52; ULK1, Unc-51-like kinase 1; OPTN, optineurin; LC3, protein 1 light chain 3; TBK1, TANK-binding kinase 1; p62, sequestosome-1; FUNDC1, FUN14 domain containing 1; BNIP3, BCL-2/adenovirus E1B interacting protein 3; Nix, Nip3-like protein X.

conditions via HIF1a signaling, whose regulation can be observed during neurogenesis and germline development. The Foxo3 transcription factor also regulates NIX expression during starvation, particularly in muscle cells. NIX levels are controlled post-translationally by SCF-FBXL4 ubiquitin E3 ligase complex, leading to proteasomal degradation [12]. Phosphorylation of serine residues near the LIR motif (Ser34 and Ser35) by ULK1 kinase enhances its ability to bind ATG8 family proteins, promoting mitophagy, although gene editing studies suggest that phosphorylation at these sites is not essential during neurogenesis [13]. Homodimerization via its C-terminal transmembrane domains is critical for NIX to interact with ATG8 proteins, facilitating mitophagy. In erythroid cells, NIX is necessary for mitochondrial clearance during red blood cell maturation, likely due to its role in inducing mitochondrial depolarization and direct interaction with LC3 and GABARAP. NIX may also promote ROS generation, which contributes to autophagy induction by inhibiting the mTOR signaling pathway and enhancing LC3 association with autophagosomal membranes.

Two models have been proposed to explain NIX-dependent mitophagy. The first model suggests that NIX triggers mitochondrial depolarization, which in turn causes mitochondrial autophagy and clearance. This model is supported by evidence that BNIP3 and NIX can trigger mitochondrial depolarization, which is sufficient

to cause mitophagy. Studies have shown that reticulocyte mitochondria depolarize over time in culture and that the mitochondrial clearance defect caused by NIX deficiency can be rescued by compounds that cause mitochondrial depolarization. However, it is also plausible that NIX-dependent mitochondrial depolarization occurs after autophagosome formation but before elimination as mitophagy in reticulocytes occurs independent of BAX and BAK [14]. The second model proposes that NIX may have a novel function of recruiting autophagy components independent of triggering mitochondrial depolarization. This model suggests that NIX functions as an adaptor protein that recruits components of the autophagy machinery to mitochondria. Preliminary studies indicate that NIX directly interacts with LC3, supporting this hypothesis. This interaction is critical for targeting mitochondria to autophagosomes in erythroid cells, suggesting a role for NIX in the specific activation of mitophagy near the mitochondrial outer membrane [15].

Bnip3-Driven Mitophagy

As mitophagy receptors, Bcl-2 homology 3 (BH3)-only protein Nix (BNIP3L) and its homologue BCL-2/adenovirus E1B interacting protein 3 (BNIP3) interacting directly with LC3 are both important for efficient turnover of mitochondria under hypoxic conditions [16]. BNIP3 is a pro-apoptotic mitochondrial protein containing a BH3 domain and a C-terminal transmembrane domain. Its expression is highly induced under hypoxic conditions via HIF1a signaling, with additional regulation during neurogenesis and germline development. Post-translational modifications of BNIP3 include ubiquitination by the FBXL4 E3 ligase complex, leading to proteasomal degradation and phosphorylation at Ser17 by ULK1 kinase and Ser24, which are crucial for its binding to ATG8 proteins and initiation of mitophagy. Homodimerization via C-terminal transmembrane domains is necessary for BNIP3 to interact with ATG8 proteins, driving mitophagy [17].

BNIP3 is expressed in various tissues under physiological conditions, including the liver, skeletal muscle, heart, kidney, and brain. Its expression is regulated by hypoxia-inducible factor-1 (HIF-1) and the Foxo3 transcription factor, with increased expression during hypoxia and starvation [18]. BNIP3 promotes mitochondrial depolarization, ROS generation, and dissociation of the Bcl-2-Beclin 1 complex, contributing to autophagy induction and recruitment of autophagy machinery to damaged mitochondria. BNIP3 has also been implicated in necrosis and autophagic cell death, differentiating its role from other BH3-only pro-apoptotic proteins [19].

FUNDC1/SRC-Driven Mitophagy

FUN14 domain containing 1 (FUNDC1), an OMM protein, plays a critical role in hypoxia-induced mitophagy. Under normal conditions, phosphorylation of tyrosine residues within the LIR motif by CK2 and Src kinases inhibits the interaction between FUNDC1 and LC3 due to steric hindrance, thus inhibiting mitophagy [20]. Upon mitophagy induction, FUNDC1 is activated through dephosphorylation at Ser13 by PGAM5 and phosphorylation at Ser17 by ULK1, enabling its interaction with ATG8 proteins. The E3 ubiquitin ligase MARCH5 ubiquitinates FUNDC1, promoting its proteasomal degradation and regulating its mitochondrial levels [21]. Unlike NIX and BNIP3, FUNDC1-mediated mitophagy does not rely on transcriptional upregulation and exhibits a stronger binding affinity with LC3B. Overexpression of FUNDC1 is sufficient to induce mitophagy in various cell lines, and its interaction with LC3 through the LIR motif is essential for this process. FUNDC1 does not promote cell death under hypoxic conditions and functions independently of Parkin, indicating a distinct mechanism from NIX- and BNIP3-mediated mitophagy.

Additional Regulatory Factors

Protein kinase C delta (PRKCD) is a kinase that plays a significant role in receptor-mediated mitophagy. It localizes to mitochondria and assists in recruiting the ULK1 complex to initiate mitophagy. This kinase is critical for the regulation of mitophagy through its phosphorylation activities. PRKCD aids in the coordination of mitophagy processes by ensuring the proper assembly and activation of the mitophagic machinery at the mitochondrial surface. It has been shown to be involved in HIF1a-induced mitophagy and is essential in various physiological contexts, including in vivo studies in zebrafish, demonstrating its importance in maintaining mitochondrial quality control [22].

Cyclin G-associated kinase (GAK)'s role in mitophagy is less well defined compared to PRKCD, but it is suggested to be crucial in autophagy processes, specifically receptor-mediated mitophagy. Inhibition of GAK results in altered mitochondrial networks that appear more fused, as well as changes in lysosomal morphology, indicating its specific function in maintaining mitochondrial dynamics and autophagic flux. GAK has been implicated in general autophagy processes, although its activity was initially thought to be dispensable for bulk or starvation-induced autophagy. Recent studies in glial cells suggest that GAK is important for overall autophagy processes, raising questions about how it functions in different cell types during mitophagy. Defining the kinase targets of GAK and its role in phosphorylating outer

Table 2. Mitophagy targets and drugs in kidney diseases: roles and mechanisms

Kidney diseases	Drug/target	Role	Mechanism
AKI			
Ischemia/ reperfusion (I/R)	FUNDC1	Protects against I/R-AKI	FUNDC1 induces mitophagy to maintain mitochondrial quality and reduce oxidative stress
	BNIP3		BNIP3 promotes mitochondrial depolarization and ROS generation
	PINK1/Parkin		PINK1/Parkin activation removes damaged mitochondria
	Drp1		Drp1 triggers mitophagy upon translocation to damaged mitochondria
Cisplatin-induced AKI	PINK1/Parkin	Protects against cisplatin-induced AKI	PINK1/Parkin enhances mitophagy to reduce oxidative stress and inflammation
	NIX (BNIP3L)		NIX promotes mitochondrial depolarization and ROS generation
	Drp1		Drp1 reduces mitochondrial fragmentation
	SFP/NGN NFs		SFP/NGN NFs inhibit mtDNA-cGAS-STING pathway and enhance mitophagy
CI-AKI	PINK1/Parkin	Protects against CI-AKI	PINK1/Parkin reduces mitochondrial ROS and NLRP3 inflammasome activation
	BNIP3		BNIP3 promotes mitophagy under hypoxia
	HIF1A		HIF1A enhances BNIP3 expression and mitophagy
	NLRP3 Inflammasome		NLRP3 inflammasome inhibition enhances mitophagy
CKD			
DN	PINK1/Parkin	Protects against DN	PINK1/Parkin enhances mitophagy, reducing oxidative stress and improving renal function
	SIRT1		SIRT1 promotes mitophagy and improves mitochondrial function
	AMPK		AMPK phosphorylates ULK1, promoting mitophagy
	mTOR		mTOR inhibition promotes interaction between ULK1 and AMPK, enhancing mitophagy
	Nrf2		Nrf2 induces mitophagy and reduces oxidative stress
Kidney fibrosis	PINK1/Parkin	Crucial in preventing fibrosis	PINK1/Parkin promotes clearance of damaged mitochondria, reducing oxidative stress
	NIX (BNIP3L)	Protects against mitochondrial dysfunction and fibrosis	NIX induces mitophagy by promoting mitochondrial depolarization and ROS generation
	SIRT1	Against kidney fibrosis	SIRT1 enhances mitophagy and improves mitochondrial function
	AMPK	Promotes mitophagy and protects against fibrosis	AMPK phosphorylates ULK1, promoting mitophagy
	mTOR	Inhibition enhances mitophagy	mTOR inhibition promotes interaction between ULK1 and AMPK, enhancing mitophagy
	Nrf2	Induces mitophagy and protects against fibrosis	Nrf2 induces mitophagy by enhancing clearance of damaged mitochondria
	Macrophages	Mitophagy mediated by PINK1/ MFN2/Parkin pathway protects against fibrosis	Macrophages regulate mitophagy and mtROS production via PINK1/MFN2/Parkin pathway
RCC			
ccRCC pRCC	–	–	–

Table 2 (continued)

Kidney diseases	Drug/target	Role	Mechanism
Inherited renal diseases			
Alport syndrome	Bardoxolone methyl (BARD)	Under evaluation for treating Alport syndrome	Activates Nrf2, which targets PINK1, enhancing mitochondrial quality control
	TJ0113	Under clinical study for Alport syndrome	Induces mitophagy, selectively eliminates damaged mitochondria, restores cell energy metabolism and homeostasis balance
ADPKD	Bardoxolone methyl (BARD)	Trial terminated due to insufficient impact on ESRD prevention	Aimed to improve renal function and manage oxidative stress via the Nrf2-PINK1 pathway
FD	–	–	–

membrane mitophagy receptors will be crucial for understanding its regulatory mechanisms. Further research is needed to elucidate its precise function and the implications of its activity in various cellular contexts [23].

Acute Kidney Injury

Based on routine healthcare data, it has been observed that the incidence of AKI in the population has significantly increased [24]. At present, there is no specific treatment available for AKI. Studies have revealed that mitochondrial loss of function and structural damage occurs earlier than the pathological manifestations of kidney injury during AKI [25]. As a result, mitochondrial dysfunction has emerged as a crucial driver of AKI and a promising therapeutic target [26]. Furthermore, the health of kidney mitochondria is a critical factor that influences the onset and recovery of AKI [27].

Ischemia/Reperfusion-Induced AKI

Ischemia reperfusion from trauma and surgery is the main risk factor of AKI, which also hinders the relevant clinical treatment [28]. Ischemia-reperfusion injury (I/R) is a pathological condition caused by the recovery of subsequent restoration of perfusion and concomitant reoxygenation to the ischemic tissue or organ [29]. It has been widely believed that renal I/R is the main cause of AKI [30] as acute tubular injury caused by ischemia and the generation of ROS by stimulated endothelial cells can lead to oxidative damage, apoptosis, and necrosis in renal tubular epithelial cells (TECs) [31]. Therefore, there is a pressing need to identify the underlying molecular mechanisms of I/R-induced AKI and develop novel targets and potent strategies to address this issue.

Mitochondrial dysfunction is closely related to the pathogenesis of I/R-AKI [32] since it generates a burst of ROS and initiates downstream tissue injury [33]. It is generally believed that pharmacological inhibition of mitochondrial fission or genetic ablation of dynamin-related protein 1 (Drp1), a key regulator in mitochondrial fission [31], could attenuate progressive kidney injury after I/R [30]. Pumilio RNA binding family member 2 (Pum2) overexpression downregulates Drp1 receptor, mitochondrial fission factor, thereby inhibiting Drp1's translocation to the mitochondria, which attenuates I/R-AKI [34, 35].

Several studies suggested that under ischemia/reperfusion (I/R) conditions, FUNDC1 and Parkin are significantly repressed, leading to inhibited mitophagy [36]. One study found that FUNDC1 deficiency impaired mitochondrial quality and resulted in excessive Drp1-dependent fission during ischemic preconditioning [37]. Another study demonstrates that BNIP3-dependent mitophagy can protect against I/R, as evidenced by the more severe kidney damage, stronger inflammation, and increased tubular cell death observed in Bnip3-KO mice after renal I/R [38]. Additionally, it has been shown that PINK1/Parkin-dependent mitophagy plays a critical role in controlling the mitochondrial quality for tubular cell viability [39]. However, one study shows that I/R can cause Drp1 to transfer to damaged mitochondria and trigger mitophagy in renal I/R [40]. The contrasting effects of Drp1 may be due to differences in the concentration of Midiv-1 used and the duration of ischemia in the experiments [33].

Despite the important role that mitophagy plays in maintaining cell homeostasis by clearing damaged mitochondria, excessive mitophagy resulting from self-amplification may contribute to cell death [41]. A study has shown that renal dysfunction may be caused by excessive mitophagy resulting from I/R. Furthermore, uncoupling protein 2 (UCP2) has a protective role against AKI by preventing loss of membrane potential and reducing subsequent mitophagy [42]. In summary, mitophagy represents a potential target for the treatment of ischemia/reperfusion-induced acute kidney injury.

Cisplatin-Induced AKI

Cisplatin is a widely used chemotherapy drug for cancer treatment, but its use can lead to significant kidney toxicity. Various studies have demonstrated that cisplatin-induced kidney toxicity is associated with mitochondrial dysfunction, elevated oxidative stress [43], inflammation [43], and imbalanced expression of endogenous antioxidant enzymes. mtDNA instability is particularly vulnerable to the effects of oxidative stress, and when mitochondria are damaged, mtDNA is released into the cytoplasm, activating the innate immune system, including the cGAS-STING pathway [44], and promoting inflammation. Recent research has shown that SFP/NGN NFs can effectively inhibit cisplatin-induced ROS accumulation and mtDNA release, while also increasing mRNA levels of SOD, NQO-1, and HO-1 and reducing levels of inflammatory factors such as IL-6 and TNF-α. Moreover, further studies have revealed that SFP/NGN NFs can enhance the expression of Pink/Parkin in renal tissue, thereby protecting kidney function by activating mitochondrial autophagy and inhibiting the mtDNA-cGAS-STING pathway [45]. There is a growing body of evidence to suggest that the induction of mitochondrial autophagy may offer protection against cisplatin-induced kidney injury [46]. For instance, the use of self-assembling silk peptide nanofibers has been shown to mitigate AKI caused by cisplatin by inhibiting the mtDNA-cGAS-STING pathway and delivering naringenin. Similarly, curcumin has been found to prevent cisplatin-induced changes in mitochondrial bioenergetics and dynamics, thereby inhibiting kidney damage. However, it should be noted that mitochondrial autophagy can be a double-edged sword. In fact, researchers using PINK1-KO rats have discovered that PINK1 deficiency can reduce mitochondrial autophagy, leading to an improvement in cisplatin-induced AKI. These findings suggest that inhibiting excessive mitochondrial autophagy may also be an effective strategy for improving cisplatin-induced AKI [47].

Contrast-Induced AKI

Contrast media are widely used in angiography and percutaneous coronary intervention. Despite advances in angiography and percutaneous coronary intervention, contrast-induced acute kidney injury (CI-AKI) is still a common cause of hospital-acquired AKI. The survey showed that the conventional methods of intravenous sodium bicarbonate and oral acetylcysteine showed no evidence of obvious benefits in preventing CI-AKI and related adverse outcomes [48]. Therefore, it is necessary to take preventive measures to reduce these potential adverse consequences [49].

The pathogenic mechanism of CI-AKI has not been fully elucidated. Some researchers believe that oxidative stress is an important driver of CI-AKI. Contrast agents can enhance oxidative stress, promote the formation of renal ROS, and induce hypoxia. Activating mitophagy can prevent tissue damage. Other studies have shown that exposure to contrast agents (iohexol and ioxamol) can induce mitophagy, mitochondrial ROS generation, and mitochondrial damage in HK-2 cells. Enhancing mitophagy can protect HK-2 cells from contrast agent-induced apoptosis while inhibiting mitophagy will exacerbate HK-2 cell damage [50].

Some researchers believe that contrast agents (iohexol) will cause mitochondrial damage in renal TECs and then induce mitochondrial ROS and NLRP3 inflammasome activation. In response, PINK1-Parkin-mediated mitophagy will be activated to repair damaged mitochondria and mitigate renal injury in CI-AKI by reducing mitochondrial ROS production and NLRP3 inflammasome activation [51]. Recent findings suggest that inhibition of mitophagy can trigger NLRP3 inflammasome activation, while hypoxia can also induce inflammation. Additionally, hypoxia-inducible factor 1A (HIF1A) can promote mitophagy during hypoxia. It is widely recognized that mitophagy can be activated through both PRKN-dependent and PRKN-independent pathways. BNIP3 serves as a crucial regulator of the PRKN-independent mitophagy pathway and is also a transcriptional target of HIF-1 [52]. Additional investigations have demonstrated that iohexol induces hypoxia and triggers the activation of the NLRP3 inflammasome. Moreover, it has been discovered that inhibiting the NLRP3 inflammasome can enhance HIF1A and BNIP3-mediated mitophagy, thereby mitigating mitochondrial damage in CI-AKI mice [53]. Hence, it can be inferred that mitophagy plays a crucial role in promoting the survival of tubular cells in the CI-AKI cell model. Given its potential significance in the context of CI-AKI, mitophagy could be explored as a promising therapeutic target.

Chronic Kidney Disease

CKD, following progressive renal dysfunction, inflammation, hemodynamic and vascular change [54], is predicted to become the 5th leading cause of death by 2040 [55]. However, the relevant knowledge about the pathological mechanisms and possible treatment of CKD is relatively few [56]. Many evidences suggest that mitochondrial dysfunction, especially mitophagy disorder, has high connection with CKD progression [57] since

kidney is the second highest mitochondrial ATP consumer in human body [58]. In addition, a temporary accumulation of damaged mitochondria can highly contribute to CKD [59], and the role of ROS is also highlighted in many studies [60].

Diabetic Nephropathy

Diabetic nephropathy (DN), a significant microvascular complication of diabetes, is the primary cause of CKD [61]. A growing body of evidence suggests that disrupted mitochondrial homeostasis plays a central role in the pathogenesis of DN, particularly altered mitophagy, which has been extensively studied [62, 63]. It is believed that mitophagy significantly decreases during DN, resulting in the accumulation of damaged mitochondria, intracellular oxidative stress, and impaired renal function [63]. In STZ-induced diabetic rat models, a decrease in PINK1 expression has been observed, indicating a reduction in mitophagy [64].

The regulation of mitophagy in DN involves several important factors, including the mammalian target of rapamycin (mTOR), adenosine 5′-monophosphate-activated protein kinase (AMPK), and sirtuin-1 (SIRT1) [65]. Research has shown that SIRT1 promotes mitophagy through the PINK1/Parkin pathway, but its activity decreases during DN due to the strict regulation of intracellular NAD+ concentrations [66]. Resveratrol, a SIRT1 agonist [67], has been found to play a significant role in treating DN. Additionally, evidence suggests that AMPK directly phosphorylates ULK1 on Ser467, Ser555, Thr574, and Ser637, while unc-51-like kinase 1 (ULK1) can assist in phosphorylating BNIP3 to promote interaction with LC3 and mitophagy. Loss of AMPK has been shown to result in defective mitophagy [68].

The researchers have reported that the activation of AMPK under hypoxic conditions is regulated by mitochondrial ROS. This activation produces an amplified signal through Ca2+/calmodulin-dependent protein kinase kinase β, which targets AMPK [69] and is downregulated in DN [70]. The activity of AMPK could lead to a decrease in forkhead box 3 (FOXO3), resulting in increased levels of endogenous antioxidants and thus attenuating DN [71, 72]. Additionally, mTOR has been found to be associated with the proliferation of tubular cells in DN. However, when the *mTOR* gene is knocked out [73], tubular injury is ameliorated. Furthermore, mTOR could inhibit mitophagy by disrupting the interaction between ULK1 and AMPK [74].

Furthermore, it is widely recognized that Nrf2 has the ability to facilitate mitophagy in the Parkin or Pink1 KD genetic backgrounds in a p62-independent manner, indicating its potential to involve other ubiquitin receptors in the mitophagy process [75]. Additionally, WJ-39, an inhibitor of aldose reductase, has been discovered to improve DN by activating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. As a result, a phase 1 clinical trial has been authorized by the National Medical Products Administration [76].

Studies indicate that the utilization of mitochondria-targeted antioxidant (mitoQ) is a promising approach for safeguarding tubular cells against oxidative damage caused by hyperglycemia. This method involves the upregulation of PINK and Parkin expression, as well as the inhibition of mitochondrial ROS production [77], which effectively reverses the decrease of mitophagy in DKD. Additionally, research has shown that placenta-derived mesenchymal stem cells possess the ability to mitigate renal injury and promote PINK1/Parkin-mediated mitophagy by activating the SIRT1-PGC-1α-TFAM pathway.

Kidney Fibrosis

Kidney fibrosis is considered as the end stage of almost all CKD, reducing the capacity for tissue repair and leading to renal failure [78, 79]. Though the molecular mechanisms and therapeutic regimens of renal tubulointerstitial fibrosis are not fully understood, many studies suggest that appropriate mitophagy could be a cell self-protection mechanism in fibrosis and a target for treatment [63, 80] since it can maintain mitochondrial homeostasis, downregulate TGF-β1/Smad signaling and alleviating renal TECs injuries in kidneys [81].

Mouse model studies confirmed that MFN1 and Parkin levels, downstream of PINK1, are reduced during kidney fibrosis [82], which happens before inflammatory and fibrotic onset [83]. Researchers find that RCAN1 attenuated renal interstitial fibrosis by regulating PINK1/Parkin-induced mitophagy by mediating LC3 accumulation and autophagosome clearance [84]. Also, melatonin improves renal fibrosis through miR-4515 upregulation and suppressive SIAH3 expression, PINK1/Parkin-mediated mitophagy promotion [85]. AMPK agonist metformin is reported to be able to alleviate renal fibrosis through the AMPK-Pink1-Parkin pathway as well [86]. Another research indicates that loss of legumain can lead to mitophagy impairment and mtROS accumulation, resulting in aging-related renal fibrosis [87].

Furthermore, it is worth noting that macrophages play a crucial role in kidney fibrosis [88]. Extensive research has been conducted to shed light on the fact that macrophage mitophagy, mediated by the PINK1/mitofusin

(MFN)2/Parkin pathway, serves as a protective mechanism against kidney fibrosis. Additionally, it has been observed that MFN2, but not MFN1, regulates mitophagy and mtROS production, thereby preventing macrophage-derived fibrotic response [81].

Renal Cancers

Renal cell carcinoma (RCC) denotes cancer that rises from renal TECs, accounting for over 90% of kidney cancers, and is identified as the most common type of urogenital cancer [89]. Some studies suggest that there is a connection between mitophagy and RCC. For example, it is reported that the knockdown of nuclear receptor subfamily 3, group C, member 1 (NR3C1) could reduce proliferation, migration, and invasion in clear cell renal carcinoma, the most common renal cancer by activating endoplasmic reticulum stress and inducing mitophagy through the ATF6-PINK1/BNIP3 [90, 91]. Furthermore, another study shows that glycerol-3-phosphate dehydrogenase 1-like (GPD1L) is positively correlated with the prognosis of RCC through the PINK1/Parkin pathway [92]. Similarly, PINK1 and PARK2 are considered to be potential prognosticators in papillary renal cell carcinoma in another report [93].

Inherited Renal Disease

Inherited renal disease is a series of diseases caused by genetic mutations, inherited from offsprings according to Mendal's genetic law. Some of these diseases have been proven to have connections with mitophagy. Alport syndrome is a progressive genetic disease that causes nephritis with sensorineural hearing loss, arising from genetic mutations in the type IV collagen alpha chain, a component of the glomerular basement membrane [94]. Though the role mitochondria playing in Alport syndrome is still unclear, agents concerning mitochondrial quality are currently under clinical evaluation [95]. Among them, Reata Pharmaceuticals nuclear submits an NDA of bardoxolone methyl (BARD) for Alport syndrome, which is a small-molecular compound that activates Nrf2 [96]. Apart from its anti-oxidative and anti-inflammatory effect, Nrf2 has also proved to be able to upregulate mitophagy by targeting PINK1 [97], indicating the play mitophagy gives to in Alport syndrome and ADPKD. However, the Food and Drug Administration (FDA) maintains that there is insufficient evidence of BARD's safety and efficacy. TJ0113 [98] has been permitted to proceed clinical study for the Alport syndrome indication by NMPA and FDA. TJ0113 is able to induce mitophagy, selectively eliminate damaged mitochondria without affecting normal mitochondria, and restore cell energy metabolism and homeostasis balance. Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary kidney disease mainly caused by variants in PKD1 (OMIM#601313) or PKD2 (OMIM#173910) [99], leading to bilateral renal cysts and progressive kidney failure. Research has been done to reveal that the impaired activity of the Nrf2 antioxidant pathway could be a driver of oxidative damage and ADPKD progression [100]. A phase 3 trial of BARD in patients separately with ADPKD, CKD, and ADPKD was conducted and terminated in May 10, 2023. The reason for its termination is that despite improving renal function, the drug did not significantly reduce the risk of ESRD development and it also did not meet some of the secondary goals, such as the time to onset of ESRD, which made it difficult to seek approval for the drug in Japan. Fabry disease (FD) is a rare X-linked disease as the second most popular lysosomal storage disorder, widely affecting renal cells, cardiac cells, and nerve cells [101]. Lysosomes are critically involved in mitophagy, making mitophagy to be a key role in FD pathophysiology. Several studies report upregulation of LC3-II levels and decreased activity of mTOR in FD, suggesting overactive mitophagy.

Conclusions

This review highlights the significance of mitophagy in kidney diseases (Table 2). The exclusion of kidney stone disease and lupus nephritis may limit the overall understanding of mitochondrial dysfunction in various kidney disorders. However, the emerging potential of targeting mitophagy in the treatment of renal diseases offers hope for patients. Several novel drugs, such as TJ0113, that are currently undergoing clinical trials, have shown promising results in promoting renal diseases, while the discontinuation of all BARD CKD programs suggests that the efficacy of indirect mitochondrial mediation is suboptimal and direct targeting of mitochondria holds greater promise. Looking ahead, the future development of drugs targeting mitophagy and their clinical practice has the potential to greatly benefit patients with kidney diseases. Further research on the molecular mechanisms and regulatory pathways of mitophagy in different kidney diseases is essential for the development of effective therapeutic interventions.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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References

1 Youle RJ, Narendra DP. Targeting mitophagy: mechanisms and therapies. Nat Rev Mol Cell Biol. 2011;12(1):9–14. https://doi.org/10.1038/nrm3028
2 Friedman JR, Nunnari J. Mitochondrial form and function. Nature. 2014;505(7483):335–43. https://doi.org/10.1038/nature12985
3 Wong HS, Dighe PA, Mezera V, Monternier PA, Brand MD. Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions. J Biol Chem. 2017;292(41):16804–9. https://doi.org/10.1074/jbc.R117.789271
4 Kim I, Rodriguez-Enriquez S, Lemasters JJ. Selective degradation of mitochondria by mitophagy. Arch Biochem Biophys. 2007;462(2):245–53. https://doi.org/10.1016/j.abb.2007.03.034
5 Pickles S, Vigié P, Youle RJ. Mitophagy and quality control mechanisms in mitochondrial maintenance. Curr Biol. 2018;28(4):R170–85. https://doi.org/10.1016/j.cub.2018.01.004
6 Bhatia D, Choi ME. The emerging role of mitophagy in kidney diseases. J Life Sci. 2019;1(3):13–22. https://doi.org/10.36069/jols/20191203
7 Choi ME. Autophagy in kidney disease. Annu Rev Physiol. 2020;82(1):297–322. https://doi.org/10.1146/annurev-physiol-021119-034658
8 Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, et al. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. 2010;8(1):e1000298. https://doi.org/10.1371/journal.pbio.1000298
9 Deas E, Plun-Favreau H, Gandhi S, Desmond H, Kjaer S, Loh SH, et al. PINK1 cleavage at position A103 by the mitochondrial protease PARL. Hum Mol Genet. 2011;20(5):867–79. https://doi.org/10.1093/hmg/ddq526
10 Lu Y, Li Z, Zhang S, Zhang T, Liu Y, Zhang L. Cellular mitophagy: mechanism, roles in diseases and small molecule pharmacological regulation. Theranostics. 2023;13(2):736–66. https://doi.org/10.7150/thno.79876
11 Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, et al. Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature. 2014;510(7503):162–6. https://doi.org/10.1038/nature13392
12 Cao Y, Zheng J, Wan H, Sun Y, Fu S, Liu S, et al. A mitochondrial SCF-FBXL4 ubiquitin E3 ligase complex degrades BNIP3 and NIX to restrain mitophagy and prevent mitochondrial disease. EMBO J. 2023;42(13):e113033. https://doi.org/10.15252/embj.2022113033
13 Rogov VV, Suzuki H, Marinković M, Lang V, Kato R, Kawasaki M, et al. Phosphorylation of the mitochondrial autophagy receptor Nix enhances its interaction with LC3 proteins. Sci Rep. 2017;7(1):1131. https://doi.org/10.1038/s41598-017-01258-6
14 Schweers RL, Zhang J, Randall MS, Loyd MR, Li W, Dorsey FC, et al. NIX is required for programmed mitochondrial clearance during reticulocyte maturation. Proc Natl Acad Sci USA. 2007;104(49):19500–5. https://doi.org/10.1073/pnas.0708818104
15 Zhang J, Ney PA. Role of BNIP3 and NIX in cell death, autophagy, and mitophagy. Cell Death Differ. 2009;16(7):939–46. https://doi.org/10.1038/cdd.2009.16
16 Hanna RA, Quinsay MN, Orogo AM, Giang K, Rikka S, Gustafsson ÅB. Microtubule-associated protein 1 light chain 3 (LC3) interacts with Bnip3 protein to selectively remove endoplasmic reticulum and mitochondria via autophagy. J Biol Chem. 2012;287(23):19094–104. https://doi.org/10.1074/jbc.M111.322933
17 Matsushima M, Fujiwara T, Takahashi E, Minaguchi T, Eguchi Y, Tsujimoto Y, et al. Isolation, mapping, and functional analysis of a novel human cDNA (BNIP3L) encoding a protein homologous to human NIP3. Genes Chromosomes Cancer. 1998;21(3):230–5. https://doi.org/10.1002/(sici)1098-2264(199803)21:3<230::aid-gcc7>3.0.co;2-0
18 Gao A, Jiang J, Xie F, Chen L. Bnip3 in mitophagy: novel insights and potential therapeutic target for diseases of secondary mitochondrial dysfunction. Clin Chim Acta. 2020;506:72–83. https://doi.org/10.1016/j.cca.2020.02.024
19 Liu K, Zhao Q, Sun H, Liu L, Wang C, Li Z, et al. BNIP3 (BCL2 interacting protein 3) regulates pluripotency by modulating mitochondrial homeostasis via mitophagy. Cell Death Dis. 2022;13(4):334. https://doi.org/10.1038/s41419-022-04795-9
20 Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, et al. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol. 2012;14(2):177–85. https://doi.org/10.1038/ncb2422
21 Chen Z, Liu L, Cheng Q, Li Y, Wu H, Zhang W, et al. Mitochondrial E3 ligase MARCH5 regulates FUNDC1 to fine-tune hypoxic mitophagy. EMBO Rep. 2017;18(3):495–509. https://doi.org/10.15252/embr.201643309
22 Laker RC, Drake JC, Wilson RJ, Lira VA, Lewellen BM, Ryall KA, et al. Ampk phosphorylation of Ulk1 is required for targeting of mitochondria to lysosomes in exercise-induced mitophagy. Nat Commun. 2017;8(1):548. https://doi.org/10.1038/s41467-017-00520-9
23 Yamamoto H, Zhang S, Mizushima N. Autophagy genes in biology and disease. Nat Rev Genet. 2023;24(6):382–400. https://doi.org/10.1038/s41576-022-00562-w
24 Sawhney S, Fraser SD. Epidemiology of AKI: utilizing large databases to determine the burden of AKI. Adv Chronic Kidney Dis. 2017;24(4):194–204. https://doi.org/10.1053/j.ackd.2017.05.001
25 Yuan L, Yuan Y, Liu F, Li L, Liu J, Chen Y, et al. PGC-1α alleviates mitochondrial dysfunction via TFEB-mediated autophagy in cisplatin-induced acute kidney injury. Aging. 2021;13(6):8421–39. https://doi.org/10.18632/aging.202653
26 Clark AJ, Parikh SM. Mitochondrial metabolism in acute kidney injury. Semin Nephrol. 2020;40(2):101–13. https://doi.org/10.1016/j.semnephrol.2020.01.002
27 Forbes JM. Mitochondria-power players in kidney function? Trends Endocrinol Metab. 2016;27(7):441–2. https://doi.org/10.1016/j.tem.2016.05.002

28 Packialakshmi B, Stewart IJ, Burmeister DM, Feng Y, McDaniel DP, Chung KK, et al. Tourniquet-induced lower limb ischemia/reperfusion reduces mitochondrial function by decreasing mitochondrial biogenesis in acute kidney injury in mice. Physiol Rep. 2022;10(3):e15181. https://doi.org/10.14814/phy2.15181
29 Omorou M, Huang Y, Gao M, Mu C, Xu W, Han Y, et al. The forkhead box O3 (FOXO3): a key player in the regulation of ischemia and reperfusion injury. Cell Mol Life Sci. 2023;80(4):102. https://doi.org/10.1007/s00018-023-04755-2
30 Malek M, Nematbakhsh M. Renal ischemia/reperfusion injury; from pathophysiology to treatment. J Renal Inj Prev. 2015;4(2):20–7. https://doi.org/10.12861/jrip.2015.06
31 Zhu DJ, Liao XH, Huang WQ, Sun H, Zhang L, Liu Q. Augmenter of liver regeneration protects renal tubular epithelial cells from ischemia-reperfusion injury by promoting PINK1/Parkin-mediated mitophagy. Front Physiol. 2020;11:178. https://doi.org/10.3389/fphys.2020.00178
32 Zheng QY, Li Y, Liang SJ, Chen XM, Tang M, Rao ZS, et al. LIGHT deficiency attenuates acute kidney disease development in an in vivo experimental renal ischemia and reperfusion injury model. Cell Death Discov. 2022;8(1):399. https://doi.org/10.1038/s41420-022-01188-x
33 Martin JL, Gruszczyk AV, Beach TE, Murphy MP, Saeb-Parsy K. Mitochondrial mechanisms and therapeutics in ischaemia reperfusion injury. Pediatr Nephrol. 2019;34(7):1167–74. https://doi.org/10.1007/s00467-018-3984-5
34 Wang J, Zhu P, Toan S, Li R, Ren J, Zhou H. Pum2-Mff axis fine-tunes mitochondrial quality control in acute ischemic kidney injury. Cell Biol Toxicol. 2020;36(4):365–78. https://doi.org/10.1007/s10565-020-09513-9
35 D'Amico D, Mottis A, Potenza F, Sorrentino V, Li H, Romani M, et al. The RNA-binding protein PUM2 impairs mitochondrial dynamics and mitophagy during aging. Mol Cell. 2019;73(4):775–87.e10. https://doi.org/10.1016/j.molcel.2018.11.034
36 Feng J, Li H, Zhang Y, Wang Q, Zhao S, Meng P, et al. Mammalian STE20-like kinase 1 deletion alleviates renal ischaemia-reperfusion injury via modulating mitophagy and the AMPK-YAP signalling pathway. Cell Physiol Biochem. 2018;51(5):2359–76. https://doi.org/10.1159/000495896
37 Wang J, Zhu P, Li R, Ren J, Zhou H. Fundc1-dependent mitophagy is obligatory to ischemic preconditioning-conferred renoprotection in ischemic AKI via suppression of Drp1-mediated mitochondrial fission. Redox Biol. 2020;30:101415. https://doi.org/10.1016/j.redox.2019.101415
38 Tang C, Han H, Liu Z, Liu Y, Yin L, Cai J, et al. Activation of BNIP3-mediated mitophagy protects against renal ischemia-reperfusion injury. Cell Death Dis. 2019;10(9):677. https://doi.org/10.1038/s41419-019-1899-0
39 Tang C, Han H, Yan M, Zhu S, Liu J, Liu Z, et al. PINK1-PRKN/PARK2 pathway of mitophagy is activated to protect against renal ischemia-reperfusion injury. Autophagy. 2018;14(5):880–97. https://doi.org/10.1080/15548627.2017.1405880
40 Li N, Wang H, Jiang C, Zhang M. Renal ischemia/reperfusion-induced mitophagy protects against renal dysfunction via Drp1-dependent-pathway. Exp Cell Res. 2018;369(1):27–33. https://doi.org/10.1016/j.yexcr.2018.04.025
41 Chang HH, Young SH, Sinnett-Smith J, Chou CE, Moro A, Hertzer KM, et al. Prostaglandin E2 activates the mTORC1 pathway through an EP4/cAMP/PKA- and EP1/Ca2+-mediated mechanism in the human pancreatic carcinoma cell line PANC-1. Am J Physiol Cell Physiol. 2015;309(10):C639–49. https://doi.org/10.1152/ajpcell.00417.2014
42 Qin N, Cai T, Ke Q, Yuan Q, Luo J, Mao X, et al. UCP2-dependent improvement of mitochondrial dynamics protects against acute kidney injury. J Pathol. 2019;247(3):392–405. https://doi.org/10.1002/path.5198
43 Mao RW, He SP, Lan JG, Zhu WZ. Honokiol ameliorates cisplatin-induced acute kidney injury via inhibition of mitochondrial fission. Br J Pharmacol. 2022;179(14):3886–904. https://doi.org/10.1111/bph.15837
44 Zhou L, Zhang YF, Yang FH, Mao HQ, Chen Z, Zhang L. Mitochondrial DNA leakage induces odontoblast inflammation via the cGAS-STING pathway. Cell Commun Signal. 2021;19(1):58. https://doi.org/10.1186/s12964-021-00738-7
45 Liu S, Gao X, Yin Y, Wang J, Dong K, Shi D, et al. Silk fibroin peptide self-assembled nanofibers delivered naringenin to alleviate cisplatin-induced acute kidney injury by inhibiting mtDNA-cGAS-STING pathway. Food Chem Toxicol. 2023;177:113844. https://doi.org/10.1016/j.fct.2023.113844
46 Ortega-Domínguez B, Aparicio-Trejo OE, García-Arroyo FE, León-Contreras JC, Tapia E, Molina-Jijón E, et al. Curcumin prevents cisplatin-induced renal alterations in mitochondrial bioenergetics and dynamic. Food Chem Toxicol. 2017;107(Pt A):373–85. https://doi.org/10.1016/j.fct.2017.07.018
47 Zhou L, Zhang L, Zhang Y, Yu X, Sun X, Zhu T, et al. PINK1 deficiency ameliorates cisplatin-induced acute kidney injury in rats. Front Physiol. 2019;10:1225. https://doi.org/10.3389/fphys.2019.01225
48 Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378(7):603–14. https://doi.org/10.1056/NEJMoa1710933
49 McCullough PA, Choi JP, Feghali GA, Schussler JM, Stoler RM, Vallabahn RC, et al. Contrast-induced acute kidney injury. J Am Coll Cardiol. 2016;68(13):1465–73. https://doi.org/10.1016/j.jacc.2016.05.099
50 Lei R, Zhao F, Tang CY, Luo M, Yang SK, Cheng W, et al. Mitophagy plays a protective role in iodinated contrast-induced acute renal tubular epithelial cells injury. Cell Physiol Biochem. 2018;46(3):975–85. https://doi.org/10.1159/000488827
51 Lin Q, Li S, Jiang N, Shao X, Zhang M, Jin H, et al. PINK1-parkin pathway of mitophagy protects against contrast-induced acute kidney injury via decreasing mitochondrial ROS and NLRP3 inflammasome activation. Redox Biol. 2019;26:101254. https://doi.org/10.1016/j.redox.2019.101254
52 Chourasia AH, Tracy K, Frankenberger C, Boland ML, Sharifi MN, Drake LE, et al. Mitophagy defects arising from BNip3 loss promote mammary tumor progression to metastasis. EMBO Rep. 2015;16(9):1145–63. https://doi.org/10.15252/embr.201540759
53 Lin Q, Li S, Jiang N, Jin H, Shao X, Zhu X, et al. Inhibiting NLRP3 inflammasome attenuates apoptosis in contrast-induced acute kidney injury through the upregulation of HIF1A and BNIP3-mediated mitophagy. Autophagy. 2021;17(10):2975–90. https://doi.org/10.1080/15548627.2020.1848971
54 Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005;365(9456):331–40. https://doi.org/10.1016/S0140-6736(05)17789-7
55 Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165–80. https://doi.org/10.1016/S0140-6736(11)60178-5
56 Xu C, Tong L, Rao J, Ye Q, Chen Y, Zhang Y, et al. Heteroplasmic and homoplasmic m.616T>C in mitochondria tRNAPhe promote isolated chronic kidney disease and hyperuricemia. JCI Insight. 2022;7(11):e157418. https://doi.org/10.1172/jci.insight.157418
57 Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet. 2018;392(10159):2052–90. https://doi.org/10.1016/S0140-6736(18)31694-5
58 Zhan M, Brooks C, Liu F, Sun L, Dong Z. Mitochondrial dynamics: regulatory mechanisms and emerging role in renal pathophysiology. Kidney Int. 2013;83(4):568–81. https://doi.org/10.1038/ki.2012.441
59 Aparicio-Trejo OE, Tapia E, Sánchez-Lozada LG, Pedraza-Chaverri J. Mitochondrial bioenergetics, redox state, dynamics and turnover alterations in renal mass reduction models of chronic kidney diseases and their possible implications in the progression of this illness. Pharmacol Res. 2018;135:1–11. https://doi.org/10.1016/j.phrs.2018.07.015

60 Gortan Cappellari G, Zanetti M, Semolic A, Vinci P, Ruozi G, Falcione A, et al. Unacylated ghrelin reduces skeletal muscle reactive oxygen species generation and inflammation and prevents high-fat diet-induced hyperglycemia and whole-body insulin resistance in rodents. Diabetes. 2016;65(4):874–86. https://doi.org/10.2337/db15-1019
61 Martínez-Castelao A, Navarro-González JF, Górriz JL, de Alvaro F. The concept and the epidemiology of diabetic nephropathy have changed in recent years. J Clin Med. 2015;4(6):1207–16. https://doi.org/10.3390/jcm4061207
62 Vasileva VY, Sultanova RF, Sudarikova AV, Ilatovskaya DV. Insights into the molecular mechanisms of polycystic kidney diseases. Front Physiol. 2021;12:693130. https://doi.org/10.3389/fphys.2021.693130
63 Yang S, Han Y, Liu J, Song P, Xu X, Zhao L, et al. Mitochondria: a novel therapeutic target in diabetic nephropathy. Curr Med Chem. 2017;24(29):3185–202. https://doi.org/10.2174/0929867324666170509121003
64 Li D, Wang L, Ou J, Wang C, Zhou J, Lu L, et al. Reactive oxygen species induced by uric acid promote NRK-52E cell apoptosis through the NEK7-NLRP3 signaling pathway. Mol Med Rep. 2021;24(4):729. https://doi.org/10.3892/mmr.2021.12368
65 Yu J, Liu Y, Li H, Zhang P. Pathophysiology of diabetic kidney disease and autophagy: a review. Medicine. 2023;102(30):e33965. https://doi.org/10.1097/MD.0000000000033965
66 Wang W, Sun W, Cheng Y, Xu Z, Cai L. Role of sirtuin-1 in diabetic nephropathy. J Mol Med. 2019;97(3):291–309. https://doi.org/10.1007/s00109-019-01743-7
67 Emerling BM, Weinberg F, Snyder C, Burgess Z, Mutlu GM, Viollet B, et al. Hypoxic activation of AMPK is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio. Free Radic Biol Med. 2009;46(10):1386–91. https://doi.org/10.1016/j.freeradbiomed.2009.02.019
68 Herzig S, Shaw RJ. AMPK: guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol. 2018;19(2):121–35. https://doi.org/10.1038/nrm.2017.95
69 Dugan LL, You YH, Ali SS, Diamond-Stanic M, Miyamoto S, DeCleves AE, et al. AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. J Clin Invest. 2013;123(11):4888–99. https://doi.org/10.1172/JCI66218
70 Zrelli H, Matsuoka M, Kitazaki S, Zarrouk M, Miyazaki H. Hydroxytyrosol reduces intracellular reactive oxygen species levels in vascular endothelial cells by upregulating catalase expression through the AMPK-FOXO3a pathway. Eur J Pharmacol. 2011;660(2–3):275–82. https://doi.org/10.1016/j.ejphar.2011.03.045
71 Kitada M, Takeda A, Nagai T, Ito H, Kanasaki K, Koya D. Dietary restriction ameliorates diabetic nephropathy through anti-inflammatory effects and regulation of the autophagy via restoration of Sirt1 in diabetic Wistar fatty (fa/fa) rats: a model of type 2 diabetes. Exp Diabetes Res. 2011;2011:908185. https://doi.org/10.1155/2011/908185
72 Wei PZ, Szeto CC. Mitochondrial dysfunction in diabetic kidney disease. Clin Chim Acta. 2019;496:108–16. https://doi.org/10.1016/j.cca.2019.07.005
73 Sakaguchi M, Isono M, Isshiki K, Sugimoto T, Koya D, Kashiwagi A. Inhibition of mTOR signaling with rapamycin attenuates renal hypertrophy in the early diabetic mice. Biochem Biophys Res Commun. 2006;340(1):296–301. https://doi.org/10.1016/j.bbrc.2005.12.012
74 Kashtan CE. Alport syndrome: achieving early diagnosis and treatment. Am J Kidney Dis. 2021;77(2):272–9. https://doi.org/10.1053/j.ajkd.2020.03.026
75 Gumeni S, Papanagnou ED, Manola MS, Trougakos IP. Nrf2 activation induces mitophagy and reverses Parkin/Pink1 knock down-mediated neuronal and muscle degeneration phenotypes. Cell Death Dis. 2021;12(7):671. https://doi.org/10.1038/s41419-021-03952-w
76 Zhou X, Liu Z, Ying K, Wang H, Liu P, Ji X, et al. WJ-39, an aldose reductase inhibitor, ameliorates renal lesions in diabetic nephropathy by activating Nrf2 signaling. Oxid Med Cell Longev. 2020;2020:7950457. https://doi.org/10.1155/2020/7950457
77 Li W, Wang Q, Du M, Ma X, Wu L, Guo F, et al. Effects of overexpressing FoxO1 on apoptosis in glomeruli of diabetic mice and in podocytes cultured in high glucose medium. Biochem Biophys Res Commun. 2016;478(2):612–7. https://doi.org/10.1016/j.bbrc.2016.07.115
78 Humphreys BD. Mechanisms of renal fibrosis. Annu Rev Physiol. 2018;80:309–26. https://doi.org/10.1146/annurev-physiol-022516-034227
79 Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389(10075):1238–52. https://doi.org/10.1016/S0140-6736(16)32064-5
80 Galvan DL, Green NH, Danesh FR. The hallmarks of mitochondrial dysfunction in chronic kidney disease. Kidney Int. 2017;92(5):1051–7. https://doi.org/10.1016/j.kint.2017.05.034
81 Bhatia D, Capili A, Nakahira K, Muthukumar T, Torres LK, Choi AMK, et al. Conditional deletion of myeloid-specific mitofusin 2 but not mitofusin 1 promotes kidney fibrosis. Kidney Int. 2022;101(5):963–86. https://doi.org/10.1016/j.kint.2022.01.030
82 Lin Q, Li S, Jin H, Cai H, Zhu X, Yang Y, et al. Mitophagy alleviates cisplatin-induced renal tubular epithelial cell ferroptosis through ROS/HO-1/GPX4 axis. Int J Biol Sci. 2023;19(4):1192–210. https://doi.org/10.7150/ijbs.80775
83 Jiménez-Uribe AP, Bellido B, Aparicio-Trejo OE, Tapia E, Sánchez-Lozada LG, Hernández-Santos JA, et al. Temporal characterization of mitochondrial impairment in the unilateral ureteral obstruction model in rats. Free Radic Biol Med. 2021;172:358–71. https://doi.org/10.1016/j.freeradbiomed.2021.06.019
84 Sang XY, Xiao JJ, Liu Q, Zhu R, Dai JJ, Zhang C, et al. Regulators of calcineurin 1 deficiency attenuates tubulointerstitial fibrosis through improving mitochondrial fitness. FASEB J. 2020;34(11). https://doi.org/10.1096/fj.202000781RRR
85 Yoon YM, Go G, Yoon S, Lim JH, Lee G, Lee JH, et al. Melatonin treatment improves renal fibrosis via miR-4516/SIAH3/PINK1 Axis. Cells. 2021;10(7):1682. https://doi.org/10.3390/cells10071682
86 Han YC, Tang SQ, Liu YT, Li AM, Zhan M, Yang M, et al. AMPK agonist alleviate renal tubulointerstitial fibrosis via activating mitophagy in high fat and streptozotocin induced diabetic mice. Cell Death Dis. 2021;12(10):925. https://doi.org/10.1038/s41419-021-04184-8
87 Wang D, Kang L, Chen C, Guo J, Du L, Zhou D, et al. Loss of legumain induces premature senescence and mediates aging-related renal fibrosis. Aging Cell. 2022;21(3):e13574. https://doi.org/10.1111/acel.13574
88 Lee SY, Kim SI, Choi ME. Therapeutic targets for treating fibrotic kidney diseases. Transl Res. 2015;165(4):512–30. https://doi.org/10.1016/j.trsl.2014.07.010
89 Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017;3:17009. https://doi.org/10.1038/nrdp.2017.9
90 Yan M, Wang J, Wang H, Zhou J, Qi H, Naji Y, et al. Knockdown of NR3C1 inhibits the proliferation and migration of clear cell renal cell carcinoma through activating endoplasmic reticulum stress-mitophagy. J Transl Med. 2023;21(1):701. https://doi.org/10.1186/s12967-023-04560-2
91 Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: the 2022 update. Eur Urol. 2022;82(4):399–410. https://doi.org/10.1016/j.eururo.2022.03.006
92 Liu T, Zhu H, Ge M, Pan Z, Zeng Y, Leng Y, et al. GPD1L inhibits renal cell carcinoma progression by regulating PINK1/Parkin-mediated mitophagy. J Cell Mol Med. 2023;27(16):2328–39. https://doi.org/10.1111/jcmm.17813
93 Simon AG, Tolkach Y, Esser LK, Ellinger J, Stöhr C, Ritter M, et al. Mitophagy-associated genes PINK1 and PARK2 are independent prognostic markers of survival in papillary renal cell carcinoma and associated with aggressive tumor behavior. Sci Rep. 2020;10(1):18857. https://doi.org/10.1038/s41598-020-75258-4

94 Daehn IS, Duffield JS. The glomerular filtration barrier: a structural target for novel kidney therapies. Nat Rev Drug Discov. 2021;20(10):770–88. https://doi.org/10.1038/s41573-021-00242-0
95 Daehn IS, Duffield JS. The glomerular filtration barrier: a structural target for novel kidney therapies. Nat Rev Drug Discov. 2021;20(10):770–88. https://doi.org/10.1038/s41573-021-00242-0
96 Song C, Zhang A, Zhang M, Song Y, Huangfu H, Jin S, et al. Nrf2/PINK1-mediated mitophagy induction alleviates sodium fluoride-induced hepatic injury by improving mitochondrial function, oxidative stress, and inflammation. Ecotoxicol Environ Saf. 2023;252:114646. https://doi.org/10.1016/j.ecoenv.2023.114646
97 Xiao L, Xu X, Zhang F, Wang M, Xu Y, Tang D, et al. The mitochondria-targeted antioxidant MitoQ ameliorated tubular injury mediated by mitophagy in diabetic kidney disease via Nrf2/PINK1. Redox Biol. 2017;11:297–311. https://doi.org/10.1016/j.redox.2016.12.022
98 Xia H, Fan MY, Cen X, Xu X, Wu R, Liu D, et al. CN115894404 B (Chinese hangzhou PhecdaMed Co Ltd; 2024.
99 Mallawaarachchi AC, Lundie B, Hort Y, Schonrock N, Senum SR, Gayevskiy V, et al. Genomic diagnostics in polycystic kidney disease: an assessment of real-world use of whole-genome sequencing. Eur J Hum Genet. 2021;29(5):760–70. https://doi.org/10.1038/s41431-020-00796-4
100 Lukas J, Giese AK, Markoff A, Grittner U, Kolodny E, Mascher H, et al. Functional characterisation of alpha-galactosidase a mutations as a basis for a new classification system in Fabry disease. PLoS Genet. 2013;9(8):e1003632. https://doi.org/10.1371/journal.pgen.1003632
101 Bertoldi G, Caputo I, Driussi G, Stefanelli LF, Di Vico V, Carraro G, et al. Biochemical mechanisms beyond glycosphingolipid accumulation in Fabry disease: might they provide additional therapeutic treatments. J Clin Med. 2023;12(5):2063. https://doi.org/10.3390/jcm12052063