Mitophagy and oxidative stress in chronic kidney disease (Review)

QUWU MUSHUO[1*], YIHUAI TIAN[1*], JIANCHUN LI[2], YANQIN QIU[1], HUI FAN[3], QIONGDAN HU[1,3] and QIONG ZHANG[1,3]

[1]Institute of Integrated Chinese and Western Medicine, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China; [2]Research Center of Integrated Traditional Chinese and Western Medicine, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China; [3]Department of Nephrology, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, Luzhou, Sichuan 646000, P.R. China

Received July 7, 2025; Accepted November 14, 2025

DOI: 10.3892/mmr.2025.13771

Abstract. Chronic kidney disease (CKD) progression is driven by a harmful interplay between impaired mitophagy and sustained oxidative stress. Under normal conditions, mitophagy serves as a protective mechanism by removing damaged mitochondria and limiting the production of reactive oxygen species. However, in CKD, a self-reinforcing cycle of mitochondrial dysfunction, defective mitophagy oxidative stress, and inflammation occurs, which promotes fibrosis. The present review examines the molecular mechanisms governing mitophagy, with a specific focus on the regulatory roles of core signaling pathways, namely the PTEN-induced kinase l/Parkin, BCL2 interacting protein 3/Nip3-like protein X and FUN14 domain-containing protein l pathways, and how their disruption contributes to CKD. The mechanistic crosstalk between mitophagy and oxidative stress is highlighted as a central pathogenic axis in CKD progression. In addition, emerging therapeutic strategies that aim to restore mitophagy and enhance antioxidant capacity are discussed, suggesting new strategies for targeted CKD treatment.

Correspondence to: Professor Qiong Zhang or Professor Qiongdan Hu, Department of Nephrology, The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University, 182 Chunhui Road, Longmatan, Luzhou, Sichuan 646000, P.R. China
E-mail: lyjean69@163.com
E-mail: huqiongdan@swmu.edu.cn

*Contributed equally

Abbreviations: CKD, chronic kidney disease; ROS, reactive oxygen species; mROS, mitochondrial ROS; ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; NLRP3, NOD-like receptor protein 3; Drp1, dynamin-related protein l; MFN1/2, mitofusin 1/2; MMP, mitochondrial membrane potential; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; IMS, intermembrane space; HIF1α, hypoxia-inducible factor 1α; ULK1, Unc-51 like autophagy activating kinase l; PINK1, PTEN-induced kinase l; p62, sequestosome 1; NBR1, neighbor of BRCA1 gene l; OPTN, optineurin; NDP52, nuclear dot protein 52; LC3, microtubule-associated protein 1 light chain 3; TBK1, TANK-binding kinase 1; BNIP3, BCL2 interacting protein 3; NIX, Nip3-like protein X; FUNDC1, FUN14 domain-containing protein l; mTOR, serine/threonine protein kinase mammalian target of rapamycin; AMPK, AMP-activated protein kinase; Keap1, Kelch-like ECH-associated protein 1; Nrf2, NF-E2-related factor 2; SOD, superoxide dismutase; GPX, glutathione peroxidase; AKI, acute kidney injury; DN, diabetic nephropathy; RTECs, renal tubular epithelial cells; UUO, unilateral ureteral obstruction; EMT, epithelial-to-mesenchymal transition

Key words: mitophagy, oxidative stress, reactive oxygen species, signaling pathways, therapeutic strategies

Contents

1. Introduction

Chronic kidney disease (CKD) is a serious progressive disorder and a major public health concern, with a global prevalence of 8-14%, affecting an estimated 700-840 million individuals worldwide (1-3). The disease typically manifests with subtle symptoms in its early stages. However, as it progresses, patients experience a gradual deterioration of kidney function, which establishes it as the third most rapidly increasing cause of mortality globally. In parallel, the economic burden of CKD has increased markedly (4).

CKD is a multifactorial chronic condition characterized by structural damage and dysfunction of the kidney (5). The renal unit is the fundamental structural and functional unit of the kidney, comprising two principal components: The glomerulus and the renal tubule. The key factors accelerating CKD progression include the loss of renal units, chronic inflammation, myofibroblast activation and extracellular matrix

deposition (6). In addition, mitochondrial dysfunction and the disruption of cellular redox homeostasis play important roles in CKD pathogenesis (7).

The treatment of CKD involves lifestyle modifications and pharmacological interventions. Standard treatments include renin-angiotensin-aldosterone system inhibitors, sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists. However, these medications have limited clinical efficacy in preventing disease progression (8,9). Therefore, the development of drugs targeting mitochondrial dysfunction and redox imbalance may be of considerable value for the improvement of CKD outcomes.

The primary function of mitochondria is adenosine triphosphate (ATP) synthesis, which is essential for the maintenance of various cellular functions and the regulation of critical processes, including cell growth, senescence and apoptosis. Impairment of this crucial function substantially affects renal physiology, contributing to the development of renal diseases (10). The kidney is among the most mitochondria-rich organs and is highly vulnerable to mitochondrial damage. Such damage compromises ATP production, causes cellular energy deficiency, and ultimately results in tubular epithelial cell atrophy or dedifferentiation (11).

Damaged mitochondria undergo depolarization, which results in a reduction of the mitochondrial membrane potential (MMP) (12). Several mechanisms, including abnormalities in mitochondrial dynamics, mutations in nuclear or mitochondrial DNA (mtDNA), nutrient deficiencies and bursts of reactive oxygen species (ROS), contribute to CKD progression, as do certain systemic conditions, such as diabetes, hypertension, aging and immune diseases (13). Mitochondrial dysfunction disrupts multiple cellular processes, leading to increased oxidative stress, chronic inflammation and fibrosis. It also triggers renal epithelial cell death and promotes microvascular damage, which collectively impair kidney function (14). Mitochondrial homeostasis and function are critically dependent on tightly regulated mitochondrial dynamics (15). Disruption of these dynamics may reduce the activity of the mitochondrial respiratory chain complex, diminish ATP generation and increase mitochondrial ROS (mROS) levels, thereby inducing oxidative damage (16).

Beyond their role as energy producers, mitochondria serve as critical regulators of immunity (17). Elevated ROS levels directly induce oxidative damage in mitochondria via the activation of proinflammatory signaling molecules, including Toll-like receptors and the NOD-like receptor protein 3 (NLRP3) inflammasome, thereby contributing to renal injury (18). Mitochondrial dysfunction regulates multiple programmed pathways, including apoptosis, pyroptosis and ferroptosis, thereby promoting tubular cell loss, inflammation and kidney dysfunction. Apoptosis is the predominant mechanism of cell death in renal tubular epithelial cells (RTECs) and podocytes (11). In addition, mitochondrial dysfunction promotes cellular senescence and influences the downstream senescence-associated phenotype (19). Senescent RTECs lose their capacity for self-repair and secrete proinflammatory cytokines, the continuous accumulation of which substantially contributes to CKD progression (20) (Fig. 1).

Mitochondria play a key role in essential cellular processes, including the tricarboxylic acid cycle, electron transport system, fatty acid β-oxidation and calcium homeostasis. These activities inherently lead to ROS generation (21). At physiological levels, ROS function as signaling molecules in various signaling pathways, while high levels are toxic to mitochondria and cells (22). Elevated ROS activate multiple inflammatory factors, and excessive inflammation promotes further ROS production, creating a mutually reinforcing cycle that accelerates CKD progression (23). Oxidative stress results from an imbalance in redox homeostasis between oxidative and antioxidant systems, which adversely affects all renal components (24). A primary source of oxidative stress is the overproduction of strongly oxidizing free radicals, such as ROS and reactive nitrogen species. Mitochondria serve as predominant intracellular producers of ROS and as one of their main targets, making them important in oxidative injury (25). Under oxidative stress conditions, ROS activate mitophagy, a process that removes damaged or excessive mitochondria. This helps to reduce further ROS production, thereby mitigating oxidative stress and safeguarding cellular components against oxidative injury (26). Although oxidative stress, mitophagy and ROS have been studied in the context of renal diseases, their interdependent roles in modulating the progression of CKD are not fully understood. By synthesizing current evidence, the present review aims to offer novel insights into the pathophysiological crosstalk among these mechanisms and to explore promising therapeutic strategies targeting these processes to ameliorate CKD.

2. Mitophagy: An overview

Definition of mitophagy. As the 'power station' of the cell, mitochondria orchestrate multiple intracellular signaling pathways, participating in amino acid metabolism, pyridine nucleotide synthesis and phospholipid modifications, which collectively influence cell survival, senescence and death (27,28). Mitochondria are dynamic organelles with a high degree of plasticity, and this adaptability is encompassed by the concept of mitochondrial dynamics. Mitochondria continuously undergo coordinated cycles of biogenesis, fusion, fission and autophagy. Mitophagy is a selective form of autophagy that eliminates damaged or superfluous mitochondria. These processes determine the morphology, quality, quantity, distribution and function of mitochondria within cells (29). The primary structural components of mitochondria are the outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM) and intermembrane space (IMS). The IMM surrounds the mitochondrial matrix and folds into invaginated cristae, markedly increasing the surface area of IMM, thereby efficiently generating ATP (28). The key mediators of mitophagy are PTEN-induced kinase 1 (PINK1), Parkin and ubiquitin chains, which promote the engulfment of damaged mitochondria by autophagosomes for lysosomal degradation (30). By contrast, mitochondrial biogenesis, a complex biological process essential for mitochondrial self-renewal, is primarily regulated by peroxisome proliferator-activated receptor-g coactivator-1 a; this process protects mtDNA and promotes dynamic cellular homeostasis (31). Mitochondrial fusion is mediated by mitofusin 1 or 2 (MFN1/2) and optic atrophy protein 1. This fusion process involves the merging of the OMM and IMM from adjacent mitochondria to create an

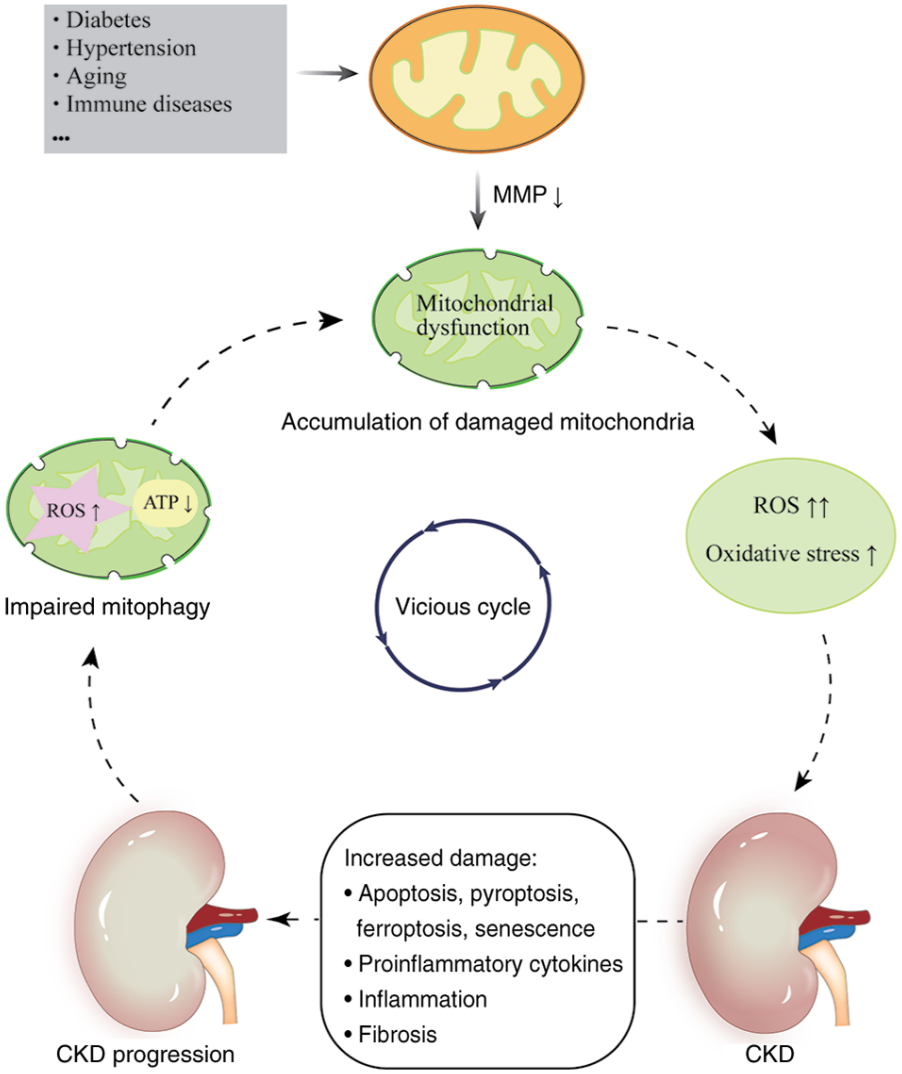

Figure 1. Schematic illustration of mitochondrial dysfunction. When mitochondria are damaged by various factors the MMP is reduced. The resulting mitochondrial dysfunction decreases ATP production, increases ROS production and oxidative stress. This triggers increased oxidative damage, renal epithelial cell death, proinflammatory cytokines activation, inflammation and fibrosis, resulting in CKD progression. MMP, mitochondrial membrane potential; ATP, adenosine triphosphate; ROS, reactive oxygen species; CKD, chronic kidney disease.

enlarged organelle. Dynamin-related protein 1 (Drp1) is the primary regulator of mitochondrial fission, a process in which the OMM and IMM of a single mitochondrion are constricted and divided to produce two daughter mitochondria (32). Notably, MFN2 functions as a mitochondrial fusion protein in its non-phosphorylated state, whereas PINK1-mediated phosphorylation converts MFN2 into a key mediator of the translocation of Parkin to damaged mitochondria (30). Mitochondrial fusion is a process of repair and renewal for the retention of mitochondria, whereas mitophagy ensures the removal of irreparably damaged mitochondria. Therefore, mitophagy, rather than mitochondrial fission, is considered the biological antithesis of mitochondrial fusion (33). The aforementioned processes of mitochondrial dynamics do not function independently; they are tightly interconnected and dynamically regulated as adaptations to cellular life activities. This integrated network of mitochondrial dynamics is essential for mitochondrial-cellular interactions and homeostasis (Fig. 2).

Autophagic processes can be categorized into three forms: Macroautophagy, microautophagy and chaperone-mediated autophagy (34). In the present review, the term autophagy refers specifically to macroautophagy, the most extensively studied form. In this process, cargo proteins are sequestered within a double-membraned autophagosome, either non-selectively, termed bulk autophagy, or through the precise elimination of specific cellular components, termed selective autophagy. Subsequently, the autophagosome is transported to the lysosomal compartment for degradation and recirculation of its contents. This process plays a crucial role in the maintenance of cellular and organismal homeostasis via a complex molecular pathway (35).

Under several pathological conditions, including elevated ROS levels, nutrient deficiencies and cellular senescence, intracellular mitochondria may undergo depolarization, a feature of mitochondrial dysfunction. To eliminate dysfunctional or excess mitochondria and maintain intracellular homeostasis, mitophagy is initiated as a cytoprotective mechanism. As discussed above, mitophagy is a selective form of autophagy in which impaired mitochondria are translocated to the lysosomal compartment, where they undergo degradation. This

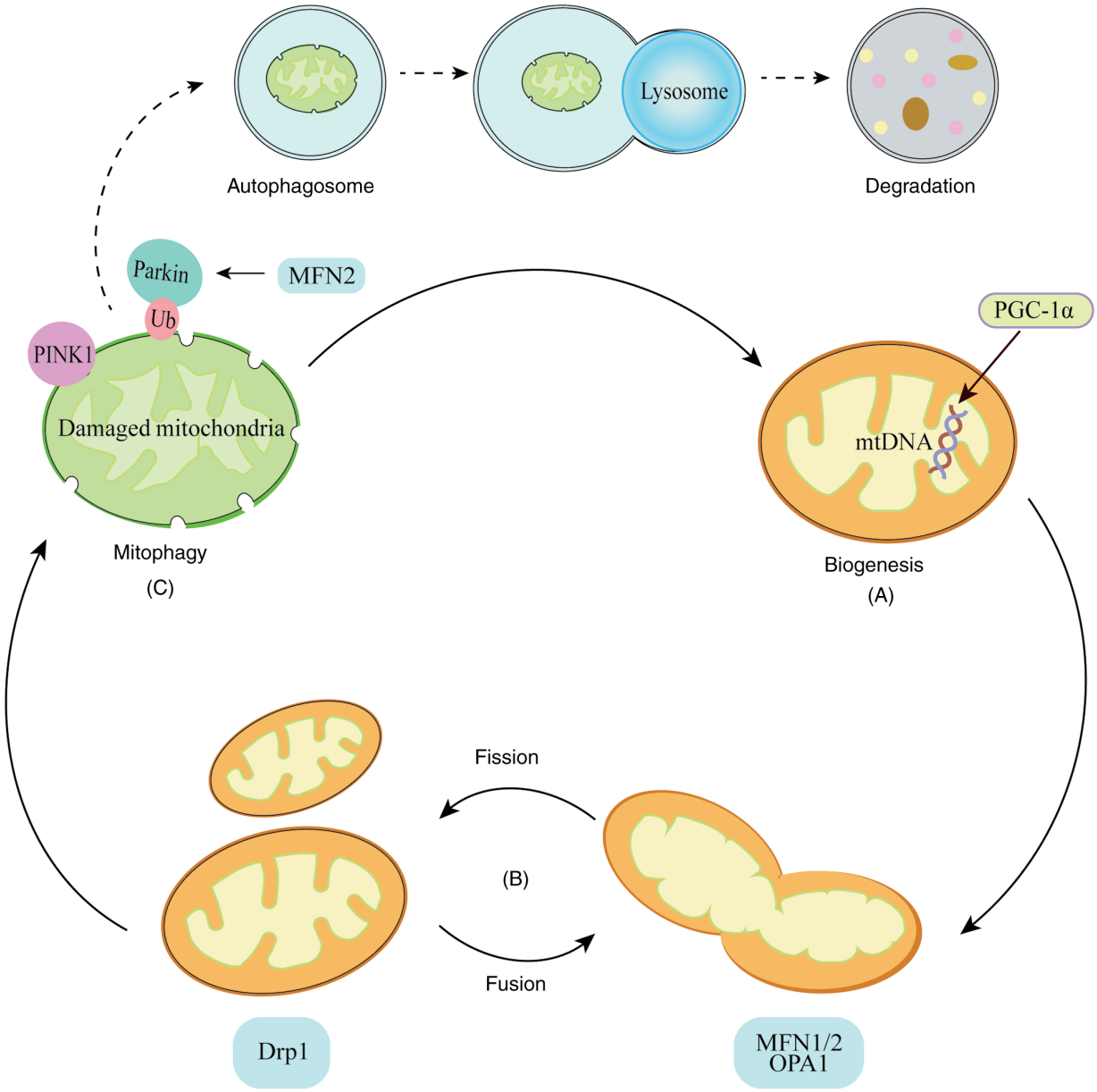

Figure 2. Schematic diagram of mitochondrial dynamics. (A) Mitochondrial biogenesis. PGC-1α is a master regulator of mitochondrial biogenesis, which controls mitochondrial self-renewal and protects mtDNA. (B) Mitochondrial fission and fusion. Fission is mainly mediated by Drp1, which severs the outer and inner mitochondrial membranes, resulting in division of the organelle into two daughter mitochondria. The primary mediators of mitochondrial fusion are MFN1, MFN2 and OPA1. (C) Mitophagy. Autophagosomes engulf the damaged mitochondria, which are targeted by PINK, Parkin and Ub, and then delivered to lysosomes for degradation. MFN2 promotes the translocation of Parkin to damaged mitochondria when it is phosphorylated by PINK1. PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; mtDNA, mitochondrial DNA; Drp1, dynamin-related protein l; MFN1/2, mitofusin 1/2; OPA1, optic atrophy protein l; PINK1, PTEN-induced kinase 1; Ub, ubiquitin.

prevents the accumulation of dysfunctional mitochondria and downstream molecular events that lead to disease progression, including oxidative stress (36).

Molecular mechanisms of mitophagy

PINK1/Parkin pathway. In 2008, Narendra *et al* (37) discovered that Parkin, an E3 ubiquitin ligase, is involved in mitochondrial depolarization and recruited to accelerate mitochondrial autophagic degradation. Subsequent studies identified key mitophagy receptors involved in this process, including sequestosome 1 (also known as p62), optineurin (OPTN) and nuclear dot protein 52 (NDP52) (36). Parkin, encoded by PRKN, functions in conjunction with PINK1, a mitochondrial-targeted serine kinase. Upon mitochondrial depolarization, Parkin is recruited to scavenge damaged mitochondria and promote mitophagy. This finding is considered a landmark discovery in mitophagy research (38). The PINK1/Parkin pathway is the most extensively studied mechanism of mitophagy, and comprises three main components: PINK1 as the mitochondrial damage sensor, Parkin as the signal amplifier and ubiquitin chains as the signal effectors (39). Upon mitochondrial damage, PINK1 accumulates at the OMM and phosphorylates ubiquitin. This phosphorylated ubiquitin activates Parkin, which subsequently adds more ubiquitin chains to OMM proteins. These chains serve as

labels for autophagy receptors in damaged mitochondria, thereby triggering selective autophagy (40) (Fig. 3).

PINK1 acts as a mitochondrial damage sensor. Its levels on mitochondria are regulated by voltage-dependent proteolysis, which ensures low expression on healthy, polarized mitochondria (41). PINK1 functions upstream of Parkin translocation and Parkin-mediated mitophagy. In dysfunctional mitochondria with low MMP, the selective accumulation of PINK1 on the OMM recruits Parkin, which initiates a series of degradation processes to clear the damaged mitochondria (41). The translocase of the outer membrane (TOM) complex, a multimeric protein assembly at the OMM, mediates the mitochondrial targeting of PINK1 (42). Under physiological conditions, TOM20 recognizes the mitochondrial targeting sequence of PINK1 and facilitates its import into the TOM40-formed translocation pore, with assistance from TOM22 and TOM70. PINK1 is ultimately delivered to the translocase of inner mitochondria membrane 23 complex at the IMM (43). Once inside, PINK1 undergoes sequential cleavage by mitochondrial processing peptidase and presenilin-associated rhomboid-like, followed by ubiquitin proteasome system-mediated degradation via the N-end rule pathway (44,45). Due to a steady balance between PINK1 import and degradation, healthy mitochondria maintain an extremely low or undetectable level of PINK1 accumulation (46). However, mitochondrial dysfunction, such as the loss of MMP induced by mtDNA mutations, mitochondrial depolarization, protein misfolding and increased ROS production, impairs the degradation process, resulting in the accumulation of PINK1 on the depolarized OMM and Parkin recruitment (47). PINK1 also phosphorylates MFN2, Parkin and ubiquitin, leading to further Parkin activation (48).

Parkin, a signal amplifier in mitophagy and a member of the RING-between-RING E3 ligase family, participates in the ubiquitin-mediated degradation and trafficking of proteins. It includes a C-terminal ubiquitin ligase domain and an N-terminal ubiquitin-like (UBL) domain (49). In healthy mitochondria, Parkin remains in an inactive conformation as a self-inhibiting dormant enzyme in the cytosolic compartment. Following mitochondrial damage, PINK1 accumulates on the OMM and phosphorylates the serine (Ser)65 residue of ubiquitin, even when present at low levels (50). Parkin is activated by two key steps. First, its UBL domain is phosphorylated at Ser65 by PINK1 kinase. Second, it binds to phosphorylated ubiquitin, These modifications induce substantial conformational changes, wherein the ubiquitin-E2 binding site of Parkin is repositioned on the RING1 domain proximal to the cysteine (Cys)431 acceptor site on the RING2 domain. This structural remodeling transforms Parkin into an active E3 ligase (51). Activated Parkin ubiquitinates various OMM proteins, which are subsequently phosphorylated by PINK1 to form phospho-ubiquitin chains that recruit autophagy receptors to induce mitophagy (52). At present, ubiquitin and the UBL domain of Parkin are the only known direct substrates of PINK1 (53).

Ubiquitin chains function as signal effectors in autophagy. When these chains are attached to OMM proteins, they are recognized by autophagy receptors, which mediate the encapsulation of damaged mitochondria into autophagosomes for lysosomal degradation. The ubiquitin chains also stimulate PINK1 kinase activity, creating an efficient feedforward loop that ensures effective mitophagy (46). Lazarou *et al* (40) demonstrated that p62 and neighbor of BRCA1 gene 1 (NBR1) are not essential for Parkin-mediated mitophagy. Instead, OPTN and NDP52 are the primary, yet redundant receptors in this pathway. Knockout of NDP52 or OPTN alone causes no defect in mitophagy. Since ubiquitin chains cannot directly bind to autophagic membranes or their associated autophagy-related protein 8 (ATG8) family proteins, molecular bridges are required to physically connect them (54). The ATG8 autophagy-related ubiquitin-like protein family includes microtubule-associated protein 1 light chain 3 (MAP1LC3, most commonly referred to as LC3) and γ-aminobutyric acid receptor-associated protein (GABARAP) subfamilies (55). LC3 shows binding affinity for multiple proteins containing a LC3-interacting region (LIR) motif, which marks ubiquitinated protein aggregates and binds to LC3 to facilitate autophagosome recruitment (56). These receptors contain a ubiquitin-binding domain to recognize ubiquitin-labeled mitochondria and a LIR motif to interact with ATG8 family proteins, forming a functional bridge between damaged mitochondria and the autophagic structures (57).

Among selective autophagy receptors, p62 was the first to be identified as playing an important role in Parkin-mediated mitophagy. Its accumulation at polyubiquitin-positive mitochondrial clusters is dependent on Parkin (36). For effective degradation, cargo proteins must be clustered into discrete compartments to enable their encapsulation by autophagosomes. p62 promotes this *in vivo* by forming droplets in which ubiquitin chains are sequestered, thereby mediating the concentration of autophagic cargo proteins and facilitating association with LC3 for delivery to lysosomes (58). While early research (59) indicated that deletion of p62 completely blocked the final clearance of damaged mitochondria, Lazarou *et al* (40) later demonstrated that p62 is dispensable for Parkin-mediated mitophagy. NBR1 is an autophagy receptor that is structurally similar to p62 and assists p62 in this process (60). The Kelch-like ECH-associated protein 1 (Keap1)-NF-E2-related factor 2 (Nrf2) system is essential for protection against oxidative and electrophilic insults (61). p62 directly interacts with Keap1 and competitively inhibits the Keap1-Nrf2 interaction, which stabilizes Nrf2 and promotes its accumulation in the nucleus. The nuclear accumulation of Nrf2 activates the transcription of numerous cytoprotective genes, including antioxidants (61,62). NBR1 is stress-inducible and indispensable for activation of the p62-Keap1-Nrf2 system (63). It induces the phase separation of p62, thereby enhancing the formation of p62 liquid droplets, while Nrf2 increases p62 transcription, establishing a positive feedback loop that continuously regulates p62 levels (63). The ATG8-binding capacity of NDP52 and OPTN is weaker than that of p62 and NBR1 (40). OPTN consists of several structural domains, including two coiled-coil (CC) domains, a leucine zipper, an LIR, a ubiquitin-binding domain and a zinc finger (ZF) domain (64). The accumulation of ubiquitin chains on damaged mitochondria triggers the activation of TANK-binding kinase 1 (TBK1), which physically associates with p62, OPTN and NDP52, and phosphorylates sites in the ubiquitin-binding domain of p62 and residues of OPTN neighboring the LIR motifs, thereby strengthening the ability of p62 and OPTN to interact with LC3 (65,66). NDP52 is a

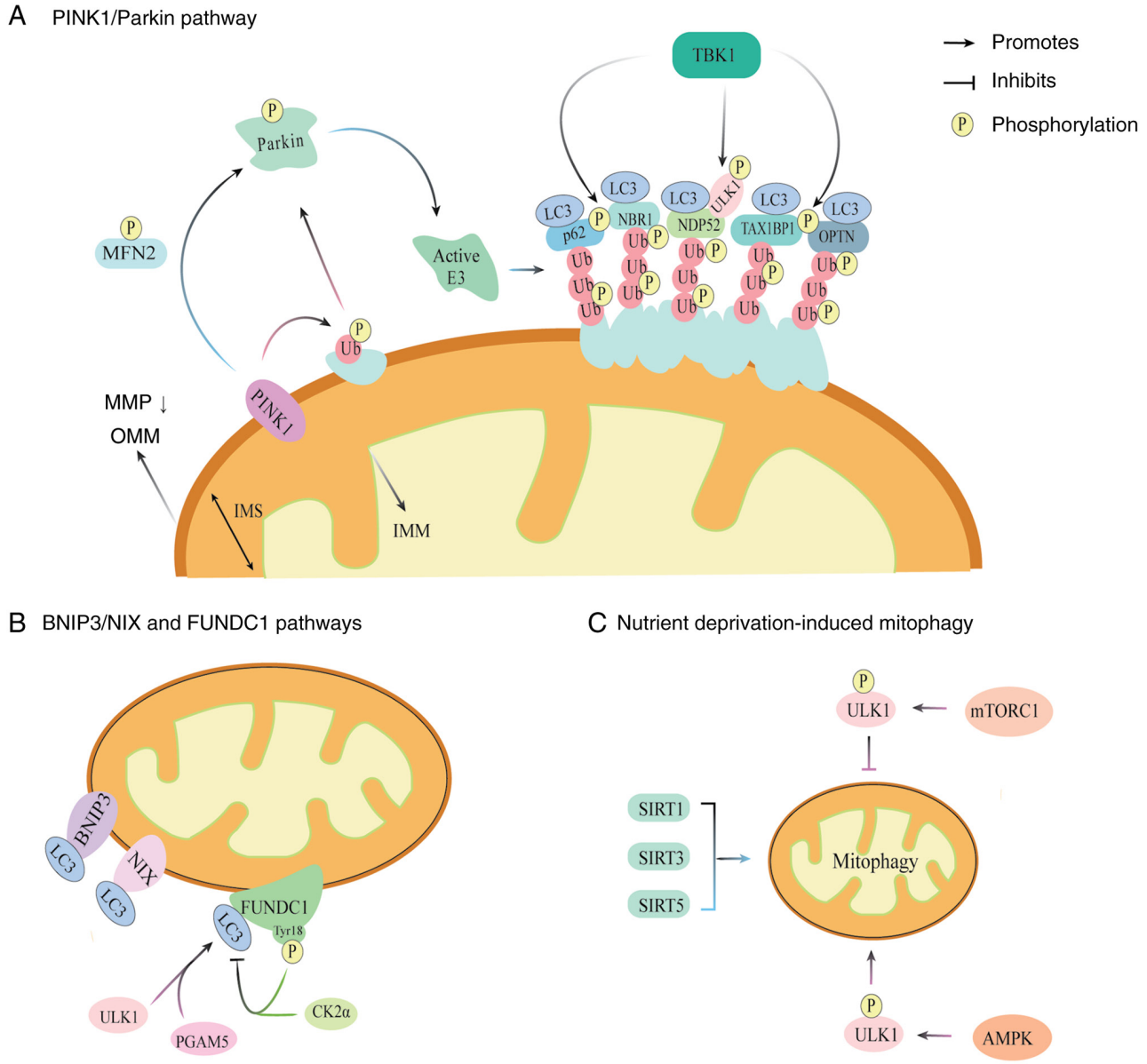

Figure 3. Molecular mechanisms of mitophagy. (A) PINK1/Parkin pathway. Among the various mitophagy pathways, the PINK1/Parkin pathway is the most well-characterized. Loss of MMP causes PINK1 to accumulate on the OMM of the depolarized mitochondria. and the recruitment of Parkin. PINK1 phosphorylates Ub and Parkin, which converts Parkin into an active E3 Ub ligase. PINK1 also phosphorylates MFN2, further promoting the recruitment of Parkin to damaged mitochondria. Ub chains are tethered to autophagy receptors, including p62, NBR1, NDP52, TAX1BP1 and OPTN, that interact with LC3 on the autophagosome. NDP52 also binds to the ULK1 complex, a process that is facilitated by the TBK1-mediated phosphorylation of autophagy receptors. (B) BNIP3/NIX and FUNDC1 pathways. The receptors BNIP3, NIX and FUNDC1 bind to LC3, to induce mitophagy. Phosphorylation of the Tyr18 residue of FUNDC1 by CK2α weakens the binding between LC3 and FUNDC1. By contract, PGAM5 and ULK1 enhance the interaction of FUNDC1 with LC3 to promote mitophagy. (C) Nutrient deprivation-induced mitophagy. Mitophagy induced by nutrient deprivation is primarily regulated by mTOR, AMPK and SIRTs. Active mTORC1 suppresses mitophagy by phosphorylating ULK1 while AMPK directly activates ULK1 through phosphorylation. SIRT1, SIRT3 and SIRT5 have been shown to promote mitophagy in animal models. PINK1, PTEN induced kinase l; MMP, mitochondrial membrane potential; OMM, outer mitochondrial membrane; Ub, ubiquitin; MFN2, mitofusin 2; p62, sequestosome 1; NBR1, neighbor of BRCA1 gene l; NDP52, nuclear dot protein 52; TAX1BP1, T-cell leukemia virus type I binding protein 1; OPTN, optineurin; LC3, microtubule-associated protein 1 light chain 3; ULK1, Unc-51 like autophagy activating kinase l; TBK1, TANK-binding kinase 1; IMM, inner mitochondrial membrane; IMS, intermembrane space; BNIP3, BCL2 interacting protein 3; NIX, Nip3-like protein X; FUNDC1, FUN14 domain-containing protein l; Tyr18, tyrosine 18; CK2α, casein kinase 2α; PGAM5, phosphoglycerate mutase family member 5; mTOR, serine/threonine protein kinase mammalian target of rapamycin; AMPK, AMP-activated protein kinase; SIRT, sirtuin mTORC1, mTOR complex 1.

multi-domain autophagy receptor, with a N-terminal SKIP carboxyl homology (SKICH) domain, central CC region and C-terminal ZF ubiquitin-binding domain (67). The SKICH domain binds to the Unc-51 like autophagy activating kinase 1 (ULK1) complex subunit RB1-inducible coiled-coil protein 1, also known as FAK family kinase-interacting protein of 200 kDa (FIP200), thereby activating cargo recruitment and autophagosome formation. TBK1 facilitates NDP52-ULK1 complex formation, further supporting the activation of mitophagy (68).

Notably in addition to the four aforementioned receptors, there is a fifth autophagy receptor, human T-cell leukemia

virus type I binding protein 1 (TAX1BP1), which is a paralog of NDP52 (53). Both NDP52 and TAX1BP1 have an atypical C-LIR motif located between the SKICH and CC domains. The atypical C-LIR motif in NDP52 preferentially binds with LC3C (69). Following OMM protein ubiquitination, TAX1BP1 is recruited to damaged mitochondria, where it interacts with LC3 via its LIR motif to initiate autophagosome formation and mitochondrial clearance (70). It has been revealed that TAX1BP1 and NBR1 colocalize, with TAX1BP1 serving as a critical organizer that directs the recruitment of upstream autophagy factors, including FIP200 and TBK1, to form autophagosomes around NBR1-marked cargo. Via these interactions, TAX1BP1 helps to tether ubiquitinated mitochondria to autophagic membranes via LC3, thereby ensuring efficient degradation (71).

BCL2 interacting protein 3 (BNIP3)/Nip3-like protein X (NIX) pathway. A secondary mitophagy mechanism, regulated by the expression thresholds of BNIP3 and NIX (also known as BNIP3 like), is known to contribute substantially to mitophagy across multiple tissues (72). Unlike other BCL2 family members, BNIP3 and NIX contain a divergent BH3 domain that is not essential for inducing apoptosis (73).

BNIP3 is an OMM protein consisting of a large N-terminal region containing an LIR motif and a characteristic C-terminal transmembrane (TM) domain (74). Bruick (75) identified that BNIP3 acts as a hypoxia-responsive gene. Under hypoxic conditions, BNIP3 promotes mitophagy by triggering mitochondrial depolarization (76). BNIP3 also interacts with PINK1 to enhance the accumulation of full-length PINK1 on the OMM, whereas the inhibition of BNIP3 promotes PINK1 proteolytic processing and suppresses PINK1/Parkin-mediated mitophagy (77). In addition, BNIP3 actively suppresses Drp1-mediated mitochondrial fusion, thereby facilitating the fragmentation and segregation of damaged mitochondria (78).

NIX is structurally similar to BNIP3, and is a single-pass OMM protein whose TM domain is essential for correct OMM targeting (79). During erythroid differentiation, NIX expression is upregulated at the transcriptional level. The deletion of NIX disrupts erythroid maturation, resulting in anemia, reticulocytosis and erythroid-myeloid hyperplasia (80). It also plays essential roles in retinal ganglion cell differentiation and in the reprogramming of somatic cells into induced pluripotent stem cells (81,82). NIX participates in mitophagy induced by hypoxia and elevated oxidative phosphorylation activity (83). It acts as a substrate of Parkin and functions downstream of the PINK1/Parkin pathway to promote mitophagy (84).

In resting cells, low levels of NIX and BNIP3 are maintained by ubiquitination and proteasomal degradation through an OMM-localized protein called SCF^{FBXL4} E3 ubiquitin ligase complex (85). Their activity in mitophagy is regulated by phosphorylation: The phosphorylation of BNIP3 at Ser17 and Ser24 within its LIR motif is essential for LC3B interaction (86), while the phosphorylation of NIX at Ser34 and Ser35 enables it to bind with GABARAP family proteins (87). Generally, the BNIP3/NIX pathway demonstrates stronger associations with development and differentiation than other mitophagy pathways (88).

FUN14 domain-containing protein 1 (FUNDC1) pathway. FUNDC1 is an integral OMM protein with a C-terminus that extends into the mitochondrial IMS and a cytosolic N-terminus containing a typical LIR (89). Under hypoxic conditions, FUNDC1 is dephosphorylated, which enhances its binding to LC3 through its typical LIR and promotes mitophagy (90), while phosphorylation inhibits this binding. Therefore, the dynamic balance between FUNDC1 phosphorylation and dephosphorylation functions as a critical switch that controls its LC3 binding capacity and subsequent regulation of mitophagy (36). A key regulatory site of FUNDC1 is tyrosine (Tyr)18, which is phosphorylated by Src kinase. This weakens the binding between LC3 and FUNDC1 due to electrostatic repulsion, thereby inhibiting mitophagy (91).

In addition to Tyr18 phosphorylation, three potential regulators of FUNDC1 activity are currently known. These are phosphoglycerate mutase family member 5 (PGAM5) and ULK1, which promote mitophagy, and casein kinase 2α (CK2α), which inhibits mitophagy (92-94). CK2α, a constitutive Ser/threonine (Thr) kinase, is a suppressor of FUNDC1 that promotes its phosphorylation at Ser13, thus effectively preventing its association with LC3 and inhibiting mitophagy (92). Chen *et al* (93) demonstrated that PGAM5, a mitochondrial phosphatase, dephosphorylates the Ser13 residue of FUNDC1, resulting in an increased association with LC3 during hypoxia or after treatment with a mitochondrial oxidative phosphorylation uncoupler (FCCP). FUNDC1 is a novel substrate of ULK1. ULK1 directly phosphorylates FUNDC1 at Ser17 under hypoxic conditions or FCCP exposure, following its recruitment to damaged mitochondria. This promotes the interaction of ULK1 with LC3, forming a bridge that links damaged mitochondria to autophagosomes (94).

Nutrient deprivation-induced mitophagy. Under conditions of nutrient or energy deprivation, mitophagy is predominantly regulated by three key pathways: Ser/Thr protein kinase mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK) and sirtuins (SIRTs) (95). AMPK and mTOR function as nutrient sensors in the kidney. In addition, mTOR complex 1 (mTORC1) serves as the primary negative modulator of mitophagy, while AMPK and SIRTs are positive regulators (95,96).

As a key regulator of anabolism, mTORC1 promotes cell growth and proliferation while concurrently inhibiting mitophagy. Under nutrient-abundant conditions, it phosphorylates ULK1 to suppress mitophagy, whereas under nutrient-limited conditions, mTORC1 is inactivated, allowing AMPK to activate ULK1 by phosphorylation, thereby inducing mitophagy (97). AMPK is a heterotrimeric complex comprising a catalytic α-subunit and regulatory β and γ subunits (98). During glucose deprivation, AMPK directly activates ULK1 via the phosphorylation of Ser317 and Ser777, to enhance mitophagy (99).

SIRTs play major roles in various physiological functions of the kidney, including DNA repair, mitochondrial metabolism, mitophagy, oxidative stress control and inflammation. SIRT dysfunction contributes to CKD pathophysiology and progression (100). Reduced SIRT1 expression or activity is associated with diminished mitophagy and exacerbated kidney disease (101,102). SIRT3, the primary mitochondrial deacetylase, is transformed from an inactive 44-kDa enzyme precursor to an active 28-kDa protein that translocates to mitochondria (103). In a sepsis model created by cecal ligation and puncture (CLP) in mice, decreased SIRT1 and SIRT3 activity was associated with mitochondrial damage (104). Another

study revealed that the activation of SIRT3 preserves mitophagy and maintains mitochondrial homeostasis in both CLP model mice and lipopolysaccharide (LPS)-treated RTECs (105). SIRT5 expression in the kidney is minimal. Polletta *et al* (106) demonstrated that the main function of SIRT5 in non-hepatic cells is the regulation of glutamine metabolism, which controls ammonia production and ammonia-induced mitophagy.

Mitophagy in CKD. Mitophagy is as a key mechanism for mitochondrial quality control that helps to maintain cellular homeostasis and protects cells by enabling them to adapt to external environmental changes. It plays a pivotal role in CKD by modulating factors associated with inflammation and fibrosis (107). Renal tubule injury is a major contributor to CKD progression (108). As the primary cellular constituents of renal tubules, RTECs are essential for both kidney repair and CKD progression, and critically determine the overall condition of the kidneys. Their innate immune functions allow them to recognize diverse stimuli and produce biologically active mediators that drive interstitial inflammation and fibrosis (108).

The unilateral ureteral obstruction (UUO) model is commonly used to study tubulointerstitial fibrosis and CKD (109). In this model, PINK1 or Parkin deficiency disrupts mitophagy, resulting in excessive mROS production, mitochondrial damage, increased TGF-β1 expression and Drp1 recruitment in RTECs, all of which promote renal fibrosis. Hypoxia-induced damage to RTECs and renal fibrosis in the UUO model are ameliorated by Drp1-Parkin-dependent mitophagy, highlighting the essential role of this process (110). In another study, it was reported that PINK1 or Parkin knockout in macrophages leads to the accumulation of damaged mitochondria and promotes their conversion to a profibrotic phenotype, which aggravates kidney fibrosis (111). In the kidneys of patients with CKD, the expression levels of the mitophagy-related proteins PINK1, Parkin and MFN2 are downregulated, which inhibits mitophagy. Furthermore, the circulating levels of C-C motif chemokine ligand 2 are increased, which recruits macrophages and exacerbates renal fibrosis. UUO models have also shown that Parkin and MFN2 expression levels are downregulated during kidney fibrosis (111). Together, these findings underscore the anti-fibrotic role of mitophagy in the repair of kidney injury and its potential to slow CKD progression.

Acute kidney injury (AKI) is a major risk factor for the development and progression of CKD (112). Following AKI, the maladaptive repair of injured tubules typically results in a sparse microvascular bed, persistent inflammation, tubular cell loss and renal fibrosis, leading to the transition of AKI to CKD (113). Proximal tubular cells contain abundant mitochondria, the dysfunction of which is a major contributor to AKI pathogenesis. Regardless of etiology, mitophagy is a vital protective mechanism in AKI (36). If mitochondrial dysfunction persists after AKI, it promotes progression to CKD via inflammatory and fibrotic pathways (114).

Cisplatin is a commonly prescribed alkylating chemotherapeutic agent that demonstrates broad-spectrum anticancer activity; however, its therapeutic potential is limited by nephrotoxic, neurotoxic and ototoxic side effects. In particular, AKI is a recognized complication of cisplatin-based chemotherapy (115). Mapuskar *et al* (116) revealed that cisplatin-induced pathological changes in mitochondrial metabolism occur during the repair phase. These are characterized by superoxide anion radical ($O_2^{\bullet-}$) accumulation, which predisposes the kidney to future injury and contribute to CKD progression. *In vitro*, Zhao *et al* (117) demonstrated that in human renal proximal tubular cells the knockdown of PINK1 or Parkin exacerbates mitochondrial dysfunction by impairing mitophagy, resulting in the accumulation of damaged mitochondria and increased cellular injury. By contrast, the overexpression of PINK1 or Parkin activates mitophagy, which alleviates cisplatin-induced mitochondrial dysfunction and cellular injury.

The NLRP3 inflammasome plays a key role in renal inflammation and pyroptosis (118). In both UUO models and hypoxic conditions, elevated mROS levels, increased accumulation of damaged mitochondria, activation of the NLRP3 inflammasome and significantly increased expression of α-SMA and TGF-β1 are observed. These changes are further intensified following BNIP3 gene deletion or silencing (119).

The activation of mitophagy can reduce pyroptosis in renal cells (120). For instance, Zn^{2+} has been shown to enhance Parkin expression by inhibiting SIRT7 activity, thereby promoting mitophagy, suppressing NLRP3 inflammasome activation and pyroptosis, and consequently protecting against sepsis-induced AKI (121).

Hypoxia-inducible factor 1α (HIF1α) is upregulated in UUO models, and functions as an upstream regulator of BNIP3. Knockout of HIF1α leads to impaired mitophagy, aggravated apoptosis and increased ROS production (122). These findings suggest that HIF1α-BNIP3-mediated mitophagy protects renal tubular cells against hypoxia-induced injury and fibrosis by reducing mROS and inhibiting NLRP3 inflammasome activation.

In the context of cisplatin-induced nephrotoxicity, Zhou *et al* (123) observed the downregulation of PINK1 and Parkin and upregulation of NIX in the kidney, indicating that the BNIP3/NIX pathway may be particularly important in cisplatin-induced mitophagy. The study also indicated that PINK1 knockout ameliorated cisplatin-induced kidney injury in rats.

Another key mitophagy pathway involves FUNDC1, which protects against mitochondrial dysfunction, cell death and renal fibrosis in CKD. In end-stage renal disease, chronic inflammation and renal injury suppress FUNDC1-mediated mitophagy, resulting in defective mitochondrial clearance, aggravated renal fibrosis and deteriorating renal function (124). Notably, the balance of mitophagy homeostasis is preserved when FUNDC1 alone is deficient, while the concurrent deficiency of both FUNDC1 and Parkin disrupts the homeostasis. Parkin compensates for the lack of FUNDC1 via compensatory upregulation, thereby sustaining basal mitophagy, which explains why baseline FUNDC1 knockout alone has little impact on renal function (125).

3. Oxidative stress: An overview

Definition of oxidative stress. The term oxidative stress was first coined by Sies and Cadenas (126) in 1985, and later defined as an imbalance between oxidants and antioxidants in

favor of oxidants, leading to a disruption in redox signaling and metabolic regulation (127). Oxidative stress contributes to disease through two distinct but interrelated mechanisms. The first involves the generation of reactive species that directly oxidize macromolecules, such as membrane lipids, structural proteins, functional enzymes and nucleic acids, resulting in abnormal cellular function or death. The second is non-physiological redox signaling, particularly involving the aberrant production of hydrogen peroxide (H_2O_2), which can disrupt redox signaling (128). Sustained oxidative stress in the kidney initiates a cascade of cellular damage, including renal ischemia, glomerular lesions, cell death, fibrosis and exacerbated inflammation. These processes are also associated with multiple CKD comorbidities, including hypertension, diabetes and atherosclerosis (129).

Mitochondria-related oxidative stress. Oxidative stress involves chemical reactions triggered by various reactive species, with ROS exerting the greatest biological impact and intracellular ROS predominantly originating from mitochondria (130). The kidney has high mitochondrial density, which renders it particularly vulnerable to oxidative stress-induced damage (11). Under physiological conditions, ROS generation and scavenging are strictly balanced. At low levels, ROS are known to affect specific signaling pathways to regulate cell proliferation, differentiation and death (129). However, ROS are generated at high levels when mitochondrial function is impaired, which creates a signal for the self-elimination of mitochondria via mitophagy. The excessive production of ROS and inability of endogenous antioxidants to remove them leads to oxidative stress (131).

The ROS family includes radical species such as $O_2^{\bullet-}$ and hydroxyl radicals ($^{\bullet}OH$), and non-radical oxidants, including H_2O_2 and singlet oxygen. Among these, $O_2^{\bullet-}$ and H_2O_2 are central to redox signaling and can exert beneficial effects at controlled levels (22,131,132). In the kidney, the major sources of ROS are NADPH oxidases (NOXs) and the mitochondrial respiratory chain (133). NOX enzymes catalyze the transfer of electrons from NADPH to molecular oxygen, which produce ROS. In addition to NOX4, which serves as a major source of ROS in the kidney, NOX1 and NOX2 contribute to vascular dysfunction and fibrosis in CKD by increasing oxidative stress (134). Furthermore, angiotensin II (AngII) serves as an early key mediator of kidney disease, which induces tubular hypertrophy and apoptosis in RTECs through ROS-mediated molecular mechanisms (135).

The maintenance of redox homeostasis is crucial for cellular function, and its disruption is a major contributor to human diseases (136). Oxidative stress in CKD arises not only from excessive ROS production but also from diminished antioxidant capacity, particularly due to impaired Nrf2 activation (137). The antioxidant system is the primary cellular defense against oxidative damage. It comprises enzymatic antioxidants, including superoxide dismutase (SOD) and glutathione peroxidase (GPX), and nonenzymatic antioxidants such as α-tocopherol (vitamin E), glutathione and bilirubin (138). These components are largely regulated by the Keap1-Nrf2 pathway. Keap1 functions as a sensor of oxidative stress, while Nrf2 is the principal regulator driving the transcription of antioxidant enzyme-encoding genes. Under oxidative stress, ROS reacts with redox-sensitive cysteine residues (Cys273 and Cys288) of Keap1 (139), altering its conformation and preventing it from binding to Nrf2, thereby affecting the autophagy receptor p62. The affinity between p62 and Keap1 is enhanced, forming a stable p62-Keap1 complex, which is subsequently degraded (140). The p62-Keap1-Nrf2 system is essential for mitophagy. The degradation of Keap1 disrupts its polyubiquitination and proteasomal degradation of Nrf2, thereby enabling Nrf2 stabilization and accumulation, leading to the sustained transcriptional activation of antioxidant genes (61).

Mitochondria are major sources of ROS due to electron leakage, primarily from respiratory chain complexes I and III. This results in incomplete oxygen reduction and the generation of $O_2^{\bullet-}$, which is rapidly converted into H_2O_2 either spontaneously or via SOD-mediated catalysis (26). The distribution of SOD is compartment-specific: SOD1 exists in both the cytosol and IMS, while SOD2 is localized in the mitochondrial matrix (141). GPX converts H_2O_2 to water. However, if not neutralized, H_2O_2 can form $^{\bullet}OH$ radicals by reacting with metal ions (142). Due to its extreme oxidative capacity, $^{\bullet}OH$ is the most destructive oxidant, which is capable of inducing oxidative DNA damage (129) (Fig. 4).

Redox regulation of mitophagy pathways. The regulation of mitophagy by redox imbalance is a dynamic, biphasic and intensity-dependent. A mild redox imbalance can activate mitophagy. In this process, the activity of the mitochondrial damage sensor PINK1 is directly regulated and activates Parkin, which initiates the ubiquitin chain labeling of outer membrane proteins, enabling them to be recognized by autophagy receptor proteins. Elevated ROS levels due to mitochondrial damage promote the oxidation and oligomerization of NDP52, an autophagy receptor essential for the efficient clearance of ubiquitin-labeled mitochondria. This enhances the initiation and efficiency of mitophagy by facilitating the selective clearance of damaged mitochondria (143). Oxidative stress activates PGAM5, which promotes the dephosphorylation of FUNDC1, enabling it to bind to LC3 and induce mitophagy (124). However, redox imbalance under sustained oxidative stress suppresses mitophagy.

In the chronic and intense oxidative stress environment of CKD, key mitophagy-associated proteins undergo excessive oxidative modification, which can lead to their inactivation. For example, PINK1 and Parkin expression is suppressed, impairing ubiquitin chain formation and consequently impeding mitophagy. This crosstalk between mitophagy and oxidative stress establishes a reinforcing cycle of damage.

Evidence from animal experiments and patient samples indicates that PINK1/Parkin pathway-mediated mitophagy is impaired in kidney fibrosis (111). Furthermore, decreased levels of mitophagy mediators, including PINK1, Parkin, p62, LC3-II and BNIP3, in muscle-derived mitochondria from patients with CKD, are associated with poor oxidative capacity (144).

In contrast with the ubiquitin-dependent pathway, receptor-mediated mitophagy is more directly regulated by oxidative stress and is independent of Parkin. Under the hypoxic, nutrient starvation and oxidative stress environment

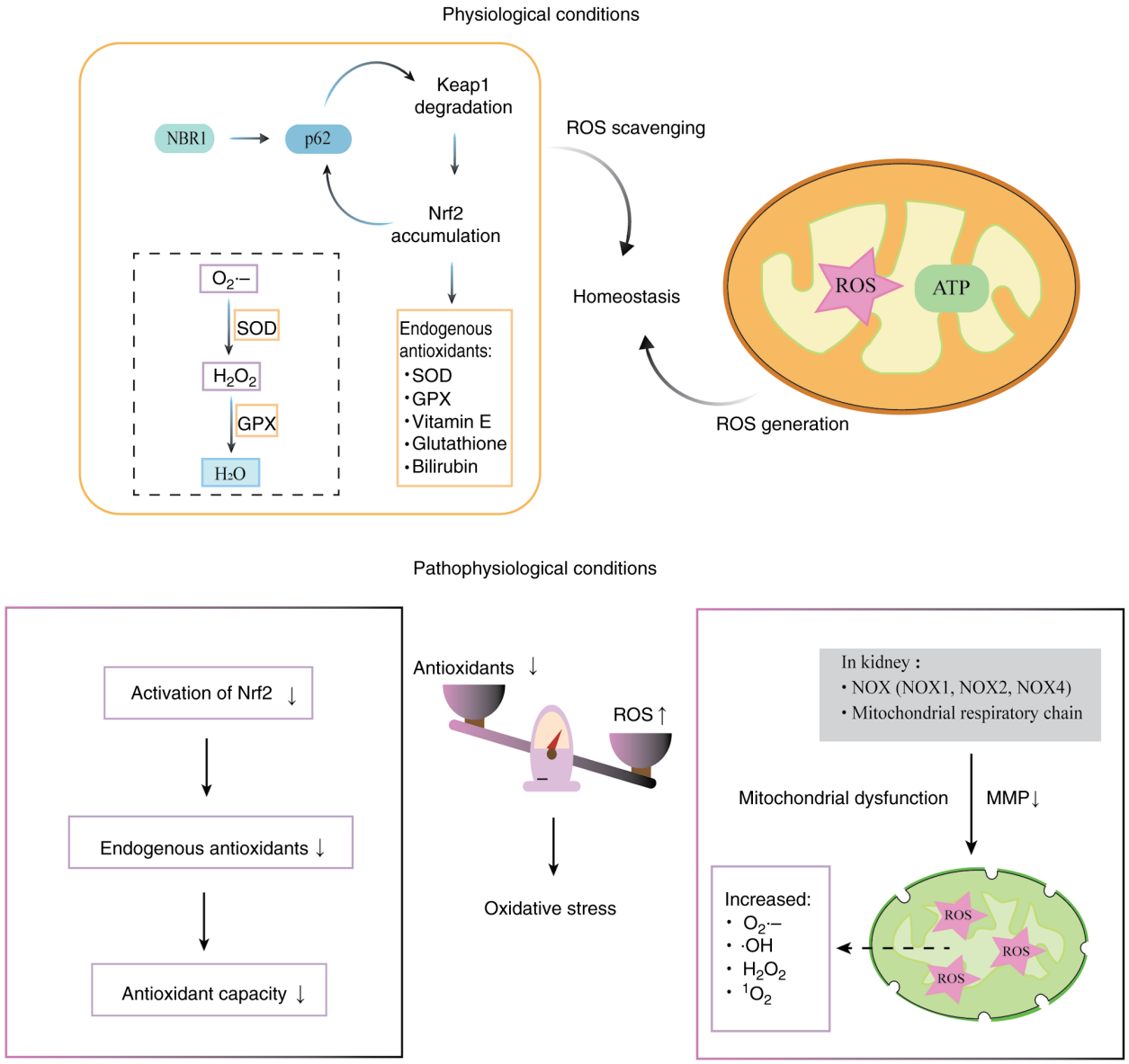

Figure 4. Diagram of mitochondria-related oxidative stress. Oxidative stress contributes to disease by two major mechanisms: ROS overproduction and the disruption of redox homeostasis. Mitochondria are the primary source of intracellular ROS. In the kidney, NOXs (NOX1, NOX2 and NOX4) and the mitochondrial respiratory chain are the major contributors to the production of ROS, which include $O_2^{\bullet-}$, $^{\bullet}OH$, H_2O_2 and $^1O_2$. Diminished antioxidant capacity, due to impaired activation of Nrf2, also contributes to oxidative stress. NBR1 induces the phase separation of p62 and enhances the formation of p62-containing liquid droplets. A positive feedback mechanism exists, in which the p62-dependent degradation of Keap1 leads to the accumulation of Nrf2, which activates the transcription of antioxidant genes, including p62. The Keap1-Nrf2 pathway regulates endogenous antioxidants, such as SOD and GPX. SOD rapidly converts $O_2^{\bullet-}$ into H_2O_2, which is then converted to water by GPX. However, if unquenched, H_2O_2 can generate •OH radicals by reacting with metal ions. ROS, reactive oxygen species; NOX, NADPH oxidase; $O_2^{\bullet-}$, superoxide anion radical; $^{\bullet}OH$, hydroxyl radical; H_2O_2, hydrogen peroxide; $^1O_2$, singlet oxygen; Nrf2, NF-E2-related factor 2; NBR1, neighbor of BRCA1 gene l; p62, sequestosome 1; Keap1, Kelch-like ECH-associated protein 1; SOD, superoxide dismutase; GPX, glutathione peroxidase; ATP, adenosine triphosphate; MMP, mitochondrial membrane potential.

of CKD, the expression levels of BNIP3 and NIX are significantly upregulated. However, high expression of BNIP3 and NIX can lead to the formation of homodimers, which disrupts the permeability of the OMM. This exacerbates ROS leakage and directly triggers mitochondrial-mediated apoptosis (73). In proteinuric mice, NIX-dependent mitophagy is considerably suppressed and associated with increased mitochondrial fragmentation, tubular epithelial cell apoptosis and loss of kidney function (145). While the activation of mitophagy within a tolerable range is protective by the removal of damaged mitochondria, excessive mitochondria injury triggers the overactivation of mitophagy and subsequent cell death.

Notably, honokiol (HKL), a pharmacologically active component of *Magnolia officinalis*, exhibits diverse therapeutic properties. Wei *et al* (146) discovered that HKL suppresses BNIP3, NIX and FUNDC1 expression and reduces AMPK activation levels in CKD models, resulting in the reduction of excessive mitophagy and induction of protective effects on the kidneys.

4. Crosstalk between mitophagy and oxidative stress in CKD.

Considerable evidence supports the crucial role of mitophagy in CKD progression, particularly in the removal of impaired

mitochondria, reduction of oxidative stress and alleviation of inflammation and fibrosis in the kidney, all of which delay CKD progression (147). However, under CKD conditions, mitophagy is impaired and mitochondrial dynamics shift toward excessive fission. Antioxidants increase mitophagy flux in animal models of CKD, supporting the impairment of mitophagy in CKD (148). In particular, five-sixth nephrectomy (5/6Nx) model animals, which are commonly used to study CKD pathophysiology, exhibit increased levels of p62. Since p62 accumulation is regarded as a marker of defective mitophagy, this further implicates impaired mitophagy in the context of CKD (149).

Although mitophagy initially acts as an adaptive, protective mechanism, it becomes dysfunctional under sustained oxidative stress. Conversely, impaired mitophagy leads to excessive ROS production. This harmful feedback cycle is a pivotal intermediary link between various initial pathologies, such as diabetes, hypertension, aging and immune diseases, and the progression of CKD (150). Diabetic nephropathy (DN) is a major contributor to end-stage kidney failure; however, current treatment strategies for DN are limited (151). There is evidence to suggest that mitophagy in tubular cells is defective in the diabetic kidney. Han *et al* (152) found that PINK1, Parkin, LC3-II and ATG5 expression levels are downregulated in the kidneys of diabetic mice, suggesting impaired mitophagy. Supporting this, patients with DN exhibit diminished circulating mtDNA levels, increased mtDNA damage and deficient mitophagy (153). The renal expression of NOX5 is upregulated in patients with DN, which induces ROS generation in podocytes and contributes to DN progression (154). Experimental models suggest that improving mitochondrial quality control can reduce tubulointerstitial fibrosis and suppress epithelial-to-mesenchymal transition (EMT)-like phenotype changes in tubular cells (155).

In hypertensive CKD, oxidative stress induces EMT and renal fibrosis. A study revealed that AdipoRon, an adiponectin receptor agonist, alleviated renal fibrosis in a mouse model of hypertension by promoting mitophagy (156). Similarly, Long *et al* (157) found that the kidneys of aging rats exhibited signs of degenerative pathology, increased oxidative stress and reduced mitophagy. Treatment with a combination of *Epimedium* dried leaves and *Ligustrum lucidum* fruits improved mitochondrial dynamics and restored mitophagy via activation of the AMPK/ULK1 pathway. Furthermore, in rats with passive Heymann nephritis, *Fangji Huangqi* (FJHQ) decoction enhanced mitophagy in podocytes by upregulating the expression of BNIP3, thereby ameliorating membranous nephropathy (158). In systemic lupus erythematosus, the mitophagy-inducing agent UMI-77 promoted mitophagy, suppressed autoimmunity, and reduced renal inflammation and ROS production, thereby preventing the progression of lupus nephritis both in patients and model mice (159). However, excessive oxidative stress can lead to excessive mitochondrial fragmentation, exceeding the mitophagic clearance capacity and leading to the accumulation of damaged mitochondria. One study showed that the activation of Drp1-dependent mitochondrial fission promoted fibrogenesis, while decreased mitochondrial fission attenuated fibrogenesis (160).

Regulated oxidative stress triggers signaling pathways that promote mitochondrial fission and mitophagy to clear damaged mitochondria and cells. This process prevents the spread of damage to neighboring mitochondria and cells. Efficient mitophagy enables the timely clearance of damaged mitochondria, characterized by reduced MMP and increased electron leakage, which are primary intracellular sources of ROS. By eliminating these mitochondria, mitophagy directly reduces ROS production at its source (161). However, because mitophagy is impaired in CKD, damaged mitochondria accumulate, leading to excessive ROS generation. Elevated ROS levels further damage healthy mitochondria and other organelles, activate inflammasomes, and promote the expression of pro-fibrotic factors, thereby exacerbating tubulointerstitial inflammation and fibrosis. This oxidative damage promotes CKD progression and is associated with a significant decline in renal function (162).

Li *et al* (110) demonstrated that mitophagy protects against uncontrolled oxidative stress in a UUO model. Whether triggered by acute or chronic injury, mitochondrial damage results in a decline in mtDNA content, ROS overproduction and reduced ATP generation, subsequently causing oxidative stress and cell injury (163).

In summary, oxidative stress can inhibit mitophagy, while impaired mitophagy exacerbates oxidative stress. This harmful feedback loop drives CKD progression.

5. Potential therapeutic strategies

Modulators of mitophagy. Oxidative stress is exacerbated by impaired mitophagy during CKD progression. Therefore, the simultaneous targeting of both aspects of this feedback loop presents a novel therapeutic strategy with potential for the treatment of CKD (Table I).

Several pharmacological agents have been identified that modulate mitophagy and thereby attenuate oxidative stress-induced renal injury. For example, magnoflorine promotes PINK1/Parkin-mediated mitophagy, thereby inhibiting NLRP3/caspase-1-mediated pyroptosis. This effects is reversed by either the genetic deletion of Parkin or use of a chemical mitophagy inhibitor, confirming that the ability of magnoflorine to inhibit NLRP3 inflammasome activation depends on mitophagy in cultured cells (164). Ruxolitinib also activates PINK1/Parkin-mediated mitophagy, thereby reducing oxidative stress, inflammation and renal fibrosis (165). Chicoric acid, a key bioactive component of chicory, stimulates Nrf2 signaling and upregulates PINK1 and Parkin expression levels in high-fat diet (HFD)-fed mice (166). Similarly, Cao *et al* (167) revealed that paeoniflorin (PF) increases the expression levels of PINK1, Parkin, BNIP3, p62 and LC3, which repairs damaged mitochondria by restoring the MMP and clearing accumulated ROS. In addition, PF ameliorates kidney inflammation by inducing the transition of macrophages to the M2 phenotype and activating mitophagy in LPS-induced murine RAW264.7 CKD models

Traditional Chinese medicine (TCM) has also been shown to regulate mitophagy. In addition to the previously mentioned FJHQ decoction, which exhibited efficacy in the treatment of membranous nephropathy, Tongluo Yishen decoction was found to improve mitochondrial dynamics and alleviate renal fibrosis by modulating PINK1/Parkin-mediated mitophagy and reducing ROS levels in UUO model rats (168). Unlike most mitophagy regulators, whose efficacy has been demonstrated

Table I. Therapeutic agents targeting mitophagy and oxidative stress.

Compound	Experimental model	Mechanism	Current status	(Refs.)
Quercetin	UUO model mice	Promotes the expression of SIRT1/PINK1 to attenuate RTEC senescence and kidney fibrosis	Preclinical	(102)
Melatonin	CLP-treated mice	Enhances the degradation of p62 via the inhibition of TFAM acetylation and subsequent SIRT3 activation	Clinical use for sleep disorders	(105)
Honokiol	Rats with adenine-induced CKD	Suppresses BNIP3/NIX, FUNDC1 and AMPK expression, reduces excessive mitophagy and protects the kidneys	Preclinical	(146)
Metformin	High-fat and streptozotocin-induced diabetic mice	Activates AMPK and promotes mitophagy through the p-AMPK-PINK1-Parkin pathway	Clinical use for type 2 diabetes	(152)
Epimedii folium and *Ligustri lucidi* fructus	Aged rats	Delay renal aging by activating the AMPK/ULK1 pathway	Preclinical stage	(157)
Fangji huangqi decoction	Passive Heymann nephritis model rats	Enhances mitophagy in podocytes by promoting the expression of BNIP3	Clinical use for edema and dysuria	(158)
UMI-77	Lupus nephritis model mice, and clinical samples	Enhances mitophagy, suppresses autoimmunity and limits renal inflammation	Preclinical	(159)
Magnoflorine	High-fat and high-fructose-fed mice	Promotes Parkin/PINK1-mediated mitophagy and inhibits NLRP3/caspase-1-mediated pyroptosis	Preclinical	(164)
Ruxolitinib	UUO model mice	Activates Parkin/PINK1 mitophagy, reduces inflammatory responses and oxidative stress	Clinical use for myeloproliferative disorders	(165)
Chicoric acid	High-fat diet-fed mice	Activates the Nrf2 pathway and increases PINK1 and Parkin expression, thereby enhancing mitophagy	Preclinical	(166)
Paeoniflorin	RAW264.7 cells stimulated with lipopolysaccharide	Upregulates PINK1, Parkin, BNIP3, p62 and LC3, increases mitochondrial membrane potential and reduces ROS accumulation	Preclinical	(167)
Tongluo yishen decoction	UUO model rats	Modulates PINK1/Parkin-mediated mitophagy and alleviates renal fibrosis	Clinical use for CKD	(168)
Rapamycin, everolimus and temsirolimus	UUO model mice	Suppresses mTORC1 and promotes AMPK-induced ULK1 activation to induce mitophagy	Preclinical	(171)
Resveratrol	5/6-nephrectomy and CLP-treated rats	Activates SIRT1/3 and reduces acetylated SOD2 levels to ameliorate oxidative stress and mitochondrial function in RTECs	Preclinical	(104, 173)
Roxadustat	Rats with renal I/R injury	Increases HIF1α protein expression and promotes HIF1α/FUNDC1-mediated mitophagy	Clinical use for renal anemia in CKD and dialysis	(174)
Uridine	Aged mice	Reduces intracellular oxidative stress, promotes the synthesis of high-energy compounds and protects cells from hypoxic damage	Preclinical	(179)

Table I. Continued.

Compound	Experimental model	Mechanism	Current status	(Refs.)
Lycopene	Mice with aristolochic acid-induced nephropathy	Activates the antioxidant system and mitophagy, upregulates levels of LC3-II and p62, exerts anti-inflammatory and anti-apoptotic effects	Preclinical	(180)
Mitoquinone	Mice with I/R injury, or infused with AngII	Decreases oxidative damage and reduces the severity of I/R injury to the kidney	Preclinical	(184, 185)
SS-31	Uninephrectomy and streptozotocin-treated mice; mice with cisplatin-induced AKI	Anti-oxidative and anti-apoptotic action via the inhibition of ROS production	Preclinical	(187, 188)
Curcumin-loaded nanodrug delivery system	Cisplatin-induced AKI	Inhibits oxidation, activates autophagy and reduces apoptosis	Preclinical	(190)

UUO, unilateral ureteral obstruction; SIRT1/3, sirtuin 1/3; PINK1, PTEN-induced kinase 1; RTEC, renal tubular epithelial cell; CLP, cecal ligation and puncture; p62, sequestosome 1; TFAM, transcription factor A, mitochondrial; SIRT3, sirtuin 3; CKD, chronic kidney disease; BNIP3, BCL2 interacting protein 3; NIX, Nip3-like protein X; FUNDC1, FUN14 domain-containing protein 1; AMPK, AMP-activated protein kinase; p-, phospho; ULK1, Unc-51 like autophagy activating kinase 1; NLRP3, NOD-like receptor protein 3; Nrf2, NF-E2-related factor 2; LC3, microtubule-associated protein 1 light chain 3; ROS, reactive oxygen species; mTORC1, serine/threonine protein kinase mammalian target of rapamycin; SOD2, superoxide dismutase 2; I/R, ischemia/reperfusion; HIF1α, hypoxia-inducible factor 1α; AngII, angiotensin II; AKI, acute kidney injury.

solely in animal and *in vitro* models, TCMs are the only mitophagy modulators supported by clinical data.

The inhibition of mTORC1 or activation of the AMPK/SIRT1 by genetic or pharmacological approaches has shown protective effects against the progression of DN in animal models (169,170). Well-known mTORC1 inhibitors include rapamycin and its analogs, everolimus and temsirolimus (171). Han *et al* (152) demonstrated that the AMPK activator metformin promotes mitophagy through the phospho-AMPK-PINK1-Parkin pathway, while concurrently attenuating oxidative stress and tubulointerstitial fibrosis in the kidneys of HFD/streptozotocin-induced diabetic mice. Transcription factor A, mitochondrial (TFAM) is essential for the initiation of mtDNA transcription (172). Melatonin has been identified as a positive regulator of PINK1 and Parkin expression, which activates upstream mitophagy. Deng *et al* (105) demonstrated that melatonin promotes p62 degradation by suppressing TFAM acetylation through SIRT3 activation, thereby enhancing mitophagy flux. Quercetin, an activator of SIRT1, attenuates RTEC senescence and kidney fibrosis by upregulating the expression of SIRT1 and PINK1 to promote mitophagy *in vivo*, as shown in an UUO model, and also enhances mitophagy in AngII-treated RTECs (102). Similarly, resveratrol activates both SIRT1 and SIRT3 to promote mitophagy (104). In another study, the administration of resveratrol to rats following 5/6Nx improved kidney function, as indicated by decreased proteinuria and lower cystatin C levels (173).

The HIF1α-FUNDC1 mitophagy axis plays a key role in hypoxia/reoxygenation (H/R)-promoted mitophagy in renal tubular cells. H/R treatment upregulates the expression of FUNDC1, while the selective inhibition of HIF1α reduces H/R-induced mitophagy (174). Notably, treatment with roxadustat further increases the expression of HIF1α *in vivo*. Zhang *et al* (174) suggested that Roxadustat may serve as a potential therapeutic agent to block the transition of AKI to CKD in future clinical applications. Currently, roxadustat is used clinically to treat renal anemia in patients with CKD and those on dialysis, and shows considerable promise as a novel mitophagy-targeting therapeutic agent for CKD.

Antioxidants. Antioxidants prevent oxidative stress by neutralizing oxidizing agents and blocking harmful oxidation by converting free radicals into nonreactive compounds (175). Uridine, a pyrimidine nucleoside composed of uracil and ribose, is important in the maintenance of cellular function and energy metabolism. It promotes the synthesis of high-energy compounds and reduces intracellular oxidative stress, thereby preventing hypoxia-induced cellular damage (176,177). In animal models of acute ischemia and ischemia/reperfusion (I/R), uridine administration has been shown to protect against injury by restoring redox balance and activating mitochondrial ATP-dependent channels (178). The levels of inflammatory factors and ROS also decrease significantly following uridine treatment (179).

Lycopene (LYC), a potent carotenoid antioxidant, exhibits multiple therapeutic effects, including anti-inflammatory, anti-apoptotic and mitophagy-modulating properties. Wang *et al* (180) demonstrated that LYC activates the Nrf2 antioxidant system and induces mitophagy to ameliorate renal

fibrosis. The study showed that LYC attenuated the aristolochic acid I-induced intracellular expression of PINK1, Parkin and TGF-β; upregulated LC3-II and p62 levels; decreased MMP; and mitigated renal fibrosis in mice by suppressing mTORC1 and promoting ULK1 activation.

Mitochondria-targeted antioxidants. Growing evidence suggests that mitochondria-targeted antioxidants have substantial therapeutic potential. Mitoquinone (MitoQ), a mitochondria-targeted antioxidant, shows therapeutic potential against the oxidative stress mediated by excessive ROS production (142). MitoQ comprises a ubiquinone moiety conjugated to a lipophilic triphenyl phosphonium (TPP) cation, which targets mitochondria. The MMP facilitates efficient cellular internalization of the TPP cation, leading to its accumulation in the mitochondrial matrix. Once inside, mitochondrial complex II reduces ubiquinone to ubiquinol, its bioactive antioxidant form, thereby counteracting oxidative damage (181,182). Due to its combination of extensive mitochondrial uptake, antioxidant recycling and localization on the matrix-facing surface of the IMM, MitoQ is substantially more effective than untargeted antioxidants in preventing oxidative damage (183). Other studies have also confirmed the ability of MitoQ to prevent MMP reduction and reduce excessive ROS production (184,185).

SS-31, another mitochondria-targeted antioxidant, contains dimethyl tyrosine residues that react with oxygen radicals, forming inactive tyrosine radical species and scavenging ROS (186). Following its accumulation on the IMM, SS-31 preserves mitochondrial structure, promotes ATP production, and inhibits ROS generation and apoptosis (187). In murine models, SS-31 demonstrates nephroprotective effects against cisplatin-induced renal damage. It exerts both antioxidant and antiapoptotic activities by modulating the mROS-NLRP3 signaling axis (188). However, preclinical studies regarding the effectiveness of SS-31 in the treatment of renal diseases are limited. Large-scale, multicenter clinical studies with a diverse range of patients are necessary to assess the efficacy, safety and tolerability of SS-31 for clinical application (189).

Nanotechnology-based delivery systems can be used to encapsulate antioxidants, with surface modifications to enable their specific uptake by mitochondria. For example, a curcumin-loaded nanodrug delivery system demonstrated protective effects on mitochondrial function and kidney tissue by scavenging excess ROS, reducing apoptosis and activating autophagy (190).

Despite these findings, the therapeutic applicability of mitochondria-targeted antioxidants in CKD warrants further investigation. The therapeutic efficacy of these antioxidants should be evaluated in multiple animal models with diverse CKD etiologies. Prior to human clinical trials, these therapies should be tested in models that most closely resemble human disease to validate their safety and efficacy, providing robust evidence to support their clinical translation.

6. Challenges and prospects

CKD is a global health issue with a complex pathogenesis involving multiple cellular and molecular processes. Attention has been focused on the roles of mitophagy and oxidative stress in CKD. A considerable body of evidence emphasizes the importance of mitophagy and oxidative stress in kidney function in healthy and disease states. Therefore, targeting mitophagy and oxidative stress has emerged as a promising approach to improve renal function and delay CKD progression.

Although targeting mitophagy and oxidative stress are promising approaches for the treatment CKD, limitations remain, and multiple challenges must be overcome before these findings can be translated into clinically effective therapies. Most current evidence is derived from animal models such as those involving UUO, I/R injury or aged mice. While these models replicate certain pathological features of CKD, they cannot fully reproduce the multifactorial course of human CKD and its long-term progression, which may involve the complex interplay of hypertension, diabetes and aging. Differences between animals and humans in drug metabolism, immune response and renal cell biology may cause strategies that are effective in animals to be ineffective or even toxic in humans. In addition, mitophagy and oxidative stress form a dynamic regulatory cycle. However, clinical methods that can dynamically and quantitatively monitor mitophagy flux in the kidney are currently lacking. Therefore, it is not yet possible to determine the optimal regulatory window for intervention in mitophagy. The excessive activation of mitophagy may lead to the unnecessary removal of healthy mitochondria, triggering cellular energy depletion, while insufficient inhibition of mitophagy fails to eliminate dysfunctional mitochondria, allowing dysfunction to persist.

To overcome these challenges, future research should focus on several aspects. First, to screen drugs and validate the underlying mechanisms, disease models that more closely resemble human physiology should be established. Kidney organoids generated from patient-derived induced pluripotent stem cells are a promising platform to simulate human-specific CKD pathological processes *in vitro*. Second, novel biomarkers that reflect *in vivo* mitophagy status and oxidative stress levels, such as mtDNA or specific mitochondrial proteins detected in blood or urine exosomes, should be identified and validated. The development of kidney-targeted nanodelivery systems is also critical, with the aim of enhancing drug accumulation in the renal tissue while reducing systemic exposure and off-target effects. Another area worthy of exploration is the integration of TCM with modern nanotechnology to design delivery carriers that, according to TCM theory, have 'kidney meridian affinity'. Finally, greater efforts should be made to discover highly specific mitophagy modulators that precisely regulate specific pathways, providing more controlled effects than those of broad-spectrum autophagy inducing agents or antioxidants.

Acknowledgements

Not applicable.

Funding

This study received support from the following sources: Sichuan Science and Technology Program (grant no. 2022YFS0621), Southwest Medical University Technology

Program (grant no. 2023QN019), National Natural Science Foundation of China (grant no. 82205002), Science and Technology Research Special Project of Sichuan Administration of Traditional Chinese Medicine (grant no. 2024MS524) and Special Project of Integrated Chinese and Western Medicine, Southwest Medical University (grant no. 2023ZYQJ04).

Availability of data and materials

Not applicable.

Authors' contributions

QM was involved in writing, reviewing and editing the manuscript, and creating visualizations. YT drafted the original manuscript and worked on visualization. JL contributed to writing, reviewing and editing, visualization and supervision. YQ and HF contributed to writing the original draft of the manuscript. QH and QZ helped to write, review and edit the manuscript, and also provided supervision and secured funding. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kovesdy CP: Epidemiology of chronic kidney disease: An update 2022. Kidney Int Suppl (2011) 12: 7-11, 2022.
2. Flythe JE and Watnick S: Dialysis for chronic kidney failure: A review. JAMA 332: 1559-1573, 2024.
3. Yang W, Wu X, Zhao M, Hu J, Lin C, Mei Z, Chen J, Zhou XJ, Nie S, Nie J, *et al*: Kidney function and cardiovascular disease: Evidence from observational studies and mendelian randomization analyses. Phenomics 4: 250-253, 2024.
4. Jha V, Al-Ghamdi SMG, Li G, Wu MS, Stafylas P, Retat L, Card-Gowers J, Barone S, Cabrera C and Garcia Sanchez JJ: Global economic burden associated with chronic kidney disease: A pragmatic review of medical costs for the inside CKD research programme. Adv Ther 40: 4405-4420, 2023.
5. Dan Hu Q, Wang HL, Liu J, He T, Tan RZ, Zhang Q, Su HW, Kantawong F, Lan HY and Wang L: Btg2 promotes focal segmental glomerulosclerosis via Smad3-dependent podocyte-mesenchymal transition. Adv Sci (Weinh) 10: e2304360, 2023.
6. Panizo S, Martínez-Arias L, Alonso-Montes C, Cannata P, Martín-Carro B, Fernández-Martín JL, Naves-Díaz M, Carrillo-López N and Cannata-Andía JB: Fibrosis in chronic kidney disease: Pathogenesis and consequences. Int J Mol Sci 22: 408, 2021.
7. Ho HJ and Shirakawa H: Oxidative stress and mitochondrial dysfunction in chronic kidney disease. Cells 12: 88, 2022.
8. Kushner P, Khunti K, Cebrián A and Deed G: Early identification and management of chronic kidney disease: A narrative review of the crucial role of primary care practitioners. Adv Ther 41: 3757-3770, 2024.
9. Zhu HZ, Li CY, Liu LJ, Tong JB, Lan ZH, Tian SG, Li Q, Tong XL, Wu JF, Zhu ZG, *et al*: Efficacy and safety of qingfei huatan formula in the treatment of acute exacerbation of chronic obstructive pulmonary disease: A multi-centre, randomised, double-blind, placebo-controlled trial. J Integr Med 22: 561-569, 2024.
10. Aranda-Rivera AK, Cruz-Gregorio A, Aparicio-Trejo OE and Pedraza-Chaverri J: Mitochondrial redox signaling and oxidative stress in kidney diseases. Biomolecules 11: 1144, 2021.
11. Doke T and Susztak K: The multifaceted role of kidney tubule mitochondrial dysfunction in kidney disease development. Trends Cell Biol 32: 841-853, 2022.
12. Lu Y, Li Z, Zhang S, Zhang T, Liu Y and Zhang L: Cellular mitophagy: Mechanism, roles in diseases and small molecule pharmacological regulation. Theranostics 13: 736-766, 2023.
13. Hoogstraten CA, Hoenderop JG and de Baaij JHF: Mitochondrial dysfunction in kidney tubulopathies. Annu Rev Physiol 86: 379-403, 2024.
14. Che R, Yuan Y, Huang S and Zhang A: Mitochondrial dysfunction in the pathophysiology of renal diseases. Am J Physiol Renal Physiol 306: F367-F378, 2014.
15. Zhan M, Brooks C, Liu F, Sun L and Dong Z: Mitochondrial dynamics: Regulatory mechanisms and emerging role in renal pathophysiology. Kidney Int 83: 568-581, 2013.
16. Palorini R, De Rasmo D, Gaviraghi M, Sala Danna L, Signorile A, Cirulli C, Chiaradonna F, Alberghina L and Papa S: Oncogenic K-ras expression is associated with derangement of the cAMP/PKA pathway and forskolin-reversible alterations of mitochondrial dynamics and respiration. Oncogene 32: 352-362, 2013.
17. Mills EL, Kelly B and O'Neill LAJ: Mitochondria are the powerhouses of immunity. Nat Immunol 18: 488-498, 2017.
18. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, *et al*: Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity 36: 401-414, 2012.
19. Miwa S, Kashyap S, Chini E and von Zglinicki T: Mitochondrial dysfunction in cell senescence and aging. J Clin Invest 132: e158447, 2022.
20. Chen K, Dai H, Yuan J, Chen J, Lin L, Zhang W, Wang L, Zhang J, Li K and He Y: Optineurin-mediated mitophagy protects renal tubular epithelial cells against accelerated senescence in diabetic nephropathy. Cell Death Dis 9: 105, 2018.
21. Bhargava P and Schnellmann RG: Mitochondrial energetics in the kidney. Nat Rev Nephrol 13: 629-646, 2017.
22. Holmström KM and Finkel T: Cellular mechanisms and physiological consequences of redox-dependent signalling. Nat Rev Mol Cell Biol 15: 411-421, 2014.
23. Yuan Q, Tang B and Zhang C: Signaling pathways of chronic kidney diseases, implications for therapeutics. Signal Transduct Target Ther 7: 182, 2022.
24. Podkowińska A and Formanowicz D: Chronic kidney disease as oxidative stress- and inflammatory-mediated cardiovascular disease. Antioxidants (Basel) 9: 752, 2020.
25. Liu X, Hussain R, Mehmood K, Tang Z, Zhang H and Li Y: Mitochondrial-endoplasmic reticulum communication-mediated oxidative stress and autophagy. Biomed Res Int 2022: 6459585, 2022.
26. Filomeni G, De Zio D and Cecconi F: Oxidative stress and autophagy: The clash between damage and metabolic needs. Cell Death Differ 22: 377-388, 2015.
27. Quintana-Cabrera R and Scorrano L: Determinants and outcomes of mitochondrial dynamics. Mol Cell 83: 857-876, 2023.
28. Kühlbrandt W: Structure and function of mitochondrial membrane protein complexes. BMC Biol 13: 89, 2015.
29. Chen W, Zhao H and Li Y: Mitochondrial dynamics in health and disease: Mechanisms and potential targets. Signal Transduct Target Ther 8: 333, 2023.
30. Dorn GW and Kitsis RN: The mitochondrial dynamism-mitophagy-cell death interactome: Multiple roles performed by members of a mitochondrial molecular ensemble. Circ Res 116: 167-182, 2015.
31. Dumesic PA, Wilensky SE, Bose S, Van Vranken JG, Gygi SP and Spiegelman BM: RBM43 controls PGC1α translation and a PGC1α-STING signaling axis. Cell Metab 37: 742-757.e8, 2025.
32. Pernas L and Scorrano L: Mito-morphosis: Mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. Annu Rev Physiol 78: 505-531, 2016.
33. Dorn GW: Evolving concepts of mitochondrial dynamics. Annu Rev Physiol 81: 1-17, 2019.

34. Garza-Lombó C, Pappa A, Panayiotidis MI and Franco R: Redox homeostasis, oxidative stress and mitophagy. Mitochondrion 51: 105-117, 2020.
35. Klionsky DJ, Petroni G, Amaravadi RK, Baehrecke EH, Ballabio A, Boya P, Bravo-San Pedro JM, Cadwell K, Cecconi F, Choi AMK, *et al*: Autophagy in major human diseases. EMBO J 40: e108863, 2021.
36. Wang S, Long H, Hou L, Feng B, Ma Z, Wu Y, Zeng Y, Cai J, Zhang DW and Zhao G: The mitophagy pathway and its implications in human diseases. Signal Transduct Target Ther 8: 304, 2023.
37. Narendra D, Tanaka A, Suen DF and Youle RJ: Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol 183: 795-803, 2008.
38. Han R, Liu Y, Li S, Li XJ and Yang W: PINK1-PRKN mediated mitophagy: Differences between in vitro and in vivo models. Autophagy 19: 1396-1405, 2023.
39. Harper JW, Ordureau A and Heo JM: Building and decoding ubiquitin chains for mitophagy. Nat Rev Mol Cell Biol 19: 93-108, 2018.
40. Lazarou M, Sliter DA, Kane LA, Sarraf SA, Wang C, Burman JL, Sideris DP, Fogel AI and Youle RJ: The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature 524: 309-314, 2015.
41. Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, Cookson MR and Youle RJ: PINK1 is selectively stabilized on impaired mitochondria to activate parkin. PLoS Biol 8: e1000298, 2010.
42. Wiedemann N and Pfanner N: Mitochondrial machineries for protein import and assembly. Annu Rev Biochem 86: 685-714, 2017.
43. Rasool S, Veyron S, Soya N, Eldeeb MA, Lukacs GL, Fon EA and Trempe JF: Mechanism of PINK1 activation by autophosphorylation and insights into assembly on the TOM complex. Mol Cell 82: 44-59.e6, 2022.
44. Lysyk L, Brassard R, Touret N and Lemieux MJ: PARL protease: A glimpse at intramembrane proteolysis in the inner mitochondrial membrane. J Mol Biol 432: 5052-5062, 2020.
45. Yamano K and Youle RJ: PINK1 is degraded through the N-end rule pathway. Autophagy 9: 1758-1769, 2013.
46. Pickrell AM and Youle RJ: The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. Neuron 85: 257-273, 2015.
47. Wang R, Zhu Y, Ren C, Yang S, Tian S, Chen H, Jin M and Zhou H: Influenza A virus protein PB1-F2 impairs innate immunity by inducing mitophagy. Autophagy 17: 496-511, 2021.
48. McLelland GL, Goiran T, Yi W, Dorval G, Chen CX, Lauinger ND, Krahn AI, Valimehr S, Rakovic A, Rouiller I, *et al*: Mfn2 ubiquitination by PINK1/parkin gates the p97-dependent release of ER from mitochondria to drive mitophagy. Elife 7: e32866, 2018.
49. Gao XY, Yang T, Gu Y and Sun XH: Mitochondrial dysfunction in parkinson's disease: From mechanistic insights to therapy. Front Aging Neurosci 14: 885500, 2022.
50. Yamano K, Matsuda N and Tanaka K: The ubiquitin signal and autophagy: An orchestrated dance leading to mitochondrial degradation. EMBO Rep 17: 300-316, 2016.
51. Zheng X and Hunter T: Parkin mitochondrial translocation is achieved through a novel catalytic activity coupled mechanism. Cell Res 23: 886-897, 2013.
52. Malpartida AB, Williamson M, Narendra DP, Wade-Martins R and Ryan BJ: Mitochondrial dysfunction and mitophagy in Parkinson's disease: From mechanism to therapy. Trends Biochem Sci 46: 329-343, 2021.
53. Matsuda N: Phospho-ubiquitin: Upending the PINK-parkin-ubiquitin cascade. J Biochem 159: 379-385, 2016.
54. Johansen T and Lamark T: Selective autophagy: ATG8 family proteins, LIR motifs and cargo receptors. J Mol Biol 432: 80-103, 2020.
55. Deretic V and Lazarou M: A guide to membrane atg8ylation and autophagy with reflections on immunity. J Cell Biol 221: e202203083, 2022.
56. Birgisdottir ÅB, Lamark T and Johansen T: The LIR motif-crucial for selective autophagy. J Cell Sci 126: 3237-3247, 2013.
57. Stolz A, Ernst A and Dikic I: Cargo recognition and trafficking in selective autophagy. Nat Cell Biol 16: 495-501, 2014.
58. Sun D, Wu R, Zheng J, Li P and Yu L: Polyubiquitin chain-induced p62 phase separation drives autophagic cargo segregation. Cell Res 28: 405-415, 2018.
59. Geisler S, Holmström KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ and Springer W: PINK1/parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol 12: 119-131, 2010.
60. Deosaran E, Larsen KB, Hua R, Sargent G, Wang Y, Kim S, Lamark T, Jauregui M, Law K, Lippincott-Schwartz J, *et al*: NBR1 acts as an autophagy receptor for peroxisomes. J Cell Sci 126: 939-952, 2013.
61. Taguchi K, Fujikawa N, Komatsu M, Ishii T, Unno M, Akaike T, Motohashi H and Yamamoto M: Keap1 degradation by autophagy for the maintenance of redox homeostasis. Proc Natl Acad Sci USA 109: 13561-13566, 2012.
62. Komatsu M, Kurokawa H, Waguri S, Taguchi K, Kobayashi A, Ichimura Y, Sou YS, Ueno I, Sakamoto A, Tong KI, *et al*: The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. Nat Cell Biol 12: 213-223, 2010.
63. Sánchez-Martín P, Sou YS, Kageyama S, Koike M, Waguri S and Komatsu M: NBR1-mediated p62-liquid droplets enhance the Keap1-Nrf2 system. EMBO Rep 21: e48902, 2020.
64. Qiu Y, Wang J, Li H, Yang B, Wang J, He Q and Weng Q: Emerging views of OPTN (optineurin) function in the autophagic process associated with disease. Autophagy 18: 73-85, 2022.
65. Matsumoto G, Wada K, Okuno M, Kurosawa M and Nukina N: Serine 403 phosphorylation of p62/SQSTM1 regulates selective autophagic clearance of ubiquitinated proteins. Mol Cell 44: 279-289, 2011.
66. Heo JM, Ordureau A, Paulo JA, Rinehart J and Harper JW: The PINK1-PARKIN mitochondrial ubiquitylation pathway drives a program of OPTN/NDP52 recruitment and TBK1 activation to promote mitophagy. Mol Cell 60: 7-20, 2015.
67. Yamano K and Kojima W: Molecular functions of autophagy adaptors upon ubiquitin-driven mitophagy. Biochim Biophys Acta Gen Subj 1865: 129972, 2021.
68. Vargas JNS, Wang C, Bunker E, Hao L, Maric D, Schiavo G, Randow F and Youle RJ: Spatiotemporal control of ULK1 activation by NDP52 and TBK1 during selective autophagy. Mol Cell 74: 347-362.e6, 2019.
69. von Muhlinen N, Akutsu M, Ravenhill BJ, Foeglein Á, Bloor S, Rutherford TJ, Freund SM, Komander D and Randow F: LC3C, bound selectively by a noncanonical LIR motif in NDP52, is required for antibacterial autophagy. Mol Cell 48: 329-342, 2012.
70. Turco E, Savova A, Gere F, Ferrari L, Romanov J, Schuschnig M and Martens S: Reconstitution defines the roles of p62, NBR1 and TAX1BP1 in ubiquitin condensate formation and autophagy initiation. Nat Commun 12: 5212, 2021.
71. Ohnstad AE, Delgado JM, North BJ, Nasa I, Kettenbach AN, Schultz SW and Shoemaker CJ: Receptor-mediated clustering of FIP200 bypasses the role of LC3 lipidation in autophagy. EMBO J 39: e104948, 2020.
72. Uoselis L, Nguyen TN and Lazarou M: Mitochondrial degradation: Mitophagy and beyond. Mol Cell 83: 3404-3420, 2023.
73. Field JT and Gordon JW: BNIP3 and nix: Atypical regulators of cell fate. Biochim Biophys Acta Mol Cell Res 1869: 119325, 2022.
74. Chen G, Ray R, Dubik D, Shi L, Cizeau J, Bleackley RC, Saxena S, Gietz RD and Greenberg AH: The E1B 19K/Bcl-2-binding protein Nip3 is a dimeric mitochondrial protein that activates apoptosis. J Exp Med 186: 1975-1983, 1997.
75. Bruick RK: Expression of the gene encoding the proapoptotic Nip3 protein is induced by hypoxia. Proc Natl Acad Sci USA 97: 9082-9087, 2000.
76. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G, *et al*: Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J 27: 433-446, 2008.
77. Zhang T, Xue L, Li L, Tang C, Wan Z, Wang R, Tan J, Tan Y, Han H, Tian R, *et al*: BNIP3 protein suppresses PINK1 kinase proteolytic cleavage to promote mitophagy. J Biol Chem 291: 21616-21629, 2016.
78. Lee Y, Lee HY, Hanna RA and Gustafsson ÅB: Mitochondrial autophagy by Bnip3 involves Drp1-mediated mitochondrial fission and recruitment of parkin in cardiac myocytes. Am J Physiol Heart Circ Physiol 301: H1924-H1931, 2011.
79. Marinković M, Šprung M and Novak I: Dimerization of mitophagy receptor BNIP3L/NIX is essential for recruitment of autophagic machinery. Autophagy 17: 1232-1243, 2021.
80. Sandoval H, Thiagarajan P, Dasgupta SK, Schumacher A, Prchal JT, Chen M and Wang J: Essential role for nix in autophagic maturation of erythroid cells. Nature 454: 232-235, 2008.
81. Xiang G, Yang L, Long Q, Chen K, Tang H, Wu Y, Liu Z, Zhou Y, Qi J, Zheng L, *et al*: BNIP3L-dependent mitophagy accounts for mitochondrial clearance during 3 factors-induced somatic cell reprogramming. Autophagy 13: 1543-1555, 2017.

82. Esteban-Martínez L and Boya P: BNIP3L/NIX-dependent mitophagy regulates cell differentiation via metabolic reprogramming. Autophagy 14: 915-917, 2018.
83. Melser S, Chatelain EH, Lavie J, Mahfouf W, Jose C, Obre E, Goorden S, Priault M, Elgersma Y, Rezvani HR, *et al*: Rheb regulates mitophagy induced by mitochondrial energetic status. Cell Metab 17: 719-730, 2013.
84. Gao F, Chen D, Si J, Hu Q, Qin Z, Fang M and Wang G: The mitochondrial protein BNIP3L is the substrate of PARK2 and mediates mitophagy in PINK1/PARK2 pathway. Hum Mol Genet 24: 2528-2538, 2015.
85. Cao Y, Zheng J, Wan H, Sun Y, Fu S, Liu S, He B, Cai G, Cao Y, Huang H, *et al*: A mitochondrial SCF-FBXL4 ubiquitin E3 ligase complex degrades BNIP3 and NIX to restrain mitophagy and prevent mitochondrial disease. EMBO J 42: e113033, 2023.
86. Zhu Y, Massen S, Terenzio M, Lang V, Chen-Lindner S, Eils R, Novak I, Dikic I, Hamacher-Brady A and Brady NR: Modulation of serines 17 and 24 in the LC3-interacting region of Bnip3 determines pro-survival mitophagy versus apoptosis. J Biol Chem 288: 1099-1113, 2013.
87. Rogov VV, Suzuki H, Marinković M, Lang V, Kato R, Kawasaki M, Buljubašić M, Šprung M, Rogova N, Wakatsuki S, *et al*: Phosphorylation of the mitochondrial autophagy receptor nix enhances its interaction with LC3 proteins. Sci Rep 7: 1131, 2017.
88. Clague MJ and Urbé S: Diverse routes to mitophagy governed by ubiquitylation and mitochondrial import. Trends Cell Biol 35: 527-538, 2025.
89. Zhang W: The mitophagy receptor FUN14 domain-containing 1 (FUNDC1): A promising biomarker and potential therapeutic target of human diseases. Genes Dis 8: 640-654, 2021.
90. Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P, Ma Q, Zhu C, Wang R, Qi W, *et al*: Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 14: 177-185, 2012.
91. Kuang Y, Ma K, Zhou C, Ding P, Zhu Y, Chen Q and Xia B: Structural basis for the phosphorylation of FUNDC1 LIR as a molecular switch of mitophagy. Autophagy 12: 2363-2373, 2016.
92. Zhou H, Zhu P, Wang J, Zhu H, Ren J and Chen Y: Pathogenesis of cardiac ischemia reperfusion injury is associated with CK2α-disturbed mitochondrial homeostasis via suppression of FUNDC1-related mitophagy. Cell Death Differ 25: 1080-1093, 2018.
93. Chen G, Han Z, Feng D, Chen Y, Chen L, Wu H, Huang L, Zhou C, Cai X, Fu C, *et al*: A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. Mol Cell 54: 362-377, 2014.
94. Wu W, Tian W, Hu Z, Chen G, Huang L, Li W, Zhang X, Xue P, Zhou C, Liu L, *et al*: ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. EMBO Rep 15: 566-575, 2014.
95. Tang C, Livingston MJ, Liu Z and Dong Z: Autophagy in kidney homeostasis and disease. Nat Rev Nephrol 16: 489-508, 2020.
96. Wullschleger S, Loewith R and Hall MN: TOR signaling in growth and metabolism. Cell 124: 471-484, 2006.
97. Hosokawa N, Hara T, Kaizuka T, Kishi C, Takamura A, Miura Y, Iemura S, Natsume T, Takehana K, Yamada N, *et al*: Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Mol Biol Cell 20: 1981-1991, 2009.
98. Herzig S and Shaw RJ: AMPK: Guardian of metabolism and mitochondrial homeostasis. Nat Rev Mol Cell Biol 19: 121-135, 2018.
99. Kim J, Kundu M, Viollet B and Guan KL: AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. Nat Cell Biol 13: 132-141, 2011.
100. Perico L, Remuzzi G and Benigni A: Sirtuins in kidney health and disease. Nat Rev Nephrol 20: 313-329, 2024.
101. Liu S, Liu Y, Li J, Wang M, Chen X, Gan F, Wen L, Huang K and Liu D: Arsenic exposure-induced acute kidney injury by regulating SIRT1/PINK1/mitophagy axis in mice and in HK-2 cells. J Agric Food Chem 71: 15809-15820, 2023.
102. Liu T, Yang Q, Zhang X, Qin R, Shan W, Zhang H and Chen X: Quercetin alleviates kidney fibrosis by reducing renal tubular epithelial cell senescence through the SIRT1/PINK1/mitophagy axis. Life Sci 257: 118116, 2020.
103. Jin L, Galonek H, Israelian K, Choy W, Morrison M, Xia Y, Wang X, Xu Y, Yang Y, Smith JJ, *et al*: Biochemical characterization, localization, and tissue distribution of the longer form of mouse SIRT3. Protein Sci 18: 514-525, 2009.
104. Xu S, Gao Y, Zhang Q, Wei S, Chen Z, Dai X, Zeng Z and Zhao KS: SIRT1/3 activation by resveratrol attenuates acute kidney injury in a septic rat model. Oxid Med Cell Longev 2016: 7296092, 2016.
105. Deng Z, He M, Hu H, Zhang W, Zhang Y, Ge Y, Ma T, Wu J, Li L, Sun M, *et al*: Melatonin attenuates sepsis-induced acute kidney injury by promoting mitophagy through SIRT3-mediated TFAM deacetylation. Autophagy 20: 151-165, 2024.
106. Polletta L, Vernucci E, Carnevale I, Arcangeli T, Rotili D, Palmerio S, Steegborn C, Nowak T, Schutkowski M, Pellegrini L, *et al*: SIRT5 regulation of ammonia-induced autophagy and mitophagy. Autophagy 11: 253-270, 2015.
107. Cui X, Zhou Z, Tu H, Wu J, Zhou J, Yi Q, Liu O and Dai X: Mitophagy in fibrotic diseases: Molecular mechanisms and therapeutic applications. Front Physiol 15: 1430230, 2024.
108. Liu BC, Tang TT, Lv LL and Lan HY: Renal tubule injury: A driving force toward chronic kidney disease. Kidney Int 93: 568-579, 2018.
109. Ohashi R, Shimizu A, Masuda Y, Kitamura H, Ishizaki M, Sugisaki Y and Yamanaka N: Peritubular capillary regression during the progression of experimental obstructive nephropathy. J Am Soc Nephrol 13: 1795-1805, 2002.
110. Li S, Lin Q, Shao X, Zhu X, Wu J, Wu B, Zhang M, Zhou W, Zhou Y, Jin H, *et al*: Drp1-regulated PARK2-dependent mitophagy protects against renal fibrosis in unilateral ureteral obstruction. Free Radic Biol Med 152: 632-649, 2020.
111. Bhatia D, Chung KP, Nakahira K, Patino E, Rice MC, Torres LK, Muthukumar T, Choi AM, Akchurin OM and Choi ME: Mitophagy-dependent macrophage reprogramming protects against kidney fibrosis. JCI Insight 4: e132826, 132826, 2019.
112. Chawla LS, Eggers PW, Star RA and Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 371: 58-66, 2014.
113. Venkatachalam MA, Weinberg JM, Kriz W and Bidani AK: Failed tubule recovery, AKI-CKD transition, and kidney disease progression. J Am Soc Nephrol 26: 1765-1776, 2015.
114. Pavlović N, Križanac M, Kumrić M, Vukojević K and Božić J: Mitochondrial dysfunction: The silent catalyst of kidney disease progression. Cells 14: 794, 2025.
115. Bhat ZY, Cadnapaphornchai P, Ginsburg K, Sivagnanam M, Chopra S, Treadway CK, Lin HS, Yoo G, Sukari A and Doshi MD: Understanding the risk factors and long-term consequences of cisplatin-associated acute kidney injury: An observational cohort study. PLoS One 10: e0142225, 2015.
116. Mapuskar KA, Wen H, Holanda DG, Rastogi P, Steinbach E, Han R, Coleman MC, Attanasio M, Riley DP, Spitz DR, *et al*: Persistent increase in mitochondrial superoxide mediates cisplatin-induced chronic kidney disease. Redox Biol 20: 98-106, 2019.
117. Zhao C, Chen Z, Xu X, An X, Duan S, Huang Z, Zhang C, Wu L, Zhang B, Zhang A, *et al*: Pink1/Parkin-mediated mitophagy play a protective role in cisplatin induced renal tubular epithelial cells injury. Exp Cell Res 350: 390-397, 2017.
118. Ludwig-Portugall I, Bartok E, Dhana E, Evers BD, Primiano MJ, Hall JP, Franklin BS, Knolle PA, Hornung V, Hartmann G, *et al*: An NLRP3-specific inflammasome inhibitor attenuates crystal-induced kidney fibrosis in mice. Kidney Int 90: 525-539, 2016.
119. Li J, Lin Q, Shao X, Li S, Zhu X, Wu J, Mou S, Gu L, Wang Q, Zhang M, *et al*: HIF1α-BNIP3-mediated mitophagy protects against renal fibrosis by decreasing ROS and inhibiting activation of the NLRP3 inflammasome. Cell Death Dis 14: 200, 2023.
120. Huang Y and Yang L: Regulation of pyroptosis and ferroptosis by mitophagy in chronic kidney disease. Zhong Nan Da Xue Xue Bao Yi Xue Ban 49: 1769-1776, 2024 (In English, Chinese).
121. Guo J, Yuan Z and Wang R: Zn^{2+} improves sepsis-induced acute kidney injury by upregulating SIRT7-mediated parkin acetylation. Am J Physiol Renal Physiol 327: F184-F197, 2024.
122. Fu ZJ, Wang ZY, Xu L, Chen XH, Li XX, Liao WT, Ma HK, Jiang MD, Xu TT, Xu J, *et al*: HIF-1α-BNIP3-mediated mitophagy in tubular cells protects against renal ischemia/reperfusion injury. Redox Biol 36: 101671, 2020.
123. Zhou L, Zhang L, Zhang Y, Yu X, Sun X, Zhu T, Li X, Liang W, Han Y and Qin C: PINK1 deficiency ameliorates cisplatin-induced acute kidney injury in rats. Front Physiol 10: 1225, 2019.
124. Li K, Xia X and Tong Y: Multiple roles of mitochondrial autophagy receptor FUNDC1 in mitochondrial events and kidney disease. Front Cell Dev Biol 12: 1453365, 2024.

125. Bi Y, Liu S, Qin X, Abudureyimu M, Wang L, Zou R, Ajoolabady A, Zhang W, Peng H, Ren J and Zhang Y: FUNDC1 interacts with GPx4 to govern hepatic ferroptosis and fibrotic injury through a mitophagy-dependent manner. J Adv Res 55: 45-60, 2024.
126. Sies H and Cadenas E: Oxidative stress: Damage to intact cells and organs. Philos Trans R Soc Lond B Biol Sci 311: 617-631, 1985.
127. Sies H, Berndt C and Jones DP: Oxidative stress. Annu Rev Biochem 86: 715-748, 2017.
128. Forman HJ and Zhang H: Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nat Rev Drug Discov 20: 689-709, 2021.
129. Modlinger PS, Wilcox CS and Aslam S: Nitric oxide, oxidative stress, and progression of chronic renal failure. Semin Nephrol 24: 354-365, 2004.
130. Murphy MP: How mitochondria produce reactive oxygen species. Biochem J 417: 1-13, 2009.
131. Zorov DB, Juhaszova M and Sollott SJ: Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 94: 909-950, 2014.
132. Sies H and Jones DP: Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nat Rev Mol Cell Biol 21: 363-383, 2020.
133. Sureshbabu A, Ryter SW and Choi ME: Oxidative stress and autophagy: Crucial modulators of kidney injury. Redox Biol 4: 208-214, 2015.
134. Sedeek M, Nasrallah R, Touyz RM and Hébert RL: NADPH oxidases, reactive oxygen species, and the kidney: Friend and foe. J Am Soc Nephrol 24: 1512-1518, 2013.
135. Leung JCK, Chan LYY, Tang SCW, Lam MF, Chow CW, Lim AI and Lai KN: Oxidative damages in tubular epithelial cells in IgA nephropathy: Role of crosstalk between angiotensin II and aldosterone. J Transl Med 9: 169, 2011.
136. Ursini F, Maiorino M and Forman HJ: Redox homeostasis: The golden mean of healthy living. Redox Biol 8: 205-215, 2016.
137. Ruiz S, Pergola PE, Zager RA and Vaziri ND: Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int 83: 1029-1041, 2013.
138. Yamamoto M, Kensler TW and Motohashi H: The KEAP1-NRF2 system: A thiol-based sensor-effector apparatus for maintaining redox homeostasis. Physiol Rev 98: 1169-1203, 2018.
139. Wakabayashi N, Dinkova-Kostova AT, Holtzclaw WD, Kang MI, Kobayashi A, Yamamoto M, Kensler TW and Talalay P: Protection against electrophile and oxidant stress by induction of the phase 2 response: Fate of cysteines of the Keap1 sensor modified by inducers. Proc Natl Acad Sci USA 101: 2040-2045, 2004.
140. Sykiotis GP and Bohmann D: Stress-activated Cap'n'collar transcription factors in aging and human disease. Sci Signal 3: re3, 2010.
141. Tretter V, Hochreiter B, Zach ML, Krenn K and Klein KU: Understanding cellular redox homeostasis: A challenge for precision medicine. Int J Mol Sci 23: 106, 2021.
142. Oyewole AO and Birch-Machin MA: Mitochondria-targeted antioxidants. FASEB J 29: 4766-4771, 2015.
143. Kataura T, Otten EG, Rabanal-Ruiz Y, Adriaenssens E, Urselli F, Scialo F, Fan L, Smith GR, Dawson WM, Chen X, *et al*: NDP52 acts as a redox sensor in PINK1/parkin-mediated mitophagy. EMBO J 42: e111372, 2023.
144. Hsu SN, Stephen LA, Phadwal K, Dillon S, Carter R, Morton NM, Luijten I, Emelianova K, Amin AK, Macrae VE, *et al*: Mitochondrial dysfunction and mitophagy blockade contribute to renal osteodystrophy in chronic kidney disease-mineral bone disorder. Kidney Int 107: 1017-1036, 2025.
145. Xu D, Chen P, Wang B, Wang Y, Miao N, Yin F, Cheng Q, Zhou Z, Xie H, Zhou L, *et al*: NIX-mediated mitophagy protects against proteinuria-induced tubular cell apoptosis and renal injury. Am J Physiol Renal Physiol 316: F382-F395, 2019.
146. Wei X, Wang Y, Lao Y, Weng J, Deng R, Li S, Lu J, Yang S and Liu X: Effects of honokiol protects against chronic kidney disease via BNIP3/NIX and FUNDC1-mediated mitophagy and AMPK pathways. Mol Biol Rep 50: 6557-6568, 2023.
147. Yang K, Li T, Geng Y, Zou X, Peng F and Gao W: The role of mitophagy in the development of chronic kidney disease. PeerJ 12: e17260, 2024.
148. Reyes-Fermín LM, Avila-Rojas SH, Aparicio-Trejo OE, Tapia E, Rivero I and Pedraza-Chaverri J: The protective effect of alpha-mangostin against cisplatin-induced cell death in LLC-PK1 cells is associated to mitochondrial function preservation. Antioxidants (Basel) 8: 133, 2019.
149. Prieto-Carrasco R, García-Arroyo FE, Aparicio-Trejo OE, Rojas-Morales P, León-Contreras JC, Hernández-Pando R, Sánchez-Lozada LG, Tapia E and Pedraza-Chaverri J: Progressive reduction in mitochondrial mass is triggered by alterations in mitochondrial biogenesis and dynamics in chronic kidney disease induced by 5/6 nephrectomy. Biology (Basel) 10: 349, 2021.
150. Wen CP, Cheng TYD, Tsai MK, Chang YC, Chan HT, Tsai SP, Chiang PH, Hsu CC, Sung PK, Hsu YH and Wen SF: All-cause mortality attributable to chronic kidney disease: A prospective cohort study based on 462 293 adults in taiwan. Lancet 371: 2173-2182, 2008.
151. Dwivedi S and Sikarwar MS: Diabetic nephropathy: Pathogenesis, mechanisms, and therapeutic strategies. Horm Metab Res 57: 7-17, 2025.
152. Han YC, Tang SQ, Liu YT, Li AM, Zhan M, Yang M, Song N, Zhang W, Wu XQ, Peng CH, *et al*: AMPK agonist alleviate renal tubulointerstitial fibrosis via activating mitophagy in high fat and streptozotocin induced diabetic mice. Cell Death Dis 12: 925, 2021.
153. Czajka A, Ajaz S, Gnudi L, Parsade CK, Jones P, Reid F and Malik AN: Altered mitochondrial function, mitochondrial DNA and reduced metabolic flexibility in patients with diabetic nephropathy. EBioMedicine 2: 499-512, 2015.
154. Holterman CE, Thibodeau JF, Towaij C, Gutsol A, Montezano AC, Parks RJ, Cooper ME, Touyz RM and Kennedy CR: Nephropathy and elevated BP in mice with podocyte-specific NADPH oxidase 5 expression. J Am Soc Nephrol 25: 784-797, 2014.
155. Sang XY, Xiao JJ, Liu Q, Zhu R, Dai JJ, Zhang C, Yu H, Yang SJ and Zhang BF: Regulators of calcineurin 1 deficiency attenuates tubulointerstitial fibrosis through improving mitochondrial fitness. FASEB J: doi: 10.1096/fj.202000781RRR.
156. Li Y, Song B, Ruan C, Xue W and Zhao J: AdipoRon attenuates hypertension-induced epithelial-mesenchymal transition and renal fibrosis via promoting epithelial autophagy. J Cardiovasc Transl Res 14: 538-545, 2021.
157. Long Y, Li Y, Ma Z, Xie Y, Zhao H, Zhang M and Liu R: Epimedii folium and ligustri lucidi fructus synergistically delay renal aging through AMPK/ULK1/Bcl2L13-mediated mitophagy. J Ethnopharmacol 346: 119668, 2025.
158. Wang Y, Ma Y, Ke Y, Jiang X, Liu J, Xiao Y, Zheng H, Wang C, Chen X and Shi M: *Fangji huangqi* decoction ameliorates membranous nephropathy through the upregulation of BNIP3-mediated mitophagy. J Ethnopharmacol 324: 117734, 2024.
159. Wang H, Shen M, Ma Y, Lan L, Jiang X, Cen X, Guo G, Zhou Q, Yuan M, Chen J, *et al*: Novel mitophagy inducer alleviates lupus nephritis by reducing myeloid cell activation and autoantigen presentation. Kidney Int 105: 759-774, 2024.
160. Wang Y, Lu M, Xiong L, Fan J, Zhou Y, Li H, Peng X, Zhong Z, Wang Y, Huang F, *et al*: Drp1-mediated mitochondrial fission promotes renal fibroblast activation and fibrogenesis. Cell Death Dis 11: 29, 2020.
161. Dröge W: Free radicals in the physiological control of cell function. Physiol Rev 82: 47-95, 2002.
162. Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, Siamopoulos KC and Tsakiris D: Oxidative stress is progressively enhanced with advancing stages of CKD. Am J Kidney Dis 48: 752-760, 2006.
163. Zhang L, Miao M, Xu X, Bai M, Wu M and Zhang A: From physiology to pathology: The role of mitochondria in acute kidney injuries and chronic kidney diseases. Kidney Dis (Basel) 9: 342-357, 2023.
164. Cheng Y, Lu Z, Mao T, Song Y, Qu Y, Chen X, Chen K, Liu K and Zhang C: Magnoflorine ameliorates chronic kidney disease in high-fat and high-fructose-fed mice by promoting parkin/PINK1-dependent mitophagy to inhibit NLRP3/caspase-1-mediated pyroptosis. J Agric Food Chem 72: 12775-12787, 2024.
165. Li H, Meng P, Meng Y, Yang Y, Zheng W, Huang H and Zhao Z: Mechanism of ruxolitinib enhancing mitophagy against renal fibrosis via PINK1/parkin pathway. Biochim Biophys Acta Mol Basis Dis 1871: 167978, 2025.

166. Ding XQ, Jian TY, Gai YN, Niu GT, Liu Y, Meng XH, Li J, Lyu H, Ren BR and Chen J: Chicoric acid attenuated renal tubular injury in HFD-induced chronic kidney disease mice through the promotion of mitophagy via the Nrf2/PINK/parkin pathway. J Agric Food Chem 70: 2923-2935, 2022.
167. Cao Y, Xiong J, Guan X, Yin S, Chen J, Yuan S, Liu H, Lin S, Zhou Y, Qiu J, *et al*: Paeoniflorin suppresses kidney inflammation by regulating macrophage polarization via KLF4-mediated mitophagy. Phytomedicine 116: 154901, 2023.
168. Jia Q, Han L, Zhang X, Yang W, Gao Y, Shen Y, Li B, Wang S, Qin M, Lowe S, *et al*: Tongluo yishen decoction ameliorates renal fibrosis via regulating mitochondrial dysfunction induced by oxidative stress in unilateral ureteral obstruction rats. Front Pharmacol 12: 762756, 2021.
169. Ren H, Shao Y, Wu C, Ma X, Lv C and Wang Q: Metformin alleviates oxidative stress and enhances autophagy in diabetic kidney disease via AMPK/SIRT1-FoxO1 pathway. Mol Cell Endocrinol 500: 110628, 2020.
170. Hong Q, Zhang L, Das B, Li Z, Liu B, Cai G, Chen X, Chuang PY, He JC and Lee K: Increased podocyte sirtuin-1 function attenuates diabetic kidney injury. Kidney Int 93: 1330-1343, 2018.
171. Galluzzi L, Bravo-San Pedro JM, Levine B, Green DR and Kroemer G: Pharmacological modulation of autophagy: Therapeutic potential and persisting obstacles. Nat Rev Drug Discov 16: 487-511, 2017.
172. Bonekamp NA, Jiang M, Motori E, Garcia Villegas R, Koolmeister C, Atanassov I, Mesaros A, Park CB and Larsson NG: High levels of TFAM repress mammalian mitochondrial DNA transcription in vivo. Life Sci Alliance 4: e202101034, 2021.
173. Wang R, Yuan W, Li L, Lu F, Zhang L, Gong H and Huang X: Resveratrol ameliorates muscle atrophy in chronic kidney disease via the axis of SIRT1/FoxO1. Phytother Res 36: 3265-3275, 2022.
174. Zhang W, Guo C, Li Y, Wang H, Wang H, Wang Y, Wu T, Wang H, Cheng G, Man J, *et al*: Mitophagy mediated by HIF-1α/FUNDC1 signaling in tubular cells protects against renal ischemia/reperfusion injury. Ren Fail 46: 2332492, 2024.
175. Sharma GN, Gupta G and Sharma P: A comprehensive review of free radicals, antioxidants, and their relationship with human ailments. Crit Rev Eukaryot Gene Expr 28: 139-154, 2018.
176. Harden TK, Sesma JI, Fricks IP and Lazarowski ER: Signalling and pharmacological properties of the P2Y receptor. Acta Physiol (Oxf) 199: 149-160, 2010.
177. Bai X, Huang D, Xie P, Sun R, Zhou H and Liu Y: Effect of uridine on mitochondrial function. Sheng Wu Gong Cheng Xue Bao 39: 3695-3709, 2023 (In Chinese).
178. Krylova IB, Selina EN, Bulion VV, Rodionova OM, Evdokimova NR, Belosludtseva NV, Shigaeva MI and Mironova GD: Uridine treatment prevents myocardial injury in rat models of acute ischemia and ischemia/reperfusion by activating the mitochondrial ATP-dependent potassium channel. Sci Rep 11: 16999, 2021.
179. Jiang N and Zhao Z: Intestinal aging is alleviated by uridine via regulating inflammation and oxidative stress in vivo and in vitro. Cell Cycle 21: 1519-1531, 2022.
180. Wang Y, Ping Z, Gao H, Liu Z, Xv Q, Jiang X and Yu W: LYC inhibits the AKT signaling pathway to activate autophagy and ameliorate TGFB-induced renal fibrosis. Autophagy 20: 1114-1133, 2024.
181. Smith RAJ, Hartley RC and Murphy MP: Mitochondria-targeted small molecule therapeutics and probes. Antioxid Redox Signal 15: 3021-3038, 2011.
182. Kelso GF, Porteous CM, Coulter CV, Hughes G, Porteous WK, Ledgerwood EC, Smith RA and Murphy MP: Selective targeting of a redox-active ubiquinone to mitochondria within cells: Antioxidant and antiapoptotic properties. J Biol Chem 276: 4588-4596, 2001.
183. James AM, Cochemé HM, Smith RAJ and Murphy MP: Interactions of mitochondria-targeted and untargeted ubiquinones with the mitochondrial respiratory chain and reactive oxygen species. Implications for the use of exogenous ubiquinones as therapies and experimental tools. J Biol Chem 280: 21295-21312, 2005.
184. Hamed M, Logan A, Gruszczyk AV, Beach TE, James AM, Dare AJ, Barlow A, Martin J, Georgakopoulos N, Gane AM, *et al*: Mitochondria-targeted antioxidant MitoQ ameliorates ischaemia-reperfusion injury in kidney transplantation models. Br J Surg 108: 1072-1081, 2021.
185. Zhu Z, Liang W, Chen Z, Hu J, Feng J, Cao Y, Ma Y and Ding G: Mitoquinone protects podocytes from angiotensin II-induced mitochondrial dysfunction and injury via the Keap1-Nrf2 signaling pathway. Oxid Med Cell Longev 2021: 1394486, 2021.
186. Reddy PH, Manczak M and Kandimalla R: Mitochondria-targeted small molecule SS31: A potential candidate for the treatment of Alzheimer's disease. Hum Mol Genet 26: 1597, 2017.
187. Hou Y, Li S, Wu M, Wei J, Ren Y, Du C, Wu H, Han C, Duan H and Shi Y: Mitochondria-targeted peptide SS-31 attenuates renal injury via an antioxidant effect in diabetic nephropathy. Am J Physiol Renal Physiol 310: F547-F559, 2016.
188. Yang SK, Han YC, He JR, Yang M, Zhang W, Zhan M, Li AM, Li L, Na-Song, Liu YT, *et al*: Mitochondria targeted peptide SS-31 prevent on cisplatin-induced acute kidney injury via regulating mitochondrial ROS-NLRP3 pathway. Biomed Pharmacother 130: 110521, 2020.
189. Zhu Y, Luo M, Bai X, Li J, Nie P, Li B and Luo P: SS-31, a mitochondria-targeting peptide, ameliorates kidney disease. Oxid Med Cell Longev 2022: 1295509, 2022.
190. Lan T, Guo H, Lu X, Geng K, Wu L, Luo Y, Zhu J, Shen X, Guo Q and Wu S: Dual-responsive curcumin-loaded nanoparticles for the treatment of cisplatin-induced acute kidney injury. Biomacromolecules 23: 5253-5266, 2022.