Mitophagy: Basic Mechanism and Potential Role in Kidney Diseases

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Key Words

Kidney diseases · Mitochondria · Mitophagy · Cell death

Abstract

Background: Mitochondria play fundamental roles in cellular metabolism, signaling, and viability. Disruption of mitochondria not only leads to dysfunction of the organelles but also activates mechanisms of cell injury and death, contributing to the pathogenesis of various diseases. ***Summary:*** Removal of damaged mitochondria is therefore crucial for cellular homeostasis and survival. Mitophagy, the selective elimination of mitochondria via autophagy, is an important mechanism of mitochondrial quality control in physiological and pathological conditions. Defects in mitophagy have been implicated in a variety of human disorders, including both acute and chronic kidney diseases. However, the role and regulatory mechanisms of mitophagy in kidney cells and tissues remain largely unknown. ***Key Message:*** This review provides updated information on mitophagy and suggests a potential role of mitophagy in renal pathophysiology.

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Introduction

Mitochondria are organelles of eukaryotic cells playing fundamental roles in cellular metabolism, especially in ATP production through oxidative phosphorylation. Mitochondria are also a major intracellular source of reactive oxygen species (ROS) in a variety of pathologic conditions including hypoxia [1], ischemia and reperfusion [2, 3], aging [4], and chemical inhibition of mitochondrial respiration [5]. Excessive mitochondrial ROS production leads to oxidative damage to cellular components that include mitochondrial proteins, lipids and DNA, which in turn leads to enhanced ROS production and further damage to mitochondria, forming a vicious cycle. Mitochondrial damage leads to the release of proapoptotic proteins, such as cytochrome c (cyt c), resulting in cell death. In addition, mitochondrial ROS production can activate the mitochondrial permeability transition (MTP) pore for cell death [6]. To ensure cellular homeostasis for viability, several mitochondrial quality control mechanisms have evolved [7, 8]. Mitophagy, the selective autophagic elimination of damaged or dysfunctional mitochondria serves as an important mitochondrial quality control mechanism. Defects in mitophagy have been associated with a variety of human disorders including cancer, heart diseases and neurodegenerative diseases [9].

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As a high metabolic demanding organ, the kidney is rich in mitochondria. Mitochondrial pathology has been implicated in the pathogenesis of both acute and chronic kidney diseases [10, 11]. As such, mitophagy may be critical to the maintenance of homeostasis in kidney cells, and disruption of mitophagy has been implicated in several kidney diseases. However, the role and regulation of mitophagy in renal physiology and pathogenesis remain largely unknown. This review aims at providing updated information on understanding mitophagy and the relevance of mitophagy in kidney diseases.

Overview of Autophagy

Autophagy is an evolutionarily conserved intracellular system for the degradation of organelles and long-life proteins. There are three types of autophagy, including macroautophagy, chaperon-mediated autophagy and microautophagy. In microautophagy, lysosomal membrane directly engulfs a portion of the cytoplasm [12]. In chaperon-mediated autophagy, cargo proteins containing a consensus KFERQ-like motif are recognized by HSPA8, and then the substrates bind to the lysosomal protein LAMP-2A followed by translocating across the lysosomal membrane for degradation [13]. Macroautophagy (hereafter referred to as autophagy) is characterized by the formation of a unique double-membrane organelle called autophagosome.

Autophagy is initiated by the nucleation of an isolation membrane, and then the isolation membrane elongates and closes to form an autophagosome. The origin of autophagosome membranes still remains controversial, but in mammalian cells, the endoplasmic reticulum seems to be the major source of autophagosome membrane [14]. Autophagosome formation is regulated by a complex molecular machinery. Among them, two ubiquitin-like conjugation systems, Atg12-Atg5 and Atg8-PE are involved in the expansion of autophagosome [15]. Autophagosome will fuse with lysosome to form a hybrid organelle named autolysosome. The cellular contents sequestered by autophagosome are degraded in autolysosome. Autophagy was considered as a nonselective bulk degradative process where the autophagosomes randomly engulf contents in the cytosol. However, it has been recently demonstrated that autophagy can specifically or selectively recognize and degrade protein aggregates, organelles or invading microbes [12]. To date, several selective types of autophagy have been verified, including the cytoplasm-to-vacuole targeting, pexophagy, ribophagy,

xenophagy and mitophagy [16]. Autophagy plays critical roles in adaptive responses to starvation and other forms of cellular stress, homeostasis, and differentiation and development [17–19]. Defects in autophagy have been implicated in a range of diseases including cancer, neurodegenerative diseases, infectious diseases, and metabolic diseases [20, 21].

Mitophagy-Autophagic Clearance of Mitochondria

Mitophagy is the selective degradation of mitochondria by autophagy. In this process, mitochondria are sequestered in autophagosomes and delivered to lysosomes for hydrolytic degradation. Mitophagy occurs physiologically and pathologically. Physiologically, Mitophagy plays essential roles in development, including the complete removal of mitochondria during erythrocyte maturation and the selective destruction of sperm-derived mitochondria after oocyte fertilization [22]. Defects in mitophagy have been implicated in a variety of pathological conditions including neurodegenerative diseases, myopathies, aging, cardiac diseases, and autoimmune diseases [9, 23]. Mitophagy shares the core molecular machinery with autophagy, and the induction and regulation of mitophagy involves a coordination of the mitochondrial dynamics machinery, specific mitophagy-initiating pathways, and the autophagy system. The work in the last few years has delineated two major mitophagy pathways that are centered on PINK1/Parkin and BNIP3/Nix [24, 25] (fig. 1).

PINK1-Parkin Pathway of Mitophagy

The most recognized mitophagy pathway in mammalian cells is mediated by two Parkinson's disease-related proteins, PINK1 and Parkin [26, 27]. PINK1 is serine/threonine kinase with a mitochondrial target sequence [26], and Parkin is a cytosol ubiquitin E3 ligase [28]. In healthy mitochondria, PINK1 is constitutively imported to the inner membrane where it is cleaved by the inner membrane presenilin-associated rhomboid-like protease PARL, and ultimately proteolytically degraded [29]. Mitochondrial depolarization prevents the import of PINK1 to the inner membrane, thereby stabilizing the full length PINK1 on the mitochondrial outer membrane [30, 31]. In this manner, PINK1 acts as a sensor of mitochondrial damage. Accumulation of full-length PINK1 on the mitochondrial surface recruits Parkin from the cytosol to

Fig. 1. Mitophagy mechanisms. **A** PINK1/Parkin-mediated mitophagy. In healthy mitochondria, PINK1 is constitutively imported into mitochondria and degraded by the inner mitochondrial membrane protease PARL. In response to mitochondrial stress, mitochondrial membrane potential ($\Delta\psi$m) is dissipated to prevent PINK1 import, leading to the accumulation of PINK1 on the mitochondrial outer membrane. PINK1 then recruits Parkin to mitochondria. Upon recruitment, Parkin ubiquitinates mitochondrial membrane proteins such as mitofusins. P62 was recruited to ubiquitinated mitochondria to promote the delivery of ubiquitinated mitochondria to autophagosome via the binding to LC3. **B** Mitophagy during reticulocyte maturation. During reticulocyte maturation, up-regulation of Nix induces mitochondrial depolarization and promotes the delivery of mitochondria to autophagosome by binding to LC3. **C** Mitophagy under hypoxia. In response to hypoxia, Nix and BNIP3 are induced. Nix and BNIP3 act as autophagy receptors to deliver mitochondria to autophagosome by binding to LC3. FUNDC1 may also act as an autophagy receptor to deliver mitochondria to autophagosome.
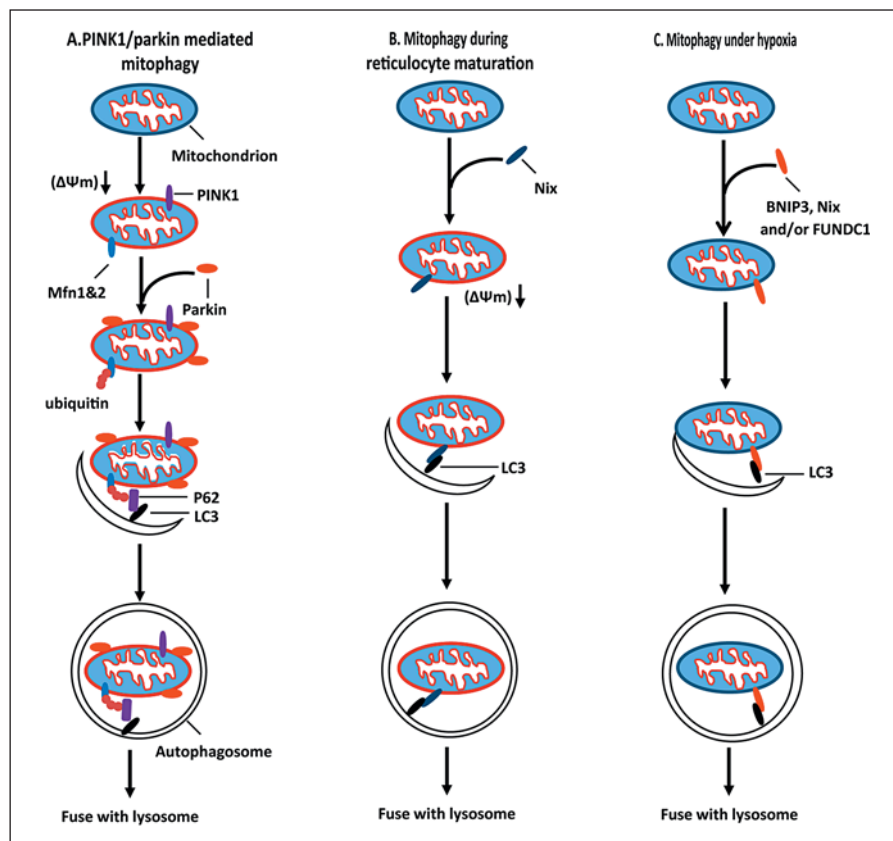
damaged mitochondria. Following the recruitment to mitochondria, Parkin ubiquitinates mitochondrial outer membrane proteins including mitofusin 1 and mitofusin 2 [32] to induce and promote the autophagic removal of mitochondria. PINK1 is necessary for Parkin-mediated mitophagy. PINK1-phosphorylated mitofusin 2 has been implicated as a Parkin receptor to attract Parkin to damaged mitochondria [33]. PINK1 is essential for activating Parkin E3 ligase activity by phosphorylating Parkin and ubiquitin [34, 35]. On the other hand, the mitochondrial deuibiquitinase USP30 opposes Parkin-mediated mitophagy [36]. In addition, some proteins such as HSPA1L, BAG4 and SIAH3 have been shown to modulate the translocation of Parkin to damaged mitochondria [37].

How are ubiquitinated mitochondria delivered to the autophagy machinery? Accumulating evidence has demonstrated that P62 (also known as SQSTM1) is essential for delivering ubiquitinated mitochondria to autophagosome via binding to LC3 [30, 38]. However, the role of p62 in Parkin-induced mitophagy remains controversial. Mitochondrial elimination has been reported to occur in the absence of p62-mediated clustering [39]. A very recent study by Wong and Holzbaur [40] showed that instead of p62, optineurin was required for autophagosome formation around damaged mitochondria in Parkin-mediated mitophagy by binding to LC3 via its LC3 interaction region (LIR) domain, and the recruitment of optineurin is independent on P62. These findings suggest Parkin can active mitophagy through recruiting preexisting phagophores via ubiquitination of outer mitochondrial membrane proteins and recruitment of receptors such as p62 and optineurin.

Parkin can also interact directly with autophagy-regulating proteins to facilitate mitophagy. For example, Van Humbeeck et al. [41] revealed that Parkin interacted with Ambra1, an activator of the Beclin1/Vps34 complex, to induce mitophagy. They showed that the interaction between Parkin and Ambra1 increased in depolarized mitochondria. Ambra1 was not required for the mitochondrial translocation of Parkin, but was critical for mitochondrial clearance through stimulating perimitochondrial nucleation of new phagophores via activating Vps34 in their immediate vicinity. These data suggest that the interaction of Parkin with Ambra1 is a key mecha-

nism for inducing the final clearance step of Parkin-mediated mitophagy. However, it is worth noting that Ambra1 was also implicated to induce Parkin- and p62-independent but LC3-dependent mitophagy [42].

In addition to Parkin, some other ubiquitin E3 ligases, including cytoplasmic E3 ligase SMURF1 and Gp78, and the mitochondrial E3 ubiquitin protein ligase 1 (Mul1) have also been implicated in mitophagy. SMURF1 [43] and Gp78 [44] participate in Parkin-dependent and -independent mitophagy, respectively. Mul1 was shown to induce mitophagy in skeletal muscles [45]. A recent study in *Drosophila* and mammalian cells revealed that Mul1 acted in parallel to the PINK1/parkin pathway in regulating mitofusin degradation and compensated for the loss of PINK1/parkin, and Mul1 did not affect Parkin-mediated mitophagy [46].

Nix- and BNIP3-Mediated Mitophagy

BCL2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3) and BNIP3-like (BNIP3L or Nix) are Bcl-2 family proteins with an atypical BH3 domain [47]. BNIP3 and Nix are mitochondrial outer membrane proteins and initially identified as pro-death proteins. Recent studies indicated that BNIP3 and Nix also mediate mitophagy in specific conditions. Nix seems indispensable for the complete mitochondrial elimination during reticulocyte maturation. In Nix-deficient mice, mitochondrial clearance in reticulocytes was dramatically inhibited or retarded [48–50]. Several studies also revealed that Nix deficiency inhibited mitochondrial depolarization, and treatment with uncoupling chemicals (e.g., CCCP) or a BH3 mimetic (e.g., ABT-737) was able to induce mitochondrial depolarization and then restored the sequestration of mitochondria into autophagosomes in Nix-deficient erythroid cells, suggesting that one mechanism for Nix induced-mitophagy is inducing mitochondrial depolarization [50]. Nix was also shown as a selective autophagy receptor for targeting mitochondria to autophagosomes via directly interacting with LC3 and GABARAP with its LIR domain [51].

Nix and BNIP3 have also been implicated in hypoxia-induced mitophagy. Under hypoxia conditions, Nix and BNIP3 are highly induced to activate mitophagy to prevent increased ROS production through elimination of damaged mitochondria, and this in turn mitigates cell death [52, 53]. Similar to Nix, BNIP3 was implicated to active mitophagy via inducing mitochondrial depolarization [54] and/or delivering mitochondria to autophago-

somes as a receptor via directly interacting with LC3 with its LIR domain [55]. In addition, as BH3-only proteins, Nix and BNIP3 can compete with Beclin-1 for binding to BCL-2 or BCL-xl leading to the release of Beclin1 [56]. Once released, Beclin1 is free to nucleate preautophagosomal membranes and induce autophagy.

In addition to BNIP3 and Nix, the integral mitochondrial outer membrane protein FUNDC1 was implicated in hypoxia-induced mitophagy through interacting with LC3 with its typical LC3-binding mitof Y(18)xxL(21) [57]. Moreover, a very recent study showed that FUNDC1 regulated ULK1 recruitment to damaged mitochondria, where ULK1 interacted and phosphorylated FUNDC1 at serine 17 to enhance FUNDC1 binding to LC3 [58]. It will be interesting to know whether FUNDC1 cooperates with BNIP3 and/or Nix to induce mitophagy under hypoxia.

Mitochondrial Fragmentation in Mitophagy

Mitochondria are highly dynamic organelles that are engaged in repeated cycles of fusion and fission. Mitochondrial fission and fusion are regulated by members of a family of conserved large GTPases. In mammals, mitochondrial fission is mediated by the cytoplasmic dynamin-related protein 1 (DRP1) [59] and the outer mitochondrial membrane protein FIS1 [60]. Mitochondrial fusion is regulated by Mfn1, Mfn2 and OPA1. Mfn1 and Mfn2 mediate outer membrane fusion, and OPA1 mediates inner membrane fusion [61, 62]. Mitochondria fuse and divide in response to cell demands and environmental changes. Under cell stress, mitochondrial fission is activated via Drp1 and fusion is arrested through the interaction of Bak, a proapoptotic Bcl-2 family protein on mitochondria, with mitofusins, culminating in mitochondrial fragmentation [63, 64]. Mitochondrial fragmentation has been identified in various human diseases, including cancer as well as neurologic and cardiovascular diseases [65, 66].

Recently, accumulating evidence has demonstrated that mitochondrial fragmentation is a prerequisite for mitophagy. The study by Twig et al. [67] revealed that fusion and fission were paired and occurred most commonly as fusion quickly followed by fission. Often, a fission event yields two types of daughter mitochondria, including hyperpolarized mitochondria and depolarized mitochondria. The depolarized daughter mitochondria have decreased levels of OPA1 and a reduced probability to fuse and will be removed by autophagy or mitophagy. Inhibition of fission reduces mitophagy, resulting in the ac-

cumulation of damaged mitochondria. Depolarization also causes the loss of Mfn1 and Mfn1 on mitochondria and thereby promotes mitochondrial fission, leading to Parkin-and/or Mul1-mediated mitophagy [46, 68]. Another study by Lee et al. [69] showed that inhibition of Drp1 or overexpression of Mfn1 prevented BNIP3-mediated mitophagy. However, although mitochondrial fragmentation promotes mitophagy, fission itself cannot induce mitophagy, for which a concomitant mitochondrial damage such as depolarization and increased ROS or other unclear signals are required [70].

MTP and Mitophagy

MTP is the result of opening mitochondria permeability transition pores in the inner membrane, which conduct all solutes less than about 1.5 KD [71]. Mitochondrial injuries from calcium overloading, ROS, and thiol cross-linking agents trigger MTP [72]. MTP causes mitochondrial depolarization, mitochondrial swelling, outer membrane rupture and consequent release of apoptogenic factors. MPT is recognized as a key event in cell death, especially necrosis.

MPT has recently been implicated in the activation of mitophagy, probably through inducing mitochondrial depolarization, a well-documented trigger of mitophagy in mammalian cells. For example, a recent study by Elmore et al. [73] showed that cyclosporin A, an immunosuppressant that blocks MPT, prevented serum deprivation and glucagon stimulated-mitochondrial depolarization and the subsequent sequestration of mitochondria into autophagosomes in hepatocytes [73, 74]. In another study, Cui et al. [75] revealed that silence of PINK1-induced mitophagy was mediated MTP in dopaminergic MN9D cells. However, no direct measurement of mitophagy was performed when MPT was inhibited in these studies. Also, it is worth noting that not all mitochondrial depolarizations are mediated by MPT.

Mitophagy and Cell Death

In general, mitophagy preserve viability by removing damaged mitochondria. However, the interplay between mitophagy and cell death is complicated [76, 77]. Firstly, many stimuli can trigger both mitophagy and cell death in the same cell. The outcome (life or death) is dependent on the degree and duration of the stress. If the stress is mild and only a subset of mitochondria is damaged, the cell can remove those mitochondria via mitophagy to preserve viability. On the other hand, when cellular stress is severe so that the number of damaged mitochondria overwhelms the capacity of mitophagy, or if mitophagy is defective, then the cell dies.

Secondly, several proteins have the capacity to regulate both mitophagy and apoptosis. For instance, Bcl-2 family proteins are involved in regulating mitophagy. Hollville et al. [78] showed that prosurvival Bcl-2 family proteins (Bcl-xL, Mcl-1, and Bcl-W) inhibit Parkin-mediated mitophagy probably by interfering with the stable recruitment of Parkin to mitochondria via direct interaction with Parkin. In a sharp contrary, BH3-only proteins (Bad, Bim, Noxa, or Puma) or a BH3 mimetic enhanced the mitochondrial translocation of Parkin leading to mitophagy activation. It is noteworthy that the effect on mitophagy may be secondary to the effect of these proteins on mitochondrial integrity and depolarization. Bcl-2 family proteins Nix and BNIP3 are proapoptotic proteins. However, as mentioned above, they both also mediate mitophagy. Moreover, BNIP3 overexpression-induced mitophagy was shown to be independent of the intrinsic apoptotic cell death pathway [54]. However, what remains unknown is exactly how these proteins switch from promoting cell death to preserving viability by regulating mitophagy.

Thirdly, apoptosis may inhibit mitophagy by cleaving autophagy proteins. For instance, Beclin1 [79, 80] and Atg5 [81] were reported to be cleaved by caspase and calpain, respectively. AMBRA1 cleavage by caspases and calpains has also been reported [82]. The cleavage of these autophagy proteins may result in the inactivation of autophagy. Moreover, some autophagy protein fragments resulting from caspase or calpain cleavage may translocate from cytosol to mitochondria, disrupting the interaction between Bcl-2 with Beclin1 and leading to augmented apoptosis [79, 81]. These studies demonstrated that when there is vast mitochondrial damage, activation of apoptosis may shut down autophagy to ensure cell death. Based on these findings, enhancement of mitophagy may provide a therapeutic strategy to protect against cell death.

Mitochondrial Pathology in Kidney Diseases

Mitochondrial pathology occurs in and is known as an important pathogenic event of kidney diseases. Firstly, mitochondrial dynamics is disrupted during kidney injury, resulting in morphological and structural changes. For example, in cisplatin-induced acute kidney injury, disruption of mitochondrial cristae and extensive mito-

chondrial swelling in proximal tubular epithelium were observed [83]. Mitochondrial fragmentation was detected in kidney tubule cells under acute and chronic kidney injury [11, 64, 66, 84, 85]. Using an in vivo multiphoton imaging technique, Hall et al. [86] showed that, in response to ischemia, the mitochondrial membrane potential dissipated rapidly, and mitochondria became shortened and fragmented in proximal tubules but not in distal tubules. Secondly, mitochondrial biogenesis in the kidney is affected during kidney injury. In a cisplatin-induced AKI model, a decreased mitochondrial mass was observed, indicating impaired mitochondrial biogenesis [83]. In a rat model with chronic cyclosporin A (CsA) treatment, mitochondrial DNA copy number, along with the expression of nuclear and mitochondrial DNA-encoded oxidative phosphorylation (OXPHOS) proteins, peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, and mitochondrial transcription factor-A (Tfam) was dramatically decreased [87]. Interestingly, in a mouse model with 5/6 nephrectomy, decreases of mitochondrial content also happened in muscles, which resulted in impaired exercise endurance, a well-documented feature in chronic kidney diseases [88]. Mitochondrial biogenesis increases the mitochondrial mass and functional capacity or helps preserve it by replacing damaged mitochondria, so defects in mitochondrial biogenesis may deteriorate kidney injury. In addition, as will be discussed later, mitochondrial degradation in the kidney was also affected during kidney injury [89].

Mitochondrial structural changes are often associated with functional impairment evidenced by reduced ATP production, excessive generation of ROS, release of proapoptotic proteins, or disturbance in calcium homeostasis, etc. [10, 90]. In the kidney, mitochondrial dysfunction is implicated in both acute and chronic kidney injury. For instance, in cisplatin-induced acute kidney injury, ATP production was affected by inhibiting complexes I–IV of the respiratory chain [91] and the electron transport chain enzyme cytochrome c oxidase [91]. Increasing evidence suggests that mitochondrial generation of ROS in response to pathogenic conditions, such as ischemia-reperfusion and hyperglycemia, plays a pathogenic role in kidney disease [92]. Release of proapoptotic proteins from mitochondrial intermembrane space resulting from permeabilization of mitochondrial outer and/or inner membrane was shown to contribute to tubular cell death that characterizes acute and chronic kidney disease [93, 94]. Collectively, mitochondrial pathology plays a pathogenic role in a variety of kidney diseases, so timely removal of damaged mitochondria is imperative to keep the kidney healthy.

Mitophagy in Kidney Diseases

Mitophagy has been implicated in several kidney disease models, including both AKI and CKD. In response to ischemia-reperfusion injury, BNIP3 was upregulated in a HIF-1-dependent manner. Interestingly, BNIP3 overexpression was shown to induce mitophagy, and inhibition of BNIP3 reduced mitophagy, suggesting BNIP3-mediated mitophagy may happen in tubular cells in AKI [95]. In the cell and mouse models of metabolic acidosis, a common complication of CKD, mitophagy was shown to be induced in proximal tubular cells, which was indispensable for maintaining mitochondrial membrane potential, morphology and functions [96], suggesting a possible link between mitophagy and metabolic acidosis. In a diabetic kidney disease model, inhibition of mitophagy and altered expression of mitophagic proteins in the kidney were observed, indicating that a disruption of renal tubular mitochondrial quality control may contribute to the pathogenesis of diabetic kidney disease [84]. In the kidney of a FSGS mouse model with autophagy deficiency in nephron and human idiopathic FSGS kidney biopsy specimens, mitochondrial dysfunction was observed, suggesting an association between mitophagy and cell injury in FSGS [97]. During renal injury induced by high-calorie diet, mitophagy was dramatically reduced accompanied by abnormal mitochondrial morphology. However, calorie restriction markedly enhanced renal autophagy and ameliorated oxidative damage in kidneys [98]. Taken together, these studies suggest that mitophagy may play a renoprotective role in both acute and chronic kidney injury. However, the regulatory mechanisms of mitophagy under these conditions remain largely unknown.

Conclusions and Future Directions

Significant progress has been made in our understanding of the roles and regulation of mitophagy in the last decade. However, many questions still remain unanswered. For example, mounting evidence supports the fact that mitophagy plays cytoprotective roles in pathological conditions, but emerging evidence also implicates that mitophagy is a possible effector of cell death programs [99]. The reason for the opposing role of mitophagy in different pathological conditions remains to be verified and delineated. Several mitophagy mechanisms have been identified, but which mechanism dominates and how they interconnect to modulate the level of mitophagy in a specific pathological condition remains largely unclear. In

addition, the molecular mechanism underlying the switch of Nix and BNIP3 from promoting cell death to preserving viability by regulating mitophagy is unclear. Mitochondrial fragmentation not only promotes mitophagy but also apoptosis [63, 100]. The determinants of the outcome (apoptosis vs. mitophagy) of mitochondrial fragmentation need to be further investigated. As to the kidney, although mitophagy has been implicated in model systems of kidney diseases, the exact role and regulatory mechanism of mitophagy under these conditions of kidney pathology remains unclear. Therefore, future studies using animal models with the deletion of mitophagy-related genes specifically in kidney tissues will be needed to further our understanding of mitophagy in kidney diseases.

Disclosure Statement

The authors have no conflicts of interest to declare.

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