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Mitophagy Pathways and Therapeutic Applications in Renal Fibrosis

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Abstract: Chronic kidney disease (CKD), a global health burden, progresses through renal fibrosis driven by mitochondrial dysfunction in metabolically active renal cells. As the kidney harbors exceptionally high mitochondrial density, defective mitophagy, a quality control mechanism for clearing damaged mitochondria have emerged as a central pathological trigger. Environmental toxins, such as perfluorinated compounds, disrupt lysosomal-mitochondrial crosstalk, exacerbating fibrotic pathways via metabolic reprogramming and sustained activation of pro-fibrotic signaling axes like FGF9/PI3K/Akt. Impaired PINK1/Parkin-mediated mitophagy permits accumulation of fragmented mitochondria, fueling oxidative stress and TGF-β/Smad3-driven epithelial-mesenchymal transition (EMT) and fibroblast activation. Recent therapeutic advances focus on restoring mitophagic flux to counteract fibrosis. Small-molecule activators (UMI-77) enhance mitochondrial clearance, attenuating NF-κB-mediated inflammation and collagen deposition. Nanotechnology-augmented mesenchymal stem cells offer targeted delivery of mitophagy modulators to damaged tubules, synergizing mitochondrial repair with anti-inflammatory effects. While preclinical studies highlight promising agents like SS-31 and MitoQ, challenges persist in achieving tissue-specific mitochondrial targeting and ensuring long-term genomic safety. This review synthesizes molecular insights into mitophagy dysregulation in fibrosis, explores innovative intervention strategies, and underscores the need for multi-omics approaches to optimize mitochondrial therapeutics. Bridging translational gaps through advanced delivery systems and patient-specific mitochondrial profiling may unlock precision therapies for halting CKD progression.

Keywords: Mitophagy; Kidney; Fibrosis; Mitochondria

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1. Introduction

Chronic kidney disease (CKD) stands as a dire global public health crisis, marked by an alarming surge in

prevalence and mortality rates. Epidemiological studies have revealed that nearly 700 million people globally, equivalent to 14.3% of the world's population, suffer from CKD, with China alone accounting for over 120 million cases. In the last 30 years, the global incidence of chronic kidney disease (CKD) has risen by nearly 30%, while the associated mortality rates have surged by over 40% [1]. Projections suggest that by 2040, CKD will become the fifth leading cause of death, up from its position as the twelfth in 2017 [2]. Renal fibrosis, a critical hallmark of CKD progression, is characterized by glomerulosclerosis, tubular atrophy, chronic interstitial inflammation, vascular lesions, and excessive extracellular matrix (ECM) deposition [3]. These structural changes impair renal function and cause systemic complications, including cardiovascular disorders. Renal fibrosis is initiated by injury, which triggers fibroblast activation via inflammatory mediators. These subsequently transform into myofibroblasts that drive excessive ECM production during tissue remodeling [4]. Myofibroblasts emerge via several cellular transdifferentiation mechanisms, such as epithelial-mesenchymal transition(EMT), endothelial-mesenchymal transition (EndMT), and macrophage-to-myofibroblast conversion [5–7]. These cells are crucial in the continuous buildup of the extracellular matrix (ECM). This process disrupts the normal structure of the renal parenchyma, reduces blood flow, and eventually leads to glomerulosclerosis and irreversible renal failure [8]. Mitochondrial dysfunction drives renal fibrosis in CKD, whereas dysregulated mitophagy exacerbates oxidative stress, inflammation, and apoptosis. This mechanistic link highlights mitophagy modulation as a promising therapeutic target, prompting current research into underlying pathways and interventions.

Autophagy maintains cellular homeostasis by recycling organelles and proteins. Activated during stress or starvation, it meets energy demands and removes damaged components. Mitophagy is a selective form of autophagy that specifically degrades mitochondria[4]. Mitophagy is crucial for mitochondrial quality control by selectively removing damaged mitochondria. Elevated mtROS levels trigger this process [9]. This process entails the encapsulation and breakdown of damaged mitochondria, thereby regulating their quantity and preserving the stability of cellular energy metabolism [10,11]. The canonical mitophagy process begins with the depolarization and destabilization of stressed mitochondria. These are then specifically recognized, enveloped by autophagosomes to form mitophagosomes, and delivered to lysosomes for final degradation [12]. However, abnormal activation of mitophagy can disrupt mitochondrial quality control, leading to imbalances that may result in cell death, tissue damage, and organ failure [13]. The kidneys are particularly active tissues for mitophagy, and research has shown that mitophagy may play a significant role in the pathogenesis of kidney diseases [14]. Elucidating mitophagy mechanisms enables targeted kidney disease therapies, thereby improving outcomes. Future research should further clarify the interplay between mitochondrial dynamics, cellular stress, and disease progression [15].

Tubular epithelial cells are highly dependent on mitochondria to support their high-energy functions. However, mitochondrial ROS production can trigger inflammatory responses and kidney injury. Under acute pathological stimuli, upregulated tubular autophagy serves as a protective mechanism against damage and subsequent fibrosis [16]. Mitochondria mediate oxidative phosphorylation; defective mitophagy disrupts tubular metabolism, impairs respiratory chain activity, and compromises acidosis adaptation. This triggers cell death, hypoxia, inflammation, and pro-fibrotic signaling, culminating in renal fibrosis. Downregulation of mitophagy mediators during fibrosis confirms that intervening in this process effectively delays disease progression [17]. Thus, elucidating mitochondrial autophagy regulatory mechanisms and their connection to renal fibrosis is essential for developing novel therapeutics. This review summarizes recent research progress, highlighting potential treatment directions and contributing to the advancement of kidney disease management.

2. Pathogenesis of renal fibrosis

Renal fibrosis, a hallmark of CKD, is characterized by tubular atrophy, extracellular matrix deposition, and myofibroblast expansion. Its pathogenesis involves multiple renal resident cells and immune effectors, particularly macrophages [18]. Tubular injury critically drives renal fibrosis by activating resident fibroblasts and pericytes. These cells enhance contractility and secrete inflammatory mediators and extracellular matrix (ECM) components for wound healing. Uncontrolled healing, however, leads to persistent ECM accumulation, causing tissue destruction, ischemia, and eventual renal failure. Understanding this interplay is vital for developing effective therapies [3].

2.1. Role of pro-fibrotic factors in renal fibrosis

2.1.1. TGF-β

Renal fibrosis is a complex process driven by various pro-fibrotic mediators, with transforming growth factor-β (TGF-β) playing a crucial role as the main orchestrator of fibrogenesis [19]. This multifunctional cytokine, produced by immune cells, endothelial cells, and fibroblasts, exerts its fibrogenic effects through different signaling pathways, TGF-β induces the synthesis of extracellular matrix (ECM) components while inhibiting matrix metalloproteinase (MMP) activity, leading to ECM imbalance [20]. It also promotes the transformation of cells into myofibroblasts, increasing cell proliferation and reducing the function of key renal cells [3]. Furthermore, TGF-β enhances the production of reactive oxygen species (ROS), fueling the activation of fibroblasts and myofibroblasts in a continuous loop [21]. TGF-β's pro-fibrotic effects predominate over its anti-inflammatory properties, establishing it as a central mediator in renal fibrosis pathogenesis. Elucidating these pathways is essential for developing targeted therapies [9].

2.1.2. NLRP3

Recent findings challenge prior views on NLRP3 in renal fibrosis. Studies show NLRP3 in renal fibroblasts promotes tubulointerstitial fibrosis via TGF-β/Smad signaling, independent of inflammasome activation. Unlike embryonic fibroblasts, renal fibroblasts express NLRP3 but do not release IL-1β upon LPS/ATP stimulation, indicating a fibrotic role that bypasses canonical IL-1β production [22].

2.1.3. Ang II

Angiotensin II (Ang II) is a potent vasoconstrictor that plays an important role in the progression of renal fibrosis [23]. There has long been evidence that Ang II receptor antagonists can improve tubulointerstitial fibrosis caused by unilateral ureteral obstruction [24]. First, an increase in Ang II levels activates the renin-angiotensin-aldosterone system (RAAS), which in turn causes renal vasoconstriction, cell proliferation, and fibroblast activation, all of which are important causes of renal fibrosis [25]. Second, Ang II can promote renal fibrosis by stimulating an increase in TGF-β [26]. In addition, angiotensin also increases the release of other growth factors, such as tumor necrosis factor-α, vascular cell adhesion molecule-1, NF-κB, endothelin, and interleukin-6, inducing oxidative stress and thereby promoting the progression of renal fibrosis [23,27].

2.1.4. MMPs

Matrix metalloproteinases (MMPs) play a crucial role in degrading extracellular matrix (ECM) proteins, with their activity controlled by endogenous inhibitors such as TIMPs [28]. Certain MMPs, including MMP-3, -10, -11, and -19, have the ability to break down various substrates like fibronectin and gelatin [29]. While MMP activation is

generally beneficial in kidney function, studies have revealed that MMP-2 and MMP-9 are upregulated during renal fibrosis progression, leading to the synthesis of α-SMA and FSP-1 in the EMT process [30]. This increased activity may be a result of MMP degradation products triggering EMT or the excessive presence of TIMPs [31]. Furthermore, MMP degradation products have been found to induce immune cell infiltration and activate pro-inflammatory pathways through cytokine cleavage, ultimately exacerbating renal fibrosis [32]. Overall, despite their essential role in ECM regulation, MMPs have been shown to contribute to the advancement of renal fibrosis through various pathways.

2.1.5. PDGFs

PDGF is widely expressed in renal cells and acts as a key profibrotic factor. Its effects drive renal fibrosis by mediating multiple profibrotic processes, including cell proliferation, migration, and extracellular matrix accumulation [33]. PDGFs recruit and proliferate mesenchymal cells, including inducing pericyte-to-myofibroblast transformation. This drives extracellular matrix accumulation, a pivotal step in advancing renal fibrosis [34]. PDGF-C is newly or overexpressed in fibrotic human renal biopsies. It directly induces fibroblast proliferation and renal interstitial fibrosis [35]. PDGF-C knockout attenuated tubulointerstitial fibrosis and myofibroblast activation in UUO-induced renal fibrosis [33]. The drug imatinib has also been shown to inhibit PDGFR tyrosine kinase activity and reduce renal fibrosis in various animal models of kidney disease [36]. PDGFs and autophagy-mediated FGF2 contribute significantly to fibroblast activation and renal fibrosis pathogenesis [37]. FGF2 is produced through autophagy after acute kidney injury and induces fibroblast activation and renal fibrosis [38]. CTGF promotes renal fibrosis by interacting with LRP6 to activate Wnt signaling, inducing pericyte and fibroblast transdifferentiation into myofibroblasts [39]. In addition, studies have shown that elevated levels of caspase-1 and the absence of PARK7 are also associated with renal fibrosis in CKD patients [40,41].

2.2. Cellular type transition in fibrosis

Renal fibrosis is a complex process involving the transformation of various cell types within the kidney. Spatial transcriptomics studies have identified mesenchymal cells, immune cells, and specific tubular epithelial cells as the main components of the human renal fibrosis niche [42]. Following tubular injury, a fibrotic niche forms where injured tubular and immune cells secrete profibrotic mediators. These mediators activate myofibroblast precursors through autocrine/paracrine pathways, driving fibrosis via activated fibroblasts [43]. The transformation of precursor cells involves processes such as epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition (EndMT), and the conversion of fibroblasts into myofibroblasts [5,6]. Macrophages are also implicated in the production of collagen I-producing myofibroblasts during renal fibrosis (MMT) [7,44]. EMT is a dynamic process in which epithelial cells acquire mesenchymal characteristics, particularly type 2 EMT, which plays a significant role in renal fibrosis, wound healing, tissue regeneration, and organ fibrosis [45]. Chronic inflammation drives fibrosis through excessive myofibroblast production and ECM deposition. In renal fibrosis, many fibroblasts originate from EMT, a process regulated by factors including TGF-β [46]. It has been confirmed in a transgenic mouse model of renal fibrosis that more than 30% of new fibroblasts originate from EMT [47]. The EMT process of renal fibrosis can be regulated by various growth factors, among which TGF-β is the key factor [48]. Inhibiting TGF-β signaling has been shown to prevent renal tubulointerstitial fibrosis and EMT, indicating its importance in the fibrotic process [49]. Endothelial cells can also undergo EndMT, contributing to renal fibrosis. Inhibition of EndMT has been shown to improve fibrosis in experimental models, highlighting its role in the pathogenesis of renal fibrosis [50,51].

Apelin can interact with FGFR1 to inhibit TGFβ-induced EndMT and reduce renal fibrosis [52]. Myofibroblasts, characterized by high α-SMA expression and excessive ECM deposition, play a crucial role in driving unresolved renal inflammation towards fibrosis [53]. The transformation of fibroblasts into myofibroblasts, a key process in renal fibrosis, is triggered by hypoxia. These myofibroblasts originate from sources like resident fibroblasts and macrophages, with erythropoietin-producing fibroblasts being a major contributor [54,55]. Myofibroblasts originate from sources such as resident fibroblasts and macrophages. Notably, erythropoietin-producing fibroblasts are a major source. Injured tubular cells secrete chemokines that polarize macrophages toward a fibrotic phenotype, thereby contributing to renal fibrosis [53]. In response to persistent injury, fibrotic macrophages release factors that activate fibroblasts, leading to ECM deposition and fibrosis progression [56]. TGF-β can also induce MMT in return, promoting the expression of profibrotic genes in kidney-infiltrating macrophages, ultimately leading to renal fibrosis [57]. Mitophagy regulates fibrosis, and its dysfunction amplifies pro-fibrotic signaling and inflammatory crosstalk in a self-reinforcing loop. Restoring mitophagy or inhibiting its aberrant pathways may enable precise treatment, making its understanding crucial for therapeutic development [15].

3. Regulation of mitophagy and its role in renal fibrosis

3.1. Regulatory mechanisms of mitophagy

Mitophagy eliminates dysfunctional mitochondria and reduces oxidative stress, thereby maintaining mitochondrial quality control and cellular homeostasis [58]. In kidney injury, mitophagy activation is critical. It reduces inflammation and apoptosis while improving energy metabolism, thereby alleviating oxidative stress, diminishing renal damage, and mitigating fibrosis [26]. Understanding mitophagy mechanisms has clinical implications for renal fibrosis treatment. Key pathways include PINK1/Parkin and receptors such as BNIP3, NIX, FUNDC1, and Cardiolipin [59]. These modulatory elements are pivotal in maintaining mitochondrial quality equilibrium and impeding the progression of renal fibrosis (**Figure 1**).

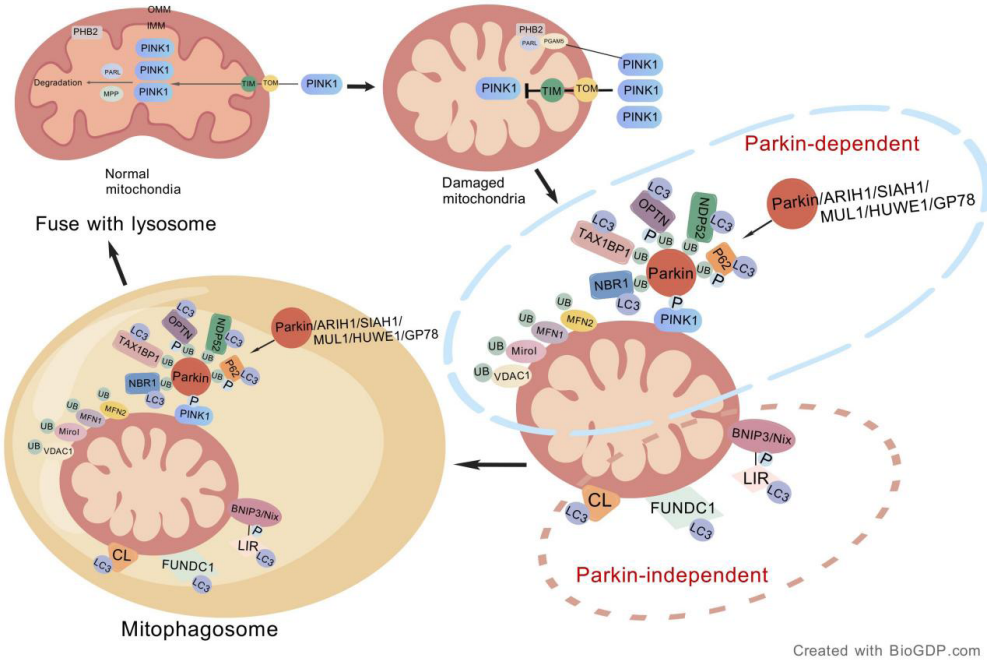

Figure 1. Schematic representation of mitophagy pathways and key regulatory components.

Mitochondrial quality control is essential for cellular health, especially under stress conditions such as membrane depolarization or oxidative damage. One crucial pathway involved in maintaining mitochondrial quality is the PINK1/Parkin-dependent pathway. When mitochondria are stressed, PINK1 stabilizes on the outer mitochondrial membrane and recruits Parkin, which transforms into an active E3 ubiquitin ligase. Parkin then tags damaged proteins on the outer membrane with phospho-ubiquitin chains, which attract autophagy receptors like OPTN and NDP52. These receptors link the damaged mitochondria to autophagosomes labeled with LC3, forming mitophagosomes that ultimately fuse with lysosomes for degradation. In specific contexts, alternative E3 ligases such as ARIH1, SIAH1, and MUL1 can also play a role in this process. Furthermore, there are Parkin-independent pathways that contribute to mitochondrial quality control. Autophagy receptors BNIP3, FUNDC1, and cardiolipin directly interact with LC3 on autophagosomes, promoting mitochondrial fission, stabilizing Parkin recruitment, and regulating mitochondrial dynamics through various phosphorylation and dephosphorylation events. Additionally, cardiolipin can bind to LC3 or Beclin-1, initiating mitophagy in response to mitochondrial damage. Overall, these pathways converge in the lysosomal degradation of damaged mitochondria, highlighting their significance in maintaining cellular homeostasis. Dysregulation of these pathways can lead to impaired mitochondrial quality control, contributing to conditions like renal fibrosis. Understanding and targeting these pathways may hold therapeutic potential for mitigating mitochondrial dysfunction and promoting overall cellular health. This figure was created with BioGDP.com.

3.1.1. The PINK1/Parkin pathway

The PINK1-Parkin pathway crucially regulates mitophagy. Here, PINK1 senses mitochondrial damage, Parkin amplifies the signal, and ubiquitin chains act as effectors to target damaged mitochondria for autophagic clearance [60]. PINK1, encoded by the PARK6 gene, is a protein kinase located in the inner mitochondrial membrane responsible for maintaining mitochondrial function in cells [38]. Parkin, an E3 ubiquitin ligase encoded by PARK2, resides inactively in the cytoplasm. Normally, PINK1 is imported into mitochondria and degraded. Upon damage, prohibitin 2 (PHB2) on the inner membrane inhibits PINK1 degradation, leading to its stabilization and accumulation on the outer mitochondrial membrane [61]. PINK1 accumulation activates Parkin, which ubiquitinates outer mitochondrial membrane proteins. Subsequent PINK1-mediated phosphorylation recruits additional Parkin, amplifying ubiquitin chain formation [62]. Parkin is then activated, ubiquitinating outer mitochondrial membrane proteins such as mitofusins and VDAC1. PINK1 phosphorylates these ubiquitinated substrates, recruiting more Parkin to amplify ubiquitin chain generation. Finally, activated Parkin binds these chains via LIR-domain proteins, enabling interaction with LC3 to initiate mitophagy [63]. These proteins have both ubiquitin-binding domains (UBDs) that recognize ubiquitinated mitochondria and interactions with ATG8 family proteins, mainly including P62, NBR1, NDP52, TAX1BP1, OPTN, TFEB, DUBs [64]. After binding to ubiquitin chains, Parkin promotes the fusion of mitochondria with autophagosomes to form mitophagosomes, which ultimately fuse with lysosomes to initiate mitophagy. In addition to the well-known Parkin, there are many E3 ubiquitin ligases similar in function to Parkin in the regulation of mitophagy, including ARIH1, SIAH1, MUL1, HUWE1, GP78, etc. [59]. The PINK1-Parkin pathway is critical for mitophagy. Though less studied, related E3 ubiquitin ligases are potential therapeutic targets for renal fibrosis. Further research to elucidate their mechanisms could reveal new treatments for mitochondrial dysfunction-related diseases.

3.1.2. Autophagy receptors in mitophagy

(1) BNIP3

BNIP3 and its homolog NIX are crucial proteins found on the outer mitochondrial membrane, both belonging to the BH3-only Bcl-2 family. Their functions in mitophagy are vital, with distinct roles depending on the cell type, n times of mitochondrial stress, these proteins undergo phosphorylation, allowing them to bind to LC3 on autophagosomal membranes and kick-start the process of phagophore encapsulation. Interestingly, BNIP3 and NIX, while sharing a similar structure, have different functions in regulating Parkin-dependent mitophagy [62,65]. BNIP3 promotes mitochondrial fission and stabilizes Parkin recruitment to isolate damaged organelles. Meanwhile, NIX acts as both a Parkin substrate and co-regulator. Following ubiquitination, NIX recruits the selective autophagy receptor NBR1, linking ubiquitinated mitochondria to the autophagic machinery [66]. In Parkin-deficient contexts, BNIP3 and NIX initiate mitophagy independently via non-ubiquitin pathways. Their hypoxia-responsive element-mediated regulation enables adaptive ischemic responses, though efficacy varies across renal cell types due to differential baseline expression.

(2) FUNDC

FUNDC1, an outer mitochondrial membrane protein, regulates mitophagy. Its three functional domains—N-terminus, transmembrane region, and C-terminus—mediate the selective degradation of damaged mitochondria [67]. The N-terminus of FUNDC1 contains an important region called the LC3 interaction region (LIR) that allows it to interact with LC3B, a key player in initiating mitophagy under hypoxic conditions [68]. FUNDC1-LC3B interaction is regulated by phosphorylation dynamics. Under basal conditions, Src kinase and CK2-mediated phosphorylation prevents FUNDC1-LC3 binding, thereby inhibiting mitophagy [69]. ULK1 phosphorylates FUNDC1 at distinct sites to promote LC3 binding and mitophagy. Conversely, PGAM5-mediated dephosphorylation in response to hypoxia or depolarization also activates mitophagy [70]. The phosphorylation status of FUNDC1 modulates its interaction with mitochondrial dynamics proteins like Drp1 and Opa1. This regulates mitochondrial fission, thereby influencing the progression of mitophagy [69,71]. Moreover, under conditions of hypoxia or mitochondrial membrane potential loss, USP19 can promote the deubiquitination of FUNDC1, leading to mitochondrial fission and subsequent mitophagy [59]. Overall, Phosphorylation, dephosphorylation, and deubiquitination of FUNDC1 critically regulate mitophagy and cellular mitochondrial homeostasis.

(3) Cardiolipin (CL)

CL is a phospholipid found in the inner mitochondrial membrane (IMM), distinguished by its unique structure of a glycerol backbone connected to two phosphatidyl groups [72]. Cardiolipin is essential for mitochondrial quality control and morphology, with its location dictating function. At the inner membrane, it cooperates with OPA1 to promote fusion, maintaining normal structure. During stress, cleaved S-OPA1 helps identify damaged mitochondria for mitophagic removal [73]. Impaired by agents like rotenone, mitochondria externalize cardiolipin to the OMM, where it binds LC3 to mark damaged organelles for cardiolipin-mediated mitophagy [74]. Additionally, Cardiolipin interacts with Beclin1 to jointly regulate mitophagy within cells [75].

New research has uncovered a network of autophagy receptors that play a crucial role in regulating mitophagy, including PHB2, autophagy/Beclin-1 regulator 1 (AMBRA1), FK506-binding protein 8 (FKBP8), BCL-2 family member MCL-1 and BCL2L13 [76–78]. These receptors interact with LC3 to regulate mitophagy.

Targeting these mechanisms may advance renal fibrosis treatment and improve kidney health.

3.2. Mitophagy and renal fibrosis

3.2.1. Mitochondrial homeostasis affects kidney function

Renal fibrosis is characterized by inflammatory cell infiltration, fibroblast activation and proliferation, extracellular matrix deposition, tubular atrophy, and microvascular rarefaction [4]. Within this harmful environment, it is common to observe mitochondrial dysfunction [79]. Kidneys eliminate metabolic waste via glomerular filtration and tubular reabsorption. Energy-intensive active transport requires efficient aerobic respiration, necessitating robust mitochondrial homeostasis and quality control for normal renal function [80]. Preserving mitochondrial integrity is therefore essential for renal health.

Mitochondrial dynamics, fission, fusion, and mitophagy maintain mitochondrial quantity and quality essential for cellular homeostasis [81]. Mitophagy serves to eliminate dysfunctional or excess mitochondria, ensuring that the optimal number is maintained within the cell [82,83]. Strikingly, mitochondrial fission is a key player in this process [84]. Regulated by DRP1 and its receptor proteins, such as Mff, Fis1, and Mid49/51, fission is essential for mitophagy to occur effectively [70]. During stress, DRP1 recruits to mitochondria to mediate fission. Inhibiting fission genetically or pharmacologically impairs mitophagy, underscoring its essential role in this process [85]. Similarly, in the renal IRI mouse model, pharmacological inhibition of fission inhibits renal IR-induced mitophagy in renal tubular cells [15]. Notably, in renal fibrosis, mitophagy-related factors including MFN2 and Parkin are downregulated, accelerating disease progression [9]. Mitophagy modulates extracellular matrix composition in mesangial cells by promoting intracellular collagen-1 degradation [4]. Noteworthy experiments with autophagy inhibitors and inducers have further elucidated the relationship between autophagy and collagen accumulation [86]. Impaired mitophagy in patients with diabetic nephropathy (DN) has been linked to enhanced renal fibrosis due to the failure to clear excessive ECM [87]. Conversely, treatment with trifluoperazine (an autophagy inducer) can also lead to a reduction in TGF-β1-induced collagen accumulation [88]. Mitophagy critically contributes to renal fibrosis pathogenesis. Modulating mitochondrial dynamics and autophagy thus represents promising therapeutic targets.

3.2.2. Mitophagy regulates inflammation to affect renal fibrosis

Inflammation plays a critical role in the development and progression of chronic kidney disease by activating fibroblasts and triggering tissue remodeling and repair which ultimately leads to fibrosis [89]. Mitochondria are key in this inflammatory process, acting as the central hub of pro-inflammatory signaling [80]. Damaged mitochondria release mtDNA that activates the NLRP3 inflammasome, leading to the production of pro-inflammatory cytokines and the initiation of inflammatory responses [90]. Mitophagy, a process that degrades damaged mitochondria containing the NLRP3 inflammasome, can inhibit inflammation and regulate immune responses, ultimately improving renal fibrosis [91]. Under renal hypoxia/obstruction, PINK1-Park2-mediated mitophagy activation in tubular epithelial cells protects against fibrosis by reducing mitochondrial damage and mtROS. Its inhibition elevates mtROS, TGF-β1, and p-Smad2/3, exacerbating fibrosis, highlighting the pathway's protective role [9]. Elucidating mitophagy's role in chronic kidney disease may inform therapeutic strategies to enhance renal function and slow progression.

3.2.3. Mitophagy regulates inflammation through TGF-β to affect renal fibrosis

Hypoxia-induced ROS in fibroblasts significantly impacts extracellular matrix synthesis, secretion, and

degradation [92]. In CKD, mitochondrial dysfunction elevates mtROS, which upregulates TGF-β1 and activates the NLRP3 inflammasome. TGF-β1 promotes EMT and fibrosis via Smad signaling while also regulating the NF-κB pathway and NLRP3 to drive inflammation, collectively accelerating renal fibrotic progression [93]. Mitochondria-targeted antioxidants such as MitoQ enhance mitochondrial antioxidant defenses, providing renal protection. For example, MitoQ improves renal function and reduces proteinuria and fibrosis in diabetic mouse models [94]. Additionally, MitoQ inhibits renal p-Smad2/3 signaling, ameliorating mitochondrial dysfunction and renal injury in a UUO-induced CKD model [4]. On the contrary, PDGFR/PI3K/AKT activation increases ROS, inhibits mitophagy, and enhances myofibroblast differentiation, accelerating renal fibrosis progression [93].

3.2.4. Mitophagy regulates inflammation through NLRP3 to affect renal fibrosis

The NLRP3 inflammasome contributes to kidney injury by inducing mitochondrial dysfunction in tubular epithelial cells and macrophages, triggering inflammatory responses that culminate in fibrosis [95]. Hypoxia induces NLRP3 mitochondrial translocation in renal tubular cells, targeting MAVS to increase ROS and dysfunction. NLRP3 also activates TGF-β/Smad signaling independently of inflammasome activity [96]. Furthermore, the NLRP3 inflammasome can activate caspase-9-dependent apoptotic signals, exacerbate kidney injury and promoting renal fibrosis [97]. Mitophagy mediated by Prohibition-2 has shown promising results in reducing mitochondrial dysfunction and NLRP3 inflammasome activation, thereby alleviating renal tubular epithelial cell injury induced by vascular endothelium [98]. Notably, the use of MitoTempo and the NLRP3 inhibitor MCC950 has been shown to significantly reduce the expression of inflammatory factors and alleviate fibrosis [99]. Inhibition of the STING-NLRP3 pathway has emerged as a crucial factor in dampening inflammatory responses and halting renal inflammation, injury, and fibrosis [100]. Recent research has highlighted the role of STING in regulating NLRP3 inflammasome activation by modulating mitochondrial function and ROS levels [101]. UroA ameliorates renal inflammation by inhibiting the STING-NLRP3 pathway and upregulating mitophagy proteins PINK1 and Parkin [102]. Upregulating PINK1/Parkin-mediated mitophagy counteracts STING-NLRP3 pathway-mediated inflammation, potentially delaying renal fibrosis. However, Parkin silencing weakens the inhibitory effect of UroA, these findings highlight mitophagy's importance in reducing renal inflammation and suggest potential therapies for kidney injury and fibrosis [62].

3.2.5. Mitophagy regulates inflammation through other pathways to affect renal fibrosis

Chronic renal inflammation drives fibrosis through mtROS overproduction and NF-κB/MCP-1 pathway activation. This recruits monocytes and activates profibrotic pathways, including plasminogen activator inhibitor-1, which inhibits plasmin and causes ECM accumulation. Subsequently, TGF-β1 induces tubular epithelial cell transformation into myofibroblasts, leading to tubulointerstitial fibrosis [4]. Autophagy proteins Beclin 1 and LC3B regulate caspase-1 activity to modulate immune responses. Their deficiency in macrophages causes mitochondrial accumulation, enhancing caspase-1 activation and inflammation [103]. Conversely, in models of chronic kidney disease (CKD), the levels of mitophagy-related proteins P62, LC3B, PINK1, Parkin, and BNIP3 are significantly lower, suggesting a potential disruption in mitophagy processes [104]. Deficiencies in BNIP3, Pink1, Park2, or Bnip3 exacerbate ischemia-reperfusion renal injury by increasing mitochondrial damage, ROS production, renal tubular apoptosis, and tubulointerstitial inflammation [99,105]. In animal models of renal vascular hypertension, impaired mitophagy, characterized by the absence of Parkin, LC3-II, and ATG5 proteins, is associated with renal fibrosis [106]. Furthermore, in aging mice, renal legumain deficiency and podocyte-specific Atg5 deletion impair

mitophagy, causing mtROS accumulation that drives glomerular lesions, proteinuria, podocyte loss, and interstitial fibrosis [107]. Mitophagy critically maintains renal cellular integrity as a homeostatic mechanism. It defends against chronic inflammation and oxidative stress, offering potential therapeutic targets for renal fibrosis [108].

3.2.6. Mitophagy regulates ROS to affect renal fibrosis

Mitophagy maintains renal health by clearing damaged mitochondria and regulating inflammation. When impaired, it triggers apoptosis, necrosis, pyroptosis, and ferroptosis, leading to epithelial cell loss and kidney disease. In chronic kidney disease, inflammation is closely linked to mitochondrial oxidative stress, as mitochondria are both a primary source and target of reactive oxygen species (ROS). Excessive mtROS disrupts cellular function and can either activate proliferation pathways or induce oxidative stress and cell death, depending on its levels. Therefore, understanding this balance is crucial. Enhancing mitophagy presents a promising therapeutic strategy to preserve mitochondrial function and prevent renal fibrosis [109,110].

Low mtROS levels are physiologically essential; however, stress-induced mtROS elevation triggers inflammation by activating pro-inflammatory genes and disrupting antioxidant defenses [111]. MtROS accumulation causes oxidative damage and cellular dysfunction. In renal ischemia-reperfusion injury, impaired mitophagy enables dysfunctional mitochondria to leak DNA into the cytoplasm, elevating mtROS, triggering inflammation, and perpetuating a cycle of renal injury [112,113]. Mitophagy is essential for proximal tubular function. Autophagy gene deficiency or downregulation impairs renal function and elevates p62 levels, indicating increased oxidative stress [114]. For instance, the downregulation of autophagy genes like PARK2 by microRNA-1224-5p and low expression of BECN1 can inhibit mitophagy, disrupting cellular homeostasis [93]. In UUO-induced renal fibrosis, PINK1 or Parkin deficiency impairs mitophagy, leading to mtROS overproduction and tubular injury that exacerbates fibrosis [114]. In UUO-induced experiments, the absence of PINK1 or Parkin and the use of mitophagy inhibitors (MDIVI) lead to excessive accumulation of abnormal mitochondria in macrophages, accelerating the transformation of macrophages into profibrotic/M2 macrophages and the progression of renal fibrosis. In contrast, the use of mitophagy activators (UMI-77) can activate mitochondrial fission and reduce profibrotic responses in renal tubular epithelial cells [62]. PINK1 deficiency impairs mitophagy, causing dysfunctional mitochondria to accumulate. This exacerbates mitochondrial oxidative stress, which can inhibit respiration and thereby worsen renal fibrosis [59]. Similarly, in renal ischemia-reperfusion injury, ROS and mtDNA damage induce epithelial-mesenchymal transition, contributing to fibrosis. Mitochondrial protection against oxidative stress attenuates this pathological process [115]. MtROS critically drive renal fibrosis; regulating mtROS to activate mitophagy may slow progression and inform therapeutic strategies (**Figure 2**).

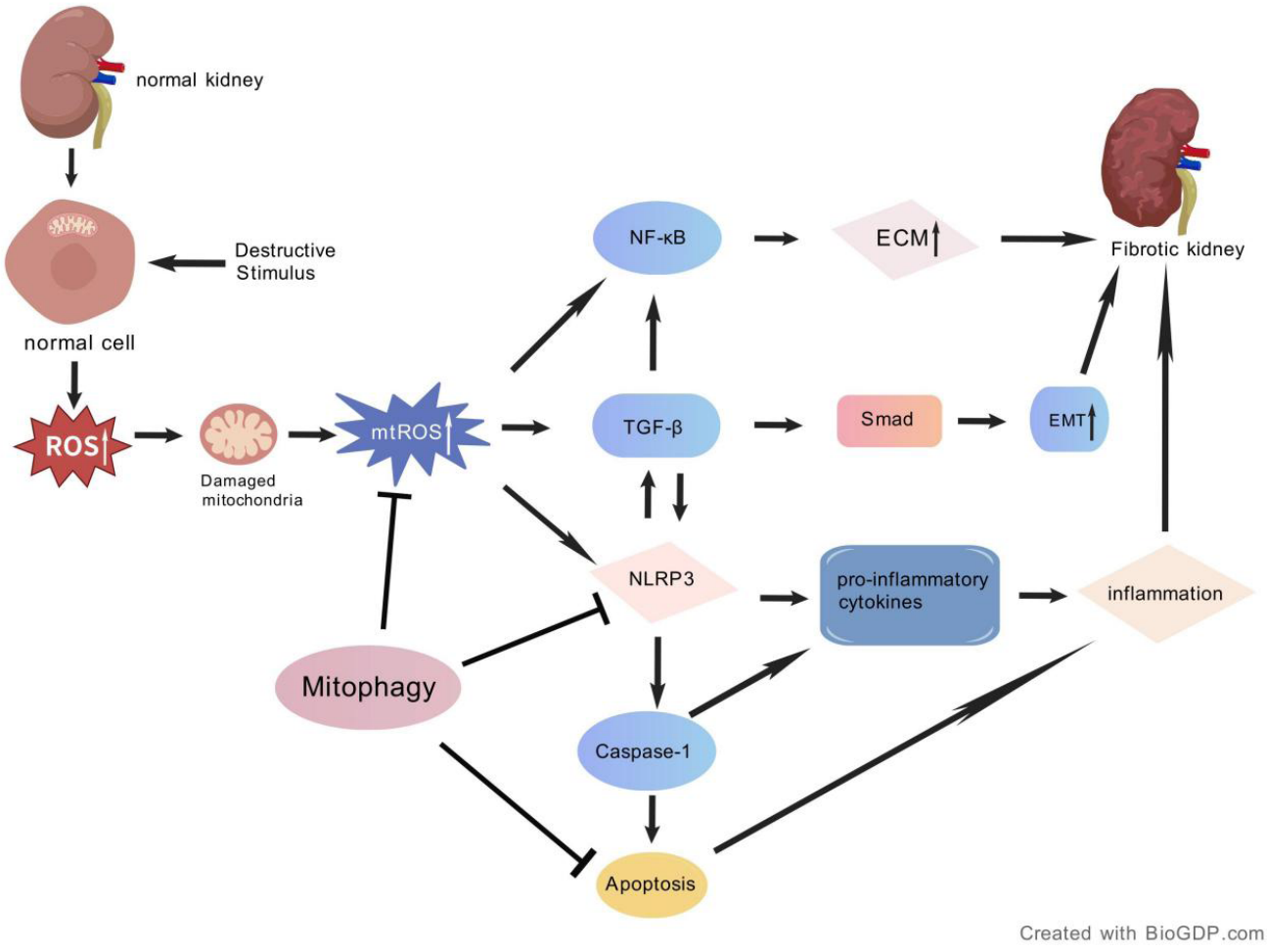

Figure 2. Mitochondrial damage and mitophagy in renal fibrosis.

Mitochondrial dysfunction and impaired mitophagy play crucial roles in the development of renal fibrosis. In a healthy kidney, a balance between fission/fusion dynamics and mitophagy ensures proper mitochondrial function, which is essential for energy production and overall renal health. However, in fibrotic kidneys, various damaging factors such as hypoxia and oxidative stress can disrupt this balance, leading to mitochondrial damage and the excessive production of mitochondrial reactive oxygen species (mtROS). The accumulation of mtROS activates pathways such as the NLRP3 inflammasome and TGF-β/Smad signaling, which contribute to the deposition of extracellular matrix (ECM), tubular atrophy, and microvascular rarefaction. Damaged mitochondria also release mtROS, triggering processes like epithelial-mesenchymal transition (EMT) and inflammation through NF-κB-mediated cytokine production. Impaired mitophagy, characterized by a decrease in key regulators like PINK1, Parkin, and BNIP3, further exacerbates mitochondrial dysfunction and promotes inflammation, apoptosis, and ECM buildup. However, therapeutic interventions that target mitophagy activation or provide antioxidants can help restore mitochondrial quality control, reduce mtROS levels, and suppress detrimental pathways like TGF-β/Smad and NLRP3. Conversely, inhibiting mitophagy can worsen inflammation and fibrosis in the kidney. Overall, understanding the intricate interplay between mitochondrial function, mitophagy, and fibrotic processes is essential for developing targeted therapies to combat renal fibrosis effectively. This figure was created with BioGDP.com.

3.3. Long-term impact of mitochondrial quality control on renal function

3.3.1. The balance of mitochondrial quality control maintains normal renal function

Mitochondrial quality control balances biogenesis with clearance via fusion/fission and mitophagy to maintain optimal function. This is especially vital in energy-intensive organs like the kidneys, which require robust quality control to meet their high metabolic demands [90,116]. Mitochondrial biogenesis plays a key role in this process, involving the replication of mitochondrial DNA and the proliferation of existing mitochondria to generate new mitochondrial mass [117]. The master regulator of mitochondrial biogenesis, PGC1α, controls the expression of various transcription factors necessary for this process, such as NRF1, NRF2, PPARα, ERR1, and YY1 [118]. Conversely, mitophagy functions to eliminate dysfunctional mitochondria, thus maintaining mitochondrial quality.

3.3.2. Mitophagy regulates renal fibrosis by affecting mitochondrial quality balance

Mitochondrial quality control is essential for maintaining cellular integrity under stress. Mitophagy, as its key component, identifies and removes severely damaged mitochondria. In kidney injury, early mitophagy induction clears damaged organelles, preventing ROS accumulation and pro-apoptotic release, thereby reducing tubular cell injury and death. Studies in obstructive kidney injury show that PINK1 or Parkin deficiency causes excessive accumulation of damaged mitochondria and mtROS in macrophages, inducing TGF-β1 expression and worsening renal injury [119]. Furthermore, Mitophagy failure in obstructive kidney injury macrophages increases Rictor expression, promoting profibrotic polarization and extracellular matrix production. Inducing tubular mitophagy prevents mitochondrial DNA release, reduces inflammation, and maintains cellular homeostasis during injury and repair [120]. Mice with TFAM-specific deletion in renal tubules exhibit abnormalities in oxidative phosphorylation (OXPHOS), low ATP levels, cell death, and renal fibrosis [113]. Activating mitophagy can help induce a metabolic switch from OXPHOS to aerobic glycolysis, aiding in tissue repair [121]. Mitochondrial protein quality control is also important in preventing the progression of renal fibrosis. Studies have shown that in renal fibrosis, impaired mitochondrial morphology and structure can be improved by increasing the expression of TNF receptor-associated protein 1 (TRAP1) [62,122]. This improvement results in reduced mitochondrial vacuolization, swelling, increased mtDNA copy numbers, and inhibition of fibrosis-related protein expression in renal tubular epithelial cells, ultimately alleviating renal fibrosis.

3.3.3. Excessive mitophagy may accelerate renal fibrosis

Mitophagy is typically considered a protective cellular response during stress. However, in kidney injury, accumulated mitochondrial damage can overwhelm this process. Excessive activation of PINK1/Parkin-mediated mitophagy, as in UUO rats, impairs mitochondrial function and exacerbates renal injury, ultimately accelerating fibrosis [123]. Research has also found that too much mitophagy can lead to mitochondrial dysfunction, but inhibiting this overactivation can have positive effects on kidney function. In a study involving CKD rats treated with HKL(C18H18O2), it was observed that the levels of BNIP3, Nix, and FUNDC1 proteins were decreased [124]. This treatment improved renal function, reduced fibrosis markers (Col-IV and α-SMA), and attenuated tubulointerstitial fibrosis, suggesting that HKL (C18H18O2) may confer renal protection by modulating excessive mitophagy in CKD rats.

Recent studies underscore the critical role of mitochondrial quality control, particularly fission, fusion, and autophagy dysregulation in renal fibrosis progression [80]. Mitochondrial fusion and fission coordinate mitochondrial quantity and architecture, whereas mitophagy selectively removes damaged organelles to limit harmful ROS overproduction [125]. These interconnected processes constitute a sophisticated quality control system

regulating mitochondrial structure, function, energy supply, and redox homeostasis in renal cells [126]. These findings suggest anti-fibrotic therapies could target mitochondrial quality control. However, challenges persist in promoting physiological mitophagy without impairing general autophagy, and in concurrently addressing mitochondrial and autophagic dysfunction in CKD [62].

4. The potential therapeutic significance of mitophagy

4.1. Therapeutic modulation of mitophagy in renal fibrosis: mechanisms and clinical prospects

Mitochondrial dysfunction critically contributes to renal injury and impaired repair. Targeting mitochondrial quality control mechanisms, particularly mitophagy, represents a promising therapeutic strategy for maintaining renal function and cellular viability [93]. Promoting mitophagy exerts antifibrotic effects on tubular cells and macrophages, thereby aiding renal repair. Furthermore, it improves mitochondrial health and reduces fibrosis in animal models, suggesting therapeutic potential. Current research therefore targets pathways like PINK1/PARK2 and BNIP3 to develop mitophagy-based interventions. Ultimately, these strategies may offer new treatments for renal fibrosis [127] (**Table 1**).

Table 1. The role of mitophagy-related pathways and regulatory mechanisms in renal fibrosis

Pathway/ Mechanism	Key Molecules/ Regulatory Nodes	Mechanism of Action	Interventions/ Drugs	Effects/Mechanism	Ref
PINK1/Parkin	PINK1, Parkin, AMPK, NR4A1-p53	Activates mitophagy to clear damaged mitochondria; AMPK-PINK1-Parkin axis improves mitochondrial dynamics	Metformin, Pioglitazone, UMI-77, Melatonin	Reduces mtROS, inhibits TGF-β/ Smad and NLRP3 pathways, alleviates fibrosis	[9,128–144]
BNIP3/Nix	BNIP3, NIX, HIF-1	Hypoxia-induced HIF-1 upregulates BNIP3/Nix, binding LC3 to initiate mitophagy; BNIP3 inhibits Opa1 and promotes Drp1-mediated mitochondrial fission	COPT, gene knockdown (UUO model)	Reduces mtROS, inhibits NLRP3 inflammation, delays fibrosis; Controversy: Partially maintains mitochondrial homeostasis indirectly via PPAR-α	[61,64–66,145]
FUNDC1	FUNDC1, ULK1, PGAM5, Drp1, Opa1	Hypoxia triggers FUNDC1 dephosphorylation (regulated by ULK1/PGAM5) to bind LC3; balances mitochondrial fission/fusion via Drp1/ Opa1 interaction	USP19 activators, hypoxia inducers (FCCP)	Promotes mitophagy, alleviates oxidative stress and fibrosis	[67–71]
Cardiolipin (CL)	CL, LC3, Beclin1	CL translocates to OMM upon mitochondrial damage, binding LC3 and Beclin1 to regulate autophagy	Rotenone,CCCP (mitochondrial stressors)	Clears damaged mitochondria, reduces ROS and inflammation	[72–75]
NLRP3 inflammasome	NLRP3, mtROS, MAVS, STING	mtROS activates NLRP3 to promote IL-1β/IL-18 secretion; STING pathway exacerbates inflammation	MCC950 (NLRP3 inhibitor),UroA (STING inhibitor)	Suppresses inflammasome activation, reduces pro-fibrotic factors	[1,95–102]
Mitochondrial dynamics	Drp1, Mff, Fis1, Opa1, MFN2	Drp1-mediated fission promotes mitophagy; MFN2 downregulation impairs fusion, increasing fragmentation	Drp1 inhibitors (Mdivi-1), MFN2 activators	Balances fission/fusion to maintain mitochondrial homeostasis	[70,82–86]
ROS Regulation	mtROS, MitoQ, MitoTEMPO	mtROS activates TGF-β/Smad and NF-κB pathways; antioxidants target ROS clearance	MitoQ, SS-31, MitoTEMPO	Improves mitochondrial function, inhibits oxidative stress and ECM deposition	[4,94–115]
ECM degradation	Beclin1, LC3B, Collagen-1	Autophagy deficiency leads to collagen-1 accumulation; autophagy inducers enhance ECM degradation	Trifluoperazine (autophagy inducer)	Reduces glomerulosclerosis and interstitial fibrosis	[4,87–89]
Other receptors	PHB2, AMBRA1, FKBP8, BCL2L13	Bind LC3 to mediate mitophagy and clear damaged mitochondria	PHB2 overexpression, Vitamin D3	Protects tubular epithelial cells, mitigates mitochondrial dysfunction	[57–59,76–79]

4.2. PINK1/Parkin pathway of mitophagy in renal fibrosis

The PINK1/Parkin pathway is implicated in mitophagy and renal fibrosis. UUO model studies demonstrate that Pink1 or Park2 deletion increases mtROS and mitochondrial damage, culminating in renal fibrosis [128]. Additionally, PINK1 promotes mitochondrial dynamics and metabolism, thereby alleviating fibrosis and enhancing the therapeutic efficacy of transplanted mesenchymal stem cells in CKD [129]. Researchers have also discovered that Pioglitazone can boost the expression of PINK1, activate mitophagy, and protect MSCs from mitochondrial dysfunction induced by the uremic toxin p-cresol (PC) [130]. Furthermore, other studies have demonstrated that mitophagy activators such as UMI-77 and the LKB1 activator PA-S14 can help reduce fibrotic responses in renal tubular epithelial cells by enhancing mitophagy in UUO mice [131,132]. Research shows that Tongluo Yishen Decoction alleviates renal fibrosis in UUO mice by downregulating Pink1/Parkin, reducing oxidative stress, and modulating mitophagy to improve mitochondrial dynamics [133]. These diverse findings underscore various potential therapeutic strategies for addressing renal fibrosis.

In diabetic kidney disease models, PINK1 deficiency impairs mitophagy, exacerbates mitochondrial dysfunction, and aggravates hyperglycemia-induced renal scarring [134]. In diabetes, sustained renal ATP production is essential for maintaining the glucose gradient; therefore, ATP deficiency can damage proximal tubular epithelial cells [135].The extent of ATP depletion directly correlates with the severity of renal PTEC injury, making it a pivotal factor in the development of kidney damage [4]. Metformin, an AMPK activator, stimulates mitophagy via the AMPK-PINK1-Parkin pathway, thereby reducing mitochondrial damage, ROS production, and renal tubular fibrosis in diabetic patients [136]. The Chinese medicine Qingre Xiaozheng Yiqi enhances PINK1/Parkin-mediated mitophagy, thereby improving renal fibrosis [137]. High glucose inactivates NR4A1-p53 signaling, enhancing Parkin transcription, mitophagy, and renal protection [138]. Glis1-regulated PGC1-α plays a critical role in the standard PINK1/Parkin-associated mitophagy, facilitating Parkin's movement to the mitochondria [139]. Melatonin has shown promise in alleviating renal fibrosis in diabetic mice by activating this pathway, which in turn restores mitochondrial function [140]. Multiple therapies mitigate diabetic nephropathy tubular injury by enhancing mitophagy. These include the MAM component PACS-2 and agents such as Finerenone and MitoQ [141–145]. Their effects highlight the central role of the PINK1-Parkin pathway and mitophagy receptors. Ultimately, modulating these pathways to preserve mitochondrial integrity represents a promising strategy for managing renal fibrosis.

4.3. BNIP3/Nix mediated mitophagy in renal fibrosis

Targeting BNIP3-mediated mitophagy represents a promising therapeutic strategy for renal fibrosis. UUO mouse studies demonstrate that BNIP3 knockdown exacerbates mitochondrial damage, NLRP3 inflammation, and fibrosis, whereas COPT-induced BNIP3 activation reduces mtROS, fibrosis markers, and apoptosis, thereby ameliorating renal injury in CKD [146]. Furthermore, BNIP3 activation also triggers PPAR-α signaling within mitochondria to sustain mitochondrial homeostasis. This process thereby suppresses mtROS, inflammatory responses, and fibrotic marker expression, slowing renal fibrosis progression. These findings underscore the complex interplay between BNIP3, mitophagy, and mitochondrial function, revealing valuable therapeutic targets [147]. Despite controversy regarding BNIP3/Nix in renal fibrosis, further mechanistic research is warranted. Ultimately, targeting this pathway holds significant promise for mitigating mitochondrial damage and tubular fibrosis.

4.4. NLRP3 pathway of mitophagy in renal fibrosis

NLRP3 inflammasome activation aggravates renal fibrosis via increased ROS. In UUO models, NLRP3 deficiency conversely enhances mitochondrial autophagy, suggesting a regulatory link [148]. HIF1α-BNIP3-mediated mitophagy mitigates renal fibrosis by suppressing mitochondrial ROS and NLRP3 inflammasome activation [1]. Furthermore, Tenuigenin alleviates tubulointerstitial fibrosis in UUO mice by inhibiting NLRP3 assembly, thereby enhancing mitophagy [149]. Targeting NLRP3 inhibition to protect mitochondrial function emerges as a viable strategy to mitigate fibrosis and preserve renal health.

4.5. Nrf2 pathway of mitophagy in renal fibrosis

Nrf2 restores mitophagy and mitochondrial dynamics balance in renal tubular cells, offering novel therapeutic strategies for CKD in animal models [143]. The natural Nrf2 activator Farrerol enhances renal tubular mitophagy via the Nrf2/PINK1 pathway, thereby eliminating damaged mitochondria and alleviating oxidative stress, inflammation, and fibrosis [150]. Furthermore, Metformin inhibits NF-κB via PP2A activation in human renal tubular cells, while targeting DRP1 and NEAT1 improves mitochondrial function under hyperglycemic conditions [136,151]. Furthermore, both PHB2 overexpression and 1,25-dihydroxyvitamin D3 mitigate ANG II-induced mitochondrial dysfunction in renal cells [60,98]. Collectively, these findings suggest Nrf2 represents a promising therapeutic target for renal fibrosis.

4.6. Other potential therapeutic approaches related to renal fibrosis improvement

Mitophagy protects kidneys against age-related inflammatory stress, whereas autophagy deficiency exacerbates age-dependent tubular injury and renal degeneration [97]. Optic nerve phosphatase upregulation enhances mitophagy in high glucose-exposed renal tubular cells, thereby reducing cellular senescence, mtROS accumulation, and NLRP3 inflammasome activation [152]. GLIS1 regulates mitochondrial quality control via PGC1-α transcription, thereby maintaining cellular homeostasis and attenuating aging-related renal fibrosis and senescence [139]. Moreover, NAD+ precursor nicotinamide mononucleotide (NMN) supplementation increases mitochondrial density and renal SIRT1 activity in aging mice, thereby ameliorating renal fibrosis [120]. These findings emphasize that mitophagy counteracts renal tubular senescence, suggesting its potential as a therapeutic approach for age-related fibrosis.

Recent advances in intercellular communication highlight mitochondrial transfer as a potential replacement for dysfunctional mitochondria [153]. Studies have demonstrated that this process can play a protective role in various organs and is particularly relevant in the context of fibrosis [154]. Mesenchymal stem cells (MSCs) have been identified as key players in facilitating the transfer of mitochondria to recipient cells through tunneling nanotubes (TNTs) [155]. Additionally, renal scattered tubular cells (STC-like cells) have shown the ability to repair damaged tubular epithelial cells (TECs) and reduce interstitial fibrosis by transferring functional mitochondria via extracellular vesicles (EVs) [156]. Furthermore, the transplantation of amniotic fluid stem cells (AFSCs) overexpressing Sirt3 has been found to maintain mitochondrial homeostasis, promote glomerular survival, and reduce renal fibrosis by activating mitophagy [153]. The role of megalin, a cell-surface endocytic receptor, in regulating mitochondrial function through extracellular signals has also been highlighted in recent research [157]. In conclusion, mitochondrial transfer represents an innovative therapeutic approach that holds promise for mitigating renal fibrosis and improving overall organ health.

5. Summary

Due to its high energy demands, the kidney is particularly susceptible to mitochondrial dysfunction, which compromises mitochondrial integrity and metabolism, leading to oxidative stress and toxic compound accumulation. This dysfunction consequently drives cell death, inflammation, fibrosis, and renal failure. Therefore, regulating mitophagy to clear damaged mitochondria is crucial for reducing oxidative stress and halting fibrosis, offering a potential therapeutic strategy for preserving kidney health.

Mitophagy has emerged as a promising therapeutic target for renal fibrosis. Key regulatory pathways include PINK1/Parkin, BNIP3, FUNDC1, and NLRP3. The canonical PINK1/Parkin pathway initiates mitophagy by promoting mitochondria-autophagosome binding, forming mitophagosomes for lysosomal degradation. Therapeutic strategies encompass upregulating Pink1/Park2, enhancing Parkin transcription, and activating PINK1/Parkin signaling to reduce mtROS, TGF-β1 expression, and Smad2/3 phosphorylation in tubular epithelial cells. Additionally, certain traditional Chinese medicine decoctions modulate mitochondrial dynamics, decrease Pink1/Parkin levels, alleviate oxidative stress, and regulate mitophagy, thereby ameliorating renal fibrosis in experimental models. Maintaining oxidative and inflammatory balance through mitophagy is key to delaying renal fibrosis. Ubiquitin-independent receptors like BNIP3, NIX, and FUNDC1 facilitate this process. Targeting BNIP3 engages both mitophagy and alternate pathways to slow fibrosis, while FUNDC1 promotes fission via deubiquitination/dephosphorylation, improving outcomes. Furthermore, FUNDC1 activation can mitigate NLRP3-mediated inflammation and enhance renal function. Alternative strategies, such as NLRP3 inhibitors or Nrf2 activators, also show promise in activating renal mitophagy and delaying fibrosis progression. Emerging avenues like mitochondrial transfer via nanomaterials or stem cells offer potential but require further refinement. Therefore, ongoing research is essential to translate these mitophagy-based therapies into effective clinical applications.

Modulating mitophagy to protect mitochondrial function in renal fibrosis is gaining traction. Although mitochondria-targeting agents, including tenuigenin, metformin, montelukast, melatonin, and certain traditional Chinese medicines show promise, clinical translation remains limited due to inadequate animal models and drug interaction uncertainties. Rigorous human trials are essential to validate these targeted drugs' efficacy and safety. Moreover, current research is primarily centered on tubular cells, creating knowledge gaps regarding mitochondrial pathology in other renal cell types. Future studies should therefore broaden their focus to investigate mitochondrial quality control across diverse renal cell types in fibrosis progression. While mitophagy activation is increasingly understood, further research into specific regulators, metabolic states, and pathway crosstalk is needed. Despite its complexity, modulating mitophagy remains a highly promising therapeutic strategy against renal fibrosis.

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