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Research advances of mitochondrial autophagy in renal diseases

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Abstract: *Kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD), are increasing in incidence and prevalence, with poor prognosis and high cost, which is a global concern[1]. Mitochondrial damage and dysfunction are involved in the development of renal diseases, and the disorder of mitochondrial homeostasis may lead to microvascular system damage, inflammation[2], fibrosis and renal failure. Recent studies have shown that mitochondrial autophagy, as an important part of maintaining mitochondrial homeostasis, can promote the clearance of diseased mitochondria and the regeneration of healthy mitochondria[3]. Therefore, this paper reviews the regulation mechanism and characteristics of mitochondrial autophagy in renal diseases, and provides new ideas and theoretical basis for the prevention and treatment of renal diseases.*

Keywords: *Autophagy, Mitophagy, kidney, renal disease*

1. Overview of Mitophagy

Mitochondria are organelles that generate energy, maintain cell redox and energy homeostasis[4], and are the main source of intracellular oxidative stress [5]. It is especially important in the metabolically active organs such as brain, heart, kidney and muscle. The kidney is one of the organs with the highest mitochondrial density [6]. From the perspective of mitochondrial density and oxygen consumption, the kidney is second only to the heart, consuming 7% of the daily ATP energy consumption of the human body [7]. This is because it takes high energy to reabsorb about 70% of the solute load and excretion filtered by glomerulus, oxidative stress increases, inflammation is decoupled from ATP oxygen consumption, which promotes mitochondrial damage and triggers mitochondrial autophagy, all of which are related to kidney diseases [8]. Autophagy is a process in which autophagy sends substances in cytoplasm to lysosomes for degradation, which can decompose cytoplasmic components for clearance and reuse [9], and can be divided into macrophage autophagy, micro autophagy and partner-mediated autophagy. The autophagy of renal tubules is the key factor to determine the prognosis of kidney [8], mainly in the proximal tubule, because the damage of renal tubules mainly occurs in the proximal part. Mitochondrial autophagy is a selective autophagy, which can remove damaged mitochondria, promote the regeneration of healthy mitochondria, maintain the functional stability of mitochondria [10], participate in regulating the inflammatory response and oxidative stress level of the body [11], and play an important role in organ level development, aging, apoptosis and diseases [12]. According to the classical process of mitochondrial autophagy, it can be divided into three steps: autophagy vesicle formation, damaged mitochondria recognition and mitochondrial autophagy formation, and mitochondrial autophagy combined with lysosomes and degraded. In short, mitochondrial dysfunction will lead to energy crisis, leading to different types of cell death (necrosis, apoptosis, scorching and iron death), affecting cell calcium level and redox state [6]. Generally speaking, mitochondrial defects in renal tubules will lead to epithelial atrophy, inflammation or cell death, which will lead to the development of renal diseases.

Maintaining mitochondrial homeostasis by balancing mitochondrial biosynthesis and eliminating damaged mitochondria is a key determinant of cell function. Damaged mitochondria can be selectively

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removed by a specific form of autophagy, which is called mitochondrial autophagy [13]. Mitochondrial autophagy is a highly selective autophagy method, which aims to remove damaged and redundant mitochondria and maintain the stability of intracellular environment. It is an important mechanism of mitochondrial quality control and an important way to maintain mitochondrial function and health.

2. Regulatory mechanism of Mitophagy in renal diseases

Different from other diseases, mitochondrial autophagy has its own characteristics in kidney diseases. Studies have found that mitochondrial autophagy can remove damaged and dysfunctional mitochondria, so the activation of mitochondrial autophagy has a protective effect on the kidney [14]. At present, there are four recognized signal pathways: PTEN-induced putative kinase 1 (PINK1)/Parkin, BINP3/NIX, FUNDC1, Beclin1 and cardiolipin, among which PINK1/Parkin is the research hotspot. This paper introduces the specific regulation mechanisms of these four signal pathways.

2.1 PINK1/Parkin signal path

At present, the research on mitochondrial autophagy mostly focuses on PINK1-PRKN pathway [15], which is also a classic way to regulate mitochondrial autophagy. PINK1, a serine/threonine kinase, is a molecular receptor of damaged mitochondria, which can be degraded by protease in mitochondrial inner membrane or matrix, and also plays an important role in this process [16]. Parkin mainly mediates substrate ubiquitination and regulates protein degradation and signal transduction. PINK1/Parkin can affect the quality control of intracellular mitochondria through the phosphorylation of mitochondrial adaptor protein mediated by PINK1 and the degradation of proteasome mediated by Parkin, thus affecting the movement of intracellular mitochondria, finally promoting the occurrence of mitochondrial autophagy, and then clearing the damaged mitochondria. In a word, PINK1/Parkin is the key signal pathway of mitochondrial quality control, and plays an extremely key role in mitochondrial autophagy.

2.2 BNIP3/NIX signal path

BNIP3 and NIX are located in the outer membrane of mitochondria. Under the condition of ischemia and hypoxia, BNIP3 induces autophagy of mitochondria in cells through the following ways [17]: BNIP3 can compete with autophagy core protein Beclin1 to bind Bcl-2 through its BH3 domain, and then induce Beclin1 to release, and free Beclin1 will activate mitochondrial autophagy; BNIP3 has a LIR sequence at the N-terminal, which can recognize and directly bind to autophagy membrane protein microtubule-associated protein I light chain 3(LC3), thus inducing mitochondrial autophagy. Therefore, BNIP3/NIX signaling pathway also plays an important role in mitochondrial autophagy.

2.3 FUNDC1 signaling pathway

FUNDC1 is located on the outer membrane of mitochondria, which is a key receptor for regulating mitochondrial autophagy and a key membrane protein for mitochondrial quality control. FUNDC1 contains three transmembrane domains and one N-terminal, which can interact with LC3 to activate mitochondrial autophagy. Studies have confirmed that gene expression can be up-regulated or down-regulated by knocking out the motifs in the interaction region of FUNDC1 or LC3, which indicates that FUNDC1 can induce mitochondrial autophagy. Under normal oxygen condition, Func1 exists in the outer membrane of mitochondria in the form of "closed loop" and is phosphorylated by tyrosine kinase at position 18 of tyrosine. At this time, the affinity between Func1 and LC3 is low, but under the condition of ischemia and hypoxia, the affinity between Func1 and LC3 is significantly increased, and Func1 can be activated by serine/threonine protein phosphatase through dephosphorylation, thus inducing mitochondrial autophagy. Based on the above research, FUNDC1 signaling pathway also plays an important role in mitochondrial autophagy.

2.4 Beclin1 signal path

Beclin1 gene is an autophagy related gene and autophagy regulatory protein, which plays an important role in mitochondrial autophagy. Studies have confirmed that Beclin1 not only participates in autophagy of cells, but also participates in autophagy of mitochondria. It was found that the expression level of Beclin1 in tissues and organs of IRI changed with the degree of IRI. Studies have shown that Beclin1 not only plays an important role in mitochondrial autophagy mediated by BNIP3-NIX signaling

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pathway, but also can interact with PINK1 and play a certain role in mitochondrial autophagy. In addition, some studies have confirmed that Beclin1-Parkin signaling pathway plays a protective role in the process of spinal cord ischemia-reperfusion injury by inducing mitochondrial autophagy. Therefore, Beclin1 signaling pathway also plays an important role in mitochondrial autophagy. Autophagic vesicles recognize damaged mitochondria and mediate their targeted clearance, which plays an important role in the regulation of mitochondrial autophagy [18].

3. The role of Mitophagy in renal diseases

Mitochondria are very important to the activity, function and viability of eukaryotic cells. Mitochondrial dysfunction involves the pathogenesis of acute kidney injury (AKI) and chronic kidney disease (CKD) [17].

3.1 Acute kidney injury

Acute renal injury is a common clinical disease, which leads to the rapid decline of renal function in a short time due to various reasons, mainly related to mitochondrial dysfunction, oxidative stress and inflammation. Renal tubular epithelial cells are rich in mitochondria, so maintaining the normal function of mitochondria is very important for renal function. In AKI, HK-2 cells are the main part of injury and death. Mitochondria break and swell, matrix vacuoles form, and mitochondrial crista disappears. Defective mitochondria are removed by mitochondrial autophagy to maintain cell integrity [19]. Studies have pointed out that abnormal mitochondrial autophagy is an important mechanism leading to the pathogenesis of AKI, and targeted intervention is expected to improve the progress of AKI [20]. In the early stage of AKI, mitochondrial autophagy is activated through PRKN-dependent signaling pathway, which removes damaged mitochondria from the electron transport chain (ETC), alleviates local inflammation and oxidative damage, and thus protects the kidney [14].

In the acute renal injury model caused by ischemia-reperfusion injury [21], PINK1-Parkin-mediated mitochondrial autophagy is activated, which protects RTEC by reducing mitochondrial injury, ROS production and inflammatory reaction. The experimental results showed that the pathological process of oxygen glucose deprivation-reoxygenation, that is, ischemia-reperfusion can activate mitochondrial autophagy mediated by PINK1, and the expression of MEG3 in renal cortex and HK-2 cells of IRI mice was significantly higher than that in sham-operated group, suggesting that MEG3 may be involved in the occurrence and development of IRI. At the same time, the down-regulation of MEG3 inhibited the apoptosis of HK-2 cells after IRI. IRI can activate mitochondrial autophagy in HK-2 cells, while inhibiting MEG3 can restore its mitochondrial autophagy activity [22].

Cisplatin is a commonly used chemotherapy drug. Because of its nephrotoxicity, it can induce mitochondrial damage and promote ROS production. Cell necrosis and inflammation in the proximal tubule are signs of cisplatin-induced AKI. Autophagy protects renal tubules from cisplatin by removing mitochondria that produce ROS [2]. Mitochondrial autophagy, as an important part of maintaining mitochondrial homeostasis, can promote the clearance of diseased mitochondria and the regeneration of healthy mitochondria. In the cisplatin-induced AKI model of mice [23], both oxidative stress and mitochondrial damage are related to the decrease of the level of sirtuin 3(SIRT3) in the kidney. Treatment with AMPK agonist AICAR can restore the expression and activity of SIRT3 in mice, improve renal function and reduce renal tubular injury. The results show that SIRT3 has protective effect on AKI, and enhancing SIRT3 to improve mitochondrial dynamics has the potential to improve the outcome of renal injury [23]. At the same time, during the treatment of cisplatin, pink1 and prkn knockout mice showed more serious renal function loss, tissue damage and apoptosis [24]. In cisplatin-induced model, knocking out PINK1 or PARK2 at the same time can cause more apoptosis, mitochondrial dysfunction and tissue damage.

Renal ischemic preconditioning (IPC) induced autophagy in mouse renal tubular epithelial cells, and then inhibited IRI[25]. PINK1 was activated during IPC, and both IPC and BECN1 peptides enhanced mitochondrial autophagy and formed mitochondria and lysosomes at the same time, suggesting that IPC may protect the kidney by activating mitochondrial autophagy.

Sepsis is the main cause of AKI, accounting for 45%-70%, with high mortality. In the mouse model of sepsis induced by lipopolysaccharide (LPS) or cecal perforation, early mitochondrial autophagy is activated, which is mainly mediated by PINK1-PARK2 pathway, among which OPTN is the main adaptor protein, which provides a mechanism for cells to remove damaged mitochondria, minimize cell damage

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and accelerate recovery [26]. The experimental results showed that the decrease of PINK1/PARK2 aggravated the mouse AKI induced by LPS or CLP, while the knock-out of PINK1/PARK2 inhibited mitochondrial autophagy, indicating that PINK1/PARK2 pathway played an important role in mitochondrial quality control, renal tubular cell survival and renal function during septic AKI [27].

After intravenous injection of iodine contrast agent, acute renal injury (CI-AKI) caused by contrast agent is more common, which mostly leads to renal failure and death [20]. Studies have shown that during CI-AKI, mitochondrial autophagy mediated by PINK1-Parkin pathway is activated to protect renal tubular epithelial cells (RTECs) from CI-AKI damage. When PINK1 or PARK2(Parkin) is inhibited, mitochondrial autophagy induced by contrast agent is eliminated. It shows that PINK1-Parkin pathway plays a leading role in mitochondrial autophagy [20]. By reducing the oxidative damage of mitochondrial ROS and DNA, and then inhibiting the activation of NLRP3 inflammatory corpuscles, the apoptosis of RTEC and the protective effect of tissue damage after contrast agent intervention on renal injury in CI-AKI mice can be prevented [28, 29].

With the phenomenon of AKI induced by renal ischemia, sepsis and nephrotoxic drugs becoming more and more common, the incidence and mortality of AKI are gradually increasing. Mitochondria is the energy center of cells, and mitochondrial dysfunction mediates oxidative stress in AKI, impaired fine energy metabolism of renal tubular epithelium, inflammatory reaction and other pathogenesis.

3.2 Chronic kidney disease

CKD is renal insufficiency lasting for more than 3 months, usually accompanied by complications, such as diabetes and hypertension. Unlike AKI, CKD is regarded as an independent, irreversible and progressive pathological state, which inevitably leads to end-stage renal disease (ESRD)[1].

Diabetic nephropathy (DN) often originates from hyperglycemia-mediated microvascular abnormalities. There is sufficient evidence that abnormal mitochondrial homeostasis plays a key role in the progress of diabetic nephropathy. Hyperglycemia leads to excessive ROS production in kidney, which leads to increased oxidative stress, such as impaired linear glutathione transport [30], increased mitochondrial activation of NAD(P)H oxidase (Nox4) ubiquitous in respiratory chain [31], and decreased stability of mtDNA against ROS production and podocyte apoptosis [32], all of which will lead to cell damage and fatal effects related to diabetic complications. Interestingly, hyperglycemia can trigger mitochondrial division, which is mediated by the phosphorylation of Rho-related spiral protein kinase 1(ROCK1)-dependent dynamic protein-related protein 1(DRP1) and its recruitment to mitochondria [32]. These results indicate that mitochondrial dynamics plays an important role in the pathogenesis of diabetic nephropathy[33]. Mitochondrial autophagy mediated by PINK1-Parkin decreased in DKD, and MitoQ can save it to reduce the apoptosis of renal tubular epithelial cells (RTEC). Autophagy or mitochondrial autophagy of DN has changed [34]. Impaired autophagy flow may lead to diabetic neuropathy complications related to extracellular matrix deposition and fibrosis.

Chronic glomerulonephritis is characterized by glomerular filtration barrier dysfunction, which is the main feature of CKD [1]. Recently, DNA-binding zinc finger protein subfamily Kruppel-like factor 6(KLF6) has been identified as a response gene that can induce early injury, and this gene encodes a key transcription regulator of podocyte mitochondrial function under stress [35]. The deletion of podocyte-specific Klf6 decreased the mitochondrial function of mice and increased the susceptibility to FSGS. Similarly, compared with healthy individuals, the podocyte-specific KLF6 expression in FSGS patients was significantly decreased. Studies have shown that KLF6 can prevent mitochondrial damage by enhancing cyt C assembly [36]. As mentioned above, the function of mpv17 is further discussed. More and more evidences show that glomerular sclerosis gene MPV17 and its encoded MPV17 protein are important factors in regulating ROS peroxisome metabolism [37]. Mpv17 was identified as an IMM localization protein in podocytes, and it was found that the loss of MPV17 was related to glomerulosclerosis. Knockout mice develop renal failure in the late stage of their life cycle (9-12 months), and glomerular lesions are caused by toxic oxidative stress and lipid peroxidation adducts. Interestingly, the expression of MPV17 decreased in some glomerular injury models and human FSGS subjects [38]. In a word, the evidence further confirms that MPV17 is very important for mitochondrial homeostasis of podocytes.

Renal fibrosis is a common manifestation of chronic kidney disease. During the development of renal fibrosis, the expression of mitochondrial autophagy in kidney decreased, including in vivo (unilateral ureteral ligation UUO) and in vitro (TGF-β treated HK-2 cells). The expressions of mitochondrial autophagy regulator 2 (MFN 2) and Parkin downstream of PINK1 are down-regulated, while the loss of

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PINK1 or Parkin will aggravate the fiber. PINK1 can phosphorylate specific mitochondrial protein MFN2, and the disappearance of MFN2 specificity will aggravate renal fibrosis, indicating that mitochondrial autophagy protects renal fibrosis through PINK1/MFN2/Parkin pathway [39]. In the case of urinary protein overload, mitochondrial dysfunction activates mitochondrial autophagy mediated by PINK1/Parkin pathway in renal tubular epithelial cells, and autophagy activation can increase adaptive response through mitochondrial autophagy. Knocking out the expression of Parkin can inhibit mitochondrial autophagy [40].

3.3 Rheumatism-related renal damage

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease, which often involves many tissues and organs of the whole body, from arthritis to pericarditis to life-threatening lupus nephritis [41]. Its pathogenesis usually involves the abnormal signal transduction of T and B cells, the production of autoantibodies and the imbalance of cytokine secretion caused by the environment [42]. Studies have shown that mitochondrial autophagy is inhibited in T cells of SLE patients and lupus susceptible mice. As an effective inducer of mitochondrial autophagy, mammalian target protein of rapamycin (mTOR) can improve the severity of diseases and mitochondrial dysfunction by inhibiting MTOR [43]. Studies have shown that up-regulating the expression of miR-155 can inhibit the PINK1/Parkin mitochondrial autophagy pathway by targeting FOXO1, thus increasing oxidative stress damage and apoptosis of podocytes [44, 45]. Therefore, mitochondrial autophagy plays a unique protective role in preventing the progress of SLE and other diseases.

3.4 Hereditary kidney disease

Polycystic kidney disease, PKD) is a common cause of end-stage renal disease [46], and its kidney contains many fluid-filled cysts. At the same time, cyst expansion can lead to local hypoxia in the kidney, thus activating hypoxia-inducible factor -1α(HIF-1α). Hypoxia, apoptosis and mTOR signal transduction are the regulatory factors of posture and the renal characteristics of PKD [47]. HIF-1α can up-regulate apoptosis and autophagy, which proves that autophagy in PKD occurs at a low level and plays a vital role under physiological conditions [48]. At the same time, studies have shown that Beclin-1 regulates the formation and maturation of autophagy, increases in Cy/Cy and cpk kidneys, and plays a pathogenic role in PKD autophagy [49].

3.5 Renal carcinoma

Renal carcinoma is a kind of malignant tumor, second only to bladder cancer, and it ranks second in China's urinary tumor group. The most common pathological type is clear cell renal cell carcinoma (ccRCC). Renal cell carcinoma (RCC), also known as renal adenocarcinoma, originated from malignant tumor of renal parenchyma urothelial cells [50]. Studies have shown that mitochondrial autophagy proteins PINK1 and Parkin participate in the occurrence and development of RCC [51]. In RCC, the expression of mitochondrial autophagy protein PINK1 in tissues is higher than that in normal tissues adjacent to cancer. On the contrary, the expression of mitochondrial autophagy protein Parkin in normal tissues adjacent to cancer is higher than that in cancer tissues, which may affect the occurrence of tumors through oxidative stress caused by ROS and MDA, and play a role in suppressing oncogenes [52].

4. Conclusions

Studies have shown that autophagy plays an important role in the process of renal injury. The autophagy level of renal tissue affects the cellular homeostasis of renal tissue, and abnormal autophagy will aggravate the damage of renal tissue and reduce renal function. Mitochondrial autophagy, as a selective gesture, can remove damaged mitochondria through the degradation and recycling of lysosomes in cells, realize the renewal of mitochondrial organelles, control the quality of mitochondria, reduce the level of ROS, maintain cell homeostasis and inhibit cell damage. Although the activation of mitochondrial autophagy has played a "double-edged sword" effect in some diseases, this mechanism is considered to be beneficial to nephropathy. In the animal model of related nephropathy, a large number of damaged mitochondria accumulate, accompanied by oxidative stress and apoptosis [53]. Therefore, paying attention to the regulatory pathway of damaged mitochondrial recognition is helpful to better understand the pathological mechanism of mitochondrial autophagy in renal diseases. In addition, there are few clinical studies on renal diseases and mitochondrial autophagy at present, so it is still a challenge

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to intervene renal diseases with mitochondrial autophagy as the target and apply it in clinic, and further research is needed in the future.

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