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Research advances of ferritinophagy in renal diseases

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Abstract: *Ferritinophagy is a selective autophagy of cell mediated by a specific cargo receptor NCOA4, which transports intracellular ferritin to lysosome-autophagy for degradation and releases free iron. Ferritinophagy is essential for the regulation of iron homeostasis. However, excessive activation of ferritinophagy can lead to intracellular iron overload ,generates Reactive Oxygen Species by the Fenton reaction of Haber-Weiss cycle, and promotes the occurrence of intracellular lipid peroxidation ,which induces cellular ferroptosis .Recently, the study of ferritinophagy has become an increasingly concerned field, and has been proved to play a crucial role in the pathological mechanisms of a variety of diseases .In this review , we will review the research progress of the role of ferritinophagy in related kidney diseases in order to provide reference for future clinical and scientific research.*

Keywords: *ferritinophagy, NCOA4, ferroptosis, iron homeostasis, kidney disease*

1. Introduction

NCOA4, also named as androgen receptor-associated protein 70 (ARA70), was originally described as a coactivator of multiple nuclear hormone receptors. Mancias at all[1]identified that nuclear receptor coactivator4(NCOA4) as a specific cargo receptor mediating ferritinophagy by proteomic analysis of purified autophagosomes. Thus discovering and naming the concept of ferritinophagy *for the first time*. NCOA4 is consider as a key regulator of ferritinophagy, which transports ferritin(mainly ferritin heavy chain 1)into lysosome-autophagy(autophagosomes)for degradation, resulting in the release of ferritin-bound iron into free iron to regulate the selective autophagy of intracellular iron metabolism. When ferritinophagy is over-activated, excessive intracellular iron deposition induces glutathione (GSH) depletion as well as reduced expression of glutathione peroxidase 4, which leads to the collapse and rupture of cellular membrane structure and ultimately leads to cellular ferroptosis. In recent years, it has been shown that ferritinophagy is involved in the pathological processes of a variety of diseases, including neurodegenerative diseases, metabolic diseases, infectious diseases, cancer and so on. In this study, we will review the potential mechanisms of ferritinophagy, the relationship between ferritinophagy and ferroptosis, and the research progress of ferritinophagy and related kidney diseases, in order to provide new potential therapeutic targets for kidney diseases.

2. The process of ferritinophagy

Ferritinophagy is a process ,in which NCOA4 , as a cargo receptor of ferritin , mediates the transport of ferritin to autophagosomes and promotes the degradation of ferritin into lysosomes to release iron ions, which includes two stages: the formation of the NCOA4-ferritin complex and degradation of ferritin[2].NCOA4 and ferritin are key regulators of ferritinophagy. NCOA4 has both an N-terminus and a C-terminus; the former binds MCM7 to control DNA replication, and the latter binds FTH1, both of which together support ferritin degradation by NCOA4[3, 4]. NCOA4 has two transcription variants: NCOA4α located in the nucleus and NCOA4β located in the cytoplasm[5]. NCOA4α protein is a protein with N- terminal domain and C- terminal domain, in which the C-terminal domain has the binding site of FTH1 and E3 ubiquitin ligase 2 (HERC2), while NCOA4β only shares the N-terminal domain and

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part of the C-terminal domain with NCOA4α[6]. Ferritin is the main form of iron storage protein, which consists of 24 ferritin heavy chain 1(FTH1) and ferritin light chain (FTL) subunits and each ferritin can store up to 4500 iron atoms[7]. It was found that only FTH participated in the process of ferritinophagy due to the difference of surface residues between FTH and FTL. In vitro assays with recombinant with FTH1 and NCOA4 showed that the C- terminal domain of NCOA4 directly interacted with the key surface arginine (R23) of FTH1. The mutant FTH1R23A blocked the interaction between FTH1 and NCOA4 in cells and inhibited the delivery of ferritin to lysosomes, which proved that the direct combination of R23 of FTH1 and C- terminal element of NCOA4 was necessary for ferritin to be delivered to lysosomes through autophagosomes [5]. FTL does not bind to NCOA4, but FTL may also play an important role in the formation of ferritin complexes, the interaction between NCOA4 and ferritin complex, and the degradation of ferritin complexes [5, 8]. NCOA4- ferritin complex can bind to protein microtubule-associated protein 1 light chain 3b (LC3B) like autophagy-related gene (ATG)8, isolate the complex in autophagosomes, and then the autophagy with lysosomes fuse to promote the degradation of ferritin and the release of iron, thus completing the ferritinophagy process[9]. The above process can be blocked by bafilomycin A1, which inhibits the fusion of autophagosomes and lysosomes, thus avoiding the degradation of ferritin and he occurrence of ferritinophagy[10]. It has also been shown that the endosome sorting complex -mediated delivery pathway for NCOA 4 and ferritin is independent of ATG 8, and it has been proved that escort-III endosome pathway mediates the rapid degradation of autophagy receptors, such as NCOA 4, p 62, TAX 1BP 1 and NDP 52 induced by starvation[11]. It can be seen that the lysosomal transport and degradation of ferritin complexes are carried out through multiple pathways, and its specific mechanisms of action need to be further elucidated.

3. Regulatory mechanism of ferritinophagy

3.1 Iron regulates ferritinophagy

The amount of iron released by ferritinophagy is regulated by the level of NCOA4[12], which in turn is strictly negatively regulated by the level of iron in cells. HERC2 is a HECT E3 ubiquitin ligase, which is related to many protein degradations, and may have multiple ubiquitination targets[13].Mancias [1] et al. showed that the content of NCOA4 depends on whether it interacts with another protein called HERC2.Research with the 293T, U2OS, HCT116, and K562 cell lines showed that when the intracellular iron level was high, the C-terminal domain of NCOA4 was recognized by the CUL7 homologous domain of HERC2, which could target the degradation of NCOA4 through the ubiquitin-proteasome system, leading to a decrease in the level of NCOA4 on the autophagosomes, thereby preventing the excessive release of iron from ferritinophagy and ferritin. Conversely, When the intracellular iron level is low, the binding of between HERC2 and NCOA4 was reduced, which results in the increase of NCOA4 levels on autophagosomes, and promotes the ferritinophagy flux to restore the intracellular free iron[5].In addition, elevated iron levels can also inhibit the binding of NCOA4 to ferritin, thus further inhibiting the occurrence of ferritinophagy[14]. It can be seen that NCOA4 level is the core factor of determining ferritinophagy flux and a key regulator of intracellular iron metabolism homeostasis.

3.2 Hypoxia regulates ferritinophagy

HIF is a key transcription factor mediating adaptation to hypoxia, hypoxia-inducible factors (HIFs) consist of HIF-1, HIF-2 and HIF-3[15, 16].Most recent studies have shown that NCOA4 is regulated by hypoxia-inducible factor (HIF). Stabilized HIF increases NCOA4 mRNA. However, this effect is attenuated when HIF-1α and HIF-2α are knocked down Meanwhile, HIF-1α and HIF-2α can bind to the region containing the NCOA4 mRNA promoter that contains the HRE motif [17].Moreover, the NCOA4 expression decrease results from impaired transcriptional regulation under hypoxia combined with its mRNA degradation by micro RNA 6862-5p, which is controlled by c-jun N-terminal kinase (JNK). FTMT and ferritin heavy chain (FTH) cooperated to protect macrophages from ferroptosis under hypoxia[3]. This suggests that the HIF-NCOA4 axis mediates ferritinophagy regulation.

3.3 Lysosome regulates ferritinophagy

At present, the mechanism of NCOA4-ferritin trafficking to the lysosome is unclear with evidence for both classical ATG8-dependent autophagic delivery to the lysosome and a non-classical ESCRT-mediated delivery system. In this pathway, ferritin transport involves the NCOA4 binding partners TAX1BP1, VPS34, ATG9A, and the ULK1 /2-FIP200 complex[11]. Contribution of each degradation

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pathway may be different according to cell type or even type of iron deprivation, e.g., one report suggests that ferroportin-mediated iron export promotes ferritin degradation by the proteasome while iron chelation agents induce degradation in the lysosome[18].Although the multiple mechanisms of ferritin degradation have been reported, it may suggest an environment-dependent pattern of ferritin turnover; NCOA4-mediated mechanism seems to be the main way of ferritin degradation.

3.4 Autophagy regulates ferritinophagy

Autophagy plays an important role in ferritinophagy, and inhibition of autophagy affects NCOA4-mediated ferritinophagy. In MEFs and HT1080 cells, NCOA4 and LC3B were co-localized, but the expression level of NCOA4 decreased. After autophagy inhibitor or genetic treatment, the decrease of NCOA4 level could be inhibited by autophagy inhibitor bafilomycin A1 or ATG3 gene knockout, indicating that autophagy may mediate the degradation of ferritin and NCOA4[19, 20].Yes-associated protein 1 (YAP1) negatively regulates autophagosome formation, and overexpression of YAP1 can also impede the NCOA4 - FTH1 interaction and affect ferritinophagy[21, 22].Moreover, NCOA4 levels increase with autophagy inhibition or ATG7 disruption. NCOA4 levels decrease over time in iron-deficient cells, similar to p62[23]. These findings suggest that autophagy plays a vital role in ferritinophagy.

3.5 HERC2-FBXL5-IPR2 regulates ferritinophagy

HERC2 regulates the steady state level of FBXL5,which catalyzes the ubiquitination and proteasomal degradation of iron regulatory protein 2 (IRP2), thus regulating cellular and systemic iron homeostasis[24] [25]. HERC2 is an FBXL5-associated protein, and Inhibition of the HERC2-FBXL5 interaction or depletion of endogenous HERC2 by RNA interference leads to the stabilization of FBXL5 and a subsequent increase in its abundance[24]. Overexpressed FBXL5 targets ferritinophagy protein 2 for proteasome degradation, and the degradation of IRP2 leads to the decrease of intracellular ferrous content, thereby increasing the iron release flux of ferritinophagy[26].Therefore, the HERC2-FBXL5-IRP2 axis plays important role in NCOA4-mediated ferritinophagy.

3.6 Other mechanisms regulate ferritinophagy

In addition, there are many factors regulating the abundance of NCOA4 and the level of ferritinophagy. ATM dominates the intracellular labile free iron by phosphorylating NCOA4, facilitating NCOA4-ferritin interaction and therefore sustaining ferritinophagy[27]. Inhibition of DNMT-1 alleviates ferroptosis through NCOA4 mediated ferritinophagy during diabetes myocardial ischemia/reperfusion injury[28]. COPZ1 knockdown also led to the increase in nuclear receptor coactivator 4 (NCOA4), resulting in the degradation of ferritin, and a subsequent increase in the intracellular levels of ferrous iron and ultimately ferroptosis. These data demonstrate that COPZ1 is a critical mediator in iron metabolism[29]. NCOA4 was upregulated by ubiquitin specific peptidase 14 (USP14) via a deubiquitination process in damaged neurons, and pharmacological inhibition of USP14 effectively reducing NCOA4 levels to protect neurons from ferritinophagy-mediated ferroptosis[30]. TRIM11 suppresses ferritinophagy through UBE2N/TAX1BP1 signaling in pancreatic ductal adenocarcinoma[31].CIRBP promotes ferroptosis by interacting with ELAVL1 and activating ferritinophagy during renal ischaemia -reperfusion injury[32]. Exosomes derived from vascular endothelial cells antagonize glucocorticoid-induced osteoporosis by inhibiting ferritinophagy with resultant limited ferroptosis of osteoblasts[33]. Small mMRi62 induces ferroptosis in pancreatic ductal adenocarcinoma (PDAC) via lysosomal degrading of NCOAE and Ferritin Heany Chain (FTH1)[34]. So far, multiple levels of ferritinophagy regulatory pathways have been found, it is necessary to further study its regulatory mechanism and the relationship between them. It is believed that focusing on this issue will be of great benefit to the clinical treatment of the disease.

4. NCOA4-mediated ferritinophagy modulates ferroptosis

Ferritinophagy is closely related to ferroptosis, and protein, which induces or participates in ferroptosis, can potentially regulate Ferroptosis pathway. Iron autophagy is closely related to iron death, and related proteins that induce or participate in iron death can potentially regulate the iron autophagy pathway. Ferroptosis is a process of iron-dependent regulated cell death mediated by lipid peroxidation that damages the cell membrane[35, 36]. Ferroptosis is distinct from other identified types of cell death

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(apoptosis, necrosis or autophagy) at the morphological level, with absence of plasma membrane rupture or blebbing, presence of small mitochondria with reduced cristae, and lack of chromatin condensation[35]. In general, the main ferroptosis-inducing event is lipid peroxidation, which is triggered by inactivation of the lipid repairing phospholipid peroxidase, GPx4 (directly by compounds such as RAS-selective lethal 3 (RSL3) and indirectly by blocking cystine metabolism and glutathione synthesis (erastin, sorafenib and BSO)), or by iron accumulation leading to ROS and lipid peroxidation production Given NCOA4-mediated ferritinophagy modulates intracellular iron levels, ferroptosis sensitivity has recently been shown to be affected by NCOA4 level[2, 19]. In cell culture models, NCOA4 depletion decreases intracellular bioavailable iron and thereby decreases sensitivity to ferroptosis-inducing insults. On the other hand, NCOA4 over-expression in cellular models increases ferritinophagy flux and thereby increases sensitivity to ferroptosis. This confirms that synthesized compound 9a directly binds to NCOA4, blocking its binding to FTH1 and thereby reducing iron levels to block ferroptosis[37]. Moreover, knockout of the NCOA4 gene blocked sideroflexin 1 (SFXN1) mediated iron overload in mitochondria, which inhibited ferroptosis [38]. In fact, treatment with sorafenib, a ferroptosis-inducing drug [39, 40], increased NCOA4 expression correlating with its role as mediator of ferroptotic cell death by promoting ferritinophagy and ROS production [41]. While the authors report upregulation of ELAVL1, a transcriptional regulator, as necessary for induction of autophagy/ferritinophagy, it is unclear whether there is a direct relationship between sorafenib, ELAVL1 function, NCOA4 expression levels, and flux through the ferritinophagy pathway [41].Interestingly, in NCOA4 knockout mice, consistent with their iron overload phenotype and elevated basal levels of tissue iron, NCOA4 depletion in mice fed with an iron-rich diet increased expression of GPx4 and SOD, likely due to overloaded FTH1 leading to iron leakage in tissues followed by upregulation of GPx4 and SOD as a compensatory mechanism to cope with oxidative stress[42].In conclusion, this data suggests that iron overload is the initiating link of ferritinophagy triggering ferroptosis. The key to regulating ferritinophagy is to affect its core substance, NCOA4, by regulating the level or hindering its binding to ferritin. In summary, NCOA4-mediated ferritinophagy plays an important role in regulating ferroptosis, mainly by regulating intracellular iron balance and affecting the production of ROS. Future studies are necessary to explore ways that ferritinophagy regulates ferroptosis and to explore intervention drugs targeting ferritinophagy to improve the ferroptosis-related pathological process in various diseases.

5. The role of ferritinophagy in related kidney diseases

5.1 Ferritinophagy and acute kidney injury

Acute renal injury (AKI), previously known as acute renal failure (ARF), is a heterogeneous critical disease with high morbidity and mortality caused by various causes such as ischemia-reperfusion injury, sepsis, nephrotoxic drugs, rhabdomyolysis and urinary tract obstruction[43]. The pathogenesis of AKI is a combination of many factors, including renal endothelial injury, microvascular dysfunction and oxidative stress, all of which will lead to the death of renal tubular epithelial cells. AKI involves a variety of cell death pathways, but its exact molecular mechanism has not been fully elucidated. Previous studies have confirmed that renal tubular epithelial cells participate in acute kidney injury by necrosis, apoptosis, pyroptosis, autophagy and ferroptosis. Recent studies have shown that ferritinophagy occurs in the kidneys of animals from AKI disease models. AKI involves multiple cell death pathways, but the exact molecular mechanisms have not been fully elucidated, and previous studies have demonstrated that renal tubular epithelial cells are involved in acute kidney injury by necrosis, apoptosis, pyroptosis, autophagy, and ferroptosis. Modalities are involved in acute kidney injury. Recently, the presence of iron autophagy has been demonstrated in the kidneys of animals from a variety of AKI disease models. During ischemia–reperfusion injury induced AKI, according to Sui et al[32], CRIBP promotes renal injury in IRI by upregulating ferroptosis, and silencing CRIBP can inhibit the occurrence of ferroptosis in HK-2 cells. Further studies revealed that CIRBP promotes ferroptosis by interacting with ELAVL1 and activating ferritinophagy during renal IR injury. Our results provide experimental evidence that ferritinophagy-mediated ferroptosis is responsible for CIRBP-enhanced renal IR injury. Meanwhile, another study on IRI, Jin et al. [44] showed that STING activated NCOA4-mediated ferritinophagy and promoted the autophagic degradation of ferritin, leading to intracellular accumulation of free iron and subsequent iron-dependent ferroptosis. We demonstrate The regulation of STING on ferroptosis is dependent on its modulation on NCOA4- mediated ferritinophagy. In addition, Su et al. [45]demonstrated that acute kidney injury (AKI) during the perioperative period,Panx1 deletion induced the expression of a cytoprotective chaperone, heme oxygenase-1 (HO-1), and inhibited ferroptinophagy via the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway. Therefore, the pannexin 1 (PANX1)-RRAS-RAF1-MAP2K1-MAP2K2-MAPK1-MAPK3 axis is expected to regulate

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ferritinophagy, thus denoting a role for ferritinophagy in AKI in the perioperative period. Deng et al. [46]showed that overexpression of the renal proximal tubule-residing myo-inositol oxygenase (MIOX) aggravates cellular redox damage and ferroptosis by promoting ferritinophagy and suppressing GPX4 activity, NADPH, and GSH levels in HK-2 cells treated with cisplatin (an in vitro model of AKI), and CD1 mice (an in vivo model of nephropathy). Therefore, MIOX may be a potential target for intervening in ferritinophagy and AKI. During LPS induced septic AKI, Tang et al. [47] showed that accompanied with reduction of cytosolic Fe2+ and lipid peroxidation accumulation, ISL could significantly inhibit the expression of HMGB1 and increased the expression of NCOA4 both in vivo and in vitro following LPS stimulation. It could be concluded that ISL might attenuate LPS induced AKI by regulating ferritinophagy-mediated ferroptosis. During patulin induced AKI, Hou at al.[48]showed that PAR-induced ferroptosis depends on the autophagy pathway. The increase of lipid peroxidation, the formation of the autophagy lysosome, and the autophagic degradation of ferritin are all important causes of ferroptosis. Concomitantly, inhibition of lipid peroxidation, chelating iron ions, and inhibition of the ferritinophagy pathway can significantly alleviate. These finding provides a potential pharmacological target for the prevention and treatment of AKI.

5.2 Ferritinophagy and chronic kidney disease

Chronic kidney disease (CKD)is a significant public health concern that affects approximately 10% of the global population[49]. The pathological progress of CKD includes progressive glomerulosclerosis, renal tubular atrophy/dilatation, renal tubular cell death and interstitial fibrosis. The most common risk factors for CKD include diabetes, hypertension, cardiovascular disease, a family history of CKD, and age greater than 60 years. The CKD rat model was established after 5/6 nephrectomy. According to the research of Wang et al. [50] , the CKD rat model showed typical characteristics of ferroptosis, such as increased iron content, oxidative stress and lipid peroxidation. Further study found that the expression of NCOA4 was up-regulated and the expression of FTH1 and FTL was down-regulated, but this situation was reversed after DFO treatment. These data show that ferritinophagy occurs in the residual kidney of CKD rats, and may cause iron overload and lead to ferroptosis in CKD patients. Therefore, down-regulating intracellular free iron by inhibiting ferritinophagy and ferroptosis may be an effective therapeutic target for CKD.

5.3 Ferritinophagy and polycystic kidney disease

Polycystic kidney disease is the most common potentially lethal single-gene inherited disease in human. Autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) are the two main forms of PKD. Polycystic kidney disease (PKD)is characterized by the proliferation of fluid-filled kidney cysts that enlarge over time, causing damage to the surrounding kidney and ultimately resulting in kidney failure. Radadiya et al [51] showed that, ferritin levels were markedly elevated in cystic kidneys of PKD mice, and CPX-O treatment reduced renal ferritin levels. The reduction in ferritin was associated with increased ferritinophagy marker nuclear receptor coactivator 4, which reversed upon CPX-O treatment in PKD mice. These data suggest that CPX-O can induce ferritin degradation via ferritinophagy, which is associated with decreased cyst growth progression in PKD mice.

5.4 Ferritinophagy and renal cell carcinoma

Renal cell carcinoma (RCC) refers is a kind of malignant tumor originated from of renal tubular epithelial cells, among which clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cell carcinoma, accounting for almost about 80-85% of RCC[52].Renal cell carcinoma is characterized by mutations in target genes involved in metabolic pathways. Metabolic reprogramming covers different processes such as aerobic glycolysis, fatty acid metabolism, and the utilization of tryptophan, glutamine, and arginine. Currently, surgery combined with targeted and immunotherapy-based comprehensive therapy is often used. However, due to the limited objective remission rate of targeted therapy and the increased drug resistance of immunotherapy, it is very necessary for RCC to urgently need new treatment methods. Mou et al.[53]showed that the gene expression level of NCOA4 was significantly lower in tumor samples in comparison to normal tissues of ccRCC on the basis of various databases including TCGA, GEO and Human Protein Atlas, which is associated with overall survival (OS) and immune cell infiltration in patients with ccRCC. By using STRING tool to analyze the PPI network of NCOA4 protein, we further found that FTL and FTH11 are the major factors regulating iron metabolism, and the increase of FTH1 mRNA levels were associated with the worse prognosis of

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RCC patients. Thus, it is plausible that NCOA4 defect reduce ferroptosis and thus possibly debilitate antitumor immune effects in ccRCC. Targeting NCOA4 may be a promising therapeutic strategy for ferroptosis-induction or/and with the combination of immunotherapy in ccRCC.

5.5 Ferritinophagy and urinary tract infections

Urinary tract infections (UTIs)are among the most frequent bacterial infections acquitted in the community and hospitals, recognized as a severe public health concern to healthcare systems around the globe. Gram-negative bacilli are the most common pathogens of UTIs, of which Escherichia coli is the most prevalent, followed by Proteus, Klebsiella, Citrobacter and so on. As uropathogens are high recurrence rates and increasing antimicrobial resistance, it may be time to explore alternative strategies for managing UTIs. Bauckman et al.[54]showed that iron overload in bladder epithelial cells induces ferritinophagy in an NCOA4-dependent manner causing increased iron availability for UPEC, triggering bacterial overproliferation and host cell death. Even moderate levels of iron is sufficient to increased autophagic flux and UPEC growth in urothelial cells。Therefore, selective inhibition of iron processing or ferritinophagy or iron chelation decreased bacterial growth in urothelial cells and reversed host cell death. In conclusion, he persistence of UPEC in BECs is involved in ferritinophagy, which promotes the death of BECs and aggravates UTIs. The inhibition of ferritinophagy and downregulation of iron content in BECs may provide new research ideas and perspectives for exploring effective antibiotic alternative therapies to prevent and treat RUTIs. Thus, ferritinophagy might be a potent driving force to induce UPEC persistence. Inhibition of the selective autophagy pathway might provide a therapeutic target to reverse host cell death and impede the development of UTIs.

6. Conclusion

Ferritinophagy is an important mechanism for regulating iron level in vivo, and it is a new special type of autophagy, which has become a research hotspot at present. It has been proved that iron is closely related to related kidney diseases. Although the molecular mechanism of ferritinophagy is still uncertain, the inhibition of ferritinophagy can prevent and reverse various related kidney diseases. In-depth study on the molecular mechanism and signal pathway of ferritinophagy in renal diseases is expected to provide a new theoretical basis for the targeted treatment of related kidney diseases in the future.

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