Kidney Diseases

Review Article

Kidney Dis 2024;10:224–236
DOI: 10.1159/000538106

Received: March 15, 2023
Accepted: February 25, 2024
Published online: March 8, 2024

A Deep Insight into Ferroptosis in Renal Disease: Facts and Perspectives

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Keywords
Ferroptosis · Metabolic pathway · Kidney diseases

Abstract
Background: Ferroptosis, a newly recognized form of programmed cell death, is distinguished by its reliance on reactive oxygen species and iron-mediated lipid peroxidation, setting it apart from established types like apoptosis, cell necrosis, and autophagy. Recent studies suggest its role in exacerbating or mitigating diseases by influencing metabolic and signaling pathways in conditions such as tumors and ischemic organ damage. Evidence also links ferroptosis to various kidney diseases, prompting a review of its research status and potential breakthroughs in understanding and treating these conditions. ***Summary:*** In acute kidney disease (AKI), ferroptosis has been confirmed in animal kidneys after being induced by various factors such as renal ischemia-reperfusion and cisplatin, and glutathione peroxidase 4 (GPX4) is linked with AKI. Ferroptosis is associated with renal fibrosis in chronic kidney disease (CKD), TGF-β1 being crucial in this regard. In diabetic nephropathy (DN), high SLC7A11 and low nuclear receptor coactivator 4 (NCOA4) expressions are linked to disease progression. For polycystic kidney disease (PKD), ferroptosis promotes the disease by regulating ferroptosis in kidney tissue. Renal cell carcinoma (RCC) and lupus nephritis (LN) also have links to ferroptosis, with mtDNA and iron accumulation causing RCC and oxidative stress causing LN. ***Key Messages:*** Ferroptosis is a newly identified form of programmed cell death that is associated with various diseases. It targets metabolic and signaling pathways and has been linked to kidney diseases such as AKI, CKD, PKD, DN, LN, and clear cell RCC. Understanding its role in these diseases could lead to breakthroughs in their pathogenesis, etiology, and treatment.

Introduction

Multiple cell death mechanisms are involved in renal diseases, such as apoptosis, necrosis, and autophagy. Different types of regulated cell death have different morphological characteristics as well as biochemical, genetic, and functional mechanisms. Many studies have shown that different drugs participate in kidney diseases by regulating apoptosis, necrosis, and autophagy in kidney cells (such as podocytes) to participate in the inflammatory response, oxidative stress, endoplasmic

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reticulum stress, and other pathways and have achieved certain therapeutic effects.

In 2012, Dixon et al. [1] first confirmed a programmed cell death (PCD) mode dependent on iron metabolism in cancer cells. Various molecules and signals involved in iron metabolism and peroxidation are critical for regulating ferroptosis. This article focuses on the latest research progress and prospects of ferroptosis in acute kidney disease (AKI), chronic kidney disease (CKD), polycystic kidney disease (PKD), diabetic nephropathy (DN), lupus nephritis (LN), and clear cell renal cell carcinoma (ccRCC) from the perspective of the metabolic mechanisms of ferroptosis and kidney diseases to provide a theoretical basis for further research on the mechanism and prevention of ferroptosis in kidney diseases.

Characteristics of Ferroptosis

Signaling pathways and molecules involved in the regulatory mechanism of ferroptosis include iron metabolism, cysteine metabolism, glutathione peroxidase 4 (GPX4) inactivation, polyunsaturated fatty acid (PUFA) synthesis, nuclear factor E2-related factors (Nrf2), p53, heat shock proteins (HSPs), iron-regulated inhibitor-1 (FSP1), AMP-activated protein kinase (AMPK) activation, and nicotinamide adenine dinucleotide phosphate (NADPH), etc. (Fig. 1).

Iron Metabolism

Iron is crucial for lipid peroxide accumulation and ferroptosis, regulating its uptake, transport, and storage for maintaining iron homeostasis. The membrane protein transferrin receptor 1 (TFR1) transports Fe^{3+} to endosomes, where it is reduced to Fe^{2+} (Fig. 2). Divalent metal transporter 1 (DMT1) releases Fe^{2+} from endosomes into intracellular iron pools. Excess iron is stored in the cytoplasm as ferritin light chain (FTL) and ferritin heavy chain 1 (FTH1). In addition, various proteins such as ferroportin 1 (FPN1) have played an important role in iron metabolism, and for more information, refer to the work of Min and colleagues [2].

Cysteine Metabolism

The cystine/glutamate reverse transporter (System Xc−) comprises the light-chain subunit (SLC7A11) and the heavy-chain subunit (SLC3A2), forming a heterodimer via disulfide bonds. This system is essential for cellular antioxidant defense, and more details can be found in the publication by Min and colleagues [2].

GPX4 Inactivation

The glutathione peroxidase (GPX) family, encompassing GPX1 to GPX8, highlights the pivotal role of GPX4 in ferroptosis (Fig. 1). GPX4, a selenium protein in mammals, repairs lipid oxidative damage by converting reduced GSH to oxidized glutathione (GSSG) and toxic lipid hydrogen peroxide (L-OOH) to nontoxic lipid alcohol (L-OH), safeguarding cell membrane integrity from oxidative interference and damage. For more detailed descriptions, refer to the work of Min and colleagues [2].

PUFA Synthesis

PUFAs, with their unstable carbon-carbon double bonds, are susceptible to lipid peroxidation, essential for ferroptosis. Acyl-CoA synthase long-chain 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are pivotal in lipid remodeling (Fig. 2) [3]. For more detailed descriptions, refer to the work of Min and colleagues [2].

Nrf2

In 2016, Sun et al. [4] showed that Nrf2 could regulate ferroptosis through the P62-KEAP1-NRF2 pathway (Fig. 2). Activation of Nrf2 promotes iron storage, reduces iron uptake by cells, and limits reactive oxygen species (ROS) production. Therefore, Nrf2 can inhibit ferroptosis. For more detailed descriptions, refer to the work of Min and colleagues [2].

P53

P53, a tumor suppressor gene activated by various stress stimuli, serves as a transcriptional inhibitor of SLC7A11, participating in ferroptosis by impeding cysteine intake and promoting its occurrence. The induction of ferroptosis by p53 involves the replacement of three lysine residues with arginine residues, resulting in an acetylated defective p53 mutant (p533KR) that robustly inhibits SLC7A11 expression without affecting other known p53 target genes associated with the cell cycle, apoptosis, or aging [5]. Consequently, p53 downregulates SLC7A11 expression, inhibiting cystine uptake by System Xc− and consequently weakening cellular antioxidant capacity, increasing lipid ROS levels, and inducing ferroptosis.

Heat Shock Proteins

HSPs, a highly conserved molecular chaperone family with immune functions, confer cell resistance to various cell death modes, including ferroptosis, through stress inhibition, antioxidation, immune

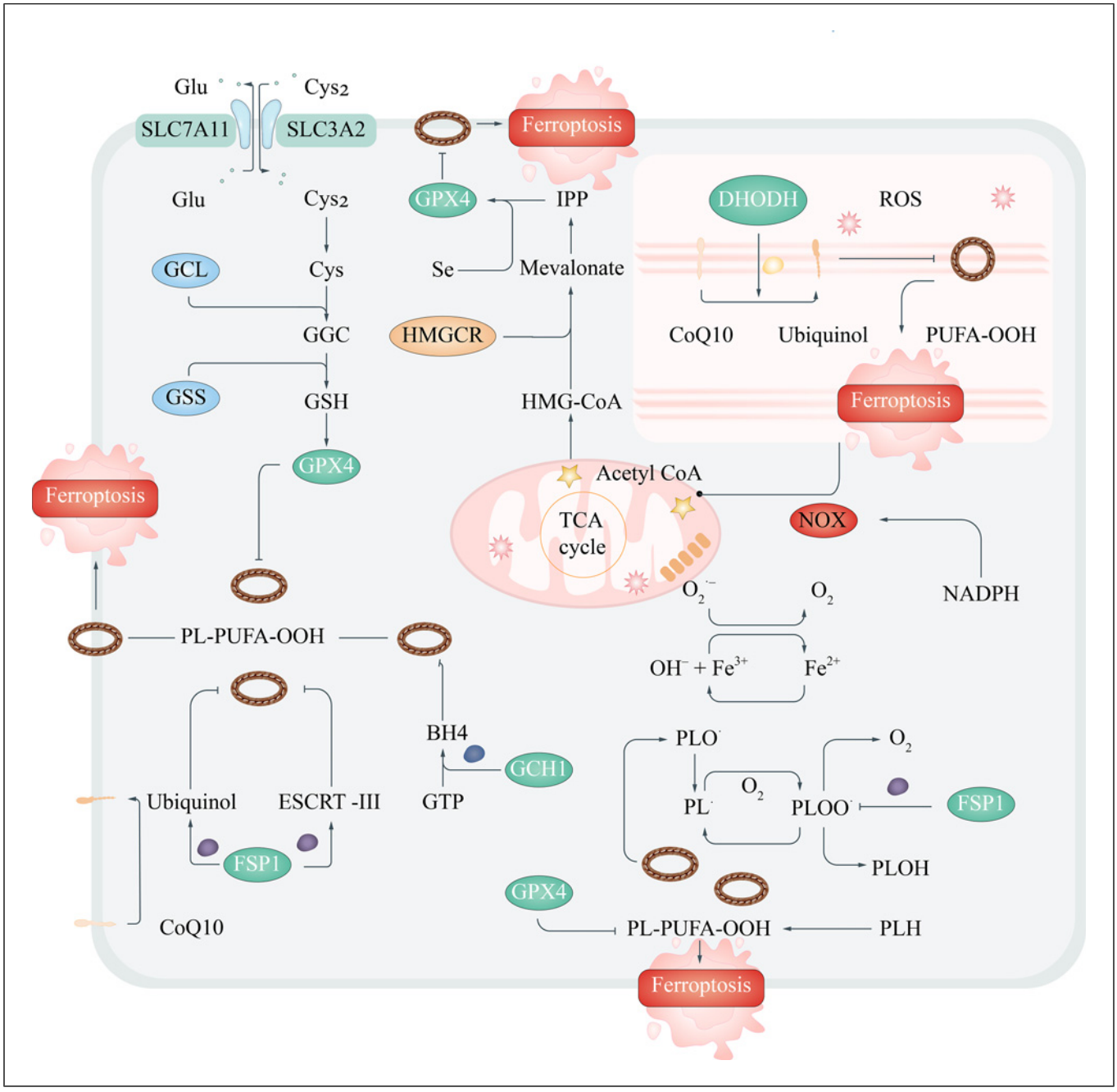

Fig. 1. Signaling pathways and key molecules that inhibit iron death and the mechanism of phospholipid peroxidation. Cys2, cystine; DHODH, dihydroorotate dehydrogenase; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; PL•, phospholipid radical; PLH, phospholipid; PLO•, alkoxyl radical; PLOH, phospholipid alcohol; PLOO•, peroxyl radical; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle.

response, and antigen presentation. Specifically, HSPB1, also known as HSP25 or HSP27, safeguards the actin cytoskeleton by curbing ferroptosis via reduced iron uptake and subsequent oxidative damage [6]. Furthermore, the HSPB1 pathway inhibits erastin-induced ferroptosis in multiple cancer cell types by mitigating iron and ROS escalation. Additionally, HSPA5 (also known as BIP or GRP78), located in the endoplasmic reticulum, binds to GPX4, significantly enhancing cellular antioxidant capacity [7].

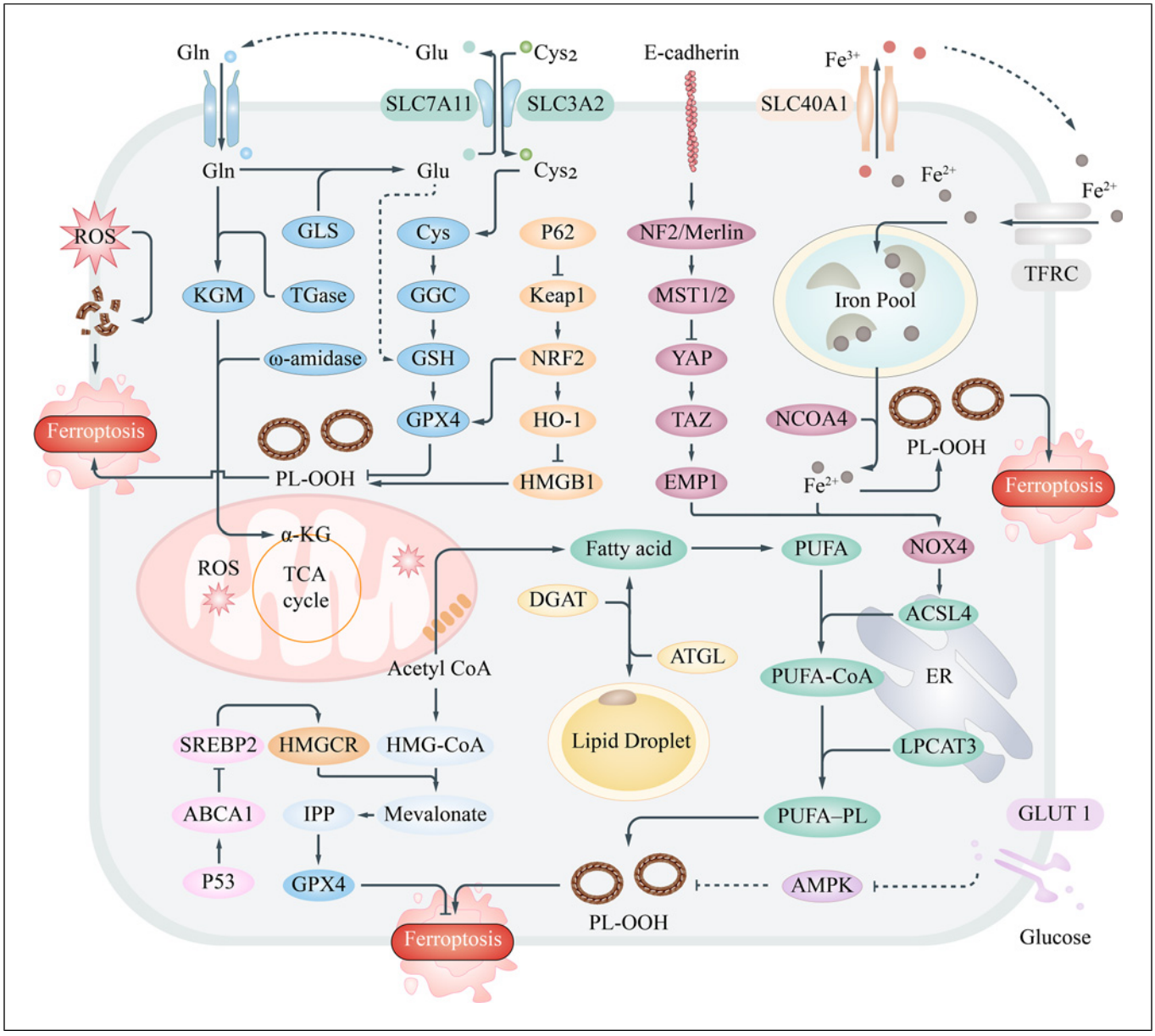

Fig. 2. Main signaling pathways that regulate ferroptosis. ACSL4, acyl-CoA synthetase long-chain family member 4; ATGL, adipose triglyceride lipase; CoQ10, coenzyme Q10; Cys2, cystine; DGAT, diacylglycerol O- acyltransferase; ER, endoplasmic reticulum; Gln, glutamine; Glu, glutamate; GLS, glutaminase; HMGCR, HMG-CoA reductase; α-KG, α-ketoglutarate; LPCAT3, lysophosphatidylcholine acyltransferase 3; NCOA4, nuclear receptor coactivator 4; NOX4, NADPH oxidase 4; PLOOH, phospholipid hydroperoxide. PUFA, polyunsaturated fatty acid; PUFA-PL, phospholipid containing polyunsaturated fatty acid chain; SREBP2, sterol regulatory element-binding protein 2; TFRC, transferrin receptor.

FSP1

Genome-wide screening revealed FSP1's role in regulating ferroptosis independent of the GSH-GPX4 pathway [8]. Intriguingly, FSP1 counteracts this effect by inhibiting GPX4 in cells, leading to ferroptosis (Fig. 1) [9]. For more detailed descriptions, refer to the work of Min and colleagues [2].

AMPK

AMPK, a vital intracellular energy metabolism sensor, orchestrates multiple metabolic pathways and balances energy supply and demand [10]. Its activation can induce or inhibit ferroptosis, possibly influenced by environmental complexity and the phosphorylation site activation level. AMPK also regulates mitochondrial stability

and triggers ferritin degradation, ROS accumulation, and ferroptosis activation [11, 12]. Studies have demonstrated AMPK as an upstream regulator of ferroptosis, with its depletion sensitizing cells to ferroptosis [13]. Another study revealed that AMPK, activated in the glucose absence, inhibits lipogenesis to attenuate ferroptosis (Fig. 2) [14]. However, conflicting conclusions may stem from the lack of ferroptosis-related biomarkers and mitochondrial phenotypic support, leaving the specific regulatory role of AMPK in ferroptosis unclear.

NADPH

As a coenzyme of GSH reductase, a reduction in NADPH plays an important role in maintaining intracellular GSH levels. The effects of classic ferroptosis inducers (erastin, RSL3, and FIN56) have been studied in a variety of cell lines, including human osteosarcoma cell lines. Intracellular NAD (H) and NADP (H) levels were significantly reduced, and ROS formation was detected [15]. In addition, recent studies have shown that NADPH provides electrons through cytochrome P450 oxidoreductase (POR) and that downstream electron receptors, such as cytochrome P450, receive electrons correspondingly, which may occur through PUFA dehydrogenation or the inhibition of Fe^{3+} conversion to Fe^{2+}, thereby triggering lipid peroxidation [16].

GCH1

An in vitro study showed that GTP cyclic hydrolase 1 (GCH1) prevented ferroptosis through its metabolites tetrahydrobiopterin (BH4) and dihydrobiopterin (BH2) (Fig. 1). For more detailed descriptions, refer to the work of Min and colleagues [2].

Hippo YAP/TAZ

High-density growth cells are generally more resistant to GPX4-induced ferroptosis than other cells. Further studies have shown that the effect of cell density on ferroptosis in epithelial cells is mediated by E-cadherin-mediated cell-cell contact, which activates the Hippo pathway through the tumor suppressor protein NF2, thereby inhibiting YAP activity [17]. The regulation of ferroptosis by cell density was also shown in renal carcinoma cells that mainly expressed TAZ but not YAP, suggesting that E-cadherin NF2 Hippo YAP/TAZ is involved in the regulation of ferroptosis (Fig. 2) [18].

Ferroptosis and Other Forms of Cell Death

Ferroptosis is a new type of iron-dependent PCD that is different from apoptosis, programmed necrosis, and pyroptosis. Morphologically, ferroptosis is characterized by mitochondrial atrophy, significant reduction and atrophy of the mitochondrial ridge, increased membrane density, and membrane rupture, while the nucleus remains normal and cell membrane density increases. Apoptosis exhibits reduced cell volume, chromatin shrinkage, nuclear fragmentation, complete membrane structure, and formation of apoptotic corpuscles. Programmed necrosis is distinguished by increased cell size, simultaneous plasma membrane rupture, abundant cell debris production, and often formation of necrosome structures.

Ferroptosis and Apoptosis

Apoptosis, a genetically regulated PCD, plays a crucial role in maintaining normal cell stability in tissues, immune and defense responses, and combatting cell damage associated with tumor occurrence and development. Recent studies have revealed a close relationship between ferroptosis and apoptosis, with ferroptosis being able to promote cell sensitivity to apoptosis and vice versa. Additionally, P53 can induce ferroptosis in tumor cells under specific conditions, presenting a potential novel therapeutic target in the form of the mixed ferroptosis/apoptosis pathway. In vivo and in vitro studies have demonstrated significant ferroptosis in MON-p53-treated cells, inhibiting tumor growth and extending the lifespan of tumor-bearing mice [19, 20].

Ferroptosis and Programmed Necrosis

Programmed necrosis exhibits the morphological traits of necrotic cells and a signaling mechanism akin to apoptosis. Ferroptosis and programmed necrosis can coexist, both observed in deceased neurons resulting from hemorrhagic stroke. Heme chloride-induced cell death led to increased mRNA levels of ferroptosis molecular markers and programmed necrosis markers [21]. In 2017, Müller et al. [22] demonstrated that ACSL4 deficiency increased MLKL, rendering cells more susceptible to ferroptosis, thereby highlighting the complementary nature of these 2 cell death pathways. Tonnus et al. [23] proposed that the depletion of NADPH by programmed necrosis renders adjacent cells sensitive to ferroptosis, suggesting an interplay between these pathways. This perspective provides a better understanding of the interconnection between ferroptosis and PCD mechanisms.

Ferroptosis and Autophagy

Autophagy, a lysosomal-dependent degradation pathway, is implicated in various diseases, including infections, immune diseases, metabolic disorders, and cancer. Recent studies have shown that autophagy can

induce ferroptosis in cancer cells by degrading ferritin [24]. Iron-mediated autophagy, facilitated by nuclear receptor coactivator 4 (NCOA4), leads to ferritin degradation and subsequent ferroptosis induction [25]. Additionally, iron-mediated autophagy increases intracellular iron concentrations through ferritin degradation, promoting ferroptosis in fibroblasts and cancer cells [26]. The interplay between ferroptosis and autophagy is further evidenced by the limitation of erastin-induced ferroptosis through the deletion of the Atg5 and Atg7 genes, reducing intracellular iron and lipid peroxidation.

Ferroptosis and Kidney Diseases

Ferroptosis and AKI

Ferroptosis has been confirmed in AKI animal models, with numerous studies highlighting the link between AKI and ferroptosis. GPX4, a key regulatory protein, influences AKI severity as its downregulation leads to spontaneous AKI in mice, while its upregulation alleviates AKI severity [27]. Additionally, CPT 2 deficiencies can induce fatty acid metabolism disorders and mitochondrial dysfunction, contributing to AKI development [28]. Nrf2 overactivation increases GSH production, preventing tubular injury, while abnormal Nrf2 function can induce ferroptosis in tubular cells [29]. Nrf2 inhibits ferroptosis by targeting HO-1 expression, and AKI exacerbation occurs after HO-1 knockdown [30]. Upregulation of HO-1 increases FtH in proximal tubules, preventing lipid oxidation and inhibiting ferroptosis, thus playing a protective role in AKI.

Exposure to IR can trigger extensive kidney cell death and a potent inflammatory response, resulting in severe acute kidney injury. In a study, Huang et al. [31] revealed that inhibiting ALR expression intensified ferroptosis in cells, leading to increased ROS and mitochondrial damage, implicating ferroptosis in IR-induced AKI mediation. Martin-Sanchez et al. [32] demonstrated the downregulation of lipid peroxidation and glutathione metabolizing proteins, characteristic of ferroptosis, in folate-induced AKI mice. In an in vivo and in vitro study, mice with acute oxalic acid poisoning exhibited calcium oxalate crystals in distal tubule epithelial cells, linked to characteristic mitochondrial permeability transition (Fig. 3) [33].

During cardiac surgery, renal IR leads to the release of free iron, causing tubular cell peroxidation and iron-dependent cell death, mitigated by early intraoperative iron-binding proteins and postoperative iron sequestration proteins [34]. Cisplatin induces renal vascular injury, reducing blood flow and causing AKI, concentrating in the S3 segment of the proximal tubule, inducing necrosis and apoptosis [35]. Hu et al. [36] demonstrated the efficacy of ferroptosis inhibitor ferrostatin-1 in reducing cisplatin-induced AKI. Rhabdomyolysis increases serum creatinine and lipid peroxidation, leading to renal tubular cell death, reversed by ferroptosis inhibitors, implicating ferroptosis in rhabdomyolysis-induced AKI due to the release of iron ions, inducing cell death (Fig. 3) [37].

The complex pathological process of AKI makes the proximal tubule segment vulnerable to diverse injuries. The specific role of ferroptosis in AKI from different causes is unclear. While research confirms ferroptosis involvement, other cell regulation modes like apoptosis and autophagy are also significant, warranting attention in the next decade.

Ferroptosis and CKD

In normal kidneys, iron regulatory proteins in proximal tubules regulate iron metabolism, but in CKD, iron regulatory protein dysfunction leads to iron deposition and Fenton reaction-mediated oxidative damage. Iron deposition is influenced by exogenous iron supplementation and endogenous iron-catalyzed responses due to ischemia and hypoxia [38].

Renal fibrosis is a prominent injury in chronic progressive kidney disease, with TGF-β1 being a crucial molecule in its pathogenesis. Evidence suggests ferroptosis's involvement in the regulatory mechanism of renal fibrosis. In a rat CKD model induced by 5/6 nephrectomy, an iron-restricted diet protected renal function and prevented hypertension and vascular remodeling, indicating ferroptosis's role in renal injury and its association with cardiovascular diseases [39]. In a mouse CKD model induced by unilateral ureteral obstruction, increased HO-1 inhibited TGF-β1 expression and proinflammatory molecules, reversing kidney injury. HO-1 deletion upregulated TGF-β1 expression, exacerbating renal fibrosis, with DFO, a ferroptosis inhibitor, preventing renal tubulointerstitial fibrosis by regulating TGF-β1-Smad signaling, oxidative stress, and the inflammatory response [40].

While the molecular mechanism of TGF-β1 and its downstream signaling pathway is well understood, the exact targeting of TGF-β by HO-1 remains unclear. Further studies are needed to determine whether ferroptosis can regulate fibrosis in CKD through other pathways.

Ferroptosis and DN

The contributory factors for DN encompass inflammation, cytokines, and genetic factors, posing a threat to vital organs like the kidneys even when blood sugar is

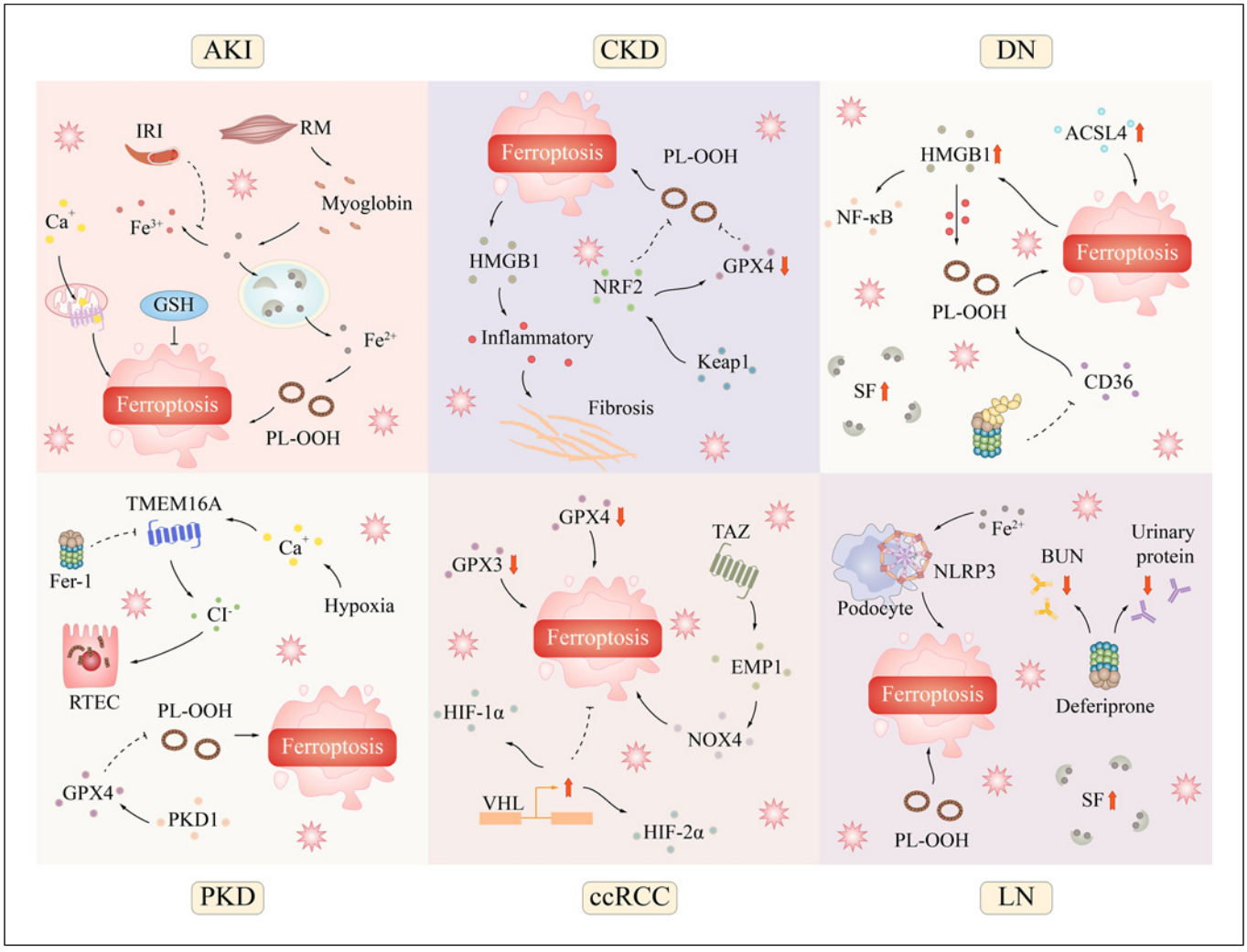

Fig. 3. Ferroptosis mediates a variety of kidney diseases, such as AKI, CKD, LN, DN, PKD, and ccRCC.

controlled. Clinical trials have shown reduced levels of SLC7A11 and GPX4, involved in ferroptosis induction, in the renal tissue of DN patients compared to other groups [41]. Similarly, in db/db diabetic mice, reduced urinary albumin excretion and superoxide production in mice on a low-iron diet indicate the involvement of ferroptosis in DN progression, with part of the ferroptosis mechanism regulating DN through oxidative stress [42].

Lipid deposits in most DN renal cells in vivo are positively correlated with CKD progression according to epidemiological studies. Arachidonic acid and phosphatidylethanolamine induce ferroptosis, with ACSL4 and LPCAT3 affecting phosphatidylethanolamine biosynthesis and remodeling, impacting PUFA transmembrane properties. Downregulating ACSL4 and LPCAT3 in DN mice inhibited ferroptosis by affecting lipid peroxidation substrate concentrations [43]. High CD36 expression in DN patients, associated with ectopic lipid deposition, can be countered to alleviate renal interstitial fibrosis [44]. CD36-knockout mice were more susceptible to CKD development, indicating its role in promoting lipid-induced ferroptosis (Fig. 3) [45].

High mobility group box-1 (HMGB1) is linked to DN dysfunction, with increased serum ferritin and HMGB1 levels in DN patients, accompanied by dysregulated iron metabolism-related molecules ACSL4 and GPX4. Downregulating HMGB1 inhibited TLR4/NF-KB axis activation and promoted Nrf2/HO-1 expression in DN renal tissue (Fig. 3) [46].

Nrf2/HO-1 regulates ferroptosis in DN kidneys. Cell experiments showed that Nrf2 knockdown increased cell sensitivity to ferroptosis under high glucose conditions,

while upregulating Nrf2 improved ferroptosis [47]. Fenofibrate treatment in diabetic mice delayed DN progression by increasing Nrf2 and inhibiting iron nutrition-related changes [47]. Bardoxolone methyl, an Nrf2 activator, completed a phase 3 clinical trial in CKD and T2DM patients, showing promise in improving the glomerular filtration rate without safety concerns [48]. Specifically expressed in DN glomeruli, HO-1 prolonged podocyte survival, with Tempol treatment delaying DN deterioration by increasing HO-1 activity in DN mice [49].

Podocytes are crucial for the glomerular filtration barrier, and their injury contributes to glomerular diseases like DN. Abnormal sensitivity to lipid accumulation in podocytes can lead to dysfunction, cytoskeletal rearrangement, inflammatory responses, and ultimately podocyte death. While there is no direct link between podocyte lipid accumulation and circulating lipid levels, podocytes express various lipid metabolism-related genes. Diabetes induces lipid metabolic reprogramming in podocytes, directly impacting lipid metabolism homeostasis and kidney function.

Recent studies have implicated ferroptosis in podocyte injury in DN, highlighting key molecular pathways and genes such as GPX4, ACSL4, and FSP1 [50]. Animal experiments have shown that DN-induced podocyte ferroptosis and oxidative stress damage can be alleviated by fisetin supplementation [51]. Targeting ferroptosis can mitigate lipotoxicity-induced podocyte damage in DN, characterized by mitochondrial oxidative stress [52].

Recent studies suggest that in addition to oxidative stress and lipid accumulation, ferroptosis may play a role in podocyte injury in DN. Further research is needed to understand this relationship fully and develop targeted therapeutic interventions.

Ferroptosis and PKD

Mutations in PKD1, PKD2, and PKHD1 genes are linked to the disease, with PKD1 influencing ferroptosis regulation in kidney tissue. PKD1 promotes cyst growth by activating cell proliferation pathways, while ferroptosis inducers like erastin can further promote cyst expansion. Additionally, TMEM16A plays a crucial role in fluid secretion into renal cysts, and interventions targeting glutathione, coenzyme Q10, or edbenzone have been implicated in PKD progression. Iron-statin 1 has shown promise in slowing PKD progression by reducing TMEM16A activation [53]. Currently, there have been few studies on ferroptosis and PKD, but many researchers have realized the impact of ferroptosis on the progression of PKD, and an increasing number of researchers believe that targeting ferroptosis may be a new therapeutic strategy for PKD treatment [54, 55].

Ferroptosis and ccRCC

Analysis of the GSCA database revealed that high SLC7A11 expression and low NCOA4 expression were associated with ccRCC patients [56]. In vitro studies demonstrated that ccRCC cells were highly sensitive to glutamine or cystine depletion, both crucial for synthesizing glutathione. Inhibiting GSH synthesis induced ferroptosis in ccRCC cells, and knockdown of glutathione peroxidases GPX3 and GPX4 increased ccRCC cell death, highlighting the importance of GSH synthesis in ccRCC cell viability and the mechanism of ferroptosis [57].

Subsequent research found that ccRCC is closely linked to von Hippel Lindau (VHL) gene mutation, impacting hypoxia-inducible factors HIF-1α and HIF-2α. Upregulation of VHL decreased ccRCC cell sensitivity to ferroptosis [57, 58]. Additionally, TAZ regulates the cell number and density via the EMP1-NOX4 signaling pathway in ccRCC, influencing cell sensitivity to ferroptosis (Fig. 3) [18].

Furthermore, abnormal mitochondrial DNA changes, particularly deletions, contribute to prostate cancer development, potentially through the impact of mitochondrial ROS mutations on cell proliferation and evasion of apoptosis. Hypoxia-induced mtROS production indirectly activates HIF-1, leading to glycolysis upregulation, mitochondrial respiration inhibition, and a cycle promoting tumor growth. These findings underscore the high dependence of cancer cells on ferroptosis-related targets like the GSH/GPX pathway, making ferroptosis induction a promising approach for urinary system tumor treatment.

Ferroptosis and LN

Clinical studies have shown significant differences in oxidative stress biomarkers like glutathione between LN and non-LN patients, indicating an imbalance in renal tissue redox status, potentially involving glomerular basement membrane peroxidation [59]. High levels of ROS were observed in the serum of patients with active LN, suggesting the involvement of ferroptosis in LN progression. Urinary transferrin and ceruloplasmin, key targets of ferroptosis regulation, were found to be expressed differently in LN patients compared to controls, further implicating ferroptosis in LN progression [60].

In animal experiments, LN mice exhibited increased intrarenal nonheme iron levels and accumulation of transferrin-bound iron. Treatment with the iron chelator deferiprone reduced proteinuria and blood urea nitrogen concentrations in LN mice, indicating the involvement of ferroptosis in LN regulation [61]. Additionally, hepcidin treatment in another animal experiment reduced renal iron accumulation and alleviated the severity of LN,

independent of glomerular immune complex deposition and circulating autoantibodies [62].

These experiments suggest the involvement of ferroptosis in LN progression, although the specific regulatory mechanism remains unclear. Some researchers have suggested that iron can directly activate the NLRP3 inflammasome, potentially contributing to the development of LN (Fig. 3) [63]. Overall, the complex etiology of LN and the discovery of ferroptosis provide a new target for LN treatment.

Therapeutic Approaches Targeting Ferroptosis

In recent years, scholars have gradually discovered some drugs associated with ferroptosis, including natural compounds, small-molecule inhibitors and inducers. In general, there have been many studies on ferroptosis in AKI, and more studies are needed to confirm that ferroptosis occurs in CKD.

Natural Compounds Targeting Ferroptosis

Wang et al. [64] observed in a mouse model that artesunate reduced fibrotic scar formation by accumulating iron and lipid peroxides. The effect was nullified by the ferroptosis inhibitor ferrostatin-1. Dihydroartemisinin induced ER stress in glioma cells, upregulating PERK-ATF4-HSPA5 expression. This led to increased GPX4 activity, preventing lipid peroxidation and protecting cells from ferroptosis [65].

In a mouse model of breast cancer, ferroptocide inhibited thioredoxin, inducing ferroptosis [66]. Baicalein blocked erastin-induced ferrous iron production, glutathione depletion, and GPX4 degradation [67]. Gastrodin and puerarin triggered various pathological conditions through ferroptosis or by inhibiting signaling pathways [68, 69].

Small-Molecule Inhibitors

Vitamin E, an antioxidant, inhibits ferroptosis by trapping peroxyl groups and directly inhibiting lipoxygenase. Liproxstatin-1 and ferrostatin-1 were identified as inhibitors of ferroptosis in ischemia-reperfusion-damaged organs [70]. Thiazolidinedione drugs like rosiglitazone suppress ACSL4 expression to counteract ferroptosis [71]. Deferoxamine and deferiprone, common iron chelators, effectively inhibit erastin-induced ferroptosis.

Small-Molecule Inducers

System Xc is a critical component of ferroptosis, and sulfapyridine, sorafenib, erastin, and their analogs can regulate ferroptosis by inhibiting System Xc [72]. Targeting the GPX family involves inhibiting GPX4 activity through direct or covalent inhibition, with representative drugs like RSL3, hexamethylmelamine, DPI family, and FIN56 [73–75]. Buthionine sulfoximine, DPI2, and cisplatin induce ferroptosis by inhibiting GSH synthesis and depleting GSH [76].

Therapeutic Approaches Targeting Ferroptosis in Kidney Diseases

Acute Kidney Disease

In folic acid-induced AKI animal experiments, an association between AKI, lipid peroxidation, and downregulated glutathione metabolic proteins was observed [32]. Ferrostatin-1 reduced histological damage, oxidative stress, and tubular cell death by inhibiting ferroptosis. IR-AKI animal experiments demonstrated that iron-dependent ferroptosis directly causes tubular necrosis [77]. The metabolically stable third-generation ferristatin, 16–86, showed a strong protective effect, even in severe IRI cases. Cisplatin-induced AKI experiments on HK-2 cells revealed that ferroptosis inhibitors reduced cell death and led to significant alterations in lipid peroxidation, GPX4 activity, NADPH, and GSH levels [78]. Ferrostatin-1 countered renal pathological changes caused by ferroptosis and its metabolic pathways. Additionally, MIOX expression profiles were found to regulate ferroptosis metabolism in mice with cisplatin-induced AKI.

Diabetic Nephropathy

Ferroptosis is crucial in DN development, and targeting it can alleviate its occurrence and progression. Fenofibrate promotes Nrf2 expression and inhibits ferroptosis in DN mice [47]. DAPA inhibits FPN ubiquitination degradation, improving DN in mice [79]. Entresto and EMPA inhibit ferroptosis in cardiomyocytes, offering new treatment possibilities for DN [80, 81].

Chinese herbal medicines and their active ingredients, such as Germacrone, quercetin, calycosin, salidroside, glabridin, platycodin D, schisandrin A, and umbelliferone, show promise in targeting ferroptosis to delay DN. These substances inhibit ferroptosis and have potential in treating DN, although further investigation into specific mechanisms is needed.

Chronic Kidney Disease

Fibrosis in kidney tissue is a typical feature of CKD, and excessive iron accumulation exacerbates the condition. In a 5/6 nephrectomy-induced CKD rat experiment, DFX treatment reduced renal type III collagen and TGF-β expression, suggesting alleviation of fibrosis through iron

chelation [82]. In a unilateral ureteral obstruction mouse model, DFO alleviated tubulointerstitial fibrosis by modulating TGF-β-Smad signaling and oxidative stress [40]. Additionally, components from Chinese herbal medicines can target ferroptosis pathways, relieving kidney tissue fibrosis [83–85].

Polycystic Kidney Disease

In PKD, the investigators found that the growth and differentiation of TMEM16A cysts are essential [54]. Glutathione, coenzyme Q10, or idebenone, as the main markers regulating ferroptosis, can delay the progression of PKD by inhibiting the expression of TMEM16A [86]. In a mouse model of PKD, the ferroptosis inhibitor Fer-1 effectively alleviated cyst deterioration compared to the controls [55]. In another animal model, the researchers found that ferritin expression was much higher in PKD mice than in healthy mice, and it was rapidly down-regulated in PKD mice after treatment with CPX-O (an iron chelator) [87]. This suggests that CPX-O delays PKD deterioration by targeting ferritin.

Renal Cell Carcinoma

Targeting ferroptosis with drugs has shown promise in treating renal cell carcinoma (RCC). RCC cells are particularly susceptible to ferroptosis, making it an attractive therapeutic target. Buthionine sulfoximine, an inhibitor of GSH synthesis, reduced tumor growth in RCC mice, suggesting its potential in treating RCC by inhibiting GSH, a ferroptosis marker [57]. Additionally, drugs from traditional Chinese medicine, such as artesunate and lycorine, have shown the ability to induce ferroptosis in RCC cells in vitro experiments [88, 89].

Overall, drug-targeted ferroptosis represents a novel and promising avenue for the treatment of kidney diseases. Continued research and clinical trials will be instrumental in further understanding the mechanisms involved and optimizing therapeutic approaches to combat this challenging disease.

Conclusion

Since its first identification in 2012, there has been a surge in studies on ferroptosis and kidney disease. This manuscript explores known regulatory mechanisms of ferroptosis and its role in kidney diseases. However, gaps persist in understanding ferroptosis's involvement in regulating kidney diseases, particularly in renal fibrosis, DN, and LN. Progress has been made on ferroptosis-related inducers and inhibitors, but clinical translation and precision drug development, including nanomedicines, are anticipated. Understanding ferroptosis's specific role in AKI and its interaction with other cell death modes, as well as its regulation of fibrosis in CKD through other pathways, remains unclear. Investigating the potential involvement of ferroptosis in kidney disease regulation through immune cells is also crucial. In-depth study of ferroptosis holds promise for new intervention targets in diagnosing and treating renal diseases.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The work was supported by the Sichuan Provincial Science and Technology Program (2021YJ0255).

Author Contributions

Zhongyu Han and Yuanke Luo were involved in the conception of the study. Yuanke Luo, Zhongyu Han, Lan Yuan, and Shiyi Zhou were involved in writing the article. Haoran Chen and Guochen Zhang were involved in the production of figures. Haoran Chen, Guochen Zhang, Luling You, Meiqi Zhang, Yumeng Lin, Lan Yuan, and Shiyi Zhou critically revised the manuscript. Zhongyu Han participated in the main work of the revision phase of the manuscript. All the authors read and approved the final manuscript.

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