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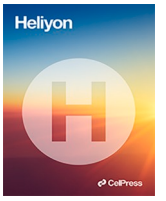

Review article

The significance of ferroptosis in renal diseases and its therapeutic potential

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ABSTRACT

Kidney diseases are significant global public health concern, with increasing prevalence and substantial economic impact. Developing novel therapeutic approaches are essential for delaying disease progression and improving patient quality of life. Cell death signifying the termination of cellular life, could facilitate appropriate bodily development and internal homeostasis. Recently, regulated cell death (RCD) forms such as ferroptosis, characterized by iron-dependent lipid peroxidation, has garnered attention in diverse renal diseases and other pathological conditions. This review offers a comprehensive examination of ferroptosis, encompassing an analysis of the involvement of iron and lipid metabolism, the System Xc^-/glutathione/glutathione peroxidase 4 signaling, and additional associated pathways. Meanwhile, the review delves into the potential of targeting ferroptosis as a therapeutic approach in the management of acute kidney injury (AKI), chronic kidney disease (CKD), diabetic nephropathy, and renal tumors. Furthermore, it emphasizes the significance of ferroptosis in the transition from AKI to CKD and further accentuates the potential for repurposing drug and utilizing traditional medicine in targeting ferroptosis-related pathways for clinical applications. The integrated review provides valuable insights into the role of ferroptosis in kidney diseases and highlights the potential for targeting ferroptosis as a therapeutic strategy.

1. Introduction

Kidney diseases are pressing global public health concern with profound implications for the well-being and livelihoods of countless individuals across the globe [1]. Furthermore, its prevalence is continuously rising, imposing substantial economic strains on countries and even families. Undoubtedly, there exists an imperative need to devise novel therapeutic approaches capable of retarding

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the progression of renal disease, mitigating the risk of cardiovascular and cerebrovascular diseases and their attendant complications, and ultimately augmenting the quality of life for afflicted patients. Thus, a comprehensive understanding of the molecular mechanisms underlying renal disease is paramount.

Cell death is an essential biological process that facilitates proper bodily development and the preservation of homeostasis. It entails the precise regulation of diverse molecular mechanisms and signifies the termination of cellular life [2–6]. Extensive literature has been dedicated to study the cell death, shedding light on various manifestations of regulated cell death (RCD) containing pyroptosis, apoptosis, ferroptosis, necroptosis, and autophagy. Among them, ferroptosis, a relatively recent form of cell death, exerts significant regulatory functions in multiple diseases such as hematological malignancies, intestinal disease, liver disease, ovarian cancer, renal failure, and nervous system diseases [7–12]. Numerous scholars have advocated for positioning ferroptosis as an important research field for enhancing treatment and prognosis of associated diseases [13]. Although some reviews have summarized the roles of ferroptosis in renal diseases [14,15], this review concludes the newest frontiers and highlights the transformation potential in clinical treatment. This review provides a succinct overview of the principal molecular mechanisms and signaling pathways linked to ferroptosis, with the objective of augmenting the comprehension regarding the connection between ferroptosis and renal diseases, while also offering valuable perspectives for the exploration of innovative treatment strategies and pharmaceutical advancements in the realm of kidney disease.

2. An overview of ferroptosis

The concept of "ferroptosis" was first coined by Dixon et al., in 2012 to depict a unique type of cell death induced by the compound erastin [16]. It is characterized by perturbations in iron and lipid metabolism within cells, leading to iron-dependent lipid peroxidation, ultimately culminating in cell death. Ferroptosis is distinguished by the presence of diminutive mitochondria exhibiting concentrated mitochondrial membrane densities and diminished or absent mitochondria cristae. Notably, the nuclear size remains unaltered. These morphological and biochemical features distinguish ferroptosis from the other four established types of cell death (Table 1) [2,4,5,17–22]. So far, ferroptosis has been proven to engage various biological pathways, such as the iron metabolism pathway, the system Xc^-/glutathione/glutathione peroxidase 4 (system Xc^-/GSH/GPX4) pathway and lipid metabolism pathway, among others [23,24].

2.1. Iron metabolism and ferroptosis

Iron is a critical component in the operation of living organisms, as it is engaged in vital cellular processes containing growth, development, respiration, erythropoiesis and metabolism. Maintaining the balance of iron metabolism is crucial for sustaining biological processes and the viability of cells. Excessive iron levels could trigger ferroptosis which generates a substantial quantity of reactive oxygen species (ROS) via the Fenton reaction (Fe^{2+}+ hydrogen peroxide (H_2O_2)→Fe^{3+}+·OH + HO-), resulting in lipid peroxidation and subsequent cell demise. Most of the iron is in the ferric (Fe^{3+}) state, which enters the endosome through the membrane protein transferrin receptor 1 (TFR1) [28]. Inside the endosome, the six-transmembrane epithelial antigen of prostate 3 (STEAP3) facilitates the conversion of Fe^{3+} to ferrous iron (Fe^{2+}) [29]. Subsequently, divalent metal transporter 1 (DMT1) translocates it to the cytoplasmic labile iron pools (LIP) and ferritin, from where it is exported by ferroportin 1 (FPN1) [30,31]. The disruption of intracellular iron homeostasis, encompassing the equilibrium between iron absorption, utilization, and recycling, may give rise to the accumulation of intracellular free iron and catalyze the Fenton reaction [18]. Hydroxyl radicals produced by Fenton's reaction further impairs cellular structure, thereby facilitating the formation of lipid ROS and eventually culminating in ferroptotic cell death (Fig. 1).

2.2. System Xc^-/GSH/GPX4 axis and ferroptosis

The System Xc^-/GSH/GPX4 axis is a core component in the enzymatic modulatory mechanism of ferroptosis. Composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), the system Xc^- functions as a heterodimer. It acts as a cystine-glutamate antiporter, exhibiting widespread distribution within phospholipid bilayers. It regulates the flow of glutamate out of cells and cystine into cells at a 1:1 M ratio to be responsible for redox balance. Cystine is converted to cysteine through reduction as it crosses the plasma membrane and enters the cell [32]. Cysteine assumes a crucial role as a limiting amino acid in the synthesis of GSH [33], which as a potent ROS scavenger and antioxidant, is regulated by the concentration of cysteine, the biological activity of glutamate-cysteine ligase (GCL) and the presence of sulfur-containing amino acid [34]. Under typical physiological circumstances, cellular GSH levels remain relatively stable, and excessive decrease of it can result in heightened oxidative stress, damage to macromolecules, and eventual cell death. Studies have shown that erastin, sulfasalazine (SAS), and sorafenib impede the synthesis of GSH by reducing the cellular concentration of cysteine through the inhibition of system Xc^-. It has also been reported that the elevated extracellular concentration of glutamate inhibits system Xc^-, thereby preventing glutamate efflux and impairing the entry of cystine into the cell. Additionally, buthionine sulfoximine (BSO) hinders the synthesis of GSH by suppressing GCL [35]. As a consequence, the depletion of intracellular GSH content generates a decline in the activity of GPX4, and the subsequent buildup of lipid peroxides and increased ROS, ultimately resulting in ferroptosis [36]. GPX4, an essential antioxidant enzyme, contains selenocysteine as its active sites and employs reduced GSH to convert hydrogen peroxide (H_2O_2) to water (H_2O), while GSH gets oxidized to glutathione disulfide (GSSG). Meanwhile, GSH, acting as an electron donor, plays a critical role in GPX4's catalytic activity, which in turn facilitates the conversion of harmful lipid hydroperoxides (LOOH) into harmless lipid alcohols (L-OH). This process leads to a reduction in phospholipid hydroperoxide levels, cellular protection against oxidative damage, and a potent defense against ferroptosis [37–40]. By

Table 1
Brief characteristics of the different types of cell death.

Death type	Ferroptosis	Apoptosis	Pyroptosis	Necroptosis	Autophagy
Morphological features	Small mitochondria, Diminished mitochondria crista, Normal nuclear size	Cellular and nuclear volume reduction, nuclear karyorrhexis, Chromatin agglutination, DNA fragmentation, apoptotic bodies formation	Cell swelling, Cell membrane incompletion, Lysis	Cytoplasm and organelles swelling, Membrane rupture, Cellular components spillover, Nuclear condensation	Double membrane autophagy, Vacuole accumulation, Nuclear condensation
Biochemical characteristic	Iron accumulation, Lipid peroxidation	DNA fragmentation	Inflammasome formation, proinflammatory factor spewing	Drop in ATP level	Raised lysosomal activity
Core components	System Xc^-/GPX4/SLC7A11/ NRF2/NCOA4/P53 /ACSL4/TFR1/FSP1 [2,4,17]	BCL-2 family/P53/CASPASE/ CDKs [25]	IL-18 [21,26] IL-1β [21,26] GSDMD [21,26] ASC/AIM2/NLRP1/NLRP3/PYRIN/NLRC4 [26]	RIPK1/RIPK3 [21,27] MLKL [27]	Multiple ATG proteins [22]

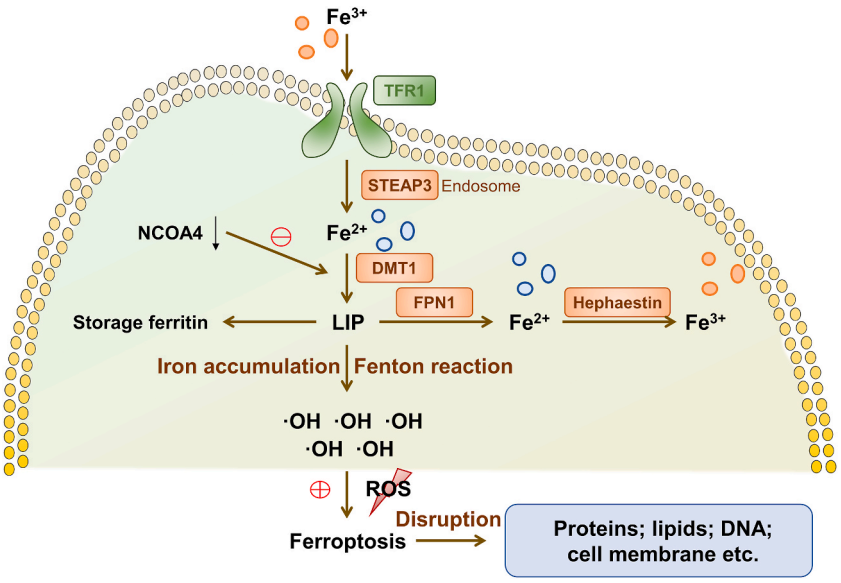

Fig. 1. Schematic illustration of the function of iron metabolism in ferroptosis. Iron overload leads to an increase in LIP and the accumulation of intracellular free iron ions, which catalyzes Fenton reaction and further promotes ferroptosis. TFR1: Transferrin receptor 1; STEAP3: Six-transmembrane epithelial antigen of prostate 3; FPN1: Ferroportin 1; DMT1: Divalent metal transporter 1; LIP: Labile iron pools; NCOA4: nuclear receptor coactivator 4.

report, the ras selective lethal 3 (RSL3) directly hinders GPX4, inducing ferroptosis in cells [41]. Additionally, lipoxygenase (LOX) stimulates cells to sustain elevated levels of hydroperoxides, which contributes to the initiation of ferroptosis [34]. To sum up, ferroptosis inducers (FINs) can be classified into two categories. Class II inducers directly impede GPX4 activity and trigger ferroptosis without consuming cellular GSH levels, such as RSL3. Conversely, class I inducers, distinct from RSL3, indirectly hinder GPX4 activity by inhibiting the system Xc^-, which subsequently reduces GSH production or depletes GSH content, ultimately culminating in ferroptosis [42,43] (Fig. 2).

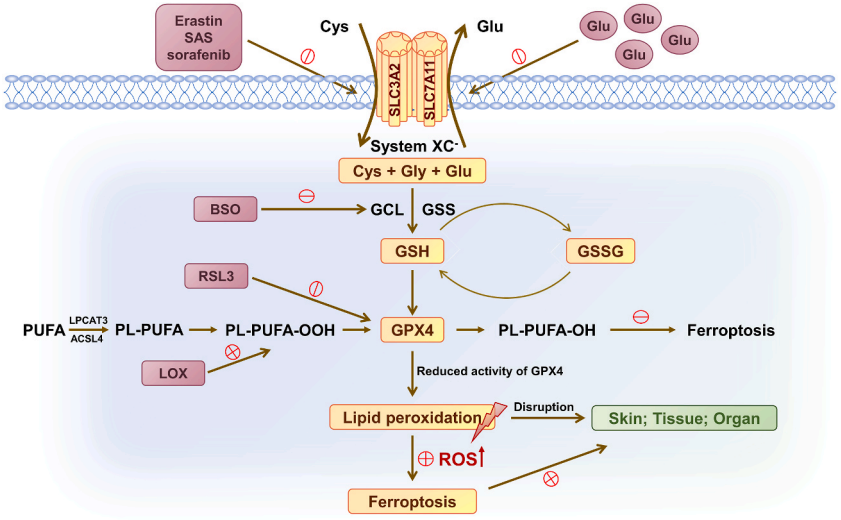

Fig. 2. System Xc^-/GSH/GPX4 axis and lipid metabolism are core regulatory mechanisms of ferroptosis. The system Xc^-/GSH/GPX4 axis can curb oxidative stress and actively opposes ferroptosis. Additionally, the certain peroxidation products catalyzed by enzymes that regulate fatty acid metabolism and phospholipid remodeling, have been identified as critical factors in the execution of ferroptosis. Cys: Cystine/cysteine; Glu: Glutamate; Gly: Glycine; SLC7A11: Solute carrier family 7 member 11; SLC3A2: Solute carrier family 3 member 2; GCL: Glutamate cysteine ligase; GSS: Glutathione synthetase; GSH: Glutathione; GSSG: Glutathione disulfide; GPX4: Glutathione peroxidase 4; PUFA: Polyunsaturated fatty acid; PL-PUFA: Phospholipid polyunsaturated fatty acid; LOOH: Lipid hydroperoxide; L-OH: Lipid alcohol.

2.3. Lipid metabolism and ferroptosis

Cell membrane integrity is contingent upon the presence of lipids. Disruption of the redox balance within organism causes extensive lipid peroxidation and subsequently ferroptosis [44]. ROS possess a propensity for reacting with polyunsaturated fatty acids (PUFAs), rendering membrane phospholipids, including biological membranes or organelle membranes, which are abundant in PUFAs, highly susceptible to ROS-induced damage [35]. This susceptibility is ascribed to the proximity of the double bond to the diallyl methylene group, making PUFAs more prone to oxidation compared to saturated fatty acids and mono-unsaturated fatty acids [7]. Lysophosphatidyl choline acyltransferase 3 (LPCAT3) and Acyl-coenzyme A (CoA) synthetase long chain family member 4 (ACSL4) are enzymes that regulate fatty acid metabolism and phospholipid remodeling during the process of ferroptosis [9]. ACSL4 is capable of catalyzing the formation of PUFA-CoA. It exhibits a preference for arachidonic acid (AA) during the esterification process with phospholipid (PL) [45]. It catalyzes the conversion of AA or adrenal acyl into their respective CoA derivatives (AA-CoA or ADA-CoA), which are then esterified by LPCTA3 to produce phosphatidyl ethanolamines (AA-PE and ADA-PE). These peroxidation products have been identified as crucial components in the execution of ferroptosis. And the phosphatidyl ethanolamines are latent targets of oxidative stress [46] (Fig. 2).

2.4. Other related signaling pathways

The tumor suppressor protein P53 have a significant impact on various cellular processes, including cell hypoxia, stress response, as well as oncogene activation. Its activation could suppress the Xc^- system, primarily by interfering with SLC7A11 transcription, leading to reduced cystine uptake, inhibited GSH synthesis, and induction of ferroptosis [47]. Moreover, P53 exhibits the capacity to augment ferroptosis through raising spermidine/spermine N1 acetyltransferase 1 (SAT1) and glutaminase 2 (GLS2) expression. However, the regulation of p53 on ferroptosis is contradictory. Some papers propose that P53 can decrease dipeptidyl peptidase-4 (DPP4) activity and up-regulate cyclin-dependent kinase inhibitor 1A (CDKN1A), which in turn inhibits ferroptosis [48]. A study identified that the mechanism by which ferroptosis-suppressing protein 1 (FSP1) inhibits ferroptosis is associated with the capture of lipid peroxyl radicals by NAD(P)H catalyzed by coenzymeQ10 (CoQ10) [49]. I It has also been reported that energy stress activates AMP-activated protein kinase (AMPK) to restrain ferroptosis. Furthermore, the involvement of mitochondria in ferroptosis induced by cysteine deprivation has been established [50]. It is widely recognized that nuclear factor erythroid 2-related factor 2 (NRF2) plays a pivotal function in preserving intracellular redox homeostasis and governing cellular oxidative stress as a prominent transcription factor. Research has demonstrated that upon ROS stimulation, NRF2 activates the expression of GPX4 to mitigate oxidative damage and ferroptosis [51]. Dimethyl fumarate (DMF) is an oral therapeutic small-molecule drug, which may prevent ferroptosis and improve AKI by inhibiting NRF2 degradation and exerting anti-peroxidation effects [52]. Meanwhile, NRF2 inhibitor also can be an effective way to induce ferroptosis in cancer cells [34](Fig. 3). Further investigation into additional mechanisms of ferroptotic cell death may be warranted in future research.

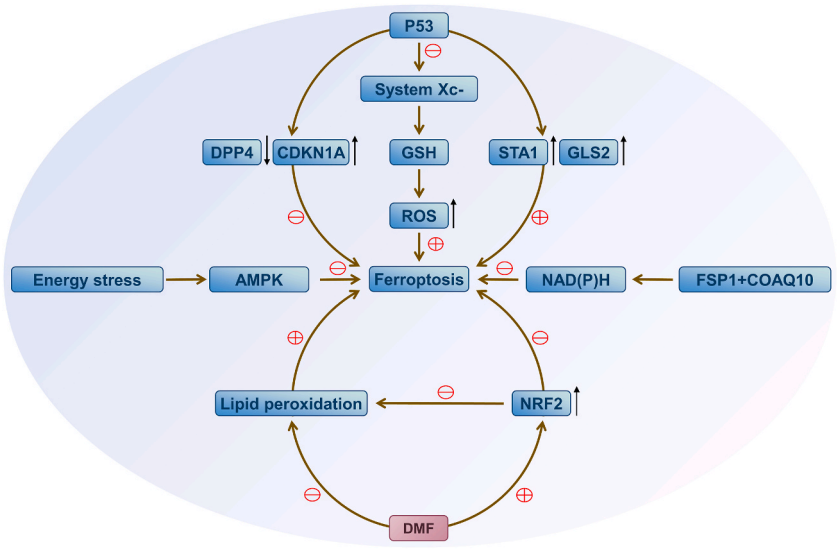

Fig. 3. Other modulated mechanisms in ferroptosis. Additional mechanisms and regulators, such as p53, FSP1, DMF, and energy stress, also contribute to the control of ferroptosis. DPP4: Dipeptidyl peptidase-4; CDKN1A: Cyclin-dependent kinase inhibitor 1A; GLS2: Glutaminase 2; SAT1: Spermidine/spermine N1 acetyltransferase 1; FSP1: Ferroptosis-suppressing protein 1; CoQ10:CoenzymeQ10; AMPK: AMP-activated protein kinase; DMF: Dimethyl fumarate; NRF2: Nuclear factor erythroid 2-related factor 2.

3. Ferroptosis in kidney diseases

3.1. The kidney as the classical organ to investigate ferroptosis in vivo

The classical organ to investigate ferroptosis in vivo is the kidney. Ferroptosis is characterized by the iron-dependent accumulation of lipid peroxidation products and lethal reactive oxygen species (ROS). The kidney is particularly susceptible to ferroptosis due to its high metabolic rate and abundant expression of lipoxygenases, which are enzymes that can promote lipid peroxidation, a key feature of ferroptosis. In addition, the kidneys are highly metabolic organs with a significant demand for oxygen, making them particularly prone to oxidative stress. This characteristic makes them a prime target for studying ferroptosis, which is driven by accumulation of lipid peroxides and reactive oxygen species (ROS).

Numerous studies have indicated that ferroptosis, characterized by aberrant iron and lipid metabolism, is present in diverse kidney diseases, including acute kidney injury (AKI), chronic kidney disease (CKD), renal cancer, polycystic kidney disease and so on. These findings imply that directing interventions towards ferroptosis could provide a novel therapeutic approach for renal disorders.

3.2. Ferroptosis and acute kidney injury

AKI frequently manifests in patients admitted to hospitals and is linked to high morbidity and mortality rates. Its incidence ranges from 5 % to 20 % among hospitalized patients and exceeds 60 % of intensive care unit (ICU) patients [53–55]. Regrettably, no targeted interventions are presently accessible to effectively alleviate AKI or facilitate recuperation. Consequently, there exists an imperative necessity to explore novel therapeutic targets and medications for addressing AKI and improving patients' prognosis. Recently, numerous studies have extensively documented and validated the significant role of ferroptosis in the pathogenesis of AKI, enhancing our understanding of its immense therapeutic potential. Iron-dependent ferroptosis has been firstly observed to precipitate the co-ordinated necrosis of renal tubules in kidney proximal tubules cell death models, ischemia-reperfusion injury and oxalate crystal-induced AKI models [56,57]. It has become evident that the extensive necrotic regions observed during tubular necrosis are derived from cells that have succumbed to ferroptosis, which might initiate cell death propagation [58–60]. Recent studies have revealed that platelet-activating factor (PAF), PAF-like phospholipids (PAF-LPLs) and human proximal tubular epithelial cell-derived small extracellular vesicles mediate synchronized tubular ferroptosis [61,62]. Ni et al. observed a notable upregulation of ferroptosis-associated genes in AKI patients [63]. Concurrently, a large number of preclinical experiments has defined that targeted inhibition of ferroptosis may confer protection against renal tubular injury in AKI [64–66]. In addition, employing AI bibliometric analysis, we conducted a comprehensive examination of the scholarly literature pertaining to ferroptosis and its correlation with the kidney, revealing that AKI has emerged as the predominant area in the past decade (Fig. 4). These investigations underscore the robust linkage between ferroptosis and AKI.

3.2.1. IR-induced acute kidney injury

Renal ischemia-reperfusion (IR) injury is a prevalent form of AKI in clinical settings. The critical determinant of its pathogenesis is renal tubular cell death. However, the effectively intervention mitigating the detrimental effects of IR injury is limited. It is reported that ferroptosis was observed in renal transplant-induced IR injury [67]. Some researchers have explored the relationship between ferroptosis and IR injury following renal transplantation, claiming that certain ferroptosis-related genes may be used to predict graft loss and delayed recovery of renal function after renal transplantation [68,69]. These studies may provide valuable insights for implementing early intervention measures, thereby enhancing the survival rate among patients undergoing renal allotransplantation.

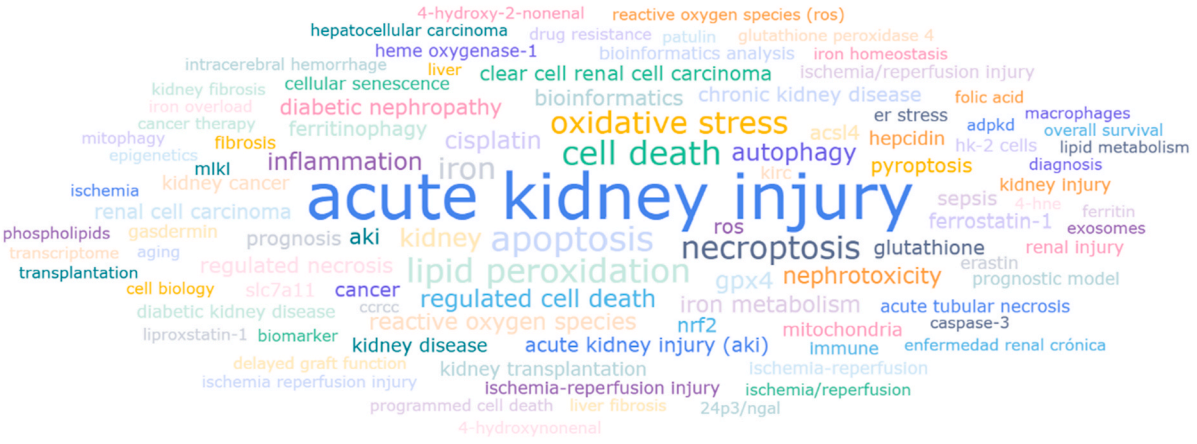

Fig. 4. Other modulated mechanisms in ferroptosis. The word cloud image generated by AI tools displays the most closely associated key terms related to ferroptosis, with "acute kidney injury" being the most prominent.

Simultaneously, Sui et al. discovered that the RNA-binding protein CIRBP activated ferritinophagy during renal IR injury through its interaction with ELAVL1 [70]. Huang et al. demonstrated that the inhibition of augmenter of liver regeneration (ALR) generated elevated levels of ROS and mitochondrial dysfunction in IR model in vitro, ultimately aggravating ferroptotic cell death [71]. Recently, dipeptidase-1 (DPEP1) that is highly expressed on proximal tubular cells and peritubular capillaries of the kidney has been identified as an important regulators of ferroptosis which can recruit neutrophils when the kidney suffers from IR injury [72–74]. In addition, research has indicated that miR-182-5p and miR-378a-3p inhibit the expression of GPX4 and SLC7A11, which subsequently promotes ferroptosis and exacerbates IR-triggered renal injury in rats [75]. Several experiments have also shown that inhibiting ferroptosis can reduce renal IR injury. A study utilizing the hypoxia-reoxygenation (HR) model system of renal tubular epithelial cells (RTECs) revealed that the inhibition of miR-3587 promoted the upregulation of heme oxygenase-1 (HO-1), thus safeguarding kidney tissues against IR-triggered ferroptosis. Su et al. have demonstrated that the silencing of Pannexin 1 also could lead to an increase in the levels of HO-1, resistance to ferroptotic cell death, and protection of renal IR injury [76]. In addition, during renal IR injury, the autophagy-mediated degradation of OTUD5, a protein that stabilizes GPX4 to prevent ferroptosis, leads to increased renal tubular cell ferroptosis and AKI [77].

Meanwhile, some studies have sought to elucidate that certain compounds or exosomes could intervene the progression of renal IR injury through the targeting of ferroptosis. Lin et al. denoted that thachrysophanol promoted GPX4 and SLC7A11 expression, thus attenuating the buildup of lipid ROS during HR and subsequently preventing ferroptosis in RTECs [78]. Zhang and his team provided initial evidence indicating that irisin could enhance the levels of GPX4 and alleviate IR-induced AKI, while the protective effect could be nullified by ferroptosis-inducing agent-RSL3 [79]. In the pioneering study examining the impact of pachymic acid (PA) on ferroptosis in IR-AKI, PA was found to enhance the NRF2 signaling pathway and increase the expression of the subsequent ferroptosis-associated proteins, including HO-1, SLC7A11 and GPX4, thus exerting a protective effect against IR injury in mice [80]. Moreover, studies have shown that XJB-5-131, as a mitochondrial-targeted nitroxide, could facilitate the repair of RTECs following IR injury through suppressing ferroptosis [81]. Of note, Sun et al. identified that the long non-coding RNA (lncRNA) taurine-upregulated gene 1 (TUG1) present in exosomes originate from human urine-derived stem cells (USC-Exo) may leading to the suppression of ACSL4-mediated ferroptosis in mice suffered IR-AKI and in human RTECs treated with HR [82]. This finding presents a novel avenue for clinical development of targeted therapeutic measures to restrain ferroptosis. In conclusion, ferroptosis is an indispensable factor in renal ischemia and perfusion injury-induced AKI.

3.2.2. Exogenous drugs/toxins-induced acute kidney injury

In addition to IR injury, current animal models of AKI can be induced by the injection of exogenous drugs or toxins through their side or poisoning effects. Previous studies have provided evidence that ferroptosis, but not necroptosis is critical in folic acid (FA)-induced AKI [83,84]. It declared the irreplaceable function of ferroptosis in FA-induced AKI. Li and colleagues discovered the occurrence of ferroptosis distinguished by reduced levels of GPX4, SLC7A11, and FSP1, along with increased concentrations of iron and malondialdehyde (MDA) in FA-AKI. Nevertheless, treatment with nuciferine effectively reversed these alterations caused by nephrotoxicity of FA, thereby yielding beneficial effects in kidneys [85]. Guo et al. identified that loss of circadian clock components Rev-erb-α/β weakened the sensitivity to FA-AKI in mice via limiting ferroptotic cell death [86]. It is well-known that FA often disrupts redox homeostasis, leading to extensive tubular necrosis and inflammation. Subsequent investigation revealed that A-lipoic acid (LA), an antioxidant, could reduce the iron overload and boost cellular response to oxidative stress in FA-AKI. Collectively, these combined effects contribute to mitigating ferroptotic damage to the kidney [87].

As known is to all, metformin has benefits for age-related disorders, however, it unexpectedly worsens acute kidney injury and mortality in mice by inducing ferroptosis and neutrophil infiltration, with the mechanism involving an iron-dependent pathway that exacerbates kidney damage [88].

Cisplatin, a commonly employed chemotherapeutic agent, exhibits remarkable efficacy in treating various solid tumors. However, high doses of cisplatin can induce evident nephrotoxicity in patients. It has been reported that ferroptosis is implicated in the pathogenesis of cisplatin-AKI and may serve as a new target for intervention [89]. Zhang et al. have identified ferroptosis as a significant mechanism contributing to the renal cell death caused by cisplatin. They further confirmed that huaier polysaccharide (HP-1) effectively inhibited ferroptotic cell death and reduced kidney damage through the activation of the NRF2/HO-1 signaling pathway [90]. Similarly, ADAMTS-13 also could counteract ferroptosis and guard cisplatin-induced nephrotoxicity through modulating the NRF2 signaling pathway [91]. Furthermore, Kim et al. verified that the administration of loganin in mice could enhance GPX4 activity, suppress ferroptosis, and consequently ameliorate kidney injury [92]. Cai et al. found that the downregulation of Sulfide:quinone oxidoreductase (SQOR) via SYVN1-mediated ubiquitination contributes to mitochondrial dysfunction and exacerbates ferroptosis and kidney damage in cisplatin-induced AKI [93]. Several studies have found that polydatin (PD) exerts multiple beneficial effects in cisplatin-AKI mouse models via preserving the balance of iron metabolism and system Xc^--GSH-GPX4 axis [94]. Li et al. demonstrated the potential of tetrahedral DNA nanostructures (TDNs) in mitigating cisplatin-induced renal injury by reducing ROS production, increasing GPX4 expression, and preventing RSL3-induced ferroptosis [95]. In addition, paricalcitol, a Vitamin D receptor (VDR) agonist, may offer protection against cisplatin stimulation by preserving GPX4 expression [96]. In summary, targeting ferroptosis may be a viable therapeutic strategy for cisplatin-triggered AKI.

It should be noted that contrast-induced-AKI (CIAKI) continues to be a dreaded complication and is a prevalent cause of the hospital-acquired AKI. A study showed that iodinated contrast medium administration to rats lacking silent information regulator 1 (SIRT1) resulted in the inadequate production GPX4, thereby exacerbating contrast-induced ferroptosis. Intriguingly, calorie restriction was found to mitigate renal damage induced by contrast medium [97]. DPEP1 plays a crucial role in the development of CIAKI through a multistep process involving immune surveillance and Nlrp3-dependent inflammation, which facilitates the reabsorption and

concentration of contrast agents in tubular epithelial cells. Linkermann et al. identify that DPEP1 contributes to dexamethasone-induced ferroptosis sensitization [98,99]. However, limited research has been conducted on the involvement of ferroptosis in CIAKI, necessitating further investigation for clarification in the future.

3.2.3. Endogenous Stimulus-induced acute kidney injury

Sepsis is a commonly encountered syndrome in clinical practice, with the kidneys being particularly vulnerable to its impact. Additionally, AKI resulting from sepsis not only heightens the risk of developing chronic diseases, but also amplifies the mortality rate among critically patients during hospitalization [100,101]. Therefore, it is imperative to prioritize the investigation of the underlying mechanism of sepsis-related AKI in order to yield favorable outcomes for patients. Xiao et al. discovered the presence of ferroptosis in sepsis-AKI and demonstrated maresin conjugates in tissue regeneration 1 (MCTR1) to restrain ferroptosis through the NRF2 signaling [102]. In another study, isoliquiritigenin (ISL) was found to protect against sepsis-AKI mimicked by lipopolysaccharide (LPS) via the preservation of iron metabolic homeostasis and the promotion of system Xc^--GSH-GPX4 axis expression [103]. Furthermore, Yao et al. proposed that the mitigation of septic kidney injury in individuals with type 2 diabetes could be achieved by targeting NADPH-induced ferroptosis [104]. 7-DHC acts as a natural anti-ferroptotic metabolite, with enzymes in distal cholesterol biosynthesis, particularly DHCR7, playing opposing roles in ferroptosis regulation, highlighting potential therapeutic strategies targeting 7-DHC levels for renal IR injury [105,106].

Numerous studies have shown that superabundant iron accumulation could evoke ferroptosis and facilitate renal damage. In rhabdomyolysis-induced AKI, Hue et al. discovered excessive iron burden and lipid peroxidation, which are hallmark features of ferroptotic cell death. They also proposed that curcumin could suppress ferroptosis-mediated cell death through enhancing the expression of HO-1, thus mitigating renal injury [107]. Conversely, Zhao et al. demonstrated that iron deficiency also could worsen rhabdomyolysis-induced AKI through augmenting specific non-heme and/or heme catalytic iron species, which subsequently activated downstream pathophysiologic mechanisms [108]. Based on the aforementioned findings, we consider that any factors that disrupt iron homeostasis, including iron deficiency or iron burden, could trigger ferroptosis via initiating oxidative damage through the disturbance of iron metabolism.

3.3. Ferroptosis and chronic kidney disease

CKD is widely acknowledged as a global health problem, with high mortality and morbidity. A notable aspect of CKD is the presence of renal fibrosis, characterized by the excessive accumulation of extracellular matrix, which severely compromises renal structure and exacerbates the decline in kidney function [109,110]. Unfortunately, the reversal of fibrosis and restoration of the original kidney function are exceedingly challenging to attain. Encouragingly, features indicative of ferroptosis have been identified in the CKD animals and patients, including downregulation of GPX and GSH expression levels, along with increased ROS concentration [111,112]. These findings hold promise for future treatments aimed at delaying the chronic progression of renal disease. In mice operated with unilateral ureteral obstruction (UUO), the ferroptosis inhibitor liproxstatin-1 (Lip-1) largely attenuate the renal fibrosis and kidney injury by relieving ferroptosis in RTECs [113]. Similar results were observed in another experiment that inhibited ferroptosis [114]. In addition, Nobiletin (Nob) may ameliorate ferroptosis-associated injury and diminish renal fibrosis and inflammation, thereby delaying the development of CKD [115]. A separate study has identified iron metabolism disorder as a prominent contributor to cellular death in the residual kidneys following 5/6 nephrectomy. Administrating cisplatin and deferoxamine could protect against the detrimental influence of renal fibrosis through preserving iron homeostasis [116]. It is well-established that the process of renal fibrosis can be exasperated by the persistent inflammation in kidney. Tocilizumab, as an emerging monoclonal antibody, binding to interleukin-6 receptor (IL-6R) and blocking the downstream signaling of IL-6, has been widely utilized in chronic inflammatory diseases. Yang et al. found that Tocilizumab mimotope could alleviate the renal fibrosis in virtue of blunting ERK signaling and lightning kidney ferroptosis. It is possible that Tocilizumab mimetic epitopes vaccine may bring inspiring efficacy for patients with CKD in the near future [117].

3.4. Ferroptosis and diabetic nephropathy

Ferroptosis has been implicated in the development of diabetic nephropathy (DN) and is anticipated to be a promising therapeutic avenue for the treatment of DN in the future [118,119]. A survey by Feng et al. suggested that ferroptosis may aggravate the renal tubular injury and thus worsen DN [120]. The down-regulation of NRF2 exacerbates ferroptotic cell death in RTECs cultured under high-glucose (HG). However, this phenomenon can be reversed by fenofibrate, which further delays the progression of DN to end-stage renal disease [121]. Similarly, there are reports indicating the involvement of high-mobility group box-1 (HMGB1) and salusin-β in the modulation of the NRF2 signaling pathway, thereby regulating HG-induced ferroptosis [122,123]. Hence, the significance of NRF2 in the occurrence of ferroptosis in diabetic renal injury is apparent. Wu et al. demonstrated the modulatory function of single-strand DNA-binding protein 1 (SSBP1) to activate the DNA-PK/P53 signaling path which may drive ferroptosis in podocytes [124]. Zhang et al. revealed that peroxiredoxin 6 (PRDX6) could reduce ferroptosis triggered by HG and prevent further deterioration of podocytes. This protective effect was potentially attributed to the involvement of the transcription factor specific protein 1 (SP1) [125]. Interestingly, advanced diabetic nephropathy, according to the research by Wang et al., may be more susceptible to ferroptosis. And they further suggested that arachidonate 15 lipoxygenase (ALOX15) is a promising target for ferroptosis [126]. Additionally, some studies have found that specific traditional medicine components could improve DN by modulating ferroptosis. For instance, glabridin (Glab) could facilitate the activation of the system Xc^--GSH-GPX4 axis, thereby reducing ferroptosis in DN and exhibiting a potential

therapeutic effect [127]. Another Study has revealed that calycosin could restore cell viability and decrease lipid ROS, thereby suppressing HG-induced ferroptosis and improving kidney damage in diabetes [128].

3.5. Ferroptosis and renal tumors

The uncontrolled proliferation of cancer cells is a prominent feature that necessitates the induction of their death in order to halt tumor progression [129]. Currently, ferroptosis, recognized as a distinct form of cell death, has emerged as a significant focus of tumor research worldwide. Ferroptosis assumes a crucial role in the treatment and prognosis of tumors by promoting malignant cell death and impeding tumor progression [130]. While still in its nascent stages, it holds substantial potential for future investigations [131]. With the gradual improvement of living standards, there has been a consistent rise in the prevalence of kidney cancers over time. Statistical data indicates that clear cell renal cell carcinoma (ccRCC) accounts for approximately 75 percent of all kidney cancer cases, establishing it as the most predominant subtype [132,133]. An abundance of lipid droplets can be observed in ccRCC, which aligns with one of the pivotal features of ferroptosis-lipid accumulation, suggesting a significant association between them [134]. Multiple studies have substantiated the occurrence of ferroptosis in ccRCC and postulated that inhibiting ferroptosis may augment the unruly amplification of renal cancer cells. Conversely, inducing ferroptosis seems to have the potential to improve patient survival, highlighting the significance of targeting iron and lipid metabolism associated with ferroptosis as an effective approach for tumor management [135–137]. Moreover, many articles have documented the utilization of ferroptosis-related genes (FRGs) for prognostic prediction in ccRCC patient [138–140]. These studies suggest a strong correlation between FRGs and immune response, clinicopathological features (such as tumor stage and grade), tumor progression, and unfavorable prognosis in ccRCC [141–143]. Examples of FRGs include kinesin family member 23 (KIF23) [144], suppressor of variegation 3e9 homolog 1 (SUV39H1) [145], and short/-branched chain acyl-CoA dehydrogenase (ACADSB) [146], among others. Meanwhile, some ferroptosis-related lncRNA (FRlncRNA) has been proven to regulate the advancement of renal cancers and act as prognostic indicators for ccRCC patients [147–149].

The System Xc^-/GSH/GPX4 axis and iron metabolism, as essential parts of the regulatory mechanism of ferroptosis, have also been widely studied in renal tumors. Ye et al. found that blocking STEAP3 expression in kidney cancer cells was observed to suppress the System Xc^-, leading to the induction of ferroptotic cell death and ultimately impeding disease progression [150]. Research has indicated that inhibiting GSH biosynthesis could induce ferroptosis in ccRCC cells, diminish the cellular viability, and hinder tumor proliferation. Therefore, the enhancement of GSH production may potentially improve the survival rate and prognosis of patients with ccRCC [151,152]. Moreover, GPX4 has been identified as an effective object for ccRCC, which underscores the importance of comprehending its underlying biological functions to advance ccRCC therapy [153]. The potential predictive value of the lipid drop-associated protein (HILPDA) in determining drug sensitivity towards GPX4 has been proposed [154,155]. FPN1 is currently the sole known iron export protein in mammals, and Zhu et al. suggested that upregulation of microRNA-4735-3p may arise ferroptosis in ccRCC through targeting FPN1 [156]. Of note, luteolin, a natural flavonoid arisen from vegetables and fruits, has been demonstrated to induce iron accumulation and trigger ferroptotic cell death by enhancing HO-1 activity in ccRCC, therefore positioning it as a prospective therapeutic agent in the future [157].

In addition, the researchers also demonstrated additional regulatory mechanisms in ferroptosis. The down-regulation of Succinate dehydrogenase (SDH) in ccRCC could decrease ferroptotic events, thus exacerbating renal tumor deterioration [158]. Zheng and colleagues emphasized that the inactive mutation of tumor suppressor KDM5C in cancer cells could lead to the reprogramming of glycogen metabolism and render the cells insensitive to ferroptosis [159]. On the contrary, the downregulation of the adipokine chemerin in cancer cells may promote fatty acid oxidation, thus aggravating ferroptosis [160]. Mou et al. proposed that the elevated expression of nuclear receptor coactivator 4 (NCOA4) in ccRCC patients could augment ferroptosis, resulting in improved overall survival rates. Furthermore, it may synergize with immunotherapy to combat tumor progression [161]. Intriguingly, Yang et al. discovered that cell density could serve as a new therapeutic strategy for renal cancer by modulating ferroptosis [162]. Certain researchers have successfully driven ferroptosis in hepatocellular carcinoma using engineered exosomes, which exhibits robust tumor targeting capacity. This innovative methodology presents a new avenue to impede the advancement of various tumors, including ccRCC [163].

4. Conclusion and perspectives

Ferroptosis is a well-regulated form of cell death distinguished by aberrant iron homeostasis and lipid peroxidation. The review primarily discusses the significance of ferroptosis in kidney disorders, elucidates the underlying mechanisms and signaling pathways, and summarizes strategies to effectively target ferroptosis in these pathological conditions. However, it's worth noting that renal diseases also encompass other forms of autonomous or interconnected RCD, including necroptosis, pyroptosis, and mitochondrial permeability transition-regulated necrosis [39,164]. Lu et al. established that the deficiency of Rheb1 (a Ras homolog enriched in the brain) in AKI rodent model, exhibited heightened mitochondrial dysfunction and tubular cell death including apoptosis, necroptosis and ferroptosis [165]. Necroptosis and ferroptosis may work together in the progression of acute renal damage [166]. Several studies have verified ferroptosis as a prominent mechanism for triggering AKI, and that necroptosis induces subsequent cell death [167]. Furthermore, A different study confirmed that oxalic acid served as an originator of autophagy in RTECs, ultimately inducing the initiation of ferroptotic cell death [168]. It has been validated that multiple cell death pathways contribute to the onset and progression of renal diseases [169]. The synergistic or antagonistic effects from different forms of cell death remain incompletely understood. A more detailed understanding of their interactions and developing efficacious treatment strategies is extremely urgent. Furthermore, the majority of investigations on ferroptosis in the kidney concentrate on AKI. However, CKD and AKI are closely intertwined, as

evidenced by numerous studies [170–172]. AKI could promote the subsequent development of CKD [173,174], while CKD itself poses a risk factor for the recurrence of AKI [175]. To date, the precise mechanism underlying the transition from AKI to CKD remains elusive. Existing research suggests that lipid accumulation, oxidative stress, inflammation and mitochondrial dysfunction implicate in the progression from AKI to CKD. Meanwhile, there exists a strong association between these factors and the occurrence of ferroptosis. It has been suggested that the likelihood of CKD development following ferroptotic cell death is higher in cases of AKI [176]. However, limited research has been conducted in this area. Consequently, a comprehensive exploration of the specific mechanism underlying ferroptosis in the progression from AKI to CKD is warranted.

Currently, researchers have discovered various inducers and inhibitors related to ferroptosis (Table 2). Notably, certain drugs already approved for clinical application, including sorafenib and sulfasalazine, have been found to possess relevant properties [177]. Additionally, Eikan Mishima et al. demonstrated some cytochrome P450 substrates drugs as anti-ferroptosis agents such as rifampicin, promethazine, omeprazole, propranolol, and thyroid hormone [178]. It means that the drug repurposing has garnered significant attention in the field. Li et al. conducted an observation wherein they found that roxadustat (FG-4592), a prolyl hydroxylase inhibitor targeting HIF, effectively mitigated ferroptosis by suppressing iron overload and lipid peroxidation [179]. It is worth mentioning that inhibitors of prolyl hydroxylase have shown certain efficacy in the treatment of clinical renal anemia [180] and COVID-19 pneumonia [181]. Besides, as previously mentioned, additional Chinese medicine or extracts derived from traditional plants may have the potential to modulate ferroptosis signaling pathways. Of note, Wang et al. [6] have reported that Quercetin (QCT) could significantly inhibit the expression of activation of transcription factor 3 (ATF3), thereby reducing ferroptosis related events. Interestingly, QCT is also a prominent constituent of “Huangkui Capsule”, a therapeutic agent utilized for renal protection.

A remarkable advancement in the field is the ongoing exploration of ferroptosis outside the laboratory, with numerous researchers boldly attempting to integrate it into clinical trials. For instance, investigators have conducted a comparative analysis of predominant alterations in SLC7A11, GPX4, and P54 among a cohort of 20 epileptic and 20 healthy children. Presently, a study in China is inquiring the involvement of PM2.5 and IL-6 in NRF2-dependent ferroptosis pathways in epileptic patients. Furthermore, another clinical trial is enrolling participants to investigate the involvement of ferroptosis in the impairment of the intestinal mucosal barrier in individuals with sepsis. Although an escalating number of researchers are actively elucidating the impact of ferropotosis on renal injury, it is pity that the clinical trials on ferroptosis and renal disease have not been conducted currently due to the following possible reasons. Firstly, the concept of ferroptosis is relatively recent, and the majority of studies to date have been preclinical, focusing on cellular or animal models. The transition from these models to human trials requires a thorough understanding of the safety, efficacy, and pharmacokinetics of potential treatments in humans, which is currently incomplete. Secondly, there is a lack of validated biomarkers to accurately identify and measure ferroptosis in patients, which is essential for the development of targeted therapies and for monitoring treatment response. Thirdly, ferroptosis involves complex cellular pathways that are not fully understood. This complexity makes it challenging to develop drugs that can specifically target ferroptosis without causing off-target effects that may lead to unintended consequences or toxicity. For instance, it is reported that ferroptotic stimuli erastin can cause DNA damage in bone marrow cells [187,188]. Fourthly, small molecule inducers or inhibitors of ferroptosis have demonstrated limitations, including suboptimal bioavailability, inadequate water solubility, and insufficient targeting capabilities, all of which constitute significant obstacles to their clinical translation [189,190].

In our opinion, the poor targeting capability and limited bioavailability could be improved by various drug delivery platforms based on nanoparticles [191,192]. Regarding the enhancement of ferroptosis monitoring capabilities, several strategies can be employed. First of all, specific biomarkers should be developed by utilizing advanced omics technologies such as genomics, proteomics, lipidomics, and metabolomics. Further, we could develop and apply advanced imaging techniques, such as magnetic resonance imaging (MRI) with iron-sensitive sequences or positron emission tomography (PET) using ferroptosis-specific probes, to visualize ferroptosis in real-time in tissues and organs. Besides, fluorescent or bioluminescent reporters can be utilized to target ferroptosis-specific markers to monitor cellular and molecular changes in vivo. Consequently, it is anticipated that a deeper understanding of therapies related to ferroptosis and their clinical implementation will be achieved in the foreseeable future, thereby potentially yielding advantageous outcomes for patient.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Mingzhu Jiang: Writing – original draft, Funding acquisition. **Shujun Wu:** Writing – original draft. **Kun Xie:** Writing – review & editing. **Gang Zhou:** Writing – review & editing. **Wei Zhou:** Validation, Investigation, Funding acquisition. **Ping Bao:** Writing – review & editing, Conceptualization.

Table 2
The small molecules and drugs that could induce/inhibit ferroptosis.

Reagents	Targets	Mechanisms	Diseases and models	References
Inducers				
Erastin,	System Xc^-	cysteine reduction	AKI; HO-$1^{-/-}$ renal proximal tubule cells	[11]
Sorafenib	System Xc-	cysteine reduction 234	Cancer; hepatocellular carcinoma (HCC) cells	[182]
BSO	GSH	GSH depletion	Renal cancer; 769P, 786-O, A-498, A704, ACHN, Caki-1, Caki-2, G401, G402, RCC4 VHL (−/−), RCC4 VHL (+/+), SK-NEP-1 and SW156 cell lines	[35]
RSL3	GPX4	GPX4 inactivation	AKI; HK2, mouse renal tubular epithelial cells	[41]
Legumain	GPX4	GPX4 inactivation	AKI; bilateral ischemia-reperfusion injury (IRI) of renal arteries or folic acid, hypoxia-induced mouse renal tubular epithelial cells	[166]
miR-182-5p, miR-378a-3p	GPX4, System Xc^-	GPX4 inactivation; SLC7A11 suppression	AKI; IR-AKI rat model; hypoxia- reperfusion induced HK-2 cells injury	[75]
miR-3587	HO-1	GPX4 inactivation; Iron accumulation	AKI; hypoxia-reoxygenation treated NRK-52E cells	[183]
Rev-erb-α/β	RORE *cis*-elements	SLC7A11 suppression; HO-1 downregulation	AKI; Folic acid (FA)-induced AKI	[86]
HMGB1	NRF2	Unknown	Diabetic nephropathy; High glucose stimulated mesangial cells	[122]
Salusin-β	NRF2	Unknown	Diabetic nephropathy; HK-2 cells exposed to high glucose	[123]
SSBP1	DNA-PK/P53	Unknown	Glomerular podocyte injury; high fructose-fed rats and high fructose-exposed podocytes	[124]
lncRNA SLC16A1-AS1	miR-1433p/ SLC7A11	System Xc^- inhibition	ccRCC; 786-O and Caki-1 cells	[149]
MicroRNA-4735-3p	SLC40A1	Unknown	ccRCC; 796-O and A498 cells	[156]
Luteolin	HO-1	Iron accumulation; GSH depletion	ccRCC; 786-O and OS-RC-2 cells	[157]
Inhibitors				
NRF2	GPX4	GPX4 activation	AKI; Cecum ligation and puncture (CLP)-induced septic-AKI (rats); LPS-induced HK-2	[51]
Liproxstatin-1	ROS	Enhanced lipid peroxidation	AKI; severe acute pancreatitis-induced AKI	[65,184]
Ferrostatin-1	ROS	Enhanced lipid peroxidation	AKI; NIH3T3, HT-1080, Murine proximal tubular epithelial cells (MCTs), Mouse embryonic fibroblasts (MEFs) from C57BL/6J mice	[185]
Vitamin K1 and its derivatives	ROS; GPX4	Enhanced lipid peroxidation; GPX4 activation	AKI; IR-AKI (C57BL/6J mice); NIH3T3, HT-1080, Murine proximal tubular epithelial cells (MCTs), Mouse embryonic fibroblasts (MEFs) from C57BL/6J mice	[185]
FSP1	CoQ10	Catalyzed NAD(P)H	AKI; Cecum ligation and puncture (CLP)-induced septic-AKI (rats); LPS-induced HK-2	[49]
MIF	Oxidative stress	Reduced oxidative stress	AKI; IR/rhabdomyolysis-AKI (mice); hydrogen peroxide (H2O2) or hypoxia in primary murine tubular epithelial cells (pmTECs)	[64]
XJB-5-131	antioxidant	GPX4 activation; ACSL4 suppression	AKI; IR-AKI (C57BL/6 mice)	[81]
lncRNA TUG1	SRSF1	ACSL4 stabilization	AKI; IR-AKI (C57BL/6 mice); H/R-treated HK-2	[82]
ALR	GSH; GPX4	Unknown	AKI; HR-treated HK-2	[71]
Irisin	GPX4, NRF2	GPX4 activation	AKI; IR-AKI (C57BL/6 mice)	[79]
Pachymic acid	GSH; GPX4; System Xc^-	GSH increase; GPX4 activation; SLC7A11 promotion	AKI; IR-AKI (C57BL/6 mice)	[80]
Thachrysophanol	ROS; GPX4; System Xc^-	GPX4 activation; SLC7A11 promotion	AKI; HR-treated HK-2	[78]
FG-4592	AKT/GSK-3β/ NRF2	Reduced iron overload and lipid peroxidation	AKI; FA-AKI (C57BL/6J mice)	[179]
A-lipoic acid	Iron; ROS; GSH; GPX4; System Xc^-	Decreased iron accumulation and oxidative stress; SLC7A11 promotion	AKI; FA-AKI (C57BL/6J mice)	[87]
Huaier polysaccharide	NRF2/HO-1	Decreased lipid peroxidation; GSH increase	Acute Cardiotoxicity; DOX-treated BALB/c mice; DOX-treated rat cardiomyocyte cell line H9c2	[90,186]
ADAMTS-13	NRF2	Unknown	AKI; Cisplatin-AKI (C57BL/6J mice)	[91]
Loganin	ERK1/2	Unknown	AKI; Cisplatin-AKI (C57BL/6J mice)	[92]
Polydatin	System Xc^--GSH-GPX4; Iron	Reduced iron accumulation; ROS suppression; GSH increase; GPX4 activation	AKI; Cisplatin-AKI (C57BL/6J mice); cisplatin-treated HK-2	[94]
TDNs	RSL3	ROS suppression; GPX4 activation	AKI; cisplatin-treated HK2	[95]
Paricalcitol	GPX4	GPX4 activation	AKI; Cisplatin-AKI (C57BL/6J mice); Cisplatin-treated HK2	[96]
Curcumin	HO-1	Increased GSH concentration	AKI; Rhabdomyolysis-AKI (C57BL/6J mice); protoporphyrin treated proximal murine tubular epithelial cells (MCTs) and HK-2	[107]
MCTR1	NRF2	Unknown	AKI; CLP-AKI (C57BL/6J mice); LPS treated HK-2	[102]

(*continued on next page*)

Table 2 (*continued*)

Reagents	Targets	Mechanisms	Diseases and models	References
Isoliquiritigenin	System Xc^--GSH-GPX4; Iron	Preserved iron homeostasis; GSH increase; GPX4 activation	AKI; LPS-AKI (C57BL/6J mice); LPS treated HK-2	[103]
Nobiletin	GPX4; Iron	Unknown	CKD; UUO-nephropathy model (C57BL/6J mice)	[115]
Tocilizumab mimotope	Iron; Lipid peroxides	Reduced lipid peroxidation and iron accumulation	CKD; UUO-nephropathy model (C57BL/6J mice)	[117]
Fenofibrate	NRF2	Unknown	Diabetic nephropathy; Streptozotocin-induced DN model (DBA/2J diabetic mice); High-glucose (HG) treated human renal proximal tubular (HK-2) cells	[121]
Peroxiredoxin 6	Specific protein 1	Unknown	Diabetic nephropathy; Streptozotocin-induced DN mice; High-glucose treated mouse glomerular podocytes MPC5	[125]
Glabridin	System Xc^--GSH-GPX4	GSH increase; GPX4 activation; SLC7A11/SLC3A2 promotion	Diabetic nephropathy; Streptozotocin-induced DN model (SD rats); High-glucose-induced NRK-52E cells	[127]
Calycosin	NCOA4	Reduced ROS	Diabetic nephropathy; High-glucose treated HK-2 cells	[128]
Quercetin	ATF3	Unknown	AKI; IR-AKI (C57BL/6J mice); Era or RSL3 treated NRK-52E cells and HK-2 cells	[6]
Dimethyl fumarate	NRF2	Increased anti-peroxidation effects	AKI; Cisplatin/FA/IR-AKI (C57BL/6J mice); Cisplatin treated HK-2 cells	[52]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] K. Kalantar-Zadeh, et al., Chronic kidney disease, Lancet 398 (10302) (2021) 786–802.
[2] Q. Feng, et al., Ferroptosis and acute kidney injury (AKI): molecular mechanisms and therapeutic potentials, Front. Pharmacol. 13 (2022) 858676.
[3] B.R. Stockwell, et al., Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease, Cell 171 (2) (2017) 273–285.
[4] J. Li, et al., Ferroptosis: past, present and future, Cell Death Dis. 11 (2) (2020) 88.
[5] D. Martin-Sanchez, et al., Ferroptosis and kidney disease, Nefrologia 40 (4) (2020) 384–394.
[6] Y. Wang, et al., Quercetin alleviates acute kidney injury by inhibiting ferroptosis, J. Adv. Res. 28 (2021) 231–243.
[7] Y. Zhao, Z. Huang, H. Peng, Molecular mechanisms of ferroptosis and its roles in hematologic malignancies, Front. Oncol. 11 (2021) 743006.
[8] D.W. Chan, et al., MAP30 protein from Momordica charantia is therapeutic and has synergic activity with cisplatin against ovarian cancer in vivo by altering metabolism and inducing ferroptosis, Pharmacol. Res. 161 (2020) 105157.
[9] M. Ou, et al., Role and mechanism of ferroptosis in neurological diseases, Mol. Metabol. 61 (2022) 101502.
[10] S. Xu, et al., The emerging role of ferroptosis in intestinal disease, Cell Death Dis. 12 (4) (2021) 289.
[11] S. Tang, X. Xiao, Ferroptosis and kidney diseases, Int. Urol. Nephrol. 52 (3) (2019) 497–503.
[12] S. Chen, et al., The emerging role of ferroptosis in liver diseases, Front. Cell Dev. Biol. 9 (2021) 801365.
[13] M.M. Capelletti, et al., Ferroptosis in liver diseases: an overview, Int. J. Mol. Sci. 21 (14) (2020).
[14] J. Li, et al., Emerging significance and therapeutic targets of ferroptosis: a potential avenue for human kidney diseases, Cell Death Dis. 14 (9) (2023) 628.
[15] H. Bayir, et al., Ferroptotic mechanisms and therapeutic targeting of iron metabolism and lipid peroxidation in the kidney, Nat. Rev. Nephrol. 19 (5) (2023) 315–336.
[16] S.J. Dixon, et al., Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 149 (5) (2012) 1060–1072.
[17] Y. Xie, et al., Ferroptosis: process and function, Cell Death Differ. 23 (3) (2016) 369–379.
[18] Y. Chen, et al., Ferroptosis: a novel therapeutic target for ischemia-reperfusion injury, Front. Cell Dev. Biol. 9 (2021) 688605.
[19] Z. Hu, et al., Emerging role of ferroptosis in acute kidney injury, Oxid. Med. Cell. Longev. 2019 (2019) 8010614.
[20] D. Tang, et al., The molecular machinery of regulated cell death, Cell Res. 29 (5) (2019) 347–364.
[21] R. Tang, et al., Ferroptosis, necroptosis, and pyroptosis in anticancer immunity, J. Hematol. Oncol. 13 (1) (2020) 110.
[22] N. Mizushima, M. Komatsu, Autophagy: renovation of cells and tissues, Cell 147 (4) (2011) 728–741.
[23] D. Tang, et al., Ferroptosis: molecular mechanisms and health implications, Cell Res. 31 (2) (2021) 107–125.
[24] X. Jiang, B.R. Stockwell, M. Conrad, Ferroptosis: mechanisms, biology and role in disease, Nat. Rev. Mol. Cell Biol. 22 (4) (2021) 266–282.
[25] B.A. Carneiro, W.S. El-Deiry, Targeting apoptosis in cancer therapy, Nat. Rev. Clin. Oncol. 17 (7) (2020) 395–417.
[26] J. Hou, J.M. Hsu, M.C. Hung, Molecular mechanisms and functions of pyroptosis in inflammation and antitumor immunity, Mol Cell 81 (22) (2021) 4579–4590.
[27] L. Galluzzi, et al., Necroptosis: mechanisms and relevance to disease, Annu. Rev. Pathol. 12 (1) (2017) 103–130.
[28] B. Borawski, J. Malyszko, Iron, ferroptosis, and new insights for prevention in acute kidney injury, Adv. Med. Sci. 65 (2) (2020) 361–370.
[29] O. Beharier, K. Kajiwara, Y. Sadovsky, Ferroptosis, trophoblast lipotoxic damage, and adverse pregnancy outcome, Placenta 108 (2021) 32–38.
[30] X. Wang, et al., Regulation of ferroptosis pathway by ubiquitination, Front. Cell Dev. Biol. 9 (2021) 699304.
[31] I. Yanatori, F. Kishi, DMT1 and iron transport, Free Radic. Biol. Med. 133 (2019) 55–63.
[32] X. Zhang, X. Li, Abnormal iron and lipid metabolism mediated ferroptosis in kidney diseases and its therapeutic potential, Metabolites 12 (1) (2022).
[33] M.J. Correia, et al., Cysteine as a multifaceted player in kidney, the cysteine-related thiolome and its implications for precision medicine, Molecules 27 (4) (2022).
[34] L. Mao, et al., The emerging role of ferroptosis in non-cancer liver diseases: hype or increasing hope? Cell Death Dis. 11 (7) (2020) 518.
[35] L.J. Su, et al., Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis, Oxid. Med. Cell. Longev. 2019 (2019) 5080843.
[36] L. Zhang, et al., Insight into the double-edged role of ferroptosis in disease, Biomolecules 11 (12) (2021).

[37] A.M. Fratta Pasini, et al., Is ferroptosis a key component of the process leading to multiorgan damage in COVID-19? Antioxidants 10 (11) (2021).
[38] M. Sarhan, et al., Immunological consequences of kidney cell death, Cell Death Dis. 9 (2) (2018) 114.
[39] D. Martin-Sanchez, et al., Targeting of regulated necrosis in kidney disease, Nefrologia 38 (2) (2018) 125–135.
[40] S. Kobayashi, et al., Carnosine dipeptidase II (CNDP2) protects cells under cysteine insufficiency by hydrolyzing glutathione-related peptides, Free Radic. Biol. Med. 174 (2021) 12–27.
[41] L. Ni, C. Yuan, X. Wu, Targeting ferroptosis in acute kidney injury, Cell Death Dis. 13 (2) (2022) 182.
[42] J.Y. Cao, S.J. Dixon, Mechanisms of ferroptosis, Cell. Mol. Life Sci. 73 (11–12) (2016) 2195–2209.
[43] J. Zhao, Y. Hu, J. Peng, Targeting programmed cell death in metabolic dysfunction-associated fatty liver disease (MAFLD): a promising new therapy, Cell. Mol. Biol. Lett. 26 (1) (2021) 17.
[44] K. Hosohata, T. Harnsirikarn, S. Chokesuwattanaskul, Ferroptosis: a potential therapeutic target in acute kidney injury, Int. J. Mol. Sci. 23 (12) (2022).
[45] A. Stamenkovic, G.N. Pierce, A. Ravandi, Phospholipid oxidation products in ferroptotic myocardial cell death, Am. J. Physiol. Heart Circ. Physiol. 317 (1) (2019) H156–H163.
[46] H. Kuwata, et al., Role of ACSL4 in the chemical-induced cell death in human proximal tubule epithelial HK-2 cells, Biosci. Rep. 42 (2) (2022).
[47] Y. Ying, B.J. Padanilam, Regulation of necrotic cell death: p53, PARP1 and cyclophilin D-overlapping pathways of regulated necrosis? Cell. Mol. Life Sci. 73 (11–12) (2016) 2309–2324.
[48] C. Ganini, et al., No time to die: how kidney cancer evades cell death, Int. J. Mol. Sci. 23 (11) (2022).
[49] X. Zhou, et al., Ferroptosis in chronic liver diseases: opportunities and challenges, Front. Mol. Biosci. 9 (2022) 928321.
[50] Y. Ma, et al., Energy metabolism as a regulator of ferroptosis, Cell Cycle 19 (22) (2020) 2960–2962.
[51] J. Wang, et al., The cross-link between ferroptosis and kidney diseases, Oxid. Med. Cell. Longev. 2021 (2021) 6654887.
[52] Y. Yang, et al., Dimethyl fumarate prevents ferroptosis to attenuate acute kidney injury by acting on NRF2, Clin. Transl. Med. 11 (4) (2021) e382.
[53] R. Bellomo, J.A. Kellum, C. Ronco, Acute kidney injury, Lancet 380 (9843) (2012) 756–766.
[54] A.S. Levey, M.T. James, Acute kidney injury, Ann. Intern. Med. 167 (9) (2017) ITC66–ITC80.
[55] P.K. Moore, R.K. Hsu, K.D. Liu, Management of acute kidney injury: core curriculum 2018, Am. J. Kidney Dis. 72 (1) (2018) 136–148.
[56] R. Skouta, et al., Ferrostatins inhibit oxidative lipid damage and cell death in diverse disease models, J. Am. Chem. Soc. 136 (12) (2014) 4551–4556.
[57] A. Linkermann, et al., Synchronized renal tubular cell death involves ferroptosis, Proc Natl Acad Sci U S A 111 (47) (2014) 16836–16841.
[58] F. Maremonti, C. Meyer, A. Linkermann, Mechanisms and models of kidney tubular necrosis and nephron loss, J. Am. Soc. Nephrol. 33 (3) (2022) 472–486.
[59] W. Tonnus, et al., Dysfunction of the key ferroptosis-surveilling systems hypersensitizes mice to tubular necrosis during acute kidney injury, Nat. Commun. 12 (1) (2021) 4402.
[60] A. Belavgeni, et al., Ferroptosis and necroptosis in the kidney, Cell Chem. Biol. 27 (4) (2020) 448–462.
[61] X. Wang, et al., Human proximal tubular epithelial cell-derived small extracellular vesicles mediate synchronized tubular ferroptosis in hypoxic kidney injury, Redox Biol. 70 (2024) 103042.
[62] Q. Zhang, et al., PAFAH2 suppresses synchronized ferroptosis to ameliorate acute kidney injury, Nat. Chem. Biol. (7) (2024) 835–846.
[63] L. Ni, et al., The correlation between ferroptosis and m6A methylation in patients with acute kidney injury, Kidney Blood Press. Res. 47 (8) (2022) 523–533.
[64] C. Stoppe, et al., The protective role of macrophage migration inhibitory factor in acute kidney injury after cardiac surgery, Sci. Transl. Med. 10 (441) (2018).
[65] D. Ma, et al., Inhibition of ferroptosis attenuates acute kidney injury in rats with severe acute pancreatitis, Dig. Dis. Sci. 66 (2) (2021) 483–492.
[66] C. Chen, et al., Legumain promotes tubular ferroptosis by facilitating chaperone-mediated autophagy of GPX4 in AKI, Cell Death Dis. 12 (1) (2021) 65.
[67] S. Granata, et al., Oxidative stress and ischemia/reperfusion injury in kidney transplantation: focus on ferroptosis, mitophagy and new antioxidants, Antioxidants 11 (4) (2022).
[68] Z. Fan, et al., A ferroptosis-related gene signature for graft loss prediction following renal allograft, Bioengineered 12 (1) (2021) 4217–4232.
[69] X. Wei, et al., Identification of subtypes and a delayed graft function predictive signature based on ferroptosis in renal ischemia-reperfusion injury, Front. Cell Dev. Biol. 10 (2022) 800650.
[70] M. Sui, et al., CIRBP promotes ferroptosis by interacting with ELAVL1 and activating ferritinophagy during renal ischaemia-reperfusion injury, J. Cell Mol. Med. 25 (13) (2021) 6203–6216.
[71] L.L. Huang, et al., Augmenter of liver regeneration protects the kidney from ischaemia-reperfusion injury in ferroptosis, J. Cell Mol. Med. 23 (6) (2019) 4153–4164.
[72] S.R. Choudhury, et al., Dipeptidase-1 is an adhesion receptor for neutrophil recruitment in lungs and liver, Cell 178 (5) (2019) 1205–1221 e17.
[73] A. Lau, et al., Dipeptidase-1 governs renal inflammation during ischemia reperfusion injury, Sci. Adv. 8 (5) (2022) eabm0142.
[74] Y. Guan, et al., A single genetic locus controls both expression of DPEP1/CHMP1A and kidney disease development via ferroptosis, Nat. Commun. 12 (1) (2021) 5078.
[75] C. Ding, et al., miR-182-5p and miR-378a-3p regulate ferroptosis in I/R-induced renal injury, Cell Death Dis. 11 (10) (2020) 929.
[76] L. Su, et al., Pannexin 1 mediates ferroptosis that contributes to renal ischemia/reperfusion injury, J. Biol. Chem. 294 (50) (2019) 19395–19404.
[77] L.K. Chu, et al., Autophagy of OTUD5 destabilizes GPX4 to confer ferroptosis-dependent kidney injury, Nat. Commun. 14 (1) (2023) 8393.
[78] C.H. Lin, et al., Nephroprotective role of chrysophanol in hypoxia/reoxygenation-induced renal cell damage via apoptosis, ER stress, and ferroptosis, Biomedicines 9 (9) (2021).
[79] J. Zhang, et al., Involvement of GPX4 in irisin's protection against ischemia reperfusion-induced acute kidney injury, J. Cell. Physiol. 236 (2) (2021) 931–945.
[80] G.P. Jiang, et al., Effects and molecular mechanism of pachymic acid on ferroptosis in renal ischemia reperfusion injury, Mol. Med. Rep. 23 (1) (2021).
[81] Z. Zhao, et al., XJB-5-131 inhibited ferroptosis in tubular epithelial cells after ischemia-reperfusion injury, Cell Death Dis. 11 (8) (2020) 629.
[82] Z. Sun, et al., Exosomal lncRNA TUG1 derived from human urine-derived stem cells attenuates renal ischemia/reperfusion injury by interacting with SRSF1 to regulate ASCL4-mediated ferroptosis, Stem Cell Res. Ther. 13 (1) (2022) 297.
[83] D. Martin-Sanchez, et al., Ferroptosis, but not necroptosis, is important in nephrotoxic folic acid-induced AKI, J. Am. Soc. Nephrol. 28 (1) (2017) 218–229.
[84] L.J. Yan, Folic acid-induced animal model of kidney disease, Animal Model Exp Med 4 (4) (2021) 329–342.
[85] D. Li, et al., Nuciferine protects against folic acid-induced acute kidney injury by inhibiting ferroptosis, Br. J. Pharmacol. 178 (5) (2021) 1182–1199.
[86] L. Guo, et al., Targeted inhibition of Rev-erb-alpha/beta limits ferroptosis to ameliorate folic acid-induced acute kidney injury, Br. J. Pharmacol. 178 (2) (2021) 328–345.
[87] X. Li, et al., A-lipoic acid alleviates folic acid-induced renal damage through inhibition of ferroptosis, Front. Physiol. 12 (2021) 680544.
[88] Z. Cai, et al., Metformin potentiates nephrotoxicity by promoting NETosis in response to renal ferroptosis, Cell Discov 9 (1) (2023) 104.
[89] Y. Ikeda, et al., Role of ferroptosis in cisplatin-induced acute nephrotoxicity in mice, J. Trace Elem. Med. Biol. 67 (2021) 126798.
[90] X. Zhang, et al., The effect of Chinese traditional medicine huaiqihuang (HQH) on the protection of nephropathy, Oxid. Med. Cell. Longev. 2020 (2020) 2153912.
[91] X. Meng, et al., ADAMTS-13-regulated nuclear factor E2-related factor 2 signaling inhibits ferroptosis to ameliorate cisplatin-induced acute kidney injuy, Bioengineered 12 (2) (2021) 11610–11621.
[92] D.U. Kim, et al., Loganin attenuates the severity of acute kidney injury induced by cisplatin through the inhibition of ERK activation in mice, Int. J. Mol. Sci. 22 (3) (2021).
[93] F. Cai, et al., Sulfide:quinone oxidoreductase alleviates ferroptosis in acute kidney injury via ameliorating mitochondrial dysfunction of renal tubular epithelial cells, Redox Biol. 69 (2024) 102973.
[94] L. Zhou, et al., Polydatin attenuates cisplatin-induced acute kidney injury by inhibiting ferroptosis, Oxid. Med. Cell. Longev. 2022 (2022) 1–14.
[95] J. Li, et al., Tetrahedral DNA nanostructures inhibit ferroptosis and apoptosis in cisplatin-induced renal injury, ACS Appl. Bio Mater. 4 (6) (2021) 5026–5032.
[96] Z. Hu, et al., VDR activation attenuate cisplatin induced AKI by inhibiting ferroptosis, Cell Death Dis. 11 (1) (2020) 73.
[97] D. Fang, et al., Calorie restriction protects against contrast-induced nephropathy via SIRT1/GPX4 activation, Oxid. Med. Cell. Longev. 2021 (2021) 2999296.

[98] A. Lau, et al., Renal immune surveillance and dipeptidase-1 contribute to contrast-induced acute kidney injury, J. Clin. Invest. 128 (7) (2018) 2894–2913.
[99] A. von Massenhausen, et al., Dexamethasone sensitizes to ferroptosis by glucocorticoid receptor-induced dipeptidase-1 expression and glutathione depletion, Sci. Adv. 8 (5) (2022) eabl8920.
[100] S. Peerapornratana, et al., Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment, Kidney Int. 96 (5) (2019) 1083–1099.
[101] J.T. Poston, J.L. Koyner, Sepsis associated acute kidney injury, BMJ 364 (2019) k4891.
[102] J. Xiao, et al., Maresin conjugates in tissue regeneration-1 suppresses ferroptosis in septic acute kidney injury, Cell Biosci. 11 (1) (2021) 221.
[103] Y. Tang, et al., Isoliquiritigenin attenuates septic acute kidney injury by regulating ferritinophagy-mediated ferroptosis, Ren. Fail. 43 (1) (2021) 1551–1560.
[104] W. Yao, et al., Inhibition of the NADPH oxidase pathway reduces ferroptosis during septic renal injury in diabetic mice, Oxid. Med. Cell. Longev. 2022 (2022) 1193734.
[105] Y. Li, et al., 7-Dehydrocholesterol dictates ferroptosis sensitivity, Nature 626 (7998) (2024) 411–418.
[106] F.P. Freitas, et al., 7-Dehydrocholesterol is an endogenous suppressor of ferroptosis, Nature 626 (7998) (2024) 401–410.
[107] M. Guerrero-Hue, et al., Curcumin reduces renal damage associated with rhabdomyolysis by decreasing ferroptosis-mediated cell death, FASEB J 33 (8) (2019) 8961–8975.
[108] S. Zhao, et al., Iron deficiency exacerbates cisplatin- or rhabdomyolysis-induced acute kidney injury through promoting iron-catalyzed oxidative damage, Free Radic. Biol. Med. 173 (2021) 81–96.
[109] P. Romagnani, et al., Chronic kidney disease, Nat. Rev. Dis. Prim. 3 (2017) 17088.
[110] M. Ruiz-Ortega, et al., Targeting the progression of chronic kidney disease, Nat. Rev. Nephrol. 16 (5) (2020) 269–288.
[111] Y. Zhang, et al., Therapeutic implications of ferroptosis in renal fibrosis, Front. Mol. Biosci. 9 (2022) 890766.
[112] J. Zhou, et al., Role of ferroptosis in fibrotic diseases, J. Inflamm. Res. 15 (2022) 3689–3708.
[113] B. Zhang, et al., Liproxstatin-1 attenuates unilateral ureteral obstruction-induced renal fibrosis by inhibiting renal tubular epithelial cells ferroptosis, Cell Death Dis. 12 (9) (2021) 843.
[114] L. Zhou, et al., Targeting ferroptosis attenuates interstitial inflammation and kidney fibrosis, Kidney Dis. 8 (1) (2022) 57–71.
[115] Y.-H. Lo, et al., Nobiletin alleviates ferroptosis-associated renal injury, inflammation, and fibrosis in a unilateral ureteral obstruction mouse model, Biomedicines 10 (3) (2022).
[116] J. Wang, et al., Ferroptosis, a new target for treatment of renal injury and fibrosis in a 5/6 nephrectomy-induced CKD rat model, Cell Death Discov 8 (1) (2022) 127.
[117] L. Yang, et al., Tocilizumab mimotope alleviates kidney injury and fibrosis by inhibiting IL-6 signaling and ferroptosis in UUO model, Life Sci. 261 (2020) 118487.
[118] S. Kim, et al., Characterization of ferroptosis in kidney tubular cell death under diabetic conditions, Cell Death Dis. 12 (2) (2021) 160.
[119] Y. Wang, et al., Ferroptosis involves in renal tubular cell death in diabetic nephropathy, Eur. J. Pharmacol. 888 (2020) 173574.
[120] X. Feng, et al., Ferroptosis enhanced diabetic renal tubular injury via HIF-1 alpha/HO-1 pathway in db/db mice, Front. Endocrinol. 12 (2021) 626390.
[121] S. Li, et al., Inhibition of ferroptosis by up-regulating Nrf2 delayed the progression of diabetic nephropathy, Free Radic. Biol. Med. 162 (2021) 435–449.
[122] Y. Wu, et al., HMGB1 regulates ferroptosis through Nrf2 pathway in mesangial cells in response to high glucose, Biosci. Rep. 41 (2) (2021).
[123] W.J. Wang, et al., Salusin-beta participates in high glucose-induced HK-2 cell ferroptosis in a Nrf-2-dependent manner, Mol. Med. Rep. 24 (3) (2021).
[124] W.-Y. Wu, et al., SSBP1 drives high fructose-induced glomerular podocyte ferroptosis via activating DNA-PK/p53 pathway, Redox Biol. 52 (2022).
[125] Q. Zhang, et al., Sp1-mediated upregulation of Prdx6 expression prevents podocyte injury in diabetic nephropathy via mitigation of oxidative stress and ferroptosis, Life Sci. 278 (2021) 119529.
[126] X. Wang, et al., Identification of genes reveals the mechanism of cell ferroptosis in diabetic nephropathy, Front. Physiol. 13 (2022) 890566.
[127] H. Tan, et al., Glabridin, a bioactive component of licorice, ameliorates diabetic nephropathy by regulating ferroptosis and the VEGF/Akt/ERK pathways, Mol Med 28 (1) (2022) 58.
[128] D. Huang, et al., Calycosin plays a protective role in diabetic kidney disease through the regulation of ferroptosis, Pharm. Biol. 60 (1) (2022) 990–996.
[129] S. Zhao, et al., Roles of ferroptosis in urologic malignancies, Cancer Cell Int. 21 (1) (2021) 676.
[130] W. Wang, et al., Identifies microtubule-binding protein CSPP1 as a novel cancer biomarker associated with ferroptosis and tumor microenvironment, Comput. Struct. Biotechnol. J. 20 (2022) 3322–3335.
[131] G. Li, et al., The research landscape of ferroptosis in cancer: a bibliometric analysis, Front. Cell Dev. Biol. 10 (2022) 841724.
[132] E. Jonasch, C.L. Walker, W.K. Rathmell, Clear cell renal cell carcinoma ontogeny and mechanisms of lethality, Nat. Rev. Nephrol. 17 (4) (2021) 245–261.
[133] H.I. Wettersten, et al., Metabolic reprogramming in clear cell renal cell carcinoma, Nat. Rev. Nephrol. 13 (7) (2017) 410–419.
[134] X. Qi, et al., The uniqueness of clear cell renal cell carcinoma: summary of the process and abnormality of glucose metabolism and lipid metabolism in ccRCC, Front. Oncol. 11 (2021) 727778.
[135] Z. Cheng, et al., Ferroptosis resistance determines high susceptibility of murine A/J strain to iron-induced renal carcinogenesis, Cancer Sci. 113 (1) (2022) 65–78.
[136] L. Dell'Atti, N. Bianchi, G. Aguiari, New therapeutic interventions for kidney carcinoma: looking to the future, Cancers 14 (15) (2022).
[137] S. Zhang, et al., Pan-cancer analysis of iron metabolic landscape across the Cancer Genome Atlas, J. Cell. Physiol. 235 (2) (2020) 1013–1024.
[138] X.L. Xing, et al., Comprehensive analysis of ferroptosis- and immune-related signatures to improve the prognosis and diagnosis of kidney renal clear cell carcinoma, Front. Immunol. 13 (2022) 851312.
[139] L. Chen, et al., Functions, roles, and biological processes of ferroptosis-related genes in renal cancer: a pan-renal cancer analysis, Front. Oncol. 11 (2021) 697697.
[140] Z. Sun, et al., Prediction of overall survival based upon a new ferroptosis-related gene signature in patients with clear cell renal cell carcinoma, World J. Surg. Oncol. 20 (1) (2022) 120.
[141] Y. Hong, et al., A novel ferroptosis-related 12-gene signature predicts clinical prognosis and reveals immune relevancy in clear cell renal cell carcinoma, BMC Cancer 21 (1) (2021) 831.
[142] J. Chen, et al., A new prognostic risk signature of eight ferroptosis-related genes in the clear cell renal cell carcinoma, Front. Oncol. 11 (2021) 700084.
[143] B. Zheng, et al., Comprehensive analysis of new prognostic signature based on ferroptosis-related genes in clear cell renal cell carcinoma, Aging (Albany NY) 13 (15) (2021) 19789–19804.
[144] X. Bai, et al., Systematic pan-cancer analysis of KIF23 and a prediction model based on KIF23 in clear cell renal cell carcinoma (ccRCC), Pharmgenomics Pers Med 14 (2021) 1717–1729.
[145] J. Wang, et al., SUV39H1 deficiency suppresses clear cell renal cell carcinoma growth by inducing ferroptosis, Acta Pharm. Sin. B 11 (2) (2021) 406–419.
[146] X. Liu, et al., Decreased expression of ACADSB predicts poor prognosis in clear cell renal cell carcinoma, Front. Oncol. 11 (2022).
[147] X.L. Xing, et al., Development and validation of ferroptosis-related lncRNAs prognosis signatures in kidney renal clear cell carcinoma, Cancer Cell Int. 21 (1) (2021) 591.
[148] Z. Zhou, et al., Identification and validation of a ferroptosis-related long non-coding RNA (FRlncRNA) signature to predict survival outcomes and the immune microenvironment in patients with clear cell renal cell carcinoma, Front. Genet. 13 (2022) 787884.
[149] Y.Z. Li, et al., Silencing lncRNA slc16a1-AS1 induced ferroptosis in renal cell carcinoma through miR-143-3p/slc7a11 signaling, Technol. Cancer Res. Treat. 21 (2022) 15330338221077803.
[150] C.L. Ye, et al., STEAP3 affects ferroptosis and progression of renal cell carcinoma through the p53/xCT pathway, Technol. Cancer Res. Treat. 21 (2022) 15330338221078728.
[151] H. Miess, et al., The glutathione redox system is essential to prevent ferroptosis caused by impaired lipid metabolism in clear cell renal cell carcinoma, Oncogene 37 (40) (2018) 5435–5450.

[152] S. Nishizawa, et al., Low tumor glutathione level as a sensitivity marker for glutamate-cysteine ligase inhibitors, Oncol. Lett. 15 (6) (2018) 8735–8743.
[153] S. Chillappagari, et al., SIAH2-mediated and organ-specific restriction of HO-1 expression by a dual mechanism, Sci. Rep. 10 (1) (2020) 2268.
[154] I. Chang, et al., SNU-333 cells as an appropriate cell line for the orthotopic renal cell carcinoma model, Technol. Cancer Res. Treat. 20 (2021) 15330338211038487.
[155] Y. Zou, et al., A GPX4-dependent cancer cell state underlies the clear-cell morphology and confers sensitivity to ferroptosis, Nat. Commun. 10 (1) (2019).
[156] C. Zhu, et al., MicroRNA-4735-3p facilitates ferroptosis in clear cell renal cell carcinoma by targeting SLC40A1, Anal. Cell Pathol. 2022 (2022) 4213401.
[157] S. Han, et al., HO-1 contributes to luteolin-triggered ferroptosis in clear cell renal cell carcinoma via increasing the labile iron pool and promoting lipid peroxidation, Oxid. Med. Cell. Longev. 2022 (2022) 3846217.
[158] J. Yang, et al., Functional deficiency of succinate dehydrogenase promotes tumorigenesis and development of clear cell renal cell carcinoma through weakening of ferroptosis, Bioengineered 13 (4) (2022) 11187–11207.
[159] Q. Zheng, et al., Deficiency of the X-inactivation escaping gene KDM5C in clear cell renal cell carcinoma promotes tumorigenicity by reprogramming glycogen metabolism and inhibiting ferroptosis, Theranostics 11 (18) (2021) 8674–8691.
[160] S.K. Tan, et al., Obesity-dependent adipokine chemerin suppresses fatty acid oxidation to confer ferroptosis resistance, Cancer Discov. 11 (8) (2021) 2072–2093.
[161] Y. Mou, et al., Low expression of ferritinophagy-related NCOA4 gene in relation to unfavorable outcome and defective immune cells infiltration in clear cell renal carcinoma, BMC Cancer 21 (1) (2021) 18.
[162] W.H. Yang, et al., The hippo pathway effector TAZ regulates ferroptosis in renal cell carcinoma, Cell Rep. 28 (10) (2019) 2501–2508 e4.
[163] J. Du, et al., Designer exosomes for targeted and efficient ferroptosis induction in cancer via chemo-photodynamic therapy, Theranostics 11 (17) (2021) 8185–8196.
[164] J.P. Garg, D. Vucic, Targeting cell death pathways for therapeutic intervention in kidney diseases, Semin. Nephrol. 36 (3) (2016) 153–161.
[165] Q. Lu, et al., Rheb1 protects against cisplatin-induced tubular cell death and acute kidney injury via maintaining mitochondrial homeostasis, Cell Death Dis. 11 (5) (2020) 364.
[166] T. Muller, et al., Necroptosis and ferroptosis are alternative cell death pathways that operate in acute kidney failure, Cell. Mol. Life Sci. 74 (19) (2017) 3631–3645.
[167] G. Cordoba-David, et al., Effective nephroprotection against acute kidney injury with a star-shaped polyglutamate-curcuminoid conjugate, Sci. Rep. 10 (1) (2020) 2056.
[168] Q. Song, et al., Oxalate activates autophagy to induce ferroptosis of renal tubular epithelial cells and participates in the formation of kidney stones, Oxid. Med. Cell. Longev. 2021 (2021) 6630343.
[169] N. Li, et al., Pathway network of pyroptosis and its potential inhibitors in acute kidney injury, Pharmacol. Res. 175 (2022) 106033.
[170] F. Guzzi, et al., Molecular mechanisms of the acute kidney injury to chronic kidney disease transition: an updated view, Int. J. Mol. Sci. 20 (19) (2019).
[171] D.A. Ferenbach, J.V. Bonventre, Acute kidney injury and chronic kidney disease: from the laboratory to the clinic, Nephrol Ther 12 (Suppl 1) (2016) S41–S48. Suppl 1.
[172] M.T. Yan, C.T. Chao, S.H. Lin, Chronic kidney disease: strategies to retard progression, Int. J. Mol. Sci. 22 (18) (2021).
[173] M.A. Kaballo, M.E. Elsayed, A.G. Stack, Linking acute kidney injury to chronic kidney disease: the missing links, J. Nephrol. 30 (4) (2017) 461–475.
[174] J. Wei, et al., New mouse model of chronic kidney disease transitioned from ischemic acute kidney injury, Am J Physiol Renal Physiol 317 (2) (2019) F286–f295.
[175] L.S. Chawla, et al., Acute kidney injury and chronic kidney disease as interconnected syndromes, N. Engl. J. Med. 371 (1) (2014) 58–66.
[176] E.F. Carney, Ferroptotic stress promotes the AKI to CKD transition, Nat. Rev. Nephrol. 17 (10) (2021) 633, 633.
[177] X. Chen, et al., Broadening horizons: the role of ferroptosis in cancer, Nat. Rev. Clin. Oncol. 18 (5) (2021) 280–296.
[178] E. Mishima, et al., Drugs repurposed as antiferroptosis agents suppress organ damage, including AKI, by functioning as lipid peroxyl radical scavengers, J. Am. Soc. Nephrol. 31 (2) (2020) 280–296.
[179] X. Li, et al., Pretreatment with roxadustat (FG-4592) attenuates folic acid-induced kidney injury through antiferroptosis via akt/GSK-3 beta/nrf2 pathway, Oxid. Med. Cell. Longev. 2020 (2020) 6286984.
[180] X. Zhu, et al., Roxadustat: not just for anemia, Front. Pharmacol. 13 (2022).
[181] A.A. Poloznikov, et al., HIF prolyl hydroxylase inhibitors for COVID-19 treatment: pros and cons, Front. Pharmacol. 11 (2021).
[182] C. Han, et al., Ferroptosis and its potential role in human diseases, Front. Pharmacol. 11 (2020) 239.
[183] W. Tao, et al., miR-3587 inhibitor attenuates ferroptosis following renal ischemia-reperfusion through HO-1, Front. Mol. Biosci. 8 (2021) 789927.
[184] X. Sheng, et al., Theoretical insights into the mechanism of ferroptosis suppression via inactivation of a lipid peroxide radical by liproxstatin-1, Phys. Chem. Chem. Phys. 19 (20) (2017) 13153–13159.
[185] B. Kolbrink, et al., Vitamin K1 inhibits ferroptosis and counteracts a detrimental effect of phenprocoumon in experimental acute kidney injury, Cell. Mol. Life Sci. 79 (7) (2022) 387.
[186] X. Ma, et al., Huaier polysaccharide attenuates doxorubicin-induced acute cardiotoxicity by regulating ferroptosis, Bull. Exp. Biol. Med. 174 (1) (2022) 37–42.
[187] L. Huang, et al., Engeletin alleviates erastin-induced oxidative stress and protects against ferroptosis via Nrf2/Keap 1 pathway in bone marrow mesenchymal stem cells, Tissue Cell 82 (2023) 102040.
[188] X. Song, et al., FANCD2 protects against bone marrow injury from ferroptosis, Biochem. Biophys. Res. Commun. 480 (3) (2016) 443–449.
[189] C. Liang, et al., Recent progress in ferroptosis inducers for cancer therapy, Adv Mater 31 (51) (2019) e1904197.
[190] T.M. Shi, X.F. Chen, H. Ti, Ferroptosis-based therapeutic strategies toward precision medicine for cancer, J. Med. Chem. 67 (4) (2024) 2238–2263.
[191] W. Qian, et al., Cyclosporine A-loaded apoferritin alleviates myocardial ischemia-reperfusion injury by simultaneously blocking ferroptosis and apoptosis of cardiomyocytes, Acta Biomater. 160 (2023) 265–280.
[192] B. Li, et al., Synchronous disintegration of ferroptosis defense Axis via engineered exosome-conjugated magnetic nanoparticles for glioblastoma therapy, Adv. Sci. 9 (17) (2022) e2105451.