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REVIEW

Molecular Mechanisms of Ferroptosis and Their Involvement in Acute Kidney Injury

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Abstract: Ferroptosis is a novel way of regulating cell death, which occurs in a process that is closely linked to intracellular iron metabolism, lipid metabolism, amino acid metabolism, and multiple signaling pathways. The latest research shows that ferroptosis plays a key role in the pathogenesis of acute kidney injury (AKI). Ferroptosis may be an important target for treating AKI caused by various reasons, such as ischemia-reperfusion injury, rhabdomyolysis syndrome, sepsis, and nephrotoxic drugs. This paper provides a review on the regulatory mechanisms of ferroptosis and its role in AKI, which may help to provide new research ideas for the treatment of AKI and future research.

Keywords: ferroptosis, iron, lipid peroxidation, molecular mechanism, acute kidney injury

Introduction

Acute kidney injury (AKI) is one of the most common clinical kidney diseases, with high morbidity and mortality worldwide. Epidemiological investigation shows that the incidence of AKI in adults and children is over 20% and 30% respectively.[1] In addition, studies show that about 5% of hospitalized patients and 30% of critically ill patients are complicated with AKI and the mortality rate is high.[2] In addition, AKI also increases the risk of patients developing chronic renal failure and uremic nephropathy.[3] The causes of AKI mainly include heart surgery, rhabdomyolysis, sepsis, and nephrotoxic drugs.[4] Few methods other than haemodialysis are currently available to make significant progress in the treatment of AKI.

In recent years, ferroptosis has become a hot research topic. Ferroptosis is a novel mode of iron-dependent cell death induced by lipid peroxidation, which is distinguished from apoptosis, necrosis, pyroptosis and autophagy, and is mainly characterised by iron accumulation and lipid peroxidation.[5] Numerous studies have found that ferroptosis is involved in a variety of diseases including neurodegeneration,[6] stroke,[7] cerebral haemorrhage,[8] and AKI[9] and that targeting the activation or inhibition of the pathways corresponding to ferroptosis can intervene in the onset and progression of disease. It was found that iron overload induced ferroptosis in renal tubular epithelial cells and was involved in the development of AKI.[10] However, ferroptosis inhibitors have shown renal protection in various animal models of AKI, which indicates that ferroptosis may play an important role in the occurrence and progress of AK.[11] Anti-ferroptosis drugs generally have the characteristics of scavenging free radicals, especially lipid peroxide free radicals, which may help to inhibit the further progress of AKI injury. Mishima et al[12] evaluated the therapeutic efficacy of cytochrome P450 family in the model of organ injury in mice, including AKI. The results showed that the increase of lipid peroxide free radicals was related to the occurrence of ferroptosis in cells, and cytochrome P450 family could effectively remove lipid peroxide free radicals and inhibit the pathological conditions related to ferroptosis. Therefore, it can be inferred that ferroptosis may be one of the key mechanisms in the occurrence and development of AKI. In this paper, the mechanism of ferroptosis is reviewed, and the research progress of ferroptosis as a potential therapeutic target of AKI is discussed.

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Ferroptosis and Its Characteristics

In 2012, Dixon et al[13] officially named this iron-dependent cell death mediated by excessive lipid peroxidation as ferroptosis for the first time. Morphologically, ferroptosis is significantly different from the previously identified modes of cell death such as apoptosis, pyroptosis, necrosis, and autophagy. Morphological features of ferroptosis cells are often characterised by loss of lipid membrane integrity and a nucleus lacking chromatin condensation. Changes in the mitochondria include a decrease in number, shrinkage in size, increased density of mitochondrial bilayers, reduction or disappearance of mitochondrial cristae, and electron microscopic observation of rupture of the outer mitochondrial membrane. Furthermore, with regard to biochemical features, ferroptosis is characterized by glutathione (GSH) depletion, glutathione peroxidase 4 (GPX4) inactivation, iron overload, and lipid peroxide accumulation.[14] Clinical studies have confirmed that ferroptosis is strongly associated with AKI[10,11] And it may become a good therapeutic target for AKI in the future with more research on ferroptosis inhibitors.[15]

Pathogenesis and Key Regulators of Ferroptosis

Although the regulatory mechanisms involved in ferroptosis as a form of programmed cell death have not been fully elucidated, with the discovery of several important mechanisms regulating ferroptosis, it has been shown that ferroptosis is closely associated with disorders of iron metabolism, imbalance of the amino acid antioxidant system and accumulation of lipid peroxides.[16] In addition, other metabolic pathways and related factors can also affect the sensitivity of cells to ferroptosis. For example, when the imbalance of iron metabolism leads to the increase of intracellular free iron, excessive ROS, and hydroxyl radical (OH) generated by Fe2+ catalyzed by the Fenton reaction will lead to the accumulation of intracellular lipid peroxides and PUFA peroxidation, which will lead to ferroptosis[17] (Figure 1).

Iron Metabolism and Ferroptosis

Disturbances in iron metabolism are key to ferroptosis.[13] Under physiological conditions, Fe3+ in the circulation is bound to transferrin, transported into the cell by transferrin receptor 1 (TFR1) on the surface of the cell membrane,[18] reduced to Fe2+ by the metal reductase STEAP3 in the nucleus, released from the nucleus by divalent metal transporter protein 1 (DMT1) and stored in the cytoplasmic unstable iron pool and ferritin, and finally exported extracellularly by ferritin-1 (FPN1).[19] If the balance between absorption, utilization, and recycling of iron is interrupted, free iron ions may accumulate and catalyze the Fenton reaction, leading to the formation of lipid ROS and ferroptosis. Silencing the gene encoding TFR1 inhibits ferroptosis in Erastin,[20] while depletion of FPN1 increases the susceptibility of cells to ferroptosis.[21] During this cycle, nuclear receptor coactivator 4 (NCOA4) acts as an adaptor protein, mediating the targeted transport of ferritin to lysosomes for autophagy degradation, thus releasing free Fe2+, which is called ferritin phagocytosis and is mainly responsible for the release and recovery of iron ions.[22] Some of this Fe2+ is transported out of the cell via FPN1 on the cell membrane to ensure that intracellular iron concentrations are kept within normal limits under physiological conditions.[23] Current evidence suggests that abnormal distribution and excess levels of intracellular iron increase the instability of the intracellular iron pool and lead to an increase in intracellular free iron.[24] Large amounts of unstable and highly reactive Fe2+ generate ROS and OH via the Fenton reaction, and the reaction products can react directly with PUFA in the plasma membrane and generate large amounts of lipid ROS,[16,17] ultimately leading to cellular ferroptosis. Therefore, Fe2+[25] is an important auxiliary factor in ROS reaction and treatment of oxidative stress. Ferritin is a kind of intracellular storage ferritin, which consists of ferritin heavy chain 1(FTH1) and ferritin light chain (FTL). FTH1 is active in iron oxidase and can convert Fe2+ into Fe3+[23] Under certain physiological and pathological conditions, upregulation of TFR expression and downregulation of ferritin (including FTH1 and FTL) expression in cells susceptible to ferroptosis leads to an imbalance in intracellular iron homeostasis, particularly an abnormal elevation in unstable iron content, which is one of the key factors affecting ferroptosis.[26] The dissolution of striated muscle can cause AKI, and the patient's condition is relieved after filtering unstable iron in peripheral blood, which reflects the close relationship between systemic iron overload and renal injury.[27] Ferrostatin-1(Fer-1) is a classic ferroptosis inhibitor. The first study found that the analogue of Fer-1, Srs11-92 (AA9), is 15 times more effective than Fer-1, and can effectively inhibit the oxidation of membrane lipids by free radicals and the ferroptosis of neurons.[28] NCOA4 was found to maintain

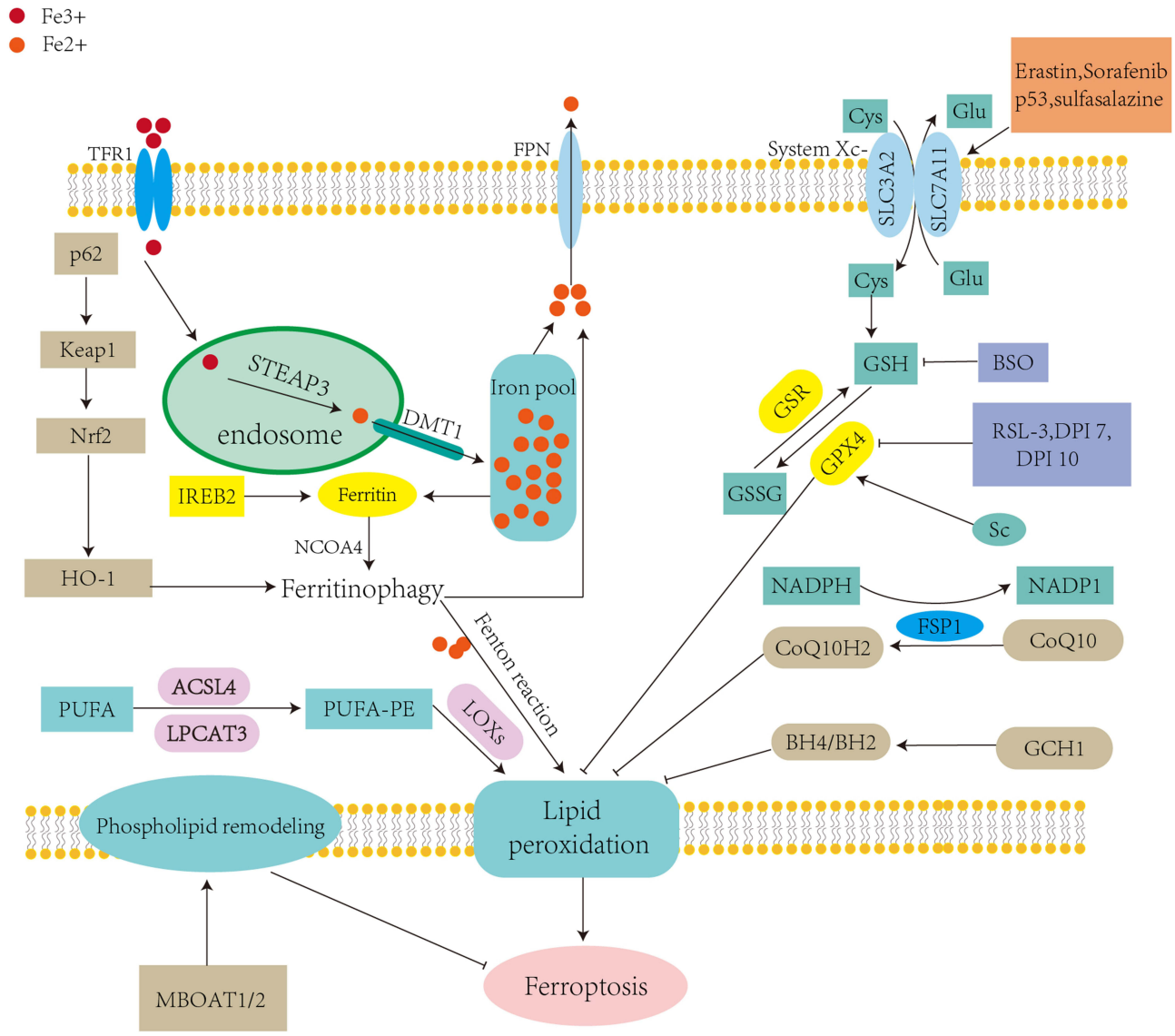

Figure 1 Regulatory mechanisms of ferroptosis. The figure shows two main types of ferroptosis regulation: The first category involves metabolic pathways, such as the aberrant iron, lipid, and amino acid metabolic pathways in ferroptosis; the second category involves signaling pathways, such as he p53, nuclear factor erythroid 2-related factor, ferroptosis suppressor protein 1, guanosine triphosphate cyclohydrolase 1 and nuclear receptor coactivator 4 pathways.

iron homeostasis by regulating ferritin phagocytosis.[22,29] Low expression of NCOA4 reduced ferritin degradation and the accumulation of active iron and ROS, thereby inhibiting cellular ferroptosis, while on the contrary, NCOA4 over-expression promoted ferritin degradation and eventually led to ferroptosis.[30]

Amino Acid Metabolism and Ferroptosis

System Xc-, also known as cystine/glutamic acid reverse transporter, is a heterodimer composed of SLC7A11 subunit and SLC3A2 subunit, and its main function is to exchange glutamic acid and cystine in and out of cells at a ratio of 1:1.[31] Cystine is reduced to cysteine after entering cells through the system Xc- and participates in the synthesis of GSH. The sulfhydryl structure of GSH can be oxidized and dehydrogenated, making GSH an important antioxidant and free radical scavenger in cells. GPX4 is a key enzyme that promotes the activity of GSH-inhibiting lipoxygenases (LOXs) and phospholipid/cardiolipid oxidation.[32] The Xc-/GSH/GPX4 axis is thought to be the main pathway involved in ferroptosis. A large number of studies have now demonstrated the association of amino acid metabolism with ferroptosis. Recent studies have found that cystine uptake mediated by SLC7A11 promotes the synthesis of GSH

and GPX4 proteins, and ultimately inhibits ferroptosis.[33] In addition, resveratrol glycosides could dose-dependently alleviate cell death induced by Erastin inhibition of the system Xc-.[34] Another study showed that the downregulation of connexin 43 could alleviate cisplatin-induced AKI by restoring SLC7A11 levels.[35] Conversely, inhibition of system Xc- promotes the development of ferroptosis, as a common foodborne mycotoxin, rod penicillin, reduces SLC7A11 activity by activating protein kinase (AMPK), mediates the formation of the beclin1-SLC7A11 complex and exacerbates nephrotoxicity in a mouse model of folic acid induction.[36] Studies have shown that YTHDC2 can target and inhibit the SLC3A2 subunit of the system Xc- thereby inducing ferroptosis.[37] Therefore, maintaining the normal function of system Xc- is essential to protect cells and tissues from ferroptosis. In addition, after knocking out the GPX4 gene in renal tubular cells in mice, researchers showed massive tubular cell death and eventually triggered AKI in mice.[38] Other studies have further demonstrated that up-or down-regulation of GPX4 expression severely affects the sensitivity of cells to ferroptosis.[39] When RSL-3 binds GPX4 it can inactivate it, thus inducing cellular ferroptosis, in agreement with the findings of the above study.[40] When system Xc- inhibition and GPX4 inactivation occurs, a decrease in PUFAs and an increase in the accumulation of lipid peroxides lead to cellular ferroptosis.[41] Irisin can attenuate ischemia-reperfusion injury (IRI)-induced AKI by upregulating GPX4 activity.[42] In addition, the oncogene p53 is also closely associated with ferroptosis, and it regulates system Xc- by suppressing the expression of SLC7A11, which affects the activity of GPX4, ultimately leading to increased lipid peroxidation and ferroptosis in cancer cells.[14] FIN56 consumes CoQ10 by binding and activating the activity of squalene synthase (SQS), promotes the degradation of GPX4, and can also lead to ferroptosis of cells.[43]

Lipid Metabolism and Ferroptosis

Lipid peroxidation is another key feature of ferroptosis. PUFAs in lipids are components of the cell membrane and are more susceptible to lipid peroxidation than monounsaturated fatty acids.[5] Thus, the amount and location of PUFAs determine the degree of cellular lipid peroxidation and ferroptosis. Acyl-CoA synthetase long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and LOXs are key enzymes in lipid oxidation, and PUFAs are converted to lipid hydroperoxides and lead to ferroptosis through esterification and oxidation by key enzymes.[44] Therefore, regulating the activity of key enzymes in the process of lipid ferroptosis would help to prevent the occurrence of ferroptosis. The accumulation of lipid peroxide, especially phospholipid peroxide, is a landmark event of ferroptosis. It was found that excessive activation of ACSL4, LPCAT3, and LOXs and the accumulation of excess Fe2+ led to high depletion of cell membrane phospholipids and accumulation of lipid peroxides, and ultimately to ferroptosis in cells.[45] In contrast, Doll et al[44] found that downregulation of ACSL4 and LPCTA3 expression contributed to the inhibition of ferroptosis, and concluded that ACSL4 was of higher value than LPCTA3.

Nuclear Factor Erythroid 2 Related Factors and Ferroptosis

Nuclear factor erythroid 2-related factor (Nrf2) is a transcription factor that can bind to nuclear factors and coordinate the expression of many important cell antioxidant genes. In general, Nrf2 exists in the form of three complexes and maintains the basic low level of the organism, for example, the protein-bound form is related to antioxidation, and the activity of Nrf2 is strictly regulated by kelch-like each-related protein 1(Keap1).[46] Under normal conditions, Nrf2 binds to Keap1 and is inactivated in the proteasome through ubiquitination and degradation.[47] Once in a state of oxidative stress, Keap1 is degraded by autophagy and Nrf2 is released.[48] Free Nrf2 rapidly translocates to the nucleus where it binds to antioxidant response elements (AREs) in the promoter region of the nucleus, driving antioxidant gene expression to balance intracellular oxidative stress and ultimately maintain cellular redox homeostasis.[49] In addition, Nrf2 can regulate many proteins and enzymes related to ferroptosis. For example, the subunit of system XC, GPX2, and GSH synthetase are all targets of Nrf2.[50] Several studies have demonstrated that Nrf2 is an important regulator of cellular ferroptosis. Enhancing Nrf2 activity in renal tubules by upregulating gene expression or pharmacological treatment may improve AKI, and targeting the Keap1-Nrf2 system may prevent the progression of renal disease.[51] To sum up, Nrf2 is closely related to cell ferroptosis.

Other Ferroptosis Mechanisms

With the rapid development of ferroptosis research, many other mechanisms related to ferroptosis have been discovered. Ferroptosis suppressor protein 1 (FSP1) was originally described as a response gene of p53, and it was found that FSP1 showed the ability to inhibit ferroptosis induced by GPX4 gene knockout.[52] FSP1 is an effective inhibitor of ferroptosis, and its main mechanism of inhibiting ferroptosis is to reduce CoQ10 with NAD(P)H and shuttle the reducing agent to the plasma membrane to prevent lipid peroxidation and resist ferroptosis. The FSP1/CoQ10 /NAD(P)H pathway exists as an independent parallel system that, together with GSH/GPX4, inhibits lipid peroxidation and ferroptosis.[53] In 2015, researchers linked P53 to cellular ferroptosis for the first time and demonstrated that p53 can regulate the expression of the SLC7A11 subunit in the system Xc-, thereby reducing GPX4 activity.[14] Lee et al[54] found that AMPK inactivation largely abrogated the protective effect of energy stress on ferroptosis-related renal IRI in vitro or in vivo. Furthermore, using CRISPR-mediated genome-wide activation screening, researchers found that guanosine triphosphate cyclic hydrolase 1 (GCH1) was similarly involved in the regulation of ferroptosis. When upregulated or silenced GCH1 could render cancer cells resistant or sensitive to ferroptosis by regulating the antioxidant tetrahydrobiopterin/dihydrobiopterin (BH4/BH2), respectively.[55] More research is needed to determine the relationship between ferroptosis and AKI and to treat AKI by developing targeted drugs that inhibit the ferroptosis signalling pathway.[56] Cellular ferroptosis occurs with rupture mediated by plasma membrane pores[57] Combination therapy with third-generation ferritin 16–86 and compounds suppressing the mitochondrial permeability transition may have a targeted therapeutic effect.[9] Similarly, it is found that the viral peptide inhibitor of ferroptosis −1 has specific inhibition on ferroptosis.[58] Dexamethasone induces ferroptosis sensitivity in renal tubular cells via glucocorticoid receptor (GR)-mediated protein dipeptidase-1 (DPEP1) expression and GSH depletion.[59]

Ferroptosis and Different Types of AKI

AKI is an acute renal insufficiency disease which can be caused by many factors. Recent studies have shown that ferroptosis is a promising therapeutic target in renal tubular injury diseases.[59,60] Thus, studies of IRI, Rhabdomyolysis (RM), Sepsis and nephrotoxic drug-induced AKI animal models provide direct evidence to confirm the involvement of ferroptosis in AKI (Figure 2).

Ferroptosis and IRI-Induced AKI

IRI is defined as tissue damage caused by the body or organ experiencing a transient reduction or cessation of blood flow for various reasons, restoration of blood supply, and then reoxygenation.[61] IRI is one of the major causes of AKI (IRI-AKI) and the pathophysiology of IRI-AKI includes mitochondrial dysfunction, ROS, and inflammatory cascade responses.[62] Ferroptosis may be a new driver of IRI-AKI. Anthocyanin −3- glucoside has anti-inflammatory and antioxidant effects in tissue IRI. After the researchers treated IRI-AKI mice with anthocyanin −3- glucoside, the results showed that the level of intracellular free iron ion decreased, the level of lipid ROS, MDA, and the expression of ACSL4 decreased, while the level of GSH and the expression of GPX4 increased, which effectively inhibited the ferroptosis of cells. Finally, the study concluded that anthocyanin −3- glucoside could reduce the ferroptosis of cells by activating the AMPK pathway and was valuable for the treatment of IRI-AKI.[63] Tonnus et al[64] showed that the inhibitor of necrotic apoptosis, necrotic inhibitor-1 (Nec-1s), can regulate ferroptosis by inhibiting RIPK1 kinase activity. At present, it is recognized that GPX4 is the key regulator of ferroptosis. Sun et al[65] found that TRIM21 can increase the ferroptosis of cells by mediating the ubiquitination degradation of GPX4. The expression of TRIM21 in mouse I/R kidney tissue is up-regulated, but when it is absent, it can effectively relieve IRI-AKI and improve renal function. The researchers found that the physiological level of selenium can reduce the ferroptosis injury caused by ischemia through TFAP2c and Sp1 to drive the transcription adaptation program and up-regulate the expression of GPX4.[66,67] Qi et al[68] similarly demonstrated the importance of GPX4 in IRI-AKI, where administration of pioglitazone treatment upregulated GPX4 gene expression and had a significant inhibitory effect on Erastin-induced cellular ferroptosis, alleviating IRI-AKI. Tonnus et al[64] demonstrated that loss of ferroptosis suppressor protein 1 (FSP1) or inhibition of selenoprotein GPX4 activity in renal IRI results in renal tubular cells that are sensitive to ferroptosis and provided further evidence that ferroptosis has

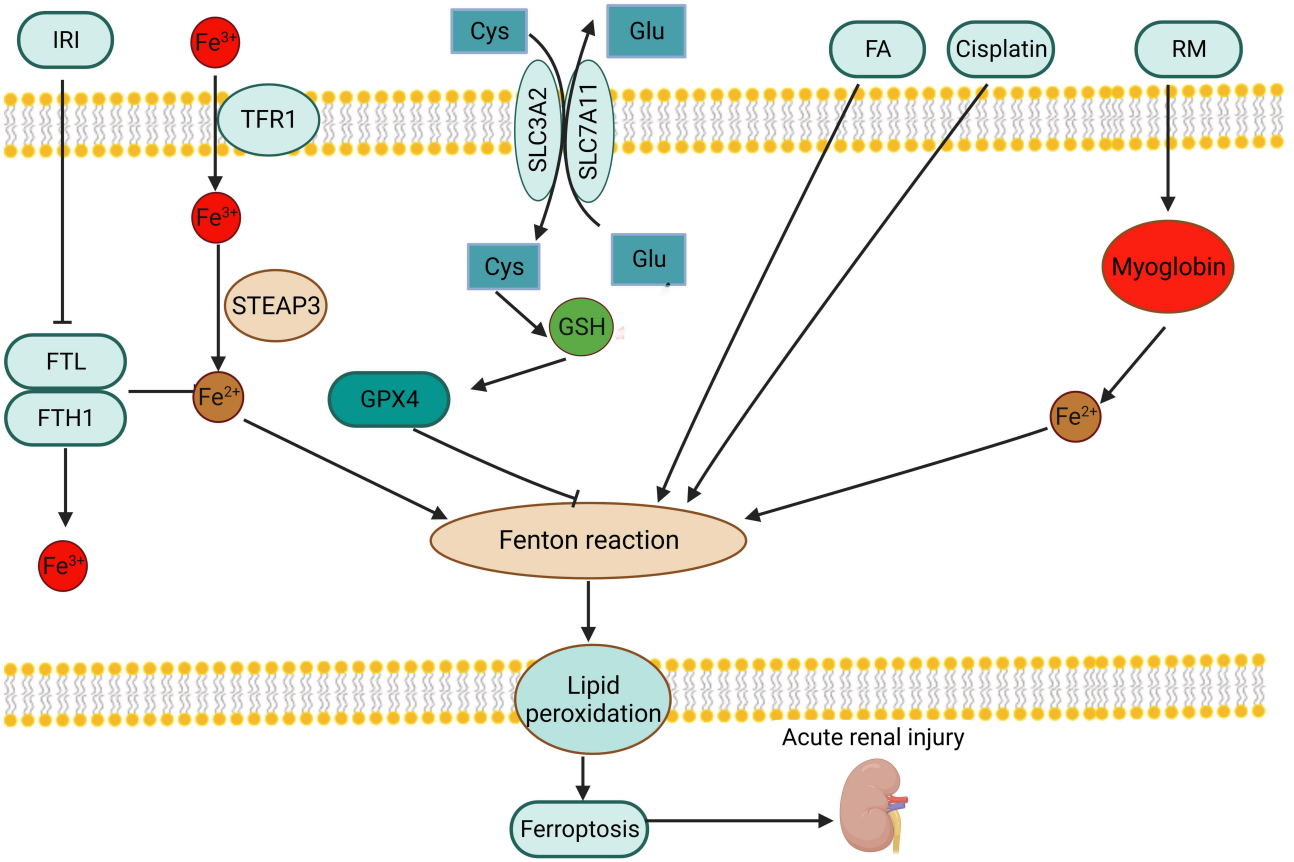

Figure 2 Regulatory mechanism of ferroptosis in AKI. This figure displays the crosstalk between IRI, RM, FA, Cisplatin and ferroptosis in AKI. Created with BioRender.com.

a genetically inherited character in AKI.Mässenhausen et al[59] found for the first time in mouse model that dexamethasone was sensitive to ferroptosis by increasing the expression of protein dipeptidase −1 and GSH depletion mediated by glucocorticoid receptor. Iron inhibitors have been considered to be important blockers of ferroptosis. Iron overload leads to ferroptosis through excessive lipid peroxidation.[64] Fer- analog UAMC-3203 is an effective ferroptosis inhibitor. Studies have shown that it is superior to Fer1 and Lip1 in reducing organ dysfunction and preventing death.[69,70] Linkermann et al[9] developed a third-generation iron inhibitor (16–86) that inhibited ferroptosis in AKI by combining treatment with drugs that inhibit mitochondrial permeability conversion, which was shown to be equally protective even in cases of severe AKI. Dong et al[71] established an IRI-AKI rat model to analyze the effects of ubiquitin-specific peptidase 7 on renal function and showed that when ubiquitin-specific peptidase 7 was inhibited, it significantly increased intracellular levels of GPX4 and SLC7A11 proteins and decreased intracellular iron ion content by reducing ubiquitination of TANK-binding kinase 1 and methylation of the FMRP translational regulator, thereby inhibiting ferroptosis and attenuating IRI-induced kidney injury. Inhibition of ubiquitin-specific protease 14 also showed similar efficacy to the treatment of IRI-AKI.[72] In addition, Wang et al[73] showed that knockdown of the ACSL4 gene significantly inhibited ferroptosis in renal tubular epithelial cells in mice with IRI-AKI. Similarly, dexmedetomidine inhibited ACSL4 activity by upregulating α2-adrenergic receptor activity and similarly attenuated ferroptosis-mediated renal injury,[74] suggesting that ACSL4 may be a key target for AKI therapy. Entacapone, an important drug as an adjunct to levodopa in the treatment of Parkinson's, was recently found to upregulate the expression of downstream SLC7A11 protein by affecting the p62-Keap1-Nrf2 pathway and significantly inhibited ferroptosis in IRI-AKI.[75] The above studies show that IRI-AKI is the most typical model of "ferroptosis" to date, and that ferroptosis is of great value in IRI-AKI, and may provides a new strategy for targeted therapy of IRI-AKI.

Ferroptosis and Rhabdomyolysis Syndrome-Induced AKI

Rhabdomyolysis (RM) is a clinical syndrome caused by the release of large amounts of intracellular material into the circulation, which is the main cause of AKI. Zarjou et al[76] knocked out the ferritin gene in mice, rhabdomyolysis occurred and AKI appeared, which indicated that ferritin played an important role in AKI. In addition, researchers delving into RM-induced AKI (RM-AKI) in rats showed significant increases in cytoplasmic and mitochondrial levels of haemoglobin and free iron, as well as in tissue levels of lipid peroxides.[77] This confirms the involvement of ferroptosis in the progression of RM-AKI. Furthermore, researchers found that iron-deficient mouse models reduced the development of RM-AKI by increasing catalytic haemoglobin iron, therefore, correcting iron deficiency may reduce the development of AKI.[78] It was found that nalmestat mesylate could inhibit the development of RM-AKI by mediating ferroptosis pathways such as glutathione metabolism and ferritin metabolism, as well as regulating the inflammatory response and associated expression of key differentially expressed genes, and it was suggested that nalmestat mesylate could be a potential target drug for the targeted treatment of RM-AKI.[79]

Ferroptosis and Sepsis-Induced AKI

Sepsis is defined as organ dysfunction caused by systemic inflammatory response of the host in response to infection, in which the kidney is one of the most commonly affected organs, which can lead to sepsis-induced AKI (SA-AKI). Guo et al[80] confirmed that the irregular immune response mediated by neutrophils and Treg cells participated in the development of SA-AKI, and was closely related to cell ferroptosis. EHT 1864 and phospholipase inhibitor (salubrinal) were effective in targeted treatment of cell ferroptosis and patients with SA-AKI. Zhou et al[81] also verified the existence of ferroptosis in the pathogenesis of SA-AKI after establishing the mouse model of SA-AKI. It was found that cationic transport regulator-like protein 1 could promote the ferroptosis of HK-2 cells by enhancing the oxidative stress induced by lipopolysaccharide. When the protein was silenced, the level of GPX4 protein in cells increased, while the levels of ACSL4 and ferritin decreased, which inhibited the ferroptosis. In addition, this study also found that n- acetylcysteine could be reversed. Melatonin is an antioxidant that regulates the sleep-wake cycle, and recent studies have found that melatonin also inhibits ferroptosis and attenuates SA-AKI by upregulating the Nrf2/HO-1 pathway.[82] The researchers found that the same regulation of cellular ferroptosis through the mmu-miR-7212-5p-Hmox1 signaling pathway and m6ARNA methylation regulators provided new insights into the regulatory mechanisms underlying the development of SA-AKI and provided new research directions for future targeted therapies for SA-AKI.[83]

Ferroptosis and Nephrotoxic Drug-Induced AKI

The use of nephrotoxic drugs is a common cause of kidney injury and is now widely used in AKI research. Features of folic acid-induced AKI (FA-AKI) include disruption of the antioxidant system and interstitial fibrosis, and ultimately tubular damage. It was found that the use of Fer-1 in FA-AKI mouse model can effectively preserve renal function and reduce oxidative stress, interstitial fibrosis, and renal tubular cell death.[84] FG-4592 is an inhibitor of the hypoxia-inducible factor prolyl hydroxylase. Li et al[85] found that FG-4592 pretreatment could be a way to reduce ferroptosis in early FA-AKI by mediating Nrf2 activation through the Akt/GSK-3β pathway, thereby delaying the progression of renal interstitial fibrosis. Huang et al[86] found that melatonin treatment attenuated hypoxia and reoxygenation or Erastin-induced ferroptosis in mouse FA-AKI tissues. RNA sequence analysis of ferroptosis-related genes showed that melatonin inhibited hypoxia and reoxygenation (HR-) to mediate the down-regulation of Nrf2 in MTEC and the up-regulation of SLC7A11 to affect oxidative stress, while specific knockdown of the Nrf2 gene increased cellular sensitivity to ferroptosis; therefore, melatonin prevents ferroptosis in AKI by acting on the Nrf2/SLC7A11 signalling pathway. In addition, it was found that aloin has certain anti-inflammatory and anti-injury activities. Hu et al[87] treated FA-AKI mice by intraperitoneal injection of aloin, and the results showed that it inhibited ferroptosis in renal tissue by activating Rev-erbα/β-SLC7A11/HO-1 signaling pathway, and protected renal function, which provided a basis for formulating targeted therapy strategies for FA-AKI.

Cisplatin is the recommended combination anti-cancer drug, and its nephrotoxic profile is of great concern - cisplatin-induced acute kidney injury (CP-AKI).[88] The accumulation of intracellular free iron mediates the excessive production of

ROS, which results in cellular ferroptosis. By constructing a quantum dot-drug conjugate compounded with carbon quantum dots, desferrioxamine, and polyethylene glycol, the researchers not only effectively scavenged excess intracellular Fe2+ and avoided the overproduction of ROS, but also had good efficacy in treating mice from CP-AKI.[88,89] Recent studies have found that dioscin can reduce the oxidative damage, apoptosis, and ferroptosis of the kidney through Nrf2/HO-1 signaling pathway, and play a protective role on CP-AKI.[90] Qi et al[91] found that CP-AKI was associated with an imbalance of ferritin metabolism in proximal tubular cells, and that administration of inositol promoted Hsc-70-interacting protein-mediated NOX4 ubiquitination, which effectively inhibited ferroptosis and improved CP-AKI. This provides new insights into the treatment of AKI.CP-AKI is mediated by both ferroptosis and mitochondrial dysfunction. 84-B10 was found to not only inhibit cisplatin-induced mitochondrial damage and mitochondrial reactive oxygen species (mtROS) production, and to restore superoxide dismutase (SODs) activity, but also to antagonise ferritinase, which showed potential for the treatment of CP-AKI.[92] In CP-AKI model, Gpx4cys/−- mice showed no difference in detection, which indicated that dysfunction of GPX4 would make renal tubules sensitive to AKI-induced necrosis.[86] The latest research found that cisplatin treatment can lead to mitochondrial damage, iron ion increase, ROS proliferation, and membrane lipid peroxidation, and can effectively inhibit ferroptosis when Fer-1 treatment is given. In addition, this study also confirmed that BNIP3 and PINK1-PARK2-mediated mitosis can regulate ROS/HO1/GPX4 pathways to inhibit ferroptosis in CP-AKI.[93] SKQ1 is a novel mitochondria-targeted antioxidant, and it was found that SKQ1 treatment significantly reversed the outcome of IRI-AKI, FA-AKI, and CP-AKI models, and the levels of biomarkers of kidney injury and inflammatory infiltration were reduced in the treated group. These results could contribute to a deeper understanding of the interactions between mitochondrial antioxidants and ferritin defense mechanisms.[94] Therefore, the future development of targeted drugs related to the inhibition of ferroptosis may be the way forward for the treatment of drug-induced AKI.

Summary

AKI is a common clinical kidney disease that can be caused by various etiologies such as IRI, RM, SA, and nephrotoxic drugs. Ferroptosis, a hot topic of research in recent years, is closely associated with the development of different types of AKI, and a number of small molecule compounds targeting ferroptosis have now demonstrated their ability to prevent and treat AKI. However, the pharmacological mechanisms, toxicity, side effects, and safe doses of the known drugs that inhibit ferroptosis in AKI remain to be further elucidated in future pre-clinical and clinical trials. To sum up, the mechanism of ferroptosis is still developing, but it plays an important role in the occurrence and development of AKI, and the future may be a good potential research direction in the treatment of AKI.

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Disclosure

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References

1. Susantitaphong P, Cruz DN, Cerda J, et al.; Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol*. 2013;8(9):1482–1493. doi:10.2215/CJN.00710113
2. Chawla LS, Bellomo R, Bihorac A, et al. Acute disease quality initiative workgroup 16. acute kidney disease and renal recovery: consensus report of the acute disease quality initiative (ADQI) 16 workgroup. *Nat Rev Nephrol*. 2017;13(4):241–257. doi:10.1038/nrneph.2017.2
3. Mehta RL, Cerdá J, Burdmann EA, et al. International society of nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet*. 2015;385(9987):2616–2643. doi:10.1016/S0140-6736(15)60126-X
4. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. *Compr Physiol*. 2012;2(2):1303–1353.
5. Yang WS, Kim KJ, Gaschler MM, et al. Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. *Proc Natl Acad Sci U S A*. 2016;113(34):E4966–75. doi:10.1073/pnas.1603244113
6. Segura-Aguilar J, Mannervik B. A preclinical model for parkinson's disease based on transcriptional gene activation via KEAP1/NRF2 to develop new antioxidant therapies. *Antioxidants*. 2023;12(3):673. doi:10.3390/antiox12030673

7. Guo J, Tuo QZ, Lei P. Iron, ferroptosis, and ischemic stroke. *J Neurochem*. 2023;165:487–520. doi:10.1111/jnc.15807
8. Wan J, Ren H, Wang J. Iron toxicity, lipid peroxidation and ferroptosis after intracerebral haemorrhage. *Stroke Vasc Neurol*. 2019;4(2):93–95. doi:10.1136/svn-2018-000205
9. Linkermann A, Skouta R, Himmerkus N, et al. Synchronized renal tubular cell death involves ferroptosis. *Proc Natl Acad Sci U S A*. 2014;111(47):16836–16841. doi:10.1073/pnas.1415518111
10. Feng Q, Yu X, Qiao Y, et al. Ferroptosis and acute kidney injury (AKI): molecular mechanisms and therapeutic potentials. *Front Pharmacol*. 2022;13:858676. doi:10.3389/fphar.2022.858676
11. Hu Z, Zhang H, Yang SK, et al. Emerging role of ferroptosis in acute kidney injury. *Oxid Med Cell Longev*. 2019;2019:8010614. doi:10.1155/2019/8010614
12. Mishima E, Sato E, Ito J, et al. Drugs repurposed as antiferroptosis agents suppress organ damage, including AKI, by functioning as lipid peroxyl radical scavengers. *J Am Soc Nephrol*. 2020;31(2):280–296. doi:10.1681/ASN.2019060570
13. Dixon SJ, Lemberg KM, Lamprecht MR, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149(5):1060–1072. doi:10.1016/j.cell.2012.03.042
14. Jiang L, Kon N, Li T. Ferroptosis as a p53-mediated activity during tumour suppression. *Nature*. 2015;520(7545):57–62. doi:10.1038/nature14344
15. Angeli JPF, Shah R, Pratt DA, et al. Ferroptosis inhibition: mechanisms and opportunities. *Trends Pharmacol Sci*. 2017;38(5):489–498. doi:10.1016/j.tips.2017.02.005
16. Chen X, Li J, Kang R, et al. Ferroptosis: machinery and regulation. *Autophagy*. 2021;17(9):2054–2081. doi:10.1080/15548627.2020.1810918
17. Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell*. 2017;171(2):273–285. doi:10.1016/j.cell.2017.09.021
18. Beguin Y, Aapro M, Ludwig H, et al. Epidemiological and nonclinical studies investigating effects of iron in carcinogenesis--a critical review. *Crit Rev Oncol Hematol*. 2014;89(1):1–15. doi:10.1016/j.critrevonc.2013.10.008
19. Zhi L, Jiao L, Rui K, et al. Lipid metabolism in ferroptosis. *Adv Biol*. 2021;5:e2100396. doi:10.1002/adbi.202100396
20. Gao M, Monian P, Quadri N, et al. Glutaminolysis and transferrin regulate ferroptosis. *Mol Cell*. 2015;59(2):298–308. doi:10.1016/j.molcel.2015.06.011
21. Geng N, Shi BJ, Li SL, et al. Knockdown of ferroportin accelerates erastin-induced ferroptosis in neuroblastoma cells. *Eur Rev Med Pharmacol Sci*. 2018;22(12):3826–3836. doi:10.26355/eurrev_201806_15267
22. Mancias JD, Wang X, Gygi SP, et al. Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. *Nature*. 2014;509(7498):105–109. doi:10.1038/nature13148
23. Cabantchik ZI. Labile iron in cells and body fluids: physiology, pathology, and pharmacology. *Front Pharmacol*. 2014;5:45. doi:10.3389/fphar.2014.00045
24. Ravingerová T, Kindernay L, Barteková M, et al. The molecular mechanisms of iron metabolism and its role in cardiac dysfunction and cardioprotection. *Int J Mol Sci*. 2020;21(21):7889. doi:10.3390/ijms21217889
25. Anderson GJ, Frazer DM. Current understanding of iron homeostasis. *Am J Clin Nutr*. 2017;106(Suppl 6):1559S–1566S. doi:10.3945/ajcn.117.155804
26. Dixon SJ, Stockwell BR. The role of iron and reactive oxygen species in cell death. *Nat Chem Biol*. 2014;10(1):9–17. doi:10.1038/nchembio.1416
27. Leaf DE, Rajapurkar M, Lele SS, et al. Iron, hepcidin, and death in human AKI. *J Am Soc Nephrol*. 2019;30(3):493–504. doi:10.1681/ASN.2018100979
28. Chen Y, He W, Wei H, et al. Srs11-92, a ferrostatin-1 analog, improves oxidative stress and neuroinflammation via Nrf2 signal following cerebral ischemia/reperfusion injury. *CNS Neurosci Ther*. 2023;29:1667–1677. doi:10.1111/cns.14130
29. Dowdle WE, Nyfeler B, Nagel J, et al. Selective VPS34 inhibitor blocks autophagy and uncovers a role for NCOA4 in ferritin degradation and iron homeostasis in vivo. *Nat Cell Biol*. 2014;16(11):1069–1079. doi:10.1038/ncb3053
30. Hou W, Xie Y, Song X, et al. Autophagy promotes ferroptosis by degradation of ferritin. *Autophagy*. 2016;12(8):1425–1428. doi:10.1080/15548627.2016.1187366
31. Sato H, Tamba M, Ishii T, et al. Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins. *J Biol Chem*. 1999;274(17):11455–11458. doi:10.1074/jbc.274.17.11455
32. Conrad M, Friedmann Angeli JP. Glutathione peroxidase 4 (Gpx4) and ferroptosis: what's so special about it? *Molecul Cellular Oncol*. 2015;2(3):e995047. doi:10.4161/23723556.2014.995047
33. Zhang Y, Swanda RV, Nie L, et al. mTORC1 couples cyst(e)ine availability with GPX4 protein synthesis and ferroptosis regulation. *Nat Commun*. 2021;12(1):1589. doi:10.1038/s41467-021-21841-w
34. Zhou L, Yu P, Wang -T-T. Wang TTPolydatin attenuates cisplatin-induced acute kidney injury by inhibiting ferroptosis. *Oxid Med Cell Longev*. 2022;2022:9947191. doi:10.1155/2022/9947191
35. Yu P, Zhang X, Liu N, et al. Pyroptosis: mechanisms and diseases. *Signal Transduct Target Ther*. 2021;6(1):128. doi:10.1038/s41392-021-00507-5
36. Chen H, Cao L, Han K, et al. Patulin disrupts SLC7A11-cystine-cysteine-GSH antioxidant system and promotes renal cell ferroptosis both in vitro and in vivo. *Food Chem Toxicol*. 2022;166:113255. doi:10.1016/j.fct.2022.113255
37. Ma L, Zhang X, Yu K, et al. Targeting SLC3A2 subunit of system XC- is essential for m6A reader YTHDC2 to be an endogenous ferroptosis inducer in lung adenocarcinoma. *Free Radic Biol Med*. 2021;168:25–43. doi:10.1016/j.freeradbiomed.2021.03.023
38. Friedmann Angeli JP, Schneider M, Proneth B, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat Cell Biol*. 2014;16(12):1180–1191. doi:10.1038/ncb3064
39. Yang WS, Stockwell BR. Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. *Chem Biol*. 2008;15(3):234–245. doi:10.1016/j.chembiol.2008.02.010
40. Yang WS, SriRamaratnam R, Welsch ME, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell*. 2014;156(1–2):317–331. doi:10.1016/j.cell.2013.12.010
41. Shui S, Zhao Z, Wang H, et al. Non-enzymatic lipid peroxidation initiated by photodynamic therapy drives a distinct ferroptosis-like cell death pathway. *Redox Biol*. 2021;45:102056. doi:10.1016/j.redox.2021.102056
42. Zhang J, Bi J, Ren Y, et al. Involvement of GPX4 in irisin's protection against ischemia reperfusion-induced acute kidney injury. *J Cell Physiol*. 2021;236(2):931–945. doi:10.1002/jcp.29903

43. Shimada K, Skouta R, Kaplan A, et al. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. *Nat Chem Biol*. 2016;12(7):497–503. doi:10.1038/nchembio.2079
44. Doll S, Proneth B, Tyurina YY, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol*. 2017;13(1):91–98. doi:10.1038/nchembio.2239
45. Kagan VE, Mao G, Qu F, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. *Nat Chem Biol*. 2017;13(1):81–90. doi:10.1038/nchembio.2238
46. Kobayashi M, Yamamoto M. Nrf2-Keap1 regulation of cellular defense mechanisms against electrophiles and reactive oxygen species. *Adv Enzyme Regul*. 2006;46:113–140. doi:10.1016/j.advenzreg.2006.01.007
47. Zhang DD, Lo SC, Cross JV, et al. Keap1 is a redox-regulated substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex. *Mol Cell Biol*. 2004;24(24):10941–10953. doi:10.1128/MCB.24.24.10941-10953.2004
48. Kaspar JW, Niture SK, Jaiswal AK. Nrf2: INrf2 (Keap1) signaling in oxidative stress. *Free Radic Biol Med*. 2009;47(9):1304–1309. doi:10.1016/j.freeradbiomed.2009.07.035
49. Kwak MK, Cho JM, Huang B, et al. Role of increased expression of the proteasome in the protective effects of sulforaphane against hydrogen peroxide-mediated cytotoxicity in murine neuroblastoma cells. *Free Radic Biol Med*. 2007;43(5):809–817. doi:10.1016/j.freeradbiomed.2007.05.029
50. Tonelli C, Chio IIC, Tuveson DA. Transcriptional Regulation by Nrf2. *Antioxid Redox Signal*. 2018;29(17):1727–1745. doi:10.1089/ars.2017.7342
51. Nezu M, Suzuki N, Yamamoto M. Targeting the KEAP1-NRF2 system to prevent kidney disease progression. *Am J Nephrol*. 2017;45(6):473–483. doi:10.1159/000475890
52. Doll S, Freitas FP, Shah R, et al. FSP1 is a glutathione-independent ferroptosis suppressor. *Nature*. 2019;575(7784):693–698. doi:10.1038/s41586-019-1707-0
53. Bersuker K, Hendricks JM, Li Z, et al. The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. *Nature*. 2019;575(7784):688–692. doi:10.1038/s41586-019-1705-2
54. Lee H, Zandkarimi F, Zhang Y, et al. Energy-stress-mediated AMPK activation inhibits ferroptosis. *Nat Cell Biol*. 2020;22(2):225–234. doi:10.1038/s41556-020-0461-8
55. Kraft VAN, Bezjian CT, Pfeiffer S, et al. GTP Cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling. *ACS Cent Sci*. 2020;6(1):41–53. doi:10.1021/acscentsci.9b01063
56. Li S, Wang R, Wang Y, et al. Ferroptosis: a new insight for treatment of acute kidney injury. *Front Pharmacol*. 2022;13:1065867. doi:10.3389/fphar.2022.1065867
57. Riegman M, Sagie L, Galed C, et al. Ferroptosis occurs through an osmotic mechanism and propagates independently of cell rupture. *Nat Cell Biol*. 2020;22(9):1042–1048. doi:10.1038/s41556-020-0565-1
58. Belavgeni A, Maremonti F, Tonnus W, et al. vPIF-1 is an insulin-like antiferroptotic viral peptide. *Proc Natl Acad Sci U S A*. 2023;120(21):e2300320120. doi:10.1073/pnas.2300320120
59. von Mässenhausen A, Zamora Gonzalez N, Maremonti F, et al. Dexamethasone sensitizes to ferroptosis by glucocorticoid receptor-induced dipeptidase-1 expression and glutathione depletion. *Sci Adv*. 2022;8(5):eabl8920. doi:10.1126/sciadv.abl8920
60. Carney EF. Ferroptotic stress promotes the AKI to CKD transition. *Nat Rev Nephrol*. 2021;17(10):633. doi:10.1038/s41581-021-00482-8
61. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nat Rev Nephrol*. 2011;7(4):189–200. doi:10.1038/nrneph.2011.16
62. Jang HR, Rabb H. The innate immune response in ischemic acute kidney injury. *Clin Immunol*. 2009;130(1):41–50. doi:10.1016/j.clim.2008.08.016
63. Du YW, Li XK, Wang TT, et al. Cyanidin-3-glucoside inhibits ferroptosis in renal tubular cells after ischemia/reperfusion injury via the AMPK pathway. *Mol Med*. 2023;29(1):42. doi:10.1186/s10020-023-00642-5
64. Tonnus W, Meyer C, Steinebach C, et al. Dysfunction of the key ferroptosis-surveilling systems hypersensitizes mice to tubular necrosis during acute kidney injury. *Nat Commun*. 2021;12(1):4402. doi:10.1038/s41467-021-24712-6
65. Sun X, Huang N, Li P, et al. TRIM21 ubiquitylates GPX4 and promotes ferroptosis to aggravate ischemia/reperfusion-induced acute kidney injury. *Life Sci*. 2023;321:121608. doi:10.1016/j.lfs.2023.121608
66. Alim I, Caulfield JT, Chen Y, et al. Selenium drives a transcriptional adaptive program to block ferroptosis and treat stroke. *Cell*. 2019;177(5):1262–1279.e25. doi:10.1016/j.cell.2019.03.032
67. Ioannou MS, Jackson J, Sheu SH, et al. Neuron-astrocyte metabolic coupling protects against activity-induced fatty acid toxicity. *Cell*. 2019;177(6):1522–1535.e14. doi:10.1016/j.cell.2019.04.001
68. Qi Y, Hu M, Qiu Y, et al. Mitoglitazone ameliorates renal ischemia/reperfusion injury by inhibiting ferroptosis via targeting mitoNEET. *Toxicol Appl Pharmacol*. 2023;465:116440. doi:10.1016/j.taap.2023.116440
69. Van Coillie S, Van San E, Goetschalckx I, et al. Targeting ferroptosis protects against experimental (multi)organ dysfunction and death. *Nat Commun*. 2022;13(1):1046. doi:10.1038/s41467-022-28718-6
70. Maremonti F, Locke S, Tonnus W, et al. COVID-19 and diabetic nephropathy. *Horm Metab Res*. 2022;54(8):510–513. doi:10.1055/a-1819-4822
71. zDong B, Ding C, Xiang H, et al. USP7 accelerates FMR1-mediated ferroptosis by facilitating TBK1 ubiquitination and DNMT1 deubiquitination after renal ischemia-reperfusion injury. *Inflamm Res*. 2022;71(12):1519–1533. doi:10.1007/s00011-022-01648-1
72. Pan J, Zhao J, Feng L, Xu X, He Z, Liang W. Inhibition of USP14 suppresses ROS-dependent ferroptosis and alleviates renal ischemia/reperfusion injury. *Cell Biochem Biophys*. 2023;81(1):87–96. doi:10.1007/s12013-022-01107-y
73. Wang Y, Zhang M, Bi R, et al. ACSL4 deficiency confers protection against ferroptosis-mediated acute kidney injury. *Redox Biol*. 2022;51:102262. doi:10.1016/j.redox.2022.102262
74. Tao WH, Shan XS, Zhang JX, et al. Dexmedetomidine attenuates ferroptosis-mediated renal ischemia/reperfusion injury and inflammation by inhibiting ACSL4 via α2-AR. *Front Pharmacol*. 2022;13:782466. doi:10.3389/fphar.2022.782466
75. Yang J, Sun X, Huang N, et al. Entacapone alleviates acute kidney injury by inhibiting ferroptosis. *FASEB J*. 2022;36(7):e22399. doi:10.1096/fj.202200241RR
76. Zarjou A, Bolisetty S, Joseph R, et al. Proximal tubule H-ferritin mediates iron trafficking in acute kidney injury. *J Clin Invest*. 2013;123(10):4423–4434. doi:10.1172/JCI67867
77. Zorova LD, Pevzner IB, Chupyrkina AA, et al. The role of myoglobin degradation in nephrotoxicity after rhabdomyolysis. *Chem Biol Interact*. 2016;256:64–70. doi:10.1016/j.cbi.2016.06.020

78. Zhao S, Wang X, Zheng X, et al. Iron deficiency exacerbates cisplatin- or rhabdomyolysis-induced acute kidney injury through promoting iron-catalyzed oxidative damage. *Free Radic Biol Med*. 2021;173:81–96. doi:10.1016/j.freeradbiomed.2021.07.025
79. Guo W, Wang Y, Wu Y, et al. Integration of transcriptomics and metabolomics reveals the molecular mechanisms underlying the effect of nafamostat mesylate on rhabdomyolysis-induced acute kidney injury. *Front Pharmacol*. 2022;13:931670. doi:10.3389/fphar.2022.931670
80. Guo G, Wang Y, Kou W, Gan H. Identifying the molecular mechanisms of sepsis-associated acute kidney injury and predicting potential drugs. *Front Genet*. 2022;13:1062293. doi:10.3389/fgene.2022.1062293
81. Zhou Z, Zhang H. CHAC1 exacerbates LPS-induced ferroptosis and apoptosis in HK-2 cells by promoting oxidative stress. *Allergol Immunopathol*. 2023;51(2):99–110. doi:10.15586/aei.v51i2.760
82. Qiu W, An S, Wang T, et al. Melatonin suppresses ferroptosis via activation of the Nrf2/HO-1 signaling pathway in the mouse model of sepsis-induced acute kidney injury. *Int Immunopharmacol*. 2022;112:109162. doi:10.1016/j.intimp.2022.109162
83. Liu B, Ao S, Tan F, et al. Transcriptomic analysis and laboratory experiments reveal potential critical genes and regulatory mechanisms in sepsis-associated acute kidney injury. *Ann Transl Med*. 2022;10(13):737. doi:10.21037/atm-22-845
84. Martin-Sanchez D, Ruiz-Andres O, Poveda J, et al. Ferroptosis, but not necroptosis, is important in nephrotoxic folic acid-induced AKI. *J Am Soc Nephrol*. 2017;28(1):218–229. doi:10.1681/ASN.2015121376
85. Li X, Zou Y, Xing J, et al. Pretreatment with roxadustat (FG-4592) attenuates folic acid-induced kidney injury through antiferroptosis via Akt/GSK-3β/Nrf2 pathway. *Oxid Med Cell Longev*. 2020;2020:6286984. doi:10.1155/2020/6286984
86. Huang YB, Jiang L, Liu XQ, et al. Melatonin alleviates acute kidney injury by inhibiting NRF2/Slc7a11 axis-mediated ferroptosis. *Oxid Med Cell Longev*. 2022;2022(83):4776243. doi:10.1155/2022/4776243
87. Hu M, An S. Ruscogenin prevents folic acid-induced acute kidney damage by inhibiting rev-erbα/β-mediated ferroptosis. *Comput Intell Neurosci*. 2022;2022:8066126. doi:10.1155/2022/8066126
88. Hu Z, Zhang H, Yi B, et al. VDR activation attenuate cisplatin induced AKI by inhibiting ferroptosis. *Cell Death Dis*. 2020;11(1):73. doi:10.1038/s41419-020-2256-z
89. Zhu Z, Liu X, Li P, et al. Renal clearable quantum dot-drug conjugates modulate labile iron species and scavenge free radicals for attenuating chemotherapeutic drug-induced acute kidney injury. *ACS Appl Mater Interfaces*. 2023;15(18):21854–21865.
90. Wang S, Zheng Y, Jin S, et al. Dioscin protects against cisplatin-induced acute kidney injury by reducing ferroptosis and apoptosis through activating Nrf2/HO-1 signaling. *Antioxidants*. 2022;11(12):2443. doi:10.3390/antiox11122443
91. Qi H, Deng F, Wang Y, Zhang H, Kanwar YS, Dai Y. Myo-inositol supplementation alleviates cisplatin-induced acute kidney injury via inhibition of ferroptosis. *Cells*. 2022;12(1):16. doi:10.3390/cells12010016
92. Fan J, Xu X, Li Y, et al. A novel 3-phenylglutaric acid derivative (84-B10) alleviates cisplatin-induced acute kidney injury by inhibiting mitochondrial oxidative stress-mediated ferroptosis. *Free Radic Biol Med*. 2023;194:84–98. doi:10.1016/j.freeradbiomed.2022.11.029
93. Lin Q, Li S, Jin H, et al. Mitophagy alleviates cisplatin-induced renal tubular epithelial cell ferroptosis through ROS/HO-1/GPX4 axis. *Int J Biol Sci*. 2023;19(4):1192–1210. doi:10.7150/ijbs.80775
94. Song J, Sheng J, Lei J, et al. Mitochondrial Targeted Antioxidant SKQ1 ameliorates acute kidney injury by inhibiting ferroptosis. *Oxid Med Cell Longev*. 2022;2022:2223957. doi:10.1155/2022/2223957