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Research Progress of Ferroptosis in Acute Kidney Injury

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Abstract: *Acute kidney injury (AKI) is an acute disease with high incidence and mortality. It is characterized by rapid deterioration of renal function and further accumulation of metabolic waste and toxins, leading to complications and dysfunction in other organs. Multiple pathogenic factors, such as rhabdomyolysis, infection, nephrotoxic drugs, and ischemia-reperfusion injury, contribute to the development and development of AKI. However, the specific mechanism is still unclear. Ferroptosis is a non-apoptotic cell death mechanism that is iron-dependent and is thought to be a process of iron accumulation and enhanced lipid peroxidation. Various studies suggest that ferroptosis plays an important role in the development of AKI. This review summarizes the potential role of ferroptosis in the pathogenesis and treatment of acute kidney injury.*

Keywords: *acute kidney injury; ferroptosis; mechanism; treat*

1. Introduction

Acute renal injury (AKI), formerly known as acute renal failure (ARF), is a common critical disease, that is caused by ischemia [1] nephrotoxic drugs, urinary tract obstruction, and other reasons, and has a high morbidity and mortality worldwide. Epidemiological investigation shows that the incidence of AKI in adults is over 20%, that in children is over 30%, and that the mortality caused by AKI in adults is as high as 23.9%[2]. AKI's high mortality, high treatment cost, and the possibility of developing chronic kidney disease (CKD) make it a major global health problem and research focus [3]. However, the specific mechanism related to the occurrence and development of AKI has not yet been determined. At present, there is no effective treatment to prevent the onset of AKI, delay its progress, and promote its repair. Apart from blood purification, few treatments have made significant progress in preventing AKI. Therefore, it is necessary to deeply study the specific pathogenesis of AKI and develop new corresponding therapies for clinical treatment. Recent studies have shown that iron death of renal tubular epithelial cells caused by iron overload positively correlates with the incidence and mortality of clinical AKI[4]. Direct evidence shows that iron death inhibitors have renal protection in various animal models of AKI, suggesting that iron death plays an important role in the occurrence and development of AKI [5]. Therefore, exploring the mechanism of iron death in AKI is of great significance for developing effective treatment strategies for AKI.

2. Definition of ferroptosis

As early as 2003, Dolma[6]and others discovered a new compound-Erastin, which has a selective lethal effect on ras-expressing cancer cells, but the way of cell death is different from that seen before. No nuclear morphological changes, DNA breakage, and caspase activation occurred, and this process could not be reversed by caspase inhibitors. Subsequently, Yang[7]and others found that this cell death mode can be inhibited by iron chelating agents and that another compound, RSL3, can cause this cell death mode. In 2012, Dixon et al. formally named this cell death iron death according to its characteristics when studying the mechanism of elastin killing RAS mutant cancer cells [8]. Iron death is a new cell death mode. Intracellular iron retention, reduced glutathione (GSH) content, and lipid reactive oxygen species (ROS) accumulation are the main characteristics of iron death [8]. The characteristics of iron death are different from other cell death types, and it has unique morphological characteristics and biological

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manifestations. Its morphological characteristics are mainly found in mitochondria, with reduced volume, increased membrane density, and decreased mitochondrial crista, but the nucleus remains normal and chromatin agglutinates [9]. Biochemistry, the consumption of intracellular glutathione (GSH), and the inactivation of glutathione peroxidase 4 (GPX4) make lipid peroxides unable to be metabolized by GPX4-catalyzed reduction reaction. Excessive accumulation of ROS can activate intracellular oxidative stress, damage protein, nucleic acid, and lipid, and eventually lead to iron death [10].

2.1. Mechanism of ferroptosis

In recent years, some molecular mechanisms and regulatory factors of iron death have been widely studied, such as iron metabolism and lipid peroxidation, cystine/glutamic acid reverse transporter (System Xc-), glutathione peroxidase 4(GPX4), tumor suppressor gene p53 and so on.

2.1.1 Iron metabolism

Iron is one of the most important trace elements in the human body, and its steady state is very important for the normal physiological function of cells [11]. In general, extracellular Fe3+ ions first bind to transferrin (TFR), then transport into cells through membrane transferrin receptor 1 (TFR1) and store in the form of ferritin complex (mainly ferritin). Fe3+ ions are reduced to Fe2+, and then transported and stored in the cell iron pool, while the excess Fe2+ ions are stored in ferritin. 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+[12]. When Fe2+ in cells is overloaded, the Fenton reaction produces a large number of free radicals, which eventually leads to lipid peroxidation and iron death [13]. Under some physiological and pathological conditions, the expression of TFR is up-regulated and the expression of ferritin (including FTH1 and FTL) is down-regulated, indicating that increasing iron intake or reducing iron storage forms can induce iron death [14]. Some iron chelating agents are closely related to the elimination of lipid peroxide free radicals, which may help to alleviate iron death-related diseases, such as AKI.

2.1.2 Lipid peroxidation

Lipid peroxidation plays a driving role in the occurrence of iron death, which can be completed by non-enzymatic or enzymatic reactions. Compared with unsaturated fatty acids and monounsaturated fatty acids, polyunsaturated fatty acids (PUFAs) are more prone to lipid peroxidation and iron death [15]. The abundance and location of PUFAs determine the degree of lipid peroxidation and iron death. Free PUFAs are substrates for synthesizing lipid signal transduction media, but they must be esterified into membrane phospholipids and oxidized to start iron death. The formation of PUFA coenzyme A derivatives is a necessary condition for iron death, and the participation of regulatory enzymes in membrane phospholipids in PUFA biosynthesis can trigger or prevent iron death[16]. ACSL4 and lysophosphatidylcholine acyltransferase 3 participate in the biosynthesis of phosphatidylethanolamine on the cell membrane. The deletion of these genes will increase the resistance of cells to iron death. In contrast, cells supplemented with arachidonic acid or other PUFAs increased their sensitivity to iron death [17][18]. Lipoxygenase (LOXs) is an important enzyme system that mediates the formation of iron death peroxide. Free PUFAs are the preferred substrate for LOX. Knocking out LOX can alleviate the damage caused by iron death. In addition, phosphatidylethanolamine can be further oxidized under the catalysis of LOXs, thus inducing cell iron death [19].

2.1.3 Amino acid metabolism

System xc- is considered an important regulator of iron death. System Xc- is an amino acid antiporter widely distributed in the phospholipid bilayer. It is an important part of the antioxidant system in cells, and it is a heterodimer composed of two subunits, SLC7A11 and SLC3A2. Cystine and glutamic acid are exchanged inside and outside the cell at the ratio of 1:1 through system xc-. The absorbed cystine is reduced to cysteine in cells and participates in the synthesis of glutathione. GSH reduces ROS and active nitrogen under the action of glutathione peroxidase (GPXs). It was found that Erastin and sulfasalazine inhibited the function of system xc- and reduced the uptake of cystine in cells, which led to the decrease of intracellular antioxidant capacity and the accumulation of lipids, thus causing cell iron death. In GPX4 knockout mice, the morbidity and mortality of AKI increased significantly. During IRI, GSH level decreased significantly, GPX4 activity decreased, iron accumulation and lipid peroxidation increased, and protein and gene expression related to iron sensitivity in renal tissue increased. To sum up, system xc- can maintain GSH levels by maintaining the balance between intracellular and extracellular cysteine and glutamic acid. Once the equilibrium state is broken, the decrease of GSH level in cells will lead to the decrease of synthesis and activity of GPX4, and eventually lead to the occurrence of cell iron death[20].

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2.1.4 GPX4

Among glutathione peroxidase (GPX) family members, GPX4 is a crucial iron death regulator. The activity of GPX4 is related to the content of glutathione (GSH). When glutathione is exhausted, the activity of GPX4 decreases or becomes inactive. As an antioxidant enzyme, GPX4 catalyzes the reduction of lipid peroxide and indirectly interferes with the Fenton reaction, which is very important for maintaining the content of hydrogen peroxide [21] in cells. High concentrations of H2O2 will produce ROS, which will rapidly oxidize fatty acids (FAs) and arachidonic acid (AA) to produce fatty toxic substances. GPX4 also converts GSH into glutathione disulfide (GSSG) and reduces cytotoxic lipid hydroperoxide (L-OOH) to corresponding alcohol (L-OH) [22], thus resisting oxidative damage. GSH reductase and NADPH/H+[23]reduce GSSG to GSH. The function of GPX4 is the core of iron death, and its significance has been gradually revealed. Inhibition of GPX4 expression or obstruction of its function may cause oxidative damage to cells or tissues. Many studies show that the antioxidant function of GPX4 is the core link to iron death [24]. Therefore, the molecules that affect the function and activity of GPX4 may significantly affect the occurrence of iron death.

2.1.5 P53

P53 is an important tumor suppressor. Besides affecting cell death, autophagy, apoptosis, and focal death, p53 is also involved in regulating cell iron death. P53 promotes iron death by decreasing the expression of SLC7A11, and it also inhibits iron death by directly down-regulating dipeptidyl peptidase 4 (DPP4) or up-regulating the expression of cyclin-dependent kinase inhibitor 1A/p21. Jiang et al. found for the first time that p53 inhibited cystine uptake by blocking SLC7A11, which led to a significant decrease in GSH and induced cell iron death [25]. Chu et al. found that knocking out arachidonic acid 12-lipoxygenase (ALOX12) specifically blocked the occurrence of iron death, which proved that p53 indirectly activated the function of ALOX12 by inhibiting SLC7A11, leading to ALOX12-dependent iron death after ROS stress [26]. Xie et al. proved that p53 can inhibit the sensitivity of tumor cells to iron death induced by erastin by blocking the activity of DPP4 [27]. Therefore, P53 may regulate iron sag in two ways, but the specific mechanism needs further study. To sum up, p53 can not only regulate apoptosis and cell cycle arrest but also inhibit the occurrence and development of tumors by regulating iron death.

3. Ferroptosis and AKI

3.1. Ferroptosis and AKI caused by rhabdomyolysis

Rhabdomyolysis (RM) can be caused by strenuous exercise; Direct trauma; Metabolic changes of muscles; Toxicity: toxic effects of chemical, physical, or biological agents; Genetic factors, and so on[28][29][30]. Renal failure caused by RM accounts for 15% of all cases of acute renal failure. Previous studies have shown that the accumulation of myoglobin (Mb) in the kidney is the core mechanism leading to renal damage. After myocyte lysis, a large number of salts, enzymes, and Mb are released in the circulation [32][33], which leads to the deposition of circulating Mb in the kidney, causing renal tubular obstruction and necrosis, and renal vascular contraction is strong [34][35]. The study on rm-induced AKI shows that the direct induction of lipid peroxidation by Fe2+ produced by Mb metabolism may be an important mechanism of rm-induced renal injury[36]. The animal model of myoglobin urine after intramuscular injection of glycerol is closely related to human RM[37]. Free iron released by Mb degradation in the kidney participates in the production of oxidized substances through the catalytic action of the Fenton reaction. Studies have shown that the use of iron chelating agent deferoxamine can alleviate renal injury in rats induced by mined [38] and prevent direct exposure to mb-induced cytotoxicity in vitro [39]. Guerrero-Hue et al. showed that iron death plays a key role in rm-induced AKI and that the death of iron death-sensitive cells can be inhibited by curcumin, a strong antioxidant[40]. In addition, Zarjou et al. reported that FTH knockout mice had higher mortality and more serious renal injury than wild-type mice in the rm-induced AKI model, indicating the protective effect of heavy chain ferritin on renal tubular injury and the role of iron ions in AKI [41]. In a word, these studies strongly indicate that iron death plays an important role in rm-induced AKI.

3.2. Ferroptosis and AKI induced by ischemia-reperfusion

Ischemia-reperfusion injury (IRI) is the most common cause of AKI, which is characterized by the sudden suspension of blood supply to renal tissue and the rapid increase of tissue injury after blood flow recovery. The clinical disease caused by this is called reperfusion syndrome. AKI is usually caused by bleeding, dehydration, postoperative hypoperfusion, sepsis, shock, and other clinical symptoms.

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Apoptosis was initially considered the main type of cell death in ischemic injury. However, later findings showed that iron death may be the main driving factor of ischemic injury [42]. The application of somatostatin in severe IRI models can protect mice from functional acute renal failure and structural organ damage [43]. Studies have shown that the low level of intraoperative iron-binding protein may reflect the impairment of the rapid processing ability of catalyzing iron release during cardiopulmonary bypass, leading to kidney damage. In iri-induced mice, the administration of somatostatin can reduce the damage to function and organs [44]. In isolated tubular cells, iron sag inhibitors can prevent hypoxia injury [45]. This indicates the importance of iron death in human ischemia-reperfusion injury and suggests that iron death may be a potential therapeutic target for kidney injury related to heart surgery or iri-induced AKI.

3.3. Renal toxic drug-induced AKI and Ferroptosis

Nephrotoxic drugs (such as folic acid and cisplatin) are another key factor causing AKI. High-dose folic acid can quickly form crystals in renal tubules, leading to AKI. Guo et al. found that lipid peroxidation occurred in the kidney tissue of mice model that induced AKI, and blocking reverb -α/β could improve folic acid-induced AKI by inhibiting iron death [46]. Martin-Sanchez et al. confirmed that in folic acid-induced AKI mice, treatment with iron death inhibitor Fer-1 can significantly alleviate renal function and reduce renal damage. Cisplatin is a commonly used anticancer drug; However, its nephrotoxicity limits its use. Previous studies have shown that the incidence of AKI induced by cisplatin is 20% ~ 30%. Recent studies have shown that cisplatin significantly induces proximal tubule injury in FTH knockout mice compared with wild-type mice [47]. Lu et al. reported that Ras homologs enriched in the brain can alleviate cisplatin-induced AKI by maintaining mitochondrial homeostasis [48]. Zhou et al. recently reported that salicylate can attenuate cisplatin-induced iron death in AKI cells by regulating the XC/GSH/GPX4 pathway and inhibiting iron metabolism disorder [49]. In summary, iron death is one of the important mechanisms of AKI induced by nephrotoxic drugs.

4. Application of AKI therapy based on Ferroptosis

AKI has always been a serious harm to world health, and it is also the focus of research. In recent years, the incidence and mortality of AKI have been on the rise, but there is still no effective prevention and treatment. To maintain the stability of renal function and protect human health, it is necessary to deeply understand the molecular mechanism of AKI and formulate appropriate therapeutic strategies to intervene and inhibit its further development. Inhibition of iron death in renal tubular epithelial cells can effectively alleviate the progress of AKI. With people gradually realizing the role of iron death in AKI, the treatment of AKI by inhibiting iron death has become a hot spot in the field of nephrology. From the point of view of treatment, in recent years, many natural and synthetic drugs have been found to induce or inhibit iron death by regulating related channels, which has great therapeutic potential for iron death-related diseases. In various proliferative diseases such as tumors, inducing iron death can promote the death of tumor cells and play an anti-tumor role. In some non-neoplastic diseases (such as ischemia-reperfusion injury, cardiovascular and cerebrovascular diseases, kidney diseases, etc.), iron death inhibitors can prevent the occurrence and development of lipid peroxidation and iron death through different targets in related pathways. At present, the main therapeutic advances include iron death inhibitors, lipid peroxidation pathway inhibitors, iron homeostasis regulators, and ROS production inhibitors. Ferritin -1 (Fer-1) can reduce lipid peroxide, scavenge oxygen free radicals, and prevent membrane lipid damage through redox reaction, thus inhibiting cell death [50]. Studies have shown that it can reduce the oxidation of alcohol by lipid peroxide (R-OOH→R-OH), and intercept and remove lipid groups by hydrogen atom transfer or direct reduction (R-O→R-OH) [51]. Somatostatin is often reported to attenuate lipid peroxidation-mediated tissue damage in various diseases, including acute kidney disease. Studies found that the use of for-1 can not only block iron death induced by rubber in vitro but also prevent renal ischemia-reperfusion injury in mice[52]. It was also found that deferoxamine can obtain 3- hydroxy diamond -1- yl, a compound with less cytotoxicity, by inhibiting lipid peroxidation, reducing the ferrous form of Mb, and inhibiting iron death, it can weaken the rhabdomyolysis induced by AKI in rats [53][54]. Lipstatin is another typical iron death inhibitor, and it is an effective spiroquindox derivative found by Qualcomm screening, which can inhibit iron death by eliminating lipid peroxide in vivo [55]. Lipstatin -1 has been reported to inhibit iron death in human renal proximal tubular epithelial cells, Gpx4-/-kidney, and iri-induced tissue injury model [56]. In addition, lipid peroxidation inhibitors, such as lysine oxidase (LOX) inhibitors, can also inhibit iron death [57]. Antioxidants and iron-chelating agents (such as vitamin E and deferoxamine ([DFO])) have also been observed to inhibit iron death by reducing the availability of iron. In addition, with the development of traditional Chinese medicine, some components

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of traditional Chinese medicine have also been proven to have anti-iron death activity, further reducing AKI kidney injury. Studies have proved that quercetin can alleviate renal injury induced by ischemia-reperfusion injury in AKI mice by inhibiting iron death. At present, several studies have been carried out to develop iron death inhibitors in various AKI animal models, but there is still a lack of clinical application potential. Therefore, clinical research on the prevention and targeted treatment of iron death in AKI should be carried out in the future.

5. Conclusions

Iron death is a recently discovered mechanism of iron-dependent non-apoptotic cell death. This paper summarizes its mechanism, characteristics, and general preliminary understanding. In AKI, it has been possible to clarify that iron death is one of the important causes of cell death. The application of small molecular iron death inhibitors to inhibit iron death is expected to be a new strategy for treating AKI. Although most of these studies on small molecular iron death inhibitors are carried out in the mouse model of AKI or in vitro experiments, future research will provide a new perspective and new strategy for the treatment of AKI to deeply explore the role of iron death in the process of AKI and rationally use iron death to regulate AKI.

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