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Research Progress of Ferroptosis in Septic Organ Damage

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Abstract: Sepsis is one of the main causes of death in severely infected patients, and the complexity of its pathogenesis increases the difficulty of clinical treatment. Ferroptosis is a new cell death mode discovered in recent years, which is closely related to the severity of sepsis. Research has found that iron accumulation can not only serve as an effective indicator for evaluating the severity of sepsis in patients, but also predict the prognosis of sepsis patients. In recent years, studies have pointed out that severe Ferroptosis exists in the body after sepsis, and inhibiting Ferroptosis is expected to become a new target for sepsis treatement. This article summarizes the evidence of Ferroptosis in sepsis organ injury, and provides new ideas for further research and treatment of sepsis.

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by the host's abnormal response to infection and can lead to multiple organ and system damage. According to statistics, there are over 31 million sepsis patients worldwide each year, and the death toll is as high as 6 million. The mortality rate of sepsis in hospitalized patients ranges from 34.9% to 66.7%. Sepsis is a group of severe clinical syndromes, and the complexity of its pathogenesis increases the difficulty of clinical treatment. Although there is a large amount of research on sepsis currently, its pathogenesis is still not fully understood. When sepsis occurs, there is a severe inflammatory response in the body, but even after the clinical application of inflammatory cytokines, the mortality rate of sepsis patients remains high [1].

Ferroptosis is a new cell death mode discovered in recent years, which is closely related to the severity of sepsis. During sepsis, iron metabolism is severely disrupted, including the transport, absorption, and excretion of iron, which can lead to the accumulation of a large amount of iron inside cells. On one hand, the accumulation of iron can activate iron-containing lipoxygenases, and on the other hand, it can catalyze the Fenton reaction to produce a large number of reactive oxygen species clusters. A large body of research has shown that iron accumulation can not only be an effective evaluation index for the severity of sepsis, but also predict the prognosis of sepsis patients. In recent years, studies have indicated that there is severe ferroptosis in the body after sepsis, and inhibiting ferroptosis may become a new target for the treatment of sepsis [2].

2. Definition of Ferroptosis and Its Main Regulation Mechanism

In 2003, Ferroptosis was observed for the first time during the treatment of cells with a cell permeable compound (Erastin). In 2012, cell death caused by reactive oxygen species (ROS) dependent lipid peroxide accumulation and Erastin-induced iron overload induced by Dixon and others, was defined as Ferroptosis， which was different from apoptosis, necrosis, autophagy or scorch. Its morphological changes were mainly the rupture and shrinkage of Outer mitochondrial membrane, the reduction and disappearae of Crista, and the hyperchromatism of mitochondria, but the nucleus did not change significantly. In contrast to autophagy, Ferroptosis does not form a typical closed bilayer membrane structure (autophagic vesicles). The regulatory pathway of Ferroptosis is very complex, and multiple metabolic pathways including iron, lipid and amino acid jointly control the sensitivity of cells to Ferroptosis.

2.1. Iron Overload

Iron homeostasis is crucial for many biological processes and cell viability in the body. Iron exists in two forms within cells: free iron and stored iron. Free iron is a divalent iron ion with redox activity, which plays a major role in iron metabolism. Most of free iron is oxidized into trivalent iron ions and stored in Ferritin. A small part of free iron is discharged through membrane iron transporter. However, excessive iron accumulation in cells, also known as iron overload, accelerates Lipid peroxidation of cell membrane, promotes mitochondrial damage, and damages tissues and organs by producing hydroxyl radicals.

There are three ways to increase intracellular free iron, namely increased cell absorption of iron, decreased storage of iron, and decreased iron efflux. Studies have found that after Ferritin autophagy is activated, Lysosome degrades Ferritin, reduces iron storage, and increases the content of free iron in cells, leading to iron overload. The intervention of iron chelator will significantly inhibit the occurrence of Ferroptosis, suggesting that iron overload is a sign of Ferroptosis and an important regulatory mechanism[3].

2.2. Lipid Peroxidation

Lipid peroxidation is a key feature of Ferroptosis. Glycerin, fatty acid, etc. can be used as raw materials to synthesize phospholipids on the cell endoplasmic reticulum, and then be transported to various biofilms to fuse with the membrane to renew the biofilm. Appropriate iron can promote the formation of phospholipids, but when iron is overloaded, the existing phospholipids on the cell membrane will undergo Lipid peroxidation, the bilayer structure and function of phospholipids will be destroyed, and eventually Ferroptosis will occur to cells.

Lipid metabolism is closely related to the sensitivity of cell Ferroptosis. Free Polyunsaturated fatty acid (PUFA), such as anthotetraenoic acid (AA) and adrenaline (AdA) phospholipids, can be oxidized by intracellular reactive oxygen species and produce lipid peroxides that cause Ferroptosis. Lipid peroxidation is a process in which ROS oxidizes biofilms. Sepsis patients can significantly increase ROS content through Fenton reaction. With the participation of iron ions, ROS accumulates on membrane lipids, leading to the formation of membrane pores, destruction of barrier function, changes in membrane permeability, and cell Ferroptosis.

2.3. Reduction (Antioxidant) System Disorder

The reduction (antioxidant) system in the human body is mainly glutathione (GSH) and Glutathione peroxidase (GPX4). GPX4 is an antioxidant enzyme necessary to maintain the redox

homeostasis of cells, has the effect of inhibiting Lipid peroxidation, and is a key regulator of Ferroptosis. Under physiological conditions, the reducing system in the body promptly reduces oxides such as ROS to harmless substances. As an important transmembrane transporter, Cystine/glutamate reverse transporter (system Xc) can mediate the exchange between extracellular Cystine and intracellular glutamate; Cystine is involved in the synthesis of glutathione. As a ligand of GPX4, GSH can play an antioxidant role with GPX4. After sepsis, the immune system of the body is disordered, leading to the imbalance of the reducing system and Ferroptosis[4].

Nuclear factor E2 related factor 2 (Nrf2) is the main upstream regulatory Signaling molecule of GPX4. When oxidative stress occurs, Nrf2 translocates to the nucleus and upregulates the expression of downstream antioxidant enzymes such as GPX4, Heme oxygenase 1 and quinone oxygen reductase 1, playing an antioxidant role. Nrf2 can clear glutamic acid and protect cells from Ferroptosis caused by Cystine deficiency. The key to maintain cell stability is to participate in various regulatory mechanisms of Ferroptosis, which is expected to provide potential targets for combating Ferroptosis [5].

3. Sepsis Organ Damage Caused by Ferroptosis

3.1. Septic Cardiomyopathy

Septic cardiomyopathy (SCM), also known as sepsis induced myocardial injury (SIMI), is a common potential complication of sepsis and a reversible left ventricular systolic dysfunction. When sepsis is combined with SCM, the prognosis is poor, and the mortality rate increases by 70% to 90%[6]. Its pathogenesis is complex and unclear. Wang et al found that in the sepsis model of mice induced by Lipopolysaccharide, the serum iron concentration increased, and the iron related protein Transferrin receptor and Ferritin increased and decreased respectively[7]. In addition, it has been reported that the iron storage function of Ferritin is crucial to prevent heart Ferroptosis and subsequent heart failure[8].

In vivo and in vitro experiments, it was found that reducing the level of iron ion can reduce the ROS level of myocardial cells, significantly reduce cardiac inflammation and dysfunction, thus improving the survival rate of SCM mice [9]; Other studies have shown that inhibition of Ferroptosis reduces myocardial injury, which may be related to inhibition of Endoplasmic reticulum stress[10]. Wei et al. reported that iris can inhibit Ferroptosis and improve mitochondrial function during sepsis. The researcher also found that the serum iris level of sepsis patients was lower than that of normal people [11].

3.2. Sepsis Induced Lung Injury

Acute lung injury (ALI) is also a common complication of sepsis, and can even cause acute respiratory distress syndrome (ARDS). Studies have shown that sepsis can increase the level of iron ions in lung epithelial cells, promote Lipid peroxidation, and increase the level of iron ions in macrophages, which can promote the migration of neutrophils, thus intensifying the inflammatory response[12].

Some studies have shown that hydrogen sulfide has a protective effect on myocardial injury in sepsis by regulating Endoplasmic reticulum stress, regulating autophagy, reducing inflammatory response and reducing apoptosis. At the same time, in the model of acute lung injury caused by sepsis, studies have shown that hydrogen sulfide can reduce Ferroptosis in acute lung injury by increasing the expression of GPX4 and SLC7A11 in the lung tissue of rats after cecal ligation perforation (CLP), And the activation of autophagy in acute lung injury can be inhibited by blocking the mTOR signaling pathway[13].

3.3. Sepsis Intestinal Injury

The intestine is the most frequently affected organ in critically ill conditions such as sepsis, and it is also the initiating organ for multiple organ failure. The gut microbiota is a complex ecosystem in the human body, including the gut microbiota, intestinal epithelial cells, and mucosal immune system. Any damage to any part can lead to intestinal dysfunction. In a healthy human body, the components of the gut microbiota work together to maintain a mutually beneficial and symbiotic balance, which is extremely important for both the host and the bacteria themselves.

Cell Ferroptosis releases too much iron in the cell to promote bacterial reproduction; At the same time, excessive iron can also promote the production of lipid peroxide raw materials, such as ROS and fatty acids, thereby exacerbating infection and leading to sepsis. Sepsis patients with iron metabolism disorder can lead to colon leakage, reduce the proliferation ability of crypt cells, damage the intestinal barrier function, increase permeability, and increase the entry of iron ions and intestinal bacteria into the portal vein; Systemic inflammatory reaction, oxidative stress and bacterial proliferation increase Ferroptosis, further cause organ damage, and form a vicious circle. The Ferroptosis of intestinal epithelial cells can destroy the intestinal barrier, promote harmful intestinal bacteria and toxins to enter the circulation and extraintestinal tissues, and inhibit Ferroptosis can reduce intestinal inflammation and barrier dysfunction in sepsis. However, the specific signaling pathway and mechanism of Ferroptosis in intestinal dysfunction in sepsis need further research.

3.4. Sepsis Liver Injury

The liver is the main metabolic and immune organ in the human body, playing a crucial role in immune defense and metabolic regulation in sepsis. The liver is also one of the most frequently damaged organs in sepsis. Liver dysfunction often occurs in the early stages of sepsis development and has been recognized as an independent risk factor for early (28 day) mortality in patients, and is significantly positively correlated with chronic (1-year) mortality[14].

It has been proved that Ferroptosis is involved in regulating liver diseases caused by iron overload, including liver fibrosis, non-alcoholic steatohepatitis, liver injury and hepatocellular carcinoma. The liver tissue of sepsis mice is oxidized and damaged. The level of unstable iron in the liver is significantly increased, resulting in Ferroptosis, which causes damage to mitochondrial function and tissue ATP synthesis, and then damages liver microcirculation, leading to perfusion failure and hepatotoxicity. Liver macrophages can promote liver iron deposition by regulating iron overload induced overexpression of HO-1, leading to a decrease in liver cell survival rate and exacerbation of liver damage. After the use of antioxidants to inhibit Ferroptosis and macrophage extracellular traps, this state can be reversed and liver injury can be alleviated[15].

3.5. Sepsis Associated Acute Kidney Injury (SA-AKI)

The incidence rate of SA-AKI in sepsis patients is as high as 40%~50%. SA-AKI can rapidly develop into renal failure or even death. Some studies have shown that iron ions are filtered in the glomerulus and reabsorbed in the renal tubules. When SA-AKI occurs, the release of intravascular hemolysis, proinflammatory factors and hemoglobin increases the content of iron ions in the kidney, causing renal iron death. The occurrence of iron death is positively related to the incidence rate and mortality of SA-AKI. In various animal models of Acute kidney injury, heme oxygenase-1, iron chelating agent or small molecule Ferroptosis inhibitor are used to reduce Acute kidney injury by inhibiting Ferroptosis of renal tubular epithelial cells, thus playing a role in renal protection.

4. Conclusions

In the past few years, Ferroptosis, as a newly discovered programmed cell death mode in the pathological process of many diseases which can lead the injury of various organs of sepsis, has been greatly expanded in the research field. However, it is unclear whether Ferroptosis can enhance or inhibit other cell death pathways such as pyroptosis. Moreover, current research is mostly based on animal or molecular level experiments, with limited clinical research. Therefore, it is necessary to further clarify the mechanism of Ferroptosis in order to carry out clinical research, which is a challenge for sepsis Ferroptosis research.

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