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Research Progress on Ferroptosis in Ischemic Cardiomyopathy

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Abstract: Ischemic cardiomyopathy (ICM) is the terminal manifestation of long-term myocardial ischemia, necrosis, and fibrosis caused by coronary artery disease, and its pathogenesis involves multiple modes of cell death. In recent years, the role of ferroptosis as an iron dependent, lipid peroxidation driven regulatory form of cell death in ICM has gradually been revealed. This article systematically reviews the molecular mechanisms of ferroptosis and its role in the occurrence and development of ICM, and explores potential therapeutic strategies targeting ferroptosis, aiming to provide new ideas for the prevention and treatment of ICM.

Keywords: Ferroptosis; Ischemic cardiomyopathy; Regulatory mechanism; Targeted therapy

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1. Introduction

Ischemic cardiomyopathy (ICM) is a common cardiovascular disease caused by long-term chronic myocardial ischemia due to coronary atherosclerosis [1]. At present, the clinical diagnostic criteria for ICM mainly include the presence of severe coronary artery disease with left ventricular dysfunction, and at least one of the following characteristics must be met.

(1) Previous history of revascularization or acute myocardial infarction (AMI);
(2) The degree of stenosis in the left main trunk or left anterior descending branch is greater than 75%;
(3) Two or more major coronary arteries have a lumen stenosis of > 75% [2].

Moreover, ICM often presents with serious complications such as arrhythmia, embolism, and heart failure, which to some extent imposes a heavy disease burden on patients and society [3]. Its pathological and physiological mechanisms involve a series of metabolic, neurohumoral, and inflammatory factors, specifically manifested as myocardial cell hypertrophy, interstitial fibrosis, oxidative stress injury, calcium homeostasis imbalance, and various forms of programmed cell death [4]. Therefore, understanding the

etiology and pathogenesis of ICM is of great significance for guiding clinical treatment and improving patient prognosis. In recent years, studies have shown that ferroptosis is involved in pathological and physiological processes such as myocardial infarction and myocardial ischemia-reperfusion injury (MIRI), both of which may lead to the development of fibrosis, suggesting that ferroptosis may play an important role in the pathogenesis of chronic ischemia hypoxia induced ICM [5]. This article focuses on the molecular mechanisms and potential therapeutic significance of ferroptosis in the occurrence and development of ICM.

2. Iron death

2.1. Overview of iron death

Iron dependent non apoptotic cell programmed cell death is a novel form of cell death that is dependent on iron, first discovered by Dixon et al. [6]. It is completely different from traditional cell apoptosis, necrosis, and autophagy, and is an iron dependent, lipid peroxidation mediated cell death mode [7]. In terms of morphology, the characteristics of ferroptosis are reflected in mitochondrial shrinkage (shrinking), increased mitochondrial membrane density, reduced or absent cristae, and rupture of the outer mitochondrial membrane [8]. In terms of biochemistry, the characteristics of iron death are reflected in iron accumulation and lipid peroxidation [9]. The mechanisms that cause ferroptosis mainly include three classic mechanisms: dysregulation of iron ion metabolism, redox disorders, and lipid peroxidation. Other factors such as coenzyme Q10, ferritin autophagy, lipid autophagy, and mitochondrial metabolic disorders can also regulate the process of ferroptosis [10].

2.2. Molecular mechanism of ferroptosis

2.2.1. Iron metabolism and iron death

Iron, as an essential trace element for the human body, plays a dual role in maintaining physiological functions of the heart: it is both indispensable and potentially toxic. Studies have shown that both iron deficiency and iron overload can have toxic effects on the heart, impair normal heart function, and induce various cardiovascular diseases. Therefore, maintaining iron homeostasis is crucial for the normal physiological activity of myocardial cells. Under physiological conditions, cellular iron uptake is mainly regulated by the plasma membrane protein transferrin receptor 1 (TFR1), which transports Fe^{3+} bound to transferrin (TF) into the cell through receptor-mediated endocytosis. Prostate six segment transmembrane epithelial antigen 3 (STEAP3) reduces Fe^{3+} to Fe^{2+}, which is then released from the nucleus into the cytoplasmic unstable iron pool and ferritin through the mediation of solute carrier family 11 member 2 (SLC11A2) (also known as divalent metal ion transporter 1 (DMT1)). Ferritin is a protein complex composed of ferritin light chain (FTL) and ferritin heavy chain (FTH) 1, which can isolate Fe^{2+} and prevent its oxidation. It is worth noting that after binding with nuclear receptor coactivator 4 (NCOA4), it can be transported to autophagosomes for lysosomal degradation (also known as ferritin autophagy), leading to the release of Fe^{2+}. Upregulation of FTL/FTH1 expression or inhibition of NCOA4 can inhibit ferroptosis. When the intracellular iron homeostasis is imbalanced and iron overload occurs, excess intracellular free Fe^{2+} will generate a large amount of reactive oxygen species (ROS) that damage the membrane system through the Fenton reaction, thereby catalyzing lipid peroxidation and ultimately triggering iron death.

2.2.2. Glutathione metabolism and iron death

The mechanism of ferroptosis is not only related to the imbalance of intracellular iron homeostasis, but also closely related to the dysfunction of the antioxidant defense system. The antioxidant system composed of glutathione (GSH) and glutathione peroxidase 4 (GPX4) as the core is an important mechanism for protecting cells from iron death. GSH, as an important intracellular antioxidant molecule, is synthesized from glutamic acid, cysteine, and glycine tripeptides under the catalysis of glutamate cysteine ligase (GCL) and glutathione synthase (GSS). Among them, cysteine serves as the rate limiting substrate for GSH synthesis, and its deficiency can directly lead to the inhibition of GSH synthesis, thereby inducing ferroptosis. System Xc - is a cysteine glutamate reverse transporter located on the cell membrane, consisting of the light chain subunit (x CT) encoded by SLC7A11 and the heavy chain subunit (4F2hc) encoded by SLC3A2. The System Xc - system can mediate cysteine uptake and glutamate efflux in a 1:1 ratio. Activation of this system can lead to an increase in intracellular cysteine concentration, which can promote downstream synthesis of GSH and GPX4. Therefore, once the activity of System Xc - decreases, the uptake of cysteine by cells will decrease, and the raw material for GSH synthesis, cysteine, will also decrease, resulting in indirect inhibition of GPX4 activity. Due to the inactivation of the System Xc -/GSH/GPX4 axis, the antioxidant stress capacity of cells decreases, leading to an increase in ROS production and accumulation, ultimately inducing ferroptosis. In recent years, studies have found that the small molecule compound Erastin can induce conformational changes in its transmembrane helical domain TM6b by specifically binding to the Phe254 site of the xCT subunit, effectively inhibiting the transport activity of System Xc -. When System Xc - system activity is inhibited by Erastin, the level of iron death in cells significantly increases. Similarly, iron death inducers such as RSL3 and FIN56 can block antioxidant defense by directly inhibiting GPX4 activity or promoting its degradation. These findings not only deepen our understanding of the molecular mechanisms of ferroptosis, but also provide new therapeutic approaches for targeted regulation of the System Xc -/GSH/GPX4 axis to intervene in ferroptosis.

2.2.3. Lipid peroxidation and ferroptosis

As mentioned earlier, the Fenton reaction caused by abnormal iron metabolism leads to an increase in ROS. The antioxidant system represented by GPX4 can eliminate the toxicity of ROS to cells, and the connection between the two is the lipid metabolism within cells. Lipid peroxidation is a hallmark of ferroptosis, and some studies suggest that lipid peroxidation can occur through two pathways:

(1) Enzymatic pathway

Mainly relying on the catalytic action of lipoxygenases (LOXs);

(2) Non enzymatic pathway

Triggered by ROS directly attacking polyunsaturated fatty acids (PUFAs).

It is worth noting that free PUFAs cannot directly induce ferroptosis and need to be activated into membrane lipids to exert their effects. This integration process is accomplished by the collaboration of two key enzymes: firstly, long-chain acyl CoA synthetase 4 (ACSL4) catalyzes the formation of CoA AA/AdA complexes between arachidonic acid (AA) or adrenal acid (AdA) and coenzyme A; Subsequently, lysophosphatidylcholine acyltransferase 3 (LPCAT3) esterifies these activated PUFAs and inserts them into cell membrane phospholipids. In the enzymatic pathway, the iron containing 15 lipoxygenase (ALOX15) first forms a complex with phosphatidylethanolamine binding protein 1 (PEBP1), which then specifically oxidizes PUFAs in phospholipids to generate phosphatidylethanolamine peroxide (PE-

PUFA-OOH), promoting the occurrence of ferroptosis. It is worth noting that the Fenton reaction and the lipoxygenase pathway generate a large amount of ROS, which attack PUFAs in membrane phospholipids, triggering a chain peroxidation reaction and forming a vicious cycle, leading to severe damage to the cell membrane structure. Overall, the accumulation of iron ions, free radical bursts, increased supply of PUFAs, and accumulation of lipid peroxides constitute the "quartet" of ferroptosis, collectively determining the fate of cell ferroptosis.

3. Iron death and ICM

Iron death is closely related to the pathogenesis of ischemic cardiomyopathy (ICM). Research has shown that the application of iron death inhibitors such as Liproxstatin-1 (Lip-1) in a mouse myocardial cell ischemia model can effectively protect myocardial cells, suggesting that iron death plays an important role in the occurrence of ICM and may provide new strategies for its treatment.

When myocardial cells are exposed to ischemia for a long time, iron metabolism imbalance, especially iron overload, can promote the generation of excessive ROS and oxygen free radicals in the oxidative system, thereby exacerbating oxidative stress, leading to myocardial cell membrane damage and cardiovascular endothelial cell dysfunction. For example, in the state of myocardial ischemia, chronic ischemia can induce stable expression of hypoxia inducible factor-1 alpha (HIF-1 alpha), thereby upregulating TfR1, promoting iron uptake in myocardial cells and causing iron overload, ultimately exacerbating ROS mediated oxidative damage. In the mouse myocardial ischemia model, downregulation of FTH expression was also observed, significantly weakening the ability of myocardial cells to bind free iron, thereby inducing increased oxidative stress and even cell death. Another study has confirmed that administering iron chelators to myocardial cells after ischemic injury can help reverse cardiac dysfunction.

Cardiomyocytes are rich in mitochondria, and their membrane structure contains a large number of PUFAs, which are susceptible to oxidative attacks. Studies have shown that under ischemic stress, the expression of ACSL4 and LPCAT3 is significantly increased, which esterifies more PUFAs and inserts them into membrane phospholipids, providing abundant substrates for lipid peroxidation. Alox15 has been identified as a key mediator of ischemia induced phospholipid peroxidation, and its derivative 15 HpETE can promote the binding of peroxisome proliferator activated receptor gamma co activator 1 alpha (PGC-1 alpha) to E3 ubiquitin ligase ring finger protein 34 (RNF34), thereby accelerating PGC-1 alpha degradation, inducing mitochondrial dysfunction, and iron death in cardiomyocytes. Knocking down Alox15 or using its specific inhibitor ML351 can significantly increase PGC-1 α levels and inhibit iron death in myocardial cells.

In ischemic cardiomyopathy, especially after myocardial ischemia-reperfusion injury (MIRI), it can be observed that the levels of ACSL4, Fe^{2+}, and malondialdehyde (MDA) in myocardial tissue increase, while the level of GPX4 decreases. Further research has shown that the protein expression and activity of GPX4 in ICM animal models and heart failure patients' myocardium are significantly reduced. The environment of ischemia, hypoxia, and oxidative stress itself can inhibit the activity of System Xc -, leading to insufficient uptake of cysteine and subsequent inhibition of GSH synthesis. At the same time, sustained oxidative stress consumes a large amount of GSH, resulting in a sharp decrease in intracellular GSH levels. Studies have shown that the specific iron death inhibitor lipoxstatin-1, which is suitable for animal models, can protect mouse myocardium from MIRI injury by downregulating voltage dependent anion channel protein 1 (VDAC1) expression and upregulating GPX4

expression.

Iron death is not an isolated event, as it forms a vicious cycle with the inflammatory immune response in ICM, jointly driving disease progression. A review suggests that ferroptosis can affect inflammatory responses through immunogenicity, and ferroptosis inhibitors may benefit cardiovascular disease patients through anti-inflammatory effects. Iron death can activate Toll like receptors (such as TLR4) by releasing damage associated molecular patterns (DAMPs) (such as high mobility group protein B1 (HMGB1) and ATP), recruit and activate innate immune cells (such as macrophages and neutrophils), trigger inflammatory responses, and release inflammatory factors such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). On the contrary, the inflammatory microenvironment further promotes ferroptosis. For example, TNF-α can downregulate the expression of System Xc - and GPX4. The inflammatory mediators released by M1 macrophages can directly damage myocardial cells and enhance their sensitivity to ferroptosis. Neutrophils exacerbate oxidative stress through myeloperoxidase (MPO).

Immune response activation is involved in the occurrence and development of various cardiovascular diseases, whether they involve congenital or adaptive immunity. A study found through the ssGSEA algorithm that various immune cells (including activated B cells, mast cells, eosinophils, monocytes, neutrophils, and Th17 cells) significantly infiltrate ICM cardiac tissue. Iron death can regulate the recruitment of neutrophils to the infarcted area, while inhibiting iron death can alleviate this process and promote repair. In addition, macrophages derived from monocytes are involved in poor ventricular remodeling, and their peripheral blood levels can serve as prognostic markers for ICM. Recent studies have also found that $CD8^+$ T cells are activated and induce cardiomyocyte apoptosis in ischemic myocardium. More noteworthy is that multiple immune checkpoints (such as PDCD1/LG2, LAG3, TIGIT) are highly expressed in ICM, which may indirectly promote ferroptosis and ventricular remodeling by inhibiting protective immune responses or enhancing inflammatory responses. This positive feedback loop of "iron death DAMPs release inflammation activation iron death exacerbation" continues to drive myocardial injury, fibrosis, and ventricular remodeling, which may be the core mechanism of ICM disease progression.

4. ICM therapy strategy targeting ferroptosis

Given the central role of ferroptosis in ICM, targeting its key components has become a highly promising therapeutic strategy. Therefore, inhibiting ferroptosis may be a promising target for treating ICM. Therefore, scientists have begun to identify a targeted anti ferroptosis method for ICM treatment. Many drugs have been believed to have therapeutic effects on ICM treatment by inhibiting ferroptosis.

4.1. Iron death inhibitors

Fer-1 and Lip-1, as classic free radical scavenging antioxidants, can directly neutralize lipid free radicals and interrupt the chain reaction of lipid peroxidation. In MIRI and ICM animal models, both exhibit significant cardioprotective effects and are currently one of the most promising candidate drugs for treatment. As a novel iron death inhibitor, polydopamine nanoparticles (PDA NPs) can inhibit the accumulation of Fe^{2+} in H9c2 cells, restore mitochondrial function, and alleviate Fe^{2+} deposition and lipid peroxidation in a mouse model of myocardial ischemia/reperfusion (I/R) injury. Atorvastatin inhibits iron death and reverses hypoxia/reoxygenation (H/R) - induced H9C2 cell damage by upregulating FPN1 expression and reducing intracellular Fe^{2+} levels. In addition,

the drug can upregulate SMAD7 expression and downregulate hepcidin expression in H/R-induced H9C2 cells, and synergistically protect the myocardium from ischemia-reperfusion injury through multiple mechanisms. At present, two clinical studies on the treatment of dilated cardiomyopathy and hypertrophic cardiomyopathy with atorvastatin have been completed. However, its application in ICM treatment has not yet entered the clinical research stage and remains a scientific issue that needs to be explored in the future.

4.2. Iron chelators

Iron chelators, such as deferoxamine, dexmedetomidine, and cyclohexanone, can effectively inhibit lipid peroxidation by reducing Fe^{2+} levels, inhibiting Fenton reaction and LOX activity. Recent studies have shown that in models of acute hemorrhagic myocardial infarction, compared to deferoxamine and Deferasirox, the iron chelator deferiprone can more rapidly alleviate bleeding, reduce inflammatory reactions, and improve chronic adverse myocardial remodeling after acute hemorrhage. Therefore, iron chelates may serve as a potential preventive treatment for acute hemorrhagic myocardial infarction. Although iron chelators have limitations in non-specific binding, which limits their widespread clinical application, current research is focused on developing iron chelators with higher myocardial targeting, or improving therapeutic specificity and safety by regulating key iron metabolism proteins (such as using NCOA4 inhibitors).

4.3. Activating agents for system Xc -

Icariin is the main flavonoid component extracted from the traditional Chinese medicine Epimedium, which has various pharmacological activities such as anti-aging, anti-inflammatory, antioxidant, and anti-fibrosis. As an effective inducer of nuclear factor E2 related factor 2 (Nrf2), icariin can upregulate GPX4 expression in cardiomyocytes, reduce ACSL4 and Fe^{2+} levels, and inhibit H/R-induced ferroptosis by activating the Nrf2/HO-1 pathway. Its derivatives icariin II and icariin also show promising drug development potential.

Xanthohumol is derived from hops and has anti-inflammatory, antioxidant, and anticancer effects. Lin et al. found that it resists ferroptosis by inhibiting lipid peroxidation and reactive oxygen species generation, chelating iron, regulating the Nrf2/GPX4 pathway, and downregulating ACSL4. However, its poor water solubility and stability limit its application.

In addition, Dexmedetomidine is a highly selective α_2 - adrenergic receptor agonist that can inhibit ferroptosis and counteract MIRI by activating the AMPK/GSK-3 β/Nrf2/SLC7A11/GPX4 pathway. Naringenin improves ischemic myocardial injury by regulating the Nrf2/SLC7A11/GPX4 axis.

5. Summary and outlook

Iron death, as a newly discovered mode of cell death, plays a central role in the pathological process of ICM. It mainly leads to the loss of myocardial cells through three major mechanisms: iron metabolism disorders, lipid peroxidation, and dysfunction of the antioxidant defense system (especially the System Xc -/GSH/GPX4 axis). More noteworthy is that a vicious cycle is formed between ferroptosis and inflammatory immune response, jointly promoting ventricular remodeling and deterioration of heart function, becoming a key driving mechanism for disease progression. Although significant progress has been made in understanding the mechanisms and preclinical interventions, translating this achievement into clinical benefits still faces multiple challenges. Firstly, there is currently a lack of specific biomarkers that can accurately and non invasively monitor the progression

of myocardial iron death, which limits early diagnosis and risk stratification of patients; Secondly, drug delivery efficiency and safety remain important issues in translational medicine, namely how to achieve heart specific delivery of iron death inhibitors and avoid potential side effects (such as tumor risk) that may arise from long-term interventions; Thirdly, existing evidence mainly comes from animal models, and the exact role of ferroptosis in human ICM and its effectiveness as a therapeutic target still need to be validated through high-quality clinical studies. In summary, ferroptosis plays an important role in the occurrence and development of ICM. Further in-depth research on its molecular mechanism and regulatory network is expected to provide new directions for clinical intervention strategies targeting ferroptosis, ultimately improving the prevention and treatment effectiveness of ICM.

Disclosure statement

The authors declare no conflict of interest.

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