Ferroptosis: Basic Mechanisms, Key-Factors and The Role of The Diseases

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Abstract. Research on the explosive growth of Ferroptosis in the past decade. Ferroptosis is the way of cell death that causes lipid peroxidation, and there are a variety of inducers for Ferroptosis that can lead to a decrease in cell antioxidant capacity and the accumulation of lipid reactive oxygen species(ROS) of through multiple regulatory pathways, which leads to cell membrane damage and eventually leads to cell oxidative death. It will lead to a series of related diseases and plays a crucial role as a tumour suppressor mechanism. In this review, the relevant regulatory mechanisms of ferroptosis (especially the conventional ferroptosis pathway) are specifically summarised and the relevant diseases associated with ferroptosis are described. Fortunately, by initiating and reducing ferroptosis, there is significant potential to treat drug-resistant malignancies, ischemic organ damage, and other degenerative disorders linked to severe lipid peroxidation. Importantly, there are still a lot of obstacles to ferroptosis, and this review offers pertinent research suggestions to overcome these problems. Lastly, this article discusses the specific applicability of ferroptosis to disease; future ferroptosis research should center on these challenges.

Keywords: Ferroptosis, lipid peroxidation, mechanisms, diseases, cancer.

1. Introduction

Cells are the basic structural and functional units inthe living organisms (except viruses). The Control of cell division, growth, proliferation and death is crucial for the research to the life process of postgraduate objects and the development of related diseases. Among them, an inevitable component of the entire life process is cell death. Whether in the physiological or pathological state, it is the basic feature of multicellular biological development, also plays an avoidable role in the development of organisms and in the maintenance of stable states. In the traditional sense, cell death consists of apoptosis and necrosis. Many studies have showed that the programmed death except apoptosis&necrosis also covers some additional modes such as autophagy, necrotic apoptosis and ferroptosis, which also have unique physiological mechanisma and characteristics recently. This article discusses a new type of cell death - ferroptosis. In 2012, the professional term was proposed firstly by Dixon but the relevant description dates back to the 1950s. In 1955 (Eagle, etc.) researchers found that a unique microscopic morphology caused by cell death with cystine deprivation. Moreover,the restoration of glutathione (GSH) can promote cell growth in 1959. After that,additional evidence from several animal studies revealed that supplementing rats with selenium-containing compounds will offset the impact of lack of vitamin E and cystine; injecting dextran iron in mice will form peroxides in adipose tissue, which weakens the process of vitamin E, and the intake of unsaturated fat will aggravate this effect[1]. The above are the pivotal contents of the development of early ferroptosis. Although it seems to have nothing to do with the current development, it outlines the basic principles. Understanding the research process of ferroptosis is important, and this article will introduce its development below. Cell ferroptosis is an unique type of non-apoptosis regulation. Its occurrence is accompanied by iron dependence. In the process of cell death, there is usually lipid peroxidisation and a large amount of iron deposition.Various cellular metabolic processes, such as redox homeostasis, mitochondrial activity, amino lipid and sugar metabolism, and iron metabolism, are responsible for its regulation. It differs from other forms of cell death in that it lacks the physical features of classic cell apoptosis as well as the swelling of the cytoplasm and organelles as well as the rupture of the cell membrane. such as cell shrinkage, chromatin condensation, formation of

apoptotic bodies and disintegration of the cytoskeleton, and classical closed bilayer membrane structures (autophagic vacuoles) do not form during ferroptosis. Morphologically speaking, ferroptosis differs from other forms of cell death in that it mostly shows up as a clear shrinking of mitochondria with increased membrane density and a decrease in or disappearance of mitochondrial cristae[2]. Understanding the internal intricate mechanisms that regulate cell death, researchers can use the accumulation of relevant knowledge to promote the prevention, diagnosis, treatment and prognosis of disease to solve its role in disease.At first, it was unclear if iron-dependent enzymes were the only ones responsible for the lipid peroxidation that causes ferroptosis, or if the labile iron pool reacted with lipid peroxides to spread these species in membranes. Research conducted in multiple labs showed that -dependent lipoxygenases frequently start ferroptosis by generating lipid peroxides, which are then multiplied by labile iron (which is not attached to enzymes) to produce excessive lipid peroxidation[3,4]. There are some different pathways to regulate the occurrence of ferroptosis such as cellular metabolic pathways and various disease-related signalling pathways. The discovery of regulating the process of cell death has led to progress in cancer treatment.[1] Among them, iron-dependent regulatory cell death forms are related to the development and treatment response of various types oftumours[1]. However, related studies have shown that ferroptosis damage favours tumour growth and that it can trigger immune mechanisms in the tumour microenvironment[5]. Most organ injuries and degenerative diseases are also caused by ferroptosis, such as drug-resistant tumour cells, especially those in the mesenchymal state and prone to metastasis, which are very prone to ferroptosis. Therefore, inducing and inhibiting ferroptosis by using the way of pharmacological regulation, it has great potential in the treatment of drug-resistant tumours, ischaemic organ damage and other degenerative diseases related to widespread lipid operoxidation [1]In this review, the development of ferroptosis and its regulatory mechanism are summarised, and also some relevant diseases are introduced for in stance, drug-resistant cancer, ischaemic organ injury and other lipid peroxide-related degenerative diseases, providing ideas for further research, aiming to help deepen the understanding of ferroptosis and the treatment of related diseases.

2. An overview of ferroptosis

Ferroptosis is a new cell death. It relies on iron content and reactive oxygen content, and iron chelation and lipophilic antioxidants inhibit iron. The abnormality of these cells is due to the loss of plasma membrane permeability due to the occurrence of strong membrane lipid peroxidation and oxidative stress.The ways to increase reactive oxygen also include excessive iron content (such as heme iron) and mitochondrial oxidation phosphorylation caused by iron overload. When the reactive oxygen content on the biofilm of iron-dead cells is higher than the clearance level of the antioxidant system, polyunsaturated fatty acids will be oxidised into lipid peroxide. The study of its mechanism focusses on oxidative damage and iron metabolism. The diseases involved in ferroptosis have been observed more than a decade ago, and the whole process has not been integrated into a unified regulatory path [6]. The mechanism of early Ferroptosis was found in the metabolism of cysteine and glutathione. During this period, it was found that phospholipid peroxidase GPX4 had the ability to prevent the accumulation of lipid peroxidation, which is the early metabolic mechanism that regulates the mechanism of ferroptosis [7]

After that, cysteine, as an important factor in regulating ferroptosis, has been continuously confirmed by many scientists: many cell lines require cysteine for survival; liver necrotic cell death depends on cysteine and involves glutathione consumption, according to research by Shiro Bannai and colleagues, a-tocopherol, an inhibitor of lipid peroxidation, can prevent cell death brought on by a deficiency in glutathione and cysteine. [8-14]. Since Ursini and others isolated an enzyme called GPX4 in 1982, the enzyme has been continuously proven to be related to lipid peroxidation and oxidative stress in the next decade [15-17]. An overview of the mechanisms about ferroptosis is given below to deepen the understanding of this mode of cell death.

2.1. Regulation and control mechanism

Ferroptosis is an iron-dependent cell death method characterised by ROS accumulation and glutathione depletion. To learn more about the mechanism related to ferroptosis, we mainly start from four characteristics (morphological characteristics, biochemical characteristics, immune characteristics, genetic characteristics). The morphological characteristics have been mentioned at the beginning. Regarding the biochemical properties, several studies indicate that iron buildup and lipid peroxidation are the two primary biochemical properties that ferroptosis is mostly associated with. Iron may directly produce an excess of ROS through the Fenton reaction, increasing oxidative damage. Furthermore, iron has the ability to catalyze the reaction of lipoxygenase ALOX or EGLN proline hydroxylase. The above-mentioned lipid peroxide is the result of a process driven by free radicals that modifies unsaturated fatty acids in biofilms and raises lipid peroxide products. Furthermore, leucocyte subgroups will die as a result of ferroptosis, which will result in a loss of immunological function. The way the immune system reacts to injured cells is dictated by ferroptosis's impact on white blood cells.

Another type of inflammatory cell death associated with DAMP or lipid oxidation products (4HNE, LTB4, etc.) following tissue damage or tumor treatment is ferroptosis. Therefore, it provides relevant ideas for the treatment of tumours and tissue injuries. Overexpression or reduction of some genes/proteins are also considered as marker factors of ferroptosis (such as p53, GPX4 and SCL7A11).

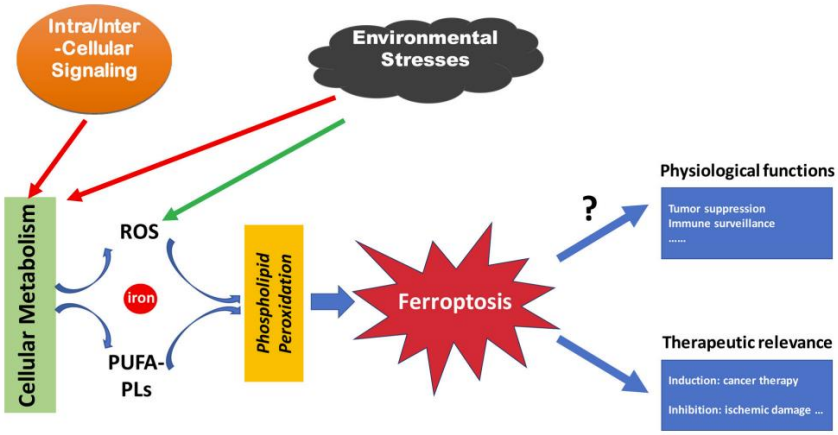

Figure 1. Ferroptosis mechanisms, biology and role in disease [1].

2.1.1 Antioxidant system regulation

Under normal circumstances, Amino acid reverse transporter one significant antioxidant system in cells is the protein system XC, which is made up of SLC3A2 and SLC7A11, the two main components. The intake of cystine is about the same as the output of glutamic acid. It can carry cystine into the cell and then be reduced to cysteine, which is needed for the cell's primary antioxidant, GSH, to synthesize. GPX4 requires GSH as a cofactor. GPX4 can catalyze the transformation of reduced GSH into oxidized GSH, and concurrently, it might lessen lipid peroxide (reduce toxic lipid peroxide to non-toxic fatty alcohol), thus reducing oxidative stress damage. Therefore, GSH plays a key role in cell antioxidant Defence. However, the concentration of the substrate cysteine limits the effectiveness of the GSH production process,so a crucial regulating component is System Xc. Erasin, a ferroptosis inducer, inhibits the intake of cysteine and targets System Xc to lower GSH synthesis.

The depletion of GSH leads to the accumulation of toxic peroxides, damage to protein and cell membranes, and subsequent cell ferroptosis [19]. Therefore, system XC- and GPX4 are important regulatory targets in ferroptosis amino acid metabolism.

In the GPXs family, there are many members,from GPX1 to GPX8. Among them, a crucial part of the ferroptosis process is played by GPX4.

GPX4 is the first central inhibitor to discover ferroptosis. GPX4 is a metabolic protein that converts GSH to oxidised glutathione GSSH. It is a key enzyme for reducing toxic peroxides. Through its

enzyme activity, it can prevent the toxicity of lipid peroxides and maintain the stable state of membrane lipid double layer [20]. Lipid ROS can build up as a result of erastin and RSL3, two ferroptosis inducers, but RSL3 is different from erastin. In its induced cell ferroptosis, the GSH level has not changed significantly. Later, it was found that the target molecule of RSL3 was GPX4. Lipid peroxides accumulated as a result of RSL3's covalent interaction with GPX4, which reduced its activity [21]. According to YANG et al. [22], cells exhibiting decreased GPX4 expression were more susceptible to ferroptosis, whereas cells exhibiting increased GPX4 expression demonstrated resistance to ferroptosis. Therefore, GPX4 is also an important regulatory protein for ferroptosis. By targeting the expression of this protein, it can achieve the purpose of promoting or inhibiting ferroptosis.

2.1.2 Regulation of lipid metabolism

Ferroptosis is mostly caused by lipid peroxidation aggregation. Polyunsaturated fatty acid (PUFAs) increases the fluidity of cell membranes, which is an important factor for primitive life to adopt environment [23]. Stable carbon-carbon double bonds, which are essential for ferroptosis and vulnerable to lipid peroxidation, are found in polyunsaturated fats (PUFAs) [24]. As an important substrate for lipid synthesis, it must be esterified to form phospholipids in cell membranes, and then oxidised to play the role of transmitting iron accumulation signals. Acyl Kievase A synthase long chain 4 (ACSL4) and haemolytic lecithatin acyltransferase 3 (LPCAT3) associated with lipid remodeling are two enzymes that play a vital role in the synthesis of PUFAs in the ferroptosis pathway [25]. The production of PUFAs is decreased when these two genes are deleted, and lower concentrations of lipid peroxide intracellular substrates, which prevents ferroptosis from occurring [26-27]; on the contrary, when arachidonic acid and other PUFAs are rich enough, ferroptosis inducers will catalyse the production of more peroxide lipids, causing more intense ferroptosis reactions in cells [2 4], this proves that Ferroptosis membrane peroxidation has PUFAs as a major target.

In addition, lipooxygenases (LOXs) can also promote the peroxidation of PUFAs and reduce the expression of LOXs, which can also effectively improve ferroptosis induced by erastin [24, 26]. Free PUFAs are the substrates for lipid peroxidisation reactions. Thus, the degree of cell lipid peroxidation will be influenced by the composition and location of PUFAs, thereby dictating the degree of ferroptosis [26]. This is another potential direction of ferroptosis regulation. Future studies may use enzymes that produce the phospholipids in PUFA membranes to either initiate or stop the ferroptosis process.

2.1.3 Iron metabolism

Ferroptosis and the buildup of lipid peroxide both depend on iron. Therefore, iron intake, transport and storage will have a certain regulatory effect on ferroptosis. The maintenance of iron homeostasis in organisms is strictly regulated. Relevant genes controlling the storage of iron ions are ferritin light chain and ferritin heavy chain1. Iron has two transformation states divalent iron (Fe2+) and trivalent iron (Fe3+). Transferrin receptor1(TFR1) is a membrane protein that ingests iron is necessary for ferroptosis. It can transport Fe3+ to the intranuclear body, and Fe3+ is further reduced to Fe2+, in the nuclear endobody. Finally, under the guidance of divalent metal transporter 1 (DMT1), the unstable iron pool in the cytoplasm receives the discharge of Fe2+ from the nucleus endosome. Ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL) are types of excess iron storage found in the cytoplasm [28]. The abnormal expression or disfunction of these iron-related proteins will increase the amount of iron ions present in the cell due to metabolic imbalance. Therefore, iron accumulation is different from the above-mentioned oxidative metabolic pathway, which is a unique mechanism for inducing ferroptosis.

In summary, antioxidant metabolism system,the fundamental metabolic pathways and processes of ferroptosis include lipid metabolism and iron metabolism.In addition, there are also FSP1/CoQ10/NADPH pathway, DHODH pathway and GCH1/BH4 pathway. Hippo-YAP signalling pathway and AMPK pathway are also involved in the regulation of ferroptosis. It was recently

reported that 1L4i also has the effect of inhibiting ferroptosis, which is a new potential ferroptosis regulation.

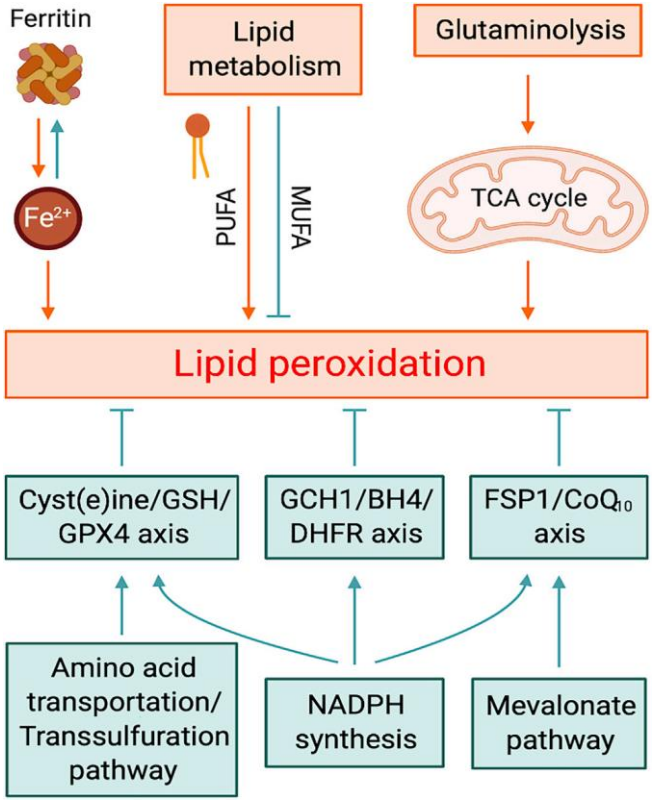

Figure 2. Metabolic basis of iron death [40].

2.2. Ferroptosis caused disease

At present, many disorders have been shown to be associated with ferroptosis. The mechanism underlying associated disorders will be better understood with additional ferroptosis study. Ferroptosis is crucial for controlling the inflammatory response and oxidative stress. More and more evidence shows that given that ferroptosis is linked to several cardiovascular conditions, including heart failure, ischemic-reperfusion injury, atherosclerosis, and stroke, ferroptosis may offer a novel therapeutic for cardiovascular illness. Not only that, it is also closely related to cancer (such as liver cancer). Here, this article outlines the increasingly close correlation between ferroptosis and Caner and Neurodegenerative diseases

2.2.1 cancer

Experiments show that the occurrence of multiple tumours is closely related to ferroptosis. One of the most prevalent malignant tumors worldwide is liver cancer. Many studies have shown that ferroptosis can regulate the growth and proliferation of tumour cells, and promote the occurrence of ferroptosis and have the obvious advantage of overcoming the resistance of traditional cancer treatment drugs [30-32]. Promoting the occurrence of ferroptosis can effectively inhibit the proliferation and progression of liver cancer cells, which is of positive clinical significance for the prevention and treatment of liver cancer [33]. Tao Lei et al. [34] found that propofol can reduce the expression of the ferroptosis gene GPX4 and thus inhibit the proliferation of liver cancer cells. In addition, a study on Hulubin B shows that Hulub mainly induces the death of Huh-7 iron in human hepatocellular carcinoma cells during the proliferation of liver cancer cells, and further experimental results confirm that its mechanisms for promoting ferroptosis include enhancing GPX4 ubiquitinisation and degradation ability and destruction of N 2 ways of rf2/heme oxygenation-1 antioxidant pathway [35]. Because pancreatic cancer cells exhibit considerable resistance to apoptosis, the identification of a novel mechanism of death holds great significance for the management of this

disease. ATR-activated ferroptosis has been identified as a potential novel target for pancreatic cancer treatment when ATR is studied for the disease [36]. Ferroptosis has also been discovered to be useful in the treatment of oesophageal, breast, and stomach cancers.The study found that a variety of inducers can induce ferroptosis as a potential anticancer therapy. The goal of the project is to transfer iron, peroxides, and other toxic compounds to destroy tumor cells via non-targeted, nanoparticle-based methods. The existence of a variety of enzymes that regulate ferroptosis enables the development of targeted therapy. The most significant target is GPX4, which is expressed in most cancer cell lines and is important for the survival of cancer cells. The particular and potentially lethal GPX4 is covalently changed by the selenocysteine residue of GPX4 and other selenium proteins that lack the GPX4 classic small molecule binding bags and current GPX4 inhibitors. In contrast to the GPX4 target, considering that the knockout mouse Slc7a11 gene will not cause major pathological changes and the expression of the SLC3A2 and/or SIc7a11 gene is negatively correlated with the clinical results of patients with melanoma and glioma, by inhibiting X. The systematic method of limiting cytocysteine is very promising. In fact, X is inhibited through pharmacology or genetics in mouse models. The system to inhibit the growth and metastasis of various tumours has had very promising results, which are both effective and low toxic. The tumour inhibits X compared with normal tissue. The system may be more susceptible because of its active metabolism and other changes, which makes it sustained oxidative stress, so it is more dependent on the detoxification function of ROS in the Xc-system. It is used to suppress X. System-based treatment methods, need. The patient's tumour tissue should be stratified and clear X. Systematic expression (for example, SLC7A11 overexpression indicates that cancer cells rely on cysteine to clear ROS) and other biomarkers previously discussed to determine the tumour's sensitivity to inhibiting the X system.Like the absence of SLC7A11, knocking out Fsp1 does not result in severe pathological alterations or embryonic death, suggesting that Fsp1 targeting offers a wide therapeutic window. FSP1 is the most highly expressed gene associated with GPX4 inhibitor resistance across 860 cancer cell types, and it is extensively expressed in the majority of cancer cell lines. Cancer cells with the GPX4 gene produce ferroptosis through iFSP1 and RSL3, whereas cancer cells without the GPX4 gene can be inactivated by the FSP-specific inhibitor iFSP1. Thus, FSP1 inhibitors may find application in clinical practice, particularly in the management of drug-resistant or dedifferentiated tumors.

2.2.2 Neurodegenerative diseases

Empirical data indicates that a multitude of neurodegenerative disorders are distinguished by the localized build-up of iron in particular regions of the central and peripheral nervous systems. Iron redistribution inside cells is typically the cause of this accumulation, which might result in Fenton reaction catalyzed by iron. Studies reveal a correlation between the development of several neurological illnesses with the build-up of iron and lipid peroxidation, which is accompanied by a decrease in GSH and GPX4 levels.The most prevalent neurodegenerative disease, Alzheimer's disease (AD), is marked by cognitive impairment. AD patients also have significantly higher iron levels in their hippocampi, which are significantly impaired [59]. Abnormalities in iron homeostasis in brain tissue can induce massive production of ROS in brain cells, ultimately causing catastrophic oxidative damage to sensitive subcellular structures [60]. These findings provide promising ideas for the treatment of neurodegenerative diseases.

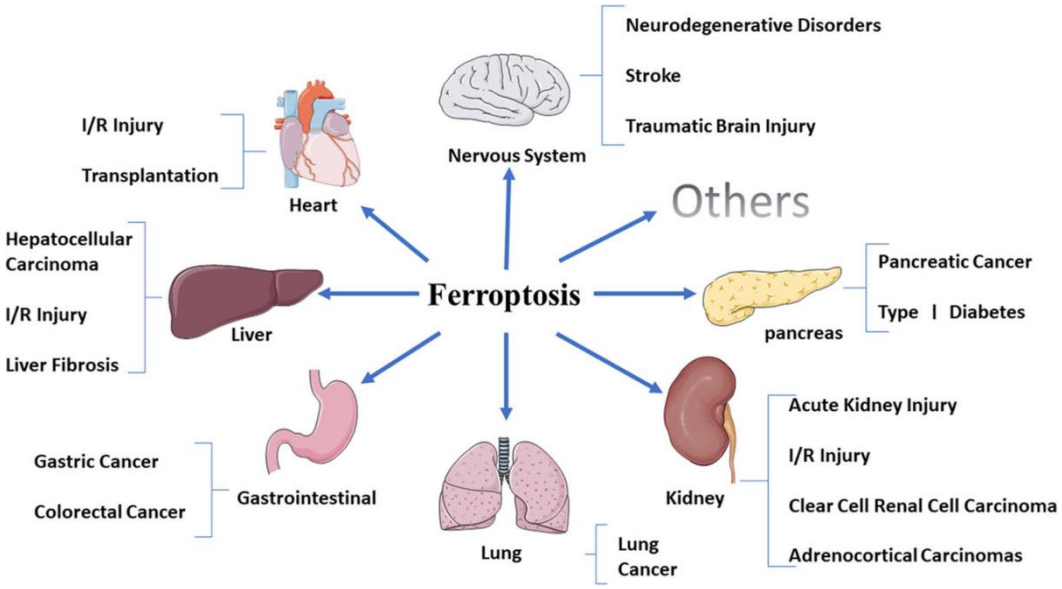

Figure 3. Ferroptosis: past, present and future [1].

2.3. Inhibitors and inducers of ferroptosis

2.3.1 ferroptosis inhibitors

According to research, Fer-1, quinodimethylacrylate, ebuselenium, butyl hydroxytoluene, alpha tocopherol, vitamin E (vitaminE), lysosome activity inhibitor [lostoxinA), pepstatinmethyle Both ster) and ammonium chloride (NH4Cl) can inhibit ferroptosis by inhibiting lipid peroxidation. Among them, Fer-1 is an alanidine-containing antioxidant. Structurally, any arylamine can inhibit ferroptosis by inhibiting lipid peroxidation. Later, the second generation (SRS1192) and the third generation (SRS16-86) Fer-1 were also found in the study, compared with Fer-1. The metabolism is more stable, and the ability to resist tissue damage is significantly increased. Dixon and others found inhibitions such as iron chelating agents such as deferrenamine, methyl sulphonic acid deferriamine and bipyridine, indicating that such iron chelating agents are also the main types of ferroptosis inhibitors. In addition, baicalein has been found to be used as a new ferroptosis inhibitor, which can not only inhibit iron accumulation, but also inhibit lipid peroxidation. Comparing its inhibitory impact to the standard ferroptosis inhibitor Fer-1, it is noticeably superior, methane defertimine, etc., which will become a strong ferroptosis injury disease. Therapeutic drugs of force [29].

2.3.2 ferroptosis inducer

The study found that ferroptosis inducers fall into two categories; regulatory oxidative stress inducers, iron metabolism inducers and other inducers. Erastin, as a regulatory oxidation inducer, can produce reactive oxygen by combining mitochondrial voltage-dependent anionchanel 2/3 (Mitochondrial voltage-dependent anionchanel 2/3, VDAC2/3) and then accelerate era. Stin induces ferroptosis. Other influencing factors such as heme oxygenase-1 (HO-1), erastin derivative (piperazine erastin), carbonyl erastin analogue imidazoleketoneerastin (IKE), s Orafenib can be used as a new type of ferroptosis inducer. Moreover, RSL3, 1S, 3R-RSL3, and the novel chemicals DPI2 and FIN56 can cause ferroptosis by preventing GPX4 from producing a large concentration of reactive oxygen species. Ma and other studies have found that siramesine can be used alone or collaboratively with lapatinib by regulating the expression of transfer rin in iron metabolism to raise the level of FeCl3 in cells and induce ferroptosis.Inducers also include cisplatin, 1,2-dioxypentacyclic compounds, etc. to induce ferroptosis, providing further methods for cancer cell research.

To sum up, at present, there is less research on ferroptosis inhibitors and inducers, mainly some experimental discoveries, and the real research in the clinical field is not in-depth enough. Therefore, we ought to keep researching ferroptosis' mechanism, master its fundamentals, and contribute to the

research and development of specific inducers and inhibitors and their investment in the research of related diseases.

3. Discussion

Ferroptosis, as a new type of cell death. The treatment of many diseases is provided as a new platform. It gradually as an important core in the emergence, development and subsequent treatment of the disease. Numerous relevant studies have demonstrated that ferroptosis occurs when tumors and degenerative illnesses are pathologically inhibited, and the inhibition and induction of ferroptosis has the potential to treat the disease. However, although ferroptosis may bring hope for future research, the research on ferroptosis is still in the initial stage, and many problems still need to be solved. First, the mechanism related to ferroptosis is not perfect. Studies show that ferroptosis is mainly regulated by SLC7A11/GSH/GPX4/FSP1/CoQH2/NAD(P)H and BH4/DHFR/GCH1. However, we still don't fully understand the downstream regulation of ferroptosis, and we don't know how cells eventually die. Current research proves that PUFA-PL peroxidation is a downstream step, which may cause membrane damage and thus destroy the integrity of the membrane. There is also another report that phospholipids containing two PUFA tails constitute ferroptosis drivers, causing membrane damage after cross-linking. In this case, the flow of the limiting membrane may be related to certain related functions. However, there may be other possibilities. I hope that the mechanism of ferroptosis can be better and more clearly explained in the following research. Second, the relevant factors that induce the trigger of ferroptosis are not fully clear. Exploring its triggers will help clarify the mechanism and conditions for the activation of ferroptosis in the physiological or pathological processes. In addition, the technology of conditional control of ferroptosis also needs to be developed to selectively activate or inhibit the occurrence of ferroptosis, which will help ferroptosis become an important treatment for cancer or other diseases. Third, mitochondrial autophagy promotes the release of free iron, thus driving lipid peroxidation to cause ferroptosis. However, there is no exact conclusion on how mitochondrial autophagy affects the occurrence of ferroptosis, which may affect ferroptosis by increasing the pressure of the endoplasmic reticule [39]. Therefore, the understanding of the relationship between the two is still shallow and needs further research to find key regulatory factors in order to provide a new direction for treatment. In a word, the study of ferroptosis should be more in-depth, explore its internal mechanism, relate to the role in related diseases, and realise the theoretical and practical value of ferroptosis, which is also its future direction.

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