

# Research progress of ferroptosis and urinary tumors

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**Abstract:** Since the researchers discovered ferroptosis in 2012, they have conducted in-depth research and exploration on the mechanism of ferroptosis and its role in tumor evolution. Ferroptosis is a new type of death that is different from apoptosis and necrosis. It is mainly dependent on the cell death caused by the increase of iron and lipid oxygen in the cell and the imbalance of redox homeostasis. After the development of urinary tumors in the middle and late stage, most patients have poor surgical results. Chemotherapy is usually given after surgery. However, some tumor cells are currently resistant to chemotherapy drugs. Therefore, the occurrence of ferroptosis increases a new idea in the treatment of urinary tumors. The purpose of this review is to outline the knowledge of ferroptosis mechanisms and regulation, its role in the growth and proliferation of urinary tumor cells and to provide new strategies for the treatment of urological tumor diseases.

*Keywords:* ferroptosis; iron-dependent cell death; urinary tumors; tumorous diseases; erastin

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## 1. Introduction

Cell death is not only the survival endpoint of all biological cells on the time axis but also plays an indispensable role in the growth and development of organisms, just as important as cell division and proliferation, and formed the natural law of biological cell life and death with cell division and proliferation. The common type of cell death is necrosis and apoptosis, in which apoptosis is programmed cell death (PCD). As researchers continue to explore cell apoptosis, many cell death patterns cannot be explained by apoptosis. Combined with the development of science and technology and the richness of research theories, many other types of cell death have been proposed, including autophagy, necroptosis, pyroptosis, mitotic catastrophe, oncosis, and ferroptosis. Among them, ferroptosis is a new type of cell death that is currently studied. It is defined as the involvement of iron ion in lipid peroxidation and mitochondrial oxidative phosphorylation in cells. Excessive iron ion can cause the production of reactive oxygen species (ROS) in cells. Once the ROS that exceeds the cell's own resistance to oxygen can cause oxidative stress, it damages the mitochondria, endoplasmic reticulum, and nucleic acids in the cell, and finally leads to cell death<sup>[1]</sup>. An important feature of tumor cells is constant growth and escape cells death. In recent years, a large number of studies have suggested that intracellular iron metabolism and iron-dependent lipid ROS metabolism abnormalities are closely related to tumor development and metastasis<sup>[2,3]</sup>. Although the specific link between ferroptosis and tumors is not clearly explained, it provides new ideas for treating tumors. In recent years, the incidence of urinary tumors has increased year by year, renal cell tumor, prostate tumor, and bladder tumor are common tumors of the urinary system, which seriously affect the quality of life of patients and threaten the lives of patients.

Through continuous research, ferroptosis may become a new method for the treatment of urinary tumors and predicting tumor prognosis.

## 2. The Origin of Ferroptosis

In the history of the discovery of iron death, the inducers of iron death were the first to appear. The inducers can induce apoptosis of tumor cells and belong to non-PCD (NPCD). In 2003, Stockwell *et al.* studied a large number of compounds in response to tumor cells through large-scale experiments and found a new compound inducer-erastin, which causes NPCD in cancer cells with RAS mutations<sup>[4]</sup>. In 2008, Yang *et al.* found RAS selective lethal3 (RSL3) and RSL5 compound inducers, which like erastin caused NPCD in tumor cells and also found that when iron chelator, deferoxamine (DFO) B-methanesulfonate, antioxidants, Vitamin E, etc., can inhibit the death of tumor cells, further indicating that this NPCD is associated with intracellular iron ions and ROS<sup>[5]</sup>. Until 2012, Dixon and Stockwell *et al.*<sup>[6]</sup> believed that ROS accumulation and iron chelator inhibit tumor cell apoptosis are closely related, RAS mutation in HT-1080 fibrosarcoma cells, and RSL after 2 h of compound erastin binding, the accumulation of cytoplasmic and lipid ROS in tumor cells increased, and the tumor cells began to separate and die after 6 h. At the same time, the addition of iron chelator DFO inhibited ROS accumulation and tumor, due to the presence of two erastin targets voltage-dependent anion channel 2 (VDAC2) and VDAC3 in mitochondria, to test that erastin acts on mitochondria and induce ROS in mitochondrial electron transport chain (ETC), HT-1080 cells were treated with erastin for 6 h, and the addition of ETC complex I inhibitor rotenone increased ROS production. Thus, Dixon and Stockwell named tumor cell apoptosis in a non-functional ETC that relies on iron-sensitive ROS accumulation in a novel cell death pattern for ferroptosis. Later, novel compound inducers including sorafenib, artemisinin, and cyclic peroxide 1,2-dioxolane also induced ferroptosis<sup>[7,8]</sup>.

## 3. Biochemical Process of Ferroptosis

System  $X_c^-$  is a cysteine-glutamate exchange transporter on the cell membrane. When glutamate is transported outside the cell, the system  $X_c^-$  can transport extracellular cysteine into the cell, cysteine, as a raw material, performs glutathione (GSH) synthesis<sup>[9]</sup>. The synthesis of intracellular GSH is essential for the protection and maintenance of cell stability as it is resistant to oxidative stress in cells. After labeling cysteine with <sup>14</sup>C, the treatment of tumor cells with erastin significantly reduced the ability of cells to uptake cysteine and synthesize GSH, demonstrating that system  $X_c^-$  is involved in ferroptosis induced by the inducer erastin<sup>[10]</sup>. By inhibiting the system  $X_c^-$ , the cyclization redox reaction results in non-procedural death. In addition, inhibition of glutathione peroxidase 4 (GPx4) can also cause iron death. GPx4 is

an enzyme that can decompose  $H_2O_2$  into water, and GSH participates as a cofactor<sup>[11]</sup>. Therefore, by consuming the GSH in the cell and reducing the activity of GPx4, the intracellular lipid ROS is increased, eventually leading to ferroptosis in the cell<sup>[12]</sup>. The GPxs family is composed of GPx1–8 members, of which GPx4 plays an important role in ferroptosis. When RSL inhibits the activity of GPx4, it can lead to the accumulation of intracellular lipid peroxide. DPI7, DPI10, and DPI12 are found through a large number of experiments, DPI13, DPI17, DPI18, DPI19, and RSL3 can also inhibit the activity of GPx4<sup>[13]</sup>. These inducers can cause apoptosis, and iron chelator and Vitamin E can inhibit cell apoptosis, further indicating that GPx4 is an important target of various inducers, and inhibition of GPx4 activity is the main cause of ferroptosis in cells. Most of the VDACS are distributed on the outer membrane of the mitochondria. When the inducer erastin binds to the mitochondrial outer membrane, it can change the permeability of the cell membrane and the selectivity of the ion channel, eventually leading to mitochondrial dysfunction and release. Finally forming an oxidation-dependent ferroptosis<sup>[14]</sup>. The study also found that P53 can inhibit systemic  $X_c^-$ , leading to cystine uptake disorders. In addition, P53 increases intracellular ROS levels and triggers intracellular stress responses, ultimately leading to ferroptosis in tumor cells<sup>[15]</sup>.

## 4. Differences between Ferroptosis and Apoptosis, Autophagy, and Pyroptosis

Typical features of ferroptosis are iron-dependent NPCD, mitochondrial atrophy in ferroptosis-death cells<sup>[6]</sup>, mitochondrial bilayer thickening, GSH depletion<sup>[16]</sup>, decreased GPx4 activity, and multigene regulation<sup>[17]</sup>. Apoptosis is the automatic death of cells in specific genes and signaling pathways after the cells are stimulated by the outside world. According to different signal sources, apoptosis is divided into endogenous and exogenous pathways. Endogenous apoptosis is mitochondria. Releases cytochrome C binds to apoptotic protease activating factor and finally initiates apoptosis; exogenous apoptosis is induced by exogenous death signals, and the two pathways must eventually undergo apoptosis by caspase hydrolysis of the substrate<sup>[18]</sup>. Typical features of apoptosis are nuclear condensation, DNA degradation, and apoptotic body formation. Autophagy includes large autophagy, small autophagy, and chaperone-mediated autophagy. In autophagy, a bilayer membrane structure enveloping organelles appears in the cytoplasm, forming autophagic vacuoles, which, in turn, bind to the lysosomal membrane, autophagy lysosomes appear, lysosome hydrolase hydrolyzes organelles, and releases nutrients for cell reuse<sup>[19]</sup>. The death of the pyroptosis has the characteristics of apoptosis and necrosis. Morphology and necrosis are similar. After external stimulation, the cell membrane ruptures, and the intracellular molecular

substances are released outside the cell, causing a local inflammatory reaction and leaving many nuclear DNA fragments, the process includes nuclear fragmentation, nuclear lysis, cell swelling and rupture, cytoplasmic leakage, and pyroptosome appearance.<sup>[20]</sup>

## 5. Regulation of Ferroptosis

The biochemical process of ferroptosis involves complex multi-gene regulation and regulation of signaling pathways. For tumor cells, positive regulation of ferroptosis is required to promote iron death of tumor cells; for normal cells, accumulation of iron ions and lipid ROS in cells can be reduced, and negative regulation of ferroptosis is required. Through a large number of studies at present, it is found that there are many ways to regulate ferroptosis and related regulators in cells.

The mevalonate (MVA) is one of the pathways for selenoprotein synthesis. The selenoprotein with selenocysteine constitutes the active center of GPx4; the selenocysteine tRNA can accurately insert selenocysteine into GPx4, statins can inhibit the MVA process, leading to loss of tRNA function and inactivation of GPx4 by selenocysteine<sup>[21]</sup>; therefore, the MVA process can activate GPx4 and inhibits ferroptosis in cells. The sulfur transfer pathway is an important process in the human body. Methionine is converted to cysteine by sulfur transfer. The important function of cysteine is to participate in the formation of GSH and antioxidant peptides. Both GSH and antioxidant peptides are substances involved in the regulation of redox reactions in cells. When oxidative stress occurs, GSH and antioxidant peptides are formed through the sulfur transfer pathway, which protects cells from oxidative substances<sup>[22]</sup>. Recent studies have found that the sulfur transfer pathway can block erastin-induced ferroptosis, but does not prevent RSL3-induced ferroptosis<sup>[23]</sup>, in conclusion, the sulfur transfer pathway is a negative regulation process that may be the cause of ferroptosis in cells, and more research is needed to prove it. Heat shock proteins (HSPs) have a protein function that stabilizes abnormal folding, and heat shock factors (HSFs) act as transfer factors to participate in the synthesis of HSPs, studies have shown that HSF1-HSPB1 can inhibit the increase of intracellular iron and ROS through complex pathways, and negatively regulate the ferroptosis of cells in various tumors<sup>[24]</sup>. Another study suggests that the MUC1-C/XCT pathway plays a negative regulatory role in breast cancer, preventing erastin-induced ferroptosis in tumor cells<sup>[25]</sup>.

Ma and Gibson *et al.* found that siramesine or siramesine combined with siramesine can control the expression of transferrin, in breast cancer cells, the concentration of FeCl<sub>3</sub> in tumor cells is increased by controlling the expression of transferrin, which ultimately leads to ferroptosis in tumor cells<sup>[26]</sup>. Lorincz and Szarka *et al.* studied the role of ferritinosis in acetaminophen-

induced cell death, research results suggest that beyond necroptosis and apoptosis, a third PCD, ferroptosis is also involved in acetaminophen-induced cell death in primary hepatocytes<sup>[27]</sup>. The discovery of these positive regulators of ferroptosis will be of great significance in the treatment of tumors, and complex processes and undetected positive modulator inducers need to be explored through more research.

## 6. Ferroptosis and Urinary Tumors

Since the discovery of ferroptosis, the study of the relationship between ferroptosis and tumor has been deepened, hoping to find new ways to treat cancer and tumor resistance, through a large number of experimental studies, ferroptosis can inhibit the growth of tumor cells and cause death<sup>[28]</sup>. In urinary tumors, related studies have reported that ferroptosis is also involved in the death of urinary tumor cells, and these findings provide new ideas for the treatment of urinary tumors. Although the study of ferroptosis and urinary tumors is in its infancy, the mechanism of ferroptosis involved in the development, treatment, and prognosis of urinary tumors has not been fully explained, ferroptosis inducers have been found in other tumors, for example, sorafenib can cause ferroptosis in tumor cells in hepatocellular carcinoma, pancreatic cancer, and renal cell carcinoma<sup>[29]</sup>. Therefore, the ongoing study of ferroptosis and urinary tumors, in the near future, ferroptosis may become a new strategy for the precise treatment of urinary tumors.

## 7. Ferroptosis and Renal Cell Tumor

Yang *et al.* found that the low expression of GSH peroxidase four can cause ferroptosis in tumor cells<sup>[12]</sup>. Among them, renal tumor cells are more likely to decrease the activity of GPXs4 than other tissue tumors induced by erastin; therefore, the discovery of ferroptosis in renal tumor cells is crucial, a new strategy for the treatment of renal tumors is provided. Garg and Vucic *et al.* studied the role of different cell death pathways and their modulators in the treatment of renal tumors, including ferroptosis<sup>[30]</sup>, studies have shown that cell survival and death are important for maintaining the development and growth of organisms, due to the complexity of renal tumors in different populations, the shortcomings of classical apoptotic pathways, and the prospect of ferroptosis as a new pathway of apoptosis are proposed. Ferroptosis is expected to become a possible treatment for kidney tumors.

## 8. Ferroptosis and Prostate Tumor

Sun and Tang *et al.*<sup>[24]</sup> studied the relationship between HSPβ-1 and iron death in prostate tumor cells. It was found that overexpression of HSPB1 inhibited iron death in erastin-induced prostate tumor cells, probably because HSPB1 phosphorylation resulted in a decrease in iron-dependent intracellular ROS species, thereby

avoiding ferroptosis. Several other studies have found that increased iron in prostate tumor cells can increase tumor cell proliferation, when an iron chelator (deferiprone [DFP]) is added, the growth of tumor cells can be inhibited. Jiang *et al.* found that the expression of ZNF217 was significantly increased in prostate cancer (PCa), further studies found that ZNF217 can cause a decrease in the content of ferroportin in cells, resulting in an increase in intracellular iron content. Promotes the growth of prostate tumor cells<sup>[31]</sup>. Koutcher *et al.* studied the effects of different concentrations of DFP in cells on PCa cell lines, it was found that the metabolism and growth of tumor cells were inhibited as the concentration of DFP increased<sup>[32]</sup>. Through the above two studies, it is found that the increase of iron content in tumor cells does not necessarily lead to the ferroptosis in cells, and there may be no iron-dependent ROS substances in the cells. According to the current research, the ferroptosis of cells depends on the increase of intracellular iron content, in addition, the intracellular iron content is reduced, which can also inhibit the growth of tumor cells; therefore, controlling the effective content of iron in cells may reach the purpose of treating tumors.

## 9. Ferroptosis and Bladder Tumor

In 1993, Seligman *et al.*<sup>[33]</sup> studied the relationship between intracellular iron ion concentration and proliferation of bladder tumors, it was found that when transferrin was combined with iron, the concentration of free iron ions in the tumor cells decreased, which was beneficial to the proliferation of bladder cancer cells, when metal gallium (Ga) and transferrin are used, it interferes with the binding of iron to transferrin, and the intracellular free iron increases, inhibiting the proliferation of bladder tumor cells, although it has not been continued to study whether intracellular free iron increase leads to ferroptosis in tumor cells, it provides new ideas for later research. Dayani and Zeltzer *et al.* proposed an increase in intracellular iron load, leading to a decrease in the protective capacity of oxygen free radicals and against oxidative stress, and an anti-tumor effect in bladder tumors<sup>[34]</sup>. Mazdak *et al.*<sup>[35]</sup> studied the role of trace elements in bladder tumors, the concentration of iron (Fe) was measured in the serum of 51 bladder tumor patients and 58 healthy volunteers, the study found that serum iron levels in patients with bladder tumors were significantly lower than those in the control group, suggesting that the decrease in serum iron levels may be the occurrence of bladder tumors. Whether the decline of serum iron will affect the decline of free iron ions in tumor cells and the mechanism of inhibiting iron death in cells still needs more research to confirm.

## 10. Summary and Outlook

Urinary tumors can be treated surgically in the early stage, and advanced tumors have lost the chance of

surgery. Most patients choose chemotherapy. The mechanism of most chemotherapeutic drugs is to destroy tumor cells, and finally, lead to apoptosis of tumor cells. However, with the prolonged use of chemotherapeutic drugs, some tumor cells are resistant to chemotherapeutic drugs, forming tumor resistance, and chemotherapy drugs lose their efficacy and cannot effectively control tumor progression. In recent years, many researchers have been searching for new ways of tumor cell apoptosis. The emergence of ferroptosis is of great significance and provides new ideas in cancer treatment and drug resistance. Researchers can develop ferroptosis inducers for certain tumors and become another way to discover new drugs for treating tumors. Although the current research on ferroptosis is deepening, the mechanism of ferroptosis and the regulation signal is complex, involving many biochemical reactions, such as how iron metabolism, lipid metabolism, and amino acid metabolism regulate the process of ferroptosis. Therefore, it needs to pass a large number. Research and explore the molecular mechanism of ferroptosis regulation signaling pathway and also have important significance for the development of new drugs for the treatment of tumors. We believe that through the continuous research of several generations, iron death will become a new method of treating tumors in the future.

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