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The main methods and application prospects of treating cancer through the induction of ferroptosis

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Abstract. The highly deadly illness known as cancer is brought on by the malignant growth of cells, and it ranks among the top causes of death globally at the moment.In recent years, research on cancer treatment drugs has emerged one after another. However, due to the continuous mutation of cancer cells, they develop resistance to traditional anti-cancer drugs, making it even more difficult to achieve a complete cure for cancer.Recent experimental studies have shown that ferroptosis,a non-apoptotic cell death pathway triggered by iron, can effectively overcome issues such as drug resistance in cancer cells, thereby achieving effective treatment for cancer. It is currently a promising therapeutic approach, and many researchers have been investigating iron death induction treatment methods.And alarge number of research papers on this novel cancer treatment method known as ferroptosis have been published.This review summarizes and introduces two treatment methods based on ferroptosis that have been extensively researched, which called therapeutic method for inducing ferroptosis using targeted nanoparticles and Methods for combining immunity and ferroptosis.,and analyzing their development prospects as well as some issues currently faced in research and suggestions for future development directions.

Keywords: ferroptosis, immunity, targeted nanoparticles.

1. Introduction

Cancer cells are a type of cell that possesses the ability to evade programmed cell death. Cancer typically arises from the loss of genes involved in the molecular mechanisms of programmed cell death, leading to resistance to apoptosis. This ability to escape programmed apoptotic cell death presents a significant challenge in current cancer treatments.

So far, tumor cells are thought to be able to retain or develop sensitivity to ferroptosis in order to avoid other types of cell death [1]. Ferroptosis is a non-apoptotic cell death pathway characterized by toxic lipid peroxidation and iron accumulation. It is able to selectively destroy tumors, effectively restraining the capabilities of cancer cells to achieve therapeutic goals, making it a highly promising alternative treatment strategy [2]. Moreover, among the several cancer drugs that have been developed so far, some are based on the induction of ferroptosis, such as Xc − transporter system (system Xc −) inhibitors, glutathione peroxidase 4 (GPX4) inhibitors, and ferroptosis inducers are ferroptosis-associated antitumor agents. Moreover, at present cisplatin, artemisinins, neratinib, lapatinib, statin, sulfasalazine, SRF, withaferin A, and zalcitabine are being tested in clinical trials for repurposing as ferroptosis inducers [3]. Moreover, Class I FINs include sorafenib, sulfasalazine and

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cisplatin, and sulfasalazine is currently applied as an immunosuppressant which can restrain System Xc- to induce ferroptosis in treating diseases such as Crohn's disease and rheumatoid arthritis, and it has already been approved for use [4]. Therefore, the development of research on ferroptosis is likely to provide significant assistance in the treatment of human cancer [3]. Research indicates that one of the primary strategies used in the present cancer therapy protocol is inducing cell death. However, due to intrinsic or acquired resistance to apoptosis-inducing drugs, the efficacy of anticancer drugs is limited. Due to the problem of drug resistance in cancer cells, it is imperative that modern medicine investigate alternate approaches that make advantage of non-apoptotic cell death to enhance treatment results, particularly by employing ferroptosis as a therapeutic strategy [3]. Currently, more and more teams are engaged in research targeting ferroptosis, such as the team of Jaewang Lee and Jong-Lyel Roh, who emphasized the importance of Ferroptosis suppressor protein 1 (FSP1)regulation and its promise as a specialized target for cancer treatment. Also discussed the latest developments in the development of FSP1 inhibitors as well as their impact on cancer therapy [5]. And the Ischemia-reperfusion (I/R) damage involved in ferroptosis affects the Wnt (A complex protein interaction network)signaling pathway, thereby influencing the treatment of diseases, among other things [6]. At the same time, there have been quite a few successful experimental examples of inducing ferroptosis in current research. For example, research showing how the tumor suppressor p53, commonly known as the "guardian" of genome stability, controls ferroptosis through transcriptional activity or a transcription-independent mechanism to preserve the integrity of cells and organisms [7]. Moreover, in lung cancer, inducing ferroptosis can leverage the prominent role of NRF2(Transcription factor nuclear factor erythroid 2-related factor 2 (NFE2L2 or NRF2)) in regulating iron metabolism, and targeting it through various treatment methods can significantly induce ferroptosis [8]. Additionally, adding ferroptosis inducers to various other traditional chemotherapy medicines enhances their anticancer effects [9]. In addition, D8+ T cells secrete interferon-gamma (IFNγ), which lead to the downregulation of SLC7A11, promoting ferroptosis in tumor cells. This indicates its role in immune surveillance. Additionally, SLC7A11 pharmacological suppression or genetic deletion causes ferroptosis, which in turn inhibits the growth of tumors [10].Therefore, given these points, it can be concluded that ferroptosis therapy is a very promising treatment method.

Currently, there are two popular treatment methods in research that are effective therapies through the pathway of ferroptosis. The first type is iron death induced by cancer-targeting nanoparticles with high efficiency in targeting cancer and minimal systemic toxicity. The second type is an innovative immunotherapy combination strategy targeting specific tumors [2], and current research has indicated that targeted nanoparticles inducing ferroptosis and treatment methods combining immunity with ferroptosis are the main research directions at present.

2. Two current important approaches to utilize ferroptosis for cancer treatment

2.1. A therapeutic method for inducing ferroptosis using targeted nanoparticles

Targeted nanoparticle therapy is a method that induces cellular ferroptosis, and its safety has been validated by multiple studies. By assembling specific biomolecules on their surface to recognize target cells, nanomaterials with a high surface/volume ratio are predicted to improve the specificity of targeted therapy, increasing medication efficacy while reducing damage to untargeted normal cells [4]. Research has shown that experimental designs have developed safe nanoparticles for clinical application, specifically nanoparticles containing iron that are dependent on iron overload and FDA-approved hyaluronic acid (FHA NPs). These FHA NPs can specifically induce the production of reactive oxygen species (ROS) and lipid peroxidation in cancer cells without affecting normal cells [2]. Moreover, FHA NP has a good anti-tumor effect and can effectively target tumor sites, demonstrating strong tumor targeting capability [2]. Another study designed iron nanoparticles based on safe ha (FHA NPs) to induce ferroptosis in order to eliminate tumors. At the same time, using this nanomedicine that reduces toxicity and enhances anti-tumor effects through iron overload disease in clinical treatment can significantly improve the quality of life for the patients undergoing treatment. At

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the same time, this efficient nano-therapy drug that induces ferroptosis is expected to be applied in the future for the treatment of various tumors and to demonstrate synergistic therapeutic effects when combined with other treatment methods [2]. However, at present, nanoparticle-based chemotherapy is still at a stage that is difficult for clinical application, mainly due to certain therapeutic limitations of the nanoparticle drugs being studied at this stage [2]. Moreover, There are many fusion methods for nanoparticle treatment, such as the use of magnetic operational nanoparticles (MNPs), which is a promising image-guided magnetic induction and combined iron-induced cancer therapy. It utilizes remotely controllable magnetic nanocarriers to provide efficient localized image-guided iron-based cancer nanomedicine [3]. Moreover, existing research has shown that in the realm of translational medicine, it has been demonstrated that MNPs' local delivery and catalytic effects in both conventional and combination cancer therapies [3]. What's more, the use of MNPs can assist in achieving targeted ferroptosis induction through further imaging in developing ferroptosis-induced cancer therapies. Specifically, ROS-producing polymeric and inorganic NPs, iron oxide NPs, and multifunctional nano-cargoes that combine an imaging element with ferroptosis activation have demonstrated excellent tumor-treating performance [3]. When combined with nanomedicine, it can reduce side effects and provide targeted non-toxicity [2],for example, low-dose ultra-small monocrystalline iron manipulable nanoparticles (NPs) can not only effectively induce ferroptosis in tumor cells and immune-mediated cell death, but also, due to their small size, the kidneys can clear the NPs more rapidly. Therefore, it is evident that the combination therapy and the ultra-small single crystal Fe NPs with irgd labeling are appropriate for clinical translation. [3].

So in light of the argument above, the treatment methods targeting ferroptosis have broad development prospects in the future of cancer therapy.

2.2. Methods for combining immunity and ferroptosis

The combination of the body's immune mechanisms and ferroptosis treatment methods can significantly enhance the efficiency of immunotherapy, thereby achieving effective treatment and elimination of cancer cells.

Research has shown that there is a certain correlation between immunotherapy and ferroptosis. This includes two situations: direct immunogenicity and the initiation of inflammatory responses that regulate other forms of necrosis in the tumor microenvironment [11]. Currently, one of the most effective methods for treating cancer is to stimulate and control the patient's immune system in order to destroy cancer cells. This has been demonstrated in several studies indicating that ferroptosis may be mediated by lipid peroxidation, which leads to the rupture of the plasma membrane, and this rupture subsequently results in the release of cytoplasmic material [3]. Many of these released substances can act as immunogenic signals and induce an inflammatory immune response. The studies *demonstrate* that making tumor cells sensitive to ferroptosis can enhance the efficacy of combination cancer immunotherapy [3]. For example, when CD8+ T cells release IFNγ, the SLC3A2 and SLC7A11 subunits of the Xc-system are reduced. This causes tumor cells to use less cystine, which in turn causes ferroptosis in tumor cells and eventually increases the effectiveness of immunotherapy [10]. Another experiment utilized the light chain (xCT, gene name SLC7A11) to induce dedifferentiation of melanoma cells activated by immunotherapy. The emergence of drug resistance, along with the cytokine IFNγ and the reduced expression of the radiation-induced ataxia-telangiectasia mutated gene (ATM), leads to heightened lipid peroxidation and ferroptosis in cancer cells. This transformation of tumor cells results in heightened susceptibility to ferroptosis induction and diminishes their overall immunosuppressive capacity. This may provide a new tool for anti-tumor immunity and could help optimize established immunotherapy approaches [11]. This emerging therapeutic strategy overcomes the limitations of traditional apoptosis-based cancer models, and ferroptosis can activate innate immunity, specifically natural killer (NK) cells, as well as adaptive immunity in cancer treatment. When combined with immunotherapy, it can effectively inhibit tumor growth, which is beneficial for better controlling and monitoring the patient's condition. Using this

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combined treatment approach is advantageous for significantly enhancing the efficacy of the treatment, creating a synergistic effect, thereby improving the effectiveness of cancer treatment [3].

As a result, this is a treatment plan with great research and application prospects.

3. Challenges and future development of using ferroptosis for cancer treatment

3.1. Challenges of using ferroptosis for cancer treatment

Disadvantages that have emerged in the current stage of research: Most of the iron death inducers currently used clinically have poor solubility, low metabolic stability and low bioavailability[3]. Moreover, studies have shown that some ferroptosis inducers can lead to increased iron buildup in the kidneys, spleen, brain and duodenum [3]. At the same time, some inducers can also induce pathological changes in healthy tissues [3]. For example, Xc − transporter system (system Xc −) inhibitors, glutathione peroxidase 4 (GPX4) inhibitors, and ferroptosis inducers are all have certain side effects while treating cancer [3] (Table 1.).

Table 1. Base principles and side effects of the three main drug types.

name	Mechanism of action	Side effects of the application
Xc − transporter system (system Xc −) inhibitors (erastin)	reduced GSH and GPX4, elevated serum iron, and malondialdehyde, followed by ferroptosis.	increased iron accumulation in the kidney, spleen, duodenum and brain. Cause a small cerebral infarction and an increase in the kidneys' glomerular capacity.
Glutathione peroxidase4(GPX4)inhibitors (RSL3)	Reduce the expression of GPX4, inducing hypertrophic death in head cancer cells and neck cancer cells.	Cells with overexpressed GPX4 exhibit resistance to RSL3, inhibiting its induced ferroptosis.
ferroptosis inducers	Treating cancer by inducing ferroptosis in cells.	cause unhealthy alterations in good cells Intestinal ischemia/reperfusion, ulcerative colitis, and cystic fibrosis can all be brought on by ferroptosis inducers, and aberrant limb development may be related to elevated iron levels.

Moreover, research has shown that using currently available iron overload disease inducers to treat cancer often struggles to achieve sufficient efficacy [3]. Non-targeted iron overload can disrupt iron homeostasis and lead to the excessive production of iron-dependent cellular reactive oxygen species (ROS) [3]. This may have an impact on the immune system and result in heart failure, leukemia, and neurological illnesses including Parkinson's disease and Huntington's disease. The process of causing iron drooping in healthy cells has the potential to trigger cancer linked to macrophages that provide iron [3]. It is also possible to trigger carcinogenesis linked to iron-supplying tumor-related macrophages by inducing iron drooping in healthy cells [3]. The fact that immunogenicity can result in cytokine release syndrome and/or aberrant inflammatory responses is now one of the major obstacles facing immunotherapy [2]. Meanwhile, the impact of immune cells on ferroptosis is somewhat related to the environment, which increases the potential instability of this treatment approach [10],and research indicates that the application environment for the treatment method of inhibiting iron overload disease, aimed at addressing the immunosuppressive effects of pathologically activated neutrophils, is limited. Due to the presence of pathologically activated neutrophils with immunosuppressive activity in tumors, there is an increased likelihood of ferroptotic cell death [10].

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This process results in the release of oxidized lipids, which restricts T cell activity and consequently promotes tumor growth, in this case, while causing ferroptosis can accelerate tumor growth, blocking it can reverse immunosuppression and slow the evolution of tumors; however, this phenomenon only occurs in the initial stages of the tumor's development. Therefore, the application of ferroptosis varies according to the environment [10]. Moreover, translational ferroptosis inducing agents has poor functionality in terms of bioavailability and has shown weak performance in experiments regarding its specificity for tumors. Research indicates that there are some uncontrollable factors associated with ferroptosis symptoms, which are related to some serious diseases like cancers, some type of nfection and cause the damage to the kidney [10]. However, the suppression of iron overload disease only shows protective effects in the early stages of tumor initiation, as once the tumor has formed, Lipostat-1 treatment cannot prevent tumor progression [10].

The results of these studies indicate that there may be a limited window of opportunity for treating the immunosuppressive effects of pathologically activated neutrophils by blocking ferroptosis [10]. A challenge of ferroptosis-inducing cancer nanomedicine is the inconsistent treatment outcomes across different tumor types. For instance, decreased iron metabolism, including the influx of iron ions, flux of iron ions, and distribution of intracellular iron ions, is one of the biochemical features of prostate cancer.[3]. It has been demonstrated that diffuse large B-cell lymphoma and renal cell carcinoma are more vulnerable to irinotecan-induced ferroptosis than other cancer cell lines from six different types of tumors, which are colon, melanoma, lung, ovary and central nervous system [3].

3.2. Future development dirsctions of using ferroptosis for cancer treatment

Research indicates that the combined effect of radiotherapy and ferroptosis can enhance the overall effectiveness of cancer treatment. However, there are still some aspects of ferroptosis for which current studies do not provide clear and definitive results, for example, methods to mitigate the targeted side effects of ferroptosis still require further research [11]. Moreover, in order to reduce side effects and harm to normal cells, future study should examine the specificity and ideal dosage of ferroptosis inducers. Additionally, since tumor cells are heterogeneous and plastic, their susceptibility to ferroptosis inducers varies, and the specific functions possessed by some cancer cells have yet to be determined. This, to some extent, hinders the application of ferroptosis in clinical practice [3]. Although most studies on hemochromatosis have been conducted in monolayer cultured cells, there are still many aspects of its role in vivo that remain unexplored. However, studies have shown that ferroptosis may be a form of immunogenic cell death (ICD) [4]. Furthermore, it is important to further study the relationship between immune interactions and ferroptosis, as this will facilitate the provision of precise treatments for each patient in the future [4]. At the same time, it is also necessary to study the combined use of various treatment methods. For example, the simultaneous combination of cisplatin (DDP) and PRLX93936 can induce ferroptosis by inhibiting GPX4. Moreover, existing research has shown that this combination therapy has performed very well in experimental results ,in the future, it is hoped that through more in-depth research, it will ultimately be applied to clinical treatment for cancer [8].

4. Conclusion and perspective

This review explains the mechanisms of ferroptosis and summarizes two currently popular approaches for applying ferroptosis in cancer treatment: the therapeutic method of targeting nanoparticles to induce ferroptosis and the treatment method that combines immunotherapy with ferroptosis.

Both methods are based on ferroptosis, which significantly differs from the traditional approach of inhibiting cancer through apoptosis. They effectively circumvent the research challenge of cancer cells developing resistance, opening up new avenues and ideas. At the same time, summarizes previous studies on treatment methods involving targeted nanoparticles that induce ferroptosis, as well as research on therapies that combine immunotherapy with ferroptosis. It provides a detailed account of the treatment principles and methods for both targeted nanoparticle-induced ferroptosis and the combination of immunotherapy with ferroptosis. It also explain the advantages demonstrated during

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the research process and related experiments, as well as areas that need improvement, along with some major issues and difficulties encountered in current ferroptosis treatment methods, and discussed and analyzed the future development direction.

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