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A New Frontier in Ferroptosis-Driven Cancer Treatment

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Abstract. Ferro ptosis, as an iron-dependent form of regulated cell death fundamentally controlled by lipid peroxidation, has been discovered to be effective in cancer therapy. However, in contrast to traditional treatment methods such as chemotherapy and radiation, ferroptosis specifically targets and destroys cancerous cells. Nevertheless, ferroptosis faces significant obstacles, including low tumour penetration, off-target toxicity, and poor solubility. Nanotechnology, namely the design of multifunctional nanoparticles (NPs), shows promise in inducing ferroptosis by several mechanisms including Fenton reactions, GPX4 inhibition, transport of lipid peroxides, and photosensitization. Significantly, the configuration of multifunctional NPs instigated ferroptosis, leading to an enhanced drug-loading system, a targeted delivery system for tumours, a synergistic combination system with other cancer therapies, and notably, additional attributes like responsiveness to stimuli. This review explains the advantages of ferroptosis-based cancer therapy over traditional methods and its potential for clinical translation. With the mentioned properties, nanotechnology can now enhance ferroptosis-based cancer therapy, leading to improved and tailored treatment techniques.

Keywords: Ferroptosis, Nanotechnology, Cancer Therapy.

1. Introduction

Ferroptosis is a type of iron-dependent programmed cell death due to lipid peroxidation [1]. Unlike the other cell death processes like apoptosis or necrosis, the accumulation of lipid peroxidation, but not caspase activation or receptor engagement, leads to ferroptosis, thereby qualifying for a unique and potentially effective anti-cancer mechanism. Since its discovery, the series of studies that followed have proven that this method is particularly effective against drug-resistant and difficult-to-treat cancers, and consequently it is of importance in further cancer treatment [2].

Though conventional therapies for cancer are capable of controlling and destroying cancerous cells, they have many limitations. The most significant of all these is the fact that such methods are often non-specific and can result in harm to normal cells, leading to moments of fatigue, nausea, and severe side effects, including hair loss, among other problems [3]. Besides, there are types of cancer that can show resistance to radiation and chemotherapy, which often results in improper treatment. In addition, the latter frequently faces problems with the complete destruction of carcinogenic cells, which could lead thereafter to the remaining presence of the disease and further, therefore, increase the chances of relapse [4]. Adverse effects are thus pronounced from radiation and chemotherapy due to lack of specific targeting only on the cells causing cancer. On the other hand, surgical intervention is limited by the extent to which the degree of malignancy has reached, as it cannot completely obliterate the cancer cells that have spread throughout the body. It is for these reasons that the development of more specific and efficient treatment of cancer is considered to be one of the most important aspects of medical research.

This review primarily elucidates the role of nanotechnology in augmenting ferroptosis in cancer therapy [1]. We will primarily cover state-of-the-art nanotechnologies that efficiently induce ferroptosis, analyzing their mode of action, targeted delivery capabilities, and therapeutic effects. The current research primarily centres around the utilization of nanoparticles to augment iron-induced cell death for cancer treatment. This approach is elucidated by Nadia Zaffaroni and Giovanni Luca Beretta in their 2021 review, which delves into the role of nanoparticles in facilitating ferroptosis and

highlights their potential to overcome the drawbacks associated with small-molecule drugs, such as systemic toxicity, limited solubility, and absence of tumor-targeting properties [5]. In this review, we will examine more developing uses and innovative tactics of nanotechnology in ferroptosis cancer therapy, focusing on the following areas:

- Exploring the design and utilization of multifunctional nanomaterials that integrate phototherapy, photodynamics, and immunotherapy.
- Enhanced Delivery Systems: Investigating novel targeted delivery methods that utilize surface modification to enhance drug concentration at the tumor location and minimize harm to healthy tissues by selectively targeting cancer cells.
- Investigate the role of nanomaterials in regulating immune cells within the tumor microenvironment, improving the efficacy of immunological therapy, and working in conjunction with ferroptosis mechanisms.
- Progress in pre-clinical and clinical research: This text discusses the introduction of new advancements in clinical and clinical research, as well as their practicality and problems in practical applications [6].

This review aims to provide a thorough grasp of how to maximize nanomaterials for therapeutic advantages by integrating current research findings from published ferroptosis and Cancer related reviews. It will include information about the year, author, and substance of these reviews.

Nanotechnology has emerged as a revolutionary method in the field of medicine, providing novel solutions to intricate obstacles in the realm of cancer therapy. Nanomaterials have several advantages in the context of ferroptosis, such as the ability to dissolve, remain stable, and increase the bioavailability of ferroptosis-inducing substances. Furthermore, nanotechnology has the potential to enhance the precision of cancer cell targeting while limiting harm to healthy cells. This can optimize the effect of treatment as well as reduce any negative impacts. Nanoparticles with innovative designs, including magnetic NPs, liposomes, and polymer-based NPs, have been created to transport iron-death activators directly to the tumor microenvironment. This approach aims to increase the local concentration of these activators and enhance the induction of ferroptosis.

This introduction explores the synergy between nanotechnology and programmed cell death in the context of cancer treatment, setting the stage for the next chapters. This review will provide a comprehensive analysis of the influence of particular materials, their uses, and potential avenues for further research.

2. Mechanism of Ferroptosis

Ferroptosis involves several key mechanisms (**Figure 1.)** [7].

First, Iron Metabolism Dysregulation leads to increased levels of Labile Iron Pool (LIP, free iron pool), which catalyses Fenton Reaction leading to Reactive Oxygen Species (ROS) production, thereby triggering lipid peroxidation. Iron intake is enhanced by transferrin endocytosis and ferritinophagy. Secondly, the polyunsaturated fatty acids (PUFAs) in the cell membrane were oxidized, leading to accumulation of lipid peroxides. Lipid peroxides are normally restored by Glutathione peroxidase 4, (GPX4) by relying on Glutatathione, GSH (Glucothiazide)[2]. Inhibition of GPX4 or depletion of glutathione leads to PLOOH accumulation and ferroptosis. Impaired Antioxidant Defense is caused by the inhibition of GPX4 or Cystine/Glutamate Antiporter (System Xc, semi-cystic acid/glutamine reverse transporter), which leads to the exhaustion of Shipped Metabolism Alterations are manifested by increased levels of Acyl-CoA Synthetase Long-Chain Family Member 4, ACSL4 (acetylase A synthetic enzyme long chain family 4), promoting the integration of PUFAs into the membrane, making them more susceptible to peroxidation. If GPX4 is suppressed, lipid peroxide will not be restored, causing it to accumulate inside the cell. This accumulation causes severe oxidative stress and membrane damage, eventually leading to ferroptosis

[7]. In short, ferroptosis is induced by iron-catalyzed lipid peroxidation, a process driven jointly by dysregulated iron metabolism, impaired antioxidant defenses (GPX4 inactivation) and lipid metabolism changes (increased PUFA oxidation sensitivity).

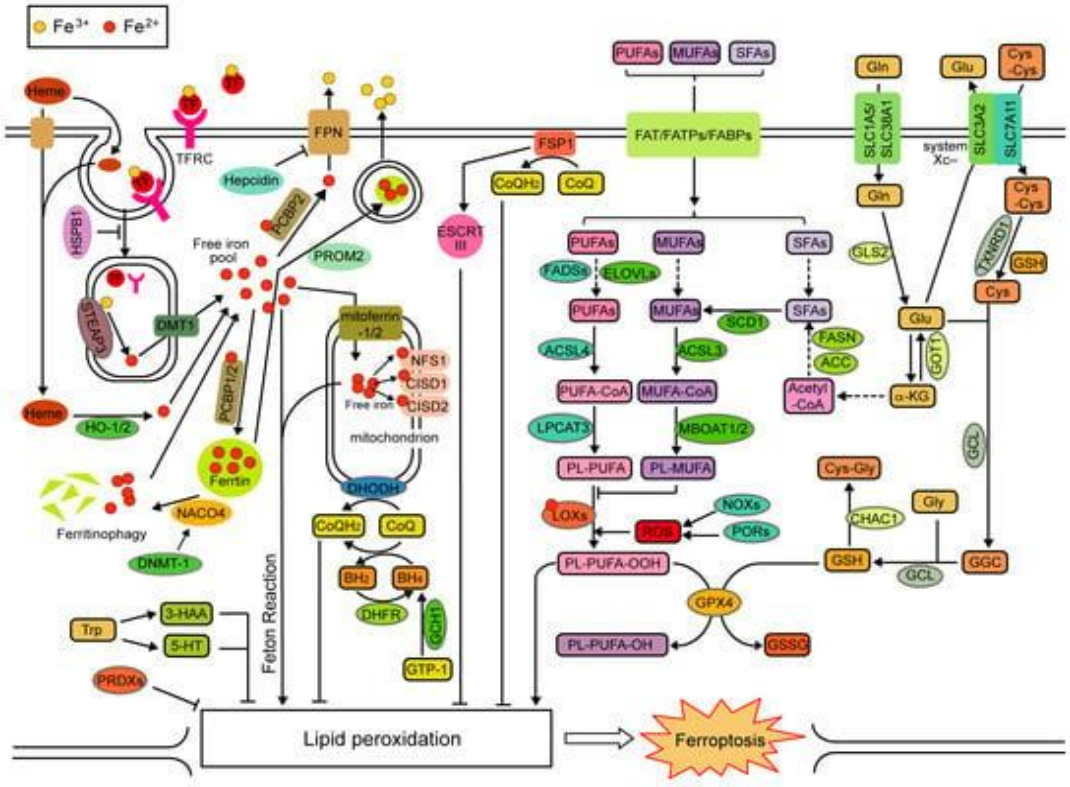

Figure 1. Mechanism of Ferroptosis [7]

3. Nanomaterial vs Ferroptosis

Mechanism

Nanomaterials can induce Ferroptosis through a variety of mechanisms:

Fenton Reaction (**Figure 2.)**: For example, Yue Ming and others published Nanozyme-enhanced ferroptosis for cancer treatment in 2024. Iron Oxide Nanoparticles, an iron-based nanomaterial, can catalyze the Fenton reaction by generating a highly reactive free-base radical (·OH) through the interaction of mercury peroxide (H_2O_2) and dioxide iron (Fe^{2+}) [8]. These basal free radicals (OH) can oxidize PUFAs in cell membranes, leading to lipid peroxidation, thereby producing a lot of ROS. These processes eventually lead to ferroptosis [9].

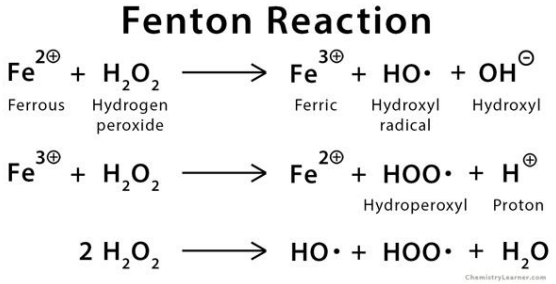

Figure 2. Chemical Formula of Fenton Reaction [9]

Glutathione Peroxidase 4(**Figure 3.)**: For example, Shumin Sun and others reported novel ferroptosis-targeted therapeutics such as Arginine-rich manganese silicate nanobubbles, erastin-loaded nanoparticles and GPX4 inhibitor- loaded nanoparticles. The direct inhibitors including RSL3, ML162, ML210 and FIN56, as well as photosensitizer-containing NPs [10]. These nanomaterials can

inhibit GPX4 through different mechanisms. GPX4 is an important antioxidant in cells, responsible for restoring lipid peroxides to non-toxic lipids. Inhibition of GPX4 thus becomes an important pathway to induced ferroptosis, especially in the treatment of cancer [11].

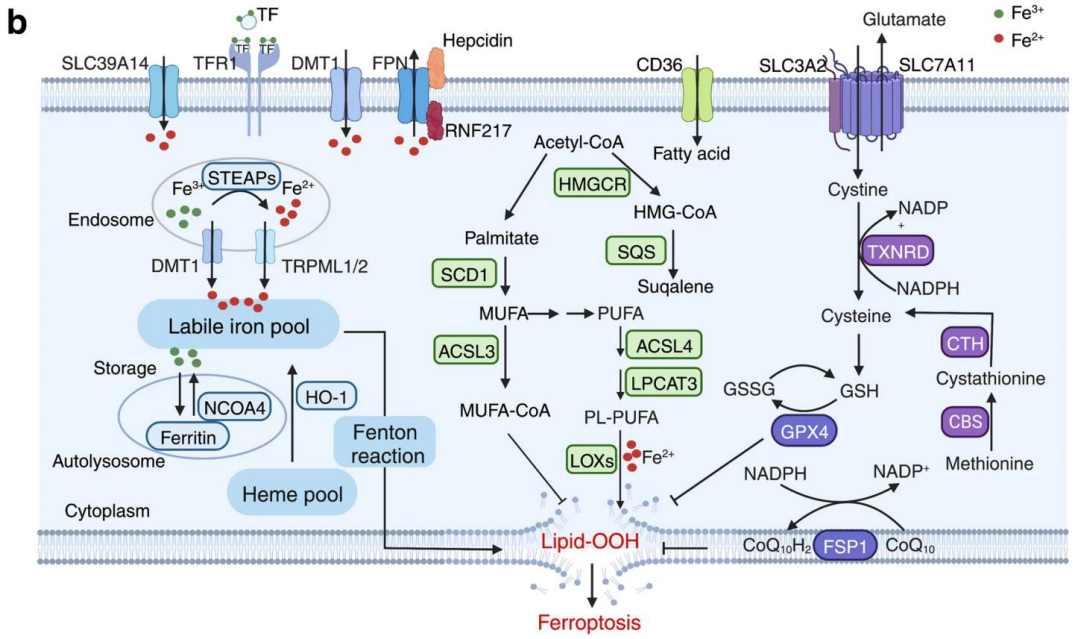

Figure 3. Mmechanism of GPX4 [11]

Delivering Lipid Peroxides (**Figure 4.)**: For example, nanomaterials can package and transport lipid peroxides or ferroptosis inducers to cancer cells, initiating the ferroptosis process. These nanomaterials include various forms of nanoparticles such as Lipid Nanoparticles, Polymeric Nanoparticles, and Inorganic NPs. These nanoparticles can effectively penetrate tumor tissue and enter cancer cells, releasing the active substances they carry. Once these Lipid Peroxides or Inducers are released, they promote Polyunsaturated Fatty Acids in the cell membrane, PUFAs (multi-unsatten fatty acids) into Lipid peroxide, producing large amounts of ROS, thereby destroying the integrity of the cellular membrane [12]. In addition, these nanomaterials can also interact with iron in cells, further promoting lipid peroxidization, eventually inducing ferroptosis in cancer cells. This mechanism provides an effective, targeted cancer treatment that produces anti-tumor effects via inducing ferroptosis of cancer cells.

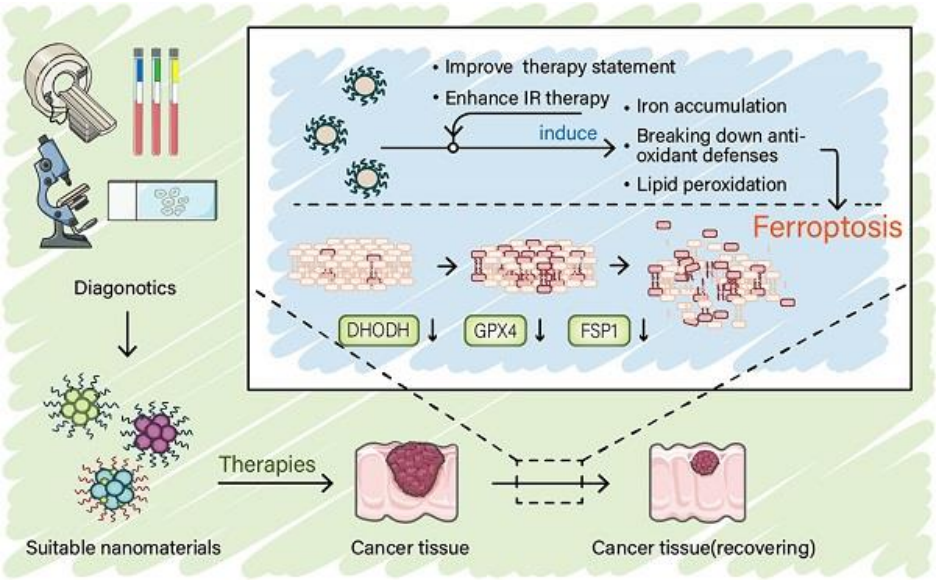

Figure 4. Delivering of Substance, Including Lipid Peroxide, to induce Ferroptosis [12]

Release of Endogenous Iron: For example, in 2022, Zhiyuan Shi and others described in iron-free multifunctional nanomaterials as ferroptotic-inducing therapy, which can trigger increased Lysosomal Membrane Permeabilization, release of Endogenous Iron Stores, and promote ferroptosis. These nanomaterials cause the Lysosomal Membranes to become unstable, causing the sealed iron to be released into the cellular tissue [13]. The iron released could get involved in the Fenton Reaction, generating ROS along with triggering lipid peroxidation. This process increases the oxidative stress in the cell, causing severe damage to the cell composition, eventually leading to ferroptosis [9]. Using this mechanism, iron-free nanomaterials can effectively induce ferroptosis in cancer cells, providing a new treatment for cancer by using the cell's own reservoir.

Photosensitivity (**Figure 5.)**: For example, in 2023 Yunpeng Huang and others, reported that nanoparticles containing photosensitive agents can produce ROS under light, thereby inducing lipid peroxide and induced ferroptosis [14]. For example, using Photodynamic Therapy, PDT, under light exposure of a specific wavelength, photosensitizers are activated, producing ROSs, such as mono-linear oxygen ($1O_2$) and phosphorus free radicals (OH), which can trigger lipid peroxide, damage cell membranes, and ultimately lead to cellular ferroptosis. Photodynamic Therapy combined with ferroptosis inducers (e.g. Erastin or RSL3) demonstrates synergistic anti-cancer effects that improve the specificity and efficiency of treatment.

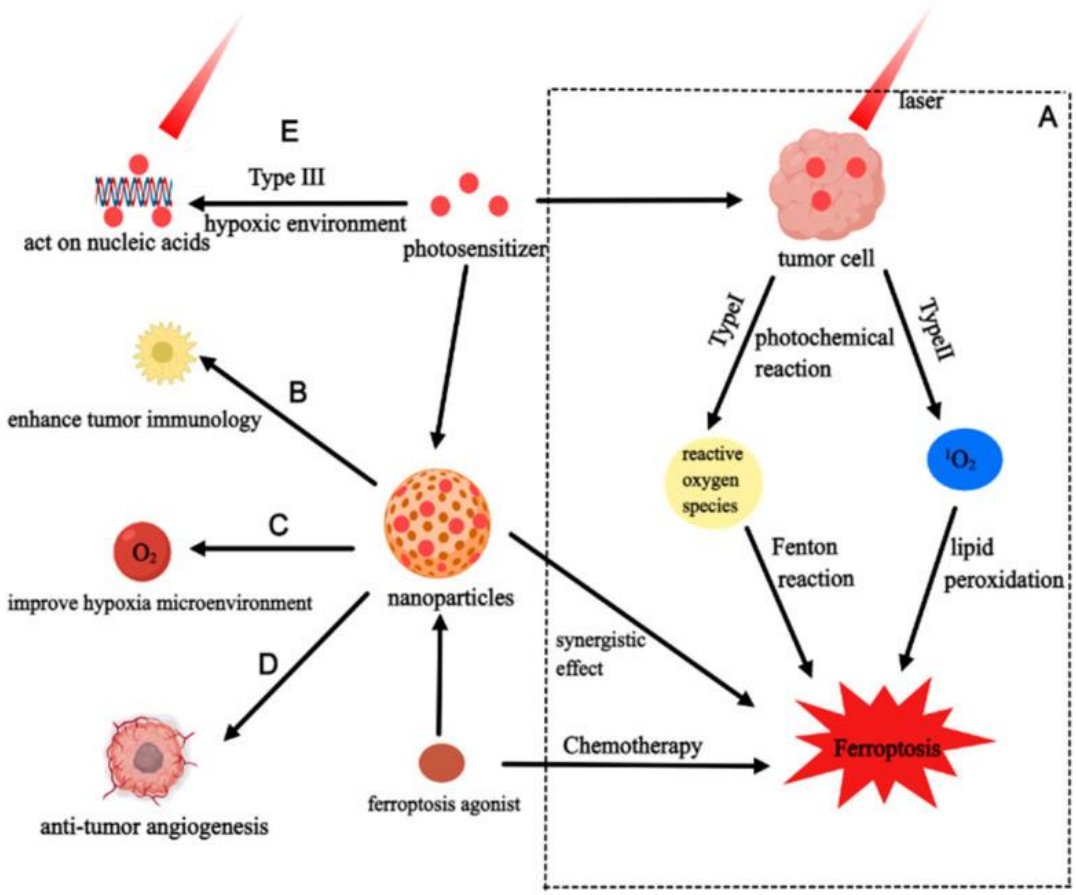

Figure 5. Mechanism of photosensitizing to cause Ferroptosis [14]

Autophagy Inhibition (**Figure 6.)**: In 2023, Qi Nie and others reported that iron oxide nanoparticles can promote the ferroptosis of cancer cells by suppressing autophagy and synergistic bundling with paclitaxel. For example, using nanoparticles containing autophagosome inhibitors, such as 3-MA (3-methyl glutamine) or Hydroxychloroquine, CQ (chlorophosome), these particles can inhibit the formation or fusion of autofagosome, increasing oxidative stress and lipid peroxidize within the cell, eventually promoting ferroptosis [15].

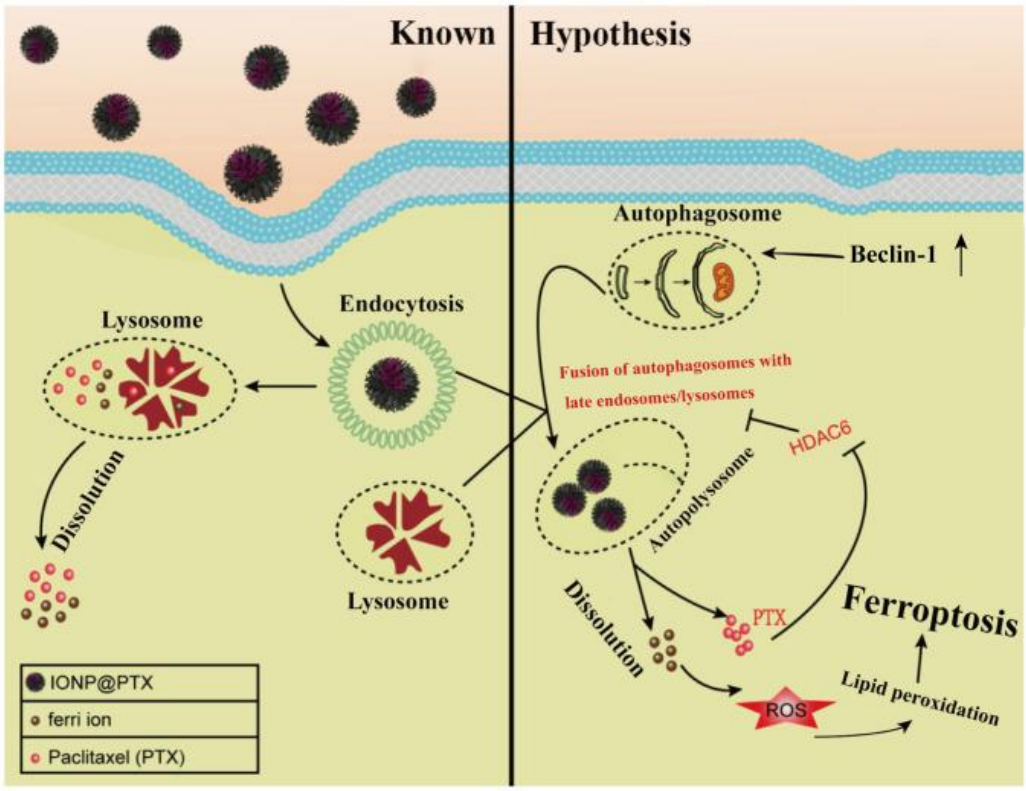

Figure 6. Mechanism of autography inhibition to cause Ferroptosis [15].

Cell Membrane Permeability: For example, in 2021 Lohans Pedrera and others used nanoparticles containing transmembrane peptides (transmembranes, such as TAT) can help ferroptosis inducers (such as Erastin) or iron ions (Fe^{2+}) to enter cells more easily. These nanoparticles can physically destroy the cell membrane or change the membrane structure, causing changes in internal cellular environment, increasing oxidative stress, and ultimately leading to ferroptosis [12][16].

Synergistic Therapy: For example, in 2023 Yunpeng Huang and others stated that nanomaterials can be designed to combine iron-death induction with other cancer treatments such as Chemotherapy, Radiotherapy and Immunotherapy to a combination of anti-tumor effects. For example, nanoparticles can simultaneously load chemotherapy drugs such as Paclitaxel (chemotherapy), iron-death inducers (RSL3), and radiotherapy sensitizers [17]. These multifunctional nanoparticles can target tumour tissue, release a variety of therapeutic drugs, accomplish multiple attacks, and enhance therapies. In addition, nanoparticles can also be used in immunotherapy, via increased immunogenicity of tumor cells, activated immune system and enhanced anti-tumor immune response.

Gene Silencing: In 2023 Xiangnan Zheng and others states that nanoparticles can carry siRNAs or gene editing tools, such as CRISPR-Cas9, silencing genes associated with ferroptosis, like GPX4. These nanoparticles were designed to specifically enter cancer cells, releasing siRNA or CRISPR-Cas9, targeting and inhibiting the expression of the GPX4 gene. This leads to ferroptosis [18].

Advantages

Nanomaterials provide several important advantages for ferroptosis cancer treatment:

Efficient Iron Ion Release and Reactive Oxygen Species (ROS) Generation

Iron-based nanomaterials can directly release high concentrations of iron ions, significantly increasing intracellular ROS levels. Therefore, this characteristic makes iron-based nanomaterials very advantageous in the induction of ferroptosis. For example, iron oxide nanoparticles can effectively trigger lipid peroxidation by releasing iron ions thereby causing ferroptosis [19]. Besides, the high porosity and good biocompatibility of MOFs have also been intensively explored in the context of ferroptosis-based cancer treatment.

Superior Drug Loading and Targeting Capabilities

Nanoparticles have shown great loading and targeting capacity, especially in cancer therapy. Surface modification of nanoparticles imparts them with the functionality of targeted delivery, enabling significantly increased drug concentrations at the tumor site, while the concentration in normal tissue decreases. For instance, polydopamine-based nanoparticles modified with polyethylene glycol (UPDA-PEG) can chelate ions of iron to enhance the release efficiency of the iron ions to conduct pH-responsive iron ion release in the tumor microenvironment [20].

Multifunctionality and Synergistic Therapeutic Effects

Nanomaterials can effectively complement a range of therapeutic procedures for the enhancement of treatment effectiveness. For instance, nanozymes, a kind of new synthesized nanomaterials, are installed with enzyme-like catalytic activity and thus are able to directly bring about ferroptosis through the regulation of the ROS levels in the tumor microenvironment [21]. In other reports, it has been indicated that nanomaterials could be used simultaneously with photothermal therapy (PTT) and chemodynamic therapy (CDT) to strengthen antitumor effects [22].

Improved Biocompatibility and Safety

Biocompatibility and safety in clinical applications are of very crucial importance in relation to nanomaterials. The use of self-assembled nanoparticles has been found to be much more biocompatible and safer due to a lesser extent of chemical modification and the use of further excipients [23]. For example, polydopamine nanoparticles are very biocompatible when in contact with the body and can be easily functionalized by simple changes of their surface, thus proving great potential in cancer therapy [24].

Addressing Drug Resistance and Enhancing Therapeutic Efficacy

Conventional small molecule ferroptosis inducers always face several problems in clinical application, such as the low water solubility, drug resistance, weak targeting capabilities, and so on. The rise of nanotechnology has opened new vistas for solving these limitations. This type of stimuli-responsive nanomaterial has some unique advantages in the field of spatial control and temporal control, releasing the medication selectively within some tumor microenvironments so as to enhance the therapy effect [25]. For example, magnetic nanotorquers generate torque under a programmed rotating magnetic field, which in turn induces release of endogenous Fe^{2+}, leading to ferroptosis [26].

Clinical Application Prospects

Although nanoparticle targeting to cancer cells holds a high degree of promise, in particular for ferroptotic-based therapy, practical implementation into the clinic raises some concerns. The complexity of the synthesis and modification process related to nanomaterials may limit their production scale-up and, consequently, clinical application. Additional research is also needed to explain the metabolic and excretory pathways of the nanomaterial in vivo, and this will ensure the safety and efficacy [23][25].

4. Conclusion

In summary, nanotechnology holds significant promise for cancer treatment by utilizing ferroptosis. The unique qualities of nanotechnology, such as targeted distribution, controlled release, multifunctional therapeutic platforms, and effectiveness, can increase the activity of ferroptosis in cancer therapy. In addition, nanoparticles have the ability to overcome the challenges posed by drug resistance and hypoxia in conventional cancer treatment. This provides more evidence of the promising potential of nanotechnology in the treatment of ferroptosis in cancer. Additionally, its capacity to enhance the immune system and regulate genes makes it a valuable candidate for cancer treatment. Nevertheless, despite its considerable potential, this technology faces many obstacles, including possible toxicity, immunological clearance, and limited tumor penetration, which require further investigation and improvement. Future research could prioritize the advancement of

nanocarriers that have improved biocompatibility and can effectively combine with other cancer treatment methods to fully explore the possibilities of ferroptosis therapy. In summary, the integration of ferroptosis cancer treatment with nanotechnology is a very promising topic that has the potential to revolutionize cancer therapeutic techniques. This advancement offers new hope to patients with drug-resistant and difficult-to-treat cancers.

Author Contribution

These authors contribute equally, and their names are listed in alphabetical order.

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