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FERROPTOSIS WITH CHEMOTHERAPY: A SYNERGISTIC APPROACH TO CANCER THERAPY

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ABSTRACT

Iron-dependent lipid peroxidation drives ferroptosis, a unique type of controlled cell death that has attracted a lot of interest due to its potential as a treatment for cancer and other illnesses. Ferroptosis, in contrast to apoptosis and necrosis, is distinguished by oxidative stress, disruption of lipid metabolism, and iron overload, providing a new way to target cancers that are resistant to treatment. The molecular processes behind ferroptosis are examined in this article, with particular attention paid to important inducers and inhibitors, including both natural and artificial substances. It also explores the possibility for synergy between ferroptosis inducers and traditional treatments like immunotherapy and chemotherapy, emphasizing their ability to boost therapeutic efficacy and go past resistance. Notwithstanding these encouraging advancements, problems with medication specificity, off-target effects, and tumour heterogeneity still exist, highlighting the need for creative fixes including patient classification based on biomarkers and sophisticated drug delivery methods. The importance of clinical trials in converting preclinical results into successful medicines is also emphasized in this article. All things considered, ferroptosis is a revolutionary new area in personalized medicine that might change cancer treatment and other fields.

KEYWORDS: Ferroptosis, Iron-dependent lipid peroxidation, Controlled cell death, Cancer treatment, Oxidative stress, Lipid metabolism.

1. INTRODUCTION

One of the main causes of mortality globally, cancer is a complex illness. A particular genetic background, long-term exposure to different environmental stressors, and an unsuitable diet are some of the contributing variables. All of the above risk factors contribute to the development of carcinogenesis by causing the accumulation of genetic alterations or mutations in certain crucial proteins in cells. A sizable section of the global population is still afflicted by disease. According to the American Cancer Society, 609,360 individuals will have lost their lives to cancer in 2022, and 1.9 million new instances of cancer will have been identified in the US.[1] The main difficulty in treating cancer is related to one of its main characteristics, namely its complex genetic background and its ability to modify it, which leads to the circumvention of traditional pharmacological treatments. This phenomenon often arises as a consequence of monotherapy, which causes the selection of random DNA mutations responsible for drug resistance.[2] Another limitation of standard chemotherapy for cancer is the occurrence of serious side effects that often limit the ability to treat this disease. These include cardiotoxicity,[3] hepatotoxicity,[4] nephrotoxicity[5] and ototoxicity.[6]

Research on cancer has increased our understanding of its molecular causes, which has made it possible to find new targets and create a vast array of treatment drugs. Nevertheless, these compounds typically fall short of two crucial requirements: i) they do not arrive at the target location in sufficient amounts, and ii) they are insufficiently potent in the tumour microenvironment. Because of these factors, even tumours that are more susceptible to chemotherapeutic drugs may experience treatment failure.[7]

Different from apoptosis, necrosis, and autophagy in terms of morphology, biochemistry, and genetics is ferroptosis, a type of cell death. Dixon identified and

discovered ferroptosis in 2012.[8] Lethal lipids and reactive oxygen species (ROS) build up in overwhelming amounts, and this accumulation is dependent on iron.[9] The mitochondria appear smaller, have a higher density of mitochondrial membranes, and have fewer or no mitochondrial cristae in ferroptotic cells. When iron chelation decreases intracellular iron levels, stops reactive radical species such radical hydroxyl from forming, and shields cells from death, the term "ferroptosis" was born.[8] Ferroptosis is a tightly controlled necrotic kind of PD that is distinct from other cell death programs such as apoptosis, anoikis, autophagy, and regulated necrosis (necroptosis, pyroptosis) at the cellular and molecular level.[10] Ferroptosis can be seen morphologically in mitochondria, which show symptoms of shrinkage, increased membrane density, and loss of well-defined mitochondrial cristae. Furthermore, it is common to find big membrane blebs.[11] The iron-dependent peroxidation of membrane lipids is a crucial factor in ferroptotic cell death.[12-15] Ferroptosis is characterized by severe phospholipid peroxidation, while other cell death mechanisms may involve mild membrane peroxidation.

Ferroptosis has a significant impact on cancer treatment. Ferroptosis, a newly discovered disorder that controls cell death, is a unique technique for eliminating cancer cells. The signalling pathways involved in ferroptosis have been compiled in this review, with an emphasis on the manner in which ferroptosis-associated medications work against cancer cells to provide a basis for cancer therapy.

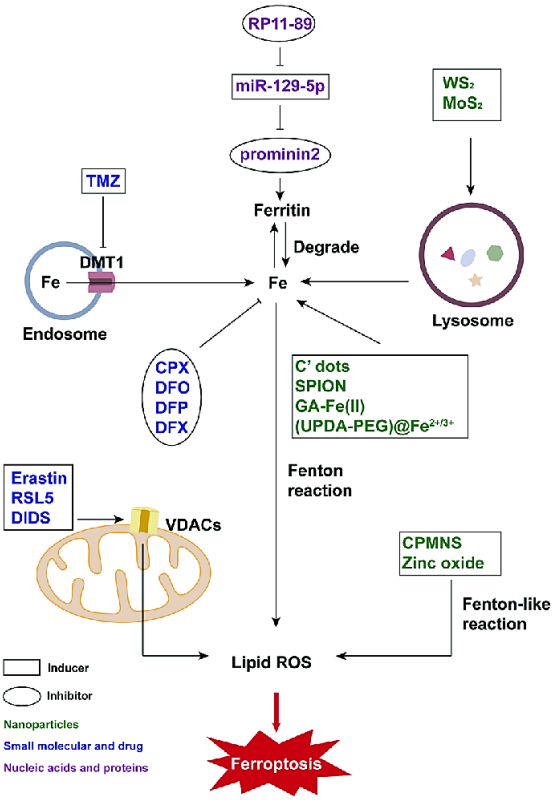

Figure 1: Ferroptosis regulators associated with iron metabolism.[16]

1.1 Mechanism of Ferroptosis

Definition: To preserve biological equilibrium and protect the body from harmful substances, a variety of human cell types self-destruct. The removal of abnormal cells is one of the many biological processes that depend on this process, known as controlled cell death (RCD). As a result, in recent years, RCD pathways—represented by apoptosis—have gained significance as a target for the creation of cancer drugs. However, many research has focused on alternate cancer cell death pathways, such as ferroptosis, because tumour cells exhibit avoidance of apoptosis, which results in resistance to therapy and return.

Ferroptosis's mechanistic understanding has advanced rapidly in recent years. Phospholipid hydroperoxides (PLOOHs), a type of lipid-based reactive oxygen species (ROS), have been identified as the executioners of ferroptosis since the system xc —GSH–GPX4 pathway was first found to play a role in suppressing ferroptosis. Ferroptosis surveillance mechanisms that are not dependent on GPX4 have been discovered more recently. In the context of ferroptosis, the mechanisms of PLOOH synthesis, namely the synthesis and activation of polyunsaturated fatty acids (PUFAs), the precursor of PLOOHs, have also been thoroughly studied. Crucially, ferroptosis and metabolic pathways are intimately related, and all of these findings agree on cellular metabolism.

1.2 Lipid peroxidation & Iron dependency

1.2.1 Lipid peroxidation

Lipid metabolism is closely associated with the process of ferroptosis. The accumulation of lipid peroxide could directly damage cellular and organelle membrane, initiating ferroptotic cell death. Polyunsaturated fatty acids (PUFAs) serve as the main substrates of lipid peroxidation during ferroptosis.[17] Thus, the extent of lipid peroxidation and the process of ferroptosis in cells largely depend on the content and localization of PUFAs. According to some reports, PUFA-phosphatidylethanolamines (PEs) esterified with arachidonoyl (AA) and adrenoyl (AdA) acyl chains are the key phospholipids in triggering ferroptosis.[18,19] The free AA/AdA could bind to coenzyme A (CoA) to form AA/AdA-CoA under the action of Acyl-CoA synthetase long-chain family member 4 (ACSL4), facilitating their esterification into phospholipids. Subsequently, lysophosphatidylcholine acyltransferase-3 (LPCAT3) catalyzes AA/AdA-CoA esterified into PEs and then the formed AA/AdA-Pes would be oxidized into lipid hydroperoxides by lipoxygenase (LOX), inducing ferroptosis.[19] Therefore, ACSL4 and LPCAT3, two enzymes involved in the biosynthesis and remodelling of PUFA-PEs in cellular membranes, are critical determinants of ferroptosis sensitivity. Genetic disruption of ACSL4 and LPCAT3 depletes the substrates for lipid peroxidation and decreases ferroptosis sensitivity.[19-21] It is reported that cells treated with arachidonic acid or other PUFA are sensitized to ferroptosis.[18] Peroxidation of n-3 and n-6 PUFA exerted selective cytotoxic effects in acidic cancer cells, leading to ferroptosis mediated antitumour effects.[22] In addition, LOXs also contribute to ferroptosis. The suppression of LOX by ferroptosis inhibitors, including vitamin E, zileuton and baicalein, can relieve ferroptosis.[23-25] However, some LOXs are essential for normal embryonic development in vertebrates. Knockdown of 12S-LOX in zebrafish could severely impair embryonic phenotype, characterized by abnormal brain, eyes, tails as well as yolk sac and pericardial oedema.[26] It is suggested that lipid metabolism is required for both ferroptosis and normal physiological function. Abnormal lipid metabolism could be a crucial trigger for ferroptosis.

1.2.2 Glutathione Peroxidase 4 (GPX4)

The selenoprotein GPX4 reduces and thereby detoxifies phospholipid hydroperoxides to the corresponding alcohols. Deletion or selective inhibition of GPX4, for example, by the tetrahydro-β-carboline RSL3L,[24] elevates lipid hydroperoxide levels and induces ferroptotic cell death.[26] GPX4 activity essentially depends on the supply of the cosubstrate GSH and therefore relies on GSH biosynthesis and regeneration as well as the cellular import of cystine via the stine/glutamate antiporter system Xc.[28] The antiporter

1. Consists of two subunits, SLC7A11 (xCT) and SLC3A2 (CD98hc or 4F2hc) that are linked via a disulfide bridge,
2. Regulates the cellular redox status, and
3. Counteracts ferroptosis.70 SLC7A11, which is unlike SLC3A2 not shared by other transporters of the heteromeric amino acid transporter family, mediates substrate specificity.
4. After cellular uptake, cystine is reduced to cysteine and subsequently transferred to GSH biosynthesis.

1.2.3 Iron dependency

Iron is a redox-active metal. Excessive iron contributes to the execution of ferroptosis through inducing the production of ROS by Fenton chain reaction. Thus, the sensitivity of ferroptosis is closely associated with iron homeostasis including iron uptake, export, storage and turnover. Iron homeostasis is a complex process, which relies on coordination of multiple genes such as IREB2 (iron responsive element binding protein 2), FTH1 (ferritin heavy chain 1), FTL (ferritin light chain), TF (transferrin), TFR1 (transferring receptor 1), FPN (ferropotein) and DMT1 (divalent metal-ion transporter-1). These genes encoded proteins could affect ferroptosis trigger via regulating intracellular iron. A recent study found that Tf and TfR1, mainly responsible for intestinal iron absorption, play the critical role in ferroptotic cell death.[29,30] Elevated plasma level of TfR1 increased the amount of intracellular iron, which might promote ferroptosis, e.g., leading to auditory cortex neurodegeneration.[31] The redundant intracellular iron is stored in ferritin which is composed of FTL and FTH1. RSL3-sensitive cells transformed with oncogenic RAS significantly could increase cellular iron level via increasing TfR1 and decreasing FTL and FTH1 mRNA expression.[29] The selective cargo receptor-nuclear receptor coactivator 4 (NCOA4)-regulated degradation of ferritin (referred to as ferritinophagy) influences the availability of labile iron and stimulates erastin-induced ferroptosis.[32-34] The bromodomain protein BRD4 inhibitor (+)-JQ1 could induce ferroptosis via ferritinophagy and regulate ferroptosis-related genes in cancer cells.[35] IREB2 is a master regulator of iron metabolism. Silencing of IREB2 by shRNA inhibits the sensitivity to erastin-induced ferroptosis in HT1080 cells.[36] Based on these findings, the cellular iron metabolism is indispensable for the induction of ferroptosis. Strategy targeting iron metabolism genes might be a promising method to treat the cancers which are drug-resistant or alleviate ferroptosis-induced diseases.

1.2.4 ROS Generation

ROS, a byproduct of aerobic metabolism, includes superoxide anion (O2 •–), hydroxyl radicals (•OH), hydrogen peroxide (H2O2) and singlet oxygen (1O2). The main cellular sources of ROS are mitochondrial metabolism and NADPH oxidase (NOX) at the cell membrane (Fig. 2). O2•– is generated by the electron transport chain on the inner membrane of the mitochondria, and its production rate depends on the mitochondrial inner transmembrane potential. In the presence of mitochondrial superoxide dismutase (SOD), O2 •– is converted into H2O2, which then diffuses from

mitochondria into the cytosol. At high iron concentrations favouring the Fenton reaction, H2O2 forms highly reactive O2 •– radicals. Catalase is responsible for converting H2O2 into water and oxygen. Mitochondrial ROS is important not only for apoptosis induction, but also for ferroptosis induction,[37–39] although the molecular switches that determine the bifurcation between these two different types of cell death remain elusive. A major regulator of ATP homeostasis, AMP-activated protein kinase (AMPK), plays a dual role in ferroptosis depending on its substrate. AMPK-mediated BECN1 phosphorylation promotes ferroptosis through the inhibition of SLC7A11 activity or the induction of autophagy[40,41] (Fig. 4a), whereas AMPK-mediated ACACA phosphorylation inhibits ferroptosis through the inhibition of fatty acid biosynthesis, 21 indicating that energy status may affect lipid biosynthesis and peroxidation during ferroptosis.

1.2.5 Ferroptosis in Cancer Biology

A major hallmark of cancer is successful evasion of regulated forms of cell death. Ferroptosis is a recently discovered type of regulated necrosis which, unlike apoptosis or necroptosis, is independent of caspase activity and receptor-interacting protein 1 (RIPK1) kinase activity. Instead, ferroptotic cells die following iron-dependent lipid peroxidation, a process which is antagonised by glutathione peroxidase 4 (GPX4) and ferroptosis suppressor protein 1 (FSP1). Importantly, tumour cells escaping other forms of cell death have been suggested to maintain or acquire sensitivity to ferroptosis. Therefore, therapeutic exploitation of ferroptosis in cancer has received increasing attention. Here, we systematically review current literature on ferroptosis signalling, cross-signalling to cellular metabolism in cancer and a potential role for ferroptosis in tumour suppression and tumour immunology.

Cell death is essential for normal development, homeostasis, and prevention of hyper-proliferative diseases like cancer. Despite success in clinical cancer treatments, resistance to existing chemotherapeutic drugs owing to genetic changes remains a problem.[42] Ferroptosis is associated with a variety of physiological and pathological processes and diseases, especially the treatment of multiple types of cancers. Numerous studies have confirmed that ferroptosis plays a key role in killing tumour cells and inhibiting tumour growth. Ferroptosis was identified as the cause for the death of several types of tumourigenic cells like non-small cell lung cancer,[43] breast cancer,[44] leukemia,[45] pancreatic cancer,[46] and hepatocellular carcinoma,[47] Consequently, ferroptosis induction may be a novel therapeutic strategy for cancer treatment.

1.2.6 Role of Ferroptosis in Tumer Microenvironment and Metabolic Reprogramming

The TME is a multifaceted ecosystem composed of tumour cells, immune cells, stroma cells, and other cells. These components not only coexist but also engage in intricate interactions that significantly influence tumour growth and progression.[49,50] Ferroptosis and the TME are connected in complex ways. On one hand, ferroptosis in cancer cells might instigate or modulate immune responses in the TME. On the other hand, the susceptibility of immune cells in the TME to ferroptosis varies significantly, and different types of immune cells can either enhance or inhibit ferroptosis in cancer cells.

Metabolic reprogramming, a hallmark of cancer, supports unrestricted proliferation, division, and metastasis of tumour cells by rewiring many metabolic pathways, such as glucose, amino acids, and lipids.[51] Previously excellent reviews have also illustrated that metabolic rewiring promotes tumorigeneses, progression, metastasis, and treatment resistance in gastrointestinal cancers.[52,53] The metabolic pattern of tumour cells is complex, with obvious heterogeneity, and different metabolic adaptation phenotypes appear owing to changes in the external environment. For example, Metastasis associated in colon cancer 1 (MACC1) is significantly upregulated to facilitate the Warburg effect and ensure gastric cancer growth in glucose deprivation-induced metabolic stress.[54] Under nutrient deprived conditions, hepatic cancer cells activate the serine biosynthesis pathway to promote cancer progression by upregulating oncogene cMyc.[55] In addition, this complex and variable metabolic pattern also exists in immune cells, which determines their differentiation and function.[56] For T-cell subsets, effector T cells prefer the glycolytic pathway for effect killing function,[56] whereas other T cells (naive, Treg, memory) usually use fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) pathways to maintain their survival.[58] Moreover, neutrophils, natural killer (NK) cells, B cells, M1 macrophages, and active dendritic cells (DCs) use the glycolytic pathway as energy supply, whereas M2 macrophages and resting DCs rely on the OXPHOS pathway.[59–62] Both tumour and immune cells need to obtain sufficient energy to survive or function through metabolic rewiring, especially glycolysis, implying that competition for nutrients between tumour and immune cells promotes immunosuppressive phenotypes.

1.2.7 Pharmacological Modulation of Ferroptosis

Table 1. Ferroptosis inducer representatives—chemical structures with the main mode of action 1 and predicted lipophilicity coefficient and potential for crossing the blood-to-brain barrier (BBB) by the program ADMET Predictor™.[63]

Here's a table summarizing non-natural inducers of ferroptosis, their mechanisms of action, and potential applications:

Table 1

Inducer	Type/Category	Mechanism of Action	Potential Applications
Erastin	Synthetic small molecule	Inhibits system Xc^-, depletes intracellular glutathione (GSH), promotes lipid peroxidation	Cancer therapy
RSL3 (RAS-selective lethal 3)	Synthetic compound	Directly inhibits GPX4, increases lipid ROS	Cancer treatment research
FIN56	Synthetic molecule	Depletes GPX4 protein levels, induces lipid peroxidation	Anticancer research
Sulfasalazine	FDA-approved drug (anti-inflammatory)	Inhibits system Xc^-, disrupts cystine uptake, depletes GSH	Potential cancer therapy, neurodegeneration studies
Ferrostatin-1 (Partial agonist)	Synthetic small molecule	Promotes lipid ROS indirectly	Research tool in ferroptosis pathways
SIR (Sorafenib)	Chemotherapy drug	Inhibits system Xc^-, promotes iron-dependent oxidative stress	Liver and other cancers
Buthionine Sulfoximine (BSO)	Chemical inhibitor	Inhibits glutathione biosynthesis, increases oxidative stress	Experimental anticancer approaches
Cisplatin	Chemotherapeutic agent	Increases ROS generation, induces lipid peroxidation	Broad-spectrum anticancer agent
Doxorubicin	Chemotherapeutic drug	Promotes ROS generation, enhances iron-catalyzed reactions	Chemotherapy for solid tumours
Arsenic Trioxide (ATO)	Chemotherapeutic agent	Increases ROS, disrupts redox balance	Leukemia therapy
Diethyl Maleate (DEM)	Chemical compound	Depletes glutathione, induces ferroptosis	Research tool for oxidative stress

Here's a table summarizing natural inducers of ferroptosis, their sources, and mechanisms of action:

Table 2

Natural Inducer	Source	Mechanism of Action	Potential Applications
Curcumin	Turmeric (Curcuma longa)	Increases lipid peroxidation, inhibits glutathione peroxidase 4 (GPX4)	Cancer therapy, anti-inflammatory uses
Quercetin	Fruits, vegetables, grains	Promotes ROS generation, inhibits ferroptosis inhibitors	Neuroprotection, anticancer effects
Resveratrol	Grapes, red wine	Enhances lipid peroxidation and iron-dependent cell death	Cardiovascular health, cancer therapy
Artemisinin	Sweet wormwood (Artemisia annua)	Produces reactive oxygen species (ROS), chelates iron	Malaria treatment, cancer applications
Celastrol	Thunder god vine (Tripterygium wilfordii)	Inhibits GPX4 and induces oxidative stress	Cancer and autoimmune diseases
Epigallocatechin Gallate (EGCG)	Green tea	Increases ROS, inhibits ferroptosis inhibitors	Anticancer, antioxidant therapy
Berberine	Berberis species	Modulates iron metabolism, induces lipid peroxidation	Antimicrobial, anticancer effects
Piperlongumine	Long pepper (Piper longum)	Promotes ROS accumulation, inhibits antioxidant systems	Cancer therapy
Baicalein	Scutellaria baicalensis	Modulates lipid peroxidation and GPX4 activity	Neurodegenerative disorders, cancer
Omega-3 Fatty Acids	Fish oil, flaxseed	Promotes lipid peroxidation, increases cell membrane instability	Cardiovascular and neuroprotective uses
Selenium Compounds	Nuts, seafood	Modulates antioxidant enzyme activity, promotes ROS generation	Antioxidant and anticancer effects

Table 2. Ferroptosis inhibitor representatives—chemical structures with the main mode of action [1] and predicted lipophilicity coefficient and potential for crossing the BBB.

Here's a table summarizing non-natural inhibitors of ferroptosis, their mechanisms of action, and potential applications:

Table 3.

Inhibitor	Type/Category	Mechanism of Action	Potential Applications
Ferrostatin-1 (Fer-1)	Synthetic small molecule	Scavenges lipid ROS, prevents lipid peroxidation	Neuroprotection, cancer therapy
Liproxstatin-1 (Lip-1)	Synthetic small molecule	Inhibits lipid peroxidation, protects against GPX4 inactivation	Neurodegenerative disease treatment
Deferoxamine (DFO)	Iron chelator	Binds free iron, reduces iron-dependent ROS generation	Neuroprotection, iron-overload therapy
Vitamin K analogs	Synthetic derivatives	Functions as radical scavengers, suppresses lipid peroxidation	Cancer therapy, cardiovascular protection
Trolox	Vitamin E analog	Antioxidant activity, scavenges lipid radicals	Antioxidant therapy, neuroprotection
α-Tocopheryl Succinate	Synthetic derivative of Vitamin E	Prevents lipid peroxidation, enhances cellular antioxidant defenses	Neurodegenerative disorders
Glutathione Ethyl Ester	Synthetic GSH precursor	Enhances intracellular glutathione levels, mitigates oxidative damage	Antioxidant research, neuroprotection
Ebselen	GPX mimic, antioxidant	Mimics GPX4 activity, reduces lipid peroxidation	Neuroprotection, inflammation control
Sodium Selenite	Inorganic selenium compound	Restores GPX4 activity, protects against oxidative damage	Antioxidant therapy, cancer research
Butylated Hydroxytoluene (BHT)	Synthetic antioxidant	Scavenges free radicals, prevents oxidative damage	Food preservation, experimental research
U73122	Phospholipase C inhibitor	Reduces lipid ROS generation, inhibits ferroptosis indirectly	Research tool in lipid peroxidation
ML162 (GPX4 inhibitor counteraction)	Synthetic molecule	Binds and stabilizes GPX4 function	Anticancer research
PD146176	Synthetic antioxidant	Scavenges lipid radicals, inhibits ferroptosis	Neuroprotective applications

Here's a table summarizing natural inhibitors of ferroptosis, their sources, mechanisms of action, and potential applications:

Table 4.

Natural Inhibitor	Source	Mechanism of Action	Potential Applications
Vitamin E (α-Tocopherol)	Nuts, seeds, vegetable oils	Scavenges lipid peroxyl radicals, inhibits lipid peroxidation	Neuroprotection, cardiovascular health
Polyphenols	Fruits, vegetables, tea	Reduces reactive oxygen species (ROS), enhances antioxidant defenses	Cancer prevention, anti-aging
N-Acetylcysteine (NAC)	Supplementation, dietary sulfur compounds	Increases glutathione levels, inhibits ferroptosis-related ROS	Neurodegenerative disease treatment
Flavonoids	Fruits, vegetables, herbs	Neutralizes ROS, protects against oxidative damage	Anti-inflammatory, cancer prevention
Selenium	Brazil nuts, seafood	Enhances GPX4 activity, reduces oxidative stress	Antioxidant and anti-inflammatory roles
Glutathione (GSH)	Synthesized in the body, dietary precursors (e.g., cysteine)	Direct inhibition of lipid peroxidation, maintains redox balance	Cancer therapy, detoxification
Coenzyme Q10 (Ubiquinone)	Meat, fish, whole grains	Functions as a lipid antioxidant, prevents lipid peroxidation	Mitochondrial protection, anti-aging
Ferulic Acid	Rice bran, whole grains	Suppresses oxidative stress, enhances antioxidant enzyme activities	Skin protection, anti-inflammatory uses
Ascorbic Acid (Vitamin C)	Citrus fruits, vegetables	Acts as an antioxidant, scavenges free radicals	Immune support, skin health

Silymarin	Milk thistle (Silybum marianum)	Inhibits lipid peroxidation, reduces ROS	Liver protection, antioxidant therapy
Astaxanthin	Microalgae, seafood (e.g., salmon, shrimp)	Prevents lipid peroxidation, reduces mitochondrial oxidative damage	Anti-inflammatory, neuroprotective uses

1.3 Combination Therapy Approach

Ferroptosis in Synergy with Radiotherapy

Head and neck squamous cell carcinoma (HNSCC) is a highly aggressive, heterogeneous tumour usually caused by alcohol and tobacco consumption, making it one of the most common malignancies worldwide. Despite the fact that various therapeutic approaches such as surgery, radiation therapy (RT), chemotherapy (CT) and targeted therapy have been widely used for HNSCC in recent years, its recurrence rate and mortality rate remain high. RT is the standard treatment choice for HNSCC, which induces reactive oxygen species production and causes oxidative stress, ultimately leading to tumour cell death. CT is a widely recognized form of cancer treatment that treats a variety of cancers by eliminating cancer cells and preventing them from reproducing. Immune checkpoint inhibitor and epidermal growth factor receptor are important in the treatment of recurrent or metastatic HNSCC. Iron death, a type of cell death regulated by peroxidative damage to phospholipids containing polyunsaturated fatty acids in cell membranes, has been found to be a relevant death response triggered by tumour RT in recent years. In the present review, an overview of the current knowledge on RT and combination therapy and iron death in HNSCC was provided, the mechanisms by which RT induces iron death in tumour cells were summarized, and therapeutic strategies to target iron death in HNSCC were explored.[64]

1.3.1 Ferroptosis in Synergy with Chemotherapy

The combination of ferroptosis inducers with chemotherapy offers a novel and synergistic approach to tackling cancer, particularly in tumours that have developed resistance to conventional treatments. By inducing ferroptosis—a unique form of cell death characterized by iron-dependent lipid peroxidation—alongside traditional chemotherapeutic agents, this strategy targets cancer cells through complementary mechanisms. Ferroptosis inducers such as Erastin disrupt cellular redox balance by depleting glutathione and impairing antioxidant defences, making cancer cells more vulnerable to oxidative stress. When paired with chemotherapy drugs like Doxorubicin, which generates reactive oxygen species and causes DNA damage, the combined stress on cellular systems overwhelms cancer cells, leading to enhanced cytotoxicity. This dual approach not only amplifies therapeutic efficacy but also exploits cancer-specific metabolic vulnerabilities, reducing the likelihood of normal cell damage. With proper optimization and patient-specific tailoring, this emerging strategy has the potential to redefine cancer therapy by offering a multi-pronged attack on malignancies.

1.3.2 Ferroptosis in Synergy with Immunotherapy and Role of Ferroptosis in Overcoming Drug Resistance

The hallmark of tumourigenesis is the successful circumvention of cell death regulation for achieving unlimited replication and immortality. Ferroptosis is a newly identified type of cell death dependent on lipid peroxidation which differs from classical programmed cell death in terms of morphology, physiology and biochemistry. The broad spectrum of injury and tumour tolerance are the main reasons for radiotherapy and chemotherapy failure. The effective rate of tumour immunotherapy as a new treatment method is less than 30%. Ferroptosis can be seen in radiotherapy, chemotherapy, and tumour immunotherapy; therefore, ferroptosis activation may be a potential strategy to overcome the drug resistance mechanism of traditional cancer treatments. In this review, the characteristics and causes of cell death by lipid peroxidation in ferroptosis are briefly described. In addition, the three metabolic regulations of ferroptosis and its crosstalk with classical signalling pathways are summarized. Collectively, these findings suggest the vital role of ferroptosis in immunotherapy based on the interaction of ferroptosis with tumour immunotherapy, chemotherapy and radiotherapy, thus, indicating the remarkable potential of ferroptosis in cancer treatment.[65]

CONCLUSION

Ferroptosis, as a distinct and regulated form of cell death, has emerged as a promising therapeutic target in the treatment of cancer and other diseases. The interplay between its inducers and inhibitors highlights the potential for precise modulation of this pathway, enabling tailored strategies to exploit ferroptosis in cancer cells while sparing healthy tissues. Combining ferroptosis-inducing agents with conventional therapies like chemotherapy, immunotherapy, or radiation amplifies therapeutic efficacy by targeting cancer's vulnerabilities, such as oxidative stress and metabolic dependencies.

However, the application of ferroptosis in clinical settings faces several challenges, including drug specificity, off-target effects, tumour heterogeneity, and resistance mechanisms. The development of reliable biomarkers to predict ferroptosis sensitivity and the design of innovative drug delivery systems are pivotal for overcoming these hurdles. Additionally, rigorous clinical trials are necessary to evaluate the safety, efficacy, and optimal protocols for combination therapies.

As research progresses, ferroptosis-based treatments hold immense potential to revolutionize cancer therapy and other fields of medicine. By addressing existing challenges and refining therapeutic strategies, ferroptosis may become a cornerstone of personalized medicine, offering hope for more effective and targeted treatments.

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64. The role of ferroptosis in radiotherapy and combination therapy for head and neck squamous cell carcinoma (Review) YU FENG1,2, XIULEI LI3, BINGWU YANG4, MAOCAI LI1, YONGYA DU5, JING WANG1, SIYU LIU1,6, LILI GONG1, LIANQING LI1 and LEI GAO7.
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