Cancer Treatment and Research Communications 43 (2025) 100913

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Ferroptosis as the new approach to cancer therapy

Oluwafemi Adeleke Ojo [a,e,*], Susan Grant [b], Pearl Ifunanya Nwafor-Ezeh [a], Tobiloba Christiana Maduakolam-Aniobi [b], Tolulope Isaiah Akinborode [c], Emmanuel Henry Ezenabor [a], Adebola Busola Ojo [d]

[a] Phytomedicine, Molecular Toxicology, and Computational Biochemistry Research Laboratory (PMTCB-RL), Department of Biochemistry, Bowen University, Iwo, Nigeria
[b] Department of Biochemistry, Landmark University, Omu-Aran, Nigeria
[c] Department of Crop Production and Soil Science, Ladoke Akintola University, Ogbomosho, Nigeria
[d] Department of Environmental Management and Toxicology, University of Ilesa, Ilesa, Nigeria
[e] Research Centre for Integrative Physiology and Pharmacology and Turku Center for Disease Modeling, Institute of Biomedicine, University of Turku, Turku, Finland

ARTICLE INFO

Keywords:
Ferroptosis
Apoptosis
Cancer
Targeted therapy

ABSTRACT

Cancer is characterized by unregulated cell proliferation, evasion of apoptosis, and a propensity for metastasis, making it a leading cause of morbidity and mortality globally. Major challenges in cancer treatment include drug resistance and tumor heterogeneity, which hinder the clinical efficacy of existing therapies. To enhance treatment outcomes, it is essential to integrate emerging biological insights and technological advancements with conventional therapeutic strategies. Recent research has identified various forms of cell death, which can be classified as either regulated or unregulated. Regulated cell death involves specific biochemical and signaling pathways, while unregulated cell death occurs passively and uncontrollably. Apoptosis, the most extensively studied form of regulated cell death, is primarily mediated by the activation of caspase proteases. Nevertheless, the resistance of many tumors to apoptotic pathways has shifted focus towards non-apoptotic forms of cell death, such as ferroptosis. Ferroptosis is an iron-dependent form of regulated necrosis characterized by extensive membrane damage resulting from lipid peroxidation. Numerous preclinical studies have demonstrated that inducing ferroptosis can significantly reduce tumor growth across a variety of cancer types. For instance, in a study involving breast cancer models, the use of ferroptosis inducers such as erastin and RSL3 led to a marked decrease in tumor volume and weight.

This review aims to explore the potential of ferroptosis as a novel therapeutic strategy in cancer treatment.

1. Introduction

Cancer encompasses a diverse group of diseases characterized by uncontrolled cell growth and proliferation. The term "cancer," derived from the Greek word "karkinos" coined by Hippocrates, the "Father of Medicine," has evolved to describe over 277 distinct types of malignancies [1,2]. Historically, the term was translated into Latin by the Roman surgeon Celsus, linking it to the brachyuran crab, a metaphor for the disease's invasive nature. Globally, cancer is the second leading cause of mortality, with 18.1 million new cases reported in 2018, the highest incidence occurring in Asia (Fig. 1) [3].

Cancer can be conceptualized as a multifaceted illness, characterized by complex tempo-spatial alterations in cell physiology that culminate in the formation of malignant tumors [4]. The pathological hallmark of cancer is neoplasia, or abnormal cell proliferation, which drives tumor invasion into surrounding tissues and distant organs, contributing significantly to patient morbidity and mortality. The transformation of normal cells into malignant cancer cells has been a focal point of biomedical research for decades [5].

In recent years, significant advances have been made in identifying therapeutic targets by elucidating the distinctions between cancer cells and their healthy counterparts. This research has led to the identification of approximately 300 genes implicated in human cancer, as cataloged in the Cancer Gene Census [6,7]. These genes predominantly play critical roles in signal transduction, cell cycle regulation, apoptosis, angiogenesis, and cellular infiltration [8]. Targeting ferroptosis in cancer stems from its unique iron-dependent, lipid peroxidation-driven cell death mechanism, offering an alternative pathway to overcome

* Corresponding author.
E-mail address: oluwafemiadeleke08@gmail.com (O.A. Ojo).

https://doi.org/10.1016/j.ctarc.2025.100913

Available online 25 March 2025

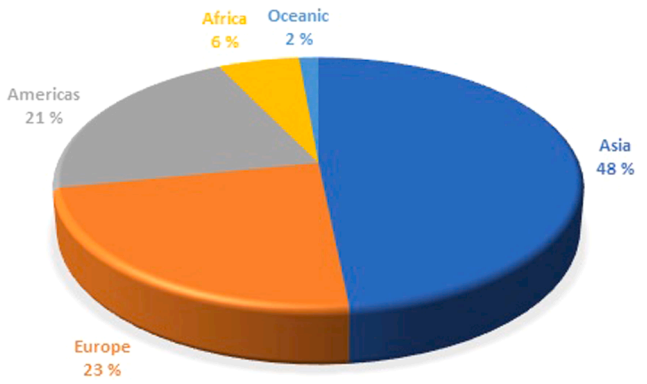

Fig. 1. Global cancer Incidence [3].

resistance to apoptosis, a common hallmark of cancer. Many tumors exhibit dysregulated iron metabolism or altered lipid composition, rendering them potentially susceptible to ferroptosis induction [9].

Furthermore, the ability of ferroptosis to elicit immunogenic cell death (ICD) presents an opportunity to synergize with immunotherapy, enhancing anti-tumor immune responses. This distinct mechanism, therefore, offers a promising avenue for novel cancer therapies. In addition, understanding the genetic and molecular underpinnings of cancer is essential for developing targeted therapies and improving patient outcomes. Ongoing research continues to uncover the complexities of cancer biology, aiming to translate these findings into effective clinical interventions.

1.1. Tumors

A tumor arises from the rapid division of cells, resulting in abnormal tissue masses or lumps [10]. Tumors can vary significantly in size, from small nodules to large masses, and can develop in virtually any part of the body.

Types of Tumors

Tumors are classified into three main categories:

1. **Benign Tumors**: These tumors are non-cancerous and do not exhibit malignant behavior. They typically grow slowly, if at all, and rarely recur after surgical removal. Common examples include hemangiomas and fibroids [11].
2. **Premalignant Tumors**: These lesions, such as cervical dysplasia and actinic keratosis, contain cells that have not yet become cancerous but possess the potential to progress to malignancy [11].
3. **Malignant Tumors**: Malignant tumors are cancerous and characterized by uncontrolled cell proliferation and the ability to metastasize to different body regions [11]. Examples include various forms of cancer, germ cell tumors, and blastomas.

1.2. Types of cancer

Cancer manifests in various forms, each with distinct characteristics and implications for treatment:

- **Breast Cancer**: This is one of the most prevalent cancers globally, primarily affecting women, though it can also occur in men [12].
- **Prostate Cancer**: Originating in the prostate gland, this cancer is common among men and varies in aggressiveness [13].
- **Basal Cell Carcinoma**: The most common form of skin cancer, it arises from basal cells in the epidermis. Early detection typically leads to successful treatment [14].
- **Melanoma**: This cancer originates in melanocytes, the pigment-producing cells of the skin [15].
- **Colon Cancer**: Also known as colorectal cancer, it begins in the large intestine and often starts as a polyp that may develop into cancer over time [16].
- **Lung Cancer**: Characterized by uncontrolled growth of abnormal lung cells, lung cancer can metastasize and is categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [17].
- **Leukemia**: This cancer involves the proliferation of abnormal white blood cells, impairing the body's ability to produce healthy blood cells [18].
- **Lymphoma**: Affecting the lymphatic system, lymphoma originates in lymphocytes and can spread to other organs. It is classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [19].

1.3. Causes of cancer

The primary cause of cancer is mutations in a cell's DNA, which can disrupt normal cellular functions and lead to uncontrolled growth [20]. These mutations can occur due to various factors, including age, environmental influences, and lifestyle choices.

Biological factors

Certain biological factors, such as age, sex, and inherited genetic abnormalities, can predispose individuals to cancer. For instance, blood cancers are more prevalent in older adults due to genetic exchanges between chromosomes [21]. The Philadelphia chromosome (Ph1), a biomarker in chronic myeloid leukemia, exemplifies how specific genetic mutations can aid in diagnosis [22].

Environmental factors

Cancer incidence varies geographically, suggesting that environmental exposures play a significant role in cancer development. Immigrants often develop cancer types prevalent in their new countries, indicating that environmental rather than inherited factors are crucial [23,24]. Notable environmental carcinogens include UV radiation and air pollutants [25].

Occupational and risk factors

Exposure to hazardous materials and chemicals in the workplace can lead to direct or indirect cellular damage, resulting in genetic mutations [26]. Such occupational hazards significantly contribute to the development of various cancers.

Lifestyle-related factors

Lifestyle choices significantly impact cancer risk. For example, smoking introduces numerous carcinogenic compounds that are strongly linked to lung cancer [27]. Other lifestyle factors, such as diet, physical activity, and alcohol consumption, also influence cancer risk.

2. Hallmark of cancer

The division, growth, stopping of development, and death of normal cells are all regulated by processes. These normal cells don't divide unless instructed to do so by neighboring cells [28]. Every tissue maintains its appropriate size and shape in compliance with the body's needs thanks to this ongoing cooperation [29]. On the other hand, cancer cells oppose this strategy; they ignore the typical growth-control signals and instead follow their own internal reproductive agenda [4].

They also possess a far more cunning characteristic: they could disperse from their original location, intruding on nearby tissues and building up into masses in other areas of the body. The deviation from this natural defense mechanisms which is very common in most Cancers leads to the development of Tumor.

2.1. Mechanisms of applying targeted therapy

Immune evasion: Both positive and negative effects on the immune system can result from tumors. Tumor cells rapidly undergo mutations that allow them to proliferate without these antigens and evade detection, but antibodies are formed when the immune system initially identifies tumor antigens [30].

Stress response: Hypoxia, or low oxygen and nutrition, stresses tumor cells and increases DNA damage. The body's defensive reaction to stress stabilizes the tumor cell and encourages the tumor's growth [31].

Stromal subversion: Entire bodily tissue is supported and connected by the stroma, an organ that serves both protective and connective functions. The extracellular matrix, which is made up of stromal cells, contains all other cells. Tumor cell signals induce stromal cell mutations via promoting angiogenesis and tumor cell motility, which permit invasion and metastasis [32].

Cytokine factors: In the context of a tumor, immune cells release cytokines, which are proteins that indicate inflammation. As a result of the inflammation that follows, immune cells release substances that encourage angiogenesis, which in turn promotes tumor growth [33].

2.2. Unprogrammed cell death

Unprogrammed cell death, also called accidental cell death or necrosis, happens when cells die without following the controlled procedures of programmed cell death, such as autophagy or apoptosis, instead of dying because of external stimuli or significant damage [34]. Among them are ferroptosis, necroptotic, and necrosis (Table 1).

Necrosis: Necrosis happens when a cell has already experienced significant damage from outside causes like trauma or infection [35]. Light or electron microscopy can be used to identify cell and organelle enlargement or rupture of surface membranes with leakage of intracellular contents, which contributes to the characterization of necrosis (derived from the Greek word "nekros," which means "death") [36]. The Greek term "oncosis" (which means "swelling") is sometimes used by researchers, however "oncotic necrosis" has also been mentioned. When organellar membranes are damaged, enzymes that degrade proteins can break out from lysosomes, enter the cytoplasm, and eventually kill cells [4]. Rapid ATP depletion coupled with metabolic failure results in necrosis, which is most frequently observed in ischemia [34]. Necrosis is characterized by cell swelling along with an uncontrollably large cell membrane rupture that causes the contents of the cell to be expelled [35].

Necroptosis: It is a mediated type of inflammatory cell death [37]. Necrosis is historically associated with unprogrammed cell death brought on by pathogen invasion or damage to the cell itself, as opposed to planned programmed cell death brought on by apoptosis [35]. The discovery of necroptosis demonstrated that necrosis is programmable in cells and that there are other ways for cells to die besides apoptosis [38]. Moreover, necroptosis' immunogenic properties make it a good option for a number of purposes, such as boosting the immune system's response to pathogens. Necroptosis is a documented defense mechanism that causes the cell to commit "cellular suicide" in a caspase-independent way when viral caspase inhibitors are present [39]. Necroptosis is only induced by TNF therapy in the presence of a pan-caspase inhibitor, such as VAD fluoroethyl ketone [40]. It takes a blocked or compromised Caspase for necroptosis to happen. Exposure to each death pathway is regulated (sometimes in opposite ways) by an interacting cluster of regulatory molecules, including FLIP, A20, and cylindromatosis deubiquitinases, as well as the cellular regulators of apoptosis proteins, cIAP1 and cIAP2 [41]

3. Ferroptosis

Dixon and colleagues coined the term ferroptosis to explain the non-apoptotic, iron-dependent mechanism of cell death characterized by intracellular lipid ROS accumulation after Dolma discovered in 2003 that their test compound "Erastin" induced cell death in cancer cells that was distinct from all other forms of cell death [42]. For both plants and animals, iron is a vital micronutrient because it is involved in several metabolic activities, including respiration, photosynthesis, and DNA synthesis. On the other hand, an excess of iron can be harmful to the body through a few ways, including cell death [43].

Uncontrolled lipid peroxidation and the ensuing membrane damage are the causes of ferroptosis, an iron-dependent mechanism of cell death [44]. It is morphologically defined by the presence of smaller-than-normal mitochondria with condensed mitochondrial membrane densities, as well as by the rupture of the outer mitochondrial membrane and the reduction or lack of mitochondrial crista [44]. In certain normal cells as well as malignant cells, it can be induced by novel chemicals or medications (such as artesunate, sorafenib, and sulfasalazine). Renal tubule cells, neurons, fibroblasts, and T cells are a few examples [45]. In terms of anatomy and biochemistry, ferroptosis is an oxidative iron-dependent mechanism that is distinct from necrosis, autophagy, and apoptosis [46].

Ferroptosis may result from internal or external causes. While inhibiting intracellular antioxidant enzyme expression or activity like glutathione peroxidase 4 (GPX4) primarily activates the intrinsic pathway, blocking the expression or activity of these same intracellular antioxidant enzymes primarily stimulates the extrinsic pathway [47]. Ferroptotic cell death can result from a variety of stressors, including radiation, hypoxia, low temperature, and high temperature, in addition to small chemicals and medications. Numerous clinical disorders, such as acute tissue injury, infection, cancer, and neurodegeneration, have been connected to this process. It has to do with mis regulated protein breakdown mechanisms like autophagy and the ubiquitin-proteasome system [48].

3.1. Hallmarks of ferroptosis

3.1.1. Morphological features

In terms of morphology, biochemistry, and genetics, ferroptosis is distinct from apoptosis, necrosis, and autophagy, according to a preliminary study. Many researchers agree that cells going through ferroptosis typically exhibit morphological alterations resembling necrosis [45]. These characteristics include mild chromatin condensation, cytoplasmic swelling (oncosis), loss of plasma membrane integrity, and enlargement of cytoplasmic organelles. Ferroptosis can occasionally be accompanied by increased autophagosomes, as well as the detachment and rounding up of cells. Notably, ferroptosis that starts in one cell has the ability to rapidly propagate to neighboring cells [48].

Ferroptotic cells typically show ultrastructural anomalies related to mitochondria, including swelling or condensation, increased membrane density, absent or diminished crista, and outer membrane rupture [45]. The part played by these organelles in ferroptosis is still up for debate, despite these notable modifications in mitochondrial morphology. In most mammalian cells, mitochondria serve as both the hub of metabolism and a significant generator of reactive oxygen species (ROS)

Table 1
Comparison of cell death mechanisms.

Feature	Apoptosis	Necrosis	Ferroptosis	Pyroptosis	Autophagy
Cell Shrinkage	Yes	No	Yes	No	No
Membrane Rupture	No	Yes	Yes	Yes	No
Inflammatory Response	No	Yes	Yes	Yes	No
Dependency on Iron	No	No	Yes	No	No
Role in Cancer Therapy	Some	None	High	Some	Some

[49]. More recent research indicates that lipid peroxidation and ferroptosis induction are dependent on mitochondria-mediated ROS production, DNA damage, and metabolic reprogramming, in contrast to an earlier study that showed the induction of ferroptosis does not require mitochondria-mediated ROS generation [49].

3.1.2. Biochemical features

Iron buildup and lipid peroxidation are the two primary biochemical features linked to ferroptosis, a ROS-dependent kind of cell death [50].

Iron accumulation: Erasin and RSL3, two traditional ferroptosis activators, enhance intracellular iron buildup while suppressing the antioxidant system [51]. Oxidative damage can be made worse by iron directly producing too many ROS through the Fenton reaction [52]. Moreover, iron may increase the activity of lipoxygenase (ALOX) and EGLN prolyl hydroxylases (often referred to as PHD), the enzymes that maintain oxygen homeostasis and cause lipid peroxidation [48]. Ferroptosis sensitivity is influenced by the interplay between cellular iron regulatory processes at the local and systemic levels. Effective inhibition of ferroptotic cell death can be achieved by targeting genes linked to iron overload or by employing iron-chelating medications (explained subsequently) [48]. The reason why iron is the only metal that may cause ferroptosis is unknown; other metals, like zinc, can also cause a Fenton reaction that produces ROS. According to one idea, iron overload causes specific downstream effectors that aid in ferroptosis to occur once lipid ROS are generated [48].

Lipid peroxidation: Lipid peroxidation, mostly affecting the cell membrane's unsaturated fatty acid content, is a free radical-induced process [53]. Lipid peroxidation produces byproducts called initially lipid hydroperoxides (LOOHs) and later reactive aldehydes, like malondialdehyde (MDA) and 4-hydroxynonenal (4HNE), which rise during ferroptosis [53]. The three distinct forms of fatty acids are saturated fatty acids (no double bond), polyunsaturated fatty acids (PUFAs, >1 double bond), and monounsaturated fatty acids (MUFAs, 1 double bond) [54]. Ferroptosis appears to be primarily dependent on the peroxidation of polyunsaturated fatty acids (PUFAs) in phospholipids by ALOXs, despite the possibility of oxidation of other cell membrane lipids such as cardiolipin, phosphatidylcholine, and phosphatidylethanolamine (PE) [55]. Cardiolipin peroxidation is absent from ferroptosis, even though mitochondria experience significant alterations during this process [48].

3.1.3. Genetic features

One potential biomarker for ferroptosis is the overexpression of specific genes or proteins, such as prostaglandin-endoperoxide synthase 2 (PTGS2/COX2), the main enzyme involved in prostaglandin synthesis [48]. However, during ferroptosis, prostaglandins are not utilized by PTGS2 as a lipid peroxidation substrate. The enzyme Acyl-CoA synthetase long-chain family member 4 (ACSL4), which is connected to fatty acid metabolism, is believed to be a specific biomarker and driver of ferroptosis because of its overexpression, which increases the PUFA content of phospholipids, which makes them susceptible to oxidation processes that result in ferroptosis [56]. But ferroptosis may not necessarily require ACSL4, therefore in certain circumstances, cells with lower levels of ACSL4 may go through ferroptosis.

The activation of genes involved in antioxidant defense (e.g., the glutathione (GSH) system, 8 coenzyme Q10 (CoQ10) system, and nuclear factor, erythroid 2-like 2 (NFE2L2, also known as NRF2) transcription pathway33) and membrane repair (e.g., the endosomal sorting complexes required for transport (ESCRT)-III pathway34) limits ferroptosis-induced membrane damage [57]. Thus, cells "decide" whether to survive or perish in response to ferroptotic stimuli by weighing the relative importance of anti-injury and injury responses.

3.1.4. Immune features

There are two parts to ferroptosis's immunological effects. First, leukocyte subset mortality and subsequent loss of immunological function can result from ferroptosis [48]. For instance, ferroptosis in T cells brought on by lipid peroxidation encourages the growth of parasitic or viral infections. More significantly, and second, ferroptosis controls how the immune system responds to dying cells or their corpses when it affects non-leukocytic cells [58]. By releasing and activating distinct damage-associated molecular pattern (DAMP) signals, various forms of cellular death can trigger distinct immunological and inflammatory reactions [59].

Ferroptosis, in general, is a kind of inflammatory cell death associated with the production, following tissue injury or tumor therapy, of lipid oxidation products (e.g., 4HNE, oxPLs, LTB4, LTC4, LTD4, and PGE2) or DAMPs (e.g., high mobility group box 1 (HMGB1) and DNA) [60]. For example, in aging and chronic disorders, the lipid peroxidation product 4HNE is a pro-inflammatory mediator that activates the nuclear factor-κB (NF-κB) pathway. Ferroptotic cells secrete HMGB1, a classic DAMP linked to several types of cell death. Then, by means of the advanced glycosylation end-product-specific receptor (AGER/RAGE), a pattern-recognition receptor, this DAMP triggers the NF-κB pathway in innate immunity, leading to the inflammation of peripheral macrophages [61]. It might be advantageous to treat inflammatory illnesses by concentrating on DAMP signaling linked to lipid metabolism.

4. Mechanisms of ferroptosis and cancer therapy

4.1. Inducing ferroptosis by suppressing GPX4 in cancer therapy

Ferroptosis, which is characterized by lipid peroxidation, is mostly regulated by GPX4. It inhibits ferroptosis and stops iron-dependent lipid reactive oxygen generation by catalyzing the conversion of R-OOH into R-OH. GPX4 is dependent on iron and reactive oxygen species (ROS) [44]. It is involved in the formation of the system xc−/GSH/GPX4 axis, which inhibits ferroptosis by fighting cellular phospholipid peroxidation [62]. One of the major obstacles preventing targeted anticancer therapy from producing better results in terms of stability and integrity is acquired drug resistance [63].

Remarkably, it has been demonstrated that cancers of the prostate, pancreas, non-small cell lung, and melanoma cells all exhibit a selective ferroptosis dependence that is exacerbated by GPX4 loss of function [64]. Higher clinical stages and selective sensitivity to ferroptosis in cancer cells with a strong mesenchymal state indicate that these cells may be susceptible to GPX4 inhibition [65]. Ionizing radiation (IR) has been found to induce ferroptosis in esophageal adenocarcinoma, breast malignancy, renal carcinoma, and fibrosarcoma in a few investigations [66]. Furthermore, it has been discovered that, in xenograft models, ferroptosis inducers that target GPX4 increase the sensitivity of radiation therapy [66]. When comparing the doxorubicin-treated animals to the naked control mice, the tumor mass made up of gpx4-knocked HCT116 (a human colon cancer cell line) cells was somewhat less [67]. As a result of GPX4′s potency as a ferroptosis inhibitor, tumor therapies are now more drug-resistant, which poses a significant challenge in clinical settings when utilizing novel molecular targets and therapeutic modalities [68].

To verify the involvement of GPX4 in carcinogenesis and test their theory that it may have a regulatory function during tumor growth, Schneider et al. conducted an experiment to inactivate GPX4 in murine embryonic fibroblasts (MEFs) [69]. In vitro inactivation of GPX4 resulted in immediate cell death. Remarkably, altered GPX4+/− generated tumor spheroids and survived in Matrigel. The mice were given subcutaneous implants of the tumor cells. Subsequently, a tumor with a robust vascular phenotype—a decrease in big diameter arteries and an increase in micro vessel density—was collected. It had the same volume and weight as tumors of the wild type. Pharmacologically suppressing 12/15-LOX reversed the phenotype and restored normal vascular morphology. Therefore, it was determined that by controlling 12/15-LOX activity, GPX4 is a crucial regulator of tumor development and vascular maturation.

Downregulating GPX4-induced antioxidation is a common strategy for GPX4-relevant cancer therapy because it is a well-known way to activate ferroptosis. According to studies, most cancer cells are thought to be under high levels of oxidative stress [70]. This suggests that to prevent oxidative damage, it is necessary to increase the ROS-scavenging ability [71]. It was discovered that ferroptosis was suppressed in cells with upregulated GPX4 expression, while it was more responsive in cells with downregulated GPX4 expression. As a ferroptosis inducer, RSL3 directly inhibits GPX4 function, which reduces antioxidant potential in cells and causes ROS to build up, ultimately resulting in ferroptosis [72]. However, DPI7 and DPI10 directly affect glutathione peroxidase, which results in ferroptosis. The amino acid selenocysteine plays a significant role in the GPX4 active group [73].

To inject selenocysteine into GPX4, selenocysteine tRNA is necessary. Mevalonate (MVA) route controls selenocysteine tRNA maturation, which affects GPX4 production. Ferroptosis is therefore regulated. Two of the most crucial elements of the MVA pathway are IPP and COQ10. Reduced selenocysteine tRNA synthesis, decreased GPX4 activity, and ferroptosis are the results of inhibiting the MVA pathway [74].

4.2. Inducing ferroptosis by suppressing system XC

System Xc- is a widely distributed amino acid anti-transporter in phospholipid bilayers. It is a heterodimer that is engaged in a significant antioxidant process in the cell, and it is made up of the SLC7A11 and SLC3A2 subunits [74]. Glutamate and cysteine are moved into and out of cells in a 1:1 ratio by machine Xc-. Cysteine that enters cells is transformed into cysteine, which is then utilized to produce glutathione (GSH) [75]. Under the direction of glutathione peroxidases, GSH reduces reactive oxygen species and nitrogen dioxide (GPXs). By preventing cystine absorption, inhibiting system Xc-activity lowers GSH production [74]. This ultimately results in a decrease in GPX activity, a decrease in the antioxidant capacity of cells, a build-up of lipid reactive oxygen species, oxidative damage, and ferroptosis. By downregulating SLC7A11 expression, P53 can also reduce lipid ROS accumulation, ferroptosis, and the antioxidant ability of cells and interfering with GPX4 action. This leads to a decline in ferroptosis, lipid ROS accumulation, and cell antioxidant capacity [76].

4.3. P53-mediated ferroptosis

Tumor suppressor genes like P53 are crucial in this regard. P53′s involvement in ferroptosis remains unknown, even though age, apoptosis, and cell cycle suppression are all significant contributors in the onset and spread of tumors [77]. Ferroptosis is aided by P53 mutants with aberrant acetylation that have recently been discovered. Fer-1, an inhibitor of ferroptosis, caused a significant reduction in the rate of cell death, and P53 also caused ferroptosis [74]. Further research indicates that P53 can impede system Xc-uptake of cystine by downregulating SLC7A11 expression, which affects GPX4 function and reduces antioxidant capacity, ROS buildup, and ferroptosis [78].

Furthermore, ferroptosis regulation is mediated by the P53-SAT1-ALOX15 pathway. P53′s transcriptional target and rate-limiting enzyme for polyamine catabolism is SAT1. In response to reactive oxygen species, SAT1 activation promotes lipid peroxidation (ROS) and ferroptosis, which is connected to the production of arachidonate lipoxygenase 15. (ALOX-15) [79].

4.4. Ferroptosis pathway

The three classes of regulatory pathways for ferroptosis are represented in the diagram. The p53 regulatory axis, the sulfur transport pathway, the MVA pathway, the glutamine pathway, and the inhibition of system Xc-are all under the direction of the GSH/GPX4 route [80]. Iron metabolism control methods include the p62-Keap1-NRF2 and HSPB1 regulatory pathways, as well as the regulation of the ATG5-ATG7-NCOA4 pathway and IREB2 in relation to ferritin metabolism [72]. The P53-SAT1-ALOX15, ACSL4, LPCAT3, and other lipid metabolism-related pathways that affect ferroptosis and lipid control are examples of the third party. By attaching itself to mitochondria, erythrin induces ferroptosis [81] (Fig. 2).

4.5. Ferroptosis and immunotherapy

The integration of ferroptosis into existing cancer treatment modalities holds significant promise can enhance anti-tumor immune responses by inducing immunogenic cell death (ICD), releasing damage-associated molecular patterns (DAMPs) that activate immune cells. This process enhances the effectiveness of immunotherapy by promoting tumor antigen presentation and T cell activation. Research highlights that combining ferroptosis inducers with immune checkpoint inhibitors can overcome tumor resistance. Studies have shown that immune cells, such as CD8+ T cells, can induce ferroptosis in tumor cells, creating a synergistic anti-tumor effect [82].

4.6. Ferroptosis and radiotherapy

When combined with radiotherapy, ferroptosis can create a synergistic effect. Radiotherapy induces oxidative stress and increases iron availability, both of which sensitize tumor cells to ferroptosis. Therefore, combining radiotherapy with ferroptosis inducers can amplify tumor cell death. Furthermore, the ICD induced by radiotherapy can be potentiated by concurrent ferroptosis, leading to a stronger anti-tumor immune response. This means, the radiation can start the process of cell death, and the ferroptosis can greatly increase the number of cells that are killed [83].

4.7. Ferroptosis and nanotherapy

Nanotherapy offers a platform for targeted delivery of ferroptosis inducers to tumor cells, minimizing off-target effects. Nanoparticles can be engineered to encapsulate and release ferroptosis-inducing agents, minimizing off-target effects and maximizing therapeutic efficacy [84]. Additionally, nanoparticles can be designed to carry multiple therapeutic payloads, enabling the simultaneous delivery of ferroptosis inducers and other anti-cancer drugs, such as immunotherapy drugs, or radiosensitizers. This allows for a very targeted approach to delivering the cell death mechanism, directly to the tumor and reduces toxicity [85].

5. Ferroptosis regulation and its role in physiological conditions

Ferroptosis, a form of regulated cell death driven by iron-dependent lipid peroxidation, is tightly controlled by the balance between pro-ferroptotic (e.g., iron availability, lipid peroxidation) and anti-ferroptotic (e.g., glutathione peroxidase 4 (GPX4), system Xc-)

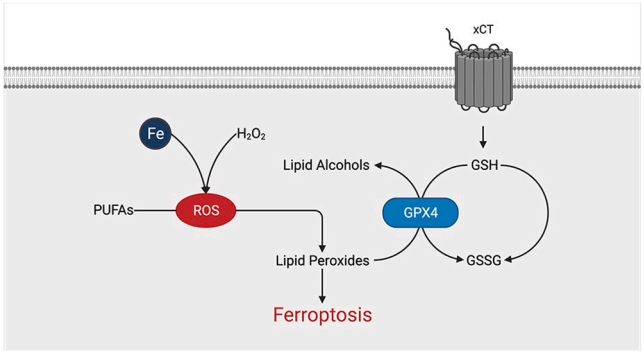

Fig. 2. Basic ferroptosis pathway. Created from biorender.com.

mechanisms. GPX4, a key regulator, detoxifies lipid peroxides, while system Xc- imports cystine, a precursor for glutathione synthesis, thus preventing ferroptosis [48]. Iron homeostasis, regulated by proteins like ferritin and transferrin, also plays a crucial role. Physiologically, ferroptosis contributes to development and tissue homeostasis, while pathologically, it's implicated in neurodegenerative diseases, ischemia-reperfusion injury, and cancer. Recent studies emphasize the crosstalk between ferroptosis and other signaling pathways, including NF-κB, p53, and the Keap1-Nrf2 pathway, which modulate its sensitivity. These interactions are critical for understanding disease progression and therapeutic targeting [86,87].

In various tumors, the role of ferroptosis is complex and context-dependent. Some tumors exhibit increased sensitivity to ferroptosis, making it a promising therapeutic target. For instance, certain cancer types with GPX4 deficiency or increased iron uptake are more vulnerable. Conversely, some tumors develop resistance through upregulation of anti-ferroptotic mechanisms or alterations in lipid metabolism [88]. The interplay between ferroptosis and the tumor microenvironment, including interactions with immune cells and stromal components, further influences its impact. Notably, ferroptosis can induce immunogenic cell death, potentially enhancing anti-tumor immune responses. Recent research has shown that ferroptosis can have a role in drug resistance, and that overcoming that resistance through ferroptosis targeted therapies is a promising area of research [85,61,89].

5.1. Preclinical evidence and translational studies on ferroptosis in cancer therapy

Preclinical evidence strongly supports the efficacy of ferroptosis induction in various cancer models. Studies have demonstrated that ferroptosis inducers can effectively suppress tumor growth in vitro and in vivo, particularly in cancer types resistant to conventional therapies. For example, research has shown that GPX4 inhibitors can induce ferroptosis and inhibit tumor progression in several cancer types, including hepatocellular carcinoma and pancreatic cancer. Additionally, combination therapies, such as ferroptosis inducers with immune checkpoint inhibitors or radiotherapy, have shown synergistic effects in preclinical settings [48,87].

Translational studies are underway to evaluate the safety and efficacy of ferroptosis-targeted therapies in clinical trials. While still in early stages, some clinical trials have been initiated to explore the potential of ferroptosis inducers in cancer patients. These studies aim to determine the optimal dosing, safety profiles, and preliminary efficacy of these agents. Biomarkers, such as GPX4 expression and iron levels, are being investigated to identify patients who may benefit most from ferroptosis-based therapies [90]. The transition from preclinical to clinical application is a critical step in realizing the therapeutic potential of ferroptosis.

6. Morphological and biochemical indications of ferroptosis

6.1. Morphological indications

Cell shrinkage: Unlike apoptosis, which often involves cell fragmentation into apoptotic bodies, ferroptotic cells typically exhibit cell shrinkage and reduced cell volume [91].
Mitochondrial changes: Mitochondria in ferroptotic cells often show specific alterations, such as a reduction in mitochondrial membrane density, smaller and more elongated shapes, and the absence of cristae or damaged cristae [92].
Membrane rupture: Cells undergoing ferroptosis may display plasma membrane damage or rupture, although this is less prominent compared to necrosis [93].

6.2. Biochemical indications

Lipid peroxidation: The build-up of oxidized lipids, especially in polyunsaturated fatty acids, is a hallmark of ferroptosis. This can be measured using specific assays like the detection of malondialdehyde (MDA) or 4-hydroxy-2-nonenal (4-HNE) [55].
Reduced glutathione levels: Ferroptotic cells often exhibit decreased levels of glutathione (GSH), a crucial antioxidant that helps protect against oxidative stress [94].

Increased Iron Levels: Ferroptosis is associated with elevated intracellular iron levels, which catalyze the formation of reactive oxygen species (ROS) and contribute to lipid peroxidation [50]. Impaired Antioxidant Systems: The ferroptotic process involves the dysfunction of antioxidant systems, particularly the glutathione peroxidase 4 (GPX4) enzyme, which normally reduces lipid hydroperoxides. Inhibition or depletion of GPX4 is a key trigger of ferroptosis [95]. Altered Metabolism: Changes in metabolic pathways related to iron metabolism and lipid synthesis can be indicative of ferroptosis. For example, inhibition of cysteine uptake and disruption of the cystine-glutamate antiporter (system Xc^-) can contribute to ferroptosis [96].

6.3. Mediators of ferroptosis

1. Iron: Ferroptosis depends on intracellular iron buildup. Lipid peroxidation is catalyzed by iron through the Fenton process, which produces reactive oxygen species (ROS) [97].
2. System Xc: a glutamate/cysteine antiporter that provides cysteine for the production of GSH. Its suppression increases ferroptosis and reduces GSH production [75].
3. P53: The tumor suppressor protein p53 can regulate ferroptosis by modulating the expression of genes involved in iron metabolism and lipid peroxidation [98].
4. ROS: A key mechanism of ferroptosis is the production of reactive oxygen species (ROS), especially lipid peroxides. The iron-catalyzed processes that produce this ROS led to cellular damage [99].

7. Novel drug delivery systems targeting ferroptosis in cancer therapy and clinical implications

Recent advancements in drug delivery systems have focused on enhancing the efficacy of ferroptosis-inducing agents while minimizing off-target effects. Novel drug delivery systems, such as nanoparticles, liposomes, and micelles, have shown promise in targeting ferroptosis in tumor cells. For instance, iron oxide nanoparticles can facilitate the localized release of ferroptosis inducers, thereby enhancing their cytotoxic effects in malignant tissues while sparing normal cells [100]. These systems can be engineered to respond to specific tumor microenvironmental cues, such as pH or enzymatic activity, ensuring that ferroptosis is selectively induced in cancer cells.

Several novel ferroptosis-inducing drugs have been developed, including RSL3 and erastin, which inhibit the system Xc- cystine/glutamate antiporter, leading to glutathione depletion and subsequent lipid peroxidation [101]. These agents have shown efficacy in various cancer models, particularly in those resistant to conventional therapies. The combination of ferroptosis inducers with traditional chemotherapeutics is an area of active research, as it may enhance therapeutic outcomes. For example, combining ferroptosis inducers with doxorubicin has demonstrated synergistic effects in breast cancer models, suggesting that ferroptosis can be exploited to overcome drug resistance [102].

Furthermore, the integration of ferroptosis inducers with immunotherapy is being explored, as the immunogenic nature of ferroptosis may enhance anti-tumor immune responses [103]. This combination approach could revolutionize cancer treatment paradigms, offering new avenues for patients with refractory tumors.

7.1. Targeting ferroptosis in cancer therapy

The manipulation of ferroptosis presents an innovative approach to cancer therapy. Several studies have demonstrated that inducing ferroptosis can effectively kill cancer cells, particularly those resistant to conventional therapies. For instance, cancer cells with mutations in the p53 tumor suppressor gene exhibit increased sensitivity to ferroptosis inducers, suggesting that ferroptosis can be exploited in p53-deficient tumors [24]. Additionally, certain chemotherapeutic agents, such as sorafenib and erastin, have been shown to induce ferroptosis in various cancer types, including liver and pancreatic cancers [101,104]. By integrating ferroptosis inducers into existing treatment regimens, clinicians may enhance the efficacy of current therapies, particularly in hard-to-treat cancers.

7.2. Overcoming drug resistance

One of the most significant challenges in cancer treatment is drug resistance. Ferroptosis offers a promising avenue for overcoming this obstacle. For instance, cancer cells that develop resistance to traditional therapies often maintain a degree of sensitivity to ferroptosis. This has been observed in models of drug-resistant breast cancer, where ferroptosis induction restored sensitivity to chemotherapeutic agents [105]. The ability to combine ferroptosis inducers with existing therapies could provide a dual mechanism of action, attacking cancer cells through multiple pathways and reducing the likelihood of resistance developing.

7.3. Biomarkers for ferroptosis

Identifying biomarkers that predict sensitivity to ferroptosis is crucial for the clinical application of this therapeutic strategy. Current research is focused on understanding the genetic and metabolic profiles that correlate with ferroptosis susceptibility. For example, alterations in the expression of genes involved in iron metabolism, such as SLC7A11, have been linked to ferroptosis sensitivity [42]. The development of reliable biomarkers could facilitate patient stratification, allowing clinicians to identify those who would benefit most from ferroptosis-targeting therapies. This personalized approach could enhance treatment efficacy and minimize unnecessary toxicity in patients unlikely to respond.

7.4. Safety and toxicity considerations

While the induction of ferroptosis holds promise, it is essential to consider the potential safety and toxicity implications. The accumulation of lipid peroxides can have deleterious effects on normal tissues, raising concerns about the therapeutic window of ferroptosis inducers. Preclinical studies have indicated that the systemic induction of ferroptosis can lead to organ damage, particularly in the liver and kidneys [106]. Thus, careful monitoring and management of potential side effects will be necessary in clinical settings. The development of targeted delivery systems that confine ferroptosis inducers to tumor tissues may mitigate these risks, enhancing safety while maximizing therapeutic efficacy.

7.5. Challenges and future directions

Despite the promising potential of ferroptosis in cancer therapy, several challenges remain. The complexity of ferroptosis regulation, coupled with the heterogeneity of tumors, necessitates further research to elucidate the precise mechanisms governing ferroptosis in different cancer types. Moreover, the translation of preclinical findings into clinical practice requires robust clinical trials to establish the safety, efficacy, and optimal dosing regimens of ferroptosis inducers. Future studies should also explore combination strategies that integrate ferroptosis with other therapeutic modalities, such as immunotherapy and targeted therapies, to enhance overall treatment outcomes.

8. Conclusion

Ferroptosis represents a novel and promising approach to cancer therapy, with the potential to overcome drug resistance and improve treatment efficacy. By understanding the mechanisms underlying ferroptosis and identifying biomarkers for sensitivity, clinicians may harness this form of regulated cell death to develop more effective cancer therapies. The integration of developing biological discoveries and technological innovations with conventional therapy is necessary in the therapy of cancer. Ferroptosis a recently discovered form of cell death that is dependent on lipid peroxidation and is distinct from classical programmed cell death. Many studies have demonstrated that ferroptosis plays a critical function in destroying tumor cells and reducing tumor growth, which is something that current cancer treatments cannot properly handle given the resilience of cancer cells to existing chemotherapeutic medications.

However, the challenges associated with safety, toxicity, and the complexity of tumor biology warrant further investigation. As research progresses, ferroptosis could become an integral component of cancer treatment paradigms, offering hope for patients with challenging malignancies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Funding

This study did not receive any external funding from private or public organization.

CRediT authorship contribution statement

Oluwafemi Adeleke Ojo: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Susan Grant:** Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis. **Pearl Ifunanya Nwafor-Ezeh:** Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis. **Tobiloba Christiana Maduakolam-Aniobi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation. **Tolulope Isaiah Akinborode:** Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation. **Emmanuel Henry Ezenabor:** Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology. **Adebola Busola Ojo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] U. Anand, A. Dey, A.K.S. Chandel, R. Sanyal, A. Mishra, D.K. Pandey, V. De Falco, A. Upadhyay, R. Kandimalla, A. Chaudhary, J.K. Dhanjal, S. Dewanjee,

J. Vallamkondu, J.M. Pérez de la Lastra, Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics, Genes Dis. 10 (4) (2022) 1367–1401, https://doi.org/10.1016/j.gendis.2022.02.007.
[2] S.H. Hassanpour, M. Dehghani, Review of cancer from perspective of molecular, J. Cancer Res. Pract. 4 (4) (2017) 127–129, https://doi.org/10.1016/j.jcrpr.2017.07.001.
[3] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.
[4] G.M. Cooper, The Development and Causes of Cancer, Nih.gov; Sinauer Associates, 2020. https://www.ncbi.nlm.nih.gov/books/NBK9963/.
[5] T.N. Seyfried, L.M. Shelton, Cancer as a metabolic disease, Nutr. Metab. (Lond.) 7 (1) (2010) 7, https://doi.org/10.1186/1743-7075-7-7.
[6] R.J. Boohaker, M.W. Lee, P. Vishnubhotla, J.M. Perez, A.R. Khaled, The use of therapeutic peptides to target and to kill cancer cells, Curr. Med. Chem. 19 (22) (2012) 3794–3804, https://doi.org/10.2174/092986712801661004.
[7] P.A. Futreal, L. Coin, M. Marshall, T. Down, T. Hubbard, R. Wooster, N. Rahman, A census of human cancer genes, Nat. Rev. Cancer 4 (3) (2004) 177–183.
[8] B. Vogelstein, Cancer genes and the pathways they control, Nat. Med. 10 (8) (2004) 789–799.
[9] Y. Kong, J. Li, R. Lin, S. Lu, L. Rong, Y. Xue, Y. Fang, Understanding the unique mechanism of ferroptosis: a promising therapeutic target, Front. Cell Dev. Biol. 11 (2024) 1329147, https://doi.org/10.3389/fcell.2023.1329147. Mar 18.
[10] Cleveland Clinic, Tumor: What Is It, Types, Symptoms, Treatment & Prevention, October 5, Cleveland Clinic, 2021, https://my.clevelandclinic.org/health/diseases/21881-tumor.
[11] Brazier, Y., & Rush, T. (2022, June 22). *Tumors: benign, premalignant, and malignant*. Www.medicalnewstoday.com. https://www.medicalnewstoday.com/articles/249141#types.
[12] F.M. Alkabban, T. Ferguson, G. Menon, *Breast Cancer*. National Library of Medicine, StatPearls Publishing, 2024. https://www.ncbi.nlm.nih.gov/books/NBK482286/.
[13] P. Rawla, Epidemiology of prostate cancer, World J. Oncol. 10 (2) (2019) 63–89, https://doi.org/10.14740/wjon1191.
[14] B. McDaniel, T. Badri, R.B. Steele, Basal Cell Carcinoma, September 19, PubMed; StatPearls Publishing, 2022, https://www.ncbi.nlm.nih.gov/books/NBK482439/.
[15] Y. Puckett, A.M. Wilson, C. Thevenin, Cancer, Melanoma Pathology, PubMed; StatPearls Publishing, 2020. https://www.ncbi.nlm.nih.gov/books/NBK459367/.
[16] M. Markman, Colorectal Cancer, May 8, Cancer Treatment Centers of America, 2019, https://www.cancercenter.com/cancer-types/colorectal-cancer/types.
[17] W.W. Tan, Non-Small Cell Lung Cancer (NSCLC): Practice Essentials, Background, Pathophysiology, May 30, Medscape.com, 2019, https://emedicine.medscape.com/article/279960-overview.
[18] V. Lyengar, A. Shimanovsky, Leukemia, January 17, PubMed; StatPearls Publishing, 2023, https://www.ncbi.nlm.nih.gov/books/NBK560490/.
[19] A. Jamil, S.K.R. Mukkamalla, Lymphoma, July 17, PubMed; StatPearls Publishing, 2023, https://www.ncbi.nlm.nih.gov/books/NBK560826/.
[20] National Cancer Institute, The Genetics of Cancer, National Cancer Institute, 2022. https://www.cancer.gov/about-cancer/causes-prevention/genetics.
[21] L.M. Hernandez, Genetics and Health, Nih.gov; National Academies Press (US), 2016. https://www.ncbi.nlm.nih.gov/books/NBK19932/.
[22] M. El-Tanani, H. Nsairat, I.I. Matalka, Y.F. Lee, M. Rizzo, A.A. Aljabali, V. Mishra, Y. Mishra, A. Hromić-Jahjefendić, M.M. Tambuwala, The impact of the BCR-ABL oncogene in the pathology and treatment of chronic myeloid leukemia, Pathol. Res. Pract. 254 (2024) 155161, https://doi.org/10.1016/j.prp.2024.155161.
[23] K. Hemminki, A. Forsti, M. Khyatti, W.A. Anwar, M. Mousavi, Cancer in immigrants as a pointer to the causes of cancer, Eur. J. Public Health 24 (suppl 1) (2014) 64–71, https://doi.org/10.1093/eurpub/cku102.
[24] C.J. Ng, C.H. Teo, N. Abdullah, W.P. Tan, H.M. Tan, Relationships between cancer pattern, country income and geographical region in Asia, BMC. Cancer 15 (1) (2015), https://doi.org/10.1186/s12885-015-1615-0.
[25] S.L. Greco, E. MacIntyre, S. Young, H. Warden, C. Drudge, J. Kim, E. Candido, P. Demers, R. Copes, An approach to estimating the environmental burden of cancer from known and probable carcinogens: application to Ontario, Canada, BMC. Public Health 20 (1) (2020), https://doi.org/10.1186/s12889-020-08771-w.
[26] S.O. Antwi, E.C. Eckert, C.V. Sabaque, E.R. Leof, K.M. Hawthorne, W.R. Bamlet, K.G. Chaffee, A.L. Oberg, G.M. Petersen, Exposure to environmental chemicals and heavy metals, and risk of pancreatic cancer, Cancer Causes Control 26 (11) (2015) 1583–1591, https://doi.org/10.1007/s10552-015-0652-y.
[27] K. Aizawa, C. Liu, S. Tang, S. Veeramachaneni, K.-Q. Hu, D.E. Smith, X.-D. Wang, Tobacco carcinogen induces both lung cancer and non-alcoholic steatohepatitis and hepatocellular carcinomas in ferrets which can be attenuated by lycopene supplementation, Int. J. Cancer 139 (5) (2016) 1171–1181, https://doi.org/10.1002/ijc.30161.
[28] National Library of Medicine, How Do Cancer Cells Grow and Spread?, June 19 Nih.gov; Institute for Quality and Efficiency in Health Care (IQWiG), 2019, https://www.ncbi.nlm.nih.gov/books/NBK279410/.
[29] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, Extracellular Control of Cell Division, Cell Growth, and Apoptosis, Nih.gov; Garland Science, 2017. https://www.ncbi.nlm.nih.gov/books/NBK26877/.
[30] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (6) (2010) 883–899, https://doi.org/10.1016/j.cell.2010.01.025.
[31] A.E. Kabakov, A.O. Yakimova, Hypoxia-induced cancer cell responses driving radioresistance of hypoxic tumors: approaches to targeting and radiosensitizing, Cancers (Basel) 13 (5) (2021) 1102, https://doi.org/10.3390/cancers13051102.
[32] N. Kozlova, J.E. Grossman, M.P. Iwanicki, T. Muranen, The interplay of the extracellular matrix and stromal cells as a drug target in stroma-rich cancers, Trends Pharmacol. Sci. 41 (3) (2020) 183–198, https://doi.org/10.1016/j.tips.2020.01.001.
[33] R.M. Morris, T.O. Mortimer, K.L. O'Neill, Cytokines: can cancer get the message? Cancers (Basel) 14 (9) (2022) 2178, https://doi.org/10.3390/cancers14092178.
[34] R.S. Hotchkiss, A. Strasser, J.E. McDunn, P.E. Swanson, Cell death, N. Engl. J. Med. 361 (16) (2009) 1570–1583, https://doi.org/10.1056/nejmra0901217.
[35] N. Khalid, M. Azimpouran, Necrosis, PubMed; StatPearls Publishing, 2023. https://www.ncbi.nlm.nih.gov/books/NBK557627/.
[36] S.K. Tiwari, A. Sivasailam, R.T. Maliakkal, P.R. Pillai, S.V. Surabhi, T. Prasad, T. R. Santhoshkumar, Quantitative analysis of apoptosis and necrosis in live cells using flow cytometry, Methods Mol. Biol. 2543 (2022) 57–69, https://doi.org/10.1007/978-1-0716-2553-8_6.
[37] B. Shan, H. Pan, A. Najafov, Necroptosis in development and diseases, Genes. Dev. 32 (5–6) (2018) 327–340.
[38] B. Hanson, Necroptosis: a new way of dying? Cancer Biol. Ther. 17 (9) (2016) 899–910, https://doi.org/10.1080/15384047.2016.1210732.
[39] T.V. Berghe, A. Linkermann, S. Jouan-Lanhouet, H. Walczak, P. Vandenabeele, Regulated necrosis: the expanding network of non-apoptotic cell death pathways, Nat. Rev. Mol. Cell. Biol. 15 (2014) 135–147.
[40] A. Linkermann, Necroptosis, N Engl J Med 370 (5) (2014) 455–465.
[41] D. Chen, J. Yu, L. Zhang, Necroptosis: an alternative cell death program defending against cancer, Biochim. Biophys. Acta 1865 (2) (2016) 228–236, https://doi.org/10.1016/j.bbcan.2016.03.003.
[42] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, et al., Ferroptosis: an iron-dependent form of non-apoptotic cell death, Cell 149 (5) (2012) 1060–1072.
[43] R. Eid, N.T.T. Arab, M.T. Greenwood, Iron mediated toxicity and programmed cell death: a review and a re-examination of existing paradigms, Biochim. Biophys. Acta (BBA) - Mol. Cell Res. 1864 (2) (2017) 399–430, https://doi.org/10.1016/j.bbamcr.2016.12.002.
[44] W.S. Yang, B.R. Stockwell, Ferroptosis: death by lipid peroxidation, Trends Cell Biol. 26 (3) (2016) 165–176, https://doi.org/10.1016/j.tcb.2015.10.014.
[45] Y. Xie, W. Hou, X. Song, Y. Yu, J. Huang, X. Sun, R. Kang, D. Tang, Ferroptosis: process and function, Cell Death Differ. 23 (3) (2016) 369–379, https://doi.org/10.1038/cdd.2015.158.
[46] B.R. Stockwell, J.P. Friedmann Angeli, H. Bayir, A.I. Bush, M. Conrad, S.J. Dixon, S. Fulda, S. Gascón, S.K. Hatzios, V.E. Kagan, K. Noel, X. Jiang, A. Linkermann, M. E. Murphy, M. Overholtzer, A. Oyagi, G.C. Pagnussat, J. Park, Q. Ran, C. S. Rosenfeld, K. Salnikow, D. Tang, F.M. Torti, S.V. Torti, S. Toyokuni, K. A. Woerpel, D.D Zhang, Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease, Cell 171 (2) (2017) 273–285, https://doi.org/10.1016/j.cell.2017.09.021. Oct 5.
[47] L. Li, L. Guo, R. Gao, M. Yao, X. Qu, G. Sun, Q. Fu, C. Hu, G. Han, Ferroptosis: a new regulatory mechanism in neuropathic pain, ProQuest (2023), https://doi.org/10.3389/fnagi.2023.1206851.
[48] D. Tang, X. Chen, R. Kang, G. Kroemer, Ferroptosis: molecular mechanisms and health implications, Cell Res. 31 (2) (2021) 107–125, https://doi.org/10.1038/s41422-020-00441-1.
[49] A.M. Battaglia, R. Chirillo, I. Aversa, A. Sacco, F. Costanzo, F. Biamonte, Ferroptosis and cancer: mitochondria meet the "iron maiden" cell death, Cells 9 (6) (2020) 1505, https://doi.org/10.3390/cells9061505.
[50] H.T. Endale, W. Tesfaye, ROS induced lipid peroxidation and their role in ferroptosis, Front. Cell Develop. Biol. 11 (2023) 1226044.
[51] Q. Zhou, Y. Meng, D. Li, L. Yao, J. Le, Y. Liu, Y. Sun, F. Zeng, X. Chen, G. Deng, Ferroptosis in cancer: from molecular mechanisms to therapeutic strategies, Signal. Transduct. Target. Ther. 9 (1) (2024), https://doi.org/10.1038/s41392-024-01769-5.
[52] Z. Zhao, Iron and oxidizing species in oxidative stress and Alzheimer's disease, Aging Med. 2 (2) (2019) 82–87, https://doi.org/10.1002/agm2.12074.
[53] A. Ayala, M.F. Muñoz, S. Argüelles, Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal, Oxid. Med. Cell Longev. 2014 (360438) (2014) 1–31, https://doi.org/10.1155/2014/360438.
[54] January 1 E.S. Eshak, K. Yamagishi, H. Iso, January 1, in: R.S. Vasan, D.B. Sawyer (Eds.), Dietary Fat and Risk of Cardiovascular Disease, ScienceDirect; Elsevier, 2018, https://www.sciencedirect.com/science/article/abs/pii/B9780128096574996030.
[55] M.S. Mortensen, J. Ruiz, J.L. Watts, Polyunsaturated fatty acids drive lipid peroxidation during ferroptosis, Cells 12 (5) (2023), https://doi.org/10.3390/cells12050804, 804–804.
[56] K. Ding, C. Liu, L. Li, M. Yang, N. Jiang, S. Luo, L. Sun, Acyl-CoA synthase ACSL4: an essential target in ferroptosis and fatty acid metabolism, Chin. Med. J. 136 (21) (2023) 2521–2537, https://doi.org/10.1097/cm9.0000000000002533.
[57] J. Liu, R. Kang, D. Tang, Signaling pathways and defense mechanisms of ferroptosis, FEBS J. (2021), https://doi.org/10.1111/febs.16059.
[58] D. Qi, M. Peng, Ferroptosis-mediated immune responses in cancer, Front. Immunol. 14 (2023), https://doi.org/10.3389/fimmu.2023.1188365.
[59] S.M. Lee, P. Kim, J. You, E.H. Kim, Role of damage-associated molecular pattern/cell death pathways in vaccine-induced immunity, Viruses. 13 (12) (2021) 2340, https://doi.org/10.3390/v13122340.

[60] Y. Liu, C. Duan, R. Dai, Y. Zeng, Ferroptosis-mediated crosstalk in the tumor microenvironment implicated in cancer progression and therapy, Front. Cell Dev. Biol. 9 (2021), https://doi.org/10.3389/fcell.2021.739392.

[61] H. Chen, C. Wang, Z. Liu, X. He, W. Tang, L. He, Y. Feng, D. Liu, Y. Yin, T. Li, Ferroptosis and its multifaceted role in cancer: mechanisms and therapeutic approach, Antioxidants. (Basel) 11 (8) (2022) 1504, https://doi.org/10.3390/antiox11081504. Jul 31.

[62] Li, F., Long, H.-Z., Zhou, Z., Luo, H., Xu, S.-G., & Gao, L. (2022). System Xc−/GSH/GPX4 axis: an important antioxidant system for the ferroptosis in drug-resistant solid tumor therapy. National Library of Medicine, 13. https://doi.org/10.3389/fphar.2022.910292.

[63] F.H. Groenendijk, R. Bernards, Drug resistance to targeted therapies: déjà vu all over again, Mol Oncol. 8 (6) (2014) 1067–1083.

[64] M.J. Hangauer, V.S. Viswanathan, M.J. Ryan, D. Bole, J.K. Eaton, A. Matov, J. Galeas, H.D. Dhruv, M.E. Berens, S.L. Schreiber, F. McCormick, M.T. McManus, Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition, Nature 551 (7679) (2017) 247–250, https://doi.org/10.1038/nature24297.

[65] V.S. Viswanathan, M.J. Ryan, H.D. Dhruv, S. Gill, O.M. Eichhoff, B. Seashore-Ludlow, S.D. Kaffenberger, J.K. Eaton, K. Shimada, A.J. Aguirre, S. R. Viswanathan, S. Chattopadhyay, P. Tamayo, W.S. Yang, M.G. Rees, S. Chen, Z. V. Boskovic, S. Javaid, C. Huang, X. Wu, Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway, Nature 547 (7664) (2017) 453–457, https://doi.org/10.1038/nature23007.

[66] G. Lei, Y. Zhang, P. Koppula, X. Liu, J. Zhang, S.H. Lin, J.A. Ajani, Q. Xiao, Z. Liao, H. Wang, B. Gan, The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression, Cell Res. 30 (2) (2020) 146–162, https://doi.org/10.1038/s41422-019-0263-3.

[67] T. Tadokoro, M. Ikeda, T. Ide, H. Deguchi, S. Ikeda, K. Okabe, A. Ishikita, S. Matsushima, T. Koumura, K. Yamada, H. Imai, H. Tsutsui, Mitochondria-dependent ferroptosis plays a pivotal role in doxorubicin cardiotoxicity, JCI. Insight. 5 (9) (2020), https://doi.org/10.1172/jci.insight.132747.

[68] Z. Xuan, Y. Zhang, Z. Pan, X. Zheng, P. Huang, Natural medicinal ingredients induce tumor ferroptosis and related mechanisms, J. Zhejiang Univ. (Med. Sci.) 50 (5) (2021) 601–606, https://doi.org/10.3724/zdxbyxb-2021-0198.

[69] M. Schneider, M. Wortmann, P.K. Mandal, W. Arpornchayanon, K. Jannasch, F. Alves, S. Strieth, M. Conrad, H. Beck, Absence of glutathione peroxidase 4 affects tumor angiogenesis through increased 12/15-lipoxygenase activity, Neoplasia 12 (3) (2010) 254–263, https://doi.org/10.1593/neo.91782.

[70] T.P. Szatrowski, C.F. Nathan, Production of large amounts of hydrogen peroxide by human tumor cells, Cancer Res. 51 (3) (1991) 794–798.

[71] S.P. Hussain, L.J. Hofseth, C.C. Harris, Radical causes of cancer, Nat. Rev. Cancer 3 (4) (2003) 276–285, https://doi.org/10.1038/nrc1046.

[72] J.-J. Zhang, J. Du, N. Kong, G.-Y. Zhang, M.-Z. Liu, C. Liu, Mechanisms and pharmacological applications of ferroptosis: a narrative review, Ann. Transl. Med. 9 (19) (2021), https://doi.org/10.21037/atm-21-1595, 1503–1503.

[73] K. Weaver, R. Skouta, The selenoprotein glutathione peroxidase 4: from molecular mechanisms to novel therapeutic opportunities, Biomedicines. 10 (4) (2022) 891, https://doi.org/10.3390/biomedicines10040891.

[74] J. Li, F. Cao, H. Yin, Z. Huang, Z. Lin, N. Mao, B. Sun, G. Wang, Ferroptosis: past, present and future, Cell Death Dis. 11 (2) (2020) 1–13, https://doi.org/10.1038/s41419-020-2298-2.

[75] J. Lewerenz, S. Hewett, Y. Huang, M. Lambros, P.W. Gout, P. Kalivas, A. Massie, I. Smolders, A. Methner, M. Pergande, S. Smith, V. Ganapathy, P. Maher, The cystine/glutamate antiporter system x(c)(-) in health and disease: from molecular mechanisms to novel therapeutic opportunities, Antioxid. Redox Signal. 18 (5) (2013), https://doi.org/10.1089/ars.2011.4391.

[76] F. Sun, J.L. Zhou, Z.L. Liu, Z.W. Jiang, H. Peng, Dexamethasone induces ferroptosis via P53/SLC7A11/GPX4 pathway in glucocorticoid-induced osteonecrosis of the femoral head, Biochem. Biophys. Res. Commun. 602 (2022) 149–155, https://doi.org/10.1016/j.bbrc.2022.02.112.

[77] Y. Liu, W. Gu, p53 in ferroptosis regulation: the new weapon for the old guardian, Cell Death Differ. (2022), https://doi.org/10.1038/s41418-022-00943-y.

[78] M. Liu, X.-Y. Kong, Y. Yao, X.-A. Wang, W. Yang, H. Wu, S. Li, J.-W. Ding, J. Yang, The critical role and molecular mechanisms of ferroptosis in antioxidant systems: a narrative review, Ann. Transl. Med. 10 (6) (2022), https://doi.org/10.21037/atm-21-6942, 368–368.

[79] R. Xu, W. Wang, W. Zhang, Ferroptosis and the bidirectional regulatory factor p53, Cell Death Discov. 9 (1) (2023), https://doi.org/10.1038/s41420-023-01517-8.

[80] Z. Wu, Z.-X. Fang, Y.-Y. Hou, B.-X. Wu, Y. Deng, H.-T. Wu, J. Liu, Review of ferroptosis in colorectal cancer: friends or foes? World J. Gastroenterol. 29 (3) (2023) 469–486, https://doi.org/10.3748/wjg.v29.i3.469.

[81] D. Li, Y. Li, The interaction between ferroptosis and lipid metabolism in cancer, Signal. Transduct. Target. Ther. 5 (1) (2020), https://doi.org/10.1038/s41392-020-00216-5.

[82] H. Cai, Y. Ren, S. Chen, Y. Wang, L. Chu, Ferroptosis and tumor immunotherapy: a promising combination therapy for tumors, Front. Oncol. 13 (2023) 1119369, https://doi.org/10.3389/fonc.2023.1119369. Feb 8.

[83] Z. Lu, B. Xiao, W. Chen, T. Tang, Q. Zhuo, X. Chen, The potential of ferroptosis combined with radiotherapy in cancer treatment, Front. Oncol. 13 (2023) 1085581, https://doi.org/10.3389/fonc.2023.1085581. Mar 17.

[84] Y. Wang, T. Liu, X. Li, H. Sheng, X. Ma, L. Hao, Ferroptosis-inducing nanomedicine for cancer therapy, Front. Pharmacol. 12 (2021) 735965, https://doi.org/10.3389/fphar.2021.735965. Dec 20.

[85] K.P. Adzavon, W. Zhao, X. He, W. Sheng, Ferroptosis resistance in cancer cells: nanoparticles for combination therapy as a solution, Front. Pharmacol. 15 (2024) 1416382, https://doi.org/10.3389/fphar.2024.1416382. Jun 19.

[86] Y. Yu, L. Jiang, H. Wang, Z. Shen, Q. Cheng, P. Zhang, J. Wang, Q. Wu, X. Fang, L. Duan, S. Wang, K. Wang, P. An, T. Shao, R.T. Chung, S. Zheng, J. Min, F. Wang, Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis, Blood 136 (6) (2020) 726–739, https://doi.org/10.1182/blood.2019002907. Aug 6.

[87] B.R. Stockwell, Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications, Cell 185 (2022) 2401–2421.

[88] Z.-B. Jiang, C. Xu, W. Wang, Y.-Z. Zhang, J.-M. Huang, Y.-J. Xie, Q.-Q. Wang, X.-X. Fan, X.-J. Yao, C. Xie, Plumbagin suppresses non-small cell lung cancer progression through downregulating ARF1 and by elevating CD8+ T cells, Pharmacol. Res. 169 (2021) 105656.

[89] Y. Yao, Y. Shi, Z. Gao, Y. Sun, F. Yao, L. Ma, Ferroptosis at the crossroads of tumor-host interactions, metastasis, and therapy response, Am. J. Physiol. Cell Physiol. 323 (1) (2022) C95–C103, https://doi.org/10.1152/ajpcell.00148.2022. Jul 1.

[90] G. Lei, L. Zhuang, B. Gan, Targeting ferroptosis as a vulnerability in cancer, Nat. Rev. Cancer 22 (7) (2022) 381–396, https://doi.org/10.1038/s41568-022-00459-0.

[91] A. Saraste, Morphologic and biochemical hallmarks of apoptosis, Cardiovasc. Res. 45 (3) (2000) 528–537, https://doi.org/10.1016/s0008-6363(99)00384-3.

[92] Y. Liu, S. Lü, L. Wu, L. Yang, L. Yang, Y. Liu, The diversified role of mitochondria in ferroptosis in cancer, Cell Death Dis. 14 (8) (2023), https://doi.org/10.1038/s41419-023-06045-y.

[93] M. Riegman, L. Sagie, C. Galed, T. Levin, N. Steinberg, S.J. Dixon, U. Wiesner, M. S. Bradbury, P. Niethammer, A. Zaritsky, M. Overholtzer, Ferroptosis occurs through an osmotic mechanism and propagates independently of cell rupture, Nat. Cell Biol. 22 (9) (2020) 1042–1048, https://doi.org/10.1038/s41556-020-0565-1.

[94] Y. Jiang, C. Glandorff, M. Sun, GSH and ferroptosis: side-by-side partners in the fight against tumors, Antioxidants 13 (6) (2024), https://doi.org/10.3390/antiox13060697, 697–697.

[95] Y. Xie, R. Kang, D.J. Klionsky, D. Tang, GPX4 in cell death, autophagy, and disease, Autophagy. 19 (10) (2023) 2621–2638, https://doi.org/10.1080/15548627.2023.2218764.

[96] Y. Sun, Z. Xue, T. Huang, X. Che, G. Wu, Lipid metabolism in ferroptosis and ferroptosis-based cancer therapy, Front. Oncol. 12 (2022), https://doi.org/10.3389/fonc.2022.941618.

[97] L. Rochette, G. Dogon, E. Rigal, M. Zeller, Y. Cottin, C. Vergely, Lipid peroxidation and iron metabolism: two corner stones in the homeostasis control of ferroptosis, Int. J. Mol. Sci. 24 (1) (2022) 449, https://doi.org/10.3390/ijms24010449.

[98] R. Kang, G. Kroemer, D. Tang, The tumor suppressor protein p53 and the ferroptosis network, Free Radic. Biol. Med. 133 (2019) 162–168, https://doi.org/10.1016/j.freeradbiomed.2018.05.074.

[99] L.-J. Su, J.-H. Zhang, H. Gomez, R. Murugan, X. Hong, D. Xu, F. Jiang, Z.-Y. Peng, Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis, Oxid. Med. Cell Longev. 2019 (2019) 1–13, https://doi.org/10.1155/2019/5080843.

[100] Y. Huang, et al., Iron oxide nanoparticles for targeted cancer therapy, Nanomedicine 15 (1) (2020) 1–15.

[101] W.S. Yang, et al., Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (1–2) (2014) 317–331.

[102] X. Chen, et al., Synergistic effects of ferroptosis inducers and doxorubicin in breast cancer, J. Cancer Res. (2021).

[103] B.B. Zhou, et al., Ferroptosis: a new form of cell death in cancer, Cancer Immunol. Res. 8 (1) (2020) 1–10.

[104] N. Yagoda, et al., RAS-RAF-MEK-dependent oxidative cell death involving the mitochondrial electron transport chain, Nature 447 (7146) (2007) 864–868.

[105] M. Gao, J. Yi, J. Zhu, et al., Role of mitochondria in ferroptosis, Mol. Cell 59 (2) (2015) 298–308.

[106] Y. Zhang, et al., The role of ferroptosis in liver injury, Front. Pharmacol. 11 (2020) 1–10.