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Ferroptosis in Cancer Research: From Lipid Peroxidation to Precision Therapeutics

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KEYWORDS

Lipid peroxidation, targeted therapy, molecular mechanisms, cancer resistance, cancer therapy, iron metabolism and antioxidants.

ABSTRACT:

Ferroptosis has emerged as a novel iron-dependent form of regulated cell death with potential in oncological therapeutics. The excessive accumulation of iron in cancer cells leads to lipid peroxidation, induced cell death. In contrast to other forms of cell death viz. apoptosis, necroptosis and autophagy, ferroptosis occurs through distinct independent biochemical pathways providing novel targets for interventional therapy.However, research gaps in understanding of mechanisms and pathways leading to ferroptosis, role of tumor microenvironment, biomarkers and the challenges involved in combining it with other cancer therapy hinder its clinical translation. A bibliometric analysis highlighted research trends to understand gaps in Ferroptosis mechanisms, cancer therapy, tumor microenvironment, biomarkers, and innovative combination therapy challenges in the last twenty years. The inclusion and exclusion criteria were set. A surge in ferroptosis research was observed in the last five years with India still trying to pace up. Patient stratification for targeted precision therapies, resistance to ferroptosis and off-target effects are a challenge for translational applications in clinics. Lipid peroxidation, iron metabolism and novel compounds controlling ferroptosis have been explored. The review explores expected research on methods for selectively activating cancer cells to undergo ferroptosis, in response to their unique metabolic and oxidative stress profile. The work also aims to identify ferroptosis as a treatment option for conventionally treated non-responsive cancers. A traverse through the available literature and ongoing research highlights the prospects of ferroptosis as a robust and targeted antineoplastic strategy, paving the way for future therapeutic innovations.

1. Introduction:

Most cancers are treated by drug therapy, radiation or surgical interventions (1, 2). However, none of these strategies is cancer cell specific and accompanied with development of comorbid conditions. The extended durations of medication result in relapse of non-responsive. Drug resistance reportedly occurs in such cases, sparing no option for treatment modalities (3). Chemotherapeutic resistance in cancer has beenan area of concern for clinicians, researchers and patients (4, 5). However, when drug resistance occurs, necrotic, autophagy and apoptotic pathways offer an opportunity to target cancer cell death (6). Necrosis is an accidental mode of cell death, while autophagy is a lysosome dependent mechanism. Apoptosis or the programmed cell death is a natural process ingrained in our genes to securely dispose, old and damaged cells (7). The key events occurring in apoptosis are DNA fragmentation, blebbing, cell fragmentation and formation of apoptotic bodies (8). Biochemical and morphological changes have been found to be highly specific, characteristic to apoptosis.

Lately, many studies have reported deviations from characteristic events of above processes indicating a parallel mechanism of cell death. “Ferroptosis”, as suggested in these studies, for such novel mechanisms of cell death is widely being investigated for cancer therapeutics (9,10). Li et al (11) extensively compared the characteristic features of different cell death processes with emphasis on ferroptosis. Unlike

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apoptosis, which relies on caspase activation, ferroptosis is characterised by lipid peroxidation and reactive oxygen species (ROS) accumulation, leading to irreversible membrane damage and cell death. Ferroptosis has been identified as a natural iron dependent cell death process, accompanied with high rates of lipid peroxidation (1, 12-15). Diverse molecules and organelles take part through various molecular networks to execute ferroptosis. The process can be GPX4-dependent and GPX4- independent antioxidant mechanisms. Several biomarkers have also been identified to monitor ferroptosis. Ferroptosis is known to occur in diseases like cancer, neurodegenerative disorders, sepsis, ischemia-reperfusion injury, autoimmune conditions and metabolic disorders (9, 16-18). The therapeutic potential of targeting this pathway for cancer treatment is widely under investigation. It may be a possible mechanism of action for chemotherapy, radiotherapy based treatment modalities (15, 19). Understanding of ferroptosis may help to devise novel pharmacological strategies in combination with immunotherapy, nanotherapy and targeted therapy (20,21).

Ferroptosis was largely undefined until 2012, when Brent Stockwell and Scott J. Dixon (22) reported its unique features and suggested its name. Prior to this year, the interest in ferroptosis largely extended to the concept of apoptosis. Apoptosiswas reported by Karl Vogt as early as in 1842 during his studies on tadpole metamorphosis. He observed the disappearance of tadpole notochord during embryonic development, but could not assign reasons for the same. Later, Kerr et al (23), provided ultrastructural evidence to prove occurrence of apoptosis in normal cells. This led to the understanding of the concept of programmed regulated cell death (11,24). However, delineation of ferroptosis from apoptosis took another four decades. Evidence proved thatferroptosis is a non-apoptotic cell death pathway (12,15,22,25).

The recognition of ferroptosis as a new form of regulated cell death made the understanding of numerous physiological and pathological processes (24). It has been suggested as a tumor suppressive mechanism for removal of cancer cells deficient in essential nutrients or challenged by infections and environmental stress (26, 27). The method is selective in targeting only the susceptible cells. Drug resistance and possible evasion of ferroptosis by cancerous cells leads to tumor progression and recurrence (28). Inducing ferroptosis may potentially reverse the pharmacological resistance by cancerous cells and help combat invasive cancers (3, 21, 29). The therapeutic advancements in cancer management need to be investigated for implications and impact of ferroptosis driven drug mechanisms. It may prove as an innovative therapy to manage drug resistance, improve drug efficacy and cancer diagnosis (26, 28).

This review consolidates recent and emerging insights into ferroptosis research, which are bound to make it an integral part of cancer therapy. A comprehensive analysis of ferroptosis mechanism, genetic factors and cellular microenvironment is done to provide a lucid understanding of differential cancer cell susceptibilities. This article aptly discusses mechanisms of ferroptosis resistance and possible approaches to overcome it, the role of hypoxia, iron metabolism and immune system in modulating tumor microenvironment to improve understanding for therapeutic applications. This review explores the novel biomarkers like specific lipid peroxidation byproducts or genetic signatures for ferroptosis sensitivity. The consolidated findings will help predict patient outcomes to ferroptosis-inducing therapies contributing to precision oncology. The potential of ferroptosis inducers for combination therapies, drug-resistant cancers has been evaluated. The insights will lead to synthesis of rational combination therapies promising clinical success. The ensuing discussion is likely to pave the way for innovative drug formulations, delivery systems, and feasible clinical applications minimizing off-target effects. Additionally, a bibliometric analysis using VOSviewer provides an overview of global research trends, identifying gaps and emerging directions in ferroptosis-related cancer therapy.

Identification of research questions-

The expanding knowledge on ferroptosis is bound to affect the future of cancer treatments. Thus, there is a need to consolidate the understanding of how ferroptosis can be manipulated to inhibit tumor growth. The following research questions are addressed to synthesize and analyze findings from existing studies on the focus area-

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- What are the mechanisms and pathways involved and how these pathways specifically contribute to ferroptosis induction?
- What strategies are being adopted to induce ferroptosis in different types of cancers?
- What is the potential of combining ferroptosis with other cancer therapies?
- What is the role of tumor microenvironment in regulating the induction and resistance to ferroptosis?
- What are the specific biomarkers for vulnerability to ferroptosis and how these can be exploited for customized clinical practices?
- What are the main challenges in incorporating ferroptosis research into clinical applications and how can these challenges be mitigated in future?

2. Methodology

Literature Search and Selection Criteria

A systematic literature review was conducted using Google Scholar and Scopus-indexed databases to identify relevant studies published between 2005 and 2025. The search keyword combinations such as Set A- "Ferroptosis + mechanisms", Set B- "Ferroptosis + Cancer Therapy", Set C- "Tumor microenvironment + Ferroptosis", Set D- "Biomarkers + clinical applications + ferroptosis", Set E- "Challenges + future directions + ferroptosis". The inclusion criteria encompassed peer-reviewed journal articles published in English, with a focus on cancer research. Non-english language publications, conference proceedings, and patents were excluded. The search strategy summary is given in Table 1.

Table 1. The search strategy summary

Items	**Specification**
Date of search (specified to date, month and year)	23-24 October 2024
Databases and other sources searched	Google Scholar citation database
Search terms used	Ferroptosis alone and in combination with molecular pathways, cancer cells, biomarkers, microenvironment, cancer therapies.
Timeframe	12 citation years from 2012-2024 for ferroptosis alone and 6 citation years from 2018-2024 for combination of keywords
Inclusion and exclusion criteria	Inclusion criteria: publications in scopus indexed journals Exclusion criteria: non-english language publications, articles outside the field of cancer research. Citations and patents excluded.
Selection process	independent process
Any additional considerations, if applicable	none

Bibliometric Analysis- The traditional literature searches were also tested with VOSviewer search for finding trends and gaps in the current publications. Data search was done with Publish or Perish on 23-24 October 2024 using keyword ferroptosis alone and in combination with molecular pathway, cancer cells, biomarkers, microenvironment, cancer therapies using google scholar. The citations and patents were excluded from the search. The total 12 citation years starting from 2012-2024 for ferroptosis alone and 06 citation years for keyword combination were considered starting from 2018-2024. Network visualization maps were created by VOSviewer version.1.6.20 with minimum cluster size: 1(for ferroptosis), 5 (for ferroptosis keyword combination), resolution: 1.00, normalization with association method, binary counting, minimum strength=0, maximum lines =1000 and visualization weights for author keyword (occurrences). Threshold Relevance Score was set by default at 60%, where only most relevant terms were selected. The data were categorized so as to answer research questions.

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Data Extraction and Analysis-

Relevant studies were categorized based on their focus areas, including mechanisms of ferroptosis, therapeutic applications, and translational challenges. Special attention was given to recent clinical trials and emerging therapeutic strategies. The findings were synthesized to provide a comprehensive understanding of ferroptosis as a precision oncology tool.

3. Results-

Conventional review analysis-

The publications increased over time, showing the emergence of ferroptosis research in 2005-2009 with a steep rise in the 2020-2025 periods as evident in Figure 1. Research hotspots include mechanisms of ferroptosis (approximately 1,50k publications), therapeutic applications, and tumor microenvironment interactions. The analysis also highlighted a disparity in global contributions, with China and the United States leading the field, while research from India and other developing regions remains comparatively limited.

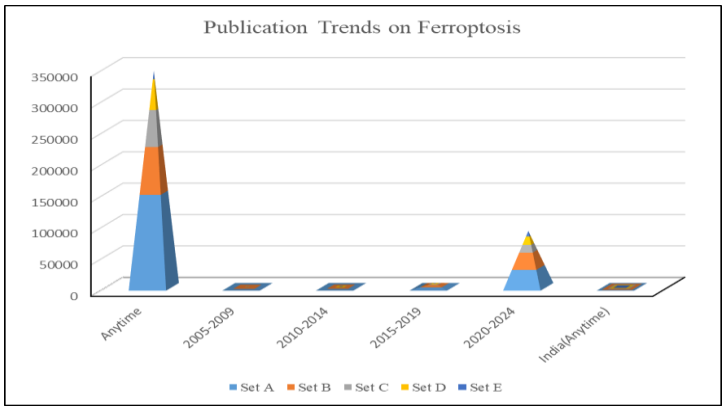

Figure 1: Summary of publications reported on Ferroptosis (as on 22-10-2024) with different sets of keywords: Set A Ferroptosis + mechanisms; Set B Ferroptosis + Cancer Therapy; Set C Tumor microenvironment + Ferroptosis; Set D Biomarkers+clinical applications + ferroptosis; Set E Challenges+futuredirections+ferroptosis

The VOSviewer analysis-

Keyword co-occurrence was used to pin down the key areas of current research trends and emerging directions. The visualization maps consisting of nodes and connecting lines represent the strength of the relationships between keywords. The repeated co-occurrences in a single document take thicker lines. The color of nodes, group the different clusters, with lighter shades illustrating predominant research directions. The VOSviewer map for keyword "Ferroptosis" resulted in a final selection of 25 items, 04 clusters, 93 links and total link strength of 166. The summary of these clusters is given in Table 2 and Figure 2.

Table 2: Summary of Clusters identified by VOS viewer for keyword ferroptosis

Cluster	No. of Items	Items (Keywords)
1	9	addition, application, cancer therapy, cardiovascular diseases, ferroptosis inducer, ferroptosis regulation, induction, molecular mechanism, regulating ferroptosis

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2	7	acsl4, cell, effect, interaction, lipid metabolism, process, sensitivity
3	5	discovery, form, iron, lipid peroxidation, regulated cell death
4	4	cell death, erastin, gpx4, peroxidation

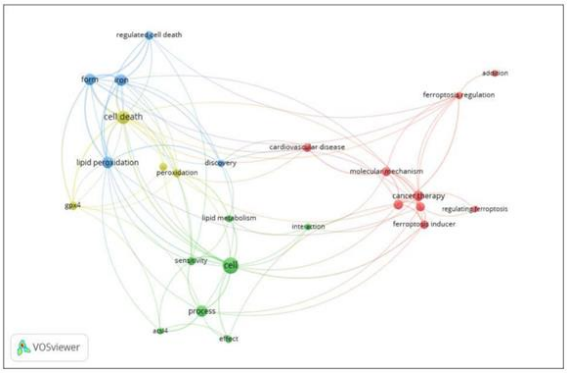

Figure 2: Visualization network maps for keyword ferroptosis

The VOSviewer map for keyword "Ferroptosis + molecular pathways, cancer cells, biomarkers, microenvironment, cancer therapies" resulted in a final selection of 38 items, 05 clusters, 263 links and total link strength of 630. The summary of these clusters is given in Figure 3 (A,B) and Table 3. The density visualization map indicated the focuses of all publications are microenvironment and prognosis of cancer using the ferroptosis biomarkers.

Table 3: Summary of clusters identified by VOSviewer for keyword ferroptosis + molecular pathways, cancer cells, biomarkers, microenvironment, cancer therapies.

Cluster	No. of Items	Items (Keywords)
1	10	breast cancer patient, gene, gene signature, identification, immune microenvironment, lung adenocarcinoma, novel biomarkers, novel ferroptosis, prognosis, validation
2	9	bladder cancer, breast cancer, cancer treatment, ferroptosis score, molecular subtype, potential target, study, t-cell, tumor microenvironment
3	8	cancer therapy, function, interaction, iron metabolism, microenvironment, regulation, small molecule, tumor cell

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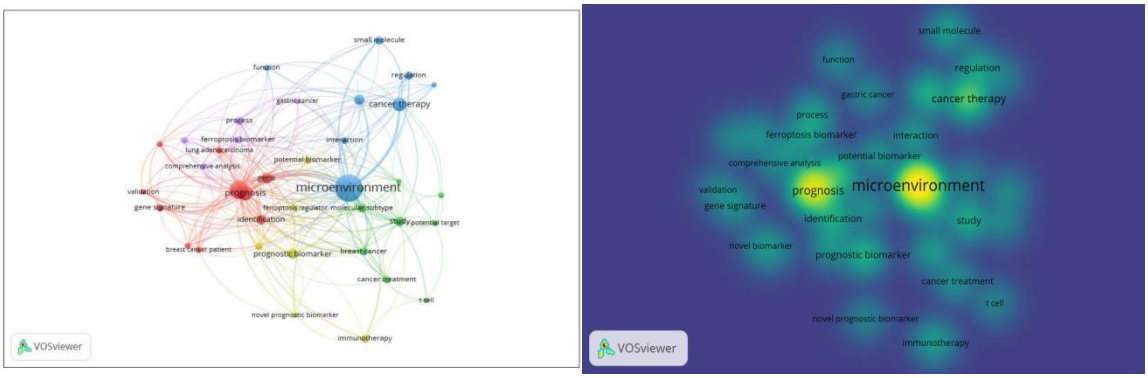
4	6	ferroptosis regulator, immune cell, immunotherapy, novel prognostic biomarker, potential biomarker, prognostic biomarker
5	5	comprehensive analysis, ferroptosis biomarker, gastric cancer, molecular function, process



(A) (B)

Figure 3: Network maps for keyword ferroptosis + molecular pathways, cancer cells, biomarkers, microenvironment, cancer therapies (A) Visualization, (B) Density

Keyword co-occurence mapping indicated strong associations between ferroptosis, lipid peroxidation, cancer resistance, and oxidative stress, underscoring the therapeutic relevance of this pathway. However, studies on clinical applications and translational challenges remain underrepresented, suggesting potential areas for future research.

Mechanisms and regulation of Ferroptosis:

Ferroptosis is an iron-dependent cell death process occurring as a result of accumulation of free iron and reactive oxygen species (ROS)(30-32). The accumulated iron catalyzes redox reactions causing oxidative stress and cytotoxicity. Iron, as a pro-oxidant, catalyzes lipid peroxidation, to generate ROS (33). In a vicious cycle, the generated ROS causes peroxidation of polyunsaturated fatty acids (PUFA) and membrane phospholipids triggering ferroptosis (32,34-36). The accumulating lipid peroxides of PUFA lead to membrane damage and cell death (37). The ROS production is prevented by sequestering of iron by ferritin and transferrin by virtue of its antioxidant nature (38).An imbalance between pro-oxidant and antioxidant properties of iron contributes to ferroptosis susceptibility. Evidence highlights the necessity of iron in lipid peroxidation, identifying it as a key vulnerability in cancer cells.

The enzymatic oxidants viz. lipoxygenases (LOXs), glutathione peroxidase 4 and non-enzymatic antioxidants take over the control of ensuing pathways (35). Lipoxygenases (LOXs) play a crucial role in formation of PUFA hydroperoxides. They inhibit the

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synthesis of antioxidant mediators like glutathione peroxidase 4 (GPX4), which otherwise would have reduced complex hydroperoxides into alcohols via Glutathione (GSH) (39). The cystine-glutamate antiporter system (system xc^-) facilitates import of cystine into the cell, a precursor for GSH synthesis (22). However, the elevated ROS levels counter system xc^- affecting GSH synthesis (40). The antioxidant defense system which is thus compromised, promotes ferroptosis. Some of the regulatory proteins like Ferroptosis suppressor protein 1 (FSP1), RAS synthetic lethal 3 (RSL3) and ferroptosis-inducing proteins (FINs) regulate the induction and progression of ferroptosis(30, 41, 42). FSP1 is an oxidoreductase which converts ubiquinone 10 (CoQ10) to CoQH2, negatively regulating ferroptosis (11). Ferroptosis is marked by structural and physiological changes in mitochondria which indicate the mitochondrial dysfunction also as a possible mechanism of ferroptosis (9, 43). The loss of cristae, metabolic energy changes, decreased glycolysis and iron metabolism inside the mitochondria cause malfunctioning of mitochondria resulting in ferroptosis(29, 34, 44).

Studies have identified p53, NRF2, RAS, ALOX family and SLC7A11 as pivotal genes modulating ferroptosis sensitivity, with mutations or overexpression in these pathways often correlating with ferroptosis induction or resistance in tumors (1, 7, 25, 45-48). Nuclear factor erythroid 2-related factor, NRF2 dysregulation promotes ferroptosis. Luo and the group reported an increase of intracellular lipid peroxidation in HEPG2 cells in response to downregulation of PRDX1 (49). RAS (Rat Sarcoma Viral Oncogene Homolog) mutations lead to ferroptosis through the RAS-BRAF-MEK-ERK pathway (1, 45).

Ferroptosis Inducers and Inhibitors:

Ferroptosis is a well-orchestrated mechanism of natural cell deathcontrolled by regulatory proteins and metabolic status of cells. Therefore, it can be induced or inhibited by some key modulators like erastin, RSL3, sulfasalazine and artemisinin, targeting the antioxidant defenses and biological membranes (21, 29, 34, 50). Erastin, a member of quinazolines, inhibits voltage dependent anion selective channels (VDACs). Sulfasalazine is known to promote ferroptosis via AKT-ERK1/2 and P53-SLC7A11 pathway (34). However, estrogen receptor inhibits transferrin receptor to adversely affect ferroptosis in breast cancer cells (51). The cystine/glutamate antiporter system xc^- is blocked by erastin as well as by sulfasalazine (5, 52). As a result, the membrane transport of cystine into the cell interior is downregulated, depleting glutathione synthesis. This reduction in antioxidant capacity sensitizes cells for lipid peroxidation and ferroptosis (32, 53). Erastin has been reported to synergisetemozolomide activity in glioma cells (54). RSL3 also targets the redox ability of cells controlled by the glutathione system, promoting lipid peroxidation (55, 56). GPX4 of the glutathione system protects cells against lipid peroxidation by reducing lipid hydroperoxides (21, 40, 53). Inhibition of GPX4 causes lipid peroxidation, disrupting cell membrane and triggering ferroptosis. The natural molecule, artemisinin, is also known to induce oxidative stress and lipid peroxidation (50). It identifies cancerous cells with altered redox balance, to selectively target them for ferroptosis (5,32). Various nanoparticles (e.g., iron oxide-based) have been developed to induce ferroptosis by delivering iron or other ferroptosis inducers to cancer cells (57).

Ferroptosis inhibitors like ferrostatins, liproxstatins or allosteric GPX4 activators, vitamin E,

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and other small molecules counter the pathways involved in ferroptosis (31,58). Fer-1, a ferrostatin, is a synthetic compound acting by scavenging of founder alkoxyl radicals generated by ferrous iron from lipid hydroperoxides. Fer-1, thus destroys the lipid hydroperoxides to prevent ferroptosis by generating an array of oxidized species (59). Liproxstatins like ferrostatins also prevent lipid peroxidation (60). Fan et al (61), concluded from their studies, Liproxstatin-1 inhibits mitochondrial lipid peroxidation in addition to recovered expression of GSH, GPX4 and ferroptosis suppressor protein 1(31).

Strategies to enhance ferroptosis in tumors:

The limitations of contemporary cancer treatment modalities have sparked the search for novel targets and molecules. Ferroptosis, identified in 2012, was not long ago considered as targeted treatment for neoplastic cells. However, now investigations are directed to find its role as an adjunct therapy for cancer treatment (53). Strategies devised to regulate ferroptosis for possible therapeutic interventions include inhibition of GPX4, reduction of glutathione, generation of ROS and free intracellular iron, triggering of anti-tumor immune response, furnishinglipids and activation of lipid peroxidation enzymes (29, 53, 62, 63).

Ferritinophagy- The free intracellular iron in excess of metabolic requirement is stored in cytoplasmic ferritin, which absorbs iron ions in the form of multimers. The lysosomes then degrade ferritin to increase free iron levels by ferritin autophagy (=ferritinophagy) resulting in increased iron storage (3). Ferritinophagy maintains iron equilibrium in the cells by recycling stored iron for cellular activities. This helps mitigate iron induced oxidative damages (29, 63, 64). Ferritinophagy inhibition could be a potential strategy to enhance ferroptosis in tumors. Ferritinophagy induces cell death by regulating lipid peroxidation, nuclear receptor coactivator 4 (NCOA4) mediated cellular autophagy and stimulation of the immune system against cancerous cells (63, 65). The immune system and lipid peroxidation pathways synergistically promote demise of cancer cells.

Promotions of lipid peroxidation by generation of ROS- ROS are physiologically important for cells. However, their imbalance leads to oxidative stress implicated in disease progression. Excessive lipid peroxidation is also a consequence of ROS generation which can lead to ferroptosis(36, 53, 66). Targeting generation of ROS in mitochondria during oxidative phosphorylation increases susceptibility to ferroptosis (43, 67, 68). Deprivation of glucose deficient cancer cells for amino acids leads to glutaminolysis promoting ferroptosis (53). NADPH oxidases (NOXs) generate ROS as part of their normal function and any means to upregulate NOXs expression results in increased ROS generation. Lipid peroxidation can be promoted by production of hydroxyl radicals. The modifications in iron metabolism, iron uptake, storage, utilization and release, generate hydroxyl radicals through iron dependent fenton reaction.

Inhibition of antioxidant pathways-Cancer cells often evade ferroptosis by activating antioxidant pathways (e.g., SLC7A11/GPX4 axis). Inhibiting these pathways may sensitize tumor cells to ferroptosis (53,64,66). Inhibiting GPX4 using compounds like RSL3 or FIN56 promotes lipid peroxidation and ferroptosis (56). Depleting Glutathione inhibits the cystine/glutamate antiporter (System Xc-), reducing glutathione levels results in lipid peroxidation buildup, enhancing

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ferroptosis. In vitro and in vivo evidence indicates a notable decrease in tumor growth in response to these inhibitors (69).

Systemic Approaches: Ferroptosis has been suggested as a part of combination therapy including chemotherapy, radiotherapy and immunotherapy to improve treatment efficiency or overcome drug resistance(3,53,70,71). The combination approaches negatively regulate anti-ferroptotic proteins such as GPX4 and solute carrier family 7 member 11(SLC7A11), with a concurrent promotion of acyl-CoA synthetase long-chain family member 4 (ACSL4) and lipid peroxidation (19,20,64,66). Studies indicate improved efficacy in challenging cancers such as glioblastoma and pancreatic cancer when combined treatments are applied (12,67). An overview of approaches applied in key cancers is summarized in table 4.

Table 4: Approaches to enhance ferroptosis in most fatal cancers

Cancer Type	Approach	Mechanism/Details	References
Breast Cancer	Targeting system Xc-	Depletes cystine levels, reducing glutathione synthesis.	72-75
	Inhibition of GPX4	Reduces lipid peroxidase detoxification, promoting ferroptosis.	
Lung Cancer	Use of ferroptosis inducers (e.g., Erastin)	Directly induces lipid peroxidation and ferroptosis.	7,18
	Iron supplementation	Increases available iron for Fenton reaction, enhancing ROS production.	
Colorectal Cancer	Combination therapy with chemotherapeutics	Enhances oxidative stress and lipid peroxidation alongside traditional treatments.	16,76
	Nutrient deprivation (e.g., cysteine)	Limits antioxidant capacity, promoting ferroptosis.	

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Prostate Cancer	Targeting androgen receptor signaling	Alters cellular metabolism, increasing sensitivity to ferroptosis.	10,47,77-79
	Lipid peroxidation inducers (e.g., ROS modulators)	Enhances oxidative damage in cancer cells.	
Pancreatic Cancer	Using small-molecule inhibitors of cystine-glutamate antiporter	Reduces GSH levels, promoting ferroptosis.	13,21,44
	Targeting mitochondrial metabolism	Disrupts energy production, leading to increased ROS and ferroptosis.	
Melanoma	Combining ferroptosis inducers with immunotherapy.	Enhances anti-tumor effects by inducing ferroptosis in resistant cells.	80-82

Role of the Tumor Microenvironment (TME)

The complex and dynamic milieu of tumors consists of stromal cells, extracellular matrix, blood vessels, signaling molecules and immune cells interacting together to influence tumor development, progression and therapeutic outcomes. Any modulation in TME disrupts tumor growth, potentially by ferroptosis and other cell death pathways.

Tumor-specific vulnerabilities to ferroptosis vary based on the context and specific cancer type- Iron metabolism lies at the crux of ferroptosis and is responsive to changes in TME (83). Ferritin sequesters immune and cancer cells of iron, promoting their survival while release of iron from stromal cells enhances susceptibility to ferroptosis. Iron supplementation in TME helps to overcome resistance to erastin induced ferroptosis (84). The dysregulated glutamine and lipid metabolism in TME makes cancer cells more susceptible to lipid peroxidation and ferroptosis (85). The lipid transporters help in influx of iron in cancer cells affecting response to ferroptosis. The reduction of ROS in TME as an outcome of hypoxia may suppress ferroptosis. Possibly the tumors stabilize hypoxia-inducible factors, affecting the iron metabolism and antioxidant systems (15, 86). The upregulated antioxidant enzyme systems result in altered susceptibility to ferroptosis. Similar to hypoxia, deficiency of other essential nutrients in TME make cells vulnerable to ferroptosis. The presence of protein products of RAS, MYC p53 and other oncogenes results in cellular resistance to ferroptosis(45, 53, 87, 88).

Biomarkers and Clinical Applications- Studies have identified lipid peroxidation byproducts, lipid hydroperoxides (e.g., malondialdehyde, 4-

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hydroxynonenal 4-HNE) as direct marker of ferroptosis (2). The upregulation of several biomarkers like ferritin, transferrin receptors, GPX4 or SLC7A11 can be used to identify susceptibility of cancer cells to ferroptosis(18, 20). Cancer patients can be categorized based on their susceptibility to ferroptosis to provide for personalized medicine. Predictive biomarkers like iron metabolism status and antioxidant capacity have helped patient stratification and optimisation of ferroptosis-based therapy responses. Survival analysis indicated that high GLMP, SLC38A6, and WDR76 expression levels are linked to poor overall survival (18).

Risks associated with ferroptosis induction in vivo- Theferroptosis activators like RSL3 or oxidized lipids can accidently lead to the death of the critical antitumor immune cells including cytotoxic CD8+ T cells, DCs (dendritic cells) and bone marrow stem cells resulting in hematopoiesis and bone marrow suppression(2,53,89). Ferroptosis inducers like other therapeutic potions pass through hepatic metabolism and renal elimination procedures, which may make these organs vulnerable to adverse side effects of ferroptosis induction. It has been found that the renal tubular cells, cardiomyocytes, neurons and glial cells are susceptible to ferroptosis (53). Metabolic syndromes like cachexia associated with chronic illnesses, such as cancer may be observed in some patients (63, 90). Ferroptosis-based treatments can contribute to weight loss and muscle wasting, typical symptoms of cachexia (53, 63). Although the cancer therapies aim to eliminate mutant cancer cells, they may affect normal cells at distant sites giving rise to new unrelated cancers (53). However, the risks can be managed by modulating the cellular environment and genetic factors responsible for ferroptosis. The off-target sites can be promoted to resist lipid peroxidation by increasing levels of glutathione and antioxidant enzymes in TME. The accumulation of free iron produced as a result of cellular homeostasis can be chelated with chelators to reduce ferroptosis in non-target cells. The other methods to prevent non-specific side effects may be by modulation of lipid metabolism, regulation of transcription factors controlling expression of antioxidant genes, or by targeted gene therapies. These strategies can be used to customize ferroptosis based therapies for novel solutions in cancer treatment.

Challenges and opportunities in targeting ferroptosis- Ferroptosis specific markers are still ill-defined in comparison to other forms of regulated cell death (91). This limits the use of ferroptosis based therapies without affecting the normal cells. Moreover the understanding of the complex tumor microenvironment, their interactions with ferroptosis inducer molecules is still in infancy, making clinical applications a distant reality (29,91). The solubility barriers, bioavailability of inducers, underlying molecular mechanisms triggering ferroptosis are evolving areas of research interest (92). As the molecular mechanisms are being explored, studies suggesting resistance to ferroptosis are also being reported. Development of models to evaluate safety and efficiency for clinical translations of ferroptotic therapy are a constraint to be addressed. Studies have found the combination of ferroptosis inducers with immunotherapies and chemotherapeutics enhances antitumor responses (62). It has been reported that RNA m6A modifications can affect the tumor sensitivity to immunological methods (71). Opportunities for development of guided tailored therapies can be realized by identifying patient-specific biomarkers. Detection of any alterations in the biomarker levels in TME can be used to predictferroptosis response. Findings indicate that certain cancer cells upregulate alternative antioxidant systems when GPX4 is inhibited. Further research is necessary to identify new inhibitors that can overcome such resistance. The resolution of challenges by researchers in understanding prognosis and TME hold promise for ferroptosis based precision cancer treatment.

4. Discussion-

The perusal of the findings from the literature has led to understanding of research focus pertaining to ferroptosis, broader implications, limitations, and future directions to be addressed.

Key Insights

Ferroptosis is a promising strategy to induce cell death in cancer cells especially those resistant to traditional therapies (70). The changes in TME viz. iron and lipid metabolism make cancer cells vulnerable to ferroptosis (33,73). The cellular antioxidant defenses like GPX4

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are potential targets to enhance susceptibility to ferroptosis. A combination of traditional and evolving strategies based on ferroptosis are bound to improve treatment outcomes. Cell death by ferroptosis has been observed in cancers of neural tissues, hepatic and renal cells. Highly dedifferentiated or mesenchymal tumors are relatively more responsive to ferroptosis. The exploitation of TME for inducing ferroptosis selectively only in cancerous cells provides an advantage to protect normal cells from potential side effects.

Gaps and Limitations- The available literature has suggestions of ferroptosis based therapies for treatment of cancers. However, a growing body of literature referring to resistance to ferroptosis cites upregulation of antioxidant pathways or metabolic alterations as contributing factors (29, 66, 93). The mitigation of these changes in TME remains a challenge as the insights into ferroptosis inducer development and their working mechanisms are still evolving. The potential targets of ferroptotic therapy and how they will affect pathways leading to lipid peroxidation and generation of ROS are being identified. The involvement of other cellular components such as mitochondria and lysosomes are not precisely known as for other cell death pathways (29, 43, 68). The heterogeneous TME poses another challenge. Hypoxic conditions, commonly found in solid tumors, can suppress ROS levels, reducing ferroptosis susceptibility. Innovative strategies to reoxygenate tumors or modify the tumor microenvironment are required to enhance ferroptosis efficacy. The lack of verifiable experimental models has led to development of off-target effects in normal tissues raising suspicions to use of ferroptosis in clinical settings. Tissues relying on similar iron and lipid metabolism pathways may be adversely affected by ferroptosis inducers. Erastin and sulfasalazine are known to affect additional regulatory pathways beyond ferroptosis making interpretation of preclinical results a challenge. An approach to personalized therapy requires identification of specific biomarkers to ascertain patient sensitivity to ferroptosis therapy. Limited number of biomarkers such as GPX4, SLC7A11 expression, and lipid peroxidation byproducts are emerging as valuable indicators of ferroptosis sensitivity (94). Stratification of patients, precise dosing and targeted delivery methods need to be developed with continuing preclinical and clinical trials to establish safe therapeutic windows.

Future Directions and Opportunities- Combining synergistic therapies like chemotherapy, radiotherapy, or immunotherapy with ferroptosis inducers holds promise for enhanced efficacy with least toxicity, especially for treatment-resistant cancers (62,70,71). The combination therapies can enable tailor drug doses for optimum therapeutic effects. The therapies are to be designed so as to target multiple ferroptosis-related pathways, overcome resistance and achieve greater selectivity for cancer cells (84,93,95). Non-coding RNAs can epigenetically modify the ferroptosis regulators to improve therapeutic modalities (20,96,97). The drug delivery vehicles like nanoparticles, liposomes, or antibody-drug conjugates can be used to enhance specificity (70). Pharmacokinetic studies are crucial for optimal dosing. Reliable preclinical models are needed to better predict ferroptosis efficacy in human cancers. Advances in 3D cultures, organoids, and patient-derived xenograft models could help bridge the translational gap and inform clinical trial design. Biomarker-guided approaches may be applied to identify patient-specific biomarkers to tailor treatment based on individual profiles. Deciphering the essential biomarkers and their role in ferroptosis may help innovate therapeutics by application of machine learning approaches (98).

Conclusion

The exploration of ferroptosis as a possible target in cancer therapy is a fast evolving regime. Ferroptosis has emerged as a potential treatment method against many malignancies. The growing understanding of molecular mechanisms involved in ferroptosis has opened up prospective intervention targets to exploit cell death mechanisms specifically in cancer cells. Cancer resistance to existing cancer therapeutic procedures limit their efficacy as a treatment modality. Ferroptosis, on the contrary utilizes unique susceptibilities of cancer cells viz. elevated iron dependency and altered redox states, to bypass mechanisms of resistance. Moreover, the treatments promoting ferroptosis are specific for cancer cells, sparing normal cells from negative side effects. These benefits favor ferroptosis to long established treatment methods. The observations for ferroptosis are in infancy

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and cannot be exactly translated to in-vivo conditions. The ferroptosis regulatory mechanisms, inconsistent cancer types and precision targeting are pronounced hurdles, before aiming at ferroptosis in cancer treatment. The ongoing research is critical to elaborate the curative strategies, optimize drug delivery systems and identify biomarkers for patient classification. The evolving understanding of ferroptosis will certainly make ferroptosis-based therapies an integral part of the oncological armory, providing hope for enhanced outcomes in cancer management. The transition from bench to bedside is fairly foreseen by incorporation of future research and clinical trials. The review provides valuable insights, analyzes the translational challenges and identifies critical future directions to hold the promise of ferroptosis becoming a part of complex anticancer therapies.

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