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Review Article

Ferroptosis as a Therapeutic Target: Advances in Drug Development for Cancer and Neurodegenerative Diseases

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ABSTRACT

Background: Ferroptosis is an iron-dependent, regulated form of cell death characterized by lipid peroxidation and oxidative stress, distinct from apoptosis and necrosis. It has emerged as a key therapeutic target in cancer and neurodegenerative diseases due to its dual role in promoting or preventing cell death. Ferroptosis inducers can eliminate drug-resistant cancer cells, while inhibitors may protect neurons in conditions like Alzheimer's and Parkinson's disease. Understanding its molecular mechanisms and pharmacological modulation offers new therapeutic possibilities. This review focuses on the pharmacological modulation of ferroptosis, its therapeutic potential in cancer and neurodegeneration, and the associated challenges in clinical translation. **Materials and Methods:** A narrative literature search was conducted in PubMed, Scopus, and Web of Science for articles published between 2015 and 2024 using the keywords ferroptosis, cancer therapy, lipid peroxidation, and neurodegeneration. Relevant preclinical and clinical studies were included. **Results:** Ferroptosis inducers like Erastin, RSL3, Sorafenib, and FIN56 sensitize cancer cells by inhibiting glutathione metabolism. Inhibitors Ferrostatin-1 and Liproxstatin-1 are neuroprotective. Though specificity, toxicity, and delivery issues persist, clinical trials attest to their promise. **Conclusion:** Ferroptosis is a novel oncology and neurology drug target. Future trials must address biomarkers, delivery systems, and their interaction with apoptosis and autophagy for the best treatment strategy.

Keywords: Ferroptosis, Cancer Therapeutics, Neurodegeneration, Lipid Peroxidation, Reactive Oxygen Species (ROS), Drug Development.

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INTRODUCTION

Ferroptosis is a regulated, specific type of cell death that is iron-dependent and has unchecked lipid peroxidation and oxidative stress, making it distinct from apoptosis and necrosis. First described by Dixon *et al*., (2012), ferroptosis was characterized as a nonapoptotic, iron-dependent death induced by the small molecule Erastin, which blocks System Xc^-, cystine-glutamate antiporter (Ma *et al*., 2021). Ferroptosis has since picked up steam as an oncology and neurodegenerative disease target for drugs because it has a two-pronged role: to induce it to kill cancer cells and to block it to rescue neurons (Li *et al*., 2020).

Molecularly, ferroptosis results from a dysbalance between antioxidant defence mechanisms and oxidative stress. Glutathione Peroxidase 4 (GPX4) is a chief regulator that protects against ferroptosis by lipid peroxide reduction. Inhibition or diminution of Glutathione, its cofactor, triggers ferroptotic death. System Xc^- plays a critical role in the import of cystine required for glutathione production; inhibition by Erastin or Sorafenib triggers glutathione deficiency and ROS accumulation (Hu *et al*., 2019). Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4) helps by PUFA-enriching membrane, making it susceptible to peroxidation. Opposing the pathway, Ferroptosis Suppressor Protein 1 (FSP1) and Coenzyme Q10 (CoQ10) block ferroptosis and sustain redox equilibrium (Kong *et al*., 2019).

Ferroptosis is especially useful in cancer therapy for drug resistance breaking in apoptosis-resistant cancers like Glio Blastoma Multiforme (GBM), Hepato Cellular Carcinoma (HCC), Pancreatic Ductal Adeno Carcinoma (PDAC), and Triple-Negative Breast Cancer (TNBC) (Zhang *et al*., 2019). Compounds like Erastin, RSL3, Sorafenib, and FIN56 have been shown to induce ferroptosis by inhibiting antioxidant pathways and iron homeostasis. RSL3 directly inhibits GPX4, whereas Sorafenib inhibits System Xc^-. Such agents may be combined with chemotherapy or immune checkpoint inhibitors to increase cancer cells' therapeutic effect and immune clearance (Chang, 2016).

Conversely, in neurodegenerative diseases such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease

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(HD), and Amyotrophic Lateral Sclerosis (ALS), ferroptosis inhibition is a therapeutic target (Zhu *et al*., 2020). Neurons, highly susceptible to oxidative damage by PUFA-rich membranes and high oxygen use, are especially vulnerable to iron-mediated ferroptotic injury. Inhibitors Ferrostatin-1 and Liproxstatin-1 block oxidative damage, and iron chelators such as Deferoxamine block limiting neurotoxicity. Excess iron in the substantia nigra in PD and lipid peroxidation in AD and HD have been demonstrated to support ferroptosis contribution to these diseases (Nassar and Blanpain, 2016).

Ferroptosis also crosstalks with apoptosis, necroptosis, and autophagy. Although apoptosis is caspase-dependent, ferroptosis provides a caspase-independent mechanism for apoptosis-resistant tumour cell death. Autophagy can induce ferroptosis by breaking down ferritin and GPX4, promoting lipid peroxidation and iron release, but it can also be protective by alleviating oxidative stress through mitophagy (Katoh, 2017).

Despite the therapeutic potential, ferroptosis is confronted with clinical hurdles such as an absence of certified biomarkers, drug selectivity, and delivery issues, especially across the blood-brain barrier. Future studies must address identifying valid biomarkers, enhancing nanoparticle-mediated delivery systems, and investigating immune system interactions. Finally, ferroptosis possesses revolutionary potential in oncology and neurology, dependent on interdisciplinarity to move research into practice (Reya *et al*., 2001).

Ferroptosis has gained increasing attention in oncology because it is implicated in iron-dependent lipid peroxidation. Wang *et al*., (2021) outlined its mechanisms and identified Erastin and RSL3 as targets of resistant cancer cells. Yang *et al*., (2020) explored the reversal of cancer stem cell resistance. Shen *et al*., (2018) identified combining ferroptosis with immunotherapy. Sun *et al*., (2023) highlighted reducing toxicity. Lu *et al*., (2018) and Tong *et al*., (2022) discussed its crosstalk with other death pathways. These findings are shown in Table 1.

MATERIALS AND METHODS

Locating Data

A comprehensive search in PubMed, Scopus, and Web of Science for articles published over the past ten years from 2015 to 2024 with keywords like ferroptosis, cancer therapy, neurodegeneration, lipid peroxidation, and oxidative stress was conducted.

Data Collection

Peer-reviewed original research, clinical trials, and extensive preclinical studies were searched with a focus on reporting mechanisms, modulators, and therapeutic uses.

Data Extraction

Key findings were compiled regarding regulatory pathways, drug targets, efficacy, toxicity, and limitations.

Merging Data

Data were analyzed for trends, gaps, and strategies in cancer and neurodegeneration to provide an evidence-based overview of ferroptosis for clinical translation.

RESULTS

Induction of Ferroptosis and Its Therapeutic Application for Cancer Treatment

Ferroptosis, an iron-dependent form of programmed cell death, is a promising target for cancer therapy due to its ability to induce death in chemotherapy-resistant cancer cells (Zhao *et al*., 2020). It is triggered by lipid peroxide excess, primarily by inhibiting Glutathione Peroxidase 4 (GPX4) or System Xc^{-}, a cystine-glutamate antiporter. GPX4 inhibitors RSL3 and ML162 interfere with antioxidant defences, while Erastin and Sorafenib inhibit System Xc^{-}, glutathione depletion, and ROS excess (Nie *et al*., 2022). These mechanisms make cancers such as Triple-Negative Breast Cancer (TNBC), Hepato Cellular Carcinoma (HCC), and Glioblastoma (GBM) ferroptosis-vulnerable. Combination with chemotherapy, radiotherapy, or immunotherapy enhances therapeutic efficacy (Lu *et al*., 2018). Radiotherapy enhances iron availability, and immune checkpoint inhibitors increase immune-mediated clearance. Tumour cells resist ferroptosis by antioxidant overexpression or FSP1 upregulation (Jiang *et al*., 2020). Strategies such as co-inhibition of GPX4 and FSP1, combination therapy, and nanoparticle drug delivery are being investigated to bypass resistance and selectively kill tumour cells with reduced toxicity (Lei *et al*., 2020), as illustrated in Table 2.

Ferroptosis in Neurodegenerative Diseases: A Double-Edged Sword

Ferroptosis is a major contributor to neurodegenerative diseases like Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD) due to its link with oxidative stress and iron dysregulation. Lipid metabolism-dependent neurons are especially susceptible to ferroptosis-induced cell death by iron overload and lipid peroxidation. Elevated iron in the substantia nigra (PD) and cortex (AD) and lipid peroxidation products like malondialdehyde and 4-hydroxynonenal in postmortem brain tissue reflect ferroptosis contribution to neuronal loss (Miller *et al*., 2020). Inhibition of ferroptosis has been recognized as an exciting neuroprotective strategy. Lipid peroxidation, oxidative stress inhibitors like Ferrostatin-1 and Liproxstatin-1, and iron chelators like Deferoxamine inhibit iron-induced damage and neuronal damage. New studies explore cerebrospinal fluid and blood-based ferroptosis biomarkers, but challenges remain in discovering blood-brain barrier–permeable inhibitors that

Table 1: Literature Review - Previous Work.

Authors (Year)	Key Finding	Research Focus	Challenges/Limitations	Future Scope
(Wang *et al*., 2021)	Identified ferroptosis mechanisms in cancer.	Ferroptosis in cancer therapy.	Drug specificity, off-target effects.	Develop combination therapies with reduced toxicity.
(Yang *et al*., 2020)	Explored ferroptosis in targeting cancer stem cells.	Overcoming cancer stem cell resistance.	Adaptive resistance mechanisms in cancer.	Enhance targeted drug delivery.
(Shen *et al*., 2018)	Discussed ferroptosis-based cancer therapies.	Ferroptosis in cancer therapy + immunotherapy.	Toxicity concerns limiting clinical use.	Clinical trials for efficacy assessment.
(Sun *et al*., 2023)	Advancements in ferroptosis-targeting drugs.	Development of ferroptosis-targeting drugs.	Toxicity, need for biomarkers.	Improve drug specificity and reduce side effects.
(Lu *et al*., 2018)	Investigated ferroptosis in cancer progression.	Ferroptosis in cancer progression.	Complexity in ferroptosis regulation.	Identify biomarkers to monitor ferroptosis.
(Tong *et al*., 2022)	Examined ferroptosis interplay with other cell death pathways.	Ferroptosis and other cell death pathways in cancer therapy.	Pathway crosstalk complicates interventions.	Explore personalized cancer therapy using ferroptosis.

This Table consolidates the ongoing research work in ferroptosis studies in a structured manner, including key findings, research areas, challenges, and opportunities.

Table 2: Ferroptosis Induction and Its Role in Cancer Therapy.

Authors	Ferroptosis Inducer	Cancer Type	Mechanism of Action	Therapeutic Outcome	Combination Therapy
(Zhao *et al*., 2020)	Erastin	Lung, Breast, Pancreatic	Inhibits System Xc^-, depleting Glutathione and inducing lipid peroxidation.	Triggers ferroptosis in apoptosis-resistant tumours, reduces tumour size.	Synergistic with chemotherapy and radiotherapy.
(Nie *et al*., 2022)	Sorafenib	Hepatocellular Carcinoma	Blocks System Xc^- reducing intracellular cystine and increasing oxidative stress.	Enhances ferroptotic cell death, limits recurrence.	Works well with immunotherapy (PD-L1 inhibitors).
(Lu *et al*., 2018)	RSL3	Glioblastoma, Melanoma	Directly inhibits GPX4, leading to toxic lipid peroxidation.	Promotes selective cancer cell death, inhibits tumour progression.	Potential combination with autophagy modulators.
(Jiang *et al*., 2020)	FIN56	Colorectal, Liver	Disrupts coenzyme Q10 synthesis, amplifying oxidative damage.	Induces cell death in treatment-resistant colorectal cancer.	Enhances response with conventional chemotherapy.
(Lei *et al*., 2020)	Ionizing Radiation	Esophageal, Head and Neck	Increases free iron levels, enhancing ROS generation.	Potentiates radiation-induced tumor suppression via ferroptotic mechanisms.	Improves effectiveness of radiotherapy in aggressive cancers.

This Table compiles key ferroptosis inducers, their molecular targets, targeted cancers, therapeutic advantages, and putative combination therapies.

preserve normal iron homeostasis. Additional studies are required to translate these results into effective neurotherapeutics (Degterev *et al.*, 2005).

Pharmacological Modulators of Ferroptosis: Advances and Challenges

Pharmacological modulation of ferroptosis has also been an effective cancer therapy and neuroprotection strategy. Ferroptosis inducers Erastin, RSL3, Sorafenib, and FIN56 inhibit System Xc^{-} or directly inhibit GPX4, resulting in lethal lipid peroxidation (Jiang *et al.*, 2021). These are especially effective against apoptosis-resistant cancer. Inhibitors Ferrostatin-1, Liproxstatin-1, and Vitamin E, however, inhibit lipid peroxidation and exhibit neuroprotection in models of Alzheimer's and Parkinson's disease. This bimodal modulation characterizes ferroptosis as a drug and a disease-preventive target (Hsieh *et al.*, 2021). Clinical use is, however, hindered by off-target toxicity, low bioavailability, and low specificity. Inducers damage normal tissue, whereas inhibitors disrupt iron homeostasis. Drug delivery is another challenge, especially across the blood-brain barrier (Koeberle *et al.*, 2023). Overcoming these challenges, research focuses on nanoparticle-based drug delivery systems, stable ferroptosis biomarkers, and best combination regimens. These are needed to safely and effectively translate ferroptosis-targeting drugs to clinical use (Consoli *et al.*, 2024), as illustrated in Table 3.

Crosstalk of Ferroptosis with Other Cell Death Models

Ferroptosis has extensive crosstalk with other controlled cell death pathways, including apoptosis, necroptosis, and autophagy, to form a highly interconnected network that controls disease progression and therapeutic response (Lee *et al.*, 2018). Different from caspase-dependent apoptosis, ferroptosis is triggered by iron loading and lipid peroxidation. However, ferroptosis serves as a backup cell death pathway in cancer cells with inhibited apoptosis, e.g., with TP53 mutations (Chen *et al.*, 2024). Necroptosis, regulated by RIPK1 and MLKL, shares overlapping oxidative stress features with ferroptosis, and one can replace the other under some tumour conditions. Autophagy has a bifunctional role in the regulation of ferroptosis: it triggers ferroptosis by degrading GPX4 and ferritin, making more iron available, but suppresses ferroptosis by mitophagy, reducing oxidative stress (Wu *et al.*, 2023). Suppression of autophagy may thus enhance the induction of ferroptosis in tumours. Such interactions illustrate the therapeutic potential of combination regimens co-targeting ferroptosis and apoptosis or autophagy pathways, particularly in therapy-resistant tumours (Ren *et al.*, 2021; Wu *et al.*, 2024). Such interaction is provided in Table 4.

Challenges with Translating Ferroptosis Research to Clinical Practice

Significant translational constraints hamper ferroptosis studies in clinic application. A lack of disease monitoring and patient stratification through ferroptosis-specific biomarkers is the biggest issue since current markers, such as lipid peroxidation and iron level, are non-ferroptosis-specific (Weiland *et al.*, 2019). Drug specificity is also a problem, with inducers of ferroptosis having the risk of targeting healthy tissues to provoke toxicity, particularly in tissues high in polyunsaturated fatty acids. Tumour heterogeneity necessitates personalized medicine, and the blood-brain barrier limits ferroptosis-targeting drugs' effectiveness in neurodegenerative diseases such as Alzheimer's and Parkinson's (Alim *et al.*, 2019).

DISCUSSION

Ferroptosis is an iron-mediated, regulated type of cell death defined by lipid peroxidation and oxidative damage, differentiating it from apoptosis and necrosis. Therapeutic uses are currently the subject

Table 3: Ferroptosis Modulation Therapies.

Authors	Compound	Molecular Target	Disease Model	Challenges	Toxicity Profile/Future Directions
(Jiang *et al.*, 2021)	Erastin	Inhibits System Xc^{-} reducing Glutathione.	Lung, Breast, Pancreatic Cancer.	Selective targeting of tumour cells.	Potential neurotoxicity: enhancing tumour selectivity.
(Hsieh *et al.*, 2021)	NRF2 Nano-Modulator	NRF2 modulation to enhance ferroptosis.	Lung Cancer	Delivery challenges, systemic toxicity.	Developing safer nano-formulations.
(Koeberle *et al.*, 2023)	FINO2	Iron-dependent lipid peroxidation.	Drug-resistant Cancers.	Bioavailability, off-target effects.	Reducing systemic toxicity, improving pharmacokinetics.
(Consoli *et al.*, 2024)	Natural Plant Extracts	Antioxidant balance disruption, ferroptosis induction.	Various solid tumours.	Variability in compound efficacy.	Standardizing dosing, exploring combination therapy.

This Figure illustrates different ferroptosis-modulating molecules, target molecules, disease models, issues of concern, toxicities, and therapeutic potential.

Table 4: Crosstalk Between Ferroptosis and Other Cell Death Pathways.

Authors	Cell Death Pathway	Molecular Mechanism	Disease Model	Therapeutic Opportunity	Combination Therapy Potential
(Lee *et al*., 2018)	Ferroptosis- Apoptosis Crosstalk	Endoplasmic reticulum stress triggers ferroptosis-induced apoptosis.	Cancer Cells (Colon, Pancreatic).	Dual modulation of ferroptosis and apoptosis to enhance therapy.	BCL-2 inhibitors and ferroptosis inducers.
(Chen *et al*., 2024)	Ferroptosis and Tumor Microenvironment	Cancer-associated fibroblasts modulate ferroptosis sensitivity.	Tumor Microenvironment in Various Cancers.	Targeting tumor-associated fibroblasts to improve ferroptosis-based treatments.	CAF inhibitors combined with ferroptosis triggers.
(Wu *et al*., 2023)	Organelle-Specific Ferroptosis and Apoptosis	Mitochondria and lysosomes regulate both ferroptosis and apoptosis.	Lung, Liver, and Brain Cancer.	Mitochondrial-targeted ferroptosis inducers for therapy.	Mitochondrial- targeting drugs plus ferroptosis agents.
(Ren *et al*., 2021)	Oxidative Stress, Ferroptosis, and Ischemic Stroke	Reactive Oxygen Species (ROS) drive both oxidative stress and ferroptosis.	Ischemic Stroke, Cardiovascular Diseases.	Antioxidant therapies that regulate ferroptosis in ischemic stroke.	Antioxidants with ferroptosis modulators.
(Wu *et al*., 2024)	Exosome-Mediated Ferroptosis Regulation	Exosomal cargo influences lipid peroxidation and ferroptosis sensitivity.	Tumor Metastasis, Drug Resistance.	Exosome-based drug delivery systems for ferroptosis regulation.	Exosome-modulating agents with ferroptosis inducers.

This bar indicates the crosstalk between ferroptosis, apoptosis, oxidative stress, and tumour microenvironment and distinguishes therapeutic applications and combination treatment strategies.

of intense scrutiny, especially in cancer and neurodegenerative diseases. Resistance mechanisms, regulation, and translational barriers must be better understood to create practical clinical applications (Zille *et al*., 2017).

In cancer, ferroptosis offers a solution against apoptosis-insensitive tumours such as Hepato Cellular Carcinoma (HCC), Glio Blastoma Multiforme (GBM), and Triple-Negative Breast Cancer (TNBC). Therapies such as RSL3, ML162, Erastin, and Sorafenib block Glutathione Peroxidase 4 (GPX4) or interfere with the cystine-glutamate antiporter System Xc^{-}, depleting Glutathione and lipid peroxidation and resulting in ferroptosis (Han *et al*., 2020). Induction of ferroptosis with inducers in combination with chemotherapy, radiotherapy, or immunotherapy is synergistic. Radiotherapy, for example, enhances the iron levels in tumours, sensitizing them to ferroptosis, and immune checkpoint blockade enables immune-mediated ferroptotic cell clearance (Bebber *et al*., 2020). Resistance in cancer cells is attained through Ferroptosis Suppressor Protein 1 (FSP1) upregulation, NRF2 antioxidant response, and heat shock protein activation. Blocking these mechanisms must be attained to optimise ferroptosis-based therapy (Kayagaki *et al*., 2011).

Ferroptosis enhances neuronal degeneration in neurodegenerative disorders due to the brain's high oxygen requirement, Polyunsaturated Fatty Acid (PUFA), and iron content. Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's Disease (HD) have been linked to ferroptosis by iron overload and lipid peroxidation markers such as Malondialdehyde (MDA) and 4-Hydroxynonenal (4-HNE) in damaged brain areas (Kayagaki *et al*., 2013). Neuroprotectants such as Ferrostatin-1, Liproxstatin-1 and iron chelators such as Deferoxamine inhibit ferroptosis by inhibiting lipid peroxidation and oxidative stress. Their therapeutic use is, however, hampered by poor ability to penetrate the Blood-Brain Barrier (BBB) and disruption of systemic iron homeostasis (Shi *et al*., 2014). Moreover, the absence of ferroptosis-specific biomarkers makes early diagnosis and monitoring difficult, and the development of BBB-permeable inhibitors and sensitive biomarkers is recommended (Wang *et al*., 2017).

Pharmacological modulation of ferroptosis has progressed with attempts to optimize inducers and inhibitors. Although drugs such as Erastin, RSL3, and FIN56 are promising in cancer, inhibitors Ferrostatin-1 and Liproxstatin-1 are neuroprotective (Rogers *et al*., 2019). Nevertheless, off-target toxicity is still problematic, particularly for non-neoplastic cells with high PUFA content. This emphasizes the need for improved drug selectivity and bioavailability. Nanoparticle-based delivery systems are being explored to enhance the specificity and minimize systemic exposure of ferroptosis-targeting therapies, including crossing BBB barriers (Liu *et al*., 2019).

Elucidation of how ferroptosis intersects with other cell death mechanisms, such as apoptosis, necroptosis, and autophagy, can yield clues for combination therapy. Autophagy can inhibit or induce ferroptosis by modulating ROS and GPX4 degradation, thus holding the potential for multi-targeted therapy (Ruan *et al*., 2018). In addition, the translation of ferroptosis-based therapies into the clinic needs the establishment of accurate diagnosis tools. Existing biomarkers such as lipid peroxidation and iron metabolism markers are non-specific, and thus, non-invasive imaging or blood-based biomarkers are urgently needed. Tumour heterogeneity is also challenging since varied cancers are differentially sensitive to ferroptosis. Personalized medicine through metabolic profiling is needed to optimise patient outcomes (Liu *et al*., 2016).

Future Directions and Key Takeaways

Future studies on ferroptosis will require focusing on improving drug specificity, reducing toxicity, and targeted delivery, primarily through nanoparticle-based systems. Combination therapy, for instance, of ferroptosis inducers with immunotherapy or apoptosis-targeting therapeutics may enhance efficacy in resistant cancers. In neurodegeneration, the discovery of ferroptosis inhibitors that can cross the blood-brain barrier is critical for the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. A critical area of progress is the discovery of ferroptosis-specific biomarkers for diagnosis, patient selection, and treatment monitoring. Elucidation of ferroptosis interactions with the immune system and cancer microenvironment may also lead to better immunotherapeutic strategies. Interdisciplinary collaborations between pharmacology, oncology, and neuroscience are critical for translation to the clinic.

CONCLUSION

Ferroptosis is a paradigm shift for anticancer and neurodegenerative disease therapeutic strategies. Iron-catalyzed and lipid peroxidation-driven is a new mechanism of apoptosis-resistant cancer cell killing, while inhibition can save neurons from death. Agents like Erastin, Sorafenib, and RSL3 are of anticancer interest, while Ferrostatin-1 and Liproxstatin-1 can provide neuroprotection. There are, however, obstacles to its therapeutic use, such as off-target toxicity, delivery constraints, and lack of effective biomarkers. Precision medicine, combination therapy, and advanced delivery systems are the key to the complete clinical potential of ferroptosis, with opportunities for more effective, specific, and personalized therapy.

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ABBREVIATIONS

ATP: Adenosine Triphosphate: **ROS:** Reactive Oxygen Species; **GPX4:** Glutathione Peroxidase 4; **FSP1:** Ferroptosis Suppressor Protein 1; **GSH:** Glutathione; **LPO:** Lipid Peroxidation; **PUFA:** Polyunsaturated Fatty Acids; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **SLC7A11:** Solute Carrier Family 7 Member 11; **FINs:** Ferroptosis Inducers; **TFRC:** Transferrin Receptor; **HCC:** Hepatocellular Carcinoma; **NSCLC:** Non-Small Cell Lung Cancer; **GBM:** Glioblastoma Multiforme; **CRC:** Colorectal Cancer; **PDAC:** Pancreatic Ductal Adenocarcinoma; **AML:** Acute Myeloid Leukemia; **TME:** Tumor Microenvironment; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **IC_{50}:** Half Maximal Inhibitory Concentration; **EC_{50}:** Half Maximal Effective Concentration; **PK/PD:** Pharmacokinetics/ Pharmacodynamics; **BBB:** Blood-Brain Barrier; **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats; **qPCR:** Quantitative PCR; **RNA-seq:** RNA Sequencing; **siRNA:** Small Interfering RNA; **WB:** Western Blot; **IF:** Immunofluorescence.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Aglietti, R. A., & Dueber, E. C. (2017). Recent insights into the molecular mechanisms underlying pyroptosis and gasdermin family functions. Trends in Immunology, 38(4), 261–271. https://doi.org/10.1016/j.it.2017.01.003

Amaravadi, R. K., & Thompson, C. B. (2007). The roles of therapy-induced autophagy and necrosis in cancer treatment. Clinical Cancer Research, 13(24), 7271–7279. https://doi.org/10.1158/1078-0432.CCR-07-1595

Bogdan, A. R., Miyazawa, M., Hashimoto, K., & Tsuji, Y. (2016). Regulators of iron homeostasis: New players in metabolism, cell death, and disease. Trends in Biochemical Sciences, 41(3), 274–286. https://doi.org/10.1016/j.tibs.2015.11.012

Bridges, R. J., Natale, N. R., & Patel, S. A. (2012). System xc(−) cystine/glutamate antiporter: An update on molecular pharmacology and roles within the CNS. British Journal of Pharmacology, 165(1), 20–34. https://doi.org/10.1111/j.1476-5381.2011.01480.x

Chang, J. C. (2016). Cancer stem cells: Role in tumor growth, recurrence, metastasis, and treatment resistance. Medicine (Baltimore), 95(1)(Suppl. 1), S20–S25. https://doi.org/10.1097/MD.0000000000004766

Chen, C., Liu, J., Lin, X., Xiang, A., Ye, Q., Guo, J., Rui, T., Xu, J., & Hu, S. (2024). Crosstalk between cancer-associated fibroblasts and regulated cell death in tumors: Insights into apoptosis, autophagy, ferroptosis, and pyroptosis. Cell Death Discovery, 10(1), 189. https://doi.org/10.1038/s41420-024-01958-9

Consoli, V., Fallica, A. N., Sorrenti, V., Pittalà, V., & Vanella, L. (2024). Novel insights on ferroptosis modulation as a potential strategy for cancer treatment: When nature kills. Antioxidants and Redox Signaling, 40 (1–3), 40–85. https://doi.org/10.1089/ars.2022.0179

Degterev, A., Huang, Z., Boyce, M., Li, Y., Jagtap, P., Mizushima, N., Cuny, G. D., Mitchison, T. J., Moskowitz, M. A., & Yuan, J. (2005). Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. Nature Chemical Biology, 1(2), 112–119. https://doi.org/10.1038/nchembio711

Fang, Y., Tian, S., Pan, Y., Li, W., Wang, Q., Tang, Y., Yu, T., Wu, X., Shi, Y., Ma, P., & Shu, Y. (2020). Pyroptosis: A new frontier in cancer. Biomedicine and Pharmacotherapy, 121, Article 109595. https://doi.org/10.1016/j.biopha.2019.109595

Hsieh, C.-H., Hsieh, H.-C., Shih, F.-S., Wang, P.-W., Yang, L.-X., Shieh, D.-B., & Wang, Y.-C. (2021). An innovative NRF2 nano-modulator induces lung cancer ferroptosis and elicits an immunostimulatory tumor microenvironment. Theranostics, 11(14), 7072–7091. https://doi.org/10.7150/thno.57803

Hu, Z., Zhang, H., Yang, S.-K., Wu, X., He, D., Cao, K., & Zhang, W. (2019). Emerging role of ferroptosis in acute kidney injury. Oxidative Medicine and Cellular Longevity, 2019, Article 8010614. https://doi.org/10.1155/2019/8010614

Jiang, M., Qiao, M., Zhao, C., Deng, J., Li, X., & Zhou, C. (2020). Targeting ferroptosis for cancer therapy: Exploring novel strategies from its mechanisms and role in cancers. Translational Lung Cancer Research, 9(4), 1569–1584. https://doi.org/10.21037/tlcr-20-341

Jiang, X., Stockwell, B. R., & Conrad, M. (2021). Ferroptosis: Mechanisms, biology and role in disease. Nature Reviews. Molecular Cell Biology, 22(4), 266–282. https://doi.org/10.1038/s41580-020-00324-8

Katoh, M. (2017). Canonical and noncanonical WNT signalling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumour plasticity [Review]. International Journal of Oncology, 51(5), 1357–1369. https://doi.org/10.3892/ijo.2017.4129

Kayagaki, N., Warming, S., Lamkanfi, M., Vande Walle, L., Louie, S., Dong, J., Newton, K., Qu, Y., Liu, J., Heldens, S., Zhang, J., Lee, W. P., Roose-Girma, M., & Dixit, V. M. (2011). Noncanonical inflammasome activation targets caspase-11. Nature, 479(7371), 117–121. https://doi.org/10.1038/nature10558

Kayagaki, N., Wong, M. T., Stowe, I. B., Ramani, S. R., Gonzalez, L. C., Akashi-Takamura, S., Miyake, K., Zhang, J., Lee, W. P., Muszyński, A., Forsberg, L. S., Carlson, R. W., & Dixit, V. M. (2013). Noncanonical inflammasome activation by intracellular LPS independent of TLR4. Science, 341(6151), 1246–1249. https://doi.org/10.1126/science.1240248

Koeberle, S. C., Kipp, A. P., Stuppner, H., & Koeberle, A. (2023). Ferroptosis-modulating small molecules for targeting drug-resistant cancer: Challenges and opportunities in manipulating redox signaling. Medicinal Research Reviews, 43(3), 614–682. https://doi.org/10.1002/med.21933

Kong, Z., Liu, R., & Cheng, Y. (2019). Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway. Biomedicine and Pharmacotherapy, 109, 2043–2053. https://doi.org/10.1016/j.biopha.2018.11.030

Lee, Y.-S., Lee, D.-H., Choudry, H. A., Bartlett, D. L., & Lee, Y. J. (2018). Ferroptosis-induced endoplasmic reticulum stress: Crosstalk between ferroptosis and apoptosis. Molecular Cancer Research, 16(7), 1073–1076. https://doi.org/10.1158/1541-7786.MCR-18-0055

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

Li, H., Yang, H., Li, P., Li, M., Yao, Q., Min, L., Zhang, Y., Wang, J., & Zheng, N. (2020). Maillard reaction products with furan ring, like furosine, cause kidney injury by triggering the ferroptosis pathway. Food Chemistry, 319, Article 126368. https://doi.org/10.1016/j.foodchem.2020.126368

Liu, X., Zhang, Z., Ruan, J., Pan, Y., Magupalli, V. G., Wu, H., & Lieberman, J. (2016). Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature, 535(7610), 153–158. https://doi.org/10.1038/nature18629

Liu, Z., Wang, C., Yang, J., Zhou, B., Yang, R., Ramachandran, R., Abbott, D. W., & Xiao, T. S. (2019). Crystal structures of the full-length murine and human gasdermin D reveal mechanisms of autoinhibition, lipid binding, and oligomerization. Immunity, 51(1), 43–49.e4. https://doi.org/10.1016/j.immuni.2019.04.017

Lu, B., Chen, X. B., Ying, M. D., He, Q. J., Cao, J., & Yang, B. (2017). The role of ferroptosis in cancer development and treatment response. Frontiers in Pharmacology, 8, 992. https://doi.org/10.3389/fphar.2017.00992

Ma, D., Li, C., Jiang, P., Jiang, Y., Wang, J., & Zhang, D. (2021). Inhibition of ferroptosis attenuates acute kidney injury in rats with severe acute pancreatitis. Digestive Diseases and Sciences, 66(2), 483–492. https://doi.org/10.1007/s10620-020-06225-2

Miller, D. R., Cramer, S. D., & Thorburn, A. (2020). The interplay of autophagy and nonapoptotic cell death pathways. International Review of Cell and Molecular Biology, 352, 159–187. https://doi.org/10.1016/bs.ircmb.2019.12.004

Nassar, D., & Blanpain, C. (2016). Cancer stem cells: Basic concepts and therapeutic implications. Annual Review of Pathology, 11, 47–76. https://doi.org/10.1146/annurev-pathol-012615-044438

Nie, Q., Hu, Y., Yu, X., Li, X., & Fang, X. (2022). Induction and application of ferroptosis in cancer therapy. Cancer Cell International, 22(1), 12. https://doi.org/10.1186/s12935-021-02366-0

Ren, J.-X., Li, C., Yan, X.-L., Qu, Y., Yang, Y., & Guo, Z.-N. (2021). Crosstalk between oxidative stress and ferroptosis/oxytosis in ischemic stroke: Possible targets and molecular mechanisms. Oxidative Medicine and Cellular Longevity, 2021, Article 6643382. https://doi.org/10.1155/2021/6643382

Reya, T., Morrison, S. J., Clarke, M. F., & Weissman, I. L. (2001). Stem cells, cancer, and cancer stem cells. Nature, 414(6859), 105–111. https://doi.org/10.1038/35102167

Rogers, C., Erkes, D. A., Nardone, A., Aplin, A. E., Fernandes-Alnemri, T., & Alnemri, E. S. (2019). Gasdermin pores permeabilize mitochondria to augment caspase-3 activation during apoptosis and inflammasome activation. Nature Communications, 10(1), 1689. https://doi.org/10.1038/s41467-019-09397-2

Ruan, J., Xia, S., Liu, X., Lieberman, J., & Wu, H. (2018). Cryo-EM structure of the gasdermin A3 membrane pore. Nature, 557(7703), 62–67. https://doi.org/10.1038/s41586-018-0058-6

Shen, Z., Song, J., Yung, B. C., Zhou, Z., Wu, A., & Chen, X. (2018). Emerging cancer therapy strategies based on ferroptosis. Advanced Materials, 30(12), Article 1704007. https://doi.org/10.1002/adma.201704007

Shi, J., Zhao, Y., Wang, Y., Gao, W., Ding, J., Li, P., Hu, L., & Shao, F. (2014). Inflammatory caspases are innate immune receptors for intracellular LPS. Nature, 514(7521), 187–192. https://doi.org/10.1038/nature13683

Sun, S., Shen, J., Jiang, J., Wang, F., & Min, J. (2023). Targeting ferroptosis opens new avenues for the development of novel therapeutics. Signal Transduction and Targeted Therapy, 8(1), 372. https://doi.org/10.1038/s41392-023-01606-1

Tong, X., Tang, R., Xiao, M., Xu, J., Wang, W., Zhang, B., Liu, J., Yu, X., & Shi, S. (2022). Targeting cell death pathways for cancer therapy: Recent developments in necroptosis, pyroptosis, ferroptosis, and cuproptosis research. Journal of Hematology and Oncology, 15(1), 174. https://doi.org/10.1186/s13045-022-01392-3

Wang, H., Cheng, Y., Mao, C., Liu, S., Xiao, D., Huang, J., & Tao, Y. (2021). Emerging mechanisms and targeted therapy of ferroptosis in cancer. Molecular Therapy, 29(7), 2185–2208. https://doi.org/10.1016/j.ymthe.2021.03.022

Wang, Y., Gao, W., Shi, X., Ding, J., Liu, W., He, H., Wang, K., & Shao, F. (2017). Chemotherapy drugs induce pyroptosis through caspase-3 cleavage of a gasdermin. Nature, 547(7661), 99–103. https://doi.org/10.1038/nature22393

Wu, J., Li, Z., Wu, Y., & Cui, N. (2024). The crosstalk between exosomes and ferroptosis: A review. Cell Death Discovery, 10(1), 170. https://doi.org/10.1038/s41420-024-01938-z

Wu, P., Zhang, X., Duan, D., & Zhao, L. (2023). Organelle-specific mechanisms in crosstalk between apoptosis and ferroptosis. Oxidative Medicine and Cellular Longevity, 2023, Article 3400147. https://doi.org/10.1155/2023/3400147

Yang, Y., Li, X., Wang, T., Guo, Q., Xi, T., & Zheng, L. (2020). Emerging agents that target signaling pathways in cancer stem cells. Journal of Hematology and Oncology, 13(1), 60. https://doi.org/10.1186/s13045-020-00901-6

Zhang, X., Du, L., Qiao, Y., Zhang, X., Zheng, W., Wu, Q., Chen, Y., Zhu, G., Liu, Y., Bian, Z., Guo, S., Yang, Y., Ma, L., Yu, Y., Pan, Q., Sun, F., & Wang, J. (2019). Ferroptosis is governed by differential regulation of transcription in liver cancer. Redox Biology, 24, Article 101211. https://doi.org/10.1016/j.redox.2019.101211

Zhao, Y., Li, Y., Zhang, R., Wang, F., Wang, T., & Jiao, Y. (2020). The role of erastin in ferroptosis and its prospects in cancer therapy. OncoTargets and Therapy, 13, 5429–5441. https://doi.org/10.2147/OTT.S254995

Zhu, Q., Shen, Y., Chen, X., He, J., Liu, J., & Zu, X. (2020). Self-renewal signalling pathway inhibitors: Perspectives on therapeutic approaches for cancer stem cells. Onco Targets and Therapy, 13, 525–540. https://doi.org/10.2147/OTT.S224465.

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