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Harnessing ferroptosis for precision oncology: challenges and prospects

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Abstract

The discovery of diverse molecular mechanisms of regulated cell death has opened new avenues for cancer therapy. Ferroptosis, a unique form of cell death driven by iron-catalyzed peroxidation of membrane phospholipids, holds particular promise for targeting resistant cancer types. This review critically examines current literature on ferroptosis, focusing on its defining features and therapeutic potential. We discuss how molecular profiling of tumors and liquid biopsies can generate extensive multi-omics datasets, which can be leveraged through machine learning-based analytical approaches for patient stratification. Addressing these challenges is essential for advancing the clinical integration of ferroptosis-driven treatments in cancer care.

Keywords Ferroptosis, Cancer, Machine learning, Liquid biopsy, Cell-free DNA, DNA methylation, Nanopore sequencing, Precision oncology

Molecular mechanisms of cell death shape anti-cancer strategies

Maintaining the balance between cell survival and death is essential for tissue homeostasis and plays a crucial role in preventing diseases, particularly cancer. The 1964 report identifying cell death as a programmed event, followed by the formal conceptualization of apoptosis in 1972, revolutionized our understanding of cellular death and unlocked new opportunities for development of targeted therapies [1, 2]. Today, an important class of targeted cancer therapeutics has emerged from our understanding of apoptosis, including Bcl-2 inhibitors such as Venetoclax [3, 4]. While inducing apoptosis remains a cornerstone of cancer therapy, resistance mechanisms and deregulation of its machinery have driven scientists to explore alternative regulated cell death pathways such as necroptosis, pyroptosis, and ferroptosis [5, 6].

Necroptosis is an inflammatory form of regulated necrosis mediated by the RIPK1-RIPK3-MLKL axis, typically activated when apoptosis is impaired [7, 8]. Pyroptosis is a gasdermin (GSDM)-dependent, inflammasome-activated process with context-dependent roles on tumor progression and immunity [9–11]. Ferroptosis is an iron-dependent, oxidative stress-driven cell death mechanism characterized by the peroxidation of polyunsaturated fatty acids (PUFAs) in cellular membranes. It differs from necroptosis and pyroptosis in its reliance on this radical chain reaction rather than on protein complex formation and subsequent signaling events mediated by, for example, caspases or kinases [12–14]. Understanding and harnessing these pathways to restore cell death function has emerged as a promising strategy in cancer treatment.

Currently, SMAC (Second Mitochondria-derived Activator of Caspases)-mimetics, such as birinapant and LCL161 [15, 16], are under clinical investigation for

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their ability to induce necroptosis in tumor cells, thereby bypassing apoptosis resistance [17–19]. Pyroptosis presents a dual role in cancer therapy: while immune-stimulating pyroptosis within tumors can be beneficial, chemotherapy-induced pyroptosis in GSDME-expressing normal tissues may result in inflammation and tissue damage [20, 21]. To mitigate these adverse effects, the concurrent use of anti-inflammatory agents, such as the NLRP3 inflammasome inhibitor RRx-001 [22, 23], is being evaluated in clinical trials for its potential to limit inflammatory damage and enhance chemoradioprotection [24]. In recent years, growing evidence has demonstrated the potential of ferroptosis in effectively eradicating both residual and therapy-resistant cancer cells [25–28]. In this review, we will focus on ferroptosis, particularly within the context of precision oncology, exploring its potential as a targeted therapeutic approach.

The rise of ferroptosis in cancer research

Ferroptosis, first conceptualized in 2012, describes a distinctive form of regulated necrotic cell death driven by iron-dependent lipid peroxidation [12, 29]. However, evidence of this cell death existed well before its formal recognition, notably in studies of oxytosis and glutamate-induced toxicity, which were linked to neuronal cell death in various neurological disorders [30–36]. These earlier observations provided crucial insights into the biology of ferroptosis and its application in neuroprotection and organ injury research.

Over the past few years, research on ferroptosis has experienced a remarkable surge, particularly in the context of cancer. Publication trends from 2012 to 2022 highlight a striking growth in studies on regulated necrosis, with ferroptosis showing the most rapid increase (Fig. 1 and SI part 1—Table S1). The number of ferroptosis-related publications has been doubling approximately every 10 months, with a similar trend in oncology, surpassing necroptosis and pyroptosis in cancer research since 2020–2021 (Fig. 1) and likely to continue outpacing the number of studies on pyroptosis across fields beyond oncology. This positions ferroptosis as a pivotal focus within the broader cell death landscape. The rapid expansion not only highlights its rising prominence but also reflects the evolving priorities of biomedical research at the intersection of cell death and disease.

Ferroptosis at the crossroads: intersecting pathways and emerging applications

A co-occurrence analysis of author keywords related to ferroptosis research (Fig. 2 and SI part 2—Table S3) reveals a dynamic and interconnected network of research fields. This analysis underscores the growing interest in studying ferroptosis alongside other regulated cell death pathways, fostering a more integrative understanding of cellular demise. Such convergence highlights how these pathways may interact or overlap within similar pathological contexts.

Main research areas and disease associations emerge within this network, with cancer standing out. Strong links to specific cancer types, such as hepatocellular carcinoma, breast, colorectal, and gastric cancers, illustrate the expanding scope of ferroptosis within oncology. Notably, half of ferroptosis-related publications focus on cancer (SI part 1—Table S1), underscoring its pivotal role in this field. How ferroptosis influences tumor immunity is also an emerging field [39–41], but it is outside the scope of this review (Fig. 2 and SI Part 2—Table S3). Beyond cancer, ferroptosis is also linked to neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, as well as to ischemia–reperfusion injuries, such as acute kidney and lung injuries. These associations highlight the relevance of ferroptosis in both acute and chronic conditions, suggesting diverse potential therapeutic applications.

Ferroptosis is highly conserved across species, from unicellular organisms to mammals, suggesting an ancient role in cellular defense and metabolic regulation [42]. Its broad pathological involvement may stem from the evolutionary pressure of atmospheric oxygen, which may have driven the emergence of ferroptosis as a lethal process and, consequently, the evolution of cellular mechanisms to counteract it for survival. Unlike apoptosis, necroptosis, or pyroptosis, ferroptosis is governed by fundamental biochemical processes regulating lipid peroxidation, rather than receptor-mediated signaling cascades [43, 44]. This core metabolic regulation also likely explains its persistence across diverse pathophysiological contexts. Evolutionarily, ferroptosis may act as a tumor-suppressive mechanism by eliminating cells with high metabolic activity, while in neurons, their high-iron demand, PUFA-rich membranes, and reliance on oxidative metabolism make them particularly vulnerable to ferroptosis, leading to neurodegeneration [45, 46].

Moreover, ferroptosis research intersects with innovative technologies such as machine learning (ML) and nanotargeting strategies (Fig. 2 and SI part 2—Table S3). ML enables more accurate modeling of biological processes, enhances drug response predictions, and optimizes precise treatment planning [47–49]. Meanwhile, nanoparticle-based delivery systems offer efficient delivery of ferroptosis-inducing agents to tumors, reducing systemic toxicity and improving therapeutic outcomes [50–52]. These advancements bring ferroptosis-based therapies closer to clinical application, showcasing the field's rapid evolution and translational potential.

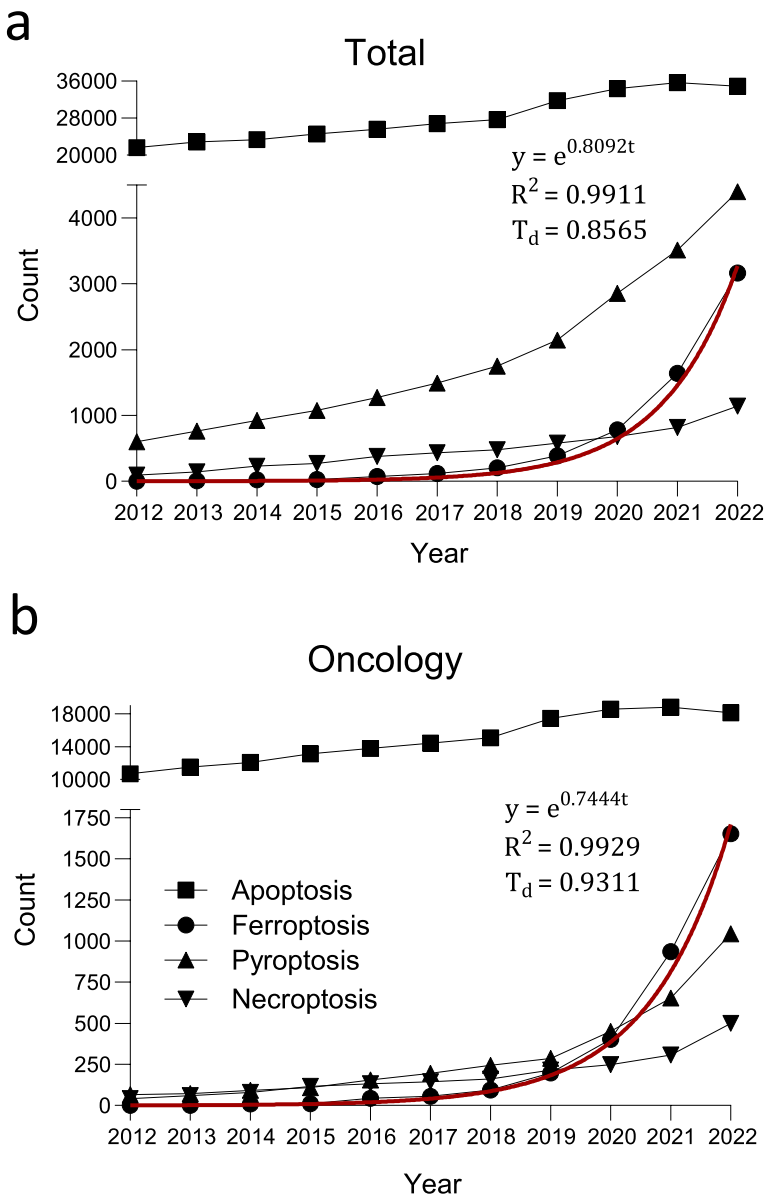

Fig. 1 Overview of publication trends from 2012 to 2022 related to specific established cell death mechanisms. **a** Total number of publications. **b** Publications focused exclusively on cancer research. In both cases, the data on ferroptosis were fitted to an exponential growth curve (curve in red: $y = y_0 e^{kt}$, where t is the time, y is the number of publication at time t, y_0 is the initial quantity in the first year considered, e is the base of the natural logarithm, and k is the growth rate constant). R^2 is the coefficient of determination and T_d, or doubling time, is a metric that quantifies the time (expressed here in years) it takes for the number of published articles on ferroptosis to double. A search for publications on these cell death subroutines was conducted in October 2024 using the Science Citation Index Expanded (SCI-EXPANDED) database of the Web of Science Core Collection (WoSCC). The retrieval formulas, adapted and expanded from Wu et al. (2023) [37], are provided in SI part 1—Advanced search formulas

Targeting ferroptosis in cancer therapy: challenges and complexities

Ferroptosis is characterized by iron-catalyzed peroxidation of PUFAs in cellular membranes, leading to cell death [12, 14]. This process is tightly regulated by iron, redox, and lipid metabolism, all of which play critical roles in determining cellular sensitivity to this form of cell death (Fig. 3) [12, 45, 53, 54]. Iron catalyzes the oxidation of PUFAs within cell membranes, generating toxic lipid peroxides that lead to lethal membrane permeabilization. GPX4, which primarily reduces lipid hydroperoxides to lipid alcohols, is crucial in detoxifying toxic lipids and preventing ferroptosis, using glutathione (GSH) as a cofactor [55]. Redox metabolites, such as vitamin E [56,

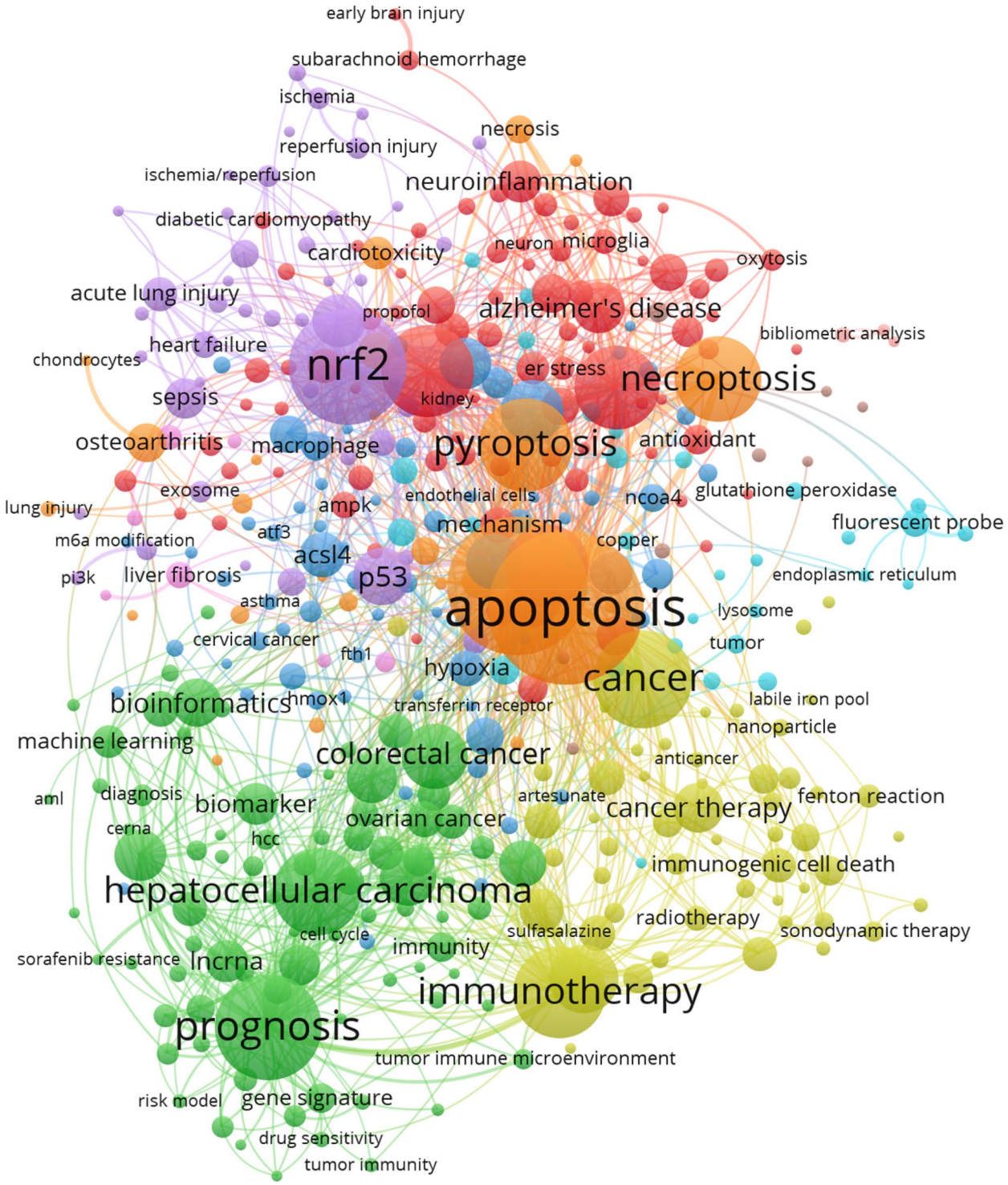

Fig. 2 A ferroptosis-based VOSviewer-generated map. Visualization is based on bibliographic data from all publications related to ferroptosis, retrieved from the Web of Science using the Science Citation Index Expanded (SCI-EXPANDED) database [38]. The map presents a co-occurrence analysis using fractional counting as the counting method, based on author keywords. To improve the visibility of co-occurrence patterns, some obvious ferroptosis-related keywords like "ferroptosis," "lipid peroxidation," "cell death," and "GPX4" were excluded from the map. A complete table containing all keywords is available in SI part 2—Table S3

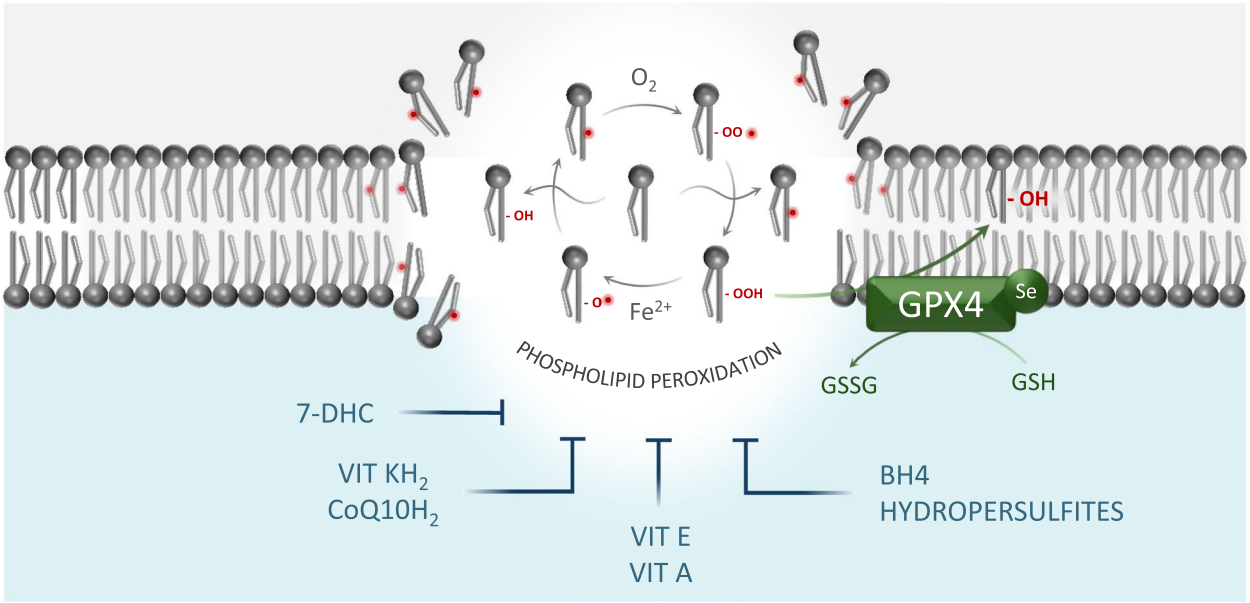

Fig. 3 Snapshot of ferroptosis execution and its major defense mechanisms.
Ferroptosis is executed by excessive peroxidation of PUFA-containing PLs within cellular membranes. This free radical chain reaction is catalyzed by O_2 and Fe^{2+}. Two major defense mechanisms suppress the process of PL peroxidation: (1) direct conversion of reactive PL-OOH to unreactive PL-OH by GPX4, and (2) dampening by an arsenal of lipophilic radical traps, such as vitamin E, A or KH_2, BH4, 7-DHC, and $CoQ10H_2$. BH4, tetrahydrobiopterin; $CoQ10H_2$, reduced form of coenzyme Q10; DHODH, dihydroorotate dehydrogenase; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione (reduced form); GSSG, glutathione disulfide (oxidized form)

57], ubiquinol ($CoQ10H_2$) [58, 59], vitamin KH_2 [60], vitamin A [61, 62], hydropersulfides [63], 7-dehydrocholesterol [64], and tetrahydrobiopterin (BH4) [65], play a crucial role in preventing ferroptosis by acting as endogenous radical scavengers.

Correspondingly, enzymes that are involved in recycling these radical scavengers effectively inhibit lipid peroxidation and ferroptosis. Among these, the FSP1/CoQ10 system functions by preventing lipid peroxidation in extramitochondrial membranes [58, 59], while DHODH acts within mitochondria, reducing the antioxidant CoQ10 in a manner akin to FSP1 [66]. GCH1/BH4 not only generates the antioxidant BH4, which functions similarly to CoQ10, but also remodels the lipid membrane environment, enhancing reduced CoQ10 and reducing PUFA-containing phospholipids (PUFA-PLs) [65, 67]. Cells with higher expression of these systems are more resistant to ferroptosis, while lower expression makes them more susceptible.

PUFA-PLs have emerged as critical determinants of cellular susceptibility to ferroptosis, as their oxidation drives the lipid peroxidation process essential for this form of cell death [54]. Recently, phospholipids with two polyunsaturated fatty acyl tails (diacyl-PUFA phosphatidylcholines: PC-$PUFA_2$s) were characterized and found to play a crucial role in regulating mitochondrial homeostasis and ferroptosis [68]. In contrast, non-oxidizable lipids such as monounsaturated fatty acids (MUFAs) confer resistance to ferroptosis, highlighting the importance of lipid composition and metabolism in regulating ferroptotic sensitivity [69]. Recent research has redefined ferroptosis not simply as a lipid peroxidation-driven cell death subroutine but as a failure in lipid quality control mechanisms [70].

On the other hand, the main challenge in studying ferroptosis, compared to other cell death pathways like apoptosis or necroptosis, lies in its highly dynamic and context-dependent nature. Unlike more defined pathways, ferroptosis does not follow a singular, linear cascade of molecular events. Instead, it is influenced by a complex interplay of iron metabolism, lipid peroxidation, and redox homeostasis, which can vary significantly depending on the cell type, tissue environment, and disease context. Therefore, a variety of metabolites and proteins can initiate or regulate ferroptosis, without any single component being necessary or universally required [43].

Furthermore, cell sensitivity to ferroptosis can vary significantly depending also on the specific induction mechanism [44]. For instance, recently, a chemical-genetic screen across different cell lines and pro-ferroptotic conditions was conducted to identify conserved regulators of ferroptosis [43, 71]. Surprisingly, only a few genes emerged as essential for ferroptosis across these

diverse contexts. The dynamism and context dependency in ferroptosis can be exemplified by the roles of ACSL4, LPCAT3, NRF2, and HMOX1. ACSL4, an enzyme key to PUFA metabolism and previously considered universally necessary for ferroptosis, was shown to be crucial only under specific conditions, particularly when ferroptosis is triggered by direct GPX4 inhibition rather than by cystine deprivation [43, 71]. LPCAT3 has a dual role in metabolizing both MUFAs and PUFAs [70, 72]; NADPH functions as a cofactor for both ferroptosis-inhibiting enzymes (e.g., FSP1) and ferroptosis-promoting enzymes (such as NOX and POR) [12, 44, 73]; and HMOX1, while part of the anti-ferroptotic Nrf2/FTH1/HMOX1 axis, can also trigger ferroptosis through increase in cellular labile iron when overactivated [50, 74].

Despite its promise as a therapeutic mechanism to target tumors resistant to conventional treatments, including apoptosis-based therapies [12, 13, 25, 50, 75], ferroptosis resistance has emerged as a critical bottleneck. Cancer cells often exhibit metabolic dependencies, such as iron, cysteine, and glutamine addiction, which coupled with the vulnerability of GSH depletion, highlight their intrinsic susceptibility to ferroptotic cell death [13, 26, 76–78]. However, experimental studies have revealed various resistance mechanisms that undermine this vulnerability, reducing the therapeutic efficacy of ferroptosis-inducing strategies. The lowered PUFA levels, reduced iron availability, and upregulated antioxidant pathways are the key ferroptosis-resistant mechanisms in cancer cells [79–84].

Therefore, in addition to strategies aimed at sensitizing cancer cells to ferroptosis, stratifying patients based on their susceptibility to ferroptosis seems crucial. In this regard, ML techniques hold promise in identifying specific biomarkers and developing prognostic and diagnostic models, as well as predictive models to estimate treatment responsiveness. Although still theoretical, these methods could enable patient stratification based on ferroptosis sensitivity, paving the way for therapeutic strategies more aligned with the principles of precision medicine.

Application of data-driven omics approaches and ML-based analytical methods in ferroptosis

The integration of datasets and ML techniques in cell death research has significantly enhanced the potential clinical impact of studies in this field. Datasets such as the Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) encompass a variety of samples, including human tissues and cell lines, offering a wealth of information that can be mined using machine learning algorithms to uncover new insights into ferroptosis [85, 86]. By interrogating these datasets, researchers can identify patterns, predict outcomes, and discover novel biomarkers or therapeutic targets with a level of accuracy and efficiency beyond what traditional methods can achieve.

ML workflow and its application in cell death research

ML encompasses a set of computational techniques that enable computers to learn from data without explicit programming. The typical machine learning process starts with data collection from the aforementioned datasets (e.g., GEO, TCGA). The collected data is then split into training and testing sets, where the training set is used to build the model, and the testing set is used to evaluate its performance. Feature selection or extraction is often performed to reduce the complexity of the data, focusing on the most relevant variables. Once trained, the model is validated on the testing set, enabling it to make predictions on new and unseen data, such as forecasting the likelihood of ferroptosis occurring in different biological contexts (SI part 1—Table S2).

The use of computational models in cell death research dates back to the 1990s, primarily focusing on apoptosis detection. These early studies used artificial neural networks (ANNs) to analyze apoptotic markers for prognostic purposes. For instance, in prostate cancer, combining clinical and apoptotic markers like Bcl-2 and p53 improved prediction accuracy [87]. ANNs were also employed to distinguish between apoptosis and necrosis in cell cultures by analyzing DNA staining and biochemical markers like LDH release [88].

Since 2020, the application of ML in cell death research has expanded to include non-apoptotic mechanisms such as ferroptosis. Similar to the approach in the 1990s, current machine learning algorithms in ferroptosis research are used to generate diagnostic, prognostic, and predictive (response to treatment) models in disease [47, 89–92]; distinguishing ferroptosis from other mechanisms of cell death [93–95]; and exploring its role in diverse pathologies [96–98]. Cancer research has garnered significant attention in this regard.

Advances in ML-driven ferroptosis research in cancer

Studies applying ML techniques to investigate ferroptosis-related biomarkers across various cancer types are concisely summarized (SI part 1—Table S2). Breast, bladder, lung, and colorectal cancers, as well as hepatocellular carcinoma, are among the most extensively studied, highlighting both the availability of public datasets and the clinical significance of these cancer types. Notably, SLC7A11, a subunit of system Xc^- involved in cystine uptake and GSH synthesis [12], has been identified as a recurrent biomarker in multiple cancer types (AML, ACC, BLCA, BRCA, HCC, ccRCC, and PRAD). Similarly,

NCOA4, a ferroptosis driver involved in ferritinophagy [99], has been found in AML, glioma, LUAD, PRAD, and ccRCC, while ACSF2, another ferroptosis driver linked to lipid metabolism [100], has been noted in BRCA, CRC, and AML. These biomarkers are crucial in regulating oxidative stress, iron homeostasis, and lipid peroxidation in ferroptosis. Their prevalence across various cancers underscores their potential as therapeutic targets, with implications for selectively inducing ferroptotic cell death.

These studies indicate an increasing trend to examine diverse cell death mechanisms simultaneously as indicators of cancer prognosis and drug sensitivity [47, 101–107]. A Cell Death Index (CDI) is often created to estimate the activity of various regulated cell death (RCD) pathways. Tumors with disrupted cell death processes are generally more aggressive, resistant to treatment, and linked to poorer patient outcomes. This reflects a shift from focusing on a single cell death mechanism to acknowledging the complex interplay of multiple processes. For instance, a study on triple-negative breast cancer (TNBC) developed a CDI by analyzing twelve RCD patterns to predict TNBC progression and drug sensitivity [47]. Among the 87 ferroptosis-related genes (FRGs) included, three ferroptosis suppressor genes (MT1G, PRKAA2, and CDKN1A) were part of the 12-gene signature constructed using LASSO Cox regression. Notably, only one gene was classified as a FRG at the time of publication. The CDI correlated with worse postoperative prognosis and resistance to standard chemotherapy, while indicating potential sensitivity to targeted therapies like palbociclib.

In line with these developments, recent research has also explored the interplay of ferroptosis with newly reported cell death subroutines, such as disulfidptosis and cuproptosis [103, 105, 108, 109]. Disulfidptosis is triggered by the accumulation of disulfide bonds, leading to cytoskeletal collapse [110], while cuproptosis involves cell death initiated by copper-induced mitochondrial protein aggregation [111, 112]. Both mechanisms share regulatory links with ferroptosis, particularly through their involvement in oxidative stress and metabolic dysfunction. In breast cancer, a model integrating these pathways has revealed their significant impacts on chemotherapy sensitivity, immune checkpoint expression, and overall prognosis in patients, with SLC7A11 playing a central role in modulating the tumor microenvironment and influencing therapeutic responses [105]. These findings underscore that our understanding of tumor biology remains incomplete without the incorporation of newly discovered cell death mechanisms and that the integration of such discoveries through machine learning could significantly enhance cancer therapy.

Challenges and future directions in ML-applied ferroptosis research

The application of the ML techniques (SI part 1—Table S2) has proven particularly effective for feature selection and improving predictive accuracy, helping identify therapeutic targets related to ferroptosis. However, most studies have focused primarily on prognostic modeling and drug sensitivity prediction, with limited attention to diagnostic applications. This focus on prognosis (Fig. 2) is partly driven by the retrospective nature of patient datasets, which can introduce bias and limit early-stage diagnostic research, as the data are often more suitable for outcome prediction rather than detecting disease at its onset.

An additional trend in ferroptosis-related prognostic model development is the predominant reliance on gene expression data (RNA sequencing), with relatively few models incorporating other omics data, such as epigenetic or proteomic data. Although gene expression data are widely used, there is growing recognition of the importance of integrating epigenomic data, particularly given the role of DNA methylation in regulating ferroptosis. For instance, DNA hypomethylation has been associated with GPX4 upregulation across various cancers, acting as a common mechanism linked to chemoresistance and poor prognosis [113]. In neuroblastoma, CBS DNA methylation status correlates with disease risk: hypermethylation predisposes to ferroptosis in low-risk cases, whereas hypomethylation upregulates CBS, activating the transsulfuration pathway and preventing ferroptosis in high-risk disease [26]. Incorporating epigenetic data could improve model accuracy by providing a more comprehensive view of cancer biology. Moreover, many studies developing these models rely on the FerrDB database, a curated resource of ferroptosis regulators and disease associations [114, 115]. While FerrDB is valuable, it primarily focuses on gene expression and may lag behind the most recent research. This underscores the need for consulting up-to-date literature to ensure all relevant findings are incorporated.

The application of ML techniques to ferroptosis in cancer remains in its early stages. As the field progresses, the development of more specialized algorithms, the integration of diverse omics datasets, and a stronger emphasis on validation and reproducibility are expected to enhance the visibility and impact of this research. This anticipated growth trajectory is rooted in the promising potential of ML to drive innovation across biomedical sciences and clinical research.

Finally, the focus on identifying ferroptosis-related signatures and prognostic biomarkers correlating with ferroptosis sensitivity or resistance from large-scale datasets reflects an increasing effort to integrate ferroptosis

research into the framework of precision oncology, as highlighted in several publications [48, 49, 102–104, 106, 116]. However, true precision oncology requires therapies tailored to a patient's current genetic and molecular tumor profile, typically derived from real-time biopsies and sequencing data [117]. In contrast, the aforementioned studies (SI part 1—Table S2) rely on pre-existing datasets rather than real-time, patient-specific data. While these studies represent an important foundational step toward incorporating ferroptosis into precision oncology, the next critical advancement will be transitioning from dataset analysis to real-time clinical applications, enabling ferroptosis research to fully influence individualized cancer treatment.

Ferroptosis in the era of precision oncology

Precision oncology offers a transformative approach to cancer treatment by tailoring therapies to the unique genetic and molecular profiles of individual tumors. By harnessing advanced molecular profiling technologies, precision oncology identifies specific mutations and biomarkers within a patient's tumor, enabling the selection of targeted therapies that directly address the underlying drivers of the disease [117–119]. This approach contrasts with traditional cancer treatments, which typically rely on classifying cancers by their tissue of origin (e.g., lung, breast, or colon cancer) and applying standard therapies, such as surgery, chemotherapy, and radiation. These conventional methods are based on average outcomes from large populations rather than individual patient characteristics. However, cancer is a highly heterogeneous disease, with tumors within the same tissue type often displaying vastly different genetic and molecular profiles [120]. This diversity means that a treatment effective for one patient may be ineffective or even harmful to another.

Emerging applications of liquid biopsy in ferroptosis research

Effective implementation of precision oncology requires a tumor sample for detailed molecular analysis. Traditionally, this has been done through a tissue biopsy, involving the surgical removal of a portion of the tumor. While tissue biopsies provide direct access to tumor cells, they come with several drawbacks. The procedure is invasive, often requiring anesthesia, and carries risks of complications. Additionally, tissue biopsies may not capture the full genetic diversity of a tumor because they only sample a specific portion, potentially missing key mutations or other molecular patterns present in different areas of the tumor [121, 122].

In contrast, liquid biopsies (LB) offer a less invasive and more comprehensive alternative. Significant advancements in liquid biopsy have led to FDA approvals of both single-gene and multigene assays for detecting alterations in cell-free DNA (cfDNA) in plasma. This represents a pivotal shift toward integrating LB as a companion diagnostic tool in targeted cancer therapies, particularly for patients with advanced-stage cancers [123, 124]. LB allows the analysis of circulating cfDNA, DNA fragments released into the bloodstream, or other bodily fluids, primarily through processes like apoptosis and necrosis, by both normal and diseased cells. A subset of cfDNA, known as circulating tumor DNA (ctDNA), is specifically derived from tumor cells. These fragments are shed into the blood, and their analysis provides a real-time snapshot of the tumor's (epi)genetic landscape across different regions and even from metastatic sites. This approach provides a more holistic view of the tumor's (epi)genetic diversity than what a tissue biopsy might capture. Analyzing ctDNA also enables continuous monitoring of the tumor's evolution over time, which is crucial for oncologists to detect changes during treatment that lead to drug resistance, assess tumor burden, and monitor residual disease after therapy [121, 125, 126]. By offering ongoing, comprehensive molecular information, LB facilitate more adaptive cancer treatment strategies, aligning closely with the goals of precision oncology.

A thorough literature search on ferroptosis and liquid biopsy yields limited results, with most studies showing co-occurrence of the terms without direct connections. However, expanding the search to ferroptosis and extracellular vesicles (EVs) isolated from serum or plasma reveals a growing area of research. These works explore how EVs, carrying molecular signatures from cancer cells or cells undergoing ferroptosis, can serve as biomarkers for disease. For example, exosomes isolated from human plasma containing different non-coding RNA molecules (miR-522, miR-4443, and circRNA_101093) have been found to drive ferroptosis resistance in patients with gastric cancer, non-small cell lung carcinoma, and lung adenocarcinoma [127–129]. This EV-based research aligns with the conceptual framework of liquid biopsy, offering a non-invasive means to monitor cell death-associated processes linked to therapy response. Interestingly, despite the clear overlap, researchers working on ferroptosis and EVs rarely refer to their studies as "liquid biopsy." This omission may reflect the nascent stage of this interdisciplinary field, highlighting a valuable connection that could enhance non-invasive cancer diagnostics and ferroptosis therapy monitoring.

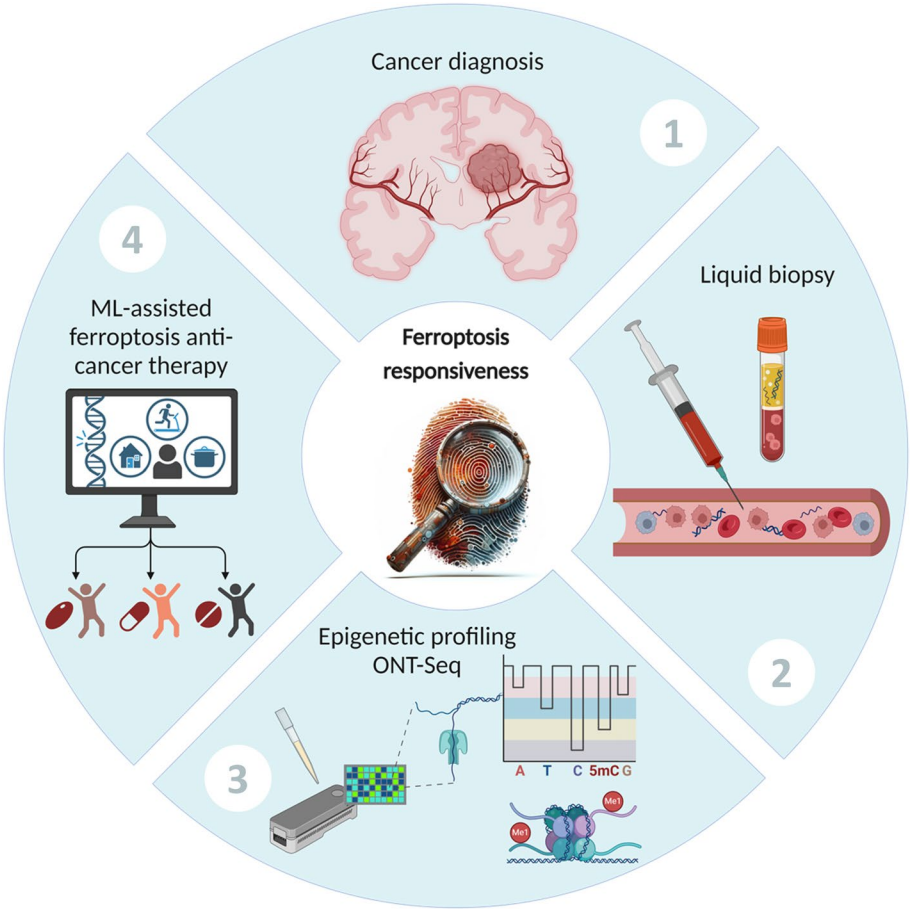

Fig. 4 A precision oncology scenario outline. A prospective workflow for ferroptosis-based cancer therapy, emphasizing the integration of liquid biopsy technology, real-time nanopore sequencing for epigenetic profiling, and machine learning (ML)-driven patient and treatment stratification based on ferroptosis responsiveness. Created with BioRender

A vision for ferroptosis integration into precision oncology practice

LB focused initially on identifying genetic markers in cfDNA, such as sex differences (prenatal testing), polymorphisms, and mutations [130]. However, by exploring non-genetic aspects like DNA methylation, fragmentation, and topology, the understanding of cfDNA has broadened, significantly enhancing the scope and applications of LB [122, 130, 131]. CpG methylation has been observed not only in gene promoters and transcription start sites but also in diverse genomic regions [132, 133]. This broader distribution underscores the potential of the epigenome as a valuable source of methylation biomarkers for different diseases.

A distinct advantage of DNA methylation patterns lies in their involvement in the early stages of cancer development. In many cancers, hypermethylation of tumor suppressor genes is an early event, often resulting in gene silencing. These changes in DNA methylation patterns can be among the first detectable signs of tumorigenesis, offering a crucial early marker for cancer detection [134–137]. Furthermore, methylation patterns in ctDNA closely mirror those of the primary tumor tissue, allowing for more universal and accurate cancer detection and even providing insights into the tumor's origin within the body [138–141]. Consequently, various cancer-specific methylation patterns in ctDNA have been investigated as potential biomarkers, with some gaining regulatory approval (CE-IVD and FDA) [142–145].

The clinical utility of ctDNA methylation as a non-invasive tool for cancer screening could extend to ferroptosis-based therapies. As exemplified earlier, specific DNA methylation patterns may serve as biomarkers for predicting a tumor's response to ferroptosis inducers. By analyzing cell-free DNA for such epigenetic modifications and employing ML models trained for stratification, clinicians can effectively predict and guide patient responses to ferroptosis-targeted treatments.

A prospective workflow for ferroptosis-based cancer therapy is outlined (Fig. 4), highlighting the integration of

liquid biopsy technology, real-time nanopore sequencing for epigenetic profiling, and ML-driven patient and treatment stratification based on ferroptosis responsiveness. While multiple DNA methylation analysis methods exist, Oxford Nanopore Technologies (ONT) stands out as a relatively underexplored yet promising portable technology. Based on third-generation sequencing, ONT enables real-time, long-read analysis of native DNA modifications without PCR amplification or bisulfite conversion. However, despite its potential for accurate epigenetic profiling through neural network-based signal interpretation, challenges with base-calling accuracy remain [146–150].

Although this discussion centers on DNA methylation, particularly through ONT sequencing, it is essential to recognize the transformative potential of integrating multi-omics technologies within the context of liquid biopsies. The field of multi-omics is rapidly advancing, pushing clinical practice toward a more robust and efficient framework for patient care. By utilizing multiple layers of molecular data, clinicians can better tailor treatments, enhance early detection, and improve prognostic accuracy, ultimately bringing the vision of ferroptosis-based precision oncology closer to reality [118, 151–154]. Interestingly, some approaches are even combining omics data with histopathological features through digital pathology analysis, enabling the identification of ferroptosis vulnerabilities for more effective stratification of breast cancer patients [155].

Ferroptosis: prospects for clinical translation

Several companies are actively developing ferroptosis-based therapeutics, focusing on both inducers for cancer treatment and inhibitors for neurodegenerative diseases and transplantation. To date, translating ferroptosis modulation into clinical applications has not been achieved, but the future appears promising.

Kojin Therapeutics is developing small-molecule inhibitors targeting glutamate-cysteine ligase (GCL), the rate-limiting enzyme in glutathione synthesis, to induce ferroptosis in solid tumors, with preclinical proof of concept established (https://kojintx.com/). Kuda Therapeutics has developed a molecule that inhibits hypoxia-inducible factor (HIF)−2α and induces ferroptosis in clear cell renal cell carcinoma (ccRCC), currently in preclinical development (https://kudatherapeutics.com/). Elucida Oncology developed C'Dots for cancer therapy and launched a therapeutic clinical trial in 2021 for FRα-overexpressing tumors [156]. Notably, while C'Dots have been shown to induce ferroptosis [51], Elucida Oncology did not explicitly link its clinical applications to ferroptosis.

On the other hand, several FDA-approved drugs, initially developed for cancer and other non-malignant conditions, have been identified as ferroptosis inducers in cancer cells, including sulfasalazine, artemisinin and its derivatives, disulfiram, lanperisone, acetaminophen, cisplatin, sorafenib, and altretamine [157, 158]. These cases illustrate that while ferroptosis-targeting therapies are not yet standard in clinical practice, existing drugs with ferroptotic activity offer significant potential for repurposing in optimized oncology treatments. This also underscores the importance of considering whether approved medications inadvertently induce ferroptosis in healthy cells, potentially leading to adverse outcomes.

On the inhibitory front, PTC Therapeutics is developing Vatiquinone (EPI-743) and Utreloxastat (PTC857), small-molecule inhibitors of 15-lipoxygenase (15-LO), an enzyme that drives lipid peroxidation and contributes to ferroptosis [159, 160]. Both compounds are advancing in clinical trials for Friedreich's ataxia and amyotrophic lateral sclerosis, respectively [161, 162]. ROSCUE Therapeutics and IRONIX Therapeutics focus on ferroptosis suppression using lipophilic radical traps, with potential applications in transplantation, multiorgan dysfunction syndrome, and neurodegenerative diseases [55, 163].

These initiatives highlight both the expanding scope of ferroptosis research and the persistent challenges in its clinical translation, including achieving selective targeting to minimize off-target toxicity, identifying reliable biomarkers to monitor ferroptotic activity in vivo, and stratifying ferroptosis-sensitive subpopulations for tailored treatments. Integrating omics-based patient profiling, liquid biopsy technologies, and machine learning-driven stratification models will be essential to overcome these hurdles and optimize safety and clinical outcomes.

We anticipate that, in the short term, several ferroptosis modulators currently in preclinical development will enter early-phase clinical trials. In the long term, ferroptosis-targeting therapies are likely to expand beyond cancer and neurodegeneration to conditions such as ischemia–reperfusion injuries and inflammatory diseases [164–166], including rheumatoid arthritis [167], inflammatory bowel disease [168, 169], metabolic dysfunction-associated steatotic liver disease (MASLD) [170], and liver fibrosis [171], driven by advances in biomarker discovery and precision medicine.

Final considerations

The literature review conducted in this article allows us to propose an evolutionary framework that highlights the progression of studies on ferroptosis, particularly in the field of oncology, structured into three fundamental stages (Fig. 5). While this framework simplifies the reality

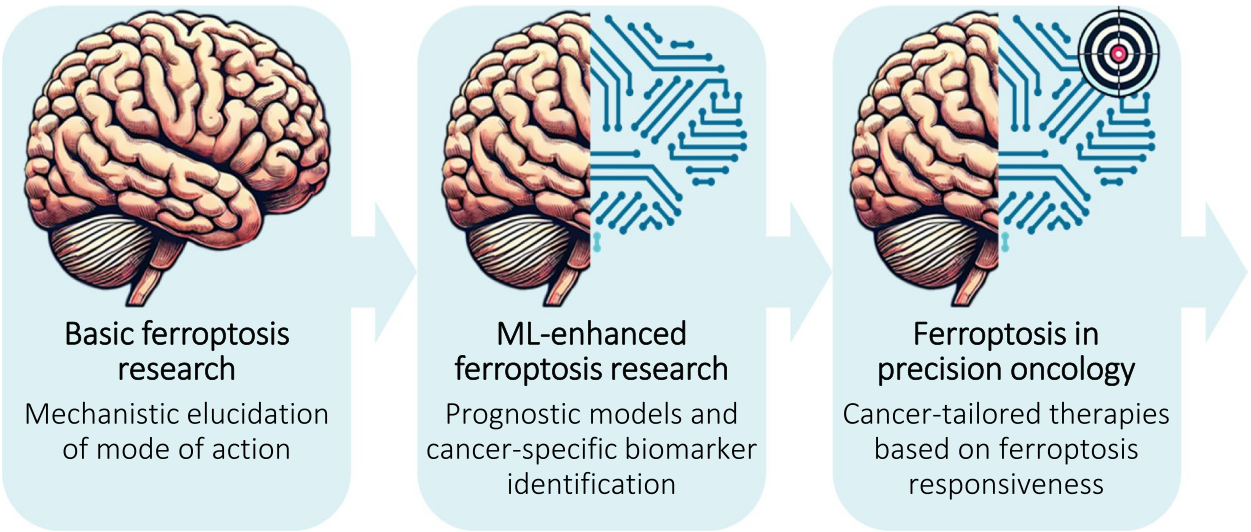

Fig. 5 Evolution of research in the field of ferroptosis. Early studies focused on elucidating the pathways that regulate ferroptosis, conceptualizing it as a distinct cell death mechanism. This foundational work continued to deepen the understanding of these pathways, consistently depicting ferroptosis as governed by well-defined molecular circuits. In parallel, machine learning-assisted investigations emerged, prioritizing the development of prognostic models for specific cancer types. Looking ahead, ferroptosis is envisioned as a key component in precision oncology, where its modulation will be leveraged for cancer therapies. Created with BioRender

of this rapidly expanding field, it offers a clear sense of the advancements achieved and where it may be headed. Importantly, these stages coexist and reinforce each other.

The first stage focused on elucidating the distinctive signaling pathways associated with ferroptosis and identifying inducers and inhibitors across various physiological and pathological contexts. Researchers initially employed various approaches, such as synthetic lethal screens [12, 172, 173] and, more recently, CRISPR screens [174–176], to pinpoint key molecular targets involved in ferroptosis. This phase is marked by significant human effort to integrate findings, as evidenced by the numerous review articles published annually (over 200 per year since 2020, exceeding 700 in the past year alone) and the development of curated databases such as FerrDB [114, 115], which consolidates knowledge about ferroptosis-related genes, compounds, and diseases.

Building on this foundational knowledge, the second stage integrated ML into ferroptosis research, allowing for the development of prognostic tools based on ferroptosis-related gene signatures in various cancer models. By establishing reliable ferroptosis signatures in specific tumor types, this phase laid the groundwork for a third, more refined stage of application.

The third phase, though still emerging, envisions the future of ferroptosis-focused cancer therapy. Real-time tumor analysis through LB and molecular profiling techniques enables a more precise understanding of individual patients' responses to ferroptosis-inducing treatments. Notably, several FDA-approved drugs have been identified as inducers [177–182], broadening therapeutic options. Additionally, high-throughput screenings aimed at discovering ferroptosis triggers further expand the pool of potential treatments. Combining epigenetic profiling with ML-driven approaches could refine patient selection, identifying those most likely to benefit from ferroptosis therapy and matching them with the most effective drugs (Fig. 4).

Another promising approach contributing to this third phase of development in ferroptosis research is the use of patient-derived xenografts (PDX), where patients' tumors are propagated through serial passages in mice (other organisms, like zebrafish, have also been used). PDX models retain the molecular, genetic, and histological heterogeneity of the original human tumors, providing a more accurate platform for studying tumor biology, drug responsiveness, predicting biomarkers of drug response, and therapeutic outcomes [183–185]. Since 2020, there has been a noticeable, though still modest, increase in the use of PDX models in cancer studies related to ferroptosis [186–191]. This emerging shift from cell line-derived xenografts (CDX), which are models developed from immortalized cancer cell lines, suggests a strategic effort to align ferroptosis research with platforms that offer greater potential for developing therapies grounded in the principles of precision oncology. However, several challenges must be addressed with PDX models, including the high cost and resources required to establish and maintain them,

the risk of stromal and genetic drift, and the use of immunocompromised mice, which may not fully capture human immune responses [183–185].

To illustrate this three-stage evolution, a conceptual journey is portrayed (Fig. 5) from traditional cell death research to a new paradigm where human expertise merges with machine learning, accelerating both discovery and therapeutic innovation. In this context, ferroptosis research advances to a new scenario where human intellect and machine learning algorithms synergize to unlock therapeutic possibilities once beyond our reach, catalyzing its integration into precision medicine.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12915-025-02154-6.

Additional file 1. Supplementary information part 1. Advanced search formulas. Supplementary information part 1. Table S1. Supplementary information part 1. Table S2.

Additional file 2. Table S3 Keywords, based on bibliographic data from all publications related to ferroptosis retrieved from the Web of Science using the Science Citation Index Expanded (SCI-EXPANDED) database, obtained from co-occurrence analysis using fractional counting based on author keywords in VOSviewer. The "Weight (link)" column quantifies the overall strength of connections (links) between a particular keyword and all the other keywords that were found in the same set of publications related to ferroptosis. Higher weights indicate the importance or centrality of a keyword within the research field.

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Authors' contributions
R.F.A. conceived the article and led its writing, I.V. contributed to the writing, I.K., B.H., and T.V.B. revised the manuscript. All authors read and approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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