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Review

Unlocking the Potential of Organoid Models in Ferroptosis: A Breakthrough in Cancer Research

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Abstract

Ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation, has emerged as a critical mechanism in cancer biology. Understanding the molecular mechanisms and experimental models of ferroptosis is essential for developing novel therapeutic strategies. Organoid models, which closely mimic the architecture and functionality of human tissues, offer a promising platform for studying ferroptosis in various cancer types. This review explores the construction and application of organoid models, highlighting their advantages in cancer research. We discuss the link between ferroptosis and organoids in various cancers, including colorectal cancer, pancreatic cancer, liver cancer, breast cancer, gastric cancer, ovarian cancer, and other cancers. Furthermore, we examine the therapeutic implications of ferroptosis in organoid models, emphasizing the potential for these models to enhance our understanding of cancer biology and improve treatment outcomes.

Keywords: Ferroptosis, Organoid Models, Cancer research

1. Introduction

The advent of organoid models has revolutionized cancer research, providing a sophisticated platform that closely mimics the in vivo environment. Organoids, derived from stem cells or primary tissues, are three-dimensional (3D) cell culture systems derived from stem cells or primary tissues, capable of self-organizing into structures that recapitulate the architecture and function of their tissue of origin(1, 2).

This has significant implications for understanding cancer biology, drug screening, and personalized medicine(3-5). This innovative technology has opened new avenues for studying complex biological processes, including regulated cell death.

Ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation, has emerged as a critical process in cancer biology(6). Unlike apoptosis or necrosis, ferroptosis is driven by the accumulation of lipid peroxides and is tightly regulated by intracellular iron metabolism and antioxidant systems, such as glutathione peroxidase 4 (GPX4) and the cystine/glutamate antiporter system Xc-(7). The interplay between ferroptosis and cancer has been extensively studied, revealing its potential to overcome drug resistance and enhance the efficacy of existing treatments. Ferroptosis has garnered significant attention in recent years due to its distinct mechanisms and implications in cancer biology.

The integration of organoid models into ferroptosis research offers unprecedented opportunities to dissect these molecular mechanisms in a more physiologically relevant context. Organoids derived from various cancer types, have demonstrated their utility in modeling tumor heterogeneity, drug responses, and disease progression(8). These models provide a robust platform for investigating the therapeutic potential of ferroptosis induction in cancer treatment.

As we delve deeper into the interplay between ferroptosis and organoid models across different cancer types, it becomes evident that these systems hold significant promise for advancing our understanding of cancer biology and developing novel therapeutic strategies. This review will explore the molecular mechanisms of ferroptosis, the construction and application of organoid models, and their implications in various cancer types, ultimately highlighting the therapeutic potential of ferroptosis in organoid-based cancer research.

2. The Link between Organoids and Ferroptosis

2.1 Construction and application of organoid models

Organoid models have revolutionized biomedical research by providing a more accurate representation of human tissues and organs in vitro(5, 9). These 3D structures are derived from stem cells or primary tissues and can mimic the architecture and functionality of their in vivo counterparts. The construction of organoid models involves several key steps, including the isolation of stem cells, embedding them in a suitable extracellular matrix, and providing the necessary growth factors and signaling molecules to promote differentiation and self-organization. For instance, pancreatic ductal adenocarcinoma (PDAC) organoids can be generated using a 3D Matrigel system, which supports the growth and differentiation of both human and mouse PDAC cells(10).

The application of organoid models extends across various fields of biomedical research, including cancer biology, drug screening, and personalized medicine. In cancer research, organoids derived from patient tumors, known as patient-derived organoids (PDOs), have been particularly valuable. These models retain the genetic and phenotypic characteristics of the original tumors, making them excellent tools for studying tumor heterogeneity, drug responses, and resistance mechanisms. Organoid models are also instrumental in understanding the molecular mechanisms underlying cancer progression and treatment resistance using organoid model of patient-derived xenografts (PDX). Furthermore, organoid models have been used to explore the interactions between cancer cells and the tumor microenvironment(11).

Currently, the construction and application of organoid models represent a significant advancement in cancer research. These models offer a more physiologically relevant platform for studying tumor biology, testing new drugs, and developing personalized treatment strategies. By faithfully recapitulating the complexity of human tissues and tumors, organoid models hold great promise for advancing our understanding of cancer and improving patient outcomes.

2.2 The potential applications of organoid models in ferroptosis

Organoid models have emerged as a revolutionary tool in cancer research, particularly in the study of ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation. The application of organoid models in ferroptosis research offers several promising avenues for understanding cancer biology and developing novel therapeutic strategies. One significant application of organoid models in ferroptosis research is their use in drug screening and development. Organoids derived from various cancer types, have been instrumental in identifying compounds that can induce ferroptosis in cancer cells(12). Accumulating findings highlight the potential of organoid models to facilitate the discovery of new ferroptosis-inducing agents and optimize existing therapies.

Another critical application of organoid models is in understanding the mechanisms of chemoresistance and developing strategies to overcome it. Chemoresistance remains a major challenge in cancer treatment, and ferroptosis has been identified as a potential pathway to sensitize resistant cancer cells to chemotherapy. Current studies underscore the utility of organoid models in elucidating the molecular underpinnings of chemoresistance and identifying novel therapeutic targets(13, 14). Organoid models also offer a valuable platform for personalized medicine, which hold great promise for tailoring treatments to achieve optimal therapeutic outcomes. Therefore, the integration of organoid technology with ferroptosis research holds great potential for advancing our understanding of cancer biology and developing innovative therapeutic strategies to combat cancer.

3. Various Cancer Organoid Models in Ferroptosis

The integration of organoid models into ferroptosis research represents a new frontier in cancer research, offering a powerful platform for elucidating complex biological processes and developing targeted therapies. In the following sections, we focus on the expanding landscape of organoid models in ferroptosis and its significant contributions in personalized medicine (Fig 1 and Tab 1).

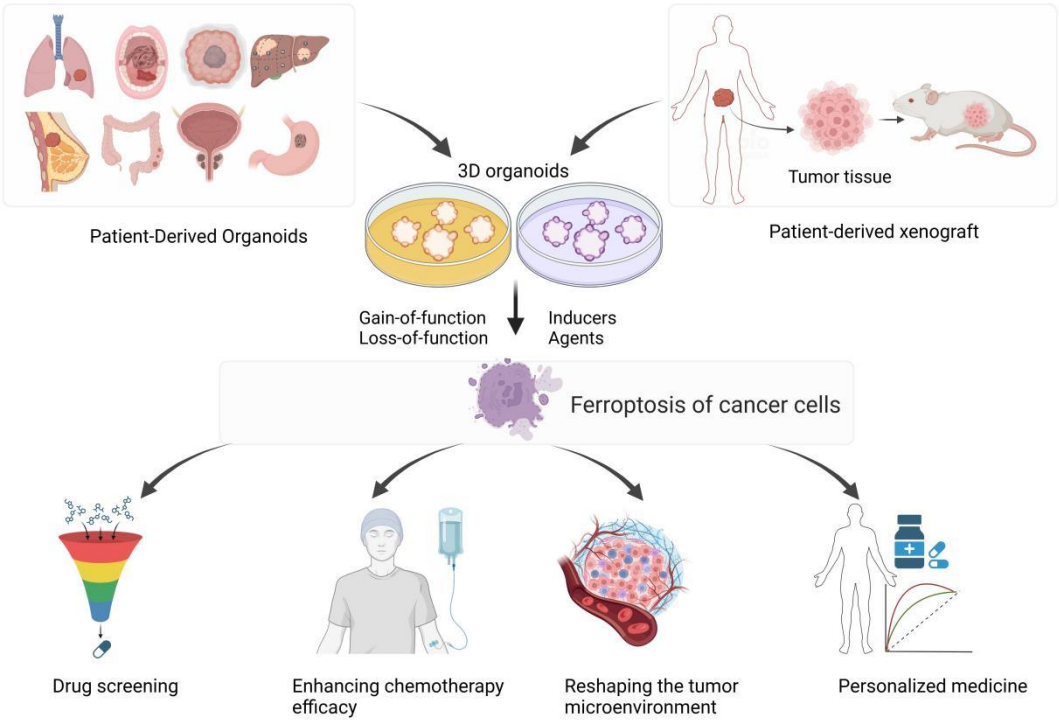

Figure 1. The roles of cancer organoid models and ferroptosis. The integration of patient-derived organoids and patient-derived xenografts into ferroptosis research, represents a new frontier in cancer research, offering a powerful platform for elucidating complex biological processes and developing therapeutic strategies.

3.1 Colorectal cancer

Colorectal cancer (CRC) has been extensively studied using organoid models to understand the mechanisms of ferroptosis and its therapeutic potential. CRC-derived organoids have shown promise in overcoming acquired drug resistance by inducing ferroptosis. For instance, studies have demonstrated that the loss of colonic epithelial Hmox1 promotes ferroptosis, suggesting a potential target for therapeutic intervention(15). Additionally, intestinal stem cell organoids have highlighted the role of IFNγ as a key cytokine capable of arresting cancer stemness and triggering GPX4-dependent ferroptosis(16). Patient-derived organoids have also been utilized to show that compounds like curcumin and

andrographis exhibit anti-tumor effects via activation of ferroptosis(12). Moreover, CRC organoids have been used to demonstrate that adipocyte-derived exosomes containing MTTP reduce ferroptosis susceptibility in CRC, promoting chemoresistance to oxaliplatin(13). These findings underscore the potential of ferroptosis as a therapeutic strategy in CRC.

Organoid models have provided valuable insights into the mechanisms of ferroptosis in CRC and its potential as a therapeutic target. Studies have shown that targeting specific pathways, such as LGR4 and β-catenin/Wnt-signaling, can overcome acquired drug resistance in CRC by inducing ferroptosis(17) . Additionally, natural compounds like andrographis have been found to sensitize CRC to chemotherapy through the activation of ferroptosis(18). The combination of Vitamin C and cetuximab has also shown promising results in inhibiting the emergence of drug-resistant cells in CRC models by triggering a synthetic lethal metabolic cell death program involving ferroptosis(19). These findings suggest that targeting ferroptosis and metabolic vulnerabilities could be effective strategies to enhance the efficacy of therapies in CRC and overcome drug resistance.

3.2 Pancreatic cancer

Pancreatic cancer, particularly PDAC, has been a challenging malignancy to treat due to its aggressive nature and resistance to conventional therapies. Organoid models derived from pancreatic cancer have provided valuable insights into the role of ferroptosis in cancer therapy. For example, elevated FSP1 has been shown to protect KRAS-mutated cells from ferroptosis during tumor initiation, highlighting a potential target for therapeutic intervention(20). Patient-derived organoids have also been used to demonstrate that targeting the MCP-GPX4/HMGB1 axis can trigger immunogenic ferroptosis, offering a novel approach to enhance anti-tumor immunity(21). Additionally, combining gemcitabine with ferroptosis inducers has been shown to enhance cytotoxic effects in SMAD4-positive organoids, suggesting a potential combination therapy for pancreatic cancer(22). These studies highlight the potential of ferroptosis as a therapeutic strategy in pancreatic cancer.

The role of ferroptosis in PDAC has been extensively studied using organoid models, which provide a physiologically relevant context to investigate chemoresistance and therapeutic responses. A study using PDAC organoids demonstrated the potential of ferroptosis inducers in overcoming chemoresistance and inhibiting tumor growth, paving the way for novel treatment strategies(10). Another study revealed the potential of small molecule chimeras, such as salinomycin derivatives and dihydroartemisinin, in inducing ferroptosis in drug-tolerant PDAC cells and organoids(23). Furthermore, the mitochondrial calcium uniporter (MCU) has been identified as a driver of metastasis and a targetable vulnerability for inducing ferroptosis in pancreatic cancer. Pharmacological inhibition of the cystine transporter SLC7A11 has been shown to effectively induce tumor regression and abrogate MCU-driven

metastasis in patient-derived organoid models(24). Therefore, organoid models provide a powerful platform for dissecting these mechanisms and identifying potential therapeutic targets. Targeting key regulators such as FSP1, MCU, and SMAD4, as well as exploiting the vulnerabilities associated with ferroptosis, holds promise for improving the treatment outcomes for pancreatic cancer patients.

3.3 Liver cancer

Liver cancer, particularly hepatocellular carcinoma (HCC), has been studied using organoid models to explore the role of ferroptosis in tumor progression and treatment. Patient-derived organoids have shown that donafenib and GSK-J4 synergistically induce ferroptosis in liver cancer by upregulating HMOX1 expression, suggesting a potential combination therapy(25). Additionally, organoid models derived from HCC patients have demonstrated that metformin can restore PPARGC1A expression and enhance ferroptosis, supporting its significance in HCC pathogenesis and therapeutic intervention(26). Furthermore, HCC organoids have been used to show that the unconventional prefoldin RPB5 interactor (URI) mediates resistance to tyrosine kinase inhibitors (TKIs)-induced ferroptosis, highlighting a potential target for overcoming drug resistance. The combination of the SCD1 inhibitor aramchol with the deuterated sorafenib derivative donafenib demonstrates potent anti-tumor effects in p53-wild type HCC organoids(27).

Additionally, combining ferroptosis induction with other therapeutic strategies, such as myeloid derived suppressor cell (MDSC) blockade, has rendered primary tumors and metastases in the liver more sensitive to immune checkpoint blockade, offering a novel approach to cancer immunotherapy. This study highlights the potential of ferroptosis-induced immune responses for the treatment of primary liver tumors and liver metastases, although it does not have the same effect on CRC organoids in subcutaneous growth but reduces their metastatic growth in the liver(28). Together, the amalgamation of ferroptosis research with organoid models opens up a promising frontier in liver cancer research. These models not only offer a more precise depiction of the tumor microenvironment but also enable the exploration of innovative therapeutic targets and strategies to address drug resistance and enhance patient outcomes.

3.4 Breast cancer

Breast cancer organoid models have provided valuable insights into the role of ferroptosis in cancer research. For instance, human TNBC organoid models have demonstrated that simultaneous inhibition of FAK and ROS1 synergistically represses tumor growth by upregulating p53 signaling and inducing ferroptosis(29). Additionally, combining anti-FGFR4 and anti-HER2 therapies has been shown to induce ferroptosis in HER2-positive breast cancer. Patient-derived xenografts and organoid experiments demonstrate the synergistic effect of combining anti-FGFR4 and anti-HER2 therapies, offering a

promising combination strategy to address resistance in HER2-positive breast cancer(30). Tamoxifen, a well-known therapeutic agent for breast cancer, has been shown to induce ferroptosis in MCF-7 breast cancer organoids. This discovery underscores the potential of ferroptosis induction in enhancing the efficacy of existing breast cancer therapies and overcoming drug resistance(31). Therefore, the integration of ferroptosis research with organoid models offers a promising frontier in breast cancer research. These models not only provide a more accurate representation of the tumor microenvironment but also facilitate the exploration of novel therapeutic targets and strategies to overcome drug resistance and improve patient outcomes.

3.5 Gastric cancer

Organoid models have also been used to explore the therapeutic implications of ferroptosis in gastric cancer. A study found that cancer-associated fibroblasts (CAFs) impair the cytotoxic function of NK cells in gastric cancer by inducing ferroptosis via iron regulation. This mechanism was elucidated using a human patient-derived organoid model, where targeting CAFs with a combination of deferoxamine and FSTL1-neutralizing antibody significantly alleviated CAF-induced NK cell ferroptosis and boosted NK cell cytotoxicity against gastric cancer(11). Inhibition of the STAT3-ferroptosis regulatory axis holds promise as a therapeutic strategy for combating chemotherapy resistance and advancing gastric cancer treatment. Targeting STAT3 with W1131 induces ferroptosis, displaying significant anti-tumor effects in various models, including organoids and patient-derived xenografts, offering a potential therapeutic approach for advanced gastric cancer(14). These findings provide new insights into the potential of ferroptosis as a therapeutic target in gastric cancer, with organoid models providing a robust platform for preclinical evaluation.

3.6 Bladder cancer

Organoid models have been employed to investigate the involvement of ferroptosis in bladder cancer (BCa) as well. For example, a recent study uncovered that Phosphoglycerate Dehydrogenase (PHGDH) upregulates the expression of SLC7A11, a component of the cystine/glutamate antiporter system Xc-, which is crucial for maintaining GSH levels and preventing ferroptosis. Further functional assays found that the PHGDH inhibitor NCT-502 induced ferroptosis in BCa cell organoid models, leading to reduced tumor growth(32). Moreover, N6-Methyladenosine (m6A) modifications influence chemoresistance by regulating RNA stability and protein levels of SLC7A11, impacting ferroptosis sensitivity in bladder cancer cells. This mechanism is swiftly induced in both cisplatin-sensitive cell lines and patient-derived organoids following short-term exposure to cisplatin, revealing a shared pathway of SLC7A11 upregulation and chemoresistance. These findings underscore the significance of epitranscriptomic plasticity as a key mechanism in rapid chemoresistance development and a promising target for

therapeutic interventions(33).

3.7 Ovarian cancer

Organoid models have provided valuable insights into the role of ferroptosis in ovarian cancer. In ovarian cancer, lipid metabolic activity and redox-driven ferroptosis are regulated by fatty acid desaturases such as SCD1 and FADS2. These enzymes balance lipid metabolism and ferroptosis, influencing cancer cell survival and proliferation. For instance, ovarian cancer organoids derived from high-grade serous ovarian cancer (HGSOC) have shown that FeNP inhibits GPX4 activity, leading to the induction of ferroptosis, suggesting a potential therapeutic approach(34). Additionally, SCD1/FADS2 fatty acid desaturases have been shown to equipoise lipid metabolic activity and redox-driven ferroptosis in ascites-derived ovarian cancer cells. Targeting lipid metabolic pathways to induce ferroptosis has shown promise in overcoming resistance to conventional therapies(35).

3.8 Other cancers

Emerging evidence from patient-derived organoid models highlights the therapeutic potential of targeting ferroptosis in other cancers. Patient-derived organoids from cholangiocarcinoma have shown that combining surufatinib with photodynamic therapy induces ferroptosis and inhibits tumor growth, suggesting a potential combination therapy(36). Glioblastoma patient-derived organoid models have demonstrated that combination treatment can enhance ferroptosis through regulating HOXM1 and GPX4 expression(37). Similarly, patient-derived organoid models from oral squamous cell carcinoma have shown that DRP1 inhibition-mediated mitochondrial elongation drives ferroptosis and abolishes cancer stemness(38). Furthermore, manoalide promotes EGFR-TKI sensitivity in lung cancer by inducing ferroptosis(39), while the AR/GPX4 axis activation and inhibition of ERO1α enhance the antitumor effects in prostate cancer and laryngeal squamous cell carcinoma, respectively(40, 41). In head and neck cancer, organoid models have been instrumental in demonstrating the synergistic effects of TrxR1 inhibition and anti-PD-1 therapy, highlighting the potential of ferroptosis induction in improving cancer treatment outcomes(42). Organoid models elucidate the role of ferroptosis in drug-tolerant persister cells and provide new avenues for cancer treatment. Collectively, integrating organoid models with ferroptosis research enhances our understanding and unveils the therapeutic potential of ferroptosis in diverse cancer types.

4. Therapeutic Implications of Ferroptosis in Organoid Models

The therapeutic implications of ferroptosis in cancer treatment have attracted considerable interest, with a particular focus on utilizing organoid models. These models serve as valuable tools in ferroptosis research, enabling drug screening, improving the effectiveness of chemotherapy, shaping the tumor

microenvironment, facilitating personalized medicine, and exploring combination therapies. This section delves into the therapeutic potential of ferroptosis as observed in organoid models, shedding light on its significance in cancer therapy.

Organoid models have emerged as a powerful tool for drug screening and development, particularly in the context of ferroptosis. These three-dimensional cultures mimic the architecture and functionality of human tissues, providing a more physiologically relevant environment compared to traditional two-dimensional cell cultures. The ability to induce ferroptosis in organoid models allows for the high-throughput screening of potential therapeutic agents that can modulate this form of cell death. For instance, studies have demonstrated the use of organoid models to identify compounds that can either induce or inhibit ferroptosis, thereby offering new avenues for cancer treatment. The use of patient-derived organoids further enhances the relevance of these models, as they can capture the genetic and phenotypic diversity of tumors, allowing for personalized medicine approaches. This capability is particularly crucial in cancers such as PDAC, where traditional treatments have limited efficacy. Recent research has shown that targeting the MCP-GPX4/HMGB1 axis in PDAC organoids can effectively trigger immunogenic ferroptosis, highlighting the potential of these models in developing novel therapeutic strategies(21).

The integration of ferroptosis in organoid models offers significant potential for enhancing the efficacy of chemotherapy. Chemoresistance remains a major hurdle in cancer treatment, and ferroptosis induction has been identified as a promising strategy to overcome this challenge. For example, in gastric cancer, the inhibition of the STAT3-ferroptosis negative regulatory axis has been shown to suppress tumor growth and alleviate chemoresistance. Organoid models derived from gastric cancer patients have been used to validate these findings, demonstrating that targeting STAT3 can induce ferroptosis and restore sensitivity to chemotherapy(14). Similarly, in colorectal cancer, the use of organoids has facilitated the study of ferroptosis pathways and their role in overcoming drug resistance, providing a robust platform for testing combination therapies that include ferroptosis inducers(17).

Organoid models are instrumental in the realm of personalized medicine, particularly for identifying predictive biomarkers of ferroptosis sensitivity. By using patient-derived organoids, researchers can assess the ferroptosis susceptibility of individual tumors, enabling the customization of treatment regimens. This approach is exemplified in studies on liver cancer, where organoids have been used to explore the role of autophagy activation and m6A modification in regulating ferroptosis. These models have revealed that high levels of m6A modification correlate with increased ferroptosis sensitivity, suggesting that m6A could serve as a predictive biomarker for ferroptosis-based therapies(43). The ability to tailor treatments based on the ferroptosis profile of a patient's tumor holds promise for

improving therapeutic outcomes and minimizing adverse effects.

The tumor microenvironment plays a critical role in cancer progression and treatment resistance. Organoid models provide a unique opportunity to study the interactions between cancer cells and the tumor microenvironment, particularly in the context of ferroptosis. For instance, in gastric cancer, CAFs have been shown to impair the cytotoxic function of NK cells by inducing ferroptosis via iron regulation. Organoid models have been used to elucidate this mechanism, demonstrating that targeting CAFs can alleviate NK cell ferroptosis and enhance anti-tumor immunity(11). These findings underscore the importance of considering the tumor microenvironment in ferroptosis-based therapies and highlight the potential of organoid models in developing strategies to modulate the tumor microenvironment for improved treatment efficacy.

The use of organoid models in ferroptosis research has opened new avenues for exploring combination therapies. Combining ferroptosis inducers with other treatment modalities, such as immunotherapy or targeted therapy, can enhance therapeutic efficacy and overcome resistance mechanisms. For example, in glioma, the inhibition of SOAT1 has been shown to increase sensitivity to ferroptosis and enhance the efficacy of radiotherapy. Organoid models have been instrumental in these studies, providing a platform to test and optimize combination therapies(44). Similarly, in breast cancer, the combination of ferroptosis inducers with traditional chemotherapeutic agents has shown promise in overcoming resistance and improving treatment outcomes(45).

5. Conclusions and Future Perspectives

The exploration of ferroptosis within the context of organoid models represents a significant advancement in cancer research, offering novel insights into the mechanisms and therapeutic potential of this form of regulated cell death. Our comprehensive review highlights the intricate molecular pathways governing ferroptosis, including the pivotal roles of intracellular iron metabolism, lipid peroxidation, GPX4, and the system Xc-. Additionally, the construction and application of organoid models have been underscored as powerful tools that bridge the gap between traditional cell lines and in vivo studies, providing a more physiologically relevant environment to study cancer biology and treatment responses.

The integration of ferroptosis research with organoid technology holds transformative potential for cancer therapeutics. Organoid models, with their ability to mimic the three-dimensional architecture and cellular heterogeneity of tumors, offer a robust platform for investigating the efficacy and mechanisms of ferroptosis-inducing agents across various cancer types. Organoid models not only enhance our understanding of ferroptosis but also pave the way for the development of more effective and targeted

cancer treatments(46). However, the heterogeneity observed in ferroptosis sensitivity across different cancer types and even within subpopulations of the same cancer underscores the need for a more nuanced understanding of the underlying mechanisms.

Balancing the diverse findings from various studies, it is evident that while the induction of ferroptosis offers a promising therapeutic avenue, the complexity of iron metabolism and redox biology necessitates a tailored approach. Future research should focus on identifying biomarkers that predict ferroptosis sensitivity and resistance, thereby enabling personalized treatment strategies. Moreover, the potential side effects of ferroptosis induction, such as unintended damage to normal tissues, warrant careful consideration and further investigation.

The convergence of ferroptosis and organoid models represents a key advancement in cancer research, deeping our comprehension of cancer therapy. Leveraging the capabilities of organoid technology enables a comprehensive exploration of ferroptosis and its therapeutic capacities, facilitating the development of more potent and personalized cancer treatments. Further investigations should focus on refining these models, investigating synergistic treatment approaches, and translating these discoveries into clinical practice, thus bridging the translational gap between laboratory and clinical settings in the battle against cancer.

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Table 1. Cancer organoid models in ferroptosis

Cancer types	Organoid models	Functions	Ref.
Colorectal cancer	CRC-derived organoid	Overcome acquired drug resistance in CRC by inducing ferroptosis	(17)
Colorectal cancer	Colonic epithelial organoids	Loss of colonic epithelial Hmox1 promotes ferroptosis	(15)
Colorectal cancer	Intestinal stem cell organoids	IFNγ as a key cytokine capable of arresting cancer stemness triggers GPX4-dependent ferroptosis	(16)
Colorectal cancer	Patient-derived organoids	Curcumin and andrographis exhibit anti-tumor effects via activation of ferroptosis	(12)
Colorectal cancer	CRC Organoids	Adipocyte-derived exosomes containing MTTP reduce ferroptosis susceptibility in CRC, promoting chemoresistance to oxaliplatin	(13)
Colorectal cancer	Patient-derived organoids	Andrographis-mediated chemosensitization in CRC via activation of ferroptosis	(18)
Colorectal cancer	CRC organoids	VitC disrupted iron homeostasis and increased ROS levels, ultimately leading to ferroptosis	(19)
Pancreatic cancer	Pancreatic organoids derived from a mouse model	Elevated FSP1 protects KRAS-mutated cells from ferroptosis during tumor initiation	(20)
Pancreatic cancer	Patient-derived organoids	Triggers immunogenic ferroptosis by targeting the MCP-GPX4/HMGB1 Axis	(21)

Pancreatic cancer	patient-derived organoids	Imidazole ketone erastin induces tumor regression and abrogates MCU-driven metastasis	(24)
Pancreatic cancer	SMAD4-positive organoids	Enhances cytotoxic effects by combining gemcitabine with ferroptosis inducers	(22)
Pancreatic cancer	PDAC organoids	Ferroptosis inducers inhibit tumor growth and overcome chemoresistance	(10)
Pancreatic cancer	PDAC organoids	the synthesis of small molecule chimeras of salinomycin derivatives and dihydroartemisinin, ccumulates in lysosomes and induces ferroptosis	(23)
Liver cancer	Patient-derived organoids	Donafenib and GSK-J4 synergistically induced ferroptosis in liver cancer by upregulating HMOX1 expression	(25)
Liver cancer	Organoid models derived from HCC patients	Metformin restores PPARGC1A expression and enhances ferroptosis.	(26)
Liver cancer	HCC organoids	Unconventional prefoldin RPB5 interactor (URI) mediates resistance to tyrosine kinase inhibitors (TKIs)-induced ferroptosis	(27)
Liver cancer	CRC organoids	Combining ferroptosis induction with MDSC blockade rendered primary tumors and metastases	(28)
Breast cancer	MCF-7 organoid models	Tamoxifen can induce ferroptosis in MCF-7 organoid models	(31)

Breast cancer	Human TNBC organoid models	Simultaneous inhibition of FAK and ROS1 synergistically repress tumor growth by upregulating p53 signaling and inducing ferroptosis	(29)
Breast cancer	Breast cancer organoids	Combining anti-FGFR4 and anti-HER2 therapies induce ferroptosis in HER2-positive breast cancer	(30)
Bladder Cancer	BCa cell organoid models	PHGDH inhibitor NCT-502 induces ferroptosis in BCa cell organoid models	(32)
Bladder Cancer	Patient-derived organoids	m6A modifications affect chemoresistance by controlling SLC7A11 protein levels, influencing ferroptosis sensitivity.	(33)
Head and neck cancer	HNSCC Organoid models	Targeting thioredoxin reductase 1 (TrxR1) induces ferroptosis and potentiates the efficacy of anti-PD-1 therapy	(42)
Gastric cancer	Patient-derived organoid model	CAFs impair the cytotoxic function of NK cells in gastric cancer by inducing ferroptosis via iron regulation	(11)
Gastric cancer	Patient-derived organoids	Inhibition of STAT3-ferroptosis negative regulatory axis suppresses tumor growth and alleviates chemoresistance	(14)
Ovarian Cancer	Ovarian cancer organoids	SCD1/FADS2 fatty acid desaturases equipoise lipid metabolic activity and redox-driven ferroptosis in ascites-derived ovarian cancer cells	(35)

Ovarian Cancer	Ovarian cancer organoids derived from HGSOC	FeNP inhibits GPX4 activity, leading to induction of ferroptosis.	(34)
Cholangiocarcinoma	Patient-derived organoids	Combining surufatinib with photodynamic therapy induces ferroptosis and inhibits tumor growth	(36)
Glioblastoma	GBM patients derived organoids (PDOs) models	Combination treatment can enhance ferroptosis through regulating HOXM1 and GPX4 expression.	(37)
Oral squamous cell carcinoma	Patient-derived organoid model	DRP1 inhibition-mediated mitochondrial elongation drives ferroptosis and abolishes cancer stemness	(38)
Lung cancer	Lung cancer organoids	MA promoted ferroptosis by targeting the NRF2-SLC7A11 axis and inducing mitochondrial Ca2+ overload-induced FTH1 pathways	(39)
Prostate cancer	Organoid cultures derived from prostate cancer cells	TQB3720 promotes ferroptosis through inhibition of the AR signaling pathway	(40)
Laryngeal squamous cell carcinoma	Organoid models derived from LSCC patients	Augmented ERO1α upon mTORC1 activation induce ferroptosis resistance and tumor progression via upregulation of SLC7A11	(41)