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Review

Ferroptosis: A Novel Mechanistic Insight and Therapeutic Opportunity in Cholangiocarcinoma

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Abstract

Cholangiocarcinoma, a malignancy of the biliary tract, remains one of the most lethal cancers with limited treatment options and poor prognosis. Emerging evidence indicates that ferroptosis an iron-dependent, oxidative form of regulated cell death, is a promising therapeutic vulnerability in Cholangiocarcinoma (CCA). This review presents an in-depth analysis of the molecular mechanisms driving ferroptosis, including iron metabolism, lipid peroxidation, and the glutathione/glutathione peroxidase 4 (GPX4) axis. It also explores the complex regulation of ferroptosis by key molecules including p53, TP53-induced glycolysis and apoptosis regulator (TIGAR), and noncoding RNAs within the CCA context. Recent computational and experimental studies have identified ferroptosis-related gene signatures and biomarkers that correlate with prognosis and therapeutic response. Moreover, ferroptosis inducers including small molecules like erastin, ras-selective lethal small molecule 3 (RSL3), and artesunate, have demonstrated potent anticancer effects in preclinical models. Nanotechnology-based strategies and gene-editing approaches offer novel delivery systems to enhance ferroptotic responses while minimizing systemic toxicity. The tumor microenvironment, particularly inflammation and immune components, further modulates ferroptosis and presents opportunities for combination therapies. This review concludes that targeting ferroptosis represents a novel and multifaceted therapeutic strategy for CCA, with the potential to synergize with chemotherapy, immunotherapy, and nanomedicine. Continued investigation into ferroptosis regulation and precision-based delivery systems could usher in a new era of effective treatments for this challenging malignancy.

Keywords

Ferroptosis, Cholangiocarcinoma, Iron metabolism, Lipid peroxidation, Ferroptosis Inducers, Nanomedicine, Immunotherapy

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1. Introduction

Cholangiocarcinoma (CCA), a malignancy arising from the epithelial cells of the bile ducts, is one of the most aggressive and lethal forms of cancer. Despite its relatively low incidence compared to other gastrointestinal tumors, CCA has garnered significant clinical attention due to its late diagnosis, rapid progression, resistance to conventional therapies, and poor prognosis with a five-year survival rate remaining below 10% [1]. Conventional treatment strategies such as surgical resection, chemotherapy, and radiotherapy often offer limited therapeutic benefit, particularly in advanced or metastatic cases [2]. The molecular heterogeneity and complex pathophysiology of CCA, which often involves chronic inflammation, altered metabolic states, and a desmoplastic tumor microenvironment, further complicate treatment and necessitate the exploration of novel therapeutic targets [3].

Recent advances in cancer biology have unveiled a non-apoptotic, iron-dependent form of programmed cell death known as ferroptosis, characterized by the accumulation of lethal lipid peroxides and oxidative damage to cellular membranes. Unlike apoptosis or necroptosis, ferroptosis is driven by distinct metabolic pathways, including dysregulated iron homeostasis, impaired antioxidant defenses (particularly the glutathione glutathione peroxidase 4 (GPX4) axis), and aberrant lipid metabolism. Notably, cancer cells including those of CCA often exhibit increased iron dependency, heightened oxidative stress, and reprogrammed lipid profiles, rendering them particularly vulnerable to ferroptotic triggers. These unique vulnerabilities have positioned ferroptosis as an attractive therapeutic mechanism, capable of overcoming resistance pathways that render traditional therapies ineffective [4].

In CCA, emerging preclinical evidence suggests a pivotal role for ferroptosis in both tumor suppression and disease progression. Studies have shown that CCA cells frequently upregulate iron transport proteins, such as transferrin receptor 1 (TfR1) and ferroptosis-resistance regulators, such as GPX4 and solute carrier family 7 member 11 (SLC7A11), highlighting a finely tuned balance between proliferation and death. Additionally, molecular regulators such as p53, TIGAR, and various noncoding RNAs have been implicated in modulating ferroptosis in CCA, underscoring the complex interplay between genetic signaling networks and redox biology. Concurrently, high-throughput transcriptomic and single-cell sequencing studies have begun to identify ferroptosis-related gene signatures that correlate with clinical prognosis and therapeutic response, paving the way for precision medicine approaches.

Beyond mechanistic insights, several ferroptosis-inducing agents including small molecules like erastin, ras-selective lethal small molecule 3 (RSL3), and artesunate have demonstrated efficacy in inducing cell death in CCA models. Furthermore, novel delivery platforms such as iron oxide nanoparticles, polymeric carriers, and gene therapy-based systems offer promising avenues for selectively enhancing ferroptotic stress in tumor cells while sparing normal tissues [5]. The tumor microenvironment, particularly immune cells and inflammatory cytokines, also plays a crucial role in modulating ferroptosis, suggesting opportunities for combination therapies that integrate ferroptosis inducers with immunotherapies or conventional chemotherapeutics.

Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation and oxidative stress, has emerged as a key tumor-suppressive mechanism distinct from apoptosis or necrosis [6]. Cancer cells often exhibit “iron addiction” and altered redox states; these features make them particularly vulnerable to ferroptosis [7]. In CCA, pathological iron metabolism and inflammation frequently co-occur during tumorigenesis, suggesting that harnessing ferroptosis could yield novel diagnostic biomarkers and therapies[8]. Indeed, recent studies report that CCA cells are highly sensitive to ferroptotic triggers and that induction of ferroptosis markedly inhibits CCA cell growth and migration. This chapter reviews the mechanistic basis of ferroptosis, summarizes experimental and computational findings in CCA, and discusses emerging therapeutic strategies including small molecules, nanomedicine, and gene-based approaches to exploit ferroptosis against CCA (Figure 1).

Emerging bioinformatics studies have identified ferroptosis-related genes that contribute to cancer progression and may serve as prognostic biomarkers or therapeutic targets. For example, computational analyses in head and neck squamous cell carcinoma (HNSCC) have implicated ferroptosis regulators such as solute carrier family 3 member 2 (SLC3A2) within cancer-associated gene networks and linked their expression to overall survival, suggesting a regulatory influence on ferroptotic pathways that include glutathione metabolism and lipid redox homeostasis. Furthermore, mechanistic reviews emphasize that glutathione peroxidases (GPXs), particularly GPX4, are central to the ferroptosis execution machinery: GPX4 uses reduced glutathione (GSH) to detoxify lipid hydroperoxides and prevent iron-dependent lipid peroxidation, thereby suppressing ferroptotic cell death in cancer cells. Dysfunction or inhibition of the system Xc-/GSH/GPX4 axis leads to accumulation of lipid reactive oxygen species (ROS) and sensitizes tumor cells to ferroptosis, a vulnerability that can be exploited therapeutically to overcome resistance to conventional treatments

CCA is a highly aggressive malignancy arising from the epithelial cells of the bile ducts and represents the second most common primary hepatobiliary cancer after hepatocellular carcinoma. Globally, the incidence of CCA ranges from 0.3 to 6 cases per 100,000 individuals per year, with markedly higher prevalence reported in Southeast Asia due to endemic risk factors such as liver fluke infection. Despite advances in diagnostic and therapeutic strategies, CCA is associated with an extremely poor prognosis, with a 5-year overall survival rate of less than 10% and a median survival of approximately 12-24 months following diagnosis. The high mortality rate is largely attributable to late-stage presentation, early metastatic spread, and limited responsiveness to conventional chemotherapy and radiotherapy, underscoring the urgent need for improved molecular biomarkers and targeted therapeutic strategies[9].

This review aims to provide a comprehensive overview of the current understanding of ferroptosis in the context of CCA. We begin by discussing the molecular mechanisms that underpin ferroptosis, followed by an in-depth examination of its regulatory networks and functional relevance in CCA[10]. We then explore the landscape of computational findings, experimental data, and emerging biomarkers that link ferroptosis to prognosis and therapy. Finally, we highlight current and prospective therapeutic strategies ranging from small molecules to nanomedicine and gene-based interventions that aim to exploit ferroptosis for the treatment of CCA. By synthesizing these multidisciplinary insights, we seek to underscore the therapeutic promise of ferroptosis and outline future directions for its clinical translation in combating this formidable malignancy.

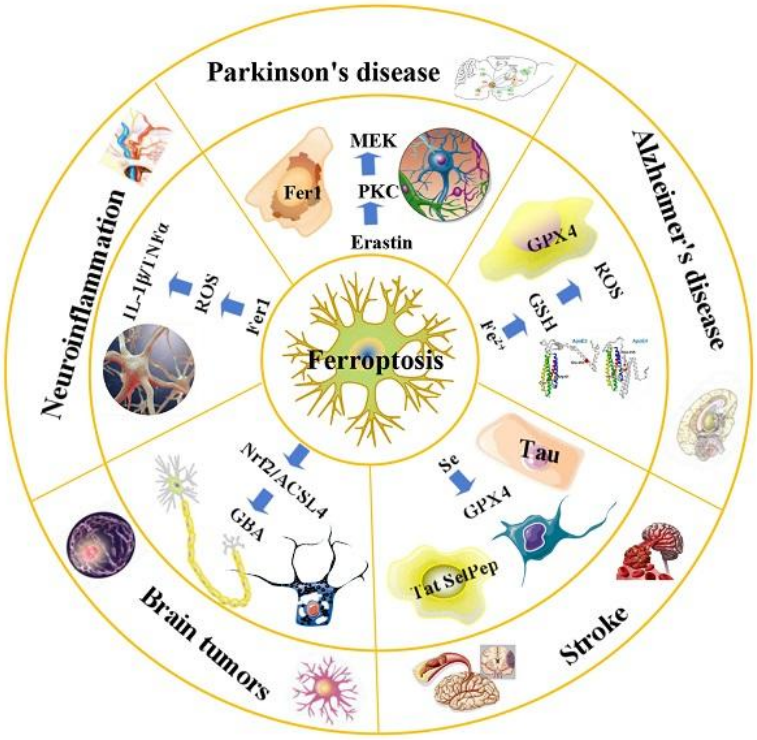

Figure 1. Different mechanism and role of ferroptosis in pathology [11].

2. Mechanisms of Ferroptosis

Ferroptosis is driven by iron-mediated ROS and lethal lipid peroxidation. Key elements include dysregulated iron metabolism (increased uptake and labile iron pool), accumulation of polyunsaturated fatty acid (PUFA) hydroperoxides, and failure of antioxidant defenses (notably the glutathione/GPX4 axis) [12].

Iron Metabolism: Cancer cells often have elevated expression of TfR1/CD71 and reduced ferritin, enabling increased Fe^{3+} uptake and higher labile Fe^{2+} via the Fenton reaction. Excess Fe^{2+} catalyzes ROS generation, driving lipid peroxidation. Disrupted iron export (via ferroportin) or storage further sensitizes cells to ferroptosis [13]. In CCA, high TfR1 expression has been observed, correlating with large tumor size and vascular invasion. TfR1-high tumors are more prone to ferroptosis, whereas TfR1 knockdown lowers intracellular Fe and suppresses ferroptosis [14].

Ferroptosis is an iron-dependent form of regulated cell death driven by lipid peroxidation and oxidative stress, directly linking iron metabolism to cancer biology. Dysregulated iron homeostasis enhances ROS generation and ferroptosis sensitivity, thereby influencing tumor progression and therapeutic response [15]. In CCA, alterations in iron metabolism contribute to aggressive disease behavior, highlighting ferroptosis as a biologically relevant and clinically exploitable pathway.

ROS and Lipid Peroxidation: ROS (superoxide, hydroxyl radicals) attack PUFA-containing membrane phospholipids (e.g., arachidonic acid-PE), generating lipid hydroperoxides. Enzymes ACSL4 and LPCAT3 incorporate PUFAs into membranes, rendering them susceptible to peroxidation. In ferroptosis, unchecked lipid peroxidation disrupts membrane integrity and leads to cell death [16]. Antioxidant systems normally detoxify these peroxides: notably, GSH and GPX4 convert lipid hydroperoxides to non-toxic alcohols. When GSH is depleted or GPX4 is inhibited, lipid ROS accumulate and ferroptosis ensues [17].

Glutathione/GPX4 Axis: The cystine/glutamate antiporter system Xc^- (SLC7A11/SLC3A2) imports cystine for GSH synthesis. Adequate GSH allows GPX4 to neutralize lipid peroxides. Inhibition of SLC7A11 or GPX4 (using compounds such as erastin or RSL3) depletes GSH or inactivates GPX4, such as triggering ferroptosis. Key regulatory

pathways (e.g., NRF2) modulate SLC7A11 and other antioxidant genes, linking ferroptosis to cellular stress responses [18].

p53 and Other Regulators: The tumor suppressor p53 can promote or inhibit ferroptosis via multiple routes. Notably, p53 represses SLC7A11 transcription, reducing cystine uptake and lowering GSH levels. p53 also upregulates ALOX12 and genes such as SAT1 and TP53INP1 to enhance ROS production and lipid peroxidation. Conversely, p53-induced TIGAR limits ROS by stimulating pentose phosphate pathway flux; TIGAR overexpression thus protects against ferroptosis [19]. In CCA, elevated TIGAR correlates with poor prognosis and ferroptosis resistance. Other ferroptosis modulators include NRF2, HIF pathways, oncogenes (e.g., YAP), and diverse noncoding RNAs that impact SLC7A11/GPX4 [20].

In addition to the canonical system Xc^-/GSH/GPX4 pathway, alternative antioxidant systems also regulate ferroptotic susceptibility. Notably, the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q10 (CoQ10) axis functions independently of GPX4 to suppress lipid peroxidation and ferroptotic cell death. FSP1 reduces CoQ10 to its antioxidant form, which scavenges lipid radicals and prevents membrane damage. Dysregulation or inhibition of this axis sensitizes cancer cells to ferroptosis, representing a potential mechanism of resistance in CCA and other malignancies [21]. Incorporating both canonical and alternative antioxidant pathways provides a more complete mechanistic framework and informs the design of strategies to overcome ferroptosis resistance in therapeutic settings [22].

FSP1/CoQ10, Lipid Remodelling: Despite the promise of ferroptosis-based therapies in CCA, several therapeutic challenges limit their clinical translation. Resistance mechanisms, including the FSP1-CoQ10 axis and adaptive lipid remodeling, can reduce ferroptotic sensitivity and contribute to treatment failure. Off-target effects, arising from systemic induction of lipid peroxidation or iron dysregulation, pose additional toxicity risks. Strategies to overcome these challenges include the use of combinatorial approaches that inhibit multiple antioxidant pathways, targeted delivery via nanocarriers to minimize systemic exposure, and biomarker-guided patient selection to identify ferroptosis-sensitive tumors [23]. Addressing these barriers is critical to maximizing therapeutic efficacy while minimizing adverse effects, thereby enhancing the translational potential of ferroptosis-based interventions in CCA [24] (Figure 2).

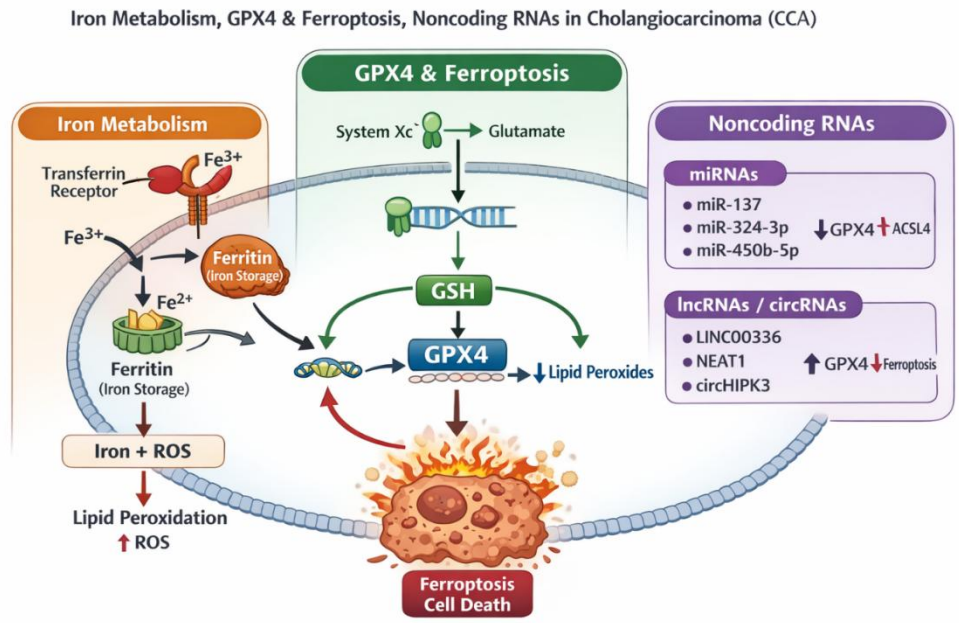

Figure 2. Interplay among iron metabolism, GPX4, and noncoding RNAs in CCA. Iron uptake, storage, and export regulate ROS and lipid peroxidation, while GPX4 detoxifies lipid peroxides via GSH. miRNAs, lncRNAs, and circRNAs modulate GPX4 and ferroptosis-related genes, collectively influencing ferroptosis sensitivity in CCA cells.

Ferroptosis is governed by the balance between iron-catalyzed ROS/lipid peroxidation and the cell's antioxidant capacity. In CCA a cancer often driven by chronic inflammation and altered metabolism these pathways are perturbed, making ferroptosis a compelling target.

3. Ferroptosis in CCA: Molecular Insights

3.1 Aberrant Iron and Antioxidant Profiles in CCA

CCA cells frequently exhibit dysregulated iron metabolism and antioxidant gene expression. High TfR1 expression in interstitial cells of Cajal (ICC) (intrahepatic CCA) tumors is associated with aggressive features and poor outcomes. *In vitro*, knocking down TfR1 lowered intracellular Fe and suppressed ICC cell proliferation, migration and invasion, indicating that CCA growth depends on iron uptake [25]. Consistent with this, treatment with the ferroptosis inducer

artesunate (which generates ROS from intracellular iron) significantly reduced ICC cell viability, whereas TfR1 knockdown blunted this effect. Thus, TfR1-mediated iron import is a double-edged sword: It drives tumor growth but also creates a vulnerability to ferroptosis [26].

In a cohort of 57 ICC patients we found that tumors with elevated GPX4 (a key ferroptosis suppressor) had larger tumor burden and markedly worse survival. Inhibition of GPX4 in ICC cell lines reduced proliferation and migration, and downregulated glucose metabolism genes (GLUT1, HIF1α) via the Akt-mTOR pathway (Figure 3) [27]. This suggests that GPX4 not only prevents ferroptotic death but also promotes metabolic reprogramming in CCA. GPX4 therefore serves as both a prognostic marker and a therapeutic target: High GPX4 predicts poor outcomes and signals ferroptosis resistance [1].

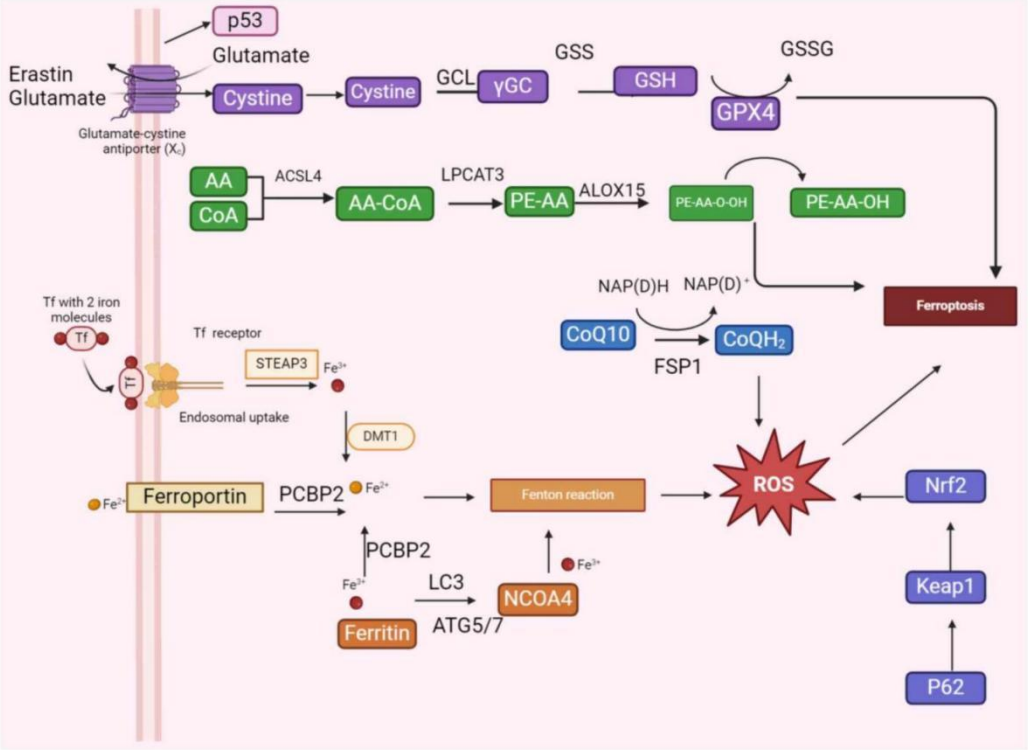

Figure 3. Integrated bioinformatics and immunoinformatics strategy for identifying prognostic biomarkers and vaccine targets in CCA. Publicly available transcriptomic datasets were retrieved and subjected to differential gene expression analysis, followed by functional enrichment analyses and protein-protein interaction (PPI) network construction to identify hub genes. Survival analysis was performed to evaluate prognostic relevance. Selected target proteins were further analyzed using immunoinformatics approaches, including epitope prediction, antigenicity, allergenicity, toxicity assessment, population coverage analysis, molecular docking, and immune simulation.

3.2 Computational Analyses and Gene Signatures

High-throughput analyses have begun to uncover gene expression patterns associated with ferroptosis in CCA. Integrated single-cell RNA-seq with bulk transcriptomic data to dissect ferroptosis heterogeneity [28]. Identified a three-gene signature (*BNIP3, TMEM107, CENPW*) linking monocyte infiltration and ferroptotic regulation that robustly predicts CCA prognosis [29]. Their single-cell data also revealed increased TNFSF13B-TFRC signaling between monocytes and cholangiocytes, implicating the tumor microenvironment in the regulation of ferroptosis. Notably, higher monocyte signatures (coupled with ferroptosis pathways) correlated with worse survival.

A novel six-gene ferroptosis-related signature for CCA by Cox regression. The signature genes included *FANCD2, PTGS2, SLC2A1, SQLE* (upregulated in tumors) and *ACO1, GOT1* (downregulated) [30]. Patients stratified by this signature showed distinct survival curves: High-risk (bad) *vs*. low-risk (good) groups. Remarkably, CCA cell lines with high risk scores were significantly more resistant to ferroptosis inducers (erastin, RSL3) than low-risk lines. This suggests that enhanced ferroptosis-protective mechanisms underlie the poor prognosis group. These computational findings underscore that ferroptosis pathway activity is intimately linked to CCA progression and can serve as a prognostic biomarker [31].

3.3 Molecular Regulators in CCA

Beyond global signatures, specific genes and noncoding RNAs in CCA regulate ferroptosis:

TP53-induced Glycolysis and Apoptosis Regulator (TIGAR): TIGAR diverts glucose to the pentose phosphate pathway, lowering ROS. The ~24% of ICC tumors overexpressed TIGAR. TIGAR high patients had significantly

shorter survival (both disease-free and overall) than TIGAR low patients [32]. *In vitro*, TIGAR knockdown in ICC cells raised ROS and lipid peroxides and decreased GPX4 levels, effectively inducing ferroptosis. The ferroptosis inducer liproxstatin reversed this effect. Moreover, combining TIGAR knockdown with cisplatin synergistically boosted ferroptosis. Thus, TIGAR overexpression in ICC confers ferroptosis resistance and worse outcomes, whereas its inhibition triggers ferroptotic death.

LncRNA/circRNA Modulators: Emerging data show that noncoding RNAs can modulate ferroptosis in CCA. The transcription factor JUND upregulates a long noncoding RNA, linc00976, in CCA. Linc00976 sponges miR-3202, leading to higher GPX4 expression. Functionally, linc00976 overexpression promoted CCA cell proliferation and metastasis while suppressing ferroptosis; conversely, linc00976 knockdown repressed tumor growth and *increased* ROS and lipid peroxidation [33]. These results demonstrate a JUND-linc00976-miR-3202-GPX4 axis that actively inhibits ferroptosis in CCA. Targeting such lncRNAs might thus restore ferroptotic sensitivity in tumors [34].

Other Pathways: The p53/GPX4/SLC7A11 axis is also implicated. Although not yet fully characterized in CCA, parallels from other cancers indicate that mutant p53 may decrease SLC7A11 and sensitize cells to ferroptosis, while wild-type p53 induction of TIGAR/G6PD can protect against it. Additionally, NF-κB signaling and autophagy-related genes (e.g., TFEB) have been suggested to intersect with ferroptosis pathways, though specific CCA data are still emerging (Figure 4) [35].

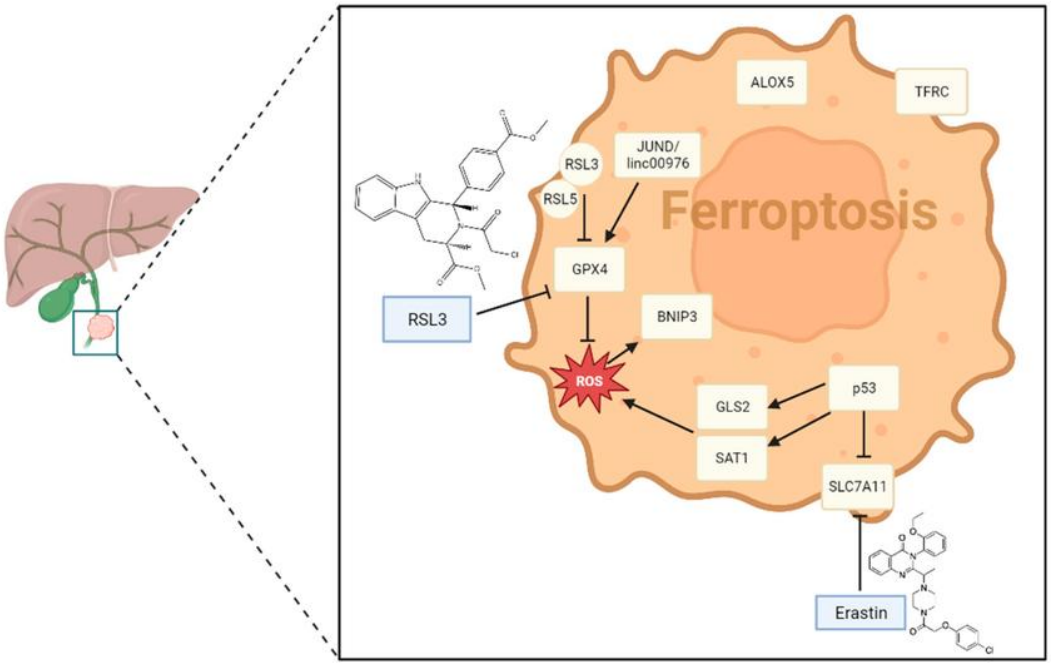

Figure 4. Key molecular regulators of ferroptosis in CCA. This schematic highlights canonical pathways, including GPX4-mediated detoxification of lipid peroxides, iron metabolism, lipid peroxidation, and regulatory influences of noncoding RNAs (miRNAs, lncRNAs, circRNAs) on ferroptosis susceptibility.

3.4 Tumor Microenvironment and Inflammation

Ferroptosis does not act in isolation; it interplays with the immune microenvironment. Single-cell study found that monocyte-derived signals (TNFSF13B) converged on TFRC (transferrin receptor) in malignant cholangiocytes, hinting that immune cells may influence tumor iron uptake [28]. CCA is often accompanied by chronic inflammation (e.g., liver flukes, hepatitis) [36], which generates ROS. Paradoxically, inflammatory cytokines can both induce ferroptosis in some contexts or promote resistance via Nrf2 activation. Combining cisplatin with artesunate not only enhanced ferroptosis but also upregulated programmed death-ligand 1 (PD-L1) on CCA cells, potentially linking ferroptosis to immunomodulation. Overall, the CCA microenvironment, rich in iron, cytokines, and immune cells, likely shapes the ferroptotic response, though much remains to be explored.

Ferroptosis in CCA is intricately linked with the tumor immune microenvironment, influencing both innate and adaptive immune responses. Ferroptotic cell death can release damage-associated molecular patterns (DAMPs) that activate monocytes and macrophages, promoting inflammatory signaling and antitumor immunity. Interestingly, treatment with ferroptosis-inducing agents, such as artesunate, has been reported to upregulate PD-L1 expression on tumor cells, potentially contributing to adaptive immune evasion [37]. This crosstalk suggests that combining ferroptosis inducers with immune checkpoint blockade may enhance antitumor efficacy. Understanding the immune-ferroptosis interplay provides a mechanistic framework for integrating ferroptosis-targeted therapies with immunotherapy, particularly in the context of CCA's immunosuppressive microenvironment [38].

4. Therapeutic Strategies Targeting Ferroptosis in CCA

The above insights suggest multiple strategies to induce ferroptosis in CCA. We outline approaches using small molecules, nanotechnology, and genetic modulation.

4.1 Small-Molecule Ferroptosis Inducers

A variety of compounds have been identified that directly or indirectly trigger ferroptosis (Figure 5). Key examples include:

System Xc^- Inhibitors (erastin derivatives): Erastin and its analogs (e.g., imidazole ketone erastin, IKE) block the cystine/glutamate antiporter, depleting GSH. In biliary tract cancer (BTC) cell lines (which include CCA cells), the IKE reduced cell viability, increased lipid ROS, and that sensitivity correlated with SLC7A11 expression [39]. Erastin analogs are prototypical ferroptosis inducers, but clinical use is limited by solubility and off-target effects.

GPX4 Inhibitors (RSL3, ML162): RSL3 covalently inhibits GPX4, causing rapid ferroptosis. The RSL3 reduced BTC cell viability and Fe^{2+} levels. Similarly, analogs like ML210 have been used to trigger ferroptosis. In CCA cells, RSL3 has been shown to induce ferroptotic markers (lipid peroxides, PTGS2 expression) [40].

Artemisinin Derivatives: Anti-malarial drugs like artesunate and dihydroartemisinin (DHA) generate cytotoxic ROS via Fenton chemistry (they contain endoperoxides that react with Fe^{2+}). In ICC cells, artesunate significantly decreased viability, and when combined with cisplatin it enhanced ferroptotic death. Artesunate also induced PD-L1, suggesting immunogenic cell death [41]. Platinated-artesunate hybrids (e.g., oxaliplatin-artesunate) are under investigation in other cancers [42].

Other Inducers: Compounds like FIN56 (depletes CoQ10 and GPX4), sulfasalazine (xCT inhibitor), sorafenib (multikinase inhibitor with off-target xCT effects in some cells), and statins (lower ubiquinone) have demonstrated ferroptotic activity in cancer models. Notably, ferroptosis inducers are being explored to overcome drug resistance and to synergize with immunotherapies [43].

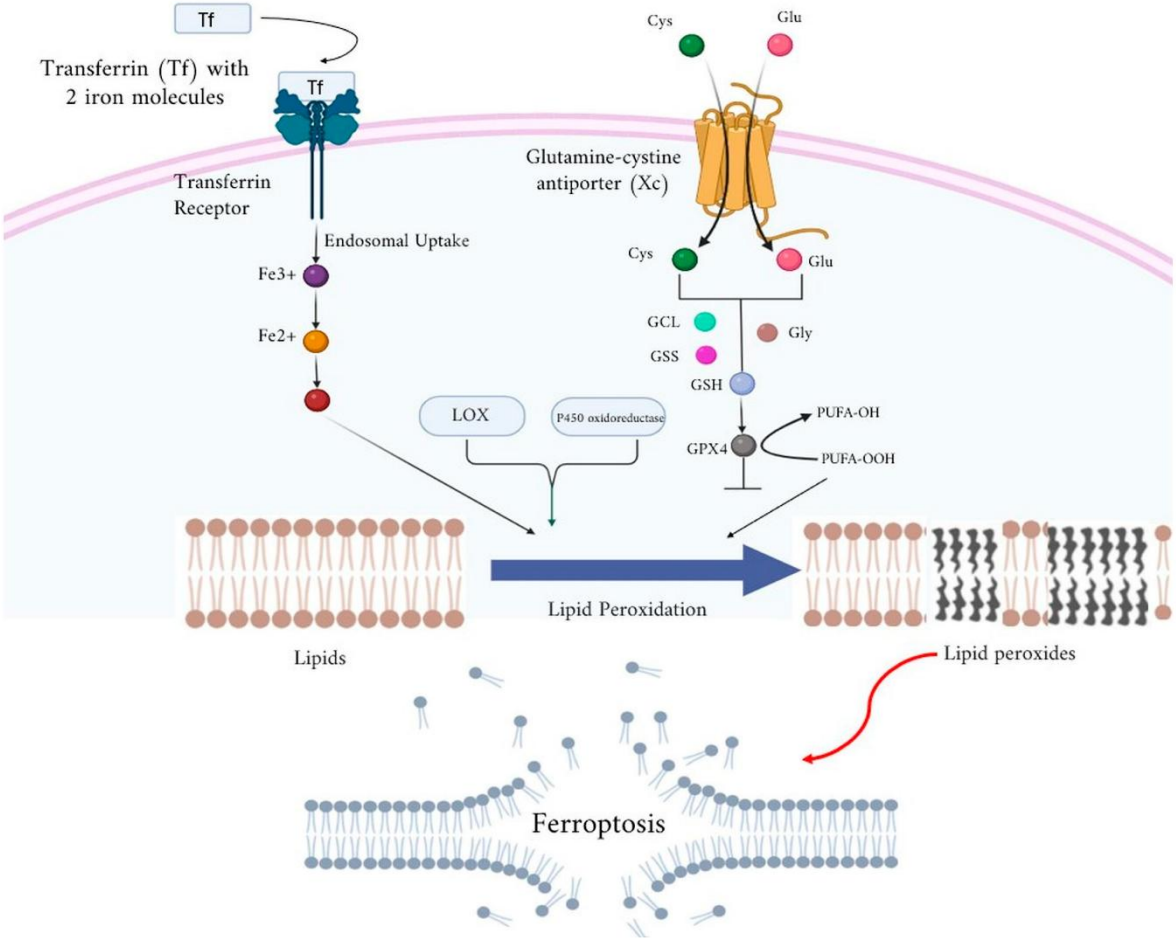

Figure 5. Small-molecule ferroptosis inducers and their therapeutic mechanisms in CCA. The diagram illustrates how agents such as artesunate, sorafenib, and erastin promote ferroptosis by targeting GPX4, system Xc^-, lipid peroxidation, and iron metabolism, highlighting their potential for CCA therapy.

These agents have shown efficacy in preclinical models of CCA/BTC (Table 1). In general, CCA cells treated with pro-ferroptotic drugs exhibit hallmark changes (↑lipid ROS, ↓GPX4, and cell death prevented by ferrostatin-1 or liproxstatin).

Table 1. Shows the Compound its targets and mechanism with remarks in CCA.

Compound	Target/Mechanism	Remarks (in CCA)	Source
Erastin/IKE (Imidazole Erastin)	Inhibits SLC7A11 (system Xc^-), depletes GSH	Potently induces ferroptosis in BTC/CCA cells; efficacy correlates with SLC7A11 and TfR1.	[44]
RSL3	Covalent inhibitor of GPX4	Induces ferroptosis (↑ROS, ↑malondialdehyde); reduces viability of BTC cells.	[5]
Artesunate (ART)	Iron-dependent ROS generation (Fenton reaction)	Decreases ICC cell viability; combination with cisplatin enhances ferroptosis and PD-L1 expression.	[45]
FIN56	Depletes CoQ10 and GPX4	Experimental ferroptosis inducer; effectiveness in CCA yet to be tested in detail.	[46]
Sulfasalazine	System Xc^- inhibitor	Blocks cystine uptake; shown to induce ferroptosis in various cancers (preclinical CCA data limited).	[47]
Liproxstatin-1 (inhibitor)	Ferroptosis inhibitor (for control)	Prevents ferroptotic death; used experimentally to confirm ferroptosis in CCA models.	[48]

4.2 Nanomedicine and Ferroptosis

Nanotechnology offers innovative ways to trigger ferroptosis selectively in tumors:

Iron-based Nanoparticles (IONPs): Superparamagnetic iron oxide nanoparticles can deliver Fe^{2+} into cancer cells. In endolysosomes, they release Fe^{2+}, promoting ROS via Fenton chemistry and causing ferroptosis. Elegantly combined IONPs with gene therapy: They used cancer-specific promoters to drive Cas13a-mediated knockdown of ferroportin (FPN) and LCN2 in tumor cells, while simultaneously delivering IONPs. This strategy substantially elevated intracellular Fe and triggered ferroptosis specifically in tumor cells, with minimal effect on normal cells. In mice, AAV delivery of this gene-nanoparticle combo "cured" treated tumors with strong growth inhibition. Although not yet tested in CCA, this proof-of-concept demonstrates how nanocarriers and nucleic acids can synergize to induce tumor-selective ferroptosis [49].

Polymeric/Liposomal Carriers: Nanocarriers can also deliver small-molecule ferroptosis drugs or prodrugs. For example, polymeric platinum (IV)-artesunate conjugates have been reported to trigger ferroptosis in colorectal cancer models. A similar strategy could be applied to CCA-encapsulating erastin or RSL3 in tumor-targeted liposomes might improve delivery and reduce toxicity. Magnetic targeting or tumor-penetrating peptides are additional tactics to enhance ferroptosis induction [50].

Exosomes and Biomimetic Systems: Tumor-derived exosomes or extracellular vesicles can be engineered to carry ferroptosis inducers or siRNAs. For instance, one could load miRNAs that targeting SLC7A11 into exosomes and deliver them to CCA. While still experimental, such biomimetic approaches could enable cell-specific modulation of ferroptosis.

Recent advances in nanomedicine offer promising strategies to enhance ferroptosis-targeted therapies in CCA. Polymeric and liposomal carriers, exosomes, and biomimetic nanoparticles have been explored for drug delivery in preclinical models of CCA, demonstrating improved tumor accumulation and reduced systemic toxicity. Additionally, novel approaches such as bile duct-targeted nanoparticles or ligands recognizing cholangiocyte-specific markers could enhance selective delivery to the biliary tract [51]. These strategies not only increase the therapeutic efficacy of ferroptosis inducers but also provide a platform for integrating combinatorial therapies, including immunomodulation. Incorporating CCA-specific nanotechnology considerations bridges the gap between preclinical research and potential clinical application, highlighting feasible translational pathways for ferroptosis-based interventions.

4.3 Nanocarriers and Systems for Ferroptosis-Based Therapy

Nanocarrier platforms, including polymeric and liposomal systems, exosomes, and biomimetic nanostructures, have emerged as promising strategies to enhance the delivery and efficacy of ferroptosis-inducing agents in cancer therapy [52]. Polymeric and liposomal carriers improve drug solubility, stability, and controlled release, thereby increasing tumor-specific accumulation while minimizing off-target toxicity [50]. Exosomes, as naturally derived vesicles, offer biocompatibility and inherent cell-targeting capabilities, facilitating efficient delivery of ferroptosis modulators to tumor cells. Biomimetic systems, designed to mimic cellular membranes or tumor microenvironments, further enhance targeting precision and therapeutic responsiveness [53]. These nanomedicine approaches not only improve the pharmacokinetic and pharmacodynamic profiles of ferroptosis inducers but also expand their translational potential for clinical applications in CCA and other malignancies [54].

Nanomedicine enables co-delivery of iron and genetic payloads to tumor cells, amplifying ferroptotic stress. Table 2 summarizes experimental ferroptosis-based nanotherapies (in various cancers) that could inspire CCA treatments.

Table 2. Experimental ferroptosis-based nanotherapies: Approaches, mechanisms, and translational insights for CCA treatment.

Approach	Mechanism	Remarks and Evidence	Source
IONP + Cas13a (AAV)	Knockdown FPN/LCN2+Fe loading	Induced robust ferroptosis in tumor cells; cured mouse xenografts; minimal effect on normal cells.	[55]
Magnetic NPs (Fe_3O_4)	Localized heat and ROS; Fenton reaction	Can synergize with hyperthermia/MRI; preclinical in lung cancer.	[56]
Pt(IV)-Artesunate nanoparticles	Ferroptotic prodrug releasing artesunate+Pt(II)	Polymer-based nanoprodrug triggered ferroptosis and apoptosis *in vitro/in vivo* (colorectal cancer).	[57]
Biomimetic vesicles	Exosomal or liposomal delivery of siRNA/drug	Could target CCA receptors (e.g., EGFR) to deliver ferroptosis inducers (conceptual).	[58]

4.4 Gene Therapy and Molecular Interventions

Gene-based strategies offer precise control over ferroptosis pathways:

CRISPR/Cas and RNA Interference: CRISPR/Cas9-based gene therapy represents a promising approach to modulate ferroptosis-related genes in CCA; however, several barriers hinder its clinical translation [59]. Efficient and tumor-specific delivery to bile duct tumors remains challenging due to the complex biliary anatomy and dense stromal microenvironment. Viral and nonviral vectors may face limitations in packaging capacity, transduction efficiency, and immunogenicity. Off-target editing is another major concern, necessitating careful design of guide RNAs and rigorous validation to prevent unintended genomic alterations [60]. Overcoming these challenges requires optimization of delivery platforms, such as liver-targeted nanoparticles, tissue-specific promoters, or exosome-mediated systems, to ensure precise, safe, and effective gene modulation for therapeutic application [61].

Gene Interference-Enhanced Ferroptosis: The Nanotherapy used a Cas13a system to knock down *FPN* and *LCN2*, starving cancer cells of iron export and binding. A similar strategy in CCA for example, using an NF-κB promoter-driven Cas13a to target *SLC7A11* or *GPX4* could further drive ferroptosis when combined with iron delivery. As demonstrated combining genetic "ferroptosis locks" with iron nanocarriers can achieve tumor-selective cell death [62].

miRNA and lncRNA Modulators: Based on the linc00976 example, one could design antisense oligonucleotides or CRISPR-based epigenetic silencing of oncogenic lncRNAs that inhibit ferroptosis. Conversely, mimics of miR-3202 (which was sponged by linc00976) could be delivered to downregulate GPX4. Such RNA therapies are in early clinical stages for other diseases and could be adapted for CCA [63].

Gene Editing for Ferroptosis Sensitivity: In principle, *ex vivo* editing of immune cells or progenitors to express ferroptosis-promoting factors might also be considered (e.g., making CAR-T cells resistant to ferroptosis in the tumor microenvironment). While speculative, these gene therapy avenues underscore the plasticity of ferroptosis regulation [64].

4.5 Combination and Multimodal Therapies

Given the interplay of pathways, ferroptosis inducers will likely be most effective in combination. Studies already highlight synergistic approaches:

Ferroptosis+Chemotherapy: Standard CCA chemotherapy (cisplatin, gemcitabine) can be combined with ferroptosis induction. Cisplatin alone modestly increased ICC cell ferroptosis, and combining it with artesunate or TIGAR knockdown greatly amplified cell death. Mechanistically, DNA damage (from cisplatin) may elevate ROS and complement ferroptotic triggers [65]. Likewise, targeting pathways that confer chemo-resistance (e.g., NRF2) might sensitize tumors to ferroptosis.

Ferroptosis+Immunotherapy: Emerging data suggest that ferroptotic cancer cells may release damage-associated signals that enhance antitumor immunity. In CCA models, artesunate + cisplatin upregulated PD-L1, implying an immune-activating milieu [66]. Combining ferroptosis inducers with checkpoint inhibitors (e.g., anti-PD-1) is an active area of research in other cancers. The goal is to induce ferroptosis in cancer cells while also relieving immunosuppression.

Ferroptosis+Targeted Photodynamic or Radiation Therapies: Ferroptosis inducers might be used alongside photodynamic therapy (PDT) or radiotherapy, both of which generate ROS. One review noted that PDT targeting p53/GPX4/SLC7A11 pathways induced ferroptosis in CCA cells. Similarly, radiation can deplete GSH and might synergize with ferroptosis inducers [67].

Multifaceted regimens that integrate ferroptosis with existing modalities hold promise. For example, a patient's tumor with high TIGAR or GPX4 expression could be treated with a ferroptosis inducer in combination with chemotherapy, while tumors with high TfR1 expression might be targeted with iron nanoparticles.

4.6 miRNA and lncRNA Modulators of Ferroptosis in Cancer Progression

In recent years, increasing evidence has highlighted the pivotal role of noncoding RNAs, particularly microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), as key regulators of ferroptosis and cancer progression. These regulatory RNA molecules modulate ferroptotic cell death primarily through post-transcriptional control of genes involved in iron metabolism, lipid peroxidation, and antioxidant defense systems, thereby influencing tumor growth, metastasis, and therapeutic resistance [68].

Several miRNAs have been reported to directly regulate core components of the ferroptosis machinery. miR-137, miR-9, and miR-424 suppress ferroptosis by targeting genes associated with iron uptake and lipid metabolism, leading to reduced intracellular iron accumulation and lipid ROS generation [69]. Conversely, ferroptosis-promoting miRNAs such as miR-324-3p and miR-15a-3p enhance ferroptotic sensitivity by downregulating glutathione peroxidase 4 (GPX4) or components of the system Xc^- cystine/glutamate antiporter, thereby impairing glutathione synthesis and antioxidant capacity. Through these mechanisms, miRNAs act as fine-tuners of ferroptosis susceptibility and contribute to cancer cell survival or vulnerability under oxidative stress conditions [70].

Long noncoding RNAs further expand the regulatory landscape of ferroptosis by functioning as molecular scaffolds, transcriptional regulators, or competing endogenous RNAs (ceRNAs). LncRNAs such as P53RRA, LINC00336, and NEAT1 have been shown to modulate ferroptosis by interacting with RNA-binding proteins or by sponging ferroptosis-related miRNAs, ultimately affecting GPX4 activity, iron homeostasis, and lipid peroxidation pathways. Dysregulated lncRNA expression has been associated with altered ferroptotic responses, aggressive tumor phenotypes, and resistance to chemotherapy across multiple cancer types [71].

Importantly, bioinformatics-driven analyses have begun to integrate miRNA-mRNA-lncRNA regulatory networks with ferroptosis-related gene signatures, providing a systems-level view of ferroptosis regulation in cancer. These multilayered regulatory interactions underscore the complexity of ferroptosis control and suggest that noncoding RNAs may serve as both biomarkers and therapeutic targets. Incorporating miRNA and lncRNA modulators into ferroptosis-focused bioinformatics frameworks enhances the biological interpretability of prognostic gene signatures and supports the development of RNA-based strategies to sensitize cancer cells to ferroptosis-inducing therapies [72].

Emerging evidence demonstrates that noncoding RNAs, including miRNAs and circRNAs, play critical roles in modulating ferroptosis in CCA [73]. For instance, miR-324-3p has been shown to enhance ferroptosis by targeting GPX4, whereas miR-137 and miR-9 suppress ferroptotic cell death through regulation of iron metabolism and lipid peroxidation. In addition to miRNAs, circRNAs such as circ-0005230 and circHIPK3 act as competing endogenous RNAs that sequester ferroptosis-related miRNAs, thereby modulating GPX4 expression and ferroptotic susceptibility [74]. These CCA-specific noncoding RNA networks integrate with canonical ferroptotic pathways and may serve as both biomarkers and therapeutic targets, providing opportunities for precision ferroptosis-based interventions.

5. Summary of Key Findings

Experimental Studies: Table 3 summarizes representative studies in CCA/BTC models. These highlight that manipulation of ferroptosis regulators (genetically or pharmacologically) alters tumor behavior. Common findings include: induction of ferroptosis markers (↑ROS, ↑MDA), reduced proliferation/migration, and correlations between ferroptosis sensitivity and expression of markers such as SLC7A11 or TfR1 [75].

Gene signatures and Prognosis: Computational analyses have identified ferroptosis-related gene signatures predictive of CCA outcomes. High-risk signatures are associated with ferroptosis resistance in cell lines, suggesting that patient stratification could guide therapy [23].

Therapeutic Agents: A growing arsenal of small molecules (e.g., erastin analogs, RSL3, artesunate) effectively induce ferroptosis in CCA models. Nano-enabled strategies and gene therapies (still largely conceptual) could enhance specificity and potency.

Challenges: Cancer cells may upregulate anti-ferroptotic pathways (e.g., GPX4, SLC7A11, NRF2) or deploy lipid remodeling to escape ferroptosis, as seen in high-risk signature cell lines. Thus, combinatorial targeting of multiple nodes (e.g., inhibiting both GPX4 and FSP1/CoQ10 pathways) may be necessary for durable response [76].

Table 3. Summary of representative ferroptosis studies in CCA models.

Model	Intervention	Key Findings	Source
BTC cell lines (CCA + GBC)	IKE (erastin), RSL3	Induced ferroptosis (↑lipid ROS, ↑Fe^{2+}); cell sensitivity correlated with CD71 (TfR1) and SLC7A11 expression. Ferroptosis effectively inhibited BTC growth.	[77]
92 ICC patients, ICC cell lines	TfR1 (CD71) IHC; siRNA knockdown; Artesunate	$TfR1^+$ tumors had a larger size/microvascular invasion and a worse prognosis. TfR1 knockdown lowered Fe and proliferation. Artesunate killed ICC cells; ferroptosis was suppressed by TfR1 knockdown. PD-L1 increased with cisplatin±artesunate.	[78]
57 ICC patient samples; ICC cell lines	GPX4 IHC; GPX4 inhibitor	High GPX4 expression in tumors correlated with multiple lesions, high FDG uptake and poor survival. GPX4 inhibition reduced ICC proliferation/migration and downregulated glycolysis genes via Aktm TOR.	[21]
CCA cohorts (TCGA, GEO); 10 CCA cell lines	Bioinformatic (LASSO model)	Six-gene FRG signature (FANCD2, PTGS2, SLC2A1, SQLE, ACO1, GOT1) stratified patients by risk. "High-risk" cell lines were more resistant to erastin/RSL3 (higher IC_{50}) than "low-risk" lines, suggesting ferroptosis resistance underlies poor prognosis.	[79]
90 ICC patients; ICC cell lines	TIGAR IHC; TIGAR siRNA; Cisplatin	TIGAR high ICC was an independent predictor of worse DFS/OS. TIGAR knockdown increased ROS/lipid peroxidation and decreased GPX4, inducing ferroptosis (reversible by liproxstatin). TIGAR KD+cisplatin caused more ferroptosis.	[21]
50 CCA patients; CCA cell lines, mice	linc00976 shRNA/overexpression	Linc00976 was upregulated in CCA and driven by JUND. Linc00976 knockdown suppressed tumor growth and promoted ferroptosis, by freeing miR-3202 to downregulate GPX4. Thus, linc00976 inhibited ferroptosis and enhanced CCA malignancy.	[80]
Murine xenograft (various human cancers)	AAV-Cas13a (FPN & LCN2 knockdown)+IONPs	Cancer-specific gene knockdown of iron export + iron nanoparticle delivery induced widespread tumor ferroptosis with minimal impact on normal cells. Treatment led to dramatic tumor regression ("durable cure") in mice.	[81]

To contextualize ferroptosis in CCA, we performed a comparative analysis of ferroptotic mechanisms across major gastrointestinal cancers, including HCC and PC. While all three malignancies are sensitive to lipid peroxidation and iron-dependent oxidative stress, CCA exhibits distinct regulation of glutathione metabolism and GPX4 activity compared with HCC and PC [82]. For example, system Xc^- expression and transferrin receptor-mediated iron uptake are more pronounced in CCA, whereas pancreatic cancer cells demonstrate heightened lipid ROS accumulation in response to ferroptosis inducers. This comparative overview, summarized in Table 4, highlights both shared and cancer-specific ferroptosis pathways, facilitating a better understanding of therapeutic vulnerabilities and guiding the design of targeted ferroptosis-based interventions across gastrointestinal cancers.

6. Clinical Translation and Future Directions

To date, clinical trials explicitly targeting ferroptosis in CCA are lacking. However, the preclinical promise has spurred interest in translational applications. Agents like sorafenib (used in HCC) and artesunate (used for malaria) are being repurposed for their ferroptotic effects in liver cancers, and it is conceivable that future trials may combine such drugs with CCA chemotherapy. Biomarkers identified in CCA (GPX4, TfR1, TIGAR, linc00976, etc,.) could guide patient selection [83]. For example, patients with GPX4 high tumors may benefit from GPX4 inhibitors or synthetic lethality strategies. The ferroptosis gene signatures (BNIP3/TMEM107/CENPW or the six-gene model) might be developed into prognostic assays to stratify patients for "ferroptosis-enhancing" therapies [84].

Several repurposed drugs with ferroptosis-inducing properties are currently being investigated in liver cancers, providing insight into translational opportunities for CCA therapy. For example, artesunate, an antimalarial agent, and sorafenib, a multikinase inhibitor, have been shown to promote ferroptotic cell death in hepatocellular carcinoma and are under evaluation in early-phase clinical trials (ClinicalTrials.gov identifiers: NCT02364835, NCT04269001) [85]. These studies highlight the potential for repositioning existing therapeutics to exploit ferroptosis pathways. Ongoing and future trials in CCA could adapt similar strategies, incorporating biomarker-driven patient selection, combination with nanocarrier delivery systems, or integration with immunotherapy, to enhance clinical efficacy and overcome resistance [86].

Novel delivery systems (e.g., nanoparticles) are on the horizon; any successful ferroptosis therapy will require tumor-targeted delivery to avoid systemic toxicity. Iron overload can damage normal tissues, so precise control is critical. Combination regimens also need optimization: for example, serial use of a ferroptosis inducer with immunotherapy may maximize cancer cell killing while minimizing harm.

The clinical translation of ferroptosis-targeted therapies in CCA holds considerable promise but faces several challenges. Patient stratification is critical, as variability in ferroptosis regulator expression and iron metabolism may influence treatment responsiveness. Advanced nanocarrier systems, including polymeric, liposomal, and exosome-based platforms, offer solutions for selective drug delivery, yet their safety, biodistribution, and immunogenicity must be carefully evaluated. Moreover, off-target effects resulting from systemic induction of lipid peroxidation or iron dysregulation present potential toxicity risks that require rigorous monitoring and dose optimization [52]. Addressing these challenges through integrated biomarker-guided patient selection, precise delivery strategies, and robust preclinical safety assessments will be essential for the successful translation of ferroptosis-based therapies from bench to bedside.

7. Key Challenges

Tumor heterogeneity (subpopulations may resistant to ferroptosis), the development of resistance (cancer cells may upregulate alternative antioxidant pathways), and the immunosuppressive microenvironment of CCA. Ongoing research into the tumor-immune-ferroptosis axis will clarify how best to integrate ferroptosis induction into comprehensive cancer therapy.

Ferroptosis represents a novel vulnerability in CCA. Mechanistic studies have revealed that CCA cells often live on a "knife's edge" of iron and redox imbalance: they upregulate iron import and antioxidant defenses to grow, but this also makes them exquisitely sensitive to ferroptotic death. Both experimental and computational evidence underscore that targeting the ferroptosis pathway whether by small molecules, nanotechnology, or gene therapy can inhibit CCA growth and metastasis. Although clinical applications are not yet realized, the accumulating data provide a strong rationale for developing ferroptosis-based therapies in CCA. Ultimately, combining ferroptosis inducers with conventional treatments or immunotherapies may open new avenues for this deadly cancer. The rigorous identification of ferroptosis-related markers and the design of multifaceted strategies will be key to translating this "iron death" insight into patient benefit.

To highlight the novelty of this review, we compared it with existing literature on ferroptosis in cancer (Table 4). Unlike previous reviews that primarily focused on general ferroptotic mechanisms or individual cancer types, our work emphasizes CCA-specific pathways, integrates computational analyses of ferroptosis-related gene signatures, and discusses translational strategies including nanocarrier-mediated delivery and immunotherapy. Additionally, this review addresses emerging regulatory layers, such as miRNA and lncRNA modulators, and provides a comparative perspective across gastrointestinal cancers [87]. This integrative approach differentiates our work by combining mechanistic insights, computational prediction, and therapeutic relevance, thereby offering a comprehensive framework for future research and clinical applications.

Table 4. Novelty and differentiation from existing reviews.

Cancer Types Covered	Therapeutic Focus	Computational/Ferroptosis Signature Analysis	Unique Contribution	Source
General cancers	Ferroptosis mechanisms	None	Overview of ferroptotic pathways across cancers	[88]
Hepatocellular carcinoma, Pancreatic cancer	Ferroptosis inducers	Limited gene analysis	Focused on therapeutic compounds and experimental studies	[89]
Multiple cancers	Lipid peroxidation and iron metabolism	None	Mechanistic review of ferroptosis regulation	[90]
CCA, Comparative analysis with HCC and pancreatic cancer	Nanocarrier-mediated ferroptosis therapy, Immunotherapy, miRNA/lncRNA modulators	Bioinformatics-based ferroptosis gene signatures, multi-omics integration	Integrates CCA-specific pathways, computational predictions, translational strategies, and comparative GI cancer analysis; emphasizes clinical translation and emerging regulatory layers	[91]

Computational Analyses and Gene Signatures

Computational analyses and ferroptosis-related gene signatures offer valuable insights into potential biomarkers and therapeutic targets in CCA. However, the robustness of these predictions depends on validation strategies and dataset quality. Many studies utilize publicly available transcriptomic datasets, which may have limited sample sizes and heterogeneous patient populations, potentially affecting generalizability [84]. Validation is typically performed using independent cohorts, in silico cross-validation, or integration with proteomic and survival data; nonetheless, experimental confirmation remains essential. Acknowledging these limitations ensures cautious interpretation of bioinformatics results and highlights the need for larger, well-characterized cohorts and functional assays to substantiate computationally derived ferroptosis signatures.

Limitations

While ferroptosis represents a promising therapeutic avenue in CCA, current evidence is subject to several limitations. Most studies rely on preclinical models, including cell lines and animal models, which may not fully recapitulate the complexity of human tumors. Clinical validation of ferroptosis-targeted interventions remains limited, and ongoing trials are sparse. Additionally, many bioinformatics analyses depend on publicly available datasets with heterogeneous patient populations and variable sample sizes, which can affect reproducibility and generalizability. Recognizing these limitations underscores the need for well-designed clinical studies, standardized datasets, and integrative experimental validation to translate ferroptosis research into safe and effective therapies for CCA.

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The Data used in this study are available in the manuscript.

Author Contributions

Syed Mudasser Ali conceptualized the study, conducted the research, and Zala Mushtaq write the manuscript.

Conflict of Interest

The author declares no conflicts of interest.

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