Ferroptosis in biliary tract cancer: Molecular mechanisms and therapeutic applications (Review)

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Abstract. Biliary tract cancer (BTC) encompasses a group of aggressive malignancies arising from the bile duct epithelium, including gallbladder cancer and cholangiocarcinoma, which are characterized by aggressive progression, frequent metastases and poor prognoses. BTC accounts for ~3% of all digestive system tumors, with a 5-year overall survival rate of <20%. BTC presents a clinical challenge. Despite multidisciplinary therapeutic approaches incorporating surgery, chemotherapy and radiotherapy, persistent obstacles, including high tumor recurrence rates (>50%) and the development of treatment resistance remains, underscoring the urgent need for novel treatment strategies such as targeted therapies and immunotherapies. Ferroptosis, a distinct mechanism of regulated cell death triggered by lipid peroxidation, serves critical roles in disease occurrence and progression. Increasing evidence supports the potential of ferroptosis as a targeted therapy in malignancies, with emerging implications for personalized BTC treatment. The present review investigated the molecular mechanisms and signaling pathways that govern ferroptosis, the advances in the understanding of ferroptosis during the initiation and progression of BTC, and the translation potential of ferroptosis for precision therapeutics. By integrating current knowledge, the present study aimed to provide theoretical suggestions for future mechanistic investigations and clinical studies of ferroptosis-based interventions for patients with BTC.

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Contents

1. Introduction

Biliary tract cancer (BTC) includes a spectrum of invasive malignancies that arise from the bile duct epithelium. It is relatively uncommon but highly heterogeneous, comprising gallbladder cancer (GBC; which arises from the gallbladder or cystic duct) and cholangiocarcinoma (CCA; which arises from the intrahepatic, perihilar or distal biliary tree). BTC accounts for <1% of all human types of cancer and ~3% of digestive system tumors globally (1,2). In recent years, the incidence of BTC has been increasing globally, particularly in Asian countries, where it represents an important health problem (3,4). Globally, adenocarcinoma accounts for ~90% of all BTC cases (5,6). BTC is usually diagnosed at advanced stage. The majority of patients with symptomatic BTC, such as those presenting with biliary obstruction, have incurable tumors with invasion of the surrounding organs, lymph nodes and distant metastases, which results in poor prognoses (2,7). At present, surgery remains the gold standard for treating early-stage tumors; however, only a limited number of patients have this opportunity (8,9). The 5-year overall survival rate of BTC is <20% for patients from the United States of America and Europe (10). Furthermore, despite undergoing curative resection with a negative margin (R0), BTC still have a high recurrence rate of >50% (8,9,11). Gemcitabine-platinum chemotherapy is a recommended first-line treatment for advanced BTC; however, its efficacy is not satisfactory (12). The emergence of targeted therapies and immunotherapies, such as Durvalumab and Pembrolizumab, has revolutionized the treatment paradigm of malignant tumors. Immunotherapy plus chemotherapy has been verified to be effective in treating BTC (13-15). Investigating the key molecular mechanisms and identifying novel therapeutic targets for BTC is imperative.

Cell death can occur either due to unregulated causes or following a regulated process (Fig. 1) (16). Unregulated cell death is the instantaneous demise of cells due to severe physical, chemical or mechanical causes. Unlike unregulated cell death, regulated cell death (RCD) is characterized by organized signaling cascades and specific molecular mechanisms, suggesting that it can be controlled (17). The process of RCD can be influenced, either delayed or accelerated, through pharmacological or genetic interventions. A study by Dixon *et al* (18) first proposed the notion of 'ferroptosis' in 2012 (19). Ferroptosis is a new type of RCD, differing from necroptosis (Fig. 1A) (20), apoptosis (Fig. 1B) (21), pyroptosis (Fig. 1C) (22) and autophagy (Fig. 1D) (23) in morphology, genetics and biochemistry (24,25). As its name implies, ferroptosis is an iron-dependent mechanism of cell death (26). Ferroptosis is triggered by lipid peroxidation (LPO), which results from an imbalanced cellular metabolism and redox homeostasis. The morphological evidence of ferroptosis includes the presence of small mitochondria with increased mitochondrial membrane densities, reduced or missing mitochondrial crista, outer mitochondrial membrane rupture and a normal nucleus (Fig. 1E) (27,28). Ferroptosis is indicated to serve an important pathophysiological role in the development and occurrence of numerous diseases, such as ischemic heart disease and acute kidney injury, but particularly in cancer (19,29). Non-small cell lung cancer, hepatocellular carcinoma, pancreatic cancer, breast cancer and renal cell carcinoma are reported to be sensitive to ferroptosis (30-34). Additionally, various ferroptosis inducers, such as sorafenib, sulfasalazine and artemisinin, demonstrate a mitigation of tumor progression (35). Due to the issue of drug resistance, there is a growing interest regarding the potential of targeting ferroptosis as a therapeutic strategy for malignancies (36-38).

The present review aimed to provide a comprehensive overview of the signaling pathways and molecular mechanisms of ferroptosis, the research progress on ferroptosis in the occurrence and development of BTC, and the potential application of ferroptosis as a targeted therapy for BTC.

2. Core mechanisms and unique features of ferroptosis

Following the first description of ferroptosis, a form of non-apoptosis and iron-dependent RCD, in 2012, there has been an increasing interest to investigate the process and regulation of ferroptosis (39). Previously, several studies investigated the mechanisms involved in ferroptosis (40-42). The present study aimed to review the core mechanisms of ferroptosis based on three aspects, namely iron metabolism, lipid metabolism and antioxidant defense systems.

Iron metabolism during ferroptosis. Iron is one of the crucial minor elements for human health, and the correct intracellular level of iron is indispensable for a well-functioning metabolic balance (43). Iron is mainly obtained from dietary intake, existing in two distinct oxidation states. These are the divalent (Fe^{2+}) and trivalent (Fe^{3+}) ions (44). The continuous interconversion of Fe^{2+} and Fe^{3+} allows iron-dependent cofactors, such as cytochrome P450s, to effectively carry out their catalytic functions in various biological processes, including nucleic acid synthesis as well as repair, epigenetic regulation and cellular respiration (45). While in the Fe^{2+} state or combined with a transporter protein, iron is primarily absorbed in the duodenum and upper jejunum epithelial cells. The less soluble Fe^{3+} ion must first be reduced to absorbable ferrous Fe^{2+} and is then transported via divalent metal transporter 1 (DMT1) into epithelial cells (46). Absorbed iron then either enters the blood circulation via ferroportin (FPN) or is stored as ferritin. Fe^{3+} is the primary form of iron in blood circulation. FPN, encoded by the transporter solute carrier family 40 member 1 gene, is the only known iron-exporting protein in mammalian cells. It is responsible for exporting Fe^{3+} to the extracellular space (47). Subsequently, multi-copper ferroxidases on the epithelial cell membrane re-oxidize Fe^{2+} to Fe^{3+}, which is then bound by transferrin (TF) and transported in the plasma (44). Lactotransferrin also contributes positively to the regulation of iron absorption by enhancing iron uptake, similar to TF (48). The majority of cells mainly obtain non-heme iron through two primary pathways that involve TF-bound iron uptake and non-TF-bound iron (NTBI) uptake. TF binds to transferrin receptor (TFR)1 and forms endosomes through clathrin-dependent endocytosis. Within cells, TF-bound iron separates, and six-transmembrane epithelial antigen of prostate 3 reduces Fe^{3+} to Fe^{2+}, which then enters the cytoplasm via DMT1 for subsequent use or storage as ferritin (49,50). When there is an iron overload, such as in hemochromatosis, excess iron surpasses the capacity of TF, resulting in the increased circulation and uptake of NTBI (forming an unstable iron pool) through transporters such as solute carrier family 39 member 14 (51). The main repository for intracellular iron is the ferritin dimer, consisting of ferritin heavy and light chains. Nuclear receptor coactivator 4 (NCOA4) increases iron levels by facilitating ferritin degradation (52-54).

Ferroptosis relies on iron, as suggested by its name. An elevated iron level in the body has a direct association with the onset of ferroptosis (18). Excessive iron levels increase the production of reactive oxygen species (ROS), leading to cell dysfunction or death, tissue damage and diseases, such as human leukocyte antigen-linked hemochromatosis and Friedreich ataxia (44). An excessive accumulation of iron can result in ferroptosis either through Fenton reactions or by activating arachidonate lipoxygenases and cytochrome P450 oxidoreductase-mediated phospholipid peroxidation metabolism (55,56). As an important step in ferroptosis, the Fenton reaction involves the non-enzymatic oxidation of organic compounds, such as polyunsaturated fatty acids (PUFAs), into inorganic states by a mixture of hydrogen peroxide (H_2O_2) and Fe^{2+} (37). Glutathione peroxidase 4 (GPX4) is the major neutralizing enzyme of phospholipid (PL) hydroperoxides (OOHs; PLOOHs). GPX4 knockdown results in an accumulation of PLOOHs, which induces an increase in lipid peroxidation and ferroptosis (57).

LPO during ferroptosis. Uncontrolled LPO represents a key hallmark of ferroptosis. A key initiation step of ferroptosis involves an excessive oxidation of PUFA-PLs (19). The susceptibility of PUFAs to peroxidation is attributed to their diallyl moieties (55). The magnitude of LPO is influenced by both the abundance and distribution of PUFAs within phospholipids (28). Arachidonic acid (AA) and adrenic acid (AdA) serve as the primary LPO substrates in ferroptosis. Acyl-CoA synthetase long-chain

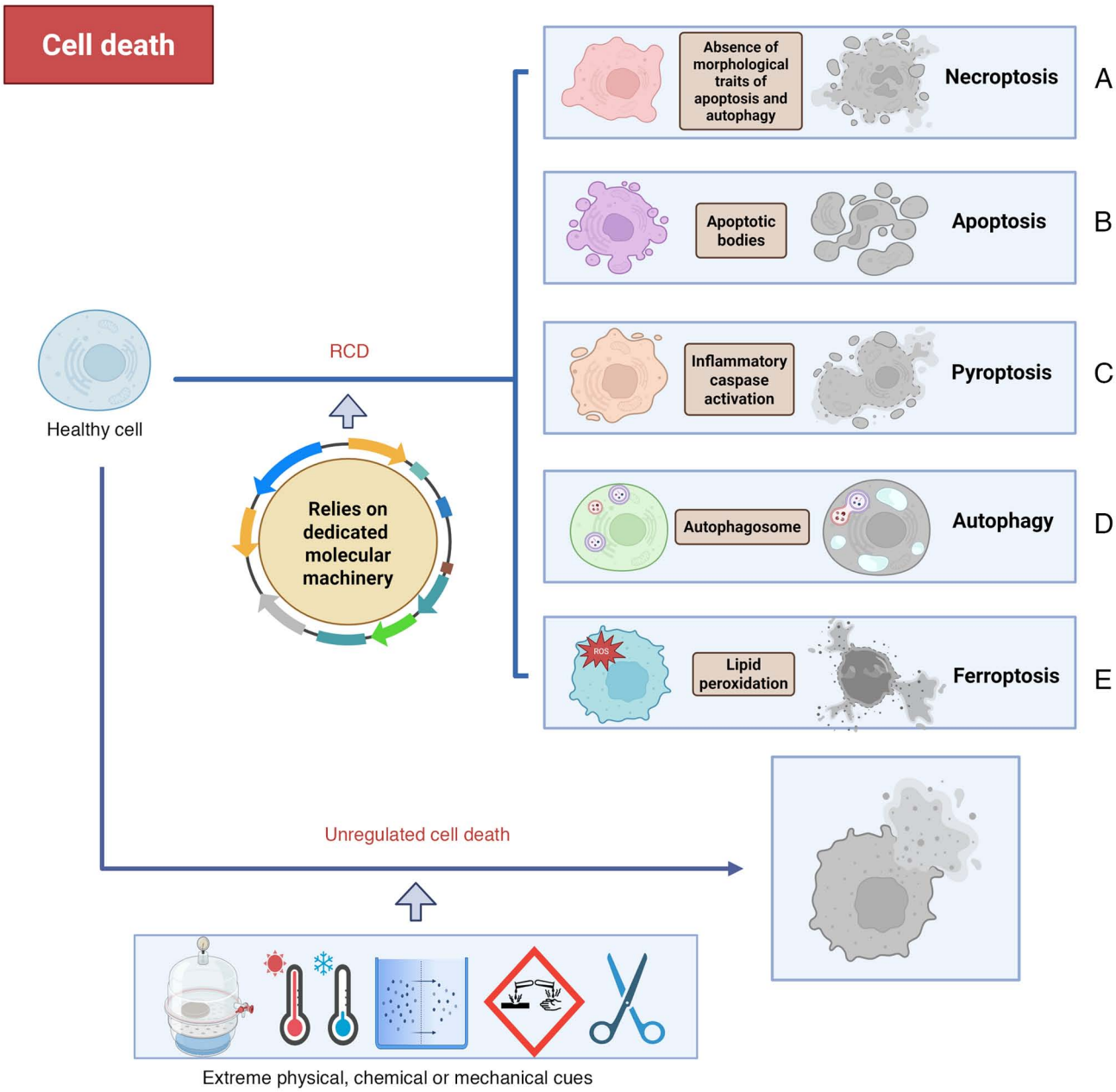

Figure 1. Main molecular mechanisms of different types of cell death. Cell death includes unregulated cell death and RCD. (A) Necroptosis is a form of RCD that is dependent on the RIPK1/RIPK3/mixed lineage kinase domain like pseudokinase signaling pathway. It is characterized by cell swelling, plasma membrane rupture and the release of damage-associated molecular patterns. (B) Apoptosis is a non-inflammatory form of RCD initiated by perturbations of the extra- or intracellular microenvironment. It is characterized by cell shrinkage, chromatin condensation, apoptotic body formation and phagocytic clearance. (C) Pyroptosis is a form of RCD activated by inflammasomes and caspases, which is characterized by plasma membrane pore formation, cell lysis and the release of proinflammatory cytokines (such as IL-1β and IL-18). (D) Autophagy is a conserved cellular self-degradation process that maintains homeostasis by sequestering damaged organelles or misfolded proteins into autophagosomes, which then fuse with lysosomes for degradation. (E) Ferroptosis is an iron-dependent RCD induced by glutathione depletion and glutathione peroxidase 4 inactivation, which leads to excessive lipid peroxidation. It is characterized by lipid oxidative damage to the plasma membrane and cell swelling and is inhibited by iron chelators and lipophilic antioxidants. Compared with necroptosis, apoptosis, pyroptosis and autophagy, ferroptosis is a new type of RCD and presents distinct morphological, genetic and biochemical characteristics. RCD, regulated cell death; RIPK, receptor-interacting protein kinase.

family member 4 (ACSL4) catalyzes the esterification of AA or AdA with CoA, generating oxidizable AA- or AdA-CoA. Subsequently, lysophosphatidylcholine acyltransferase 3 (LPCAT3) facilitates the PL remodeling of AA- or AdA-CoA and membrane phosphatidylethanolamine (PE) into AA- or AdA-PE, anchoring it to the cell or mitochondrial membranes (58). Conversely, acyl-CoA synthetase long-chain family member 3 (ACSL3) and stearoyl-CoA desaturase 1 (SCD1) confer cellular resistance to ferroptosis by catalyzing the synthesis of monounsaturated fatty acid (MUFA) and the displacement of PUFAs from plasma membrane phospholipids (55,59,60). Subsequently, 15-lipoxygenase (LOX) then oxidizes AA-PE or AdA-PE to PL-PUFA-OOHs, which acts as a ferroptosis signal (58). However, 12-LOX can mediate the ACSL4-independent pathway of LPO production via the p53/solute carrier family 7 member 11 (SLC7A11)/12-LOX axis (61).

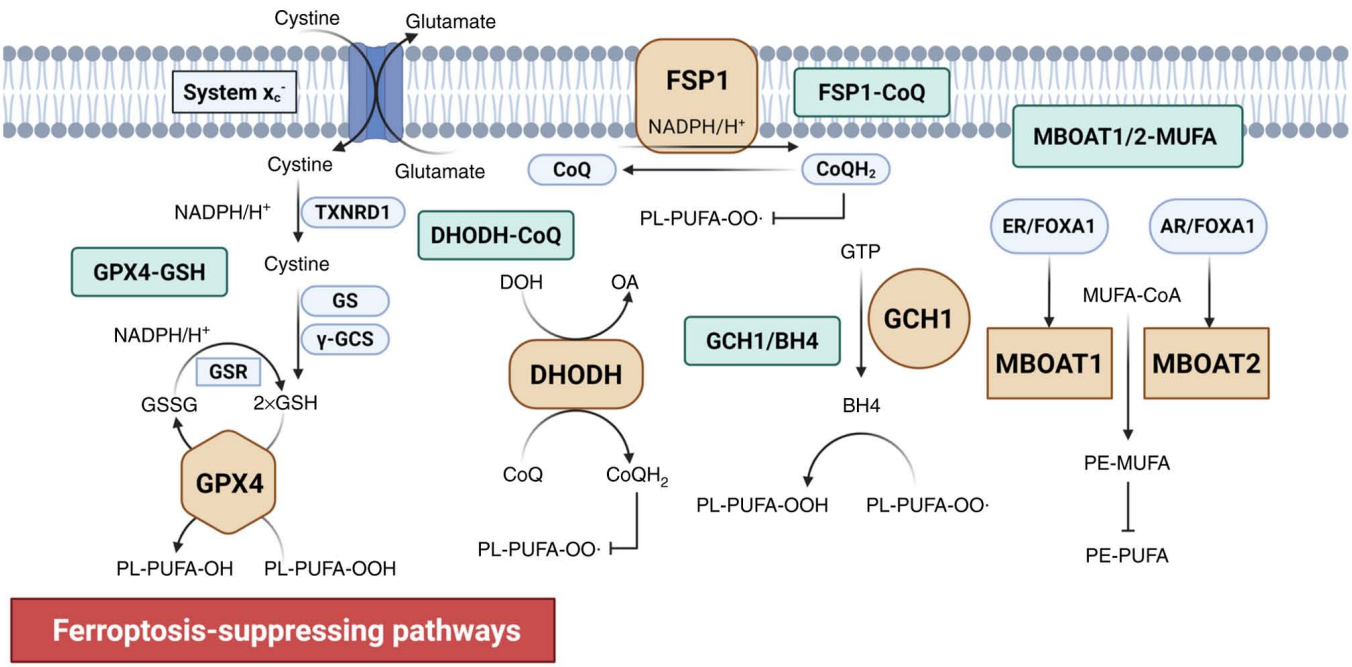

Figure 2. Antioxidant systems that suppress ferroptosis. Pathways of the antioxidant system include the SLC7A11-GSH-GPX4, FSP1-CoQ-NAD(P)H, GCH1-BH4, DHODH-$CoQH_2$ and MBOAT1/2-MUFA pathways. The SLC7A11-GSH-GPX4 axis transports cystine into cells via SLC7A11 (a component of system Xc^-) for GSH synthesis. Subsequently, GPX4 uses GSH to scavenge lipid peroxides, which serves as the core antioxidant defense axis for ferroptosis inhibition. In the FSP1-CoQ-NAD(P)H pathway, NAD(P)H serves as the energy source, FSP1 reduces CoQ to $CoQH_2$ and $CoQH_2$ directly binds lipid free radicals and inhibits lipid peroxidation. Therefore, the FSP1-CoQ-NAD(P)H pathway acts as a ferroptosis defense pathway independent of GSH. In the GCH1-BH4 system, GCH1 catalyzes the production of BH4, which reduces lipid peroxidation by stabilizing the lipid bilayer structure, chelating free iron or directly scavenging free radicals. Therefore, the GCH1-BH4 system exerts antioxidant and ferroptosis-inhibiting effects. In the DHODH-$CoQH_2$ system, DHODH participates in pyrimidine synthesis in mitochondria using CoQ as an electron acceptor, while reducing CoQ to $CoQH_2$. Subsequently, $CoQH_2$ inhibits lipid peroxidation, forming a mitochondrial-level antioxidant defense mechanism. In the MBOAT1/2-MUFA system, MBOAT1/2 catalyzes the combination of MUFA with phospholipids to form MUFA-containing phospholipids, which can resist lipid peroxidation and enhance the cell anti-ferroptosis capabilities at the membrane structure level. SLC7A11, solute carrier family 7 member 11; System Xc^-, cystine/glutamate antiporter; GSH, glutathione; GPX4, glutathione peroxidase 4; FSP1, ferroptosis inhibitory protein 1; CoQ, ubiquinone; GCH1, GTP cyclic hydrolase 1; BH4, tetrahydrobiopterin; DHODH, dihydroorotate dehydrogenase; $CoQH_2$, ubiquinol; MBOAT1/2, membrane-bound O-acyltransferase domain-containing 1/2; TXNRD1, thioredoxin reductase 1; ER, estrogen receptor; AR, androgen receptor; FOXA1, forkhead box protein A1; GS, glutathione synthetase; GSR, glutathione reductase; GSSG, glutathione disulfide; γ-GCS, γ-glutamylcysteine synthetase; MUFA, monounsaturated fatty acid.

Antioxidant defense systems

SLC7A11-glutathione (GSH)-GPX4 axis. The SLC7A11-GSH-GPX4 axis is the principal antioxidant defense system (62). The cystine/glutamate antiporter (system Xc^-), located on the cell membrane, consists of solute carrier family 3 member 2 (SLC3A2) and SLC7A11 subunits. System Xc^- facilitates the 1:1 exchange of extracellular cystine and intracellular glutamate. Intracellular cystine is reduced to cysteine, a precursor for GSH synthesis. GSH serves as an essential cofactor for GPX4. GPX4 uses GSH to reduce PL-PUFA-OOH to non-toxic alcohol phospholipid hydroxides, thereby halting the LPO chain reaction (63,64). The activity of SLC7A11 is downregulated by TP53, BRCA1-associated protein 1 and beclin-1, and upregulated by nuclear factor erythroid 2-related factor 2 (Nrf2) (65) (Fig. 2).

Ferroptosis inhibitory protein 1 (FSP1)-ubiquinone (CoQ)-NAD(P)H pathway. FSP1 is a GSH-independent ferroptosis suppressor, acting in parallel to GPX4. When GPX4 is knocked out, FSP1 (also known as apoptosis-inducing factor mitochondrial-associated protein 2) is activated as a compensatory antioxidant system. FSP1 is located on the plasma membrane and uses NAD(P)H to reduce CoQ to ubiquinol ($CoQH_2$), which acts as an antioxidant by binding to radicals. This neutralizes lipid peroxide free radicals and blocks the propagation of LPO (66,67) (Fig. 2).

GTP cyclic hydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) system. The GCH1-BH4 system is another important GPX4-independent ferroptosis inhibitor. GCH1 prevents ferroptosis via the synthesis of its metabolic derivatives, BH4 and dihydrobiopterin (BH2), and lipid remodeling. GCH1 overexpression selectively protects those PLs containing two PUFA chains from degradation, which potentially has two simultaneous mechanisms: i) Acting as an antioxidant that directly binds to radicals; and ii) contributing to the synthesis of CoQ (68,69) (Fig. 2).

Dihydroorotate dehydrogenase (DHODH)-$CoQH_2$ system. The DHODH-$CoQH_2$ system is a ferroptosis defense pathway, which is localized in the mitochondria and independent of cytosolic GPX4 or FSP1. Knocking out DHODH markedly induces mitochondrial LPO, inducing ferroptosis in cancer cells with low GPX4 expression levels. Furthermore, combining inhibitors of DHODH (such as brequinar) with inducers of ferroptosis (such as sulfasalazine) induces mitochondrial LPO and ferroptosis in malignancies with high GPX4 expression levels synergistically (70). Mechanistically, DHODH suppresses ferroptosis at the mitochondrial inner membrane by reducing CoQ to $CoQH_2$, which is a parallel mechanism to the mitochondrial GPX4 pathway (70) (Fig. 2).

Membrane-bound O-acyltransferase domain-containing (MBOAT)1/2-MUFA system. As PL-modifying enzymes, MBOAT1 and MBOAT2 function as GPX4/FSP1-independent ferroptosis suppressors. MBOAT1 and 2 inhibit ferroptosis by remodeling PLs by selectively incorporating MUFAs into lyso-PE. This increases the cellular MUFA-PE levels and decreases the PUFA-PE levels (71). However, MBOAT1 and 2 function as sex hormone-dependent regulators, and their transcription is upregulated by androgen and estrogen receptors (71) (Fig. 2).

3. Ferroptosis and the tumor microenvironment (TME)

The TME serves pivotal roles in the initiation, progression, metastasis and therapeutic resistance of tumors (72-75). It is a dynamic interacting network that is comprised of diverse cellular components, including malignant cells, immune cells, cancer-associated fibroblasts and endothelial cells, alongside acellular elements such as the extracellular matrix, cytokines and metabolites (76). Ferroptosis engages in a complex bidirectional crosstalk with the TME, particularly through metabolic reprogramming and immunomodulation, which regulates BTC malignancy and treatment responses (77,78).

Ferroptosis in malignant cells modulates antitumor immunity within the TME through immunogenic signaling (79,80). Previous evidence indicates that ferroptotic cancer cells release damage-associated molecular patterns (DAMPs), a hallmark of immunogenic cell death (ICD), which function as endogenous adjuvants to potentiate antitumor immunity (81,82). As well as the classic DAMPs, such as high mobility group protein 1 (83-85), adenosine triphosphate (86,87), calcium reticulum protein (84,86) and the recently identified proteoglycan decorin (88), ferroptotic cancer cells release immunomodulatory cytokines such as C-X-C motif chemokine ligand 1 (CXCL1), tumor necrosis factor (TNF) and interferon (IFN)-β, that contribute to the remodeling of the TME (89). However, whether ferroptosis is a classic form of ICD is still an ongoing scientific debate (89). In addition, the specific role of ferroptotic cancer cells in antitumor immunity is also contradictory. A previous study demonstrates that tumor cell competition for cystine compromises the function of CD8+ T cells within the TME. Cystine deprivation triggers glutamate accumulation, which potentiates CD36-mediated LPO (90). However, ferroptotic cells can activate antitumor immunity by expressing 1-steaoryl-2-15-HpETE-sn-glycero-3-PE. This serves as a signal that mediates phagocytosis by engaging Toll-like receptor 2 on macrophages (91) and enhancing the activities of natural killer cells (92).

Immune cells exhibit differential susceptibility to ferroptosis within the TME, and their functional heterogeneity enables distinct populations to either potentiate or suppress ferroptosis in malignant cells (80). CD8+ T cells exhibit an increased sensitivity to GPX4 inhibition compared with malignant cells, resulting in a premature impairment of antitumor immunity prior to notable tumor cell death (93). However, these effector lymphocytes demonstrate relative resistance to system Xc^- inhibitors, such as sulfasalazine, as inhibition of system Xc^- did not affect T cell proliferation and antitumor immune responses (94). Activated CD8+ T cells with high expression levels of fatty acid transporter CD36 increases the risk of LPO and ferroptosis (95). Compared with tumor-derived CD8+ T cells, tumor-infiltrating regulatory T cells (Tregs) typically have reduced levels of LPO, suggesting that they are less prone to ferroptosis in the TME (93). However, system Xc^- inhibitors rarely impair the viability of Tregs (96). Tumor-associated macrophages (TAMs) are one of the most abundant types of immune cells in the TME and include the proinflammatory antitumor M1 and anti-inflammatory protumor M2 types (97,98). The sensitivity of these two types of cells to ferroptosis is different due to the high levels of inducible nitric oxide synthase and nitric oxide-free radicals in M1 type compared with M2 type TAMs (99). Another group of immune-suppressive cells, namely myeloid-derived suppressor cells (MDSCs), exhibit notable resistance to ferroptosis, which is associated with the upregulation of system Xc^- and neutral ceramidase N-acylsphingosine amidohydrolase expression levels (100).

Metabolic reprogramming is a defining hallmark of malignancy, triggering cancer metastasis, aggressiveness and therapeutic resistance (101). Remodeled metabolic environments and immunosuppressive environments enable cancer cells to evade RCD (78). This metabolic reprogramming extends beyond canonical adaptations such as the Warburg effect (in which preferential glycolysis reduces mitochondrial ROS generation), and includes the suppression of pyruvate dehydrogenase, limiting the acetyl-CoA flux for PUFA biosynthesis, which is critical for ferroptosis (102-104). Within the TME, MDSCs increase immunosuppression through IL-6/JAK2/STAT3-mediated SLC7A11 upregulation, which depletes the extracellular cystine pools (105). This metabolic competition induces a GSH deprivation-induced ferroptosis in CD8+ T cells, further inactivating antitumor immunity (90).

To resist ferroptosis, cancer cells use lipid metabolic reprogramming as a defense strategy via two primary mechanisms: i) PL membrane restructuring via the activation of the sterol regulatory element-binding protein-1-SCD1 axis, replacing oxidation-vulnerable PUFAs with MUFAs (106); and ii) mevalonate pathway-derived antioxidant production, such as isopentenyl pyrophosphate from cholesterol metabolism, which neutralizes lipid peroxides (107,108). Iron homeostasis is also inhibited through TFR1-mediated uptake and ferritin heavy chain (FTH)-dependent storage, which reduces the levels of cytotoxic free Fe^{2+} (109,110). Furthermore, gut microbiota-derived metabolites, such as short-chain fatty acids (such as butyrate) and tryptophan metabolites (such as indole-acrylic acid), also affect the TME and influence the resistance of cancer cells to ferroptosis (111,112).

4. Epigenetic regulation in ferroptosis

Epigenetic regulation is a heritable mechanism that regulates the expression of genes through chemical modifications without altering the DNA sequence. It primarily involves DNA methylation, histone modifications, non-coding RNA (ncRNA)-mediated regulation and RNA methylation (113).

Several key genes are dynamically controlled by DNA methylation. For example, in normal tissues, the core enzyme GPX4, which is essential for eliminating lipid peroxides, has notably reduced expression levels due to transcriptional repression caused by the hypermethylation of CpG islands within its

promoter region compared with cancer tissues. This suppression increases cellular susceptibility to ferroptosis (114-117). By contrast, the promoter of the system Xc^- light chain subunit SLC7A11 is frequently hypomethylated, leading to its elevated expression levels (118,119). This enhances cystine uptake and GSH synthesis, which inhibits ferroptosis. Furthermore, hypermethylation of the FSP1 promoter results in a reduction to its expression levels, which sensitizes cells to ferroptosis (120,121).

RNA methylation, the most abundant post-transcriptional modification in eukaryotic mRNA, also contributes to ferroptosis regulation. AlkB homolog 5 regulates glutamate-cysteine ligase modifier subunit (GCLM) mRNA levels though N^6-methyladenosine (m^6A) modification of GCLM and YTH m^6A RNA binding protein-mediated decay of GCLM, which regulates ferroptosis (122). Additionally, methyltransferase-like protein 16 (METTL16) serves a role in ferroptosis and tumorigenesis by catalyzing the m^6A modification of Sentrin/small ubiquitin-like modifier-specific protease 3 mRNA and regulating the stability of lactotransferrin (123).

Histone modifications serve an important role in shaping chromatin structure. It exerts precise transcriptional control over ferroptosis-associated genes, such as SLC7A11 and ACSL3, and impacts gene expression and cancer development (124-126). p53 promotes the nuclear translocation of a histone H2B monoubiquitylation (H2Bub1) deubiquitinase, ubiquitin-specific protease 7 (USP7), which negatively regulates H2Bub1 levels. The interaction between p53 and USP7 reduces the occupancy of H2Bub1 at the regulatory region of SLC7A11, leading to transcriptional repression of SLC7A11and enhancing the ferroptosis induction sensitivity of cells (125). Histone acetylation and methylation also demonstrate bidirectional regulatory effects on ferroptosis (126-129).

ncRNAs regulate the expression of ferroptosis-associated genes via post-transcriptional regulation, forming protein-RNA interaction networks. Specifically, microRNA (miR)-137/miR-9 and miR-15a-5p promote ferroptosis by targeting SLC7A11 and GPX4 mRNA, respectively (130,131), whereas miR-27a and miR-4717 exert anti-ferroptosis effects by targeting ACSL4 and NCOA4 (132,133). Long ncRNAs (lncRNAs) also participate in ferroptosis regulation by acting as protein decoys, chromatin modifiers or miRNA sponges (134,135).

Ferroptosis induction has emerged as a novel strategy to overcome tumor therapy resistance (35,36). However, tumor cells establish complex ferroptosis defense networks by remodeling immune-metabolic environments, notably elevating the threshold for ferroptosis initiation (78). The development of this resistance limits the clinical application of ferroptosis-inducing therapies (78). However, a series of innovative strategies have been developed, providing a theoretical foundation for designing effective treatments to circumvent resistance. Recently identified, reversible palmitoylation modification of GPX4 is a key regulator of ferroptosis. The palmitoylation inhibitor 2-bromopalmitate notably enhances the antitumor efficacy of ferroptosis inducers by inhibiting GPX4 palmitoylation (136). Furthermore, targeted protein degradation represents an emerging therapeutic paradigm. The GPX4-targeted autophagy-targeting chimera (GPX4-AUTAC), based on selective autophagic degradation, induces ferroptosis and demonstrates antitumor activity *in vitro*, *in vivo* and in patient-derived organoids (137). In addition, proteolysis-targeting chimeras that target GPX4/DHODH have also been designed (138,139). The use of combination strategies that target immune checkpoints alongside ferroptosis inducers are also gaining attention (140). Furthermore, the development of novel nanodrug delivery systems offers additional approaches to overcome chemoresistance, such as high-density lipoprotein nanoparticles with dual metabolic disruption (selenium deprivation and LPO) (141) and antibody-targeted nanoplatforms (such as Fe-MOF@Erastin@Herceptin), which deliver ferroptosis inducers (such as erastin) specifically to tumor cells (142).

5. Targeting ferroptosis in BTC therapy

Ferroptosis is demonstrated to have therapeutic potential in various types of cancer, including hepatocellular carcinoma, lung carcinoma, lymphoma, pancreatic ductal carcinoma and renal cell carcinoma (30-34). BTC is an uncommon type of gastrointestinal malignancy that has a poor prognosis. In the early stages of disease, surgical resection with negative margins can effectively treat BTC (8,9). For unresectable and metastatic disease, gemcitabine and cisplatin chemotherapies plus immunotherapy (such as with Durvalumab or Pembrolizumab) are the only preferred regimens approved by the National Comprehensive Cancer Network (143,144). With the increasing number of patients with BTC, investigating novel targets and alternative options is crucial. Ferroptosis, which is considered to be one of the most promising potential antitumor methods, can affect the occurrence and development of BTC by regulating intracellular iron and ROS levels, providing new treatment options for patients with BTC (70,124,145). The following section primarily concentrates on the advancements in ferroptosis-associated research in BTC, including potential therapeutic targets, treatment options and associated mechanisms (Table I; Fig. 3).

TP53 is acknowledged as a classic tumor suppressor gene, which serves important roles in controlling the cell cycle, cell proliferation and cell death (146,147). TP53 serves a role in controlling the susceptibility to ferroptosis via both transcription-dependent and transcription-independent mechanisms (148). Shank-associated RH domain interacting protein (SHARPIN) is a crucial part of the complex responsible for activating the linear ubiquitin chain, which inhibits ferroptosis through the p53/SLC7A11/GPX4 signaling pathway and promotes cell proliferation in CCA. Silencing the SHARPIN gene results in the suppression of p53 ubiquitination and degradation, as well as a decreased expression of SLC7A11, GPX4, superoxide dismutase (SOD)-1 and SOD-2. Targeting SHARPIN may serve as a potential strategy benefiting CCA treatment (149). Human hydroxysteroid dehydrogenase-like 2 (HSDL2) is also a regulator of cancer progression and lipid metabolism. Knocking down HSDL2 promotes CCA progression by inhibiting ferroptosis through the p53/SLC7A11 axis (150). As a member of Runt-domain family, Runt-related transcription factor 3 (RUNX3) has a reduced expression level in GBC. This downregulation, mediated by promoter DNA hypermethylation, is notably associated with adverse outcomes in patients with GBC. RUNX3 activates the transcription of

Table I. Targeting ferroptosis in biliary tract cancer.

Tumor type	Agent	Target	Mechanism	Characteristics	(Refs.)
CCA	-	SHARPIN	Regulates P53/SLC7A11/GPX4 signaling.	-	(149)
CCA	-	HSDL2 (knockdown)	Inhibits P53 pathway and upregulates SLC7A11.	-	(150)
CCA	-	JUND/linc00976	Regulates miR-3202/ GPX4 axis.	-	(163)
CCA	AS-252424	ACSL4	Regulates immune microenvironment and metabolism.	-	(168)
CCA	-	ACSL3	Regulates the levels of MUFAs.	-	(173)
CCA	-	IDH1	Sensitizes cells to erastin-induced ferroptosis.	-	(193)
CCA	-	FBXO31	Facilitates the proteasomal degradation of GPX4 and sensitizes cancer stem cells-like cells to cisplatin.	-	(164)
CCA	-	GOLPH3	Facilitates the expression of SLC7A11.	-	(152)
CCA	-	METTL16	Promotes the expression of ATF4 via m^6A modification.	-	(158)
CCA	Liquidambaric acid	STAMBPL1	Liquidambaric acid binds to STAMBPL1, which inhibits Nrf2 de-ubiquitination.	Triterpenoid compound	(206)
CCA	HiPorfin	P53	HiPorfin activates the P53/SLC7A11/ GPX4 axis.	-	(213)
CCA	Hypericin	AKT/mTORC1	Hypericin inhibits the AKT/mTORC1/ GPX4 axis.	-	(214)
CCA (iCCA)	Quercetin	NF-κB	Quercetin inhibits the NF-κB pathway.	Flavonoid	(201)
CCA (iCCA)	Simvastatin	AKT	Simvastatin inhibits the pPCK1-pLDHA-SPRINGlac axis.	-	(208)
CCA (iCCA)	-	METTL3	Promotes the expression of Nrf2 via m^6A modification.	-	(157)
CCA (iCCA)	-	TIGAR (knockdown)	Decreases the expression of GPX4 and elevates the levels of ROS and lipid peroxidation.	-	(153)
CCA (iCCA)	-	TFR	Regulates the intracellular iron levels.	-	(176)
CCA (iCCA)	-	Hsa_circ_0050900 (knockdown)	Inhibits the expression of SLC3A2 by sponging hsa-miR-605-3p.	-	(175)
CCA (iCCA)	-	ETV4/ALYREF	Facilitates glycolytic metabolism and regulates PKM2 transcription and stabilization.	-	(177)
CCA (iCCA)	-	CircFOXP1 (encoding circFOXP1-231aa)	Interacts with OTUD4 and regulates the protein stability of NCOA4.	-	(174)
CCA (iCCA)	-	PAX8-AS1	Mediates the PAX8-AS1/GPX4 axis.	-	(165)
CCA (dCCA)	-	AKR1C1	Downregulates CYP1B1 mRNA levels and the cAMP-PKA signaling pathway.	-	(178)
GBC	Lithocholic acid	GLS	Lithocholic acid promotes glutaminase-mediated glutamine metabolism.	Bile acids	(209)
GBC	-	RUNX3	Activates the p53/SLC7A11 signaling pathway.	-	(151)
GBC	-	TFAP2A	TFAP2A knockdown suppresses the Nrf2 signaling axis.	-	(156)
GBC	Isoliquiritigenin	HMOX1/GPX4	Activates the p62-Keap1-Nrf2-HMOX1 signaling pathway and downregulates GPX4 expression levels.	Flavonoid	(205)

Table I Continued. Targeting ferroptosis in biliary tract cancer.

Tumor type	Agent	Target	Mechanism	Characteristics	(Refs.)
GBC	-	SIRT3	Inhibits AKT-dependent mitochondrial metabolism.	-	(172)
GBC	Wu-Mei-Wan	STAT3	Downregulates the expression of STAT3 and enhances the sensitivity of GBC cells to gemcitabine.	TCM formulation	(207)

BTC, biliary tract cancer; GBC, gallbladder cancer; CCA, cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; dCCA, distal cholangiocarcinoma; SHARPIN, shank-associated RH domain interacting protein; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; HSDL2, hydroxysteroid dehydrogenase-like 2; ACSL4, acyl-CoA synthetase long-chain family member 4; ACSL3, acyl-CoA synthetase long-chain family member 3; MUFA, monounsaturated fatty acid; IDH1, isocitrate dehydrogenase 1; FBXO31, F-box protein 31; GOLPH3, golgi phosphoprotein 3; METTL16, methyltransferase-like protein 16; ATF4, activating transcription factor 4; m^6A, N6-methyladenosine; STAMBPL1, signal transducing adaptor molecule binding protein like 1; Nrf2, nuclear factor erythroid 2-related factor 2; METTL3, methyltransferase like 3; TIGAR, TP53-induced glycolysis and apoptosis regulator; ROS, reactive oxygen species; TFR, transferrin receptor; SLC3A2, solute carrier family 3 member 2; ETV4, E26 transformation-specific variant 4; ALYREF, Aly/REF nuclear export factor; OTUD4, OTU domain-containing protein 4; NCOA4, nuclear receptor coactivator 4; PAX8-AS1, paired box 8-antisense RNA 1; CYP1B1, cytochrome P450 family 1 subfamily B member 1; GLS, glutaminase; RUNX3, runt-related transcription factor 3; TFAP2A, transcription factor activating enhancer-binding protein 2 α; HMOX1, haem oxygenase-1; SIRT3, sirtuin 3; TCM, traditional Chinese medicine.

inhibitor of growth protein 1, which leads to the suppression of SLC7A11 through a p53-dependent pathway and the induction of ferroptosis (151). Golgi phosphoprotein 3 also promotes CCA malignancy by inhibiting ferroptosis through SLC7A11 upregulation (152). Additionally, TP53-induced glycolysis and apoptosis regulator (TIGAR) is associated with adverse outcomes and ferroptosis resistance in patients with intrahepatic CCA (iCCA). *TIGAR* encodes an enzyme responsible for regulating glycolysis and scavenging ROS. Knockdown of TIGAR reduced the expression of GPX4, a key inhibitor of ferroptosis (153). Furthermore, combining TIGAR knockdown with cisplatin treatment synergistically induces a notable increase in ferroptosis (153).

The transcription factor Nrf2 controls the expression of genes involved in counteracting oxidative and electrophilic stresses, which serves a role in regulating the cellular antioxidant response (154,155). A study by Huang *et al* (156) reports that transcription factor activating enhancer-binding protein 2 α (TFAP2A) may serve a role as a regulator of ferroptosis in GBC via the Nrf2 signaling pathway. GBC cells exhibit elevated levels of TFAP2A, compared with non-tumorigenic human intrahepatic bile duct cells (H69), and knocking down TFAP2A lead to a decrease in GBC cell proliferation, migration and invasion, as well as a decreased expression of oxidative stress-associated genes, such as heme oxygenase 1 and Nrf2. A study by Zheng *et al* (157) demonstrates high methyltransferase-like 3 expression levels in cisplatin-resistant iCCA cells compared with parental cells. This upregulation enhances m^6A modifications, leading to the inhibition of ferroptosis and a resistance to cisplatin through the stabilization of Nrf2 mRNA and an increase in the Nrf2 protein expression levels. Additionally, overexpression of METTL16 in patients with CCA is associated with poor prognosis. Mechanistically, METTL16 increases the m^6A modifications of activating transcription factor 4 (ATF4) mRNA, which increases the expression of ATF4 and subsequently results in the suppression of ferroptosis (158).

At present, GPX4 is recognized as the only enzyme with the ability to directly reduce complex phospholipid hydroperoxide (159). Therefore, GPX4, which is responsible for the efficient removal of phospholipid hydroperoxides, is critical for cell survival (160). When GPX4 fails to effectively remove PLOOHs, there is an increase in LPO and ferroptosis (57,161). GPX4 is also one of the important adverse prognostic indicators in iCCA (162). A study by Lei *et al* (163) demonstrates that JUND enhances the transcription of linc00976, which promotes the development of CCA and prevents ferroptosis by regulating the miR-3202/GPX4 axis. F-box protein 31 (FBXO31) stimulates the ubiquitination process of GPX4 and consequently promotes the degradation of the GPX4 proteasome, which enhances the occurrence of ferroptosis. Additionally, FBXO31-upregulated cancer stem cell-like cells present enhanced sensitivity to cisplatin compared with control cells (164). In addition, lncRNA paired box 8-antisense RNA 1 binds to p62 and activates Nrf2, which promotes GPX4 transcription and stabilizes GPX4 mRNA by interacting with insulin-like growth factor 2 mRNA binding protein 3. This inhibits ferroptosis and promotes resistance to gemcitabine and cisplatin. Treatment with JKE-1674 (1 μM), a GPX4 inhibitor, combined with gemcitabine (5 μM) and cisplatin (10 μM) exhibits an improved antitumor potential in preclinical models of both subcutaneous tumor and orthotopic mice models, compared with gemcitabine and cisplatin therapy (165).

Previous studies reveal ACSL4 promotes ferroptosis by catalyzing the esterification of long-chain PUFAs into PUFA-CoA, which serve as substrates for LPO (166,167). Data from the Gene Expression Omnibus and The Cancer Genome Atlas databases demonstrates that there is a higher level of ACSL4 in CCA compared with normal adjacent tissues. Additionally, ACSL4 levels are associated with the prognosis of patients with CCA as well as the immune infiltration in CCA (168). Targeting the ACSL4 pathway may be an anti-cancer approach. A study by Liao *et al* (169) reveals that, via ACSL4-dependent lipid reprogramming, IFNγ from

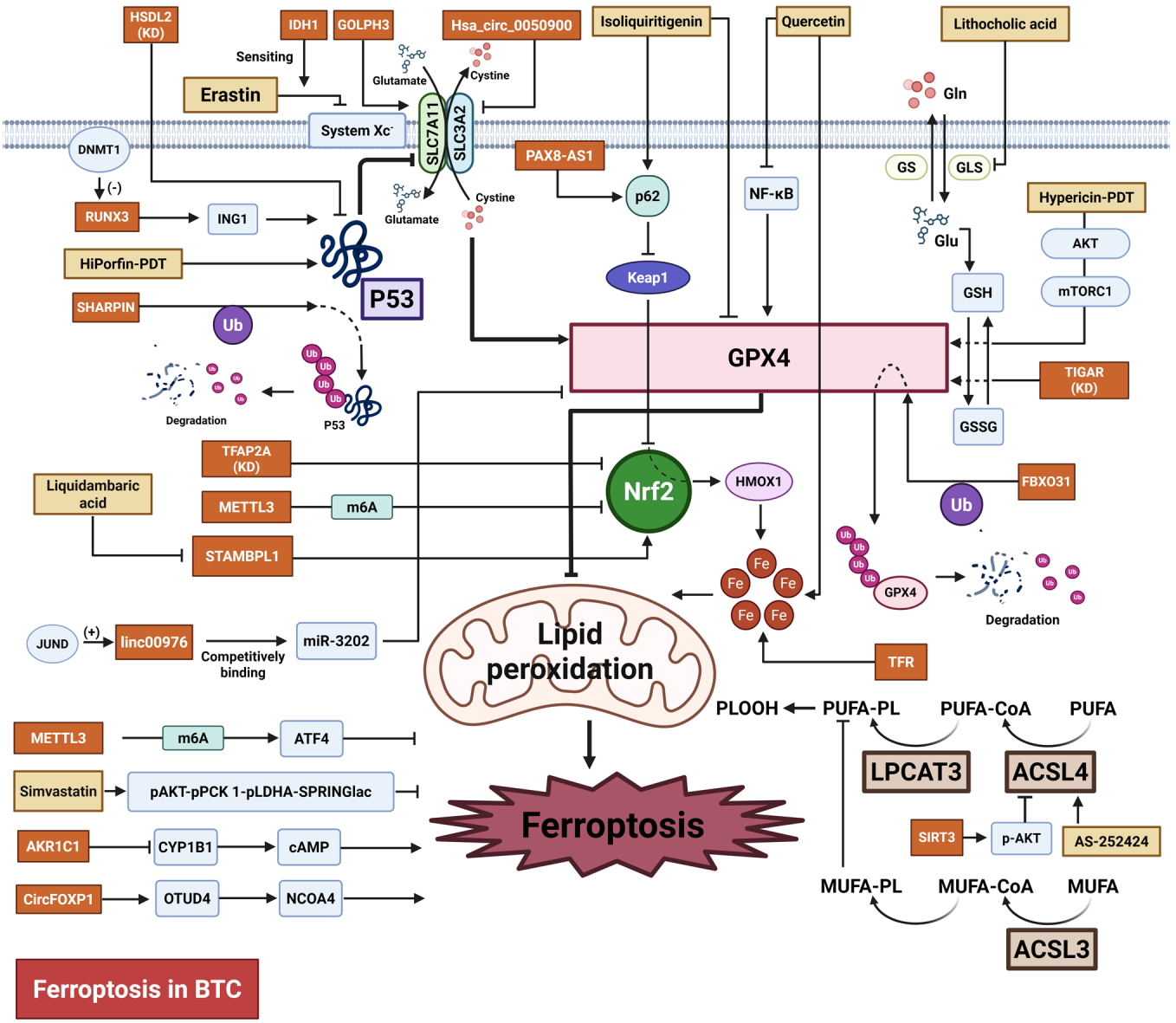

Figure 3. Main regulatory network of ferroptosis in BTC. Multiple molecules including system Xc^- and GPX4, as well as signaling pathways involving p53, Nrf2 and NF-κB, are involved in the processes of ferroptosis induction and inhibition. Substances such as isoliquiritigenin, quercetin and lithocholic acid influence ferroptosis-related processes. These regulatory mechanisms control lipid peroxidation and ferroptosis in BTC. BTC, biliary tract cancer; SHARPIN, shank-associated RH domain interacting protein; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; HSDL2, hydroxysteroid dehydrogenase-like 2; DNMT1, DNA methyltransferase 1; ING1, inhibitor of growth 1; ACSL4, acyl-CoA synthetase long-chain family member 4; ACSL3, acyl-CoA synthetase long-chain family member 3; LPCAT3, lysophosphatidylcholine acyltransferase 3; MUFA, monounsaturated fatty acid; IDH1, isocitrate dehydrogenase 1; FBXO31, F-box protein 31; GOLPH3, golgi phosphoprotein 3; METTL16, methyltransferase-like protein 16; ATF4, activating transcription factor 4; m^6A, N6-methyladenosine; STAMBPL1, signal transducing adaptor molecule binding protein like 1; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; METTL3, methyltransferase like 3; TIGAR, TP53-induced glycolysis and apoptosis regulator; TFR, transferrin receptor; SLC3A2, solute carrier family 3 member 2; ETV4, E26 transformation-specific variant 4; ALYREF, Aly/REF nuclear export factor; OTUD4, OTU domain-containing protein 4; NCOA4, nuclear receptor coactivator 4; PAX8-AS1, paired box 8-antisense RNA 1; CYP1B1, cytochrome P450 family 1 subfamily B member 1; GS, glutathione synthetase; GSSG, glutathione disulfide, GLS, glutaminase; GSH, glutathione; RUNX3, runt-related transcription factor 3; TFAP2A, transcription factor activating enhancer-binding protein 2 α; HMOX1, haem oxygenase-1; SIRT3, sirtuin 3; STAT3, signal transducer and activator of transcription 3; PDT, photodynamic therapy; Ub, ubiquitin.

cytotoxic T lymphocytes and AA from the TME induce tumor cell ferroptosis. Furthermore, cancer cells that derive from migration exhibit a higher ferroptosis sensitivity and PUFA lipid contents compared with primary-tumor-derived cells. This supports the possibility of targeting ferroptosis in the treatment of cancer (170). Specific and targeted inhibitors of ACSL4 with anti-ferroptosis function such as AS-252424 have been screened and identified (171). In GBC, sirtuin 3 has tumor suppressive effects through the induction of the expression of ACSL4 and AKT-dependent ferroptosis, and inhibition of the epithelial-mesenchymal transition (172). Another member of the acyl-CoA synthetase long chain family, ACSL3, synthesizes MUFAs that suppress PUFAs peroxidation, which confers ferroptosis protection. Furthermore, ACSL3 is an unfavorable prognostic biomarker in patients with CCA and a mediator of ferroptosis resistance in CCA cells. Therefore, ACSL3 may be a potential therapeutic target (173).

Furthermore, several other factors potentially regulate ferroptosis sensitivity. For example, circular (circ)forkhead box protein P1 and *Homo sapiens*_circ_0050900 affect ferroptosis by interacting with OTU domain-containing protein 4 and regulating SLC3A2, respectively (174,175). TFR modulates the ferroptosis sensitivity of cells by regulating intracellular iron levels. Additionally, TFR is also an adverse prognostic factor in patients with iCCA (176). The regulatory importance of the E26 transformation-specific variant 4-ALY/REF export factor-pyruvate kinase M2 and Aldo-keto reductase family 1 member C1-cytochrome P450 family 1 subfamily B member 1-cAMP axes also warrant attention (177,178). Additionally, gut microbiotas inhibit ferroptosis in iCCA by altering glutamine metabolism through the regulation of the activin receptor-like kinase 5/NADPH oxidase 1 axis (179).

Ferroptosis serves a role in the pathogenesis, progression and treatment resistance of BTC. Furthermore, accumulating evidence demonstrates that ferroptosis-associated indicators are notably associated with patient prognosis and represent potential prognostic biomarkers (Table II). Techniques such as RNA sequencing and immunohistochemistry reveal elevated expression of ferroptosis-associated markers, including ACSL3/4, SLC7A11 and GPX4, in BTC tumor tissues compared with normal adjacent tissues, which is notably associated with poorer clinical outcomes (168,173,176,180-183). By contrast, isocitrate dehydrogenase 1 (IDH1) mutations are associated with a more favorable prognosis in BTC (183,184). In addition, other key ferroptosis-associated markers, such as LPCAT3 and FSP1, are also associated with prognosis in various solid tumors including ovarian cancer and lung adenocarcinoma; however, their clinical validation in BTC requires further investigation (185-192). Taken together, these ferroptosis-associated indicators may serve as novel prognostic markers for BTC, potentially offering a new perspective for precise prognosis assessment and individualized treatment strategies. Furthermore, integrating these indicators to establish multi-parameter prognostic models may enhance the accuracy of existing BTC prognostic assessment systems.

In addition to conventional GPX4 inhibitors and system Xc^- inhibitors, numerous other compounds have the potential to induce and notably contribute to the ferroptosis process in BTC. A number of these compounds can function independently, while others require co-administration with traditional chemotherapies, inducers and technologies.

Erastin, an inducer of ferroptosis, specifically inhibits system Xc^- (18). A study by Su *et al* (193) demonstrates that IDH1 mutations suppress CCA progression through erastin-induced ferroptosis. Erastin-treated IDH1 mutation cells have increased numbers of propidium iodide-positive cells, increased levels of lipid ROS and decreased cell viability compared with that in erastin-treated wild type cells. However, IDH1 mutation-targeted inhibitors, such as ivosidenib (AG-120), demonstrates notable clinical efficacy in CCA and are, at present, incorporated into second-line therapy. Therefore, the feasibility of combining ferroptosis inducers with IDH1-targeted agents requires further investigation (12,194). Furthermore, erastin and lenvatinib combined with photodynamic therapy (PDT) can increase ROS levels and inhibit antioxidant systems intracellularly, thereby enhancing the induction of ferroptosis in CCA cells (195).

Traditional Chinese medicine (TCM) is currently recognized as a viable complementary treatment in malignancies (196). Accumulating evidence demonstrates that TCM can notably enhance the chemosensitivity of a patient, potentiate the antitumor efficacy of therapeutic agents and mitigate treatment-associated adverse effects in cancer management (197,198). Quercetin (QE), a flavonoid in flowers, stems and leaves of various plants, possesses the ability to impede the progression of breast and colon cancer by interrupting the cell cycle (199,200). Previous studies demonstrate that QE induces ferroptosis in iCCA cells by inhibiting the NF-κB signaling pathway, which inhibits iCCA cell invasion (201,202). Isoliquiritigenin (ISL), also known as 2',4',4-trihydroxychalcone, is also a type of flavonoid and is extracted from the root of the liquorice plant. ISL induces apoptosis and inhibits proliferation in tumors (203,204). A study by Wang *et al* (205) reveals that ISL triggers ferroptosis in GBC by activating the p62-Kelch-like ECH-associated protein 1-Nrf2-haem oxygenase-1 (HMOX1) signaling pathway and reducing the expression of GPX4. Silencing HMOX1 or increasing GPX4 expression levels decreases the susceptibility of GBC cells to ISL-induced ferroptosis and enhances the survival of GBC cells (205). Another naturally occurring triterpenoid compound named liquidambaric acid (LCD) also exhibits notable therapeutic potential. LCD can bind to and inhibit signal transducing adaptor molecule binding protein like 1, which stabilizes Nrf2 through de-ubiquitination, and notably enhances CCA cell proliferation and migration while impeding ferroptosis (206). Wu-Mei-Wan, a long-utilized TCM formula, demonstrates potential efficacy as a second-line GBC therapy. It enhances gemcitabine chemosensitivity and induces ferroptosis through phosphorylated (p)-STAT3-mediated transcriptional regulation of ferroptosis-associated targets, downregulating GPX4, HIF-1α and FTH1, while upregulating ACSL4 (207).

At present, chemoimmunotherapy is the first-line treatment option for BTC due to the durvalumab plus gemcitabine and cisplatin in advanced BTC and KEYNOTE-966 studies (143,144). A study by Zhu *et al* (208) reveals that, in AKT-hyperactivated iCCA, the p-AKT-p-phosphoenolpyruvate carboxykinase 1 (PCK1)-p-lactate dehydrogenase A-SPRINGlac axis is a driver of ferroptosis resistance. This combines p-PCK1-mediated glycolytic activation and mevalonate flux reprogramming. However, simvastatin treatment effectively reverses this resistance, underscoring its therapeutic potential for improving the chemoimmunotherapy efficacy through ferroptosis sensitivity (208).

In addition, metabolic products such as lithocholic acid (LCA) are reagents involved in inhibiting tumorigenesis. A study by Li *et al* (209) reveals that LCA induces ferroptosis in GBC by suppressing glutaminase-mediated glutamine metabolism, which may be a tumor-suppressive mechanism with therapeutic potential.

PDT is a treatment modality that selectively destroys tumor tissue through the light activation of photosensitizers and release of ROS (210). The tumor-selective destruction capacity of PDT minimizes damage to healthy tissues, which suggests it may be a potential antitumor therapeutic strategy (211,212). The first-generation photosensitizer-HiPorfin-mediated

Table II. Ferroptosis-associated biomarkers in BTC.

Biomarker	Tumor type	Clinical validation in BTC	Validation method	Expression level in tumor	Prognostic association	(Refs.)
ACSL3	CCA	Yes	RNA-sequencing and survival analysis.	High	Poor	(173)
ACSL4	CCA	Yes	IHC and survival analysis.	High	Poor	(168)
SLC7A11	CCA	Yes	IHC and survival analysis.	High	Poor	(180)
CHAC1	CCA	Yes	IHC and survival analysis.	High	Poor	(180)
GPX4	CCA	Yes	IHC and survival analysis.	High	Poor	(183)
ACC	CCA	Yes	IHC and survival analysis.	High	Poor	(181)
TFR1	CCA	Yes	IHC and survival analysis.	-	Poor	(176)
Nrf2	GBC	Yes	IHC and survival analysis.	High	Poor	(182)
IDH1	BTC	Yes	PCR and survival analysis.	-	Well	(184)
DHODH	Esophageal cancer	No	IHC and survival analysis.	High	Poor	(185)
STARD7	Hepatocellular carcinoma	No	RNA-sequencing and survival analysis.	High	Poor	(186)
GCL	Hepatocellular carcinoma	No	IHC and survival analysis.	High	Poor	(187)
ATF4	Gastric cancer	No	IHC and survival analysis.	High	Poor	(188)
SCD1	Breast cancer	No	IHC and survival analysis.	High	Poor	(189)
GCH1	Breast cancer	No	RNA-sequencing and survival analysis.	High	Poor	(190)
LPCAT3	Ovarian cancer	No	IHC and survival analysis.	-	Well	(191)
FSP1	Lung cancer	No	IHC and survival analysis.	-	Well	(192)

BTC, biliary tract cancer; CCA, cholangiocarcinoma; GBC, gallbladder cancer; IHC, immunohistochemistry; ACSL3, acyl-CoA synthetase long-chain family member 3; ACSL4, acyl-CoA synthetase long-chain family member 4; TFR, transferrin receptor; SLC7A11, solute carrier family 7 member 11; CHAC1, glutathione-specific γ-glutamylcyclotransferase1; GPX4, glutathione peroxidase 4; ACC, acetyl-CoA carboxylase; IDH1, isocitrate dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; LPCAT3, lysophosphatidylcholine acyltransferase 3; SCD1, stearoyl-CoA desaturase 1; GCH1, GTP cyclic hydrolase 1; DHODH, dihydroorotate dehydrogenase; STARD7, steroidogenic acute regulatory protein-related lipid transfer domain containing 7; FSP1, ferroptosis inhibitory protein 1; GCL, glutamate cysteine ligase; ATF4, activating transcription factor 4.

PDT promotes the apoptosis and ferroptosis of CCA cells through the activation of the p53/SLC7A11/GPX4 signaling pathway (213). Furthermore, the second-generation photosensitizer-Hypericin-mediated PDT induces ferroptosis in CCA by inhibiting the AKT/mTORC1/GPX4 signaling pathway (214). These findings provide possible insights into individualized precision therapy for CCA. Furthermore, combination strategies represent novel therapeutic paradigms for BTC. Surufatinib (SUR), a multi-targeted kinase inhibitor, has comparable clinical efficacy in patients with advanced CCA compared with regorafenib, which is one of the recommend regimens used for subsequent-line therapy of BTC (12,215). Mechanistically, both SUR and PDT induce ferroptosis through the upregulation of ACSL4 and

suppression of GPX4, and their effect is synergistically enhanced during combination treatment (215). In addition, an integrated nanotherapeutic platform known as CMArg@Lip has been successfully developed for combined PDT and gas therapy. This platform encapsulates the photosensitizer, NO gas-generating agent and Nrf2 inhibitor with ROS-responsive liposomes, which enables it to effectively address the challenges of tumor hypoxia and the antioxidant microenvironment (216).

6. Conclusions and perspectives

Ferroptosis, an iron-dependent, LPO-driven form of RCD, is a research focus in BTC therapeutics. Accumulating evidence demonstrates marked vulnerability of BTC cells to ferroptosis, unveiling novel avenues for targeted treatment. Despite promising advances, challenges persist. While core ferroptosis pathways, such as the GPX4-GSH axis and system Xc^- regulation, are delineated, the integrated regulatory network, particularly crosstalk with metabolic reprogramming and TME interactions, is yet to be fully elucidated. At present, clinically applicable biomarkers for predicting ferroptosis sensitivity are lacking, which hampers patient stratification. Furthermore, current ferroptosis inducers, such as erastin analogs and RSL3 derivatives, have limitations in tumor specificity, systemic toxicity and pharmacokinetic profiles.

Future studies should prioritize the following: i) Systematic investigations of ferroptosis synergism with immune checkpoint inhibitors and molecular-targeted agents, using multiomics approaches to decipher resistance mechanisms; ii) development of integrated biomarker panels incorporating genetic, epigenetic and microenvironmental features for precision patient stratification; iii) therapeutic validation through physiologically relevant platforms, including patient derived organoids, orthotopic BTC models and humanized mouse systems simulating tumor-stroma crosstalk; and iv) engineering of tumor-targeted nano-formulations, such as the CMArg@Lip platform, to enhance the tumor-targeted delivery of ferroptosis inducers while mitigating off-target effects.

In summary, bridging mechanistic insights from laboratory studies with rationally designed clinical trials incorporating biomarker-driven enrollment may highlight ferroptosis modulation as a potnetial therapeutic paradigm for BTC.

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Availability of data and materials

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Authors' contributions

RZ and YD contributed to literature searching and screening, manuscript drafting and revision of the manuscript. SY and HH contributed to the revision of the manuscript. FLi and FLiu contributed to the study design and revision of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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