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Research Progress on Ferroptosis in the Occurrence, Development and Treatment of Hepatocellular Carcinoma

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Abstract: *Hepatocellular carcinoma (HCC) is [1]the most common and most lethal primary liver cancer globally, characterized by complex pathogenesis, difficult early diagnosis, frequent therapeutic resistance, and poor overall prognosis. As a novel iron-dependent form of programmed cell death, ferroptosis has attracted extensive attention in the field of tumor biology in recent years. This paper systematically summarizes the molecular regulatory mechanisms of ferroptosis in HCC, including abnormal alterations in core pathways such as iron metabolism, lipid peroxidation, and glutathione peroxidase 4 (GPX4), as well as its regulatory effects on tumor proliferation, metastasis, and the immune microenvironment. Meanwhile, this review focuses on the potential value of ferroptosis in reversing therapeutic resistance in HCC. In addition, this paper also summarizes the application prospects of ferroptosis-related gene-based biomarkers in the diagnosis and prognostic evaluation of HCC, as well as the latest research progress of ferroptosis-targeting therapeutic strategies (such as GPX4 inhibitors, system xc^- inhibitors, iron nanomedicines, etc.), providing new ideas and potential intervention targets for the precise treatment of HCC.*

Keywords: *Hepatocellular Carcinoma; Ferroptosis; Lipid Peroxidation; GPX4; Targeted Therapy*

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy globally and the third leading cause of cancer-related death, with particularly high incidence rates in East Asia, Africa, and Southern Europe. 75% of cases are associated with HBV/HCV infection, alcoholism, and metabolic syndrome[1]. HCC accounts for 75% of primary liver cancers, with a 5-year survival rate of only 2.4% for advanced-stage disease[2]. It is characterized by rapid progression, poor prognosis, and susceptibility to resistance against conventional therapies[3]. Current diagnostic methods (e.g., serum AFP testing, imaging) lack sufficient sensitivity for early screening. Although progress has been made in early diagnosis and local treatments (e.g., surgical resection, ablation, liver transplantation), most patients are diagnosed at an advanced stage and can only receive systemic therapy. While first-line targeted agents (e.g., sorafenib, lenvatinib) combined with immune checkpoint inhibitors (e.g., atezolizumab + bevacizumab) can prolong survival, the overall objective response rate remains below 30%, and acquired resistance is nearly inevitable. Sorafenib, a first-line targeted drug, offers limited survival extension, along with issues of resistance and toxicity[4]. First-line targeted drugs like sorafenib and lenvatinib extend survival by only a few months, and only 15-20% of patients respond to immune checkpoint inhibitors (ICIs). Formally named in 2012, ferroptosis is an iron-dependent, lipid peroxidation-driven, non-apoptotic cell death form, first defined by Dixon et al. Given the high reactive oxygen species (ROS) load and unique iron metabolism characteristics of HCC cells, inducing ferroptosis has emerged as a novel strategy to overcome treatment resistance, providing a new direction for HCC therapy. Therefore, exploring novel mechanisms of HCC progression and developing new therapeutic strategies is urgently needed. Ferroptosis is a non-apoptotic, iron-dependent, programmed cell death form first proposed by Dixon et al. in 2012. Its core features are the lethal accumulation of lipid peroxides and oxidative damage to the cell membrane. Morphological and biochemical markers include mitochondrial shrinkage, reduced cristae, accumulation of ferrous iron (Fe^{2+}), reactive oxygen species (ROS), and lipid peroxides[5,6]. Key pathways include: Iron metabolism: TFR1 mediates iron uptake, STEAP3 reduces Fe^{3+} to Fe^{2+}, iron catalyzes ROS generation via the Fenton reaction, and ferritinophagy (mediated by NCOA4) releases

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free iron, promoting lipid peroxidation; CISD1, CP, PCBP1, etc., regulate iron homeostasis. Lipid metabolism: ACSL4 and LPCAT3 catalyze polyunsaturated fatty acids (PUFAs) to form lipid peroxides, and the PEBP1/15-LO complex promotes oxidation. Antioxidant systems: The GSH/GPX4 pathway: SLC7A11 mediates cystine uptake for GSH synthesis, GPX4 clears lipid peroxides; ATF3, NRF2, etc., regulate its expression. The FSP1/CoQ10 pathway: Independent of GPX4, it functions by regenerating CoQ10 or repairing membrane damage to inhibit ferroptosis[7]. Other pathways: DHODH, GCH1/BH4, etc., influence ferroptosis by regulating mitochondrial redox balance. In HCC, ferroptosis has been confirmed to be closely related to tumor initiation, progression, metastasis, and treatment resistance. As the liver is a central organ for iron storage and metabolism[8], HCC cells often exhibit iron metabolism disorders and redox imbalances, making them highly sensitive to ferroptosis inducers. Inducer classification: Class 1: e.g., erastin and sulfasalazine (SAS), inhibit System Xc^- (SLC7A11/SLC3A2), blocking cystine uptake and depleting GSH; Class 2: e.g., RSL3, directly inhibit GPX4 activity, leading to lipid peroxidation[9] . However, tumor cells can also evade ferroptosis by upregulating anti-ferroptosis molecules such as GPX4 and SLC7A11 (xCT), thereby acquiring resistance and a more aggressive malignant phenotype. Therefore, targeting ferroptosis pathways holds promise as a novel strategy to overcome HCC resistance and inhibit tumor progression. This review systematically summarizes the research progress on ferroptosis in HCC, covering molecular mechanisms, biological functions, immune regulation, drug resistance, and clinical translation.

2. Molecular Mechanisms of Ferroptosis in Hepatocellular Carcinoma

2.1 Abnormal Regulation of Iron Metabolism and Lipid Peroxidation

Iron homeostasis imbalance: Fe^{2+} catalyzes ROS generation via the Fenton reaction, promoting lipid peroxidation. Hepcidin maintains liver iron homeostasis by regulating the iron exporter ferroportin (FPN).Lipid peroxidation: ACSL4/LPCAT3 catalyze the esterification of polyunsaturated fatty acids (PUFAs) into phospholipids, which are then oxidized by lipoxygenases (ALOXs) into lipid peroxides (LPO)[10]. Ferroptosis: An iron-dependent programmed cell death characterized by lipid peroxidation and glutathione (GSH) depletion, involving disturbances in iron, lipid, and amino acid metabolism, closely linked to inflammatory responses[11]. As a form of programmed necrotic cell death dictated by iron-dependent phospholipid peroxidation, ferroptosis requires iron ions (Fe^{2+}/Fe^{3+}), ROS, and PUFA-phospholipids as essential mediators and substrates, and ultimately results in the loss of membrane integrity via the accumulation of phospholipid hydroperoxides (PLOOH) [12]. It is a programmed necrotic cell death dictated by iron-dependent phospholipid peroxidation.. Key triggers: peroxidation of PUFA-containing phospholipids (PUFA-PLs) in the presence of reactive iron (Fe^{2+}/Fe^{3+}), via non-enzymatic (Fenton reaction) or enzymatic (e.g., lipoxygenases ALOXs, cytochrome P450 oxidoreductase POR) pathways. Execution marker: accumulation of phospholipid peroxidation products (PLOOH) disrupting membrane integrity, leading to cell death [13].Sorafenib and erastin inhibit the cystine/glutamate transporter SLC7A11, causing GSH depletion and inactivation of GPX4, which cannot clear lipid peroxides. Abnormal mitochondrial morphology (shrinkage, increased membrane density) is a hallmark feature . Regulatory hubs: Pro-death factors: PUFA-PLs (e.g., those containing arachidonic acid AA/adrenic acid AdA), reactive iron, POR/ALOXs. Anti-death mechanisms: GPX4 reduces PLOOH; pathways like FSP1-CoQ10, DHODH, GCH1-BH4 terminate chain reactions via radical-trapping [14] . Long-chain acyl-CoA synthetase 4 (ACSL4) activates unsaturated fatty acids like arachidonic acid and incorporates them into membrane phospholipids, acting as a key driver of ferroptosis. Mevalonate pyrophosphate decarboxylase (MVD) in the mevalonate pathway can activate both the GSH/GPX4 and CoQ10/ferroptosis suppressor protein 1 (FSP1) defense systems by regulating GPX4 synthesis and coenzyme Q10 (CoQ10) generation, helping HCC cells resist ferroptosis.

2.2 Core Regulatory Roles of GPX4 and System xc^-

Antioxidant system inhibition: GPX4/GSH, FSP1/CoQ10, and GCH1/BH4 are the three major anti-ferroptosis pathways. GPX4 deficiency leads to accumulation of lipid peroxides .GPX4-GSH axis: This is the most classic regulatory pathway of ferroptosis. System Xc^- (composed of SLC7A11 and SLC3A2) transports extracellular cystine into the cell for GSH synthesis, while GPX4 utilizes GSH to clear lipid peroxides. When System Xc^- is inhibited, methionine can generate cysteine to maintain GSH synthesis; knockout of CBS/CTH promotes ferroptosis [15]. GPX4 relies on GSH to reduce LPO, serving as the primary mechanism inhibiting ferroptosis. SLC7A11-mediated cystine uptake is the rate-limiting step for GSH synthesis; drugs like sorafenib induce ferroptosis by inhibiting this system. Non-GPX4

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dependent pathways:FSP1-CoQ10 pathway: FSP1 regenerates CoQ10 in an NADPH-dependent manner to clear lipid radicals.GCH1-BH4 pathway: Tetrahydrobiopterin (BH4) acts as a radical-trapping agent inhibiting lipid peroxidation.DHODH-CoQH2 system: Mitochondrial dihydroorotate dehydrogenase (DHODH) inhibits ferroptosis by reducing CoQH2 [16] . EGFR signaling stabilizes DHODH via TOM20-mediated phosphorylation of LOXL3 and inhibits ferroptosis [17].HCC cells often evade ferroptosis by upregulating SLC7A11 and GPX4 expression, inhibiting lipid peroxidation accumulation, which supports their proliferation, invasion, and metastasis [18] . This classic antioxidant pathway relies on GSH to reduce PLOOH . GPX4 reduces lipid peroxides to harmless alcohols using reduced GSH.PTMs of GPX4:Succination: Fumarate succinates GPX4 at Cys93, inhibiting its enzyme activity.Ubiquitination: TRIM46 and FBXO31 promote K48-linked ubiquitination and degradation of GPX4, inducing ferroptosis[19]. OTUB1 stabilizes GPX4 via deubiquitination, inhibiting ferroptosis.Phosphorylation: CKB phosphorylates GPX4, inhibiting its degradation and promoting HCC growth.Sorafenib inhibits SLC7A11, depleting GSH, but activation of NFE2L2/NRF2 can restore antioxidant defenses [20] .

2.3 Cross-talk between Ferroptosis and Other Cell Death Pathways

(1) Ferroptosis: Defined in 2012, dependent on iron ions (Fe^{2+}/Fe^{3+}) and lipid peroxidation (PLOOH) leading to membrane rupture. Key pathway: SLC7A11-GSH-GPX4 axis. Targeting GPX4 or cystine metabolism can induce ferroptosis in cancer cells, e.g., using drugs RSL3 and erastin.(2) Cuproptosis: Trigger mechanism: copper ionophores (e.g., elesclomol) transport copper to mitochondria, triggering toxicity due to mitochondrial Cu^{2+} overload [21,22] . Feature: associated with metabolic shift in glucose metabolism. Novel mechanism: copper causes mitochondrial proteotoxic stress by aggregating lipoylated TCA cycle proteins (e.g., DLAT).(3) Disulfidptosis: Mechanism: In SLC7A11-high cells under glucose abundance, NADPH (from pentose phosphate pathway PPP) reduces cystine; under glucose starvation, cystine accumulation leads to abnormal actin disulfide bond formation and cytoskeletal collapse. Regulatory factor: Rac1-WRC-Arp2/3 complex promotes branched actin polymerization, accelerating disulfide bond formation.(4) Alkaliptosis: Unique feature: induced by drug JTC801 triggering intracellular alkalinization, without lipid peroxidation or necrosome formation, and not blocked by inhibitors of other known death pathways. Potential mechanism: associated with inhibition of opioid receptor-like protein 1 (ORL1), but specific metabolic targets need exploration.All involve imbalances in key metabolites (iron, copper, cystine, pH) and are linked to cancer metabolic reprogramming [22]. Ferroptosis: Iron-dependent lipid peroxidation-driven; features mitochondrial cristae reduction, membrane rupture, and inhibition of GSH/GPX4 antioxidant system. Key regulators: SLC7A11 (System Xc^-), ACSL4 (promotes lipid peroxidation), and NRF2/KEAP1 pathway (antioxidant defense). Pyroptosis: Mediated by Gasdermin (GSDM) family (e.g., GSDMD, GSDME), activating caspase-1/4/11 via inflammasomes, releasing IL-1β/IL-18. Pathways: canonical (caspase-1/GSDMD), non-canonical (caspase-4/5/11), and alternative (caspase-3/8 activating GSDME).Necroptosis: Triggered by RIPK1/RIPK3/MLKL signaling axis, forming the necrosome, leading to membrane rupture and release of inflammatory factors[23]. Ferroptosis is regulated by the activation of TLR3 and TNF-α, as well as NF-κB signaling [24].

3. Role of Ferroptosis in Immune Regulation and Drug Resistance in Hepatocellular Carcinoma

3.1 Impact of Ferroptosis on the Tumor Immune Microenvironment (TIME)

The bidirectional regulatory role of ferroptosis in the tumor microenvironment (TME). Cellular interactions in the TME:Cancer-Associated Fibroblasts (CAFs): Secrete FGF5 to inhibit tumor cell ferroptosis; exosomal miR-522 promotes chemoresistance by inhibiting ALOX15; enhance cystine supply via TGF-β pathway. Exo-miR-125b inhibits HCC metastasis by targeting SMAD2. HCC cells secrete Exo-miR-1247-3p to activate NFs conversion into CAFs, promoting tumor progression via IL-6/IL-8 [25] .Tumor-Associated Macrophages (TAMs): Dynamic regulation of macrophages: Polarization phenotypes: M1 (pro-inflammatory) secrete IL-6, TNF-α; M2 (anti-inflammatory) secrete IL-10, TGF-β. Functional networks: Iron cycle releases free iron via erythrophagocytosis (Nramp1-mediated); Inflammatory regulation: ROS activates NF-κB via NOX2/GGT pathway. Bidirectional interaction mechanisms: Impact of ferroptosis on macrophages: Polarization regulation: Iron overload promotes M1 polarization via ROS/p53 acetylation. Recruitment signals: HMGB1 and oxidized phospholipids (e.g., SAPE-OOH) activate macrophages via TLR2/AGRE pathway. Regulation of ferroptosis by macrophages: iron exerts a biphasic regulatory effect on macrophage function. On one hand, it supports the activity of

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hemoproteins such as iNOS and NOX2, enhancing STAT1-dependent nitric oxide production and M1-type antimicrobial responses. On the other hand, iron accumulation suppresses STAT1/3 activation, downregulates iNOS transcription, and promotes anti-inflammatory pathways involving HO-1, IL-10, and STAT3 [26].T Lymphocytes: $CD8^+$ T cells trigger ferroptosis by inhibiting SLC7A11 or activating ACSL4 via IFNγ .SLC7A11 (also known as xCT) serves as the key functional subunit of the system xc^- transporter located on the plasma membrane. It forms a heterodimeric complex with SLC3A2, responsible for the 1:1 exchange transport of extracellular cystine into the cell and intracellular glutamate out of the cell. This process constitutes the core metabolic hub of the cellular antioxidant system: imported cystine is rapidly reduced to cysteine, the rate-limiting precursor for GSH synthesis. GSH, one of the most crucial intracellular antioxidant molecules, acts as an essential substrate for GPX4, protecting cells against lipid peroxidation and ferroptosis [27] . Cholesterol in the TME promotes $CD8^+$ T cell ferroptosis via CD36. GPX4 deficiency leads to Treg cell ferroptosis, enhancing anti-tumor immunity [28] . $CD8^+$ T cells induce tumor ferroptosis by downregulating SLC7A11 via IFNγ, but Treg cells are resistant to ferroptosis due to high GPX4 expression [29] . Existing drug modifications: Cisplatin combined with ω-3 fatty acids enhances GPX4 inhibition. Radiotherapy promotes ferroptosis by upregulating ACSL4 .

3.2 Ferroptosis-Mediated Therapeutic Resistance in Hepatocellular Carcinoma

HCC resistance results from dynamic interactions between the TME and intrinsic tumor cell mechanisms (e.g., genetic mutations, epigenetic regulation, metabolic adaptation) .
Mechanisms of resistance to targeted therapy in HCC: Abnormal signaling pathways: EGFR amplification, compensatory activation of PI3K/AKT and Wnt/β-catenin pathways ; Upregulation of FGFR4 and c-MET mediates lenvatinib resistance. Tumor Microenvironment (TME): Hypoxia promotes angiogenesis and EMT via HIF-1α/2α; TAMs secrete IL-6/CXCL1, enhancing stemness and sorafenib resistance. Epigenetic regulation: DNA methylation (e.g., RASSF1A silencing) and YTHDF1-mediated m6A modification (NOTCH1 stabilization) drive resistance .Mechanisms of chemotherapy resistance: Multidrug resistance (MDR): ABC transporter (e.g., MRP1/2) overexpression leading to drug efflux; 5-FU resistance linked to PI3K/PDK1/ROCK1 pathway activation. Apoptosis evasion: p53 mutations, Bcl-2 family overexpression (e.g., Mcl-1) inhibiting chemotherapy-induced cell death. Ferroptosis resistance: YAP/TAZ-SLC7A11 axis restores glutathione homeostasis, counteracting sorafenib-induced ferroptosis. Mechanisms of immunotherapy resistance: Immunosuppressive TME: Tregs inhibit $CD8^+$ T cell function via CTLA-4/PD-1 and IL-10/TGF-β; MDSCs promote immune desert via lactate/GPR81 axis. Checkpoint molecule regulation: PD-L1 glycosylation and CD73 upregulation enhance immune escape via AKT pathway. Metabolic reprogramming: Lactate from the Warburg effect is exported via MCT4, suppressing NK cell cytotoxicity and promoting M2-TAM polarization. Other resistance mechanisms: Autophagy and ER stress (ERS): MALAT1-miR216b axis regulates autophagy promoting 5-FU resistance[30]; ERS enhances survival via PERK/ATF4 pathway. Non-coding RNAs: circRNA-SORE stabilizes YBX1 promoting sorafenib resistance; LINC01134 mediates oxaliplatin resistance via SP1/p62 axis.Cancer Stem Cells (CSCs): Wnt/β-catenin and Hippo pathways maintain stemness, leading to targeted therapy failure. Mechanisms to overcome resistance: Metabolic reprogramming: ABCC5 upregulates SLC7A11 via PI3K-AKT-NRF2 axis; GSTZ1 deletion activates NRF2/GPX4 pathway; ferroptosis induction (e.g., GPX4 inhibition) can overcome chemotherapy resistance [31] .Cellular interactions: FAM134B-mediated reticulophagy weakens sorafenib-induced ferroptosis .Recently discovered RCDs (necroptosis, pyroptosis, ferroptosis, cuproptosis) offer new targets to overcome cancer therapy resistance . Chemotherapy drugs (e.g., cisplatin, temozolomide) can induce pyroptosis (GSDME-dependent), but after resistance, elevated autophagy shifts cell death towards ferroptosis (e.g., Haloperidol combination therapy via NCOA4 upregulation). Resistant tumors with high autophagy can be targeted to induce ferroptosis (e.g., Fin56 combined with mTOR inhibitors) [32]. Modulating cell death mode switching can break resistance bottlenecks. KRAS mutant tumors depend on autophagy for survival, but excessive activation of ferritinophagy can trigger ferroptosis. Integrated strategies: Targeting key ferroptosis pathways (GPX4/NRF2, iron metabolism, p53) combined with immunotherapy or nanotechnology can overcome resistance [33] .

4. Ferroptosis-Related Biomarkers and Targeted Therapeutic Strategies

4.1 Role of Ferroptosis-Related Genes in HCC Diagnosis and Prognosis

Ferroptosis-related genes (e.g., SLC7A11, GPX4, ACSL4) and ncRNAs (e.g., circIL4R, GABPB1-

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AS1) can serve as prognostic markers for HCC [34] .Dual role of ferroptosis in HCC: Pro-tumorigenic role: Iron overload and chronic liver disease (e.g., hereditary hemochromatosis, NASH) may promote hepatocarcinogenesis via ferroptosis.Anti-tumor potential: HCC cells, due to high iron demand and GPX4/SLC7A11 overexpression, are sensitive to ferroptosis, making it a therapeutic target [35] . Prognostic models based on ferroptosis and immune-related genes can predict patient survival and immunotherapy response. Lipid peroxidation products (4HNE, MDA) and PRDX3 hyperoxidation have been proposed as ferroptosis-specific markers .Regulatory mechanisms of ferroptosis in HCC:(1) Iron metabolism-related targets: FPN (regulated negatively by hepcidin) maintains liver iron homeostasis; FPN dysregulation linked to HCC progression. TFR1 (transferrin receptor) regulates hepatocyte iron uptake, associated with HBV-related HCC prognosis. FBXL5-IRP2 axis: FBXL5 loss leads to iron metabolism disorders, promoting DEN or HCV-induced HCC.(2) Lipid metabolism and oxidative stress: ACSL4 promotes PUFA synthesis via c-Myc/SREBP1 pathway, enhancing HCC sensitivity to ferroptosis. NRF2 pathway: p62-Keap1-NRF2 axis inhibits ferroptosis by activating antioxidant genes like HO1, linked to HCC drug resistance. HSPB1: Phosphorylated HSPB1 reduces ROS accumulation via p38 MAPK pathway, protecting HCC cells from ferroptosis .

4.2 Therapeutic Strategies Targeting Ferroptosis and Clinical Progress

Targeted drugs: Natural compounds:Artesunate: Enhances sorafenib-induced ferritinophagy-dependent ferroptosis by regulating labile iron pools (LIPs) and lysosomal iron release, synergizing with sorafenib . Formosanin C: Induces ferritin degradation via NCOA4.Heteronemin (isoprenoid): Induces ferroptosis and apoptosis via ROS-p38/JNK pathway .Traditional Chinese Medicine components (e.g., Poriacein C, Prunella vulgaris extract): Downregulate GPX4 or upregulate ACSL4 . Synthetic drugs: Sorafenib: Induces ferroptosis by inhibiting system Xc^- [36] , but resistance is common (e.g., MT1G upregulation via NRF2 confers resistance) . Sorafenib's effect is limited by resistance mechanisms (e.g., activation of NRF2/MT-1G pathway). Mechanisms of sorafenib resistance related to ferroptosis include: Hippo-YAP/TAZ-ATF4-SLC7A11 pathway: In resistant HCC, YAP/TAZ nuclear translocation activates ATF4, which binds TEAD to promote SLC7A11 transcription, increasing GSH synthesis and inhibiting ferroptosis.LIFR-NF-κB-LCN2 pathway: Low LIFR expression activates NF-κB via SHP1, upregulating the siderophore protein LCN2, which inhibits transferrin receptor activity, reduces iron uptake, and weakens sorafenib-induced ferroptosis.Keap1-Nrf2 antioxidant system: Activation of NRF2 target genes (MT-1G, ABCC5) and FACT complex-mediated NRF2 transcription prolongation inhibit ferroptosis.ETS1-miR-23a-3p-ACSL4 axis: Sorafenib activates transcription factor ETS1, upregulating miR-23a-3p, which targets and inhibits ACSL4, thereby suppressing ferroptosis [37] .Lenvatinib: It was reported that lenvatinib might trigger ferroptosis by suppressing the FGFR/system xc-/GPX4 pathway [38] .Disulfiram: A copper ionophore that antagonizes NRF2 to enhance lipid peroxidation. Haloperidol: A sigma-1 receptor antagonist that inhibits GPX4.Nanotechnology applications: Fe(III)-shikonin nanoparticles simultaneously induce ferroptosis and necroptosis. Prussian blue nanoparticles (HMPB) loaded with sorafenib for pH-responsive release to enhance targeting. Manganese silicate nanoparticles (MMSNs) deplete GSH and induce ferroptosis [39].MnMSN@SFB depletes GSH and inhibits System xc^-.MIL-101(Fe)@sorafenib synergizes with iRGD for targeted delivery, enhancing lipid peroxidation. Exosomes (ExosCD47) loaded with erastin and photosensitizers induce ferroptosis via chemo-photodynamic therapy .Other targets (drugs under development): ACSL4 (promotes PUFA synthesis, enhances sensitivity), CISD1 (mitochondrial iron-sulfur protein; inhibition enhances erastin-induced ferroptosis), Lactate metabolism (inhibits ferroptosis via HCAR1/AMPK/SREBP1/SCD1 axis) .Combination therapy strategies: Supplementation with ω-3 fatty acids (e.g., DHA) synergizes with sorafenib to inhibit tumor growth. Targeting NRF2 or MT-1G can reverse sorafenib resistance. Ferroptosis inducers combined with immunotherapy (e.g., PD-1 inhibitors) hold promise . Immunomodulation: CD133+ HCC stem cells resist ferroptosis by upregulating GSH; the SLC7A11 inhibitor sulfasalazine can reverse this.Key regulatory molecules:p53: Bidirectionally regulates ferroptosis by inhibiting SLC7A11, activating SAT1/ALOX15, or upregulating GLS2. Promotes ferroptosis by inhibiting SLC7A11 or activating ALOX12, but can also delay it via DPP4 inhibition or CDKN1A .NRF2: Activates antioxidant genes (HO1, FTH1) and MT-1G, inhibiting ferroptosis and mediating sorafenib resistance. YAP/TEAD: Upregulates TFRC to promote ferroptosis, but can also induce resistance via SLC7A11 .ACSL4: Promotes PUFA synthesis via c-Myc/SREBP1 pathway, enhancing ferroptosis sensitivity.GPX4: Selenium-dependent enzyme; its deficiency leads to lipid ROS accumulation. Other regulators: HSPB1 (phosphorylation reduces iron uptake, inhibits ferroptosis); TRIM25 (activates NRF2 pathway by ubiquitinating and degrading Keap1, protecting cells from ER stress injury).

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5. Conclusion and Future Perspectives

This review elaborates on the molecular mechanisms and therapeutic potential of ferroptosis in HCC, emphasizing strategies to overcome drug resistance and combine with immunotherapy/radiotherapy by targeting ferroptosis. Insufficient targeting of ferroptosis may damage normal tissues (e.g., heart, kidney). Future research needs to address selectivity and toxicity to advance ferroptosis from basic research to clinical translation. Biomarkers: ACSL4, GPX4, and lipid peroxidation products (e.g., 4-HNE) may serve as predictive markers for ferroptosis sensitivity. Expression of ACSL4, SLC7A11, and G6PD is significantly associated with HCC prognosis . Future multi-omics approaches are needed to develop specific ferroptosis inducers and biomarkers, providing new ideas for advanced HCC treatment. Clinical therapeutic potential of ferroptosis: Immunotherapy: $CD8^+$ T cells inhibit SLC7A11 via IFN-γ, promoting ferroptosis and enhancing PD-1 inhibitor efficacy. Radiotherapy: Radiation induces ferroptosis by inhibiting SLC7A11 or activating ACSL4, overcoming radioresistance. Nanotherapy: Manganese-doped mesoporous silica nanoparticles enhance ferroptosis by depleting GSH and inducing lipid peroxidation. Natural drugs: Artesunate combined with sorafenib synergistically induces ferroptosis by promoting ferritin degradation (ferritinophagy) .Patients with advanced HCC are prone to resistance to targeted drugs like sorafenib and immunotherapies [40]. Combining ferroptosis induction with radiotherapy, immunotherapy, or nanomedicine may break the treatment bottleneck for HCC. Clinical translation challenges: Toxicity of ferroptosis inducers (e.g., GPX4 inhibitors) and tumor heterogeneity. Optimizing personalized therapy by integrating ferroptosis-related genes and immune microenvironment characteristics is needed. Bekric et al. systematically elaborated the dual role and therapeutic potential of ferroptosis in HCC, emphasizing that targeting key ferroptosis pathways (e.g., GPX4, NRF2) can overcome drug resistance and promoting clinical translation by combining with nanotechnology/immunotherapy. Ferroptosis regulates HCC progression and drug resistance through multiple pathways. Induction strategies (drugs, nanotechnology, immune combinations) show broad therapeutic prospects, but further clarification of mechanisms, optimization of targeting, and validation of clinical translation potential are required.

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