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Research Progress on the Role of Ferroptosis in the Development of Oxaliplatin Resistance in Gastric Cancer

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Abstract

Gastric cancer is one of the most common malignant tumors of the digestive tract, with a low rate of early detection and an unsatisfactory overall prognosis in advanced stages. Oxaliplatin-based regimens are widely used in the treatment of advanced gastric cancer; however, acquired resistance limits sustained therapeutic benefit and adversely affects recurrence and survival outcomes. Ferroptosis, a form of regulated cell death (RCD) characterized by iron-dependent lipid peroxidation, is jointly regulated by the System Xc^--GSH-GPX4 axis, the FSP1-CoQ10 pathway, and signaling pathways such as p53, and is also influenced by exosomal signaling and metabolic reprogramming within the tumor microenvironment (TME). Current studies indicate that the development of oxaliplatin resistance in gastric cancer is often accompanied by activation of antioxidant systems, elevation of the lipid peroxidation threshold, and suppression of ferroptosis. Induction of ferroptosis through natural compounds or combination strategies has been shown, under certain conditions, to enhance the cytotoxicity of oxaliplatin and partially reverse resistant phenotypes. This review focuses on the molecular mechanisms underlying ferroptosis, summarizes the characteristics of aberrant ferroptosis regulation in gastric cancer, outlines the major pathways through which ferroptosis participates in oxaliplatin resistance, discusses strategies for reversing resistance by inducing ferroptosis, and explores the potential of ferroptosis-related molecules as predictive biomarkers and targets for clinical translation.

Keywords

Gastric Cancer, Ferroptosis, Oxaliplatin, Drug Resistance, Tumor Microenvironment

1. Introduction

Gastric cancer is one of the most common malignant tumors of the digestive tract, and the global disease burden remains substantial, with both incidence and mortality consistently ranking among the leading cancers worldwide. Epidemiological and mechanistic studies indicate that Helicobacter pylori infection, unhealthy dietary patterns, smoking, and alcohol consumption are closely associated with chronic gastric mucosal inflammation, and lesions may gradually progress from chronic gastritis to atrophy, intestinal metaplasia, and dysplasia, ultimately developing into gastric cancer. Early-stage patients may achieve favorable outcomes through endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), whereas advanced-stage patients mainly rely on systemic therapy to prolong survival and improve quality of life. In systemic treatment, oxaliplatin-based combination chemotherapy is widely applied, often combined with 5-fluorouracil (5-FU) to form the FOLFOX regimen for advanced gastric cancer. Although objective responses can be achieved in some patients, therapeutic efficacy varies markedly, and acquired resistance has become a major factor limiting long-term benefit [1]. Evidence suggests that resistance involves multilayered molecular regulation, including aberrant expression of non-coding RNAs, alterations in redox homeostasis, and metabolic reprogramming, and the underlying mechanisms remain under continuous investigation [2].

According to the Nomenclature Committee on Cell Death (NCCD), cell death can be classified into regulated cell death (RCD) and accidental cell death (ACD), and RCD, also termed programmed cell death (PCD), includes autophagy, pyroptosis, and ferroptosis. Ferroptosis is a form of RCD characterized by iron-dependent lipid peroxidation, distinct from apoptosis and necrosis, and its occurrence is closely associated with intracellular iron homeostasis and antioxidant systems. Recent studies have shown that modulation of ferroptosis can influence tumor cell responses to chemotherapeutic agents, and decreased ferroptosis sensitivity is associated with chemotherapy tolerance [3]. Experimental findings demonstrate that induction of ferroptosis can enhance the cytotoxicity of oxaliplatin; for example, baicalin promotes ferroptosis via a p53-related pathway and increases the sensitivity of resistant cells to oxaliplatin, while disulfiram combined with oxaliplatin induces lipid peroxidation and suppresses tumor cell proliferation. Other studies indicate that long non-coding RNAs can inhibit ferroptosis through regulation of key protein post-translational modifications, thereby enhancing oxaliplatin resistance. These findings suggest that ferroptosis may play an important role in the development of oxaliplatin resistance in gastric cancer.

Based on current evidence, a systematic review of the molecular mechanisms of ferroptosis and its aberrant regulation in gastric cancer may help clarify the biological basis of oxaliplatin resistance and provide theoretical support for identifying novel therapeutic targets.

2. Molecular Mechanisms of Ferroptosis in Gastric Cancer

2.1. Basic Biological Characteristics of Ferroptosis

2.1.1. Mechanisms of Iron-Dependent Lipid Peroxidation

The key biochemical event in ferroptosis is the sustained accumulation of iron-dependent lipid peroxidation within membrane systems. Polyunsaturated fatty acids (PUFAs) in membrane phospholipids are highly susceptible to hydrogen abstraction by free radicals, and amplification of the peroxidation chain reaction results in alterations in membrane structure and permeability, ultimately leading to cellular damage [4]. Pharmacological evidence shows that iron chelators and lipophilic radical-trapping antioxidants reduce lipid peroxidation levels and attenuate ferroptotic phenotypes, supporting the central role of iron and lipid peroxidation in ferroptosis.

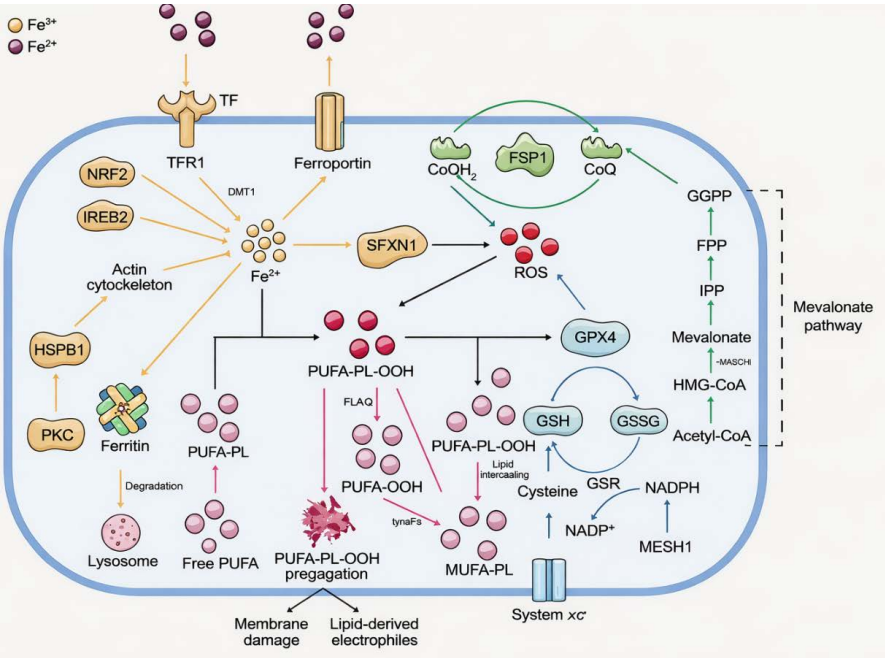
The supply of membrane phospholipid substrates is associated with lipid remodeling processes. ACSL4 (acyl-CoA synthetase long-chain family member 4) and LPCAT3 (lysophosphatidylcholine acyltransferase 3) facilitate the incorporation of PUFAs into phospholipid pools, and increased availability of oxidizable substrates promotes the initiation and maintenance of lipid peroxidation, thereby modulating cellular sensitivity to ferroptosis. Elevated levels of free ferrous iron (Fe^{2+}) enhance the Fenton reaction, generating reactive radicals that promote the formation of PL-PUFA-OOH (phospholipid hydroperoxides). Increased membrane oxidative stress becomes more difficult to terminate, enabling lipid peroxidation to surpass the tolerance threshold and drive ferroptosis.

Propagation of lipid peroxidation may occur through non-enzymatic free radical chain reactions or through enzymatic oxidation. Lipoxygenases (LOXs) catalyze the oxidation of specific lipid substrates and generate lipid hydroperoxides, and evidence supports their involvement in amplifying peroxidation and modulating the ferroptosis threshold [5]. On the detoxification side, glutathione peroxidase 4 (GPX4) uses reduced glutathione (GSH) as an electron donor to convert PL-PUFA-OOH into PL-PUFA-OH (reduced phospholipid alcohols), thereby limiting the peroxidation chain reaction and reducing membrane damage [6] When GSH supply is insufficient or GPX4 activity is impaired, lipid hydroperoxides accumulate, membrane injury worsens, and cells are more likely to enter a ferroptotic phenotype (**Figure 1**).

2.1.2. Iron Homeostasis Imbalance and the Fenton Reaction

Iron is an essential trace element required for cellular metabolism and proliferation. Under physiological conditions, iron levels are tightly regulated to prevent oxidative toxicity. Once iron homeostasis is disrupted, ferroptosis-related damage may accumulate [8]. The iron homeostasis network primarily includes iron uptake, storage, and export. The transferrin receptor (TFR1) mediates iron import, ferritin ensures safe iron storage, and ferroportin facilitates iron export to maintain intracellular stability. In ferroptosis models, expansion of the labile iron pool (LIP) is often associated with increased susceptibility to cell death. Iron chelation

attenuates ferroptotic phenotypes, indicating that free iron plays a critical role in the lethal process.



When System Xc⁻ supports cystine uptake and GSH synthesis, GPX4 reduces PL-PUFA-OOH to PL-PUFA-OH and restrains lipid peroxidation, while free iron promotes PL-PUFA-OOH generation through the Fenton reaction and LOX-associated oxidation, leading to membrane damage and changes in ferroptotic susceptibility. System Xc⁻: cystine/glutamate antiporter; cystine; GSH: glutathione; GPX4: glutathione peroxidase 4; PUFA: polyunsaturated fatty acids; ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; LOXs: lipoxygenases; Fenton rxn: Fenton reaction; PL-PUFA-OOH: phospholipid hydroperoxides; PL-PUFA-OH: reduced phospholipid alcohols; CoQ10: coenzyme Q10; NRF2: nuclear factor erythroid 2-related factor 2; ferritinophagy.

Figure 1. Overview of iron-dependent lipid peroxidation in ferroptosis (reproduced from Stockwell *et al.*) [7].

When intracellular ferrous iron (Fe^{2+}) increases in the presence of hydrogen peroxide (H_2O_2), the Fenton reaction generates highly reactive hydroxyl radicals (·OH). These radicals initiate membrane lipid free radical chain reactions and promote sustained accumulation of lipid peroxides. Enhanced iron uptake, increased ferritin degradation, or impaired iron export collectively elevate LIP levels, amplifying oxidative stress within membrane systems and facilitating the crossing of the ferroptotic threshold. From a cellular perspective, iron-dependent oxidative damage is not restricted to a single organelle. Lipid peroxidation propagates across multiple membrane structures, leading to permeability alterations consistent with the morphological and biochemical characteristics of ferroptosis.

Ferritinophagy represents an important mechanism influencing the LIP. Nuclear receptor coactivator 4 (NCOA4) functions as a cargo receptor for ferritinoph-

agy and mediates ferritin delivery to lysosomes, resulting in iron release. Increased iron release enhances substrate availability for the Fenton reaction and promotes lipid peroxidation [9]. Quantitative proteomic studies have identified NCOA4 as a key regulator of ferritin turnover. Changes in NCOA4 levels modify cellular responses to iron load and oxidative injury, thereby linking iron metabolism to ferroptosis sensitivity. Global regulation of iron metabolism is also influenced by hepcidin, iron regulatory proteins, and transcriptional networks. Disruption of the dynamic balance between iron input and output strengthens the coupling between free iron and reactive oxygen species (ROS) generation, driving the ferroptotic reaction cascade. Within the integrated ferroptosis framework, iron homeostasis imbalance and lipid peroxidation are mutually reinforcing processes. Iron provides the conditions for radical generation, while peroxidation products exacerbate membrane damage, ultimately determining cell fate.

2.1.3. Regulatory Role of the Antioxidant System

The occurrence of ferroptosis depends not only on iron burden and the availability of lipid peroxidation substrates, but also on the integrity of intracellular antioxidant systems. Weakening of antioxidant defenses significantly reduces the capacity to clear lipid peroxides and promotes ferroptotic phenotypes. Among various regulatory axes, glutathione peroxidase 4 (GPX4) occupies a central position. GPX4 utilizes reduced glutathione (GSH) as an electron donor to convert membrane lipid hydroperoxides into relatively stable lipid alcohols, thereby limiting the propagation of peroxidation chains and maintaining membrane stability. Genetic or pharmacological inhibition of GPX4 leads to rapid lipid peroxide accumulation and heightened sensitivity to iron-dependent oxidative injury, establishing GPX4 as a key suppressor of ferroptosis.

Beyond the GPX4-GSH axis, ferroptosis suppressor protein 1 (FSP1) has been identified as an independent inhibitor of ferroptosis [10]. FSP1 promotes the reduction of coenzyme Q10 (CoQ10) and enhances membrane antioxidant capacity, thereby suppressing lipid peroxidation independently of GPX4 and forming a parallel regulatory pathway. Loss of FSP1 increases sensitivity to lipid peroxidation stress, whereas overexpression reduces ferroptotic cell death, suggesting a compensatory role within the ferroptosis regulatory network. Further studies indicate that enhancement of the CoQ redox cycle can partially compensate for GPX4 dysfunction, demonstrating that multiple antioxidant pathways cooperate to maintain membrane lipid homeostasis [11].

The cystine glutamate antiporter (System Xc^-) functions upstream in antioxidant regulation. SLC7A11, a key subunit of System Xc^-, mediates cystine uptake and supports GSH synthesis. Adequate GSH supply sustains GPX4 activity and suppresses lipid peroxidation amplification. Alterations in SLC7A11 expression influence cellular tolerance to oxidative stress, and evidence suggests that this pathway is associated with ferroptosis sensitivity and therapeutic responses in various cancers. Collectively, the GPX4-GSH axis, the FSP1-CoQ10 pathway, and System Xc^- regulation constitute an integrated antioxidant defense network. Im-

pairment at any node may lead to insufficient lipid peroxide clearance and promote ferroptosis.

2.2. Core Regulatory Pathways of Ferroptosis

The core regulatory pathways of ferroptosis revolve around redox homeostasis, membrane lipid peroxidation levels, and iron availability. Among them, the System Xc^--GSH-GPX4 axis plays a pivotal role, and changes in pathway activity are closely associated with cellular tolerance to lipid peroxidation stress. System Xc^- consists of SLC7A11 (xCT) and SLC3A2, and is responsible for cystine uptake and GSH synthesis. When GSH supply is sufficient, GPX4 reduces membrane lipid hydroperoxides and limits membrane damage expansion. Suppression of SLC7A11 or insufficient cystine supply reduces GSH levels and restricts GPX4 antioxidant capacity, thereby facilitating lipid peroxide accumulation and promoting ferroptosis.

p53 provides an important transcriptional link in ferroptosis regulation. By repressing SLC7A11 expression and reducing cystine uptake, p53 decreases antioxidant substrate availability, making lipid peroxidation stress more difficult to buffer and increasing ferroptosis sensitivity [12]. This regulatory mode connects tumor suppressive signaling with metabolic dependency. Changes in this pathway influence cellular survival decisions under stress and suggest potential value for SLC7A11 in evaluating therapeutic responses.

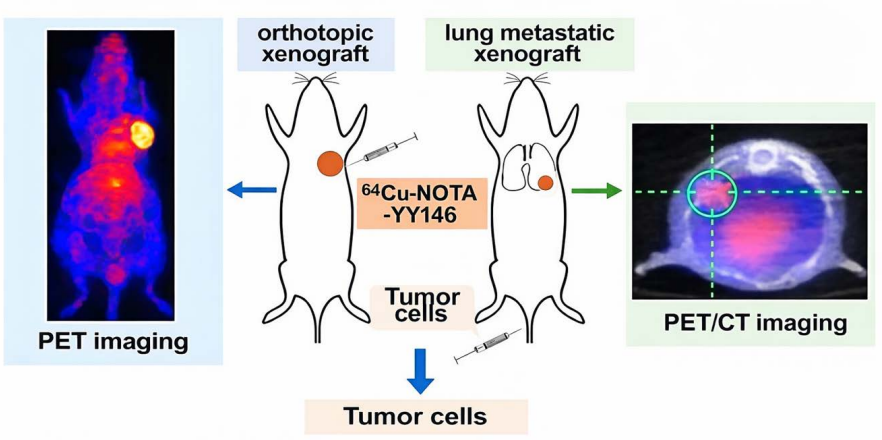
In addition to the GPX4-dependent main axis, the FSP1-CoQ10 pathway represents a significant parallel defense mechanism. FSP1 maintains CoQ10 in a reduced state and scavenges lipid radicals, partially restricting membrane peroxidation chain reactions even when GPX4 function is impaired. The existence of this pathway indicates that ferroptosis suppression is not controlled by a single node. GPX4 and FSP1 form complementary defense systems, and the overall antioxidant capacity more accurately reflects the true threshold that determines cell fate.

At the translational level, imaging and distribution assessment of SLC7A11 (xCT) have been used to link molecular mechanisms with therapeutic responses. A related review presents schematic workflows of radiolabeled probes in xenograft models using PET and PET/CT imaging, including comparisons between orthotopic and metastatic models, emphasizing the value of membrane protein target visualization for drug delivery and efficacy evaluation. This approach aligns with the core ferroptosis pathway framework. Activity of SLC7A11-related pathways may serve as an observable indicator of antioxidant capacity and can be integrated into research models evaluating ferroptosis sensitivity and resistance tendencies (**Figure 2**).

2.3. Aberrant Regulation of Ferroptosis in Gastric Cancer

In gastric cancer tissues, ferroptosis-related genes and pathways frequently exhibit dysregulated expression. Redox homeostasis and iron metabolic balance are reprogrammed, leading to alterations in the lipid peroxidation threshold and influ-

encing cellular survival advantages. Multi-omics analyses and review data suggest that antioxidant axes such as SLC7A11/GPX4 are up-regulated in a subset of gastric cancer samples. Enhanced lipid peroxide clearance capacity is associated with reduced ferroptosis susceptibility and correlates with malignant progression.



PET: positron emission tomography; PET/CT: positron emission tomography/computed tomography; System Xc^-: cystine/glutamate antiporter; xCT: SLC7A11; GSH: glutathione; GPX4: glutathione peroxidase 4; FSP1: ferroptosis suppressor protein 1; CoQ10: coenzyme Q10; cystine.

Figure 2. Schematic workflow of PET and PET/CT imaging for SLC7A11/xCT-related targeting (reproduced from Koppula *et al.*) [13].

The non-coding RNA (ncRNA) network is closely coupled with ferroptosis regulation. miRNAs, lncRNAs, and circRNAs may target antioxidant genes, iron metabolism-related genes, or key lipid metabolic enzymes, thereby modulating GSH supply, GPX4 activity, and membrane phospholipid composition, ultimately shaping ferroptosis-resistant phenotypes. Within the framework of digestive tract tumor research, ncRNA-mediated post-transcriptional regulation is considered to exert amplification effects. Minor fluctuations at critical nodes may shift the overall antioxidant system, enabling gastric cancer cells to better adapt to sustained oxidative stress.

The tumor microenvironment plays an important role in the aberrant regulation of ferroptosis in gastric cancer. Cancer-associated fibroblasts (CAFs) can transfer miR-522 via exosomes and suppress ALOX15 expression, resulting in decreased PUFA-associated lipid peroxidation and inhibition of ferroptosis. Under chemotherapeutic stress, this process is further enhanced and associated with acquired resistance. This mechanism highlights the role of intercellular communication in shaping the ferroptosis threshold. Microenvironmental signals may exert rapid protective effects through downregulation of key lipid peroxidation enzymes, thereby reducing cellular responsiveness to pro-oxidative therapies.

Metabolic and energy-sensing pathways within gastric cancer cells also participate in aberrant ferroptosis regulation. TENT5B has been reported to enhance the stability of PRKAA2 mRNA and up-regulate its expression to promote cell fer-

roptosis, leading to the decrease of proliferation and migration ability of gastric cancer cells. These findings suggest that AMPK-related energy stress pathways influence ferroptosis sensitivity and contribute to tumor progression [14]. Such regulatory routes intersect with antioxidant axes and lipid substrate supply pathways. Alterations in energy status may affect membrane lipid remodeling and ROS tolerance, resulting in multilayered coupling in ferroptosis regulation.

2.4. Relationship between Ferroptosis and Chemotherapeutic Response in Gastric Cancer

The response of gastric cancer to chemotherapy is closely associated with intracellular redox homeostasis. Ferroptosis, characterized by the accumulation of lipid peroxidation, can influence the outcome of chemotherapy-induced cellular damage. Reduced ferroptosis sensitivity is often accompanied by weaker chemotherapeutic responses and increased likelihood of resistance. Exosomal miR-522 secreted by CAFs in the tumor microenvironment downregulates ALOX15 and suppresses lipid peroxidation. Inhibition of ferroptosis under these conditions facilitates the development of acquired chemoresistance, suggesting that the microenvironment modulates drug sensitivity through regulation of key lipid peroxidation nodes.

In studies related to oxaliplatin treatment, the induction of ferroptosis has been employed to enhance chemotherapeutic efficacy. Certain drugs or natural compounds influence Nrf2/HO-1 or p53-related pathways, alter antioxidant capacity, and promote lipid peroxide accumulation, thereby increasing the cytotoxic effect of oxaliplatin. Polyene phosphatidylcholine can competitively bind to specific domains of Nrf2 and KEAP1, thus activating the Ferroptosis pathway mediated by Nrf2/HMOX1 to reverse the resistance of gastric cancer cells to oxaliplatin, indicating that the antioxidant transcription network is functionally related to Ferroptosis and may be pharmacologically regulated to reduce the risk of oxaliplatin chemotherapy resistance in patients. Baicalin activates p53-related ferroptosis in oxaliplatin-resistant cell models and enhances chemosensitivity, manifested by elevated lipid peroxidation markers and weakened antioxidant defenses, suggesting that ferroptosis pathways represent actionable targets for resistance intervention.

Evidence from combination strategies further supports the coupling between ferroptosis and chemotherapeutic response. Co-administration of disulfiram and oxaliplatin increases lipid ROS levels and downregulates GPX4 and SLC7A11 expression in gastric cancer cells, leading to enhanced cell death and indicating the involvement of ferroptosis. These findings provide experimental support for the strategy of combining chemotherapeutic agents with ferroptosis induction. Overall, chemotherapeutic responsiveness in gastric cancer is influenced by the status of ferroptosis pathways. Microenvironment-mediated suppression of ferroptosis may attenuate drug efficacy, whereas pharmacological induction of ferroptosis can enhance oxaliplatin-associated cytotoxicity, providing a logical foundation for resistance reversal and combination therapy strategies.

3. Mechanisms of Ferroptosis in the Development of Oxaliplatin Resistance in Gastric Cancer

3.1. Molecular Basis of Oxaliplatin Resistance

3.1.1. Enhanced DNA Damage Repair Mechanisms

After entering the nucleus, oxaliplatin forms platinum-DNA adducts that hinder replication fork progression and trigger DNA damage responses. Cellular survival outcomes are closely associated with the efficiency of damage removal. In clinical samples and translational studies, elevated expression of nucleotide excision repair (NER)-related molecules, such as excision repair cross-complementing gene 1 (ERCC1), is frequently associated with poor responses to 5-fluorouracil (5-FU)/oxaliplatin-based chemotherapy, suggesting that enhanced DNA damage repair constitutes a key foundation for resistance [15].

Enhanced DNA repair capacity is reflected not only by increased levels of key repair proteins but also by faster and more stable repair processes. Platinum-DNA adducts are more readily recognized and excised, the duration of cell cycle arrest is shortened, and death signaling is attenuated. Under resistant conditions, DNA damage response networks are coupled with redox homeostasis. Oxidative stress may influence repair protein activity and cell fate pathways. Resistant cells tend to simultaneously strengthen repair capacity and antioxidant buffering, thereby reducing the accumulation of irreversible damage induced by chemotherapy.

Epigenetic regulation and transcriptional remodeling may influence tumor cell adaptation to stress. Studies have shown that the demethylase J MJ D3 upregulates ALOX5 and alters ferroptosis sensitivity, suggesting that stress-related gene networks can be reprogrammed and affect therapeutic response patterns [16]. Such remodeling may coexist with enhanced DNA repair within the same tolerance framework. Enhanced DNA repair and alterations in ferroptosis pathways may act synergistically during resistance development. Increased repair capacity reduces lethal genomic damage, while strengthened antioxidant defenses lower lipid peroxidation pressure, ultimately attenuating the cytotoxic effects of platinum-based therapy.

3.1.2. Activation of Antioxidant Systems and Tolerance to Oxidative Stress

Oxaliplatin treatment elevates intracellular reactive oxygen species (ROS), and enhanced oxidative stress promotes lipid peroxidation while interfering with multiple stress-response pathways. The development of resistance is often accompanied by upregulation and remodeling of antioxidant capacity. Under these conditions, increased cystine uptake mediated by System Xc^- (SLC7A11/SLC3A2) provides sufficient substrates for glutathione (GSH) synthesis. Glutathione peroxidase 4 (GPX4) more efficiently clears lipid peroxides, thereby increasing the threshold of oxidative stress tolerance. When SLC7A11 or GPX4 remains highly active, lipid ROS fail to accumulate persistently, membrane damage signaling is attenuated, and chemotherapy-induced cell death becomes less likely.

Autophagy-related regulation is coupled with antioxidant networks. The interaction between p62 and Keap1 affects Nrf2 (nuclear factor erythroid 2-related factor 2) activity. Upregulated Nrf2 promotes the expression of antioxidant genes such as SLC7A11 and GPX4, reducing ferroptosis-related lipid peroxidation stress and contributing to resistant phenotypes [17]. Intervening in autophagy and modulating the p62-Keap1-Nrf2-GPX4 axis can alter ferroptosis sensitivity and influence the intensity of oxaliplatin-induced stress responses, suggesting a shared molecular basis between oxidative stress tolerance and resistance formation. This tolerant state is characterized by accelerated ROS clearance, reduced formation of terminal lipid peroxidation products, and enhanced adaptation to sustained chemotherapy exposure.

Pharmacological or nutritional interventions may also modulate oxidative stress and ferroptosis through the Nrf2/HO-1 (HMOX1) axis. Changes in Nrf2 activity simultaneously affect antioxidant gene expression and iron metabolism-related genes, thereby influencing oxaliplatin responsiveness. Polyene phosphatidylcholine has been reported to enhance the efficacy of oxaliplatin through Nrf2/HMOX1-mediated Ferroptosis, indicating that changing the Nrf2-mediated Ferroptosis pathway under certain conditions enhances chemotherapy sensitivity rather than simply promoting drug resistance. Overall, activation of antioxidant systems and tolerance to oxidative stress are achieved through the System Xc^--GSH-GPX4 axis and Nrf2-associated transcriptional programs. Suppressed lipid peroxidation limits full activation of ferroptosis and offsets the cytotoxic effects of oxaliplatin.

3.1.3. Metabolic Reprogramming and Resistance Formation

Resistance under oxaliplatin stress is frequently accompanied by metabolic reprogramming. Energy supply modes and reducing equivalent distribution are restructured, enabling cells to maintain survival and proliferation under sustained drug pressure. Metabolic reprogramming involves not only adaptive changes in glycolysis and mitochondrial function but also reinforcement of lipid metabolic pathways. Fatty acid oxidation (FAO) is activated and assumes a greater role in energy provision and homeostatic maintenance.

In gastrointestinal tumor models, oxaliplatin induces upregulation of FAO rate-limiting enzymes such as CPT1B and CPT2. Enhanced fatty acid catabolism reshapes NADPH levels and redox balance, buffers ROS stress, reduces apoptotic tendencies, and decreases oxaliplatin sensitivity [18]. This pattern suggests that FAO not only provides ATP but also enhances antioxidant capacity by sustaining reducing equivalents. Lipid peroxidation becomes more difficult to accumulate and is coupled with decreased ferroptosis sensitivity.

The tumor microenvironment may also drive metabolic reprogramming and consolidate resistant phenotypes. Mesenchymal stem cell-related signals induce upregulation of lncRNA MACC1-AS1 and promote FAO-dependent stemness and chemoresistance. Inhibition of FAO weakens resistance phenotypes and enhances the antitumor efficacy of combination chemotherapy [19]. Metabolic re-

programming may overlap with epigenetic and post-transcriptional suppression of ferroptosis. lncRNA BASP1-AS1 promotes PCBP2 K115 lactylation and suppresses ferroptosis, thereby enhancing oxaliplatin tolerance. Metabolic status and cell death thresholds are thus coordinately adjusted within a unified tolerance framework.

3.2. Key Role of Ferroptosis Suppression in Oxaliplatin Resistance

The development of oxaliplatin resistance is often accompanied by suppression of ferroptosis pathways. Lipid peroxidation fails to accumulate persistently, the cell death threshold is elevated, and drug cytotoxicity is weakened. When the System Xc^--GSH-GPX4 axis remains highly active, enhanced cystine uptake, increased GSH synthesis, and strengthened GPX4-mediated clearance of lipid peroxides terminate membrane peroxidation chain reactions more efficiently, preventing full activation of ferroptosis. Autophagy-related regulation further amplifies this protective effect. Activation of the p62-Keap1-Nrf2-GPX4 axis upregulates antioxidant gene expression and enhances oxidative stress tolerance, limiting ferroptosis-related damage accumulation and accompanying resistant phenotypes.

The tumor microenvironment shapes ferroptosis resistance through paracrine mechanisms. CAF-derived exosomal miR-522 downregulates ALOX15 and suppresses lipid peroxidation, facilitating acquired chemoresistance. This effect becomes more pronounced under chemotherapeutic stress and correlates with reduced treatment efficacy [20]. This mechanism underscores that ferroptosis suppression is not merely an intracellular event. Microenvironmental signals establish an extrinsic protective barrier at key lipid peroxidation nodes, making oxaliplatin-induced oxidative damage less likely to translate into effective cell death.

Post-transcriptional modifications and non-coding RNA regulation may also stabilize ferroptosis suppression. lncRNA BASP1-AS1 drives PCBP2 K115 lactylation and inhibits ferroptosis, thereby conferring stronger oxaliplatin tolerance in gastric cancer cells. These findings suggest that ferroptosis suppression can be stably maintained by specific molecular axes and constitutes an important component of resistance [21]. Within this framework, System Xc^--mediated substrate supply, Nrf2-driven antioxidant transcriptional programs, microenvironment-derived suppression of lipid peroxidation enzymes, and lncRNA-mediated protein modifications collectively sustain reduced ferroptosis activity and form a critical foundation for resistance.

3.3. Strategies to Reverse Oxaliplatin Resistance by Inducing Ferroptosis

Strategies aimed at inducing ferroptosis to reverse oxaliplatin resistance focus on increasing lipid peroxidation and weakening antioxidant defenses, thereby restoring vulnerability to oxidative damage in resistant cells. Combination approaches have gained support in multiple studies. Co-treatment with disulfiram and oxaliplatin elevates lipid ROS levels and downregulates GPX4 and SLC7A11 expres-

sion, leading to enhanced cell death and implicating ferroptosis involvement. These findings suggest that adding ferroptosis-inducing interventions to conventional chemotherapy may produce sensitization effects and improve resistant phenotypes [22].

Interventions targeting the Nrf2/HO-1 (HMOX1) network have likewise been used to enhance oxaliplatin efficacy. Polyene phosphatidylcholine promotes the sensitivity of oxaliplatin through ferroptosis mediated by Nrf2/HMOX1, which indicates that the regulation of oxidative stress transcription reaction may be transformed into ferroptosis induction and chemotherapy resistance reduction under certain conditions [23]. These findings also indicate that ferroptosis induction is not equivalent to simple inhibition of Nrf2. The timing and intensity of pathway modulation may determine whether outcomes manifest as protective or cytotoxic effects. Combination strategies should therefore align with the stress context of drug exposure to achieve stable benefits.

Reviews of pharmacological interventions from both conventional and traditional medicine perspectives suggest that various small-molecule compounds can induce ferroptosis by modulating iron metabolism, lipid peroxidation, and antioxidant systems. Combination chemotherapy studies are increasing, with key issues focusing on optimal dosing windows, toxicity boundaries, and in vivo delivery efficiency. Standardized evaluation may facilitate clinical translation [24]. Overall, current strategies can be summarized as promoting lipid peroxidation, inhibiting the System Xc^--GSH-GPX4 defense axis, modulating p53 or Nrf2-related pathways, and combining these approaches with oxaliplatin to restore ferroptosis susceptibility and enhance chemotherapeutic response.

3.4. Ferroptosis as a Predictive Biomarker and Clinical Translation Prospects

Ferroptosis-related molecules may provide insights for stratification and therapeutic response prediction in gastric cancer. Differences in gene expression in clinical samples are associated with immune characteristics. Transcriptome-based analytical frameworks suggest prognostic variation, indicating that ferroptosis signaling and the tumor immune microenvironment may jointly contribute to risk stratification. Bioinformatic analyses stratified by HMGA2 expression levels reveal differences in immune cell infiltration and significant associations with ferroptosis-related genes. Survival analyses further demonstrate prognostic disparities between groups, supporting the incorporation of ferroptosis features into prognostic assessment [25].

Tissue-detectable indicators offer practical advantages for clinical translation. Differential expression of PCBP1 and STUB1 in gastric cancer tissues can be validated by immunohistochemistry and correlates with clinicopathological characteristics. Correlation analyses suggest their involvement in ferroptosis regulatory networks and association with tumor aggressiveness, providing a feasible basis as candidate biomarkers [26]. The potential value of such markers lies in relatively

mature detection methods and manageable costs. Combined with staging and treatment strategies, they may assist in follow-up planning and recurrence risk assessment. However, larger sample sizes and multicenter validation are required to enhance reliability.

Beyond static biomarkers, ferroptosis-related pathways may predict treatment responses and guide combination strategies. The ENT5B-PRKAA2 axis is related to ferroptosis, and the up-regulation of ENT5B promotes ferroptosis and affects cell proliferation and migration, indicating that the molecular axis coupled with ferroptosis may be used as a classification index for selecting beneficiaries. At the translational level, the synergy between ferroptosis induction and immunotherapy or chemotherapy has become an emerging research direction. Interactions between regulated cell death (RCD) and tumor immunity may influence therapeutic outcomes. Ferroptosis-inducing agents combined with immune checkpoint inhibitors (ICIs) are considered worthy of exploration [27].

In addition, natural compounds are also used as sensitizers. Baicalin activates p53-related pathways and promotes ferroptosis in oxaliplatin-resistant gastric cancer cells, characterized by increased lipid peroxidation markers and compromised antioxidant systems. Resistant cells exhibit enhanced responsiveness to oxaliplatin and more pronounced growth inhibition [28]. Such strategies emphasize modulation of key pathway nodes within tolerable dosage ranges to achieve sensitization, providing potential directions for long-term combination therapy.

Current challenges include the standardization of indicators and dynamic monitoring. High sample heterogeneity and differences in detection platforms complicate interpretation. Single molecules are unlikely to capture the full biological state. Multi-marker combined models and stratification strategies may better meet clinical demands. Future research should focus on reproducible detection panels, threshold settings directly associated with clinical endpoints, and validation in prospective cohorts. Such efforts may promote the transition of ferroptosis biomarkers from correlation to applicability and support individualized therapeutic decision-making.

4. Conclusion

Accumulating evidence indicates a close association between ferroptosis and oxaliplatin responsiveness in gastric cancer. Resistance development is frequently accompanied by enhanced antioxidant defenses such as the System Xc^--GSH-GPX4 axis, elevation of the lipid peroxidation threshold, and microenvironment-mediated suppression of key lipid peroxidation nodes via exosomal signaling. Sustained repression of ferroptosis thus becomes a critical foundation for resistance. Existing studies demonstrate that pharmacological agents or natural compounds that induce ferroptosis can enhance oxaliplatin cytotoxicity and improve resistant phenotypes in cellular and animal models. Combination strategies appear feasible but require careful consideration of therapeutic windows, toxicity limits, and delivery efficiency. Ferroptosis-related molecules are associated with immune infil-

tration patterns, tissue expression differences, and metabolic axes, indicating potential value as biomarkers for risk stratification and therapeutic response prediction. However, current evidence levels and standardization remain limited. Multicenter cohorts, unified detection systems, and validation strategies integrating mechanistic insights with clinical endpoints are necessary to advance ferroptosis-targeted interventions and biomarkers from research to clinical application.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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