Current Cancer Research

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Review

Exosome-Mediated Ferroptosis Regulation in Gastric Cancer: Mechanisms, Challenges, and Therapeutic Potential

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Abstract

Gastric cancer (GC) persists as one of the foremost contributors to cancer-associated morbidity and mortality worldwide, with limited effective therapies for advanced disease stages. Recent progress in cancer biology has spotlighted ferroptosis–an iron-dependent, regulated mode of cell death–as a promising avenue for therapeutic intervention. Exosomes–small extracellular vesicles that mediate intercellular communication–have emerged as pivotal modulators of ferroptosis through the transfer of bioactive molecules such as lipids, proteins, and RNAs. In the context of GC, exosomes influence critical metabolic pathways including iron homeostasis, oxidative stress, and lipid peroxidation, thereby contributing to tumor progression, metastasis, and therapeutic resistance. This review endeavors to comprehensively elucidate the current understanding of exosome-mediated ferroptosis regulation in gastric cancer, delineate the underlying molecular mechanisms, and to assess their potential as novel diagnostic and therapeutic targets. The review further highlights existing knowledge gaps and suggests.

Keywords

Biomarker, Exosomes, Ferroptosis, Gastric Cancer, Non-Coding RNAs

Article History

Received: 12 March 2025
Revised: 29 April 2025
Accepted: 30 April 2025
Available Online: 9 May 2025

1. Introduction

Gastric cancer ranks among the most frequently diagnosed malignancies and constitutes a major contributor to cancer-related mortality on a global scale. According to 2020 statistics, it was identified as the fifth most commonly occurring cancer and the fourth leading cause of cancer-associated deaths worldwide [1]. In spite of advancements across various therapeutic modalities, including surgery, chemotherapy, radiotherapy, and immunotherapy, the high rates of recurrence and metastasis continue to compromise patient outcomes, often leading to a poor prognosis.

Recent advancements in the classification of GC into distinct molecular subtypes have paved the way for more personalized treatment approaches [2]. Additionally, research into the tumor microenvironment has provided valuable insights into the mechanisms of tumor growth and identified new therapeutic targets [3]. The investigation of exosome-mediated ferroptosis regulation in GC is motivated by the ongoing challenges in treating the disease, particularly its high relapse and metastasis rates, despite advances in conventional therapies.

The initial identification of exosomes occurred in the early 1980s, when they were first characterized as vesicles responsible for cellular waste disposal [4]. Nevertheless, it was not until the early 2000s that studies began to uncover their critical function as mediators of intercellular communication, especially within the context of cancer biology [5]. In 2012, Dixon et al. first introduced the concept of ferroptosis, a distinct form of programmed cell death driven by iron dependency, clearly differentiating it from traditional modes of cell death such as apoptosis and necrosis [6]. Over the last decade, growing evidence has underscored the pivotal roles of both exosomes and ferroptosis in cancer development and resistance. Only recently have researchers begun to investigate the intersection of these two fields, especially their relevance in gastrointestinal malignancies such as GC [7,8]. GC remains a significant healthcare burden globally, both in terms of mortality and economic impact due to the high costs of treatment and long-term care. This research aims to provide potential solutions to reduce recurrence and improve survival rates, thus alleviating this societal burden. This growing area of research has established a foundation for investigating the regulation of ferroptosis by exosomes as a novel therapeutic approach in GC, with particular emphasis on overcoming treatment resistance and addressing tumor heterogeneity [9,10].

Exosomes within the tumor microenvironment have become recognized as vital contributors, holding a pivotal role in tumor progression and metastasis. Considering the essential function of the tumor microenvironment in the progression of GC, recent studies have increasingly focused on investigating its components, with particular attention to extracellular vesicles (EVs) that are instrumental in promoting tumor progression and metastasis.

A variety of cell types release nanoscale vesicular structures, enclosed by lipid membranes, into the extracellular environment. All life forms, from bacteria to eukaryotic organisms, produce these vesicles and release them under both normal and pathological conditions [11]. Once thought to be mere cellular waste, EVs have now been recognized as essential mediators of intercellular communication through recent scientific investigations. By serving as carriers, EVs facilitate the transfer of diverse molecular cargos–including nucleic acids, proteins, and lipids–between cells, thereby modulating a wide array of biological processes. EVs transport proteins associated with cell signaling, receptor activity, and enzymatic functions, as well as genetic material like miRNA, mRNA, and DNA [12]. Exosomes can either facilitate or inhibit disease progression through these substances. They participate in various biological and pathological processes, including stem cell preservation, tissue repair, immunological surveillance, tumor metastasis, and pathogen interactions [13]. EVs are involved in a range of biological and pathological processes, including stem cell maintenance, tissue regeneration, immune surveillance, tumor metastasis, and interactions with pathogens.

Ferroptosis, recently described as a distinct form of regulated cell death, is initiated by iron-dependent lipid oxidation and has gained significant research interest over the past years. This pathway differs from other cell death processes, such as apoptosis, necrosis, and autophagy, based on both morphological features and underlying molecular mechanisms [14]. Ferroptosis serves as an important regulatory mechanism in the progression of multiple diseases, including GC, and has been associated with tumor resistance [10]. Although initial investigations primarily focused on exosomes released by active or apoptotic cells, more recent studies have begun to explore the complex interplay between exosomes and ferroptosis [15,16].

This review explores the evolving relationship between exosomes and ferroptosis in GC, emphasizing the molecular mechanisms involved and their implications for tumor progression and therapeutic resistance. Specifically, we highlight how exosomal cargo influences pathways related to iron homeostasis, lipid oxidative degradation, and redox imbalance, all of which are central to ferroptotic regulation. By synthesizing the latest findings, this review provides an integrated perspective on the exosome–ferroptosis axis and discusses its implications for future research and therapeutic development in GC. Despite considerable progress, important gaps remain–particularly regarding the specificity of molecular mechanisms, and clinical applicability–which this review aims to critically address.

2. Origin and Formation of Exosomes

The generation of exosomes remains under active investigation, with the endosomal sorting complex essential for transport (ESCRT) machinery recognized as one of the primary pathways involved [17]. In 2001, the identification of the ESCRT-I complex was a significant breakthrough, as it was shown to play a central role in the sorting and formation of exosomes [18]. Following this discovery, further research identified additional related complexes, such as ESCRT-II and ESCRT-III, both of which contribute to the overall process of exosome biogenesis [19]. The ESCRT machinery functions by recognizing ubiquitinated cargo and facilitating the deformation of the cell membrane. In simple terms, ESCRT-0 identifies the ubiquitinated cargo, initiating the signaling cascade. Subsequently, ESCRT-I and ESCRT-II associate with the cargo, forming an enriched region around it, before ESCRT-III recruits enzymes responsible for removing ubiquitin from the cargo. These actions allow the cargo to be packed into budding vesicles, which grow into multivesicular bodies (MVBs) over time [20].

Once MVBs are formed, they undergo further maturation. Small guanosine triphosphatases (GTPases) such as Rap5 and Rap7 are crucial in transitioning early endosomes into MVBs, regulating their development and maturation [21]. Mature MVBs can either merge with the plasma membrane, resulting in the release of exosomes into the extracellular space, or fuse with lysosomes for subsequent degradation [22,23]. Rab GTPases, including Rab27A and Rab27B, regulate the movement of MVBs toward the cellular membrane, where fusion occurs with the outer cell membrane via the SNARE complex, resulting in exosome release (Figure 1) [24]. Additionally, the deubiquitinating enzyme USP8, associated with endosomal membranes, plays a regulatory role in controlling the degradation of MVBs by modulating the levels of the APP intracellular domain (AICD) protein [25].

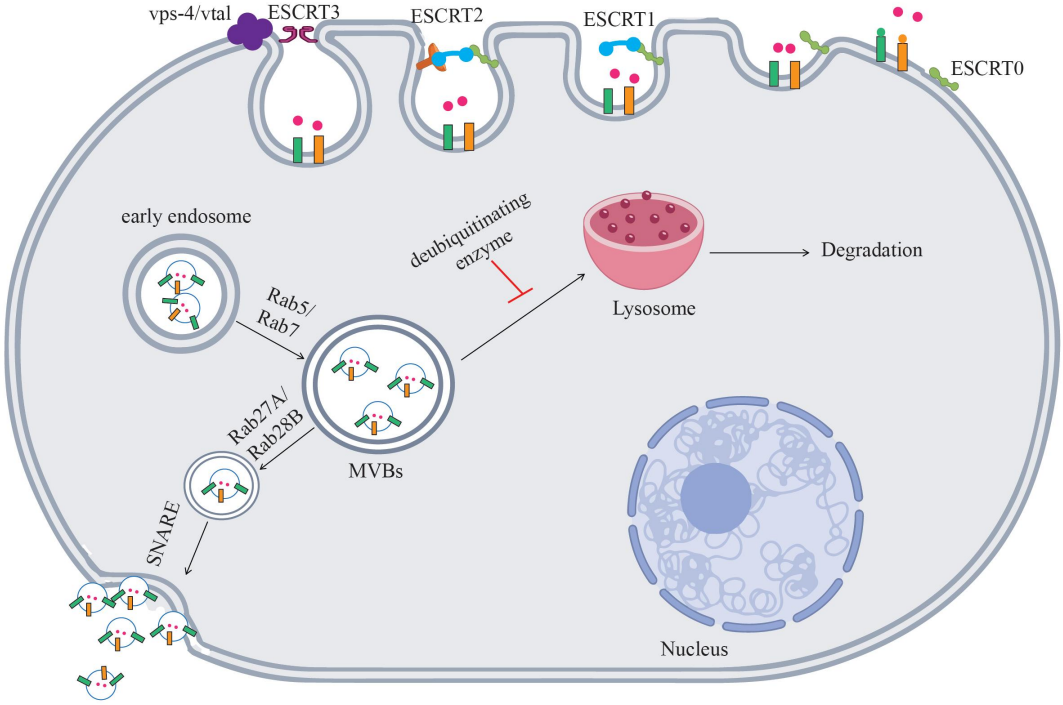

Figure 1. Exosome formation occurs through an ESCRT-dependent pathway, involving cargo sorting, the maturation of MVBs, and their merging with the cellular membrane to facilitate extracellular release.

EVs are present in numerous body fluids, derived from diverse cell types, and serve as crucial mediators of intercellular communication. Platelets, immune system components, and tumor cells are major contributors within the pool of circulating EVs, with platelets being particularly prolific in the circulatory system [26]. While most EVs in the blood originate from hematopoietic cells, additional cell populations—including adipocytes, cardiomyocytes, and tumor cells—contribute to EV release as well [27].

Cancer cells, in particular, have been shown to extensively release EVs, both into the bloodstream and surrounding tissues, which can modify the tumor milieu and drive the advancement of disease. In addition, stem cells, including embryonic and mesenchymal stem cells, secrete EVs that influence cellular behavior, tissue repair, and immune modulation. These different sources show how distinct EVs are, which could help with diagnosing and treating a number of illnesses, such as cancer and immune system problems [28,29].

3. Molecular Composition and Functional Roles of EVs

EVs represent intricate nanoscale entities built from a diverse array of molecular components, all originating from their parent cells. The type of cell and the surroundings will greatly affect the particular content of these vesicles [30]. The

molecular cargo carried by EVs is influenced by their subtype: larger EVs are typically enriched in DNA, CD9, and Annexin A1, while smaller EVs tend to have higher concentrations of CD63 and CD81 [31].

One particularly intriguing aspect of EVs is the presence of DNA, which has become a subject of growing research interest. EVs can contain different genetic materials, including circular forms, single- and double-stranded sequences, mitochondrial genomes, as well as extrachromosomal circular DNA (eccDNA) [32]. These DNA molecules reflect the genetic composition of the cells from which the EVs originate and play an important role in horizontal gene transfer. This transfer may enhance genetic variability and promote the dissemination of oncogenes, a phenomenon particularly significant in cancer development [33]. For minimally invasive diagnostic approaches, such as liquid biopsy, tumor-derived EVs have been shown to harbor tumor-specific genetic alterations, including point mutations and gene amplifications, making them highly valuable [34].

Mitochondrial DNA encapsulated within EVs has been linked to cellular stress responses and may play a role in modulating immune signaling pathways [35]. The diverse roles of DNA in EVs make it a crucial area of study for both understanding their physiological functions and for their potential use in diagnostics and therapeutic interventions.

In addition to DNA, EVs carry a variety of RNA species, which can be transferred between cells, potentially triggering phenotypic alterations in target cells [36]. These encompass messenger RNAs (mRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), microRNAs (miRNAs), and piwi-interacting RNAs (piRNAs). Non-coding RNAs (ncRNAs)—including miRNAs, lncRNAs, and circRNAs—are RNA transcripts that, rather than encoding proteins, function primarily to regulate gene expression. For example, miRNAs modulate gene expression by associating with mRNAs and preventing their translation. LncRNAs play roles in transcriptional regulation and chromatin remodeling, while circRNAs can act as miRNA sponges. Among these, miRNAs are particularly abundant and have been found to make up about 40% of all RNA reads in plasma EVs [37,38]. CircRNAs alongside lncRNAs have been shown to perform functional roles within EVs, impacting a range of biological processes, such as tumor development [39,40]. Through horizontal transfer, these RNA molecules can regulate gene expression in recipient cells, making EVs significant players in cellular communication. This further underscores their promise as candidates for therapeutic intervention or as biomarkers for disease diagnosis and monitoring.

EVs are enriched with various lipid species, such as saturated fatty acids, cholesterol, ceramide, sphingomyelin, and phosphatidylserine. Among these, ceramide is the predominant lipid and plays a critical role in EV formation during their biogenesis [41]. Compared to the membrane of their parent cells, EVs exhibit a distinct lipid composition, characterized by elevated levels of gangliosides, cholesterol, di-saturated lipids, and sphingomyelin [42]. This specific lipid signature of EVs has been associated with the stimulation of signaling pathways that promote cancer-associated phenotypes [43]. Phosphatidylserine, a lipid molecule present on the outer membrane of EVs, has emerged as a potential biomarker for cancer, owing to its connection with changes in the cell membrane of cancer cells [44].

Proteins are another important component of EVs, the exact make-up of which is conditionally and type-specific [45]. EVs are enriched with a wide array of proteins, including membrane-associated, cytosolic, extracellular matrix (ECM)-linked, and serum-derived proteins [46]. Prominent proteins within EVs comprise tetraspanins like CD82, CD81, CD63, and CD9, which play crucial roles in vesicle biogenesis and membrane merging. Additional significant proteins consist of MVB-associated molecules, including ALG-2-interacting protein X (ALIX), Rab proteins, and tumor susceptibility gene 101 (TSG101) family members, along with stress-related chaperones such as heat shock protein 70 (HSP70) and heat shock protein 90 (HSP90), both of which participate in cellular stress responses [47,48]. Moreover, EVs transport various growth factors and cytokines, such as vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), and tumor necrosis factor-alpha (TNF-α), all of which can modulate tumor progression and immune system activities [49].

Cell adhesion molecules, including integrins and intercellular adhesion molecule-1 (ICAM-1), as well as proteins associated with antigen presentation, such as MHC class I and II complexes, are also present in EVs, contributing significantly to immune regulation [50]. Furthermore, signaling molecules like Ras family proteins, GTPases, RhoA, Harvey rat sarcoma virus oncogene homolog (HRas), and proto-oncogene tyrosine-protein kinase Src (Src) are frequently detected, where they impact cellular behaviors and mediate intercellular communication. Structural proteins like actins, tubulins, and vimentin are also commonly found in EVs, reflecting their role in maintaining cell shape and facilitating vesicle transport [51].

Membrane proteins, in particular, are of great interest as potential biomarkers for disease. These proteins often reflect the specific pathological state of the donor cell, making them useful for disease diagnosis. For instance, EVs enriched with elevated amounts of programmed death-ligand 1 (PD-L1) and oncogenic receptors have been implicated in promoting cancer progression, facilitating angiogenesis, and enabling immune escape, thus positioning them as crucial targets for cancer treatment [52,53]. The broad spectrum of proteins, lipids, and nucleic acids carried by EVs highlights their potential to act as potent platforms for elucidating disease mechanisms and advancing both diagnostic and therapeutic approaches (Figure 2).

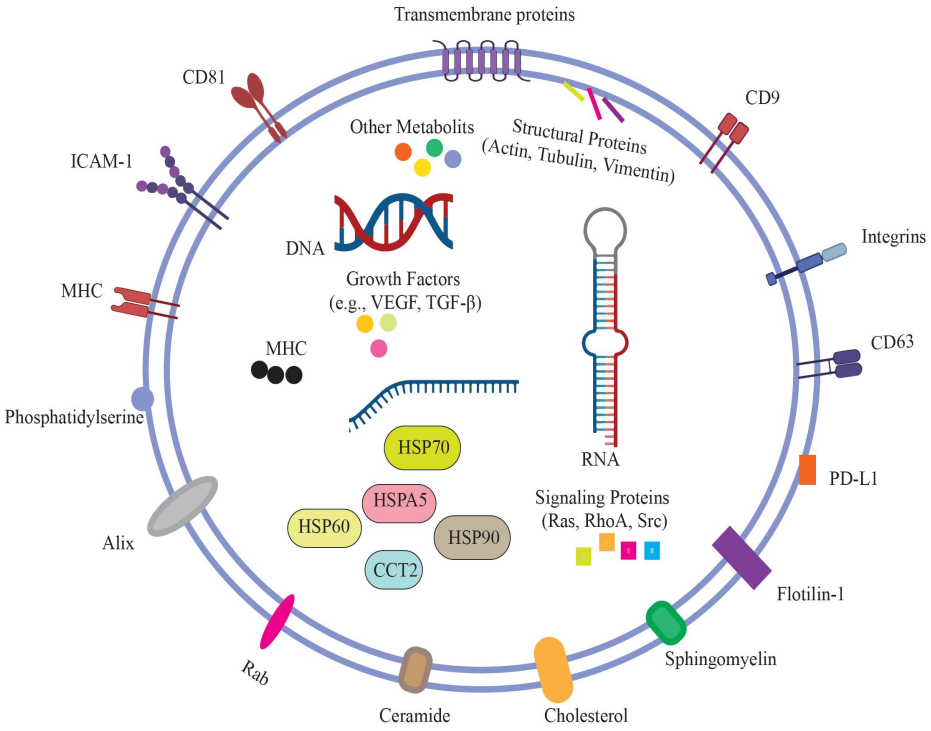

Figure 2. Molecular composition of EVs. The figure illustrates representative surface and internal components commonly found in EVs, including lipids (e.g., cholesterol, ceramide, phosphatidylserine, sphingomyelin), transmembrane proteins (e.g., CD9, CD63, CD81, integrins, ICAM-1, PD-L1), cytosolic proteins (e.g., HSP70, HSP90, HSP60, HSPA5, CCT2), signaling proteins (e.g., Ras, RhoA, Src), structural proteins (e.g., actin, tubulin, vimentin), and various nucleic acids (DNA, RNA). Growth factors such as VEGF and cytokines like TGF-β are also carried within EVs and contribute to their functional roles in intercellular communication.

In conclusion, their capacity to modulate recipient cell functions positions them as pivotal contributors to both normal physiological activities and pathological states, with a notable emphasis on cancer. Exploring the molecular cargo of EVs offers significant potential for enhancing our comprehension of disease mechanisms and for driving the development of novel diagnostic and therapeutic strategies.

4. Ferroptosis: Mechanisms and Implications in Disease

Ferroptosis entails an iron-dependent mechanism that results in the degradation of cellular membranes and consequent cellular demise [54]. The fundamental processes driving ferroptosis include disturbances in lipid and iron homeostasis, resulting in the production of reactive oxygen species (ROS) and subsequent lipid peroxidation. Morphologically, ferroptotic cells exhibit unique features such as mitochondrial contraction, loss of membrane integrity, and organelle swelling, contrasting with the nuclear fragmentation characteristic of other cell death pathways [55,56].

A hallmark of ferroptosis is the oxidative degradation of lipids, particularly targeting polyunsaturated fatty acid (PUFA) residues, particularly those incorporated into phospholipids in cellular membranes, are oxidized by ROS. This process leads to the accumulation of lipid peroxides, compromising membrane stability and eventually causing cell death [57]. Enzymes such as lysophosphatidylcholine acyltransferase 3 (LPCAT3) and Acyl-CoA synthetase long-chain family member 4 (ACSL4) play crucial roles in regulating the integration of PUFAs into cellular membranes, thereby increasing their vulnerability to oxidative damage. Recognized as a key enzyme involved in lipid peroxidation, 15-lipoxygenase (15-LOX) stands out because it changes arachidonic acid (AA), which is a key part of starting ferroptosis [58].

Iron is essential for ferroptosis, functioning as a cofactor in the Fenton reaction, which produces highly reactive hydroxyl radicals that drive lipid peroxidation. Disruptions in iron homeostasis, such as excessive intracellular iron accumulation, exacerbate ROS generation, leading to ferroptosis. The cellular uptake of iron is initiated by transferrin receptor 1 (TFR1), which mediates the transport of ferric iron (Fe^{3+}) into the cell, where it is subsequently reduced to ferrous iron (Fe^{2+}) by enzymes such as metal reductases [59]. Once inside the cell, Fe^{2+} can catalyze lipid peroxidation through the Fenton reaction. Conversely, ferroportin (FPN1), the sole recognized iron exporter in mammals, regulates iron export and is essential for regulating cellular iron homeostasis. Disruptions in this process can cause iron overload and enhanced susceptibility to ferroptosis [60].

In addition to iron metabolism and lipid peroxidation, ferroptosis is closely governed by antioxidant defense systems, notably glutathione peroxidase 4 (GPX4). GPX4 plays an essential role in shielding cells from oxidative stress by converting lipid peroxides into harmless lipid alcohols [61]. The enzyme depends on glutathione (GSH), an antioxidant that is synthesized in part by the System xc– transport system. This system imports cysteine, which is necessary for

GSH synthesis, into the cell. When GSH levels are depleted or GPX4 activity is inhibited, lipid peroxides accumulate, initiating ferroptosis (Figure 3) [62].

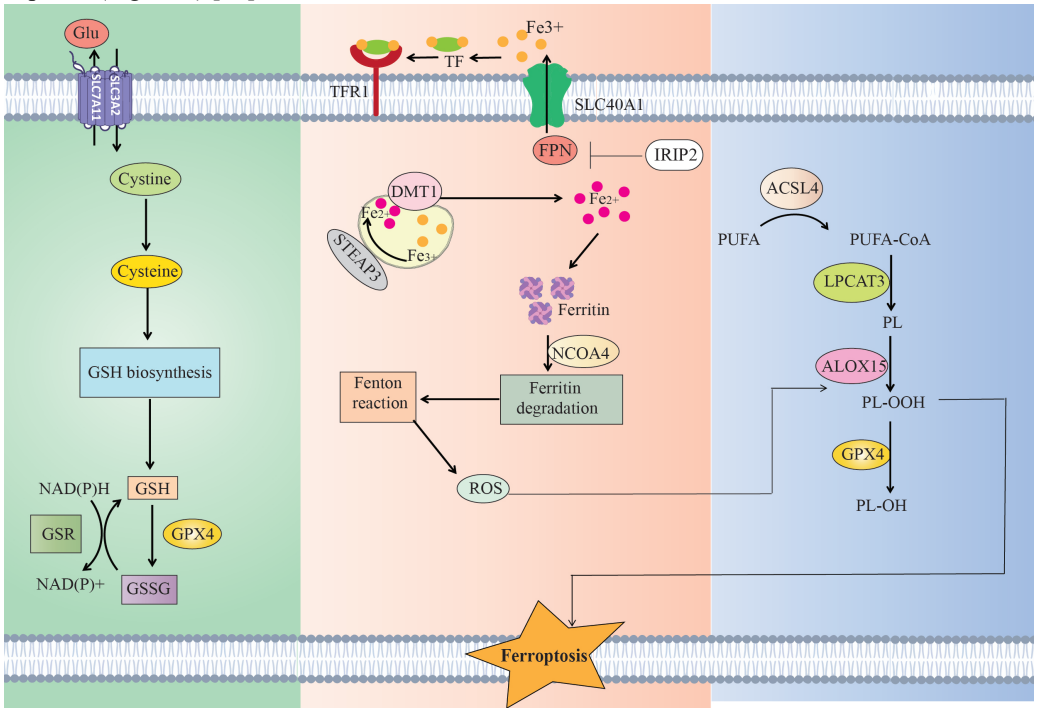

Figure 3. Ferroptosis represents a controlled mode of cell death, distinguished by excessive lipid peroxidation and iron accumulation. This process leads to the buildup of ROS as a result of disturbances in lipid and iron metabolic pathways. Key regulators include TFR1 for iron uptake, FPN1 for iron export, and GPX4, which protects against oxidative damage. Inhibition of antioxidant defenses, particularly GPX4 depletion, results in uncontrolled lipid peroxidation, loss of membrane integrity, and induction of ferroptotic cell death.

Given its dependence on iron metabolism and lipid oxidative damage, ferroptosis represents a unique vulnerability that can be therapeutically targeted, particularly in cancer and neurodegenerative diseases. The intricate balance between ferroptosis-inducing factors and protective antioxidant mechanisms determines cellular fate, making it a critical process in normal physiology as well as in disease states. Within cancer biology, ferroptosis exhibits a dual function–serving as a tumor-suppressive mechanism while also being circumvented by malignant cells through adaptive metabolic changes [63]. Understanding the regulatory networks governing ferroptosis provides valuable insights into novel therapeutic strategies aimed at restoring ferroptotic sensitivity in resistant tumor cells, including GC [10]. Furthermore, growing evidence underscores the involvement of EVs, particularly exosomes, in modulating ferroptosis through the transfer of key molecular regulators, reinforcing the need for further investigation into their therapeutic potential.

5. Role of Exosomes in Ferroptosis Regulation

Exosomes serve as crucial mediators in transporting molecular cargo that influences the regulation of ferroptosis-related gene activity within target cells. Considering the pivotal involvement of ferroptosis in tumor development, a deeper understanding of how exosomes contribute to ferroptosis modulation is essential [6].

5.1 Exosome-Mediated Inhibition of Ferroptosis

Exosomes regulate ferroptosis by modulating intracellular iron homeostasis and influencing the Fenton reaction, leading to the generation of ROS and initiating lipid oxidative damage. Exosomes mitigate ferroptosis by reducing intracellular iron concentration, thus limiting ROS generation through this reaction [6]. Exosomes regulate intracellular iron concentrations by suppressing two pivotal proteins involved in iron trafficking, namely divalent metal transporter 1 (DMT1) and iron regulatory protein 2 (IRP2).

The uptake of Fe^{3+} through the transferrin receptor (TFRC) and its subsequent reduction to Fe^{2+} mediated by six-transmembrane epithelial antigen of prostate 3 (Steap3) is followed by the release of iron from endosomes via DMT1. This mechanism accelerates ferroptosis by enhancing the Fenton reaction. Given the pivotal role of DMT1 in preserving iron homeostasis, its downregulation leads to a reduction in intracellular iron levels, thereby attenuating ferroptosis [64]. Exosomal miR-23a-3p, a microRNA originating from human umbilical cord blood mesenchymal stem cells (HUCB-MSCs), suppresses ferroptosis by targeting DMT1, a major protein involved in iron regulation [65]. Similarly, miR-19b-3p, present in exosomes derived from adipose-derived stem cells (ADSCs-19bM-Exos), modulates IRP2 expression [66]. Overexpression of IRP2 enhances TFRC levels and reduces ferroportin, leading to iron retention. Conversely, its suppression decreases intracellular iron transport, ultimately reducing ferroptosis susceptibility [66]

Exosomes also inhibit ferroptosis by interfering with ferritinophagy, a process that regulates iron metabolism by controlling the degradation of ferritin and influences ferroptosis susceptibility. When activated excessively, it elevates intracellular free iron levels, thereby inducing ferroptosis [67,68]. Nuclear receptor coactivator 4 (NCOA4) functions as a key mediator of ferritinophagy by directing the delivery of ferritin heavy chain 1 (FTH1) to autophagosomes, where lysosomal degradation subsequently releases iron [69]. Exosomes originating from vascular endothelial cells (EC-Exos) suppress ferroptosis by interfering with ferritinophagy [70].

5.2 Exosomal Activation of Ferroptosis Defense Mechanisms

Exosomes also stimulate ferroptosis defense mechanisms, notably through the upregulation of GPX4, a major antioxidant enzyme that neutralizes lipid peroxidation and prevents the onset of ferroptosis. Several studies indicate that exosomes promote GPX4 expression, thereby strengthening cellular resistance against ferroptosis [70]. Plasma-derived exosomes (RP-Exos) enhance the expression of GPX4 and suppress lipid peroxidation at the level of the plasma membrane [71].

Another ferroptosis-inhibitory mechanism involves exosomal regulation of ferroptosis suppressor protein 1 (FSP1), which operates alongside GPX4 to protect against oxidative damage. In non-small-cell lung cancer (NSCLC), the delivery of exosomal miR-4443 from cisplatin-resistant cells to cisplatin-sensitive counterparts leads to the downregulation of methyltransferase-like 3 (METTL3), which subsequently elevates FSP1 mRNA expression and attenuates ferroptosis [65].

5.3 Exosomal Modulation of Ferroptosis Through Alternative Pathways

Exosomes derived from cancer-associated fibroblasts (CAFs) can modulate ferroptosis via miR-522, which inhibits arachidonate 15-Lipoxygenase (ALOX15), a key enzyme involved in lipid hydroperoxide production and ferroptosis regulation. ALOX15, an enzyme activated through iron-catalyzed reactions, facilitates the buildup of lipid hydroperoxides, ultimately triggering ferroptosis. CAF-derived exosomal miR-522 suppresses ALOX15 expression in GC cells, thereby diminishing lipid ROS buildup and inhibiting ferroptosis. In contrast, elevated levels of exosomal miR-522 have been shown to promote ferroptosis by inhibiting ALOX15 function [72].

Exosomes can also influence ferroptosis through miRNA-mediated signaling, such as the activation of the AMPK pathway by miR-30e-5p, which reduces oxidative stress and enhances cellular resilience [73]. miR-30e-5p inhibits SP1, which normally represses AMPK activation. Since AMPK counteracts ferroptosis by phosphorylating acetyl-CoA carboxylase (ACC), its activation suppresses lipid peroxidation and enhances cellular resistance to ferroptosis. By downregulating SP1, EPC-derived exosomal miR-30e-5p facilitates AMPK phosphorylation, which in turn boosts metabolic stability and enhances oxidative stress resilience, thereby reducing ferroptosis susceptibility [73].

Long non-coding RNAs found in exosomes, such as Mir9-3hg, influence (peroxiredoxin 6) PRDX6 expression and shield cells against ferroptosis caused by oxidative stress. The Pumilio RNA-binding family member 2 (Pum2)/PRDX6 axis is employed by lncRNA Mir9-3hg, derived from bone marrow mesenchymal stem cells (BMSCs), to suppress ferroptosis in cardiomyocytes [74]. lncRNA Mir9-3hg downregulates Pum2, a regulatory factor that binds to the PRDX6 promoter and inhibits its transcription. Since PRDX6 serves as a ferroptosis suppressor, its upregulation by exosomal lncRNA Mir9-3hg effectively prevents ferroptosis [75].

These insights highlight the intricate relationship between exosomes and ferroptosis, identifying potential therapeutic targets for cancer treatment and ferroptosis-associated disorders.

6. Crosstalk between Exosomes and Ferroptosis in Gastric Cancer

Exosomes, EVs facilitating intercellular communication, significantly impact ferroptosis regulation in GC. By transferring a variety of molecular cargoes, including miRNAs, lncRNAs, circRNAs, and specific proteins, exosomes influence essential cellular activities such as lipid metabolic pathways, regulation of iron balance, and management of oxidative stress [76,77]. These regulatory mechanisms are crucial in modulating tumor development and contributing to therapy resistance. Comprehensive understanding of these interactions offers critical insights for developing novel therapeutic strategies aimed at restoring ferroptosis sensitivity and enhancing treatment efficacy.

6.1 MicroRNA-Mediated Regulation of Ferroptosis

Exosomal miRNAs suppress ferroptosis by modulating key signaling pathways involved in lipid peroxidation, oxidative damage, and iron metabolism. miR-522 derived from CAFs inhibits ALOX15, thereby reducing lipid ROS accumulation and enhancing chemoresistance [72]. Similarly, exosomal miR-21 suppresses PTEN expression, thereby activating the PI3K/AKT signaling cascade and mitigating ferroptosis triggered by oxidative stress [78]. Additionally, miR-23a promotes tumor survival by suppressing PTEN activity and triggering the AKT signaling pathway, thereby enhancing angiogenesis and resistance to ferroptosis [79].

GC cell-derived miR-214-3p confers resistance to apatinib treatment by targeting ACSL4, reducing ferroptosis-inducing efficacy [80]. Moreover, miR-19b-3p from adipose-derived stem cells and miR-23a-3p from mesenchymal stem cells inhibit ferroptosis by regulating iron metabolism through IRP2 and DMT1, respectively [81]. Natural compounds, such as QZJWD, target miR-199-3p, reversing its inhibitory effect on ACSL4 and promoting ferroptosis. Bioengineered exosomes originating from mesenchymal stem cells, modified to overexpress miR-149-5p and deliver siRNA targeting MKL-1, have demonstrated significant therapeutic potential by efficiently inducing ferroptosis and suppressing tumor growth [82].

6.2 LncRNA-Mediated Regulation of Ferroptosis

Exosomal lncRNAs significantly influence ferroptosis through interactions with lipid metabolism pathways and regulatory proteins. LncFERO enhances the translation of SCD1 via hnRNPA1 recruitment, stabilizing lipid membranes and reducing ferroptotic cell death. Chemotherapy-induced upregulation of hnRNPA1 increases lncFERO secretion, amplifying chemoresistance [83]. Similarly, lnc-ENDOG-1:1 upregulates SCD1 expression, enhancing tumor resistance against oxidative stress-induced ferroptosis [84]. Conversely, CAF-derived exosomal lncRNA DACT3-AS1 activates SIRT1, thereby increasing GC cell sensitivity to oxaliplatin-induced ferroptosis [85].

6.3 Circular RNA (circRNA)-Mediated Regulation of Ferroptosis

Exosomal circRNAs modulate ferroptosis through regulatory interactions with miRNAs and immune response pathways. CircPDSS1, elevated in GC, acts as a sponge for miR-1278, leading to upregulation of GOT1, impairing NK cell function and suppressing ferroptosis [86]. CircHIPK3 contributes to cisplatin resistance by suppressing autophagy-dependent ferroptosis via the miR-508-3p/Bcl-2/beclin1/SLC7A11 signaling cascade, highlighting the diverse functions of circRNAs in GC development and chemotherapy resistance [87].

6.4 Protein-Mediated Regulation of Ferroptosis via Exosomes

Specific proteins within exosomes intersect critically with ferroptosis regulatory pathways, highlighting potential therapeutic targets. Heat shock proteins (HSP70 and HSP90) modulate cellular stress responses influencing lipid peroxidation and ferroptotic sensitivity [88]. Proteins integral to exosome biogenesis, including ALIX, TSG101, and Rab GTPases, indirectly influence ferroptosis by altering lipid dynamics and cargo loading [31]. Furthermore, ferroptosis regulators such as GPX4, ACSL4, and SLC7A1(may be modulated by exosomal proteins, thereby affecting tumor cell survival [88]. A comprehensive investigation of protein-mediated interactions may unveil new therapeutic strategies to address treatment resistance and enhance clinical prognosis in GC (Figure 4).

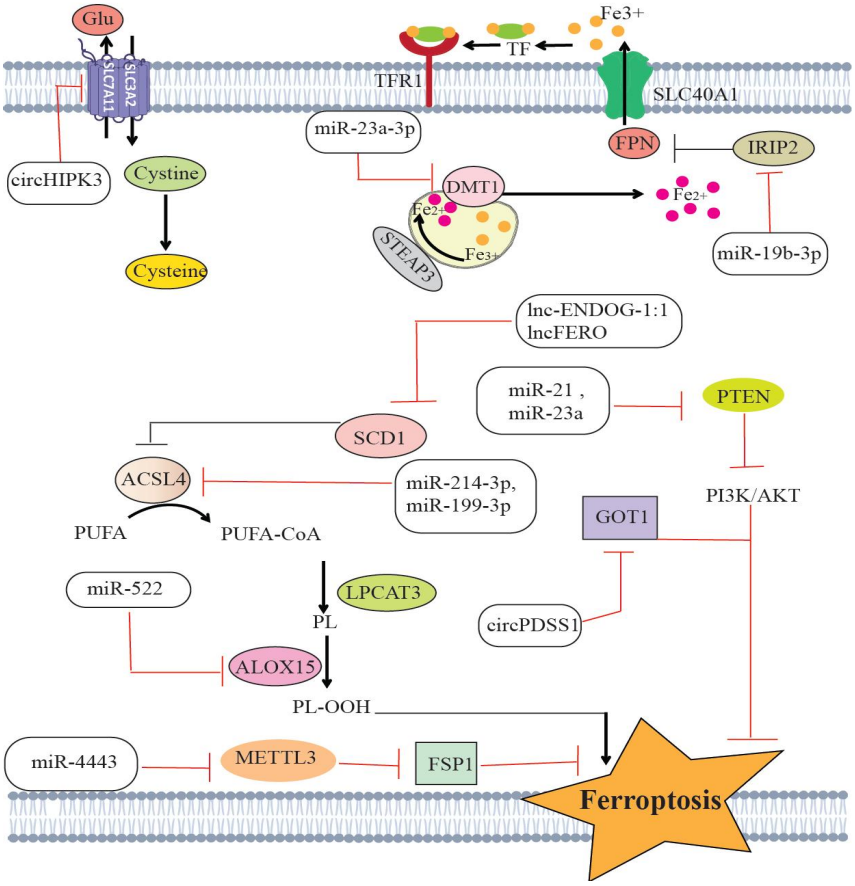

Figure 4. The involvement of exosomal non-coding RNAs in GC through modulation of the ferroptosis pathway.

6.5 Emerging Role of hnRNAs in Ferroptosis Regulation

Although less characterized, heterogeneous nuclear RNAs (hnRNAs) are gaining attention as modulators of ferroptosis. These RNAs frequently associate with RNA-binding proteins such as hnRNPA1, modulating the stability and translation of transcripts involved in ferroptosis. For example, hnRNPA1 contributes to the upregulation and exosomal secretion of lncFERO, which enhances SCD1 expression and suppresses ferroptosis [83]. Additional research is required to clarify the broader function of hnRNAs in the regulation of ferroptosis mediated by exosomes in GC.

7. Therapeutic Applications of Exosome-Mediated Ferroptosis

GC continues to pose a significant clinical challenge because of its frequent relapse and resistance to chemotherapy. Recent investigations underscore the significance of exosomal ncRNAs in modulating ferroptosis within GC. Targeting these exosomal ncRNAs or their pathways could enhance ferroptosis and improve the effectiveness of chemotherapy, offering potential new treatment options for GC patients.

7.1 Exosome-Mediated Ferroptosis Regulation

A major advancement in understanding ferroptosis regulation in GC has been the recognition of exosomal lncRNAs and their influence on ferroptosis modulation. In a study by Zhang et al., attention was directed toward lncFERO, an exosomal lncRNA originating from GC cells. They demonstrated that lncFERO interacts with mRNA and recruits hnRNPA1, promoting lipid metabolism dysregulation and suppressing ferroptosis. The study further revealed that lncFERO secretion was induced by chemotoxicity, enhancing stemness and chemotherapy resistance in GC stem cells [83]. This finding suggests that targeting the lncFERO/hnRNPA1/SCD1 signaling axis may represent a promising therapeutic approach to counteract chemotherapy resistance in GC.

Further studies on CAFs, which play a critical role in the tumor microenvironment, have highlighted their contribution to ferroptosis regulation through exosomal ncRNAs. Qu et al. investigated DACT3-AS1, an exosomal lncRNA secreted by CAFs, and observed that it inhibited cell proliferation, reduced migratory capability, and limited invasive behavior in GC cells. Notably, DACT3-AS1 promoted sensitivity to oxaliplatin by inducing ferroptosis, demonstrating the potential of CAF-derived exosomal lncRNAs in enhancing chemotherapy sensitivity and reversing drug resistance in GC [85].

Similarly, miR-522, secreted by CAFs and delivered via exosomes, was shown to inhibit ferroptosis by targeting ALOX15, a key enzyme involved in lipid peroxidation. This suppression of ferroptosis resulted in acquired resistance to chemotherapy drugs like cisplatin and paclitaxel, further emphasizing the role of CAF-derived exosomal miR-522 in mediating chemotherapy resistance in GC [85].

CircHIPK3, another exosomal RNA, has been associated with cisplatin resistance in GC. Zhang et al. demonstrated that circHIPK3 suppresses autophagy-dependent ferroptosis via the miR-508-3p/Bcl-2/beclin1/SLC7A11 signaling axis, with serum-derived exosomal circHIPK3 emerging as a promising non-invasive biomarker for assessing cisplatin resistance [72]. This study emphasizes the potential of exosomal circHIPK3 as a tool for monitoring therapeutic response and addressing drug resistance in GC treatment.

Another study by Wang et al. explored the exosomal miR-214-3p secreted by GC cells and its impact on vascular endothelial cells. Their findings revealed that miR-214-3p suppresses ACSL4, a crucial enzyme participating in lipid peroxidation during ferroptosis, consequently diminishing ferroptosis in endothelial cells and impairing the therapeutic efficacy of apatinib, a third-line treatment for advanced GC [80]. The study proposed that suppression of miR-214-3p could reinstate the anti-angiogenic activity of apatinib, offering a potential approach to improve the effectiveness of GC treatments.

7.2 Non-Exosome-Dependent Ferroptosis Regulation

Besides exosome-mediated mechanisms, non-exosomal pathways also significantly contribute to the regulation of ferroptosis in GC. For example, miR-375 has been reported to diminish the stemness of GC cells by promoting SLC7A11-dependent ferroptosis. Ni et al. demonstrated that miR-375 directly targets SLC7A11, a critical regulator of ferroptosis, thereby lowering both stemness and chemoresistance in GC cells. This study highlights the therapeutic potential of modulating the miR-375/SLC7A11 axis to decrease GC cell stemness and enhance chemotherapy response [89].

Further studies have investigated competing endogenous RNA (ceRNA) networks that regulate ferroptosis in GC. Jin et al. identified a ceRNA network involving genes such as TXNIP, TSC22D3, GABARAPL1, and CAV1. These genes exhibited differential expression in GC, and their levels correlated with patient prognosis. This ceRNA network may regulate ferroptosis and could be targeted for therapeutic intervention in GC [90].

Researchers explored how Helicobacter pylori infection contributes to GC progression by modulating ferroptosis. Their findings revealed that H. pylori virulence factors influence glutathione metabolism, ROS production, and lipid oxidation, thereby modulating ferroptosis in gastric epithelial cells. This crosstalk between H. pylori and ferroptosis underscores the potential application of ferroptosis inducers or inhibitors as therapeutic strategies for managing H. pylori-associated

GC. MT1G, a metallothionein, was found to regulate ferroptosis and autophagy in GC [91]. Meng et al. demonstrated that MT1G overexpression inhibited cell proliferation and migration while promoting ferroptosis by reducing GPX4 and SLC7A11 expression. Their study proposed that MT1G might function as a therapeutic target to promote ferroptosis in GC [92]. Finally, NEK2, a protein kinase, was shown by Wu et al. to affect ferroptosis sensitivity in GC. Suppression of NEK2 was found to enhance ferroptosis by upregulating HMOX1 expression via activation of the Keap1/Nrf2 signaling pathway [93]. This study presents NEK2 as a potential target for enhancing ferroptosis sensitivity and improving GC treatment outcomes.

The studies emphasize the complex and multifaceted role of ferroptosis in GC and its regulation by both exosomal and non-exosomal mechanisms. Exosomal ncRNAs such as lncFERO, DACT3-AS1, miR-522, circHIPK3, and miR-214-3p play critical roles in modulating ferroptosis and drug resistance in GC. These findings suggest that targeting exosomal ncRNAs or their associated pathways could provide novel therapeutic strategies to overcome chemotherapy resistance and improve treatment efficacy. Additionally, non-exosomal mechanisms, including the regulation of ferroptosis by genes like SLC7A11, TXNIP, and TSC22D3, also offer valuable insights into potential therapeutic targets. For future studies, non-exosome-dependent ferroptosis regulation mechanisms can be further explored by incorporating exosomes. Overall, the regulation of ferroptosis in GC, through both exosomal and non-exosomal pathways, holds significant promise for the development of more effective treatment strategies for GC patients.

8. Research Gaps and Challenges

While the relationship between exosomes and ferroptosis in GC has attracted growing interest, numerous unresolved questions continue to impede progress in this area. One major limitation lies in the insufficient understanding of the precise exosomal carg–particularly microRNAs, lipids, and proteins–and their specific molecular targets within ferroptosis-related pathways. While studies have highlighted exosomal miR-522 as a modulator of ferroptosis in GC by targeting ALOX15, the involvement of other regulators such as GPX4 in this context remains to be elucidated [88].

The lack of standardized protocols for isolating and characterizing exosomes has substantially restricted the ability to reproduce and compare findings across different studies. Methods including ultracentrifugation, polymer-assisted precipitation, and microfluidic technologies produce exosomal populations with differing purity, size distribution, and cargo characteristics, thereby introducing considerable heterogeneity in experimental results [94]. Moreover, despite the growing interest in exosome-mediated ferroptosis, most functional evidence remains restricted to *in vitro* systems using GC cell lines, with relatively few studies utilizing *in vivo* models that accurately mimic the tumor microenvironment [95,96].

Another critical challenge lies in the translation of mechanistic findings into clinical applications. While the potential of using exosomes as vehicles for ferroptosis induction is theoretically promising, significant challenges remain, including issues related to exosome loading, targeting specificity, immune evasion, and large-scale production. Furthermore, the role of exosome-mediated ferroptosis within the complex and immunologically diverse TME, especially under hypoxic conditions in GC, has yet to be systematically examined [97,98].

9. Future Perspectives on Exosomal Ferroptosis Modulation

Ferroptosis has emerged as a crucial aspect of cancer research, with exosomes–membrane-bound vesicles facilitating intercellular communication–playing a pivotal role in modulating this form of regulated cell death [99]. Despite significant advancements in understanding exosome-mediated ferroptosis suppression, multiple knowledge gaps persist, necessitating further investigation into unexplored regulatory mechanisms, therapeutic innovations, and their diagnostic and prognostic implications.

One critical area requiring further exploration is the mechanistic underpinnings of exosomal ferroptosis suppression. While GPX4 overexpression has been extensively studied in ferroptosis resistance, Other critical elements of the Xc-GSH-GPX4 axis, such as SLC7A11 and solute carrier family 3 member 2 (SLC3A2), are still inadequately characterized within the exosomal framework. Likewise, emerging evidence indicates that exosomal miR-4443 regulates FSP1 via m6A modification, playing a role in the development of cisplatin resistance in NSCLC [100]. However, whether miR-4443 influences additional ferroptosis-related pathways remains an open question. Additionally, the guanosine triphosphate cyclohydrolase 1 (GCH1)–tetrahydrobiopterin (BH4) pathway, a recently identified ferroptosis defense system, has not been extensively explored concerning exosomal interactions. Other molecules, such as ALOX15, AMP-activated protein kinase (AMPK), and PRDX6, have been implicated in exosome-ferroptosis interactions, but a more comprehensive understanding of their regulatory networks is required [101,102].

From a therapeutic standpoint, exosomes present both challenges and opportunities in cancer treatment. On one hand, they mediate ferroptosis resistance and drug resistance, while on the other, they offer potential as targeted drug-delivery vehicles. In NSCLC, exosomal miR-4443 contributes to cisplatin resistance by modifying FSP1, suggesting that restoring METTL3/FSP1-mediated ferroptosis could potentially overcome drug resistance [100]. Another promising therapeutic avenue involves targeting prominin-2 (PROM2), which facilitates iron export through exosomes, preventing ferroptosis and supporting tumor survival. Heat shock factor 1 (HSF1) has been identified as a positive regulator of

PROM2, making it a potential therapeutic target to sensitize chemo-resistant tumors to ferroptosis-inducing drugs [101,102]. Nevertheless, additional studies are required to better define the specificity and ensure the safety of these interventions.

Additionally, exosomes are gaining recognition as natural carriers for therapeutic agents due to their biocompatibility and targeted delivery potential [103]. Current efforts focus on loading erastin, a system Xc− inhibitor, into exosomes to induce ferroptosis in cancer cells. This strategy can be further expanded by incorporating additional ferroptosis-inducing compounds. For example, temozolomide, a frontline chemotherapeutic agent for glioblastoma, has been implicated in ferroptosis induction through DMT1 modulation, presenting a potential avenue for combining standard chemotherapies with exosome-based therapies [104].

Beyond therapeutic applications, exosomes are emerging as valuable diagnostic and prognostic tools in cancer research. Liquid biopsy techniques leveraging exosomal biomarkers offer non-invasive cancer detection and monitoring. Ferroptosis-associated exosomal markers have been implicated in multiple malignancies, including hepatocellular carcinoma (HCC) and prostate cancer [105,106]. Lipidomic profiling of exosomes from patient plasma has shown promise in enhancing early HCC detection in individuals with cirrhosis, while molecular lipids in urinary exosomes have demonstrated potential as prostate cancer biomarkers [107].

A notable prognostic example involves pancreatic ductal adenocarcinoma (PDAC), where oxidative stress induces autophagy-dependent ferroptosis and the subsequent release of exosomal KRASG12D. These KRASG12D-containing exosomes stimulate fatty acid oxidation pathways driven by signal transducer and activator of transcription 3 (STAT3) and induce the polarization of tumor-associated macrophages toward an M2-like phenotype, which is associated with unfavorable clinical outcomes [108]. The ability to track such ferroptosis-related exosomal markers highlights their potential in refining cancer diagnostics and prognostic assessments across diverse tumor types.

Taken together, exosomes represent a promising frontier in ferroptosis research, with implications spanning mechanistic discoveries, therapeutic advancements, and diagnostic innovations. Future studies should focus on uncovering novel exosome-mediated regulatory pathways, developing exosome-based drug delivery systems, and establishing ferroptosis-related exosomal biomarkers for precision oncology. Expanding our understanding of these areas will support the advancement of exosome-mediated ferroptosis modulation toward clinical implementation, potentially enhancing cancer therapies and patient outcomes.

10. Conclusions

Exosomes are pivotal in regulating ferroptosis in GC, functioning as essential mediators of intercellular communication and impacting tumor metabolism, cell survival, and resistance to therapy. By transferring regulatory molecules such as miRNAs, lncRNAs, and proteins, exosomes suppress ferroptotic cell death through the regulation of lipid peroxidation, iron homeostasis, and antioxidant defenses. These mechanisms not only facilitate tumor progression but also contribute to chemoresistance and immune evasion, posing significant challenges in cancer treatment.

Given their role in ferroptosis inhibition, exosomes have emerged as potential therapeutic targets. Strategies aimed at disrupting exosome-mediated suppression of ferroptosis–such as blocking the secretion of oncogenic miRNAs, restoring oxidative lipid damage, or employing engineered exosomes for drug delivery–offer promising directions for cancer therapy. Furthermore, exosomes hold significant potential as non-invasive biomarkers, providing valuable insights into tumor dynamics and treatment responses through liquid biopsy approaches. Moving forward, further exploration of exosome-ferroptosis interactions will be essential to develop effective therapeutic interventions. A deeper understanding of these mechanisms could lead to novel strategies that enhance ferroptosis sensitivity, improve treatment efficacy, and ultimately contribute to better clinical outcomes in GC.

Competing Interests

The authors declare no competing interests

Authors' Contributions

Z.R. and F.S. contributed to the conceptualization, writing the original draft, review, editing, and approved the final manuscript.

Abbreviations

ALOX15: Arachidonate 15-Lipoxygenase
AMPK: AMP-Activated Protein Kinase
BMSC: Bone Marrow Mesenchymal Stem Cell
CAF: Cancer-Associated Fibroblast
circRNA: Circular RNA

DMT1: Divalent Metal Transporter 1
ECM: Extracellular Matrix
EV: Extracellular Vesicle
FPN1: Ferroportin 1
FSP1: Ferroptosis Suppressor Protein 1
GC: Gastric Cancer
GPX4: Glutathione Peroxidase 4
GSH: Glutathione
HCC: Hepatocellular Carcinoma
ICAM-1: Intercellular Adhesion Molecule 1
IRP2: Iron Regulatory Protein 2
lncRNA: Long Non-Coding RNA
LPCAT3: Lysophosphatidylcholine Acyltransferase 3
MVB: Multivesicular Body
mRNA: Messenger RNA
NSCLC: Non-Small Cell Lung Cancer
NCOA4: Nuclear Receptor Coactivator 4
PDAC: Pancreatic Ductal Adenocarcinoma
PRDX6: Peroxiredoxin 6
PUFA: Polyunsaturated Fatty Acid
ROS: Reactive Oxygen Species
SCD1: Stearoyl-Coenzyme A Desaturase 1
SNARE: Soluble N-ethylmaleimide-Sensitive Factor Attachment Protein Receptor
SP1: Specificity Protein 1
STAT3: Signal Transducer and Activator of Transcription 3
TFRC: Transferrin Receptor
TME: Tumor Microenvironment
VEGF: Vascular Endothelial Growth Factor

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