The putative role of ferroptosis in gastric cancer: a review

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Ferroptosis is a unique cell death modality triggered by iron-dependent lipid peroxidation, with cysteine metabolism and glutathione-dependent antioxidant defence responses as the primary triggering mechanisms. Ferroptosis is an independent tumour suppression mechanism and has been implicated in various disorders. In tumourigenesis, ferroptosis plays a dual role in promoting and inhibiting tumours. P53, NFE2L2, BAP1, HIF, and other tumour suppressor genes regulate ferroptosis, releasing damage-associated molecular patterns or lipid metabolites to influence cellular immune responses. Ferroptosis is also involved in tumour suppression and metabolism. The combination of amino acid, lipid, and iron metabolism is involved in the initiation and execution of ferroptosis, and metabolic regulatory mechanisms also play roles in malignancies. Most investigations into ferroptosis in gastric cancer are concentrated on predictive models, not the underlying processes. This review investigates the underlying mechanisms of ferroptosis, tumour suppressor genes, and the tumour microenvironment. ***European Journal of Cancer Prevention*** **32: 575–583 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Gastric cancer is a heterogeneous disease characterized by numerous genetic mutations and epigenetic alterations that disrupt the balance between oncogenic and tumour suppressor pathways. This imbalance causes gastric cancer cell proliferation and cancer cell death. Ferroptosis is a controlled form of cell death that differs morphologically, biochemically, and genetically from apoptosis, necrosis, and necroptosis. It is characterized by iron-dependent reactive oxygen species (ROS) generation, lipid peroxidation, and iron accumulation (Chen *et al*., 2021a). Ferroptosis-related genes can be classified into three categories: drivers that promote ferroptosis, suppressors that inhibit ferroptosis, and markers that regulate ferroptosis. These genes regulate ferroptosis and other cellular processes (Zhou and Bao, 2020). Ferroptosis may play a role in tumour formation and the resistance of certain cancers, including gastric cancer, to medications, and therefore targeting ferroptosis may be an effective therapeutic strategy for gastric cancer (Alvarez *et al*., 2017; Zhang *et al*., 2020a). Hence, this review focuses on the correlation between ferroptosis and gastric cancer from several perspectives, including ferroptosis mechanisms, tumour suppressor genes, the tumour microenvironment (TME), and metabolic regulation.

Ferroptosis is a novel form of cell death

Ferroptosis mechanisms that have been discovered thus far are primarily based on cysteine metabolism and glutathione-lysine antioxidant defence (Table 1 and Fig. 1). Cysteine, a critical amino acid for cell viability, generally enters cells in dimerized and oxidized forms. The glutamate/cystine antiporter (System XC-), a cystine-glutamate antiporter encoded by the SLC7A11 gene, which encodes the System XC-substrate-specific subunit that mediates the uptake of extracellular cystine in exchange for intracellular glutamate release (Lin *et al*., 2020). SLCA711 expression is closely controlled by oncoproteins [such as nuclear factor erythroid 2-related factor 2 (NRF2)] and tumour suppressors (including p53, BAP1, and ARF). Rastin was first described as a System XC inhibitor that efficiently inhibits cellular cystine absorption and depletes glutathione, which is a typical ferroptosis inducer (Yagoda *et al*., 2007). Glutathione is also an essential cellular antioxidant that maintains cellular redox equilibrium and protects cells from oxidative damage (Ursini and Maiorino, 2020). Inactivation of the glutathione-dependent phospholipid peroxidase GPX4 leads to an imbalance in the antioxidant defence system, leaving cells vulnerable to lipid peroxidation and ultimately leading to ferroptosis (Forcina and Dixon, 2019). In addition, the cysteine-tRNA synthetase CARS has been identified as essential for ferroptosis (Hayano *et al*., 2016). CARS inhibition led to increased transcriptional upregulation of serine metabolism and transsulfuration pathway components, making methionine available for cysteine production. This process maintained the stability of cysteine and glutathione levels. ACSL4 is also a crucial component in ferroptosis, contributing to the oxidation of membrane phospholipids, which may influence ferroptosis activation (Feng *et al*., 2021). FSP1 is a ferroptosis inhibitor that exerts effects independent of the canonical GPX4 signalling pathway. A study found that

Fig. 1

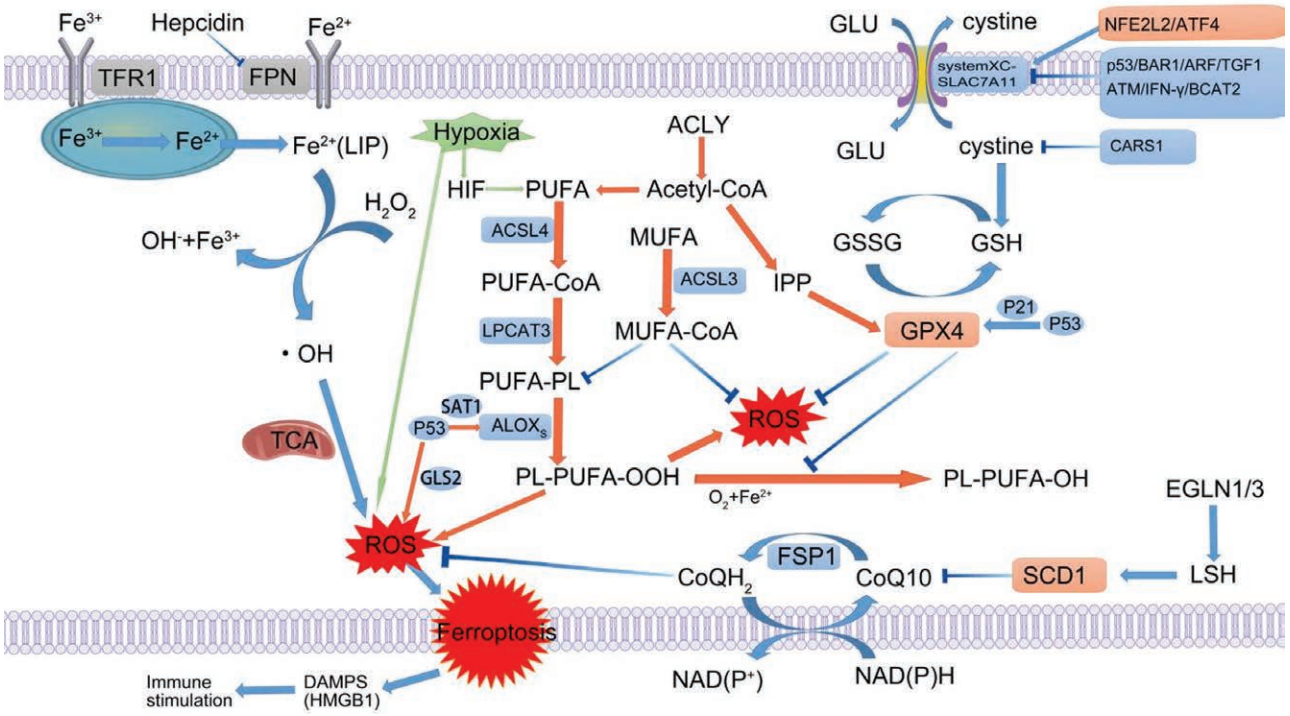

Diagram of the core regulatory mechanism of tumor ferroptosis (green is the effect of hypoxia on ferroptosis, orange is the effect of lipid metabolism on ferroptosis). ACLY, ATP citrate lyase; ACSL4, acyl-CoA synthetase long-chain family member 4; AGEs, advanced glycation end products; ALOXS, arachidonate lipoxygenase; ARF, cyclin-dependent kinase inhibitor 2A; BCAT2, branched chain amino acid transaminase 2; CARS1, cysteinyl-tRNA synthetase; CRC, colorectal cancer; DAMPS, damage- associated molecular patterns; DPP4, dipeptidyl peptidase 4; DUSP1, dual-specificity phosphatase 1; EGLN1, egl-9 family hypoxia-inducible factor 1/3; EGLN1/3, Egl-9 family hypoxia-inducible factor 1/3; EMT, epithelial–mesenchymal transition; FASN, fatty acid synthase; Fe2+, ferrous iron; Fe3+, ferric iron; FPN, ferroportin; FSP1, ferroptosis suppressor protein 1; GC, gastric cancer; GLS2, glutaminase 2; Glu, glutamate; GPX4, glutathione peroxidase; GSH, L-glutathione; GSSG, L-glutathione oxidized; HIF, hypoxia- inducible factor; IFN-γ, interferon-γ; IPP, intracisternal A particle-promoted polypeptide; LIP, labile iron pool; LPCAT3, lysophosphatidylcholine acyltransferase 3; LSH, lymphoid tissue-specific helicase; MUFA, monounsaturated fatty acid; NFE2L2, nuclear factor, erythroid 2-like 2; NOX4, NADPH oxidase 4; PUFA, polyunsaturated fatty acid; PUFA-PL, phospholipid with polyunsaturated fatty acid; RLS, reactive lipid species; ROS, reactive oxygen species; SCD1, steroyl CoA desaturase; SLC7A11, solute carrier family 7 member 11; SNPs, single-nucleotide polymorphisms; TANs, tumour-associated neutrophils; TCA, mitochondrial tricarboxylic acid cycle; TFR1, transferrin receptor 1; TME, tumour microenvironment; TRAIL, TNF-related apoptosis-inducing ligand; TXNIP, thioredoxin-interacting protein; VCAM-1, vascular cell adhesion molecule-1.

the myristoylation of FSP1 was essential to the ability of FSP1 to inhibit ferroptosis. FSP1 prevents ferroptosis by lowering CoQ10 levels and preventing lipid oxidation (Bersuker *et al*., 2019; Doll *et al*., 2019). Hence, ferroptosis is related to various pathophysiological processes and diseases, including cancer, type II diabetes, cardiovascular disease, and neurodegeneration (Stockwell *et al*., 2017; Sha *et al*., 2021). Furthermore, because tumour cells with specific oncogenic mutations are highly susceptible to ferroptosis, inducing ferroptosis in these tumour cells might result in a robust therapeutic response.

Ferroptosis is a nontumourigenic tumour suppression mechanism

Ferroptosis is a tumour-suppressing process that may influence numerous biological features of cancers, including the epithelial–mesenchymal transition (EMT), immunological responses, genomic alterations, disease progression, and drug resistance (Granofszky *et al*., 2018; Chen *et al*., 2021b). High iron levels in cancer cells enhance the proliferative and anabolic/metabolic activities of the cancer cells, and sensitivity to ferroptosis induction is associated with an increased iron requirement (Battaglia *et al*., 2020). Tumour cells alter ferroptosis sensitivity by changing iron consumption patterns, autophagy, and mitochondrial iron levels (Battaglia *et al*., 2020; Liu *et al*., 2020). Mesenchymal dedifferentiated cancer cells and EMT/metastasis-prone cancer cells were identified as relatively susceptible to ferroptosis (Viswanathan *et al*., 2017; Guan *et al*., 2021). These findings demonstrate that ferroptosis activation in tumour cells, as mediated through, for example, GPX4 and ACSL4, lowers the tumour necrosis rate and invasiveness; however, the physiological role of ferroptosis in tumour suppression and the genetic mechanisms involved in overcoming this tumour-suppressing process remain unknown.

Table 1 The action pathway of ferroptosis core gene

	Suppressor	Driver
Iron absorption and efflux		Tfr1, Tfr2, DMT1
Iron storage		Ferritin
Ferriregulatory protein	FBXL5	IRP1, IRP2
Heat shock protein	HSF-1, HSBP1, HSPA5	
Iron autophagy regulatory factor		NCOA4
Redox-regulated	NRF2, GPX4, FSP1, HO-1 NQO1, CISD1	ALOXs, PEBP1, NOXs DPP4/CD26, VDAC2/3
Glutathione steady-state regulation	SLC7A11, MUC1, GCLC	SLC1A5, GLS2, CARS, CHAC1
Lipid metabolism regulation	LSH/HELLS, SCD, FADS2	ACSL4, ACSL3, LPCAT3, CS
Regulation of glucose metabolism	PHGDH, G6PD, ME1	PHKG2
The mevalerate pathway	HMGCR	SQLE, SQS
Transcription factor	STAT3, ATF4, HIF1A	ATF3, BACH1, P53, ATF4, HIF1A, ZEB1, NRF2, YAP/TAZ

DPP4, dipeptidyl peptidase 4, LSH, lymphoid-specific helicase.

Ferroptosis and tumour suppressor genes

The p53 tumour suppressor pathway is inactivated in cancer (Kastenhuber and Lowe, 2017). Many p53 functions, including its involvement in cell cycle arrest, senescence, and apoptosis, have been linked to tumour suppression, including ferroptosis-mediated through regulation of SLC7A11 transcription (Kang *et al*, 2019). Thus, ferroptosis may be necessary for tumour suppression, particularly in the absence of modulators of cell cycle arrest, senescence, or apoptosis. In addition to regulating SLC7A11, p53 can induce SAT1 expression, enhancing ALOX15 activity, which modifies tumour cell sensitivity to ferroptosis (Ou *et al*., 2016). PTGS2 and CBS, two ferroptosis markers, have also been identified as p53 target genes (Enache *et al*., 2018); however, p53 can also inhibit ferroptosis in certain cancer cells by regulating p21 or dipeptidyl peptidase 4 (DPP4) expression (Xie *et al*., 2017; Venkatesh *et al*, 2020). The cell cycle regulatory protein p21 is an essential p53 target gene because it can slow the cell cycle and initiate the replacement of the raw materials needed to generate nucleic acids, NADPH, and glutathione, preventing ferroptosis (Venkatesh *et al*, 2020). The p53 protein may also directly bind DPP4 in the nucleus, preventing it from binding NOX1 in the cytoplasm and reducing the ferroptosis rate (Xie *et al*., 2017). These findings suggest the complicated roles played by ferroptosis in cancer, highlighting the need for further research. P53 is not the sole tumour suppressor that regulates ferroptosis. Similar to p53, BAP1 is commonly deleted or mutated in human malignancies (Carbone *et al*., 2020). BAP1, a tumour suppressor, has been shown to reduce SLC7A11 expression and promote ferroptosis by regulating H2A ubiquitination at the SLC7A11 promoter (Zhang *et al*., 2019).

NFE2L2 is a master regulator of oxidative stress signalling and exhibits a dual function in tumour development. Low constitutive NFE2L2 activity favours early carcinogenesis, whereas high constitutive NFE2L2 activity promotes tumour progression and therapeutic resistance (Dodson *et al*., 2019).

NFE2L2 expression in cancer cells is regulated by KEAP1-mediated protein degradation and the transcriptional modulation of oncogene signalling pathways such as KRAS-BRAF-MYC (Rojo de la Vega *et al*., 2018). The NFE2L2 signalling pathway has been demonstrated to inhibit ferroptosis by transactivating cytoprotective genes linked to iron metabolism (SLC40A1, MT1G, HMOX1, and FTH1) and glutathione metabolism (SLC7A11, GCLM, and CHAC1) and genes encoding ROS detoxification enzymes (TXNRD1, AKR1C1, AKR1C2, SESN2, GSTP1, and NQO1) (Anandhan *et al*., 2020). NFE2L2 promotes SLC7A11 expression and activity, whereas TP53, BAP1, and BECN1 exert the opposite effects (Sun *et al*., 2016). During ferroptosis, glutathione levels are altered through this dual-regulation mechanism. Other glutathione sources include the transsulfuration pathway, which is inhibited by aminoacyl-tRNA synthetases such as CARS1. Notably, single-nucleotide polymorphisms in CARS1 (rs384490, rs729662, rs2071101, and rs7394702) increase the risk of gastric cancer (Tian *et al*., 2017).

HIF promotes tumour growth and treatment resistance (Lee *et al*, 2021). HIF1 and EPAS1 expression is upregulated in many cancers and is linked to poor patient outcomes (Ivan and Kaelin, 2017). HIF seems to exhibit a dual function in cancer cell ferroptosis regulation. On the one hand, iron phagocytosis is inhibited by hypoxia, while mitochondrial ferritin expression is increased (Fuhrmann *et al*., 2020). On the other hand, EPAS1 activation increases lipid- and iron-regulator gene expression in tumours, making these tumours more susceptible to ferroptosis and increasing ROS levels via irreversible cysteine oxidation (Singhal *et al*., 2021). Therefore, effective control of HIF-mediated signalling is essential for maintaining lipid homeostasis and regulation of ferroptosis.

Ferroptosis and the tumour microenvironment

Ferroptosis promotes and suppresses tumour growth by releasing damage-associated molecular patterns (DAMPs) into the TME and activating immune responses to trigger ferroptosis (Murao *et al*., 2021). DAMPs may cause immunogenic cell death, boosting antitumour immunity; however, DAMPs stimulate inflammatory responses that promote tumour development, indicating that ferroptosis influences the TME and that cancer cells may regulate ferroptosis (Sun *et al*., 2020a). In pancancer analyses, tumours sensitive to ferroptosis exhibited more CD8 + T cells (Tang *et al*., 2020). CD8 + T lymphocytes may secrete interferon γ to inhibit SLC3A2 and SLC7A11 expression and cystine absorption by tumour cells (Wang *et al*., 2019). Immune cells such as T cells, B cells, and macrophages

undergo ferroptosis under specific circumstances, controlling tumour immunity. Reduced production of cytotoxic cytokines due to ferroptosis driven by T-cell CD36 expression and coupled with anti-PD-1 leads to diminished T-cell antitumour effects (Ma *et al*., 2021).

HMGB1 is released by ferroptotic cancer cells and promotes inflammatory responses in macrophages by binding to advanced glycation end products (AGEs). This ferroptosis-mediated inflammatory response is limited by the genetic and pharmacological inhibition mediated by the HMGB1-AGE pathway. Furthermore, pancreatic cancer cells may secrete exosomes carrying KRAS-G12D, and these exosomes are engulfed by macrophages. The uptake of AGEs leads to M2 macrophage polarization and tumour growth promotion (Wen *et al*., 2019; Dai *et al*., 2020). In addition to the aforementioned proteins, a complex network of nonproteinaceous DAMPs (such as ATP, host DNA, and lipid mediators) may be produced during ferroptosis and influence antitumour immunity (Shi *et al*., 2022). The long-term effects of ferroptosis on tumour immunity depend on interactions between cancer cells and various immune cell subsets. For example, the lymphatic system promotes tumour spreading by boosting ACSL3-dependent monounsaturated fatty acid (MUFA) synthesis (Quan *et al*., 2021); however, the role played by neutrophils in cancer remains controversial (Shaul and Fridlender, 2019; Yee *et al*., 2020). Early tumour development attracts neutrophils to damaged tissues, creating a positive feedback loop and leading to tumour necrosis (Yee *et al*., 2020). In contrast, neutrophils in various cancers are called tumour-associated neutrophils and are closely associated with poor prognosis in various advanced cancers, such as gastric cancer and colorectal cancer (CRC) (Mizuno *et al*., 2019; Wang *et al*., 2020b).

Neutrophils can promote tumour growth by releasing cytokines that affect the extracellular matrix, stimulating angiogenesis and regulating the behaviours of other inflammatory cells. They can also absorb and store iron and export proteins. Neutrophil cytotoxicity may lead to anticancer effects. Studies on neutrophil-induced cytotoxicity revealed that neutrophil-derived ROS, TNF-related apoptosis-inducing ligand, and hydrogen peroxide are critical for neutralizing granulocyte-mediated tumour cell death (Yuan *et al*., 2018); however, not all mature neutrophils can induce cell death. High-density mature neutrophils can lead to tumour cell death, but low-density or immature neutrophils exert no impact (Sagiv *et al*., 2015). Activated mature neutrophils promote ferroptosis by transporting myeloperoxidase-containing granules into tumour cells (Yee *et al*., 2020).

Ferroptosis is related to tumour suppression and metabolism

Recent studies have shown that ferroptosis involves pathways linking tumour suppression and metabolism. The initiation and execution of ferroptosis depend on the interaction between amino acid metabolism, lipid metabolism, and iron metabolism pathways, and metabolic regulators also play roles in tumours.

Ferroptosis and amino acid metabolism

Amino acids are essential substances metabolized by almost all types of cells. Recent tumour metabolomic research has linked numerous amino acids to cancer growth and diverse metabolic signatures in tumour cells, indicating their possible roles as biomarkers and keys to disease aetiologies. Wiggins *et al.* (2015) observed that gastric cancer patients presented with lower tyrosine, phenylalanine, and tryptophan levels. Citrulline, valine, tryptophan, and histidine levels were considerably reduced in gastric cancer patients, whereas increased levels of isoleucine and lysine were observed (Miyagi *et al*., 2011). Jing *et al.* (2018) discovered that gastric cancer patients presented with lower glutamine, histidine, arginine, and tryptophan levels and higher ornithine concentrations, and these markers showed excellent specificity and sensitivity for use in discriminating gastric cancer from stomach ulcers. Specifically, leucine, threonine, and serine are potential biomarkers for early gastric cancer (Liu *et al*., 2018).

Furthermore, arginine has been reported to be a prognostic factor for gastric cancer (Shi et al., 2021). Tumour cells overexpress amino acid transporters to accommodate increases in amino acid requirements. The cationic amino acid transporter PQLC2 is involved in the cysteine depletion process and is considered a possible therapeutic target in gastric cancer (Jeung *et al*., 2019).

In ferroptosis, cystine is transported by system XC- to produce glutathione. Recent research based on CRISPR/Cas9 editing revealed a previously unknown ferroptosis inhibitor, BCAT2, which controls intracellular glutamate levels, activates selective antagonistic system Xc inhibition and protects liver and pancreatic cancer cells against ferroptosis *in vitro* and *in vivo* (Wang *et al*., 2021a). ATF4, a ferroptosis inhibitor, has also been identified as a promoter of gastric cancer progression, possibly by regulating amino acid metabolism and autophagy pathways (Wang *et al*., 2021b).

Ferroptosis and lipid metabolism

The regulation of lipid metabolism, such as lipid uptake, synthesis, and hydrolysis, is essential for maintaining cellular homeostasis. Lipid production, storage, and degradation are closely linked to ferroptosis and lipid peroxidation (Röhrig and Schulze, 2016). Moreover, tumour cells also activate adipogenesis to maintain their high metabolic demands (Snaebjornsson *et al*., 2020). Therefore, lipid metabolism plays a role in ferroptosis and carcinogenesis.

Lipid peroxides form some of the ROS found in all living organisms and are the principal inducers of ferroptosis

(Latunde-Dada, 2017). In the presence of ferrous iron, LPO is transformed into alkoxy radicals, which then combine with polyunsaturated fatty acids (PUFAs) to initiate a lipid radical chain reaction resulting in hydroxy fatty acid or reactive hazardous aldehyde production. These reactive lipid species may induce toxicity, stimulate lipid peroxidation, alter critical proteins, or drive cell death signalling cascades (Higdon *et al*., 2012). Exogenous MUFAs and PUFAs regulate intracellular lipid peroxidation and hence influence cell ferroptosis susceptibility (Yang *et al*., 2016). Exogenous MUFAs may displace PUFAs from phospholipids in the plasma membrane, reducing their oxidation susceptibility (Magtanong *et al*., 2019).

Cancer cell lipid metabolism is dynamically interconnected to the TME (Vriens *et al*., 2019). Oncogenic signalling and lipid metabolism promote cancer cell growth, survival, proliferation, migration, invasion, and metastasis. Induction of extracellular fatty acid transporters (CD36, SLC27, FABPs) (Su and Abumrad, 2009) and stromal cells (adipocytes and fibroblasts) may encourage tumour cells to take up extracellular fatty acids and trigger mitotic signalling (Ladanyi *et al*., 2018; Auciello *et al*., 2019). Cachexia cancer cells quickly release factors that cause excessive fatty acid oxidation (FAO) in human myotubes, causing oxidative stress, p38 activation, and decreased muscle growth (Fukawa *et al*., 2016). High levels of saturated membrane lipids due to lipid accumulation in gastric cancer patients protect cancer cells from ROS-induced damage (Kopecka *et al*., 2020).

Lipid metabolism genes may play roles in cancer promotion. Reduced production of ATP citrate lyase, which is a catalyst for the first reaction in de-novo fat synthesis, decreases the viability of tumour cells and limits their proliferation, invasion, and metastasis (Khwairakpam *et al*., 2020). Inhibition of the fatty acid synthase gene reduces the fatty acid synthesis rate and increases malonyl-CoA build-up, which inhibits carnitine palmitoyltransferase-mediated FAO. Furthermore, FAO may lead to ATP and NADPH production, eliminating potentially toxic lipids and causing subsequent cell cycle arrest and tumour cell apoptosis (Carracedo *et al*., 2013; Schroeder *et al*., 2021). Sun *et al.* (2020b) found that overexpression of fat cell differentiation-related proteins may induce cellular hypoxia, decreasing the ferroptosis rate and increasing gastric cancer cell proliferation and apoptosis.

The ACSL protein family is involved in critical lipid metabolism pathways such as peroxisome adipocytokine signalling pathway. Furthermore, the PPAR signalling pathway regulates fatty acid metabolism. Notably, GPX4 has been found to activate NRF2 and inhibit the expression of vascular cell adhesion molecule-1, contributing to tumour metastasis and angiogenesis (Song and Long, 2020). The iron-dependent enzymes Egl-9 family hypoxia-inducible factor 1/3 and c-Myc directly induce the expression of chromatin remodelling factor lymphoid-specific helicase (LSH) by inhibiting HIF-1α. Increasing the LSH levels can upregulate the expression of genes involved in lipid metabolism, such as SCD1 and FADS2, and reduce the ferroptosis rate by inhibiting the accumulation of lipid peroxides and intracellular iron (Jiang *et al*., 2017).

Ferroptosis and iron metabolism

Iron is an essential element in all living organisms. The capacity of iron to be oxidized and reduced makes it ideal as an electron transporter and a cofactor in various biochemical reactions, including DNA synthesis, mitochondrial respiration, host defence responses, and cell signalling. Moreover, disrupted iron redox may lead to ROS formation, adversely affecting genome stability and inducing malignant transformation. Therefore, abnormal iron metabolism plays a significant role in the development and growth of tumours (Yang *et al*., 2016; Wang *et al*., 2018). Iron homeostasis in the TME or in tumour cells is related to tumour development (Hassannia *et al*., 2019).

Substantial oxidative stress disrupts the regulatory function of ferritin, causing the release of large quantities of iron, which leads to excessive iron build-up in cells and low ferroportin levels. Iron-dependent lipid peroxidation is promoted by high TfR expression levels (Verma *et al*., 2020). Intracellular ROS may be produced in several ways. The Fenton reaction, in which ferrous iron reacts with hydrogen peroxide to generate hydroxyl radicals that participate in the ROS reaction, is a crucial regulator of ferritin degradation and TfR1 expression during ferroptosis. ROS-induced autophagy is another critical regulator of ferritin degradation and TfR1 expression during ferroptosis (Park and Chung, 2019). Iron is also an essential cofactor of several ROS-producing enzymes (Liu *et al*., 2022).

In addition to the involvement of iron metabolism alteration in ferroptosis, genes that regulate iron metabolism can regulate ferroptosis. Hepcidin is a gene crucial for regulating iron metabolism and is mainly expressed in cells that have been exposed to iron, such as hepatocytes, intestinal epithelial cells, and macrophages in the reticuloendothelial system. Hepcidin binds to transferrin (ferroportin) on the cell surface, causing transferrin breakdown and reducing iron production.

Ferroportin levels are quickly stabilized when hepcidin levels are low and iron is transferred to plasma. When hepcidin expression is high, ferroportin is inactivated, and iron absorption into plasma is inhibited. As a result, elevated hepcidin levels have been reported in several tumour types, and hepcidin inhibits ferroportin-mediated iron export (Ginzburg, 2019). By establishing a ferroportin-deficient mouse model to mimic hepcidin hyperactivation in CRC, Schwartz *et al.* (2021) discovered that ferroportin-deficient individuals and tumour tissue exhibited considerably increased iron reserves.

This study shows that intestinal epithelial hepcidin-ferroportin signalling is essential for CRC development and progression.

Ferroptosis and gastric cancer

In addition to the aforementioned interactions involved in ferroptosis and tumours, ferroptosis may play a role in the occurrence and development of gastric cancer mediated through *Helicobacter pylori* infection and gastric cancer-related molecules (Lopez and Skaar, 2018).

Ferroptosis and *H. pylori* infection

More than 60% of gastric cancers are closely related to infection with *H. pylori*, a gram-negative, active, microaerophilic, and spiral-shaped bacterium (Matsunaga *et al*., 2018). The only natural host of *H. pylori* is the human stomach, where it causes gastric cancer by producing specific toxic factors such as cytotoxin-related gene A, vacuolar cytotoxin A, and outer membrane protein. The WHO has classified *H. pylori* as a Grade 1 carcinogen (Crowe, 2019). An imbalance in iron metabolism is currently thought to induce ferroptosis and increase the risk of gastric cancer (Wei *et al*., 2020); however, multiple mechanisms may link iron metabolism, *H. pylori* infection, and cancer development; whether *H. pylori* is the primary cause of the underlying aberrant iron metabolism in gastric cancer is debated. *H. pylori* infection accelerates carcinogenesis by increasing pathogen virulence (Noto *et al*., 2013) and is related to iron shortage, a higher plasma sTfR level, and a higher sTfR/log ferritin ratio (Enko *et al*., 2019). Iron shortage enhances *H. pylori* cag pathogenicity island expression coupled with toxin VacA released by *H. pylori* to induce transmutation. Because ferritin receptors are mislocalized in the basolateral membrane, not the apical surface, *H. pylori* receive iron from transferrin to survive (Flores *et al*., 2017). In addition, the interplay of dyslipidaemia with *H. pylori* infection can promote gastric cancer progression by inducing TH17 cell differentiation and activation (Liu *et al*., 2017). Although the association between *H. pylori*, gastric cancer, and ferroptosis is widely acknowledged, further study is needed to understand the relevant processes.

Ferroptosis-related molecules and gastric cancer prognosis

Recent research shows that ferroptosis is linked to the development of gastric cancer, but the possible mechanism of ferroptosis in gastric cancer cells has not been fully explained (Table 2). Studies have shown that four gastric cancer cell lines (AGS, SNU-1, Hs-746 T, and HGC-27 cells) are all sensitive to erastin (Wang *et al*., 2021c). Moreover, ferroptosis is the primary form of erastin-induced gastric cancer cell death (Hao *et al*., 2017). Xiao *et al*. (2021) found that gastric cancer-associated TMEs can be classified into EMT-like, microsatellite instability-like, and metabolite-like types. In each subtype, a different set of enriched pathways is activated, and a different survival rate is associated with each type. Therefore, the identification of gastric cancer subtypes with varying ferroptosis rates has important clinical implications (Xiao *et al*., 2021). In addition, some genes have been found to play essential roles in regulating ferroptosis in gastric cancer. For example, CDO1 (Hao *et al*., 2017) and ALOX15 (Zhang *et al*., 2020a) can promote the ferroptosis of human gastric cancer cells, while SCD1 (Wang *et al*., 2020a), PLIN2 (Sun *et al*., 2020b), and GDF15 (Chen *et al*., 2020a) inhibit ferroptosis of human gastric cancer cells. Notably, ferroptosis-related genes were discovered as indicators of gastric cancer diagnosis and prognosis in prognostic models (Huo *et al*., 2021; Jiang *et al*., 2021; Liu *et al*., 2021b, 2021c; Wang *et al*., 2021d).

Three separate studies revealed that the expression levels of ZFP36 and MYB are reliable predictors of clinical outcomes. ZFP36, also known as tristetraprolin, is an RNA-binding protein that downregulates TWIST1 and SNAI1 expression to initiate the mesenchymal-epithelial transition (Yoon *et al*., 2016). ZFP36 binds to PRC1 mRNA, limiting tumour development and enhancing 5-Fu sensitivity by downregulating PRC1 expression (Chen *et al*., 2020b). ZFP36 also protects cells against ferroptosis by regulating cellular responses to oxidative stress (Zhang *et al*., 2020b).

MYB is a well characterized proto-oncogene protein that controls various signalling pathways involved in cell differentiation, survival, and proliferation and plays a critical role in carcinogenesis in multiple cancer types (Fry and Inoue, 2019). MYB expression in gastric cancer cells can be targeted and inhibited by miR-139-5p, promoting gastric cancer cell proliferation and metastasis (Xie *et al*., 2021). Exosomes transport miR-130a from gastric cancer cells to vascular cells by targeting c-MYB *in vivo* and *in vitro* to enhance angiogenesis and tumour progression (Yang *et al*., 2018). Furthermore, c-Myb promotes the transcription of CDO1 and the expression of GPX4 during ferroptosis (Hao *et al*., 2017).

Dual-specificity phosphatase 1 (DUSP1) is an oncogene, and increasing evidence suggests that it is involved in tumour cell proliferation, differentiation,

Table 2 Prognostic model results associated with ferroptosis in gastric cancer

Author	Gene	
Wang C	*SLC1A5*, *ANGPTL4*, *CGAS*	Yang *et al.* (2018)
Chen L	*GABARAPL1*, *ZFP36*, *DUSP1*, *TXNIP*, *NNMT*, *MYB*, *PSAT1*, *CXCL2*	Lopes *et al.* (2017)
Wang F	*AKAP12*, *DUSP1*, *EFNA3*, *LOX*, *PIM1*, *SERPINE1*, *STC1*, *ZFP36*	Peng *et al.* 2020
Liu G	*TCFBR1*, *MYB*, *NFE2L2*, *ZFP36*, *TF*, *SLC1A5*, *NF2*, *NOX4*	Teng *et al.* (2018)
Huo J	*NOX4*, *NOX5*, *GLS2*, *MYB*, *TGFBR1*, *NF2*, *AIFM2*, *ZFP36*, *SLC1A4*, *TXNIP*, *CXCL2*, *HAMP*, *SP1*	Schröder *et al.* (2020)

DUSP1, dual-specificity phosphatase 1; NOX4, NADPH oxidase 4; TXNIP, thioredoxin-interacting protein.

transformation, cell cycle arrest, and apoptosis by regulating the MAPK signalling pathway (Lopes *et al*., 2017; Peng *et al*., 2020). The expression of DUSP1 is more significant in the early stages of gastric cancer than in the late stages of the disease. Furthermore, it has been closely associated with the drug resistance of gastric cancer cells (Teng *et al*., 2018).

Thioredoxin-interacting protein (TXNIP) is a metabolic protein involved in redox homeostasis and several biological processes, making it a tumour suppressor in many malignancies, although it is expressed at low levels in numerous human cancers and tumours (Schröder *et al*, 2020). TXNIP overexpression reduces tumour growth and metastasis in transplant models (Park *et al*., 2018), while TXNIP deficiency has been shown to promote gastric cancer development through ROS signalling (Lee *et al*., 2010). NADPH oxidase 4 (NOX4) controls the generation of ROS and lipid peroxides. NOX4 expression has been linked to the aetiology, development, and prognosis of several cancer types. For example, overexpression of NOX4 promotes CRC progression and is associated with poor prognosis (Lin *et al*., 2017). The NOX4 gene is also often deleted in individuals with liver cancer, indicating that NOX4 may reduce tumour growth by mediating TGF-1-induced apoptosis (Herranz-Itúrbide *et al*., 2021). Although the mechanism of NOX4 action in gastric cancer is still unclear, studies have shown that NOX4 can significantly promote the proliferation and invasion of gastric cancer cells (Gregg *et al*., 2014).

The degree of information on identified ferroptosis-related genes varies greatly due to differences in the databases and assessment methodologies used in individual studies. Therefore, whether these ferroptosis-related genes can be used to diagnose or predict the prognosis of gastric cancer in the early stages remains unclear.

Summary

Ferroptosis, an iron-dependent controlled form of cell death caused by lipid peroxide build-up, is linked to several disorders and exhibits a tumour suppressor function. Many studies have linked ferroptosis to tumour incidence, growth, invasion, and metastasis, particularly in TME and immunotherapy studies. Gastric cancer is one of the most prevalent digestive tract cancers, and the role played by ferroptosis in gastric cancer incidence and progression remains unknown. This article summarizes the correlations identified between ferroptosis and gastric cancer by describing related mechanisms and their relationships with the TME and metabolic regulation, which contribute to future research on the mechanism of ferroptosis in gastric cancer tissue.

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Conflicts of interest

There are no conflicts of interest.

References

Alvarez SW, Sviderskiy VO, Terzi EM, Papagiannakopoulos T, Moreira AL, Adams S, *et al.* (2017). NFS1 undergoes positive selection in lung tumors and protects cells from ferroptosis. *Nature* **551**:639–643.

Anandhan A, Dodson M, Schmidlin CJ, Liu P, Zhang DD (2020). Breakdown of an ironclad defense system: the critical role of NRF2 in mediating ferroptosis. *Cell Chem Biol* **27**:436–447.

Auciello FR, Bulusu V, Oon C, Tait-Mulder J, Berry M, Bhattacharyya S, *et al.* (2019). A stromal lysolipid-autotaxin signaling axis promotes pancreatic tumor progression. *Cancer Discov* **9**:617–627.

Battaglia AM, Chirillo R, Aversa I, Sacco A, Costanzo F, Biamonte F (2020). Ferroptosis and cancer: mitochondria meet the 'iron maiden' cell death. *Cells* **9**:1505.

Bersuker K, Hendricks JM, Li Z, Magtanong L, Ford B, Tang PH, *et al.* (2019). The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis. *Nature* **575**:688–692.

Carbone M, Harbour JW, Brugarolas J, Bononi A, Pagano I, Dey A, *et al.* (2020). Biological mechanisms and clinical significance of BAP1 mutations in human cancer. *Cancer Discov* **10**:1103–1120.

Carracedo A, Cantley LC, Pandolfi PP (2013). Cancer metabolism: fatty acid oxidation in the limelight. *Nat Rev Cancer* **13**:227–232.

Chen L, Qiao L, Bian Y, Sun X (2020a). GDF15 knockdown promotes erastin-induced ferroptosis by decreasing SLC7A11 expression. *Biochem Biophys Res Commun* **526**:293–299.

Chen W, Chen M, Zhao Z, Weng Q, Song J, Fang S, *et al.* (2020b). ZFP36 binds with PRC1 to inhibit tumor growth and increase 5-fu chemosensitivity of hepatocellular carcinoma. *Front Mol Biosci* **7**:126.

Chen X, Yu C, Kang R, Kroemer G, Tang D (2021a). Cellular degradation systems in ferroptosis. *Cell Death Differ* **28**:1135–1148.

Chen X, Kang R, Kroemer G, Tang D (2021b). Broadening horizons: the role of ferroptosis in cancer. *Nat Rev Clin Oncol* **18**:280–296.

Crowe SE (2019). Helicobacter pylori infection. *N Engl J Med* **380**:1158–1165.

Dai E, Han L, Liu J, Xie Y, Zeh HJ, Kang R, *et al.* (2020). Ferroptotic damage promotes pancreatic tumorigenesis through a TMEM173/STING-dependent DNA sensor pathway. *Nat Commun* **11**:6339.

Dodson M, Castro-Portuguez R, Zhang DD (2019). NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. *Redox Biol* **23**:101107.

Doll S, Freitas FP, Shah R, Aldrovandi M, da Silva MC, Ingold I, *et al.* (2019). FSP1 is a glutathione-independent ferroptosis suppressor. *Nature* **575**:693–698.

Enache AO, Stepan AE, Mărgăritescu C, Pătraşcu V, Ciurea RN, Simionescu CE, *et al.* (2018). Immunoexpression of p53 and COX-2 in basal cell carcinoma. *Rom J Morphol Embryol* **59**:1115–1120.

Enko D, Wagner H, Kriegshäuser G, Wögerer J, Halwachs-Baumann G, Schnedl WJ, *et al.* (2019). Iron status determination in individuals with Helicobacter pylori infection: conventional vs. new laboratory biomarkers. *Clin Chem Lab Med* **57**:982–989.

Feng J, Lu PZ, Zhu GZ, Hooi SC, Wu Y, Huang X-W, *et al.* (2021). ACSL4 is a predictive biomarker of sorafenib sensitivity in hepatocellular carcinoma. *Acta Pharmacol Sin* **42**:160–170.

Flores SE, Aitchison A, Day AS, Keenan JI (2017). Helicobacter pylori infection perturbs iron homeostasis in gastric epithelial cells. *PLoS One* **12**:e0184026.

Forcina GC, Dixon SJ (2019). GPX4 at the crossroads of lipid homeostasis and ferroptosis. *Proteomics* **19**:e1800311.

Fry EA, Inoue K (2019). c-MYB and DMTF1 in cancer. *Cancer Invest* **37**:46–65.

Fuhrmann DC, Mondorf A, Beifuß J, Jung M, Brüne B (2020). Hypoxia inhibits ferritinophagy, increases mitochondrial ferritin, and protects from ferroptosis. *Redox Biol* **36**:101670.

Fukawa T, Yan-Jiang BC, Min-Wen JC, Jun-Hao ET, Huang D, Qian C-N, *et al.* (2016). Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. *Nat Med* **22**:666–671.

Ginzburg YZ (2019). Hepcidin-ferroportin axis in health and disease. *Vitam Horm* **110**:17–45.

Granofszky N, Lang M, Khare V, Schmid G, Scharl T, Ferk F, *et al.* (2018). Identification of PMN-released mutagenic factors in a co-culture model for colitis-associated cancer. *Carcinogenesis* **39**:146–157.

Gregg JL, Turner RM 2nd, Chang G, Joshi D, Zhan Y, Chen L, *et al.* (2014). NADPH oxidase NOX4 supports renal tumorigenesis by promoting the expression and nuclear accumulation of HIF2α. *Cancer Res* **74**:3501–3511.

Guan D, Li C, Li Y, Li Y, Wang G, Gao F, *et al.* (2021). The DpdtbA induced EMT inhibition in gastric cancer cell lines was through ferritinophagy-mediated activation of p53 and PHD2/hif-1α pathway. *J Inorg Biochem* **218**:111413.

Hao S, Yu J, He W, Huang Q, Zhao Y, Liang B, *et al*. (2017). Cysteine dioxygenase 1 mediates erastin-induced ferroptosis in human gastric cancer cells. *Neoplasia* **19**:1022–1032.

Hassannia B, Vandenabeele P, Vanden Berghe T (2019). Targeting ferroptosis to iron out cancer. *Cancer Cell* **35**:830–849.

Hayano M, Yang WS, Corn CK, Pagano NC, Stockwell BR (2016). Loss of cysteinyl-tRNA synthetase (CARS) induces the transsulfuration pathway and inhibits ferroptosis induced by cystine deprivation. *Cell Death Differ* **23**:270–278.

Herranz-Itúrbide M, López-Luque J, Gonzalez-Sanchez E, Caballero-Díaz D, Crosas-Molist E, Martín-Mur B, *et al*. (2021). NADPH oxidase 4 (Nox4) deletion accelerates liver regeneration in mice. *Redox Biol* **40**:101841.

Higdon A, Diers AR, Oh JY, Landar A, Darley-Usmar VM (2012). Cell signalling by reactive lipid species: new concepts and molecular mechanisms. *Biochem J* **442**:453–464.

Huo J, Wu L, Zang Y (2021). Eight-gene prognostic signature associated with hypoxia and ferroptosis for gastric cancer with general applicability. *Epigenomics* **13**:875–890.

Ivan M, Kaelin WG Jr (2017). The EGLN-HIF O2-sensing system: multiple inputs and feedbacks. *Mol Cell* **66**:772–779.

Jeung YJ, Lee K, Lee HJ, Kim E, Son MJ, Ahn J, *et al*. (2019). Cationic amino acid transporter PQLC2 is a potential therapeutic target in gastric cancer. *Cancer Sci* **110**:1453–1463.

Jiang Y, Mao C, Yang R, Yan B, Shi Y, Liu X, *et al*. (2017). EGLN1/c-Myc induced lymphoid-specific helicase inhibits ferroptosis through lipid metabolic gene expression changes. *Theranostics* **7**:3293–3305.

Jiang X, Yan Q, Xie L, Xu S, Jiang K, Huang J, *et al*. (2021). Construction and validation of a ferroptosis-related prognostic model for gastric cancer. *J Oncol* **2021**:6635526.

Jing F, Hu X, Cao Y, Xu M, Wang Y, Jing Y, *et al*. (2018). Discriminating gastric cancer and gastric ulcer using human plasma amino acid metabolic profile. *IUBMB Life* **70**:553–562.

Kang R, Kroemer G, Tang D (2019). The tumor suppressor protein p53 and the ferroptosis network. *Free Radic Biol Med* **133**:162–168.

Kastenhuber ER, Lowe SW (2017). Putting p53 in context. *Cell* **170**:1062–1078.

Khwairakpam AD, Banik K, Girisa S, Shabnam B, Shakibaei M, Fan L, *et al*. (2020). The vital role of ATP citrate lyase in chronic diseases. *J Mol Med (Berl)* **98**:71–95.

Kopecka J, Trouillas P, Gašparović AC, Gazzano E, Assaraf YG, Riganti C (2020). Phospholipids and cholesterol: inducers of cancer multidrug resistance and therapeutic targets. *Drug Resist Updat* **49**:100670.

Ladanyi A, Mukherjee A, Kenny HA, Johnson A, Mitra AK, Sundaresan S, *et al*. (2018). Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. *Oncogene* **37**:2285–2301.

Latunde-Dada GO (2017). Ferroptosis: role of lipid peroxidation, iron and ferritinophagy. *Biochim Biophys Acta Gen Subj* **1861**:1893–1900.

Lee JH, Jeong EG, Choi MC, Kim S-H, Park J-H, Song S-H, *et al*. (2010). Inhibition of histone deacetylase 10 induces thioredoxin-interacting protein and causes accumulation of reactive oxygen species in SNU-620 human gastric cancer cells. *Mol Cells* **30**:107–112.

Lee SH, Golinska M, Griffiths JR (2021). HIF-1-independent mechanisms regulating metabolic adaptation in hypoxic cancer cells. *Cells* **10**:2371.

Lin XL, Yang L, Fu SW, Lin W-F, Gao Y-J, Chen H-Y, *et al*. (2017). Overexpression of NOX4 predicts poor prognosis and promotes tumor progression in human colorectal cancer. *Oncotarget* **8**:33586–33600.

Lin W, Wang C, Liu G, Bi C, Wang X, Zhou Q, *et al*. (2020). SLC7A11/xCT in cancer: biological functions and therapeutic implications. *Am J Cancer Res* **10**:3106–3126.

Liu J, Wang H, Chen G, Yang M, Wu ZX, Ericksen RE, *et al*. (2017). The synergy of Helicobacter pylori and lipid metabolic disorders in induction of Th17-related cytokines in human gastric cancer. *J Cancer Metastasis Treat* **3**:169–176.

Liu J, Lin S, Li Z, Zhou L, Yan X, Xue Y, *et al*. (2018). Free amino acid profiling of gastric juice as a method for discovering potential biomarkers of early gastric cancer. *Int J Clin Exp Pathol* **11**:2323–2336.

Liu J, Kuang F, Kroemer G, Klionsky DJ, Kang R, Tang D (2020). Autophagy-dependent ferroptosis: machinery and regulation. *Cell Chem Biol* **27**:420–435.

Liu J, Kang R, Tang D (2022). Signaling pathways and defense mechanisms of ferroptosis. *FEBS J* **22**:7038–7050.

Liu G, Ma JY, Hu G, Jin H (2021). Identification and validation of a novel ferroptosis-related gene model for predicting the prognosis of gastric cancer patients. *PLoS One* **16**:e0254368.

Liu SJ, Yang YB, Zhou JX, Lin Y-J, Pan Y-L, Pan J-H (2021c). A novel ferroptosis-related gene risk signature for predicting prognosis and immunotherapy response in gastric cancer. *Dis Markers* **2021**:2385406.

Lopes LJS, Tesser-Gamba F, Petrilli AS, de Seixas Alves MT, Garcia-Filho RJ, Toledo SRC (2017). MAPK pathways regulation by DUSP1 in the development of osteosarcoma: potential markers and therapeutic targets. *Mol Carcinog* **56**:1630–1641.

Lopez CA, Skaar EP (2018). The impact of dietary transition metals on host-bacterial interactions. *Cell Host Microbe* **23**:737–748.

Ma X, Xiao L, Liu L, Ye L, Su P, Bi E, *et al*. (2021). CD36-mediated ferroptosis dampens intratumoral CD8+ T cell effector function and impairs their antitumor ability. *Cell Metab* **33**:1001–1012.e5.

Magtanong L, Ko PJ, To M, Cao JY, Forcina GC, Tarangelo A, *et al*. (2019). Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. *Cell Chem Biol* **26**:420–432.e9.

Matsunaga S, Nishiumi S, Tagawa R, Yoshida M (2018). Alterations in metabolic pathways in gastric epithelial cells infected with Helicobacter pylori. *Microb Pathog* **124**:122–129.

Miyagi Y, Higashiyama M, Gochi A, Akaike M, Ishikawa T, Miura T, *et al*. (2011). Plasma free amino acid profiling of five types of cancer patients and its application for early detection. *PLoS One* **6**:e24143.

Mizuno R, Kawada K, Itatani Y, Ogawa R, Kiyasu Y, Sakai Y (2019). The role of tumor-associated neutrophils in colorectal cancer. *Int J Mol Sci* **20**:529.

Murao A, Aziz M, Wang H, Brenner M, Wang P (2021). Release mechanisms of major DAMPs. *Apoptosis* **26**:152–162.

Noto JM, Gaddy JA, Lee JY, Piazuelo MB, Friedman DB, Colvin DC, *et al*. (2013). Iron deficiency accelerates Helicobacter pylori-induced carcinogenesis in rodents and humans. *J Clin Invest* **123**:479–492.

Ou Y, Wang SJ, Li D, Chu B, Gu W (2016). Activation of SAT1 engages polyamine metabolism with p53-mediated ferroptosis responses. *Proc Natl Acad Sci U S A* **113**:E6806–E6812.

Park E, Chung SW (2019). ROS-mediated autophagy increases intracellular iron levels and ferroptosis by ferritin and transferrin receptor regulation. *Cell Death Dis* **10**:822.

Park JW, Lee SH, Woo GH, Kwon H-J, Kim D-Y (2018). Downregulation of TXNIP leads to high proliferative activity and estrogen-dependent cell growth in breast cancer. *Biochem Biophys Res Commun* **498**:566–572.

Peng W, Zhang C, Peng J, Huang Y, Peng C, Tan Y, *et al*. (2020). Lnc-FAM84B-4 acts as an oncogenic lncRNA by interacting with protein hnRNPK to restrain MAPK phosphatases-DUSP1 expression. *Cancer Lett* **494**:94–106.

Quan J, Bode AM, Luo X (2021). ACSL family: the regulatory mechanisms and therapeutic implications in cancer. *Eur J Pharmacol* **909**:174397.

Röhrig F, Schulze A (2016). The multifaceted roles of fatty acid synthesis in cancer. *Nat Rev Cancer* **16**:732–749.

Rojo de la Vega M, Chapman E, Zhang DD (2018). NRF2 and the hallmarks of cancer. *Cancer Cell* **34**:21–43.

Sagiv JY, Michaeli J, Assi S, Mishalian I, Kisos H, Levy L, *et al*. (2015). Phenotypic diversity and plasticity in circulating neutrophil subpopulations in cancer. *Cell Rep* **10**:562–573.

Schröder J, Schumacher U, Böckelmann LC (2020). Thioredoxin interacting protein (TXNIP) is differentially expressed in human tumor samples but is absent in human tumor cell line xenografts: implications for its use as an immunosurveillance marker. *Cancers (Basel)* **12**:3028.

Schroeder B, Vander Steen T, Espinoza I, Venkatapoorna CMK, Hu Z, Silva FM, *et al*. (2021). Fatty acid synthase (FASN) regulates the mitochondrial priming of cancer cells. *Cell Death Dis* **12**:977.

Schwartz AJ, Goyert JW, Solanki S, Kerk SA, Chen B, Castillo C, *et al*. (2021). Hepcidin sequesters iron to sustain nucleotide metabolism and mitochondrial function in colorectal cancer epithelial cells. *Nat Metab* **3**:969–982.

Sha W, Hu F, Xi Y, Chu Y, Bu S (2021). Mechanism of ferroptosis and its role in type 2 diabetes mellitus. *J Diabetes Res* **2021**:9999612.

Shaul ME, Fridlender ZG (2019). Tumor-associated neutrophils in patients with cancer. *Nat Rev Clin Oncol* **16**:601–620.

Shi L, Liu Y, Li M, Luo Z (2022). Emerging roles of ferroptosis in the tumor immune landscape: from danger signals to antitumor immunity. *FEBS J* **13**:3655–3665.

Shi LY, Wang YY, Jing Y, Xu M-H, Zhu Z-T, Wang Q-J (2021). Abnormal arginine metabolism is associated with prognosis in patients of gastric cancer. *Transl Cancer Res* **10**:2451–2469.

Singhal R, Mitta SR, Das NK, Kerk SA, Sajjakulnukit P, Solanki S, *et al*. (2021). HIF-2α activation potentiates oxidative cell death in colorectal cancers by increasing cellular iron. *J Clin Invest* **131**:e143691.

Snaebjornsson MT, Janaki-Raman S, Schulze A (2020). Greasing the wheels of the cancer machine: the role of lipid metabolism in cancer. *Cell Metab* **31**:62–76.

Song X, Long D (2020). Nrf2 and ferroptosis: a new research direction for neurodegenerative diseases. *Front Neurosci* **14**:267.

Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, *et al*. (2017). Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell* **171**:273–285.

Su X, Abumrad NA (2009). Cellular fatty acid uptake: a pathway under construction. *Trends Endocrinol Metab* **20**:72–77.

Sun X, Ou Z, Chen R, Niu X, Chen D, Kang R, *et al*. (2016). Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells. *Hepatology* **63**:173–184.

Sun Y, Chen P, Zhai B, Zhang M, Xiang Y, Fang J, *et al*. (2020a). The emerging role of ferroptosis in inflammation. *Biomed Pharmacother* **127**:110108.

Sun X, Yang S, Feng X, Zheng Y, Zhou J, Wang H, *et al*. (2020b). The modification of ferroptosis and abnormal lipometabolism through overexpression and knockdown of potential prognostic biomarker perilipin2 in gastric carcinoma. *Gastric Cancer* **23**:241–259.

Tang R, Hua J, Xu J, Liang C, Meng Q, Liu J, *et al*. (2020). The role of ferroptosis regulators in the prognosis, immune activity and gemcitabine resistance of pancreatic cancer. *Ann Transl Med* **8**:13471347.–134711347.

Teng F, Xu Z, Chen J, Zheng G, Zheng G, Lv H, *et al*. (2018). DUSP1 induces apatinib resistance by activating the MAPK pathway in gastric cancer. *Oncol Rep* **40**:1203–1222.

Tian T, Xiao L, Du J, Zhu X, Gu Y, Qin N, *et al*. (2017). Polymorphisms in CARS are associated with gastric cancer risk: a two-stage case-control study in the Chinese population. *Gastric Cancer* **20**:940–947.

Ursini F, Maiorino M (2020). Lipid peroxidation and ferroptosis: The role of GSH and GPx4. *Free Radic Biol Med* **152**:175–185.

Venkatesh D, Stockwell BR, Prives C (2020). p21 can be a barrier to ferroptosis independent of p53. *Aging (Albany, NY)* **12**:17800–17814.

Verma N, Vinik Y, Saroha A, Nair NU, Ruppin E, Mills G, *et al*. (2020). Synthetic lethal combination targeting BET uncovered intrinsic susceptibility of TNBC to ferroptosis. *Sci Adv* **6**:eaba8968.

Viswanathan VS, Ryan MJ, Dhruv HD, Gill S, Eichhoff OM, Seashore-Ludlow B, *et al*. (2017). Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway. *Nature* **547**:453–457.

Vriens K, Christen S, Parik S, Broekaert D, Yoshinaga K, Talebi A, *et al*. (2019). Evidence for an alternative fatty acid desaturation pathway increasing cancer plasticity. *Nature* **566**:403–406.

Wang S, Luo J, Zhang Z, Dong D, Shen Y, Fang Y, *et al*. (2018). Iron and magnetic: new research direction of the ferroptosis-based cancer therapy. *Am J Cancer Res* **8**:1933–1946.

Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, *et al*. (2019). CD8+ T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature* **569**:270–274.

Wang C, Shi M, Ji J, Cai Q, Zhao Q, Jiang J, *et al*. (2020a). Stearoyl-CoA desaturase 1 (SCD1) facilitates the growth and anti-ferroptosis of gastric cancer cells and predicts poor prognosis of gastric cancer. *Aging (Albany NY)* **12**:15374–15391.

Wang Y, Zhai J, Zhang T, Han S, Zhang Y, Yao X, *et al*. (2020b). Tumor-associated neutrophils can predict lymph node metastasis in early gastric cancer. *Front Oncol* **10**:570113.

Wang K, Zhang Z, Tsai HI, Liu Y, Gao J, Wang M, *et al*. (2021a). Branched-chain amino acid aminotransferase 2 regulates ferroptosis cell death in cancer cells. *Cell Death Differ* **28**:1222–1236.

Wang M, Lu Y, Wang H, Wu Y, Xu X, Li Y (2021b). High ATF4 expression is associated with poor prognosis, amino acid metabolism, and autophagy in gastric cancer. *Front Oncol* **11**:740120.

Wang J, Wang T, Zhang Y, Liu J, Song J, Han Y, *et al*. (2021c). CPEB1 enhances erastin-induced ferroptosis in gastric cancer cells by suppressing twist1 expression. *IUBMB Life* **73**:1180–1190.

Wang F, Chen C, Chen WP, Li Z-L, Cheng H (2021d). Development and validation of a novel ferroptosis-related gene signature for predicting prognosis and the immune microenvironment in gastric cancer. *Biomed Res Int* **2021**:6014202.

Wei J, Gao X, Qin Y, Liu T, Kang Y (2020). An iron metabolism-related SLC22A17 for the prognostic value of gastric cancer. *Onco Targets Ther* **13**:12763–12775.

Wen Q, Liu J, Kang R, Zhou B, Tang D (2019). The release and activity of HMGB1 in ferroptosis. *Biochem Biophys Res Commun* **510**:278–283.

Wiggins T, Kumar S, Markar SR, Antonowicz S, Hanna GB (2015). Tyrosine, phenylalanine, and tryptophan in gastroesophageal malignancy: a systematic review. *Cancer Epidemiol Biomarkers Prev* **24**:32–38.

Xiao S, Liu X, Yuan L, Chen X, Wang F (2021). Expression of ferroptosis-related genes shapes tumor microenvironment and pharmacological profile in gastric cancer. *Front Cell Dev Biol* **9**:694003.

Xie Y, Zhu S, Song X, Sun X, Fan Y, Liu J, *et al*. (2017). The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity. *Cell Rep* **20**:1692–1704.

Xie Y, Rong L, He M, Jiang Y, Li H, Mai L, *et al*. (2021). LncRNA SNHG3 promotes gastric cancer cell proliferation and metastasis by regulating the miR-139-5p/MYB axis. *Aging (Albany NY)* **13**:25138–25152.

Yagoda N, von Rechenberg M, Zaganjor E, Bauer AJ, Yang WS, Fridman DJ, *et al*. (2007). RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels. *Nature* **447**:864–868.

Yang WS, Kim KJ, Gaschler MM, Patel M, Shchepinov MS, Stockwell BR (2016). Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis. *Proc Natl Acad Sci U S A* **113**:E4966–E4975.

Yang H, Zhang H, Ge S, Ning T, Bai M, Li J, *et al*. (2018). Exosome-derived miR-130a activates angiogenesis in gastric cancer by targeting C-MYB in vascular endothelial cells. *Mol Ther* **26**:2466–2475.

Yee PP, Wei Y, Kim SY, Lu T, Chih SY, Lawson C, *et al*. (2020). Neutrophil-induced ferroptosis promotes tumor necrosis in glioblastoma progression. *Nat Commun* **11**:5424.

Yoon NA, Jo HG, Lee UH, Park JH, Yoon JE, Ryu J, *et al*. (2016). Tristetraprolin suppresses the EMT through the down-regulation of Twist1 and Snail1 in cancer cells. *Oncotarget* **7**:8931–8943.

Yuan X, Gajan A, Chu Q, Xiong H, Wu K, Wu GS (2018). Developing TRAIL/TRAIL death receptor-based cancer therapies. *Cancer Metastasis Rev* **37**:733–748.

Zhang Y, Koppula P, Gan B (2019). Regulation of H2A ubiquitination and SLC7A11 expression by BAP1 and PRC1. *Cell Cycle* **18**:773–783.

Zhang H, Deng T, Liu R, Ning T, Yang H, Liu D, *et al*. (2020a). CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. *Mol Cancer* **19**:43.

Zhang Z, Guo M, Li Y, Shen M, Kong D, Shao J, *et al*. (2020b). RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells. *Autophagy* **16**:1482–1505.

Zhou N, Bao J (2020). FerrDb: a manually curated resource for regulators and markers of ferroptosis and ferroptosis-disease associations. *Database (Oxford)* **2020**:baaa021.