SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 18: 2159-2164, 2019

The role of ferroptosis in digestive system cancer (Review)

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Received December 20, 2018; Accepted June 11, 2019

DOI: 10.3892/ol.2019.10568

Abstract. Ferroptosis is a type of regulated cell death dependent on iron and reactive oxygen species. Ferroptosis is distinct from other cell death modalities, including apoptosis, autophagy and necrosis. Dysregulated ferroptosis has been implicated in a number of diseases, including neuropathy, ischemia reperfusion injury, acute kidney failure and cancer. The digestive system consists of several organs. The morbidity and mortality rates of digestive system cancer are high. The current review summarizes the role of ferroptosis in digestive system cancer. A large number of molecules, including tumor protein p53, retinoblastoma protein, nuclear factor E2-related factor 2, KH RNA binding domain containing signal transduction associated 1, cysteine dioxygenase type 1, metallothionein-1G, nuclear receptor coactivator 4, CDGSH iron sulfur domain 1, heat shock protein family A (Hsp70) member 5 and acyl-CoA synthetase long chain family member 4, regulate ferroptosis in digestive system cancer. Drugs such as cisplatin, baicalein, haloperidol, artesunate, piperlongumine, saponin and bromelain may cause cancer cell death by inducing ferroptosis. An improved understanding of ferroptosis in digestive system cancer may give rise to novel diagnostic and making therapeutic strategies.

Contents

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Key words: ferroptosis, regulated cell death, digestive cancer

1. Introduction

Ferroptosis is a novel form of regulated cell death (RCD) that was described in 2012 (1). Ferroptosis involves the accumulation of lipid peroxidation products and reactive oxygen species (ROS) derived from iron metabolism. Ferroptosis is morphologically, biochemically and genetically distinct from other pathways for RCD, including necroptosis, apoptosis and autophagy (2). Amino acid, iron and lipid metabolism are involved in the process of ferroptosis. Glutamate and glutamine are pivotal regulators of ferroptosis (3). During normal physiological function, extracellular glutamate induces ferroptosis. Lipid metabolism may affect the sensitivity of cells to ferroptosis. Polyunsaturated fatty acids are susceptible to lipid peroxidation and are required for ferroptosis (4). Iron is involved in the accumulation of lipid peroxides and ferroptosis. Iron import, export, storage and turnover influence the sensitivity of cells to ferroptosis (5). Several molecules, including voltage dependent anion channel (VDAC) 2/3, glutathione peroxidase 4 (GPX4), heat shock protein β-1, nuclear factor E2-related factor 2 (NRF2), NADPH oxidase, the tumor suppressor p53 (TP53) and solute carrier family 7 member 1 (SLC7A1), regulate ferroptosis through the direct or indirect targets of iron metabolism as well as lipid peroxidation (2).

Previous studies demonstrated that ferroptosis participated in diverse diseases, including neuropathy (1,6), ischemia reperfusion injury (3) acute kidney failure (6-8) and cancer (3). Sorafenib was revealed to induce ferroptosis in hepatocellular carcinoma (HCC) and several studies have subsequently investigated the mechanism of ferroptosis in HCC (9-11). The digestive system comprises several organs and the incidence of cancer in the digestive system is high. The current review presents the role of ferroptosis in digestive system cancer.

2. Ferroptosis in digestive system cancer

Ferroptosis was revealed to be involved in various types of digestive system cancer, excluding esophageal and biliary system cancer (9,12-15). The mechanisms of ferroptosis in digestive system cancer are presented in Table I and Fig. 1.

Gastric cancer. Studies investigating ferroptosis in gastric cancer are lacking. Human cysteine dioxygenase 1 (CDO1) converts cysteine to taurine (16); therefore, an increase in CDO1 activity is expected to decrease cellular cysteine levels. Cysteine is required for glutathione (GSH) synthesis

and increased CDO1 activity may decrease the synthesis of GSH and promote ferroptosis (16). Hao *et al (*12) revealed that that silencing of CDO1 in gastric cancer cells reduced the erastin-induced ferroptosis by restoring cellular GSH, which prevented ROS generation and lipid peroxidation. MYB proto-oncogene transcription factor, which interacts with the CDO1 promoter as a transcription factor, regulated CDO1 and GPX4 expression during ferroptosis (12). Further investigation is required to identify the role and underlying mechanism of ferroptosis in gastric cancer.

Colon cancer. Previous studies investigating the role of ferroptosis in colon cancer have largely focused on TP53 (13,17-19). TP53 is an evolutionarily conserved protein involved in the regulation of cell proliferation, death and differentiation and metabolism. TP53 may initiate cell-cycle arrest and induce apoptosis in response to stress stimuli by means of the transcriptional and transcription-independent processes (17). Additionally, the induction of ferroptosis may contribute to the oncosuppressive activities of TP53 (13). Furthermore, TP53 was revealed to promote ferroptosis by means of a transcription-dependent process (20). Xie *et al* (20) revealed that TP53 constrained erastin-stimulated ferroptosis through the inhibition of dipeptidyl-peptidase-4 (DPP4) function in a transcription-independent manner in colorectal cancer. Silencing of TP53 facilitated plasma membrane-associated DPP4-dependent lipid peroxidation, and thus prevented nuclear accumulation of DPP4. As a result, SLC7A11 expression was increased which resulted in ferroptosis (20). Furthermore, the TP53-independent p53 upregulated modulator of apoptosis axis was implicated in ferroptosis induction in human colon cancer HCT116 cells (19).

The role of TP53 in ferroptosis may provide a therapeutic target for colon cancer. Albiziabioside A, a saponin derivative, suppressed the expression of GPX4, and together with the accumulation of lipid peroxidation products, resulted in ferroptosis by TP53 activation (21). Cisplatin induced ferroptosis by depleting GSH and inactivating GPX4 in A549 and HCT116 cells, suggesting that ferroptosis may be a novel target in cancer therapy (22). Bromelain exhibited anticancer effects in Kras mutant human colorectal carcinoma cells by upregulating the expression of acyl-CoA synthetase long chain family member 4, which acted as a ferroptosis target (23).

Defective ribosome biogenesis was reported in colon cancer lacking TP53 (24). 5-fluorouracil induced ribosomal protein L3 (RPL3) activation in TP53-/- colon cancer cells by inhibiting the expression of cystathionine-β-synthase (24), which may subsequently influence the cysteine level. Additionally, RPL3 decreased the expression of cysteine/glutamate antiporter and induced ferroptosis in TP53-mutated lung cancer cells (25). Ribosomal protein-dependent pathways are associated with ferroptosis and may be potential targets of anticancer drugs.

Pancreatic cancer. Pancreatic cancer is one of the most l*ethal* types of digestive malignancies, and current chemotherapeutic drugs are often ineffective. Previous studies suggested that certain natural plant extracts possess a potential therapeutic effect in pancreatic cancer cells by inducing ferroptosis (15,18,26,27). The combination of cotylenin A (CN-A) and phenethyl isothiocyanate synergistically induced pancreatic cancer cell death by the generation of ROS, which drives ferroptosis (26). In addition, artesunate (ART) induced ferroptosis by ROS generation and lipid peroxidation in KRAS-activated human pancreatic ductal adenocarcinoma (PDAC) and the AT-induced ferroptosis was inhibited by ferrostatin-1. Notably, ART did not exert an effect on non-neoplastic human pancreatic ductal epithelial cells (27). This suggests that ART may be a candidate for pancreatic cancer therapy by inducing ferroptosis. Piperlongumine (PL) induces human pancreatic cancer cell line death by substantially increasing the intracellular ROS level. This effect was inhibited by ferroptosis inhibitors and iron chelators but not apoptosis or necrosis inhibitors, suggesting that PL induced cell death by ferroptosis (15). Furthermore, the aforementioned study revealed that triple combined therapy with PL, CN-A and sulfasalazine had a high efficacy in pancreatic cancer *in vitro* (15). Baicalein inhibited erastin-induced ferroptosis by preventing GSH depletion and GPX4 degradation in pancreatic cancer cells (18).

Previous studies have investigated the mechanism of ferroptosis in pancreatic cancer cells (14,28,29). Heat shock protein family A (Hsp70) member 5 (HSPA5) negatively regulated ferroptosis in human PDAC cells through the HSPA5-GPX4 signaling pathway, which mediated ferroptosis resistance (14). The inhibition of the HSPA5-GPX4 signaling pathway improved gemcitabine sensitivity through the disinhibition of ferroptosis *in vitro* and *in vivo* (14). Nuclear receptor coactivator 4 (NCOA4) was revealed as the cargo receptor mediating ferroptosis (28). Silencing of NCOA4 inhibited ferritin degradation and suppressed ferroptosis while the overexpression of NCOA4 augmented ferritin degradation and promoted ferroptosis in human pancreatic cells (30). Lipoxygenase inhibitors prevented pancreatic cell ferroptosis induced by erastin as well as the ferroptosis inhibitor RSL3. In addition, treatment of the human pancreatic cancer cell line Panc-1 with arachidonate 15-lipoxygenase-activating compounds accelerated ferroptosis (29). The TP53-independent PUMA axis was implicated in ferroptosis in human pancreatic cancer cells as well as the previously mentioned colon cancer cells (19).

HCC. The majority of previous studies associated with ferroptosis involved the investigation of HCC (10,31,32). Sorafenib, a multikinase inhibitor, is used for the treatment of advanced HCC and is currently being investigated as a ferroptosis inducer (2,9). Mechanistically, sorafenib induces ferroptosis as a form of regulated cell death in HCC. Sorafenib inhibits the initiation of translation mediated by the rapamycin kinase signaling pathway which is considered to constitutes an important role in the initiation of ferroptosis in HCC (11). Iron metabolism is identified as a vital mediator of ferroptosis and the iron chelator deferoxamine prevents sorafenib from inducing oxidative stress in HCC cells (31). CDGSH iron sulfur domain 1 (CISD1) is an iron-possessing external mitochondrial membrane protein that modulates mitochondrial iron uptake and respiration (33). A previous study revealed that CISD1 decreased ferroptotic cell death in HCC cells by regulating iron metabolism and preventing mitochondrial damage in ferroptosis (32). In addition to iron metabolism regulating ferroptosis, lipid metabolism may serve an important role in the regulation

Table I. Mechanisms of ferroptosis in digestive system cancer.

Author, year	Cancer type	Mechanism	(Refs.)
Hao *et al*, 2017	Gastric cancer	Silencing cysteine dioxygenase type 1 inhibited ferroptosis by restoring cellular GSH and preventing ROS generation.	(12)
Wei *et al*, 2018	Colon cancer	Suppressed the expression of GPX4 and induced the accumulation of lipid peroxidation products by activating TP53.	(21)
Xie *et al*, 2017		TP53 limited erastin-induced ferroptosis by blocking dipeptidyl peptidase 4 activity in a transcription-independent manner.	(20)
Guo *et al*, 2018		Cisplatin induced ferroptosis via GSH depletion and GPX4 inactivation.	(22)
Hong *et al*, 2017		TP53-independent PUMA axis is involved in ferroptosis in human colon cancer HCT116 cells.	(19)
Park *et al*, 2018		Bromelain increased erastin-induced ferroptosis by increasing acyl-CoA synthetase long chain family member 4 in Kras mutant human colorectal carcinoma cells.	(23)
Kasukabe *et al*, 2016	Pancreatic cancer	Cotylenin A and phenethyl isothiocyanate induced ferroptosis by generating ROS.	(26)
Zhu *et al*, 2017		HSPA5 inhibited ferroptosis via the HSPA5-GPX4 signaling pathway.	(14)
Eling *et al*, 2015		Artesunate induced ferroptosis through ROS generation and lipid peroxidation.	(27)
Xie *et al*, 2016		Baicalein inhibited erastin-induced ferroptosis by preventing GSH depletion and GPX4 degradation.	(18)
Yamaguchi *et al*, 2018		Piperlongumine induced ferroptosis through ROS generation.	(15)
Hou *et al*, 2016		Knockdown of ATG5 and ATG7 limited erastin-induced ferroptosis and overexpression of NCOA4 increased ferritin degradation and promoted ferroptosis.	(30)
Shintoku *et al*, 2017		Lipoyxgenase inhibitors prevented pancreatic cell ferroptosis and arachidonate 15-lipoxygenase-activating compounds accelerated ferroptosis.	(29)
Hong *et al*, 2017		TP53-independent PUMA axis is involved in ferroptosis.	(19)
Zhang *et al*, 2018	HCC	Increased expression of ELAV like RNA binding protein 1 through inhibition of the ubiquitin-proteasome pathway in ferroptosis.	(38)
Sun *et al*, 2016		p62 expression prevented NRF2 degradation and enhanced NRF2 nuclear accumulation through inactivation of kelch like ECH associated protein 1 in HCC cells treated with a ferroptosis inducer.	(10)
Yuan *et al*, 2016		CDGSH iron sulfur domain 1 inhibited ferroptosis by protecting against mitochondrial lipid peroxidation.	(32)
Bai *et al*, 2017		Haloperidol increased the cellular levels of Fe^{2+} and lipid peroxidation and promoted ferroptosis.	(9)
Louadre *et al*, 2013		Iron chelator deferoxamine inhibited ferroptosis by preventing oxidative stress in HCC cells.	(31)
Ou *et al*, 2017		LDL-DHA nanoparticles induced ferroptotic cell death by blocking GPX4.	(34)
Houessinon *et al*, 2016		MT1 constituted a biomarker of altered redox metabolism and ferroptosis in HCC cells exposed to sorafenib.	(44)
Sun *et al*, 2016		Inhibition of MT-1G enhanced the anticancer activity of sorafenib *in vitro* and in tumor xenograft models.	(45)
Dehart *et al*, 2018		Erastin and erastin-like compounds caused HCC ferroptosis by opening voltage gated anion channels.	(41)
Sauzay *et al*, 2018		Sorafenib inhibited the initiation of translation and the mechanistic target of rapamycin kinase signaling cascade.	(11)
Louadre *et al*, 2015		Reduced levels of etinoblastoma protein increased ferroptosis induction upon exposure to sorafenib.	(42)

GSH, glutathione; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; TP53, tumor protein 53; HSPA5, heat shock protein family A (Hsp70) member 5; NRF2, nuclear factor, erythroid 2 like 2; HCC, hepatocellular carcinoma; MT, metallothioneinl LDL_DHA low-density lipoprotein-docohexaenoic acid; PUMA, p53 upregulated modulator of apoptosis.

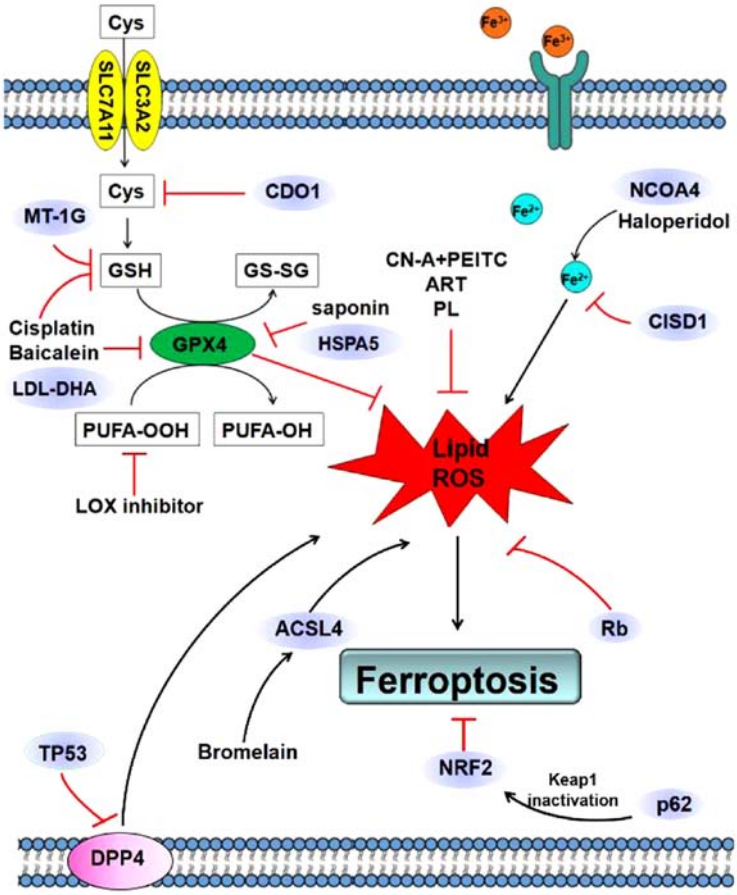

Figure 1. Signaling pathways regulating ferroptosis in cancer of the digestive system.

of ferroptosis (31). Low-density lipoproteins-docosahexaenoic acid nanoparticles stimulated ferroptosis by promoting lipid peroxidation, depleting glutathione and inactivating the lipid antioxidant GPX4 in a rat hepatoma model, HCC cell lines and human HCC tumor xenografts in mice (34).

NRF2 is implicated in several types of cancer, including HCC (35-37). RF2 is involved in ferroptosis in HCC cells. When HCC cells were exposed to a ferroptosis inducer, p62 expression decreased NRF2 degradation and increased NRF2 nuclear accumulation by inactivating Kelchlike ECH-associated protein 1 (KEAP1). Knockdown of p62 in HCC cells promoted the anticancer function of erastin and sorafenib by inducing ferroptosis (10). Activating the p62-KEAP1-NRF2 signaling pathway may thus protect against ferroptosis in HCC cells (10). Furthermore, NRF2 determined the therapeutic efficacy of ferroptosis-targeted therapies in HCC cells (10).

Zhang *et al* (38) revealed that ELAV-like RNA binding protein 1 (ELAVL1) serves an important role in the regulation of ferroptosis in liver fibrosis and hepatocarcinoma. When erastin was exposed to ferroptosis-inducing compounds, ELAVL1 protein expression was significantly increased due to inhibition of the ubiquitin-proteasome pathway (38). The σ 1 receptor (S1R) is present in the mitochondrial membrane and endoplasmic reticulum and modulates oxidative stress (39,40). Haloperidol, an S1R antagonist, significantly increased the cellular concentration of Fe^{2+} as well as lipid peroxidation, and accordingly promoted erastin-and sorafenib-induced ferroptosis (9). Furthermore, erastin, coupled with other erastin-like lead compounds, induced HCC ferroptosis through the opening of VDACs, which increased the membrane potential, mitochondrial ROS and oxidative stress-induced cell death (41).

Louandre *et al* (42) revealed that HCC cells with decreased expression of retinoblastoma protein (Rb) manifested a 2-to 3-fold increase in ferroptotic cell death induced by sorafenib compared with controls, highlighting the function of Rb in determining the susceptibility of HCC cells to sorafenib as well as regulating ferroptosis. However, clinically-applicable biomarkers reflecting the susceptibility of cancer cells to sorafenib are still in shortage (43). Microarray analysis and subsequent experiments revealed that metallothionein (MT)-1 may be a biomarker of modified redox metabolism as well as ferroptosis in HCC cells exposed to sorafenib (44). Furthermore, MT-1G may serve as a potential therapeutic target for overcoming sorafenib resistance in human HCC cells (45). Additionally, knockdown of MT-1G by RNA interference augmented glutathione depletion and lipid peroxidation, which promoted sorafenib-induced ferroptosis (45).

3. The association between ferroptosis and other forms of regulated cell death

While ferroptosis is distinct from other forms of regulated cell death, including apoptosis, necrosis and autophagy, it is connected with other types of cell deaths (19,30).

Apoptosis. ART and erastin, which are common ferroptosis inducers, enhance tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in human pancreatic cancer PANC-1 and BxPC-3 cells as well as human colon cancer HCT116 cells (19). An increased activation of caspase 8/9/3, regarded as the hallmark of apoptosis, was observed in the aforementioned study. *In vitro,* the ferroptotic agents stimulated endoplasmic reticulum (ER) stress in human colon cells (46). Furthermore, they increased the activation of the death receptor 5 via the TRAIL and initiated apoptosis (46).

Autophagy. A recent study revealed that autophagy was conducive to ferroptosis by degrading ferritin in cancer cells. Knockdown of autophagy-related (ATG) 5 and ATG7 limited erastin-stimulated ferroptosis by reducing the intracellular ferrous iron concentration and lipid peroxidation (30). ELAVL1 is a positive regulator of ferroptosis by inhibiting the ubiquitin-proteasome pathway. Upregulated ELAVL1 expression revealed increased autophagosome production coupled with autophagic flux. ELAVL1 promoted autophagy by binding to the adenine uracil-rich region in the 3'-untranslated region of beclin 1 (BECN1) mRNA, resulting in BECN1 overexpression (38).

ER stress. Previous studies have revealed that inhibiting cystine-glutamate exchange with the aid of ferroptotic agents activates an ER stress feedback loop and upregulates the glutathione-specific γ glutamylcyclotransferase 1 gene (47,48). Hong *et al* (14) demonstrated that the unfolded protein response was detected in ART-treated colon cancer cells, suggesting that the ferroptotic agent induced ER stress. Furthermore, the ER stress markers HSPA5 and DNA damage inducible transcript 3 were detected in ferroptotic agent-treated HCT116 cells, suggesting that ferroptotic agents induce ER stress (14,19). Additionally, ART-induced ER stress was inhibited by iron chelators and lipid peroxidation inhibitors, including ferrostatin-1 and lipoxstatin-1.

4. Conclusions

The digestive system consists of a number of organs and cancer of the digestive system has a relatively high morbidity and mortality rates. Furthermore, patients with digestive system cancer have a poor quality of life. Ferroptosis, which is a novel form of regulated cell death, is implicated in several types of digestive system cancer, excluding esophageal and biliary system cancer. As described in the present review, iron, lipid and amino acid metabolism are involved in ferroptosis. Molecules involved in ferroptosis in digestive system cancer, include TP53, Rb, NRF2, p62, CDO1, MT-1G, NCOA4, CISD1 and HSPA5. Several drugs, such as cisplatin, baicalein, haloperidol, ART, PL, bromelain and saponin, induce cancer cell death by ferroptosis in the digestive system and exert therapeutic effects. Nevertheless, the signaling pathways and major transcriptional regulators of ferroptosis in digestive system cancer remain unknown. Further studies are required to establish the roles of ferroptosis in metastasis, energy metabolism, autophagy and drug resistance. Furthermore, the elucidation of molecular pathways underlying ferroptosis in digestive system cancer may provide novel therapeutic targets and improve the prognosis of patients with digestive system cancer.

Acknowledgements

Not applicable.

Funding

The present review was supported by the National Natural Science Foundation of China (grant no. 81600509) and the Youth Incubation foundation of Tianjin Medical University General Hospital (grant no. ZYYFY2016020).

Availability of data and materials

Not applicable.

Authors' contributions

YS and RL conceived and designed the review. YS and HY drafted the manuscript. KJ and BMW critically revised the article for intellectual content. All the authors approved the final version of manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

Not applicable.

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