

Frontiers of Ferroptosis in Cancer Treatment

Durr-e-shahwar Malik¹, Mirna Azalea Romero², Saiyada Fatima Maida Halim³, Deena ElSORI⁴, Lara Youssef⁵, Ishmuratova Margarita Yulaevna⁶, Uteuliyev Yerzhan Sabitaliyevich⁷, Rukset Attar^{8*}

¹Institute of Pharmaceutical Sciences, PUMHSW, Nawabshah, Pakistan

²Facultad de Medicina, Universidad Autónoma de Guerrero, Laboratorio de Investigación Clínica, Av. Solidaridad S/N, Colonia Hornos Insurgentes, cp 39300, Acapulco, Guerrero México

³Rashid Latif Medical College, Lahore, Pakistan

⁴Faculty of Resilience, Rabdan Academy, Abu Dhabi, United Arab

⁵Department of Biomedical Sciences, Faculty of Medicine and Medical Sciences, University of Balamand (UOB), Al-Kurah, Lebanon

⁶E. A. Buketov Karaganda University, Kazakhstan

⁷Scientific Center for Innovative Technologies and Research, Kazakhstan

⁸Department of Obstetrics and Gynecology, Yeditepe University, Turkey

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ABSTRACT

Recent phenomenal advancements in genomic and proteomic technologies and rapid breakthroughs in the interpretation of large gene expression datasets have enabled scientists to comprehensively characterize the gene signatures involved in ferroptosis. Ferroptosis is an iron-dependent form of non-apoptotic cell death that has gained the worthwhile attention of both basic and clinical researchers. Ferroptosis has dichotomous, context-dependent functions both as a tumor suppressor and promoter of carcinogenesis. Essentially, pharmacological modulation of ferroptosis by its induction as well as its inhibition holds enormous potential to overcome drug resistance and to improve the therapeutic potential of chemotherapeutic drugs in a wide variety of cancers.

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Introduction

Rapidly evolving resistance against malignant cancer is a major concern in molecular oncology. Studies have shown that intra and inter-tumor heterogeneity, loss of apoptosis and deregulation of signaling cascades play a central role in different steps of carcinogenesis (1-4). The ability of signaling cascades to regulate different steps of cancer development and progression also presents an Achilles heel, as their misexpression has major pathological consequences in carcinogenesis and metastasis (5-17). The translation of laboratory-directed therapies into clinical benefits is very challenging. Additionally, the pivotal role of epigenetics, epithelial to mesenchymal transition and non-coding RNAs is also very exciting and has been extensively explored (18-20). Seemingly, cancer is a multifaceted disease with surprisingly multifactorial effects.

Programmed cell death is an inevitable physiological event in the cell cycle that determines

the fate of the cell. Conventionally, the cell death mechanism involves apoptosis, autophagy, and necroptosis. Ferroptosis is a newer non-apoptotic, iron-dependent form of cell death that is characterized by the accumulation of lipid reactive oxygen species (21-23). Ferroptosis can be induced in cancer cells *via* natural or artificial stimuli to induce cell death. Since ferroptosis may lead to the elimination of malignant cells, it has gained attraction as a tumor-suppressive mechanism. The role of ferroptosis in the pathogenesis of cancer is poorly understood and understudied (24). As an alternative cell death pathway, triggering ferroptosis is also a promising approach to overcoming the resistance of cancer cells to apoptosis. Morphological characteristics of the conventional cell death mechanisms involve loss of the permeability of cell wall, shrinkage of cell, distortion of cell organelles and formation of autophagic vacuoles. In contrast, ferroptosis induce cell death by the condensation of mitochondria, the disintegration of mitochondrial cristae and rupture of

*Corresponding author. E-mail: ruksetattar@hotmail.com
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mitochondrial membrane (25).

In 2003, Dolma and colleagues discovered that erastin is a new compound capable of inducing cell death in RAS-expressing cells but the mechanism was morphologically different and was irresponsive to caspase inhibitors (26). Later it was found that this form of cell death can be reversed by iron-chelating agents and interestingly found out another compound RSL3 that was capable of inducing a similar kind of cell death (26)(27). In 2008, Yang (27) validated that iron-chelating agents can inhibit this form of cell death while in 2012 the terminology of ferroptosis was coined by Dixon for erastin-induced cell death in RAS mutated cells (28). To our interest, mammalian cancer cells have exhibited this form of cell death in response to various small molecules such as erastin, RSL-3, ML162, FIN56. Ferroptosis embarks the presence of iron and the accumulation of ROS. Relevantly, the induction of ferroptosis by these small molecules was reversed by iron-chelating agents or lipophilic antioxidants.

A strong relationship between ROS generation and cancer progression has made it an important therapeutic target. ROS generation can not only lead to the resistance of chemotherapies but can promote the aggressiveness of cancer by various pathways. Elevated levels of ROS can modify DNA, and proteins leading to the activation of various oncogenic pathways that can promote tumorigenesis (29). Moreover, ROS-mediated angiogenesis can occur by modulating various endothelial growth factors. It can further increase the migration and invasion of cells by regulating various enzymes and cytoskeleton (30).

Basic mechanisms involved in ferroptosis

The membranes of mammalian cells are rich in phospholipids with one or more polyunsaturated fatty acid (PUFA) chains (31). Ferroptosis is driven by the peroxidation of the PUFA chain. Ferroptosis inducing small molecules inhibits a phospholipid peroxidase i.e glutathione peroxidase 4 (GPX4) resulting in the toxic accumulation of lipid peroxides that induce ferroptosis. The role of PUFAs was confirmed by various studies when ferroptosis was prevented by knocking out genes (e.g., *ACSL4*, *LPCAT3*) essential for the integration of activated PUFAs in membrane phospholipids (PL) (32). However, the molecular

mechanisms behind the oxidation of PUFAs are still unknown.

Phosphorylase kinase G2 (PHKG2) regulates the iron availability to lipoxygenase enzymes that further initiate peroxidation of PUFA at the bis-allylic position leading to ferroptosis. Moreover, PUFA oxidation and ferroptosis can be blocked by pre-treating cells with PUFAs containing heavy hydrogen isotope deuterium at the site of peroxidation, suggesting PUFA peroxidation by PHKG2 is critical for the induction of ferroptosis (33). Further in the endoplasmic reticulum, oxidation of phospholipids is specifically at arachidonoyl (C20:4) or adrenoyl (C22:4) fatty acyl chains and can be inhibited by acyl-CoA synthase 4 (*ACSL4*) to reverse ferroptosis (34).

One of the vital mechanisms of ferroptosis induction is the inhibition of the cystine-glutamate antiporter system (x_c^-) that regulates the exchange of cysteine and glutathione (GSH) across the membrane. System x_c^- is composed of two subunits i.e light chain subunit SLC7A11 (xCT) and heavy chain subunit SLC3A2. While SLC7A11 is specific to system x_c^- (35). Importantly, SLC7A11 is overexpressed in a wide range of tumors and has been shown to induce oncogenic Ras transformation (36) making it an attractive target in cancer therapeutics (37). Ferroptosis can be initialized by inactivation of the system x_c^- , which leads to a reduction in the synthesis of glutathione GSH, the cofactor of an antioxidant enzyme GPX4 (glutathione peroxidase-4) or by direct inactivation of GPX4 (38,39). The GPX4 defense system is an antioxidant that detoxifies various lipid peroxides and studies have shown that it is the key driver of ferroptosis. Its inhibition finally leads to an increase in iron-dependent lipid peroxidation. A number of ferroptosis-inducing small molecules as erastin, sulfasalazine, and sorafenib utilize this mechanism. Notably, cancer cells that overexpress GSH and system Xc^- expression are highly resistant to chemotherapies (40).

As ferroptosis is iron-dependent cell death and the presence of free iron along with PUFAs is critical. The iron-dependent lipoxygenase enzymes oxidize membrane PUFAs for the production of oxidized lipid species that further induces cell death. The fact was validated when iron chelators such as ciclopirox and deferoxamine suppressed ferroptosis by modulating the generation of lipid ROS. Interestingly, the

transport of iron into the cell is the form of iron-transferrin complexes and this process is specifically up-regulated in various cancers and the downregulation of transferrin receptors inhibited ferroptosis.

As already discussed, GPX4 is the main negative regulator of ferroptosis and its inhibition alone is sufficient for inducing this form of necrotic cell death (shown in Figure 1). But the innate repair mechanisms to neutralize lipid hydroperoxides in PUFAs protects against ferroptosis. Stoppage of ferrostatin-1 (ferroptosis inhibitor) dosage caused significant tumor regression selectively in the GPX4-knockout xenografts, but GPX4-wild-type xenografts continued to undergo rapid growth (41). This was attributed to a number of endogenous repair mechanisms that protects the cell from iron-dependent cell death. Recent studies have shown that various endogenous inhibitors as Liproxstatin-1 or ferrostatin-1 were able to inhibit ferroptosis-induced cell death, suggesting the possible role of various antioxidant pathways in the defense against iron-dependent cell death and loss of repair of hydroperoxides is critical for ferroptosis induction.

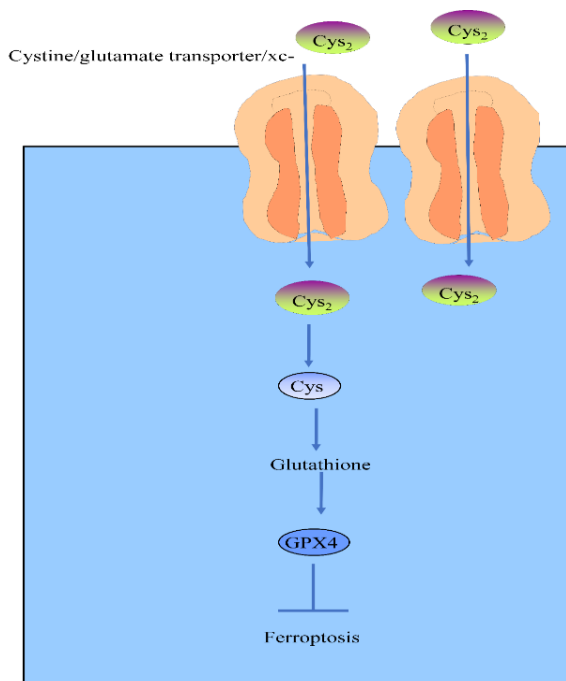


Figure 1. shows the underlying mechanisms of ferroptosis.

Tumor suppression and ferroptosis

The link between ferroptosis and cancer was first identified when the tumor-suppressive activity of p53

mutant mice was observed. p53 is an important tumor suppressor gene. p53 induces the DNA-damage-response pathway including DNA repair, apoptosis, cell-cycle arrest, and/ or senescence (42). In non-transformed, un-stressed cells, the amount of p53 protein is generally kept low. p53 is an important tumor suppressor gene. p53 induces the DNA-damage-response pathway including DNA repair, apoptosis, cell-cycle arrest, and/ or senescence (42). In non-transformed, un-stressed cells, the amount of p53 protein is generally kept low. It has long been considered that p53 mainly exerts its tumor-suppressive function via the above-mentioned mechanisms. Interestingly, the acetylation-defective mutant p53^{3KR} is unable to induce these classical p53 functions, but still maintains its anti-tumor activity (43, 44). Inhibition of the GSH/GPX4 defense system finally leads to an increase in iron-dependent lipid peroxidation. It has been shown that p53 inhibits the expression of SLC7A11, a component of the Xc⁻ system, thereby accelerating ferroptosis. p53 caused transcriptional downregulation of SLC7A11. Furthermore, overexpression of SLC7A11 rescued these cells from p53^{3KR}-mediated ferroptotic death. Upon p53^{3KR} expression induced by tetracycline, growth of H1299 p53^{-null} cells was drastically reduced in xenografted mice. However, tumor-suppressive effects of p53^{3KR} were abolished to a greater extent upon SLC7A11 overexpression (43, 44). In addition, p53 can also enhance ferroptosis by regulating SAT1 (spermidine/spermine N¹-acetyltransferase) in multiple cancer cells including breast cancer (45) or by regulating GLS2 (glutaminase 2) (46,47). Conversely, p53 can also negatively regulate ferroptosis, e.g. by p53-p21-dependent upregulation of intracellular GSH (48). p53 function in ferroptosis seems to be regulated by posttranslational modification(s). p53 Ser46 phosphorylation has been recently reported to trigger ferroptosis following cisplatin treatment (49-50), but the underlying mechanism is unclear.

Role of ferroptosis in various types of Cancers

Pancreatic cancer

Pathologically, the most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC) with a high prevalence of kRas mutations (51). Since ferroptosis was originally investigated to be a

dependent phenomenon, therefore, its role in PDAC is critical. The role of ferroptosis in PDAC is tricky with dual effects on the growth of cancer. The induction of ferroptosis in pancreatic cancer cells has been shown through various complex mechanisms. The role of the antioxidant enzyme GPX4 in ferroptosis has already been discussed and it has been established prognostic factor in pancreatic cancer patients. In a recent study, the impact of GPX4 depletion upregulated 8-OHG release leading to the activation of the DNA sensor pathway (TMEM173/STING-dependent), resulting in the infiltration of macrophages and the activation of kRas-driven PDAC in mice. Infiltration of tumor-associated macrophages was increased in Kras-driven and GPX4 depleted mice. TMEM173 depletion protected against GPX4 depletion-induced cancer progression and decreased infiltration of TAMs in Kras-driven mice. Overall, ferroptosis inhibitors suppressed kRas-mediated oncogenesis, revealing the possible role of targeting ferroptosis to regulate tumor progression in the pancreas (52). In another study, zalcitabine-an anti-HIV drug-induced mitochondrial damage and ferroptosis by activating the ALOX5 pathway in pancreatic cancer. Zalcitabine failed to reduce the size of tumors in mice subcutaneously implanted with ALOX5-knockdown, STING1-knockdown or ATG5-knockdown-PANC1 cancer cells (53). Further, high dose rapamycin-induced degradation of GPX4. GPX4-knockdown MIAPaCa2 or PANC1 cells were found to be more sensitive to rapamycin-mediated tumor-suppressive effects (54).

Traditionally, artesunate is an anti-malarial drug but later has shown antitumor potential. Artesunate-induced ferroptosis in pancreatic ductal adenocarcinoma (PDAC) cells that are resistant to apoptosis, indicating a possible pathway for the treatment of tumors resistant to apoptosis (55). Promisingly, potent antitumor effects were seen with the co-treatment of cotylenin A and phenylethyl isothiocyanate (PEITC) mainly by inducing ROS in pancreatic cancer cells. Cotylenin A and Piperlongumine synergistically induced the death of pancreatic PANC-1 and MIAPaCa-2 cancer cells. Further studies have shown a more potent combination of Piperlongumine, CN-A and sulfasalazine that has better ferroptosis-inducing effects (56).

Breast cancer

As discussed previously GPX4 inhibition is the primary mechanism for the induction of ferroptosis. Importantly, a number of studies have shown that inhibition of GPX4 can induce ferroptosis in resistant breast tumors as they rely on GPX4 for survival. A group of resistant cells in high-mesenchymal state cells were found following lapatinib treatment in HER2-amplified breast cancer cell lines. Importantly, the author named this highly resistant population as persister cells and importantly they were highly dependent on GPX4 for survival and further, GPX4 inhibitors eliminated these persister cells by inducing ferroptosis (57). This implicates the significance of ferroptosis in overcoming resistance to breast cancer therapies.

In a range of breast carcinoma cell lines (MCF-7, MDA-MB-231, ZR-75 and SKBr3), co-treatments of siramesine and lapatinib triggered ferroptosis by up surging intracellular iron levels and ROS (58). The co-administration of siramesine and lapatinib can up-regulate intracellular iron levels by targeting transferrin and ferroportin leading to ROS-mediated ferroptosis in breast cancer cells. This induction was reversed by iron chelators (59). Yet, in another study, ferroptosis in TNBCs was induced by the depletion of cysteine which plays a critical role in GPX4 synthesis. Ferroptosis was induced via the GCN2-eIF2 α -ATF4-CHAC1 pathway. The restoration of this pathway was shown with ferrostatin-1, necrostatin-1, RIP1 knockdown and deferoxamine (an iron chelator) to emphasize that stress response pathways were specifically involved (60).

Accumulating evidence provided evidence about gefitinib resistance in triple-negative breast cancer (TNBC) and a recent study has shown that induction by ferroptosis by inhibiting GPX4 sensitized TNBC to gefitinib (61).

Sulfasalazine SAS preferentially triggered ferroptosis in breast cancer cells with lower estrogen receptor expression by inhibiting GPX4 and xCT while inducing transferrin receptor and divalent metal transporter 1 (62). Another study revealed that metformin could trigger ferroptosis by decreasing the protein stability of SLC7A11 by blocking the UFMylation process. The author further emphasized that SAS and metformin can have a synergetic effect on inducing ferroptosis and inhibiting the invasiveness

of breast cancer. SLC7A11 knockdown caused a significant increase in the sensitivity of cancer cells to metformin and enhanced the production of lipid ROS. Metformin and sulfasalazine combinatorially inhibited the growth of tumors in mice subcutaneously implanted with T47D cells (63). More recently, curcumin has been shown to exhibit its anti-tumor effects by inducing ferroptosis in breast cancer cells (64). Promisingly, the anaesthetic agent ketamine showed anti-proliferative effects by inhibiting KAT5/GPX4 axis that further triggering ferroptosis. Ketamine exerted inhibitory effects on GPX4 expression by attenuating KAT5 on the promoter regions of GPX4 by reducing the levels of H3K27ac (65).

Ovarian Cancer

Ovarian cancer is a lethal and therapeutically challenging disease (66-69).

As explained in previous paragraphs about the potent role of p53 in regulating ferroptosis. Here in a recent study, Human Serum Incubated-Superparamagnetic Iron Oxides induced ferroptosis in ovarian cancer cells by the transfer of free iron to mitochondria and intracellular accumulation while the p53 gene augmented this effect by the down-regulation of SLC7A11 and GPX4 in ovarian cancer cells (70). The role of p53 in relation to ferroptosis in ovarian cancer is still under-studied and warrants the need for further investigations.

Accumulating evidence suggests that transcriptional co-activator with PDZ binding motif (TAZ) can regulate the invasiveness of ovarian cancer and is an important target to combat chemotherapeutic resistance (71). In a recent study, Yang and colleagues have shown that the activation of TAZ can induce ferroptosis in ovarian cancer cells by regulating the ANGPTL4-NOX gene pathway (72). Platinum-tolerant cancer cells poses challenges to chemotherapies in ovarian cancers and interestingly these cells were more responsive to GPX4 inhibitors leading to ferroptosis induction. FZD7 overexpression not only promoted proliferation rates of OVCAR5 and SKOV3 cancer cells but also enhanced platinum resistance. There was an evident reduction in the levels of GPX4 in FZD7 knockdown cells. Importantly, a notable reduction in growth rates of

tumors was reported in mice inoculated with FZD7 knockdown OVCAR5 cancer cells (73).

Lung Cancer

Largely, lung cancer is classified into two groups; small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Importantly, 88% of the NSCLC overexpresses and they are more dependent on iron as transferrin protein is overactive (74). Cisplatin is the primary adjuvant chemotherapy in NSCLC but it has shown frequent resistance. Induction of ferroptosis by GPX4 inhibition improved the response of cisplatin in a number of lung cancer cell lines and in xenograft mice models (75). In another study, combining cisplatin with ferroptosis activator RSL3 induces ferroptosis through ferritinophagy.

However, the resistance is a complex phenomenon but following cisplatin treatment leads to the over-activation of NRF2/xCT pathway that has been frequently associated with the resistance. Notably, a low dose of cisplatin in combination with ferroptosis activators i.e erastin/sorafenib notably improved the prognosis of failed cisplatin therapy (76). Moreover, combining erastin with radiotherapy helps the combat radio-resistance in NSCLC cells (77).

Urologic Cancers

Ferroptosis can implicate the treatment of various urologic cancers as prostate cancer, kidney cancer, and bladder cancer. Prostate cancer (PC) is not only a malignancy but a lipid metabolic disorder. Ferroptosis has been identified to play a critical role in the pathophysiology of prostate cancer. Importantly, PC cells were found to be more sensitive to ferroptosis inducers compared to non-cancer prostate cells. Resistant PCs exhibited higher sensitivity to erastin and RSL3. The author suggested the therapeutic potential role of erastin and RSL3 as adjuvant therapy with anti-androgen therapy. Combinatorial treatment with erastin/RSL3 and enzalutamide synergistically inhibited the growth of tumors in xenografted animal models (78). Iron-dependent death can improve the prognosis of anti-androgen therapy in prostate cancer by its antiproliferative effects. Bicalutamide-iron combinations efficaciously impaired tumor expansion while single agents did not inhibit tumor growths

(79). In a comprehensive statistical study utilizing genomic and clinical cohorts on various ferroptosis-related genes, AIFM2 and NFS1 were found to be highly correlated with ferroptosis in prostate cancer. NFS1 and AIFM2 knockdowns remarkably hampered the expansion of tumor mass in experimental mice (80).

Foods high in dietary polyunsaturated fatty acid (PUFA) are linked with a reduced risk of PC and an enzyme 2,4-Dienoyl-CoA reductase 1 (DECR1) that is involved in PUFA oxidation is frequently up-regulated in PCs. Interestingly, deletion of DECR1 leads to the accumulation of PUFAs that induces lipid peroxidation and ferroptosis (81). Knockdown of DECR1 increases the susceptibility of castration-resistant PCs to ferroptosis by up-regulating lipids detoxifying enzymes (82). PANX2-a protein coding gene was found to be significantly up-regulated in PCs and has been identified as a potent marker correlated with ferroptosis (83). PANX2 was shown to regulate the nuclear factor erythroid 2-related factor 2 (NRF2) and antioxidant response of NRF2 protects cancer cells against ferroptosis by regulating SLC7A11. In PCs, silencing of PANX2 inhibited NRF2 leading to ferroptosis (83).

Hippo-YAP/TAZ is composed of kinase cascade that triggers cell growth. Hippo pathway and ferroptosis are highly sensitive to cell density and an up-regulated TAZ expression is linked with increased sensitivity to ferroptosis (84). In Renal carcinoma cells (RCCs), cell density-mediated ferroptosis was mediated by a TAZ-EMP1-NOX4 pathway, implying the role of iron-dependent death in the treatment of resistant renal carcinoma (85). In renal carcinoma cells, lycorine treatment regulated the key markers of ferroptosis by decreasing the expression of GPX4 and increasing the expression of acyl-CoA synthetase long-chain family member 4 (ACSL4) in RCCs (86).

Bioinformatically, the relationship between ferroptosis and bladder cancer has been established by a number of studies (87-89). A natural product baicalin was found to induce ferroptosis in bladder cancer cells 5637 and KU-19-19 by regulating ferritin heavy chain 1 (FTH1). Intraperitoneally injected Baicalin induced regression of the tumor mass in mice inoculated with KU-19-19 cells (90). Fin56 which is a type 3 ferroptosis inducer promotes GPX4 degradation and triggers ferroptosis in bladder cancer

cells. Also, Torin 2 which is a potential mTOR inhibitor promotes autophagy and when combined with Fin56 had a synergistic cytotoxic effect on the bladder cancer cells. This suggests the combined therapy of ferroptosis inducers and mTOR inhibitor has therapeutic potential for the treatment of bladder cancer (91).

Role of ferroptosis in various cancer therapies

The role of ferroptosis in radiotherapy gained attention when exposed to ionizing radiation (IR) was shown to induce ferroptosis and was frequently linked with better survival following radiotherapies (92, 93). Substantial evidence exists between ferroptosis and the prognosis of IR in diverse cancer models. In cell culture and xenograft models of breast cancer, lung cancer, oesophageal cancer, ovarian cancer, sarcoma, and glioblastoma, ferroptosis inducers improved the radiosensitivity of IR by the inactivation of SLC7A11 or GPX4 (94,95). In both in-vitro and in-vivo models of lung adenocarcinoma, treatment with erastin improved the sensitivity of X-ray irradiation by the depletion of glutathione (96). Following radiation therapy, the use of polyphenol gallic acid decreased the survival of breast cancer and melanoma cells mainly by inhibiting GPX4 activity (97).

Only a few studies hint at a possible role of ferroptosis in immunotherapies and yet more intensive research is required to establish this relationship. In a notable work by Wang et al published in Nature has shown that immunotherapy can activate CD8+ T cells leading to secretion of IFN γ that further suppresses the expression of SLC7A11 and SLC3A2 that regulates the system Xc that further resulting in JAK (Janus kinase) -STAT1 (signal transducer of the transcription 1) mediated ferroptosis in cancer cells. Further, it was shown that the expression of the anti-ferroptosis gene SLC7A11 is negatively correlated with IFN γ expression in cancer cells, CD8+ T cell counts, and prognosis of cancer patients (98). These findings have been repeatedly mentioned as a breakthrough in the field of immunotherapy that needs further investigations.

One of the major challenges of anti-tumor therapies is resistance. Ferroptosis has gained attention for enhancing the sensitivity of resistant cancer therapies and a number of anticancer drugs as iron activators, GSH inhibitors and NRF2 inhibitors have been

developed that suppress oncogenesis by activating iron-dependent cell death or ferroptosis (99).

Recent data has shown that ferroptosis inducers can up-regulate the cytotoxicity of cisplatin that otherwise exhibits frequent resistance (76). Ferroptosis agonist i.e erastin, sorafenib triggered ferroptosis through NRF2/SLC7A11 pathway in cisplatin-resistant non-small cell lung cancer cells (76). Further, STAT3 inhibitor BP-1-102 induced ferroptosis by interrupting STAT3/NRF2/GPX4 signals in osteosarcoma cells. Collectively, the findings indicated that ferroptosis agonists and STAT3 inhibitors caused re-activation of ferroptosis in cisplatin-resistant cells and consequently increased sensitivity to cisplatin (100).

Mechanistically, artesunate has been shown to induce ferroptosis by upregulating NCOA4-mediated ferritinophagy, promoting lysosomal activity leading to increased intracellular iron levels and regulating iron-related genes. Further artesunate has been repeatedly shown to potentiate the anticancer potential of other chemotherapeutic agents. For instance, artesunate-mediated ferroptosis induction increased the sensitivity of cisplatin in resistant head and neck cancer cells by inhibiting NRF2 pathway (101). Sorafenib is the first-line chemotherapeutic drug used against advanced hepatocellular carcinoma. Artesunate potentiates the effects of sorafenib by inducing ferroptosis by the activation of lysosomal cathepsin B/L, ferritin degradation and peroxidation of lipid (102). Previously, clinical trials on artesunate showed that it improved the survival of cancer patients and recent data has shown its potential role in facilitating ferroptosis, therefore, further studies are required to harness its true potential. Further, Siramesine an antidepressant drug and lapatinib which is a tyrosine kinase inhibitor have been shown to possess iron activating potential. As indicated above in the breast cancer section, both drugs potentially improve the efficacy of chemotherapies by reducing resistance and relapse of tumors.

As cancer cells are sporadically proliferating, they are highly dependent on iron for their growth and survival. A number of cancer cell lines have reported up-regulation of TFR and down-regulation of FPN. Balance in the metabolism of iron plays integral role in improving the resistance of chemotherapies (103). It is important to note that drug-resistant tumors overexpress transferrin receptor (TFR) and ferritin and

less ferroportin-1 (FPN, the iron transport protein) compared to non-resistant as transport of iron plays a critical role is ferroptosis resistance. The decrease in intracellular free iron leads to resistance toward iron-dependent cell death. Conversely, ferroptosis sensitivity can be augmented by TFR overexpression leading to up-regulation in iron uptake, blocking FPN that impairs iron export and inhibiting ferritin that reduces iron storage. It has long been established through various studies that inhibition of TFR is linked with combating resistance to chemotherapies (104, 105). For instance, it was shown that liposomes co-encapsulating doxorubicin and verapamil that targets TFR showed high efficacy to combat chemotherapeutic resistance in hematologic malignancy cells (105). As already discussed, targeting TFR induces ferroptosis, this implicates the role of TFR to improve the response of chemotherapeutic drugs in breast cancer.

Detailed Mechanistic Insights about Ferroptosis:

N6-methyladenosine (m6A), an essential RNA modification is catalyzed principally by METTL3-METTL14 methyltransferase complexes. IGF2BPs belong to the family of m6A readers and promote the storage and stability of their target mRNAs in an m6A-dependent manner. METTL3 stabilized SLC7A11 by IGF2BP. IGF2BP2 overexpression caused significant reversal of the inhibitory effects of METTL3 silencing on the mRNA stability of SLC7A11 (106).

AGAP2-AS1, a long non-coding RNA has been shown to fuel the proliferation ability of melanoma cells. AGAP2-AS1 knockdown markedly enhanced erastin-directed ferroptotic death in melanoma cells. AGAP2-AS1 increased mRNA stability of SLC7A11 by IGF2BP2 in melanoma cells (Fig.2) (107).

PCDHB14 (Protocadherin beta-14) is a tumor suppressor and reported to be transcriptionally upregulated by p53. As SLC7A11 is a negative regulator of ferroptosis and NFKB (p65) has been shown to transcriptionally upregulate SLC7A11. PCDHB14 promoted E3 ubiquitin ligase RNF182-induced ubiquitylation and degradation of p65 (Fig.2) (108).

ALKBH5) is a m6A demethylase and promotes destabilization of target mRNAs by demethylation. Inhibition of ALKBH5 markedly abrogated the

sensitivity of HPSCC cells to ferroptosis. However, ALKBH5 overexpression sensitized HPSCC cells to RSL3. More importantly, RSL3 considerably induced regression of tumor mass in mice inoculated with ALKBH5 overexpressing- HPSCC cells. NFE2L2/NRF2 is degraded by KEAP1 but inactivation of KEAP1 relieves KEAP1-mediated inhibitory effects on NFE2L2/NRF2. Inactivation of NFE2L2/NRF2 signaling has been reported to maximize anti-tumor effects of ferroptosis inducers. ALKBH5 overexpression considerably abrogated binding ability of IGF2BP2 to 3'UTR of NRF2 mRNA. Intraperitoneal injections of NRF2 inhibitor (ML385) proficiently inhibited the weights and growth of tumors in mice inoculated with ALKBH5-silenced cells (109).

Inhibition/inactivation of FGFR4 significantly reduced the recruitment of β -catenin/TCF4 complexes to promoter regions of SLC7A11 and Ferroportin-1. Selective inhibitor of FGFR4 (Roblitinib) in combination with trastuzumab synergistically inhibited the growth of palpable tumors in mice inoculated with MDA-MB-361 or rSKBR3 cancer cells. FGFR4 inhibition caused considerable suppression in the levels of p-GSK-3 β , β -catenin, SLC7A11 and Ferroportin-1 (110).

CCR4-NOT complexes are recruited to poly(A) tails of mRNAs by PABPC1 (poly(A)-binding protein 1) for de-adenylation of mRNAs, or is recruited directly by YTHDF2 to trigger the process of destabilization of m6A-modified mRNAs. Shortening of the poly(A) tails (de-adenylation) has been demonstrated to repress expression by decreasing the stability of target mRNAs. Knocking down of CNOT1, a large scaffold subunit of the CCR4-NOT complex led to significant increase in the length of poly(A) tail of SLC7A11 in HuH6 cells. There was an evident increase in the length of SLC7A11 poly(A) tails upon the overexpression of IGF2BP1 and reduced profoundly upon knockdown of IGF2BP1. IGF2BP1 competitively interacted with PABPC1 and blocked interaction of the CCR4-NOT complexes with PABPC1 (Fig.2) (111).

Phosphorylation of DRP1 (Dynamin-related protein 1) at serine-637 inactivates it. DRP1 inactivation by phosphorylation at Serine-637 was repressed in erastin-induced ferroptotic death. DRP1 dephosphorylation at Serine-637 in GBM cells

potently induced ACSL4-mediated ferroptosis. HSP90 co-localized with ACSL4 and DRP1 in the outer membranes of mitochondria. Calcineurin dephosphorylated DRP1 at Serine-637 and HSP90 interacted with calcineurin and stimulated its functions. In PL1 cells, HSP90 knockdown increased phosphorylation of DRP1 at serine-637 and reduced the levels of calcineurin and ACSL4. However, active DRP1 and HSP90 substantially enhanced the thermal stability of ACSL4. Overexpression of HSP90 and ACSL4 maximized erastin-induced shrinkage of PG7-derived glioma tumors (112).

KAT6B (Lysine Acetyltransferase 6B) is a negative regulator of ferroptosis. Erastin-mediated ferroptosis was blocked in KAT6B-overexpressing-U251 and LN229 cells. KAT6B knockdown potently abolished the enrichment of histone H3 lysine 23 acetylation and RNA polymerase II on promoter region of STAT3 in LN229 and U251 cells (113).

NF κ B activating protein (NKAP), an RNA-binding protein binds effectively to m6A-containing sites of SLC7A11 transcripts and increased protein levels of SLC7A11. Sulfasalazine-mediated tumor growth inhibition was noted to be more pronounced in subcutaneous xenograft models inoculated with NKAP-silenced U87MG cells. Sulfasalazine also efficiently inhibited tumor growth in an orthotopic intracranial animal model inoculated with NKAP-silenced U87MG cells. NKAP recruited the splicing factor SFPQ for the recognition of alternative splice sites after binding to m6A sites. SFPQ is a splicing factor and participates in the regulation of oncogenic transcriptome. NKAP-directed recruitment of SFPQ promoted the mechanism of alternative transcription termination site (TTS) and promoted maturation of mRNA (114).

There was a significant reduction in the weights and volume of tumors in mice orthotopically implanted with LINC01564-silenced LN229 cells into the brain. SRSF1 overexpression increased the levels of NRF2 as well as its target genes. LINC01564 promoted the stability of MAPK8 mRNA by recruitment of SRSF1. LINC01564 promoted MAPK8-mediated phosphorylation of NRF2 for the activation of the target genes (Fig.2). Likewise, there was a significant impairment of tumor growth in mice orthotopically implanted with MAPK8-silenced LN229 cells (115).

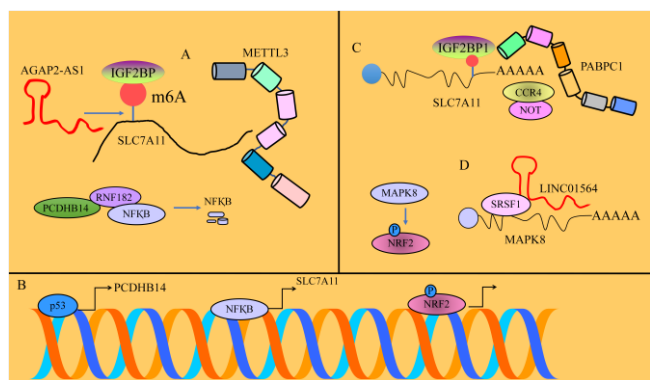


Figure 2. Diagrammatic representation of interplay among different signaling molecules for the regulation of ferroptosis. (A) METTL3 induced m6A modifications of SLC7A11. These modifications are read by IGF2BPs. IGF2BP2-controlled the stability of SLC7A11 mRNA. AGAP2-AS1 increased mRNA stability of SLC7A11 by IGF2BP2 (B) PCDHB14 (Protocadherin beta-14) is transcriptionally upregulated by p53. NFKB (p65) transcriptionally upregulates SLC7A11. PCDHB14 promoted RNF182-induced ubiquitylation and degradation of p65. (C) IGF2BP1 competitively interacted with PABPC1 and blocked interaction of the CCR4-NOT complexes with PABPC1. (D) LINC01564 promoted the stability of MAPK8 mRNA by recruitment of SRSF1. LINC01564 promoted MAPK8-mediated phosphorylation of NRF2 for the activation of the target genes.

Conclusions

We have witnessed incredible and ever-growing interest among clinical and basic researchers in characterization of regulators of the ferroptosis in cancer and in reaping the full benefits of this wealth of information to improve cancer prevention and treatment. Ferroptosis has a highly context-dependent and complex role in carcinogenesis and metastasis. Design and development of translational anticancer agents is challenging and relies on continuing research for a better understanding of the regulatory mechanisms and signaling pathways which mechanistically modulate ferroptosis.

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Not applicable.

Interest conflict

The authors declare that they have no conflict of interest.

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