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Ferroptosis and its facet in Cancer therapy

Abstract

Ferroptosis is a regulated process impelled by iron-dependent lipid peroxidation. It is a new type of cell destruction processes including apoptosis, autophagy and necrosis. It demonstrates mainly the contraction of mitochondria and expansion of mitochondrial membrane density which does not lead to any alteration in morphology. Due to the malfunctioning of ferroptosis several disorders arise which includes damage of one or more nerve which leads to numbness and muscle weakness whereas ischemia reperfusion injury, acute kidney failure and cancer also occurs. Also, ferroptosis is induced in large number of cancer cells through series of small molecules which helps in to bringing out this process. In scientific research and medicine many findings contribute in the chance of defeating cancer by genetic or pharmacological interference with ferroptosis cell death which is appealing for various researches. There are multiple pathways and cell organelles which plays a role in ferroptosis regulation. Ongoing studies on ferroptosis have demonstrated its role in humans though its mechanism is not yet clear. Recently, various studies have encouraged the role of this newly emerged cell death process and also showed some effective usage in the treatment of cancer. Here, we review the mitochondrial aspect of ferroptosis as well as discuss on the role of ferroptosis in Cancer cell therapy. We will also aim on the future scope of ferroptosis in the treatment of Cancer as well as discuss about the problems related to its clinical role which may trigger the cancer cell therapy.

Keywords: iron-dependent lipid peroxidation, necrosis, apoptosis, autophagy, mitochondrial membrane, cancer cells, multiple signalling pathways

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Introduction

The term ferroptosis was first demonstrated by Dixon in 2012.[1] He described it as a novel cell death which was distinct from autophagy and apoptosis. Unlike other cell death, this is an iron and reactive oxygen species (ROS) dependent cell death and mostly, causes cytological changes. This includes shrunken mitochondria cristae, shredded outer mitochondrial membrane and membrane was compressed which causes change in the mitochondrial function.[2–6] Due to the occurrence of oxidative stress and intense lipid peroxidation these deformities arise from the loss of selective permeability of plasma membrane. There are crucial regulators of ferroptosis which includes glutamate and glutamine.[3] Ferroptosis occurs extracellularly along with typical physiological function. Sensitivity of cells to ferroptosis may affect the lipid metabolism. Ferroptosis also requires polyunsaturated fatty acids as they are susceptible to lipid peroxidation.[4] Due to iron involution in the collection of lipid peroxide, ferroptosis occurs.[5] Several molecules are involved in the modulation of ferroptosis are: 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).[6] It has explained in previous studies that ferroptosis played an important role in varied diseases including Cancer,[7] acute kidney failure,[8–10] neuropathy[1,8] ischemia reperfusion injury.[7]

Role of mitochondria

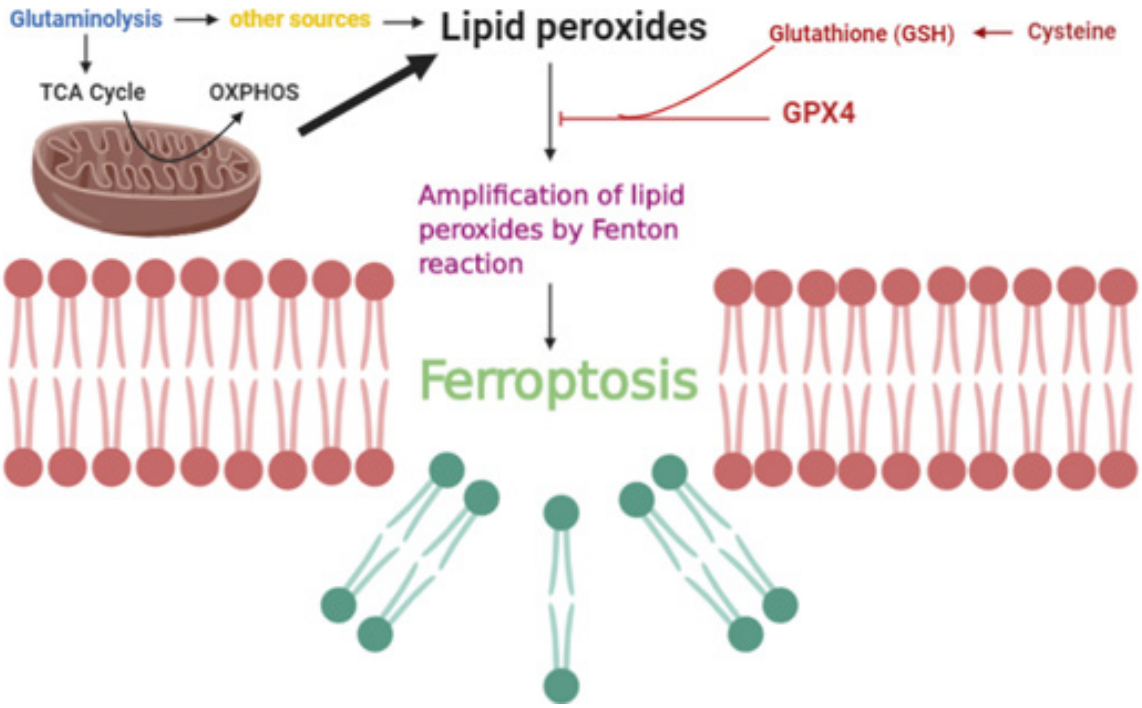
As we know that, mitochondria have an important function in generating ATP through OXPHOS which is the basic requirement for most of the normal cell types.[7,11] This mechanism is determined by the rate of ROS production.[12] Mitochondria plays a main function in the tissue homeostasis and also causes crucifixion of several types of regulated cell death which includes extrinsic and intrinsic apoptosis and autophagy.[13,14] In an experimental coronation of ferroptosis through pharmacological xCT inhibition demonstrated to bring out mitochondrial fragmentation, mitochondrial ROS production, loss of the mitochondrial membrane potential (MMP) and ATP depletion.[2,6,11,15–17] Therefore, there is a necessity of enhancing mitochondrial metabolism for crucifixion of ferroptosis,[6] reduction of mitochondria via Parkin-mediated mitophagy in vitro or suppression of OXPHOS rescued cells from ferroptosis elicited by cystine deprivation or erastin.[11] Thereby, due to oxidative stress and induction of ferroptosis causes mitochondrial DNA (mtDNA)-depleted ρ0 cells to remain susceptible towards them.[18] Therefore, it is still controversial that the role of mitochondria is involved in ferroptosis of all cell types or not and there may be cell-specific variations same as explained type I and type II cell events in extrinsic apoptosis.[19] Meanwhile, BH3-interacting domain death agonist (BID) which is a Bcl-2 family member is split into shortened Bid (tBID) which has important role in extrinsic apoptosis type II cells and it was demonstrated for the necessity of erastin-induced ferroptosis and oxytosis in neurons.[16]

Ferroptosis: overview in oncogenic selective cell death

At first in small molecules particularly targeting Harvey rat sarcoma viral oncogene homolog (HRAS)G12V-mutant human foreskin fibroblasts (BJeLR) where ferroptosis was first originated as a component of synthetic fatality screen.[20] Then two classes of small molecules were described, first class is described by Xc-inhibitor which has erastin and sulfasalazine and another class is described by GPX4 inhibition which has RSL3.[2,21] It was observed that due to increase in the intracellular iron levels of HRAS-mutant cells it was shown that HRASG12V selectivity was explained to stem from a higher expression of transferrin receptor TFRC.[21]

It was also demonstrated that the higher sensitivity to eras tin and the silencing of KRAS by small hairpin (sh) RNA leads to the reduction of eras tin's potency in Kirsten sarcoma viral oncogene homolog (KRAS)-mutant Calu-1 lung cancer cells. Also, in the treatment upon shRNA-mediated suppression of BRAF in A-673 cells which supresses an activating BRAFV600E mutation, showed more resistant to eras tin.[2] Also, by increasing the activity of mitogen-activated protein kinase Pathway (MAPK), it was shown that human mammary epithelial (HME) cells expressing mutant epithelial growth factor receptor (EGFR) were much more sensitive to cystine deprivation-induced ferroptosis which encourages an increased ferroptosis sensitivity of oncogene-expressing cells.[22] Additionally, it was presented that the level of MAPK pathway activity in non-small-cell lung cancer (NSCLC) cell lines, interacts with sensitivity to ferroptosis induced by cystine deprivation.[22]

Few Studies are also going on oncogenic RAS isoforms and introduction of cellular ROS aside from carry out the potential effects of ferroptosis. In this view, due to ROS production the oncogenic expression of NRASG12D and HRASG12V was and also causes a p38 mitogen-activated protein kinase (MAPK)-mediated oxidative stress response.[23] Furthermore, the RAS-stimulated ROS production is mediated by PI3K/Rac1 and RAF/MEK/ERKRAS-effector pathways regulation which activates of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-oxidases (NOX).[24,25] KRAS also improved its activation and supported the cellular transformation by changing the location of p47phox, which is a sub- unit of NADPH oxidase 1 (NOX1) and shifting it to the plasma membrane.[26] Also, in the background of arresting tumour suppressor p16 results in up-regulation in NADHPH oxidase 4 due to KRASG12V expression.[27] Thereby, oncogenic RAS isoforms may also have an impact in ferroptosis and lipid peroxidation by boosting up the delivery into the normal cellular ROS pool. This has been shown that due to the introduction of ROS belonging to acute oncogenic RAS over expression in vitro helps in cellular transformation at the rate of raised ROS. Still, there is a doubt arises by means of what the tumours expressing oncogenic KRAS from the remote site would manage ROS in vivo. An appealing context in respect NRF2, which acts as a transcription factor which also activates antioxidant defence genes shows that expression of KRASG12D, BRAFV619E and MYCERT2 oncogenes from their respective remote site induces nuclear NRF2.[28,29]



Cysteine deprivation

Active mitochondria	→	Rapid exhaustion of GSH by GPX4	→	Potent ferroptosis
Inactive mitochondria	→	Slow exhaustion of GSH by GPX4	→	Diminished ferroptosis

Figure 1 This shows that mitochondria play an essential role in cysteine-deprivation elicited ferroptosis but not in GPX4 inhibition elicited ferroptosis. The mitochondrial TCA cycle and electron transport chain encourage cysteine-deprivation elicited ferroptosis by delivering a main origin for cellular lipid peroxide production. Also, a component of the TCA namely fumarate hydratase may help in the anti-tumour role in mitochondrial mediated ferroptosis.

Mostly, NRF2 helps in the positive regulation of various genes namely glutamate-cysteine ligase catalytic subunit (GCLC) and glutamate-cysteine ligase modifier subunit (GCLM) and acts as a transcription factor during GSH (Figure 1) synthesis and also xCT.[30–32] Also, NRF2 enhances expression of Ferritin (FTH)[33] which acts like a hunter for active iron thereby, improving its protecting function in ferroptosis. It was also seen that in chronic liver cancer, hepatocytes became more sensitive to ferroptosis inducers at the time of removal or inhibition of NRF2.[33,34] Also, the expression of the ATP binding cassette (ABC)-family transporter which acts as a multidrug resistance protein 1(MRP1) is monitored by NRF2 when it merges with KEAP1 which is a tumour suppressor protein.

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Thereby, intervening glutathione efflux, MRP1 was able to sensitise to ferroptosis.[35] In human malignant lung carcinoma due to which cellular rates of glutamino lysis increases also, shows simultaneous elevation of KEAP1 and KRAS mutations.[36] Also, activation of NRF2 by withaferin A resulting in the induction of its actual target gene heme oxygenase 1(HMOX1). In neuroblastoma, HMOX1 brings out a plenty of iron from cytosol by catalysing its release from heme promoting ferroptosis.[37] Therefore, NRF2 activation results in cell type specific ferroptosis and expression of HMOX1 gene can also influence opposing results for ferroptosis.

Cancer treatment and therapeutics

Ferroptosis sensitivity of various types of carcinoma cells was significantly distinct from one other. In a committee of various cancer cell lines called NCI-60 of US National Cancer Institute Developmental Therapeutics Program. Among all the eight tissues, diffuse large B cell lymphomas and Renal cell carcinoma showed more susceptibility to erastin-induced ferroptosis than other six tissues namely: the breast, lung, colon, melanocytes, central nervous system, and ovary.[6] There was controversy that the susceptibility of various cell lines to ferroptosis is distinct to each other due to the of the change in their essential metabolic state. In many studies, ferroptosis has been described as a major element in inhibiting cancer growth as well killing the carcinoma cells. Thereby, diagnosis is a better attempt than following same typical chemotherapy method. Therefore, summarization of all the achievable means of ferroptosis is an effective approach towards the treatment of various cancer types and also in clinical application.

Discovery of human epidermal growth factor receptor (HER1/HER2) tyrosine kinase inhibitor Lapatinib which has a high mesenchymal state and it was also selectively sensitised to the interference of ferroptosis brings out the discovery of ferroptosis-inducing therapy (FIT) which showed its effectiveness in various types of cancer treatment.[38,39] For first time studies also showed that the cells which are free from other ways of killing but those are selectively sensitised to ferroptosis. Recently, immunotherapy is developed which demonstrated sensitization of tumour cell ferroptosis. In regard of xCT which is abnormally expressed in many cancers and inducing ferroptosis may be not much efficient for cancer. There are two major inducers namely RSL3 and erastin have poor solubility of water and it is metabolically instable which makes it inappropriate for the in vivo application so, it does not match up to pharmacokinetic standards.[39,40,41] Many attempts were taken for in vivo application of erastin in order to avoid this obstacle and show erastin more relevant. One of the approaches was regarding triple-negative breast cancer (TNBC)cells which were treated with erastin which were wrapped in exosomes covered with folate to specifically target folate receptor-overexpressing TNBC.[42] Another approach was shown anti-tumour activity of stable form of erastin called piperazine-coupled erastin in a xenograft model using human fibrosarcoma HT-1080 cells.[18,40] Also, in a SU-DHL-6DLBCL xenograft model imidazole-ketone erastin, a metabolically stable variant of erastin has demonstrated to reduce tumour growth.[41] Although for enhancing clinical application, small molecule backbones for RSL3 and erastin will have to be more advance. Also, there are many drugs which are certified by food and drug administration (FDA) determines its function by ferroptosis induction in various cancer types. One of the drugs is Sorafenib, which is a multi-kinase inhibitor approved by FDA and helps in the treatment of hypernephroma and also in liver cancer which is also called HCC. Thereby, Sorafenib is demonstrated to inhibit system xc-.[43] Additionally, ferropstatin-1 and iron-chelators suppresses sorafenib by inducing cell death in HCC.[44] Tumour suppressor retinoblastoma protein (RB1) suppresses ferroptosis induced by sorafenib treatment was also explained[45] which indicates a potential biomarker for sorafenib treatment-induced ferroptosis.

Another drug called Sulfasalazine (SAS) which was an FDA-approved drug was speculated to act as an anti-inflammatory drug for the treatment of rheumatoid arthritis and inflammatory bowel diseases (Crohn, ulcerative colitis).[46] The targets of SAS are arachidonat-5-lipoxygenase (ALOX-5),[47] cyclooxygenase2 (COX-2)[48] and nuclear factor 'kappa-light-chain-enhancer'(NF-κB) which were described.[49] It has also been explained that these inhibit the system xc- subunit xCT and adequately induce ferroptosis in non-Hodgkin lymphoma cells.[46] Altretamine (hexamethyl melamine) which is also FDA-approved alkylating antineoplastic drug which helps in the treatment of ovarian cancer.[50] It has also demonstrated that inhibition of GPX4 (Figure 2) helps in adequately destroying U-2932 DLBCL cells in vitro.[51] Moreover, Statins namely cerivastatin and simvastatin, have been explained in inducing ferroptosis in the human fibro sarcoma cell line HT-1080 by blocking the mevalonate pathway and thus helps in reducing the synthesis of CoenzymeQ10.[38] Hence, the induction of ferroptosis may determine the treatment efficiency and also there are various drugs which of several already certified as cancer drugs which may diminish the clinical development approach for the therapeutic induction of ferroptosis in human cancers.[52,53]

Conclusion and perspective

According to the studies, we have seen that ferroptosis is giving us a new and great advance in anti-tumor therapies as well as many encouraging findings have shown the efficiency of ferroptosis in achieving the goal. Currently, various experiments are focusing on the removal of cancer cells those are resistant in nature and for carrying out this appealing approach, ferroptotic cell death is playing a new and remarkable role. Importantly, it has been advised that to obtain a mesenchymal cell state (e.g., epithelial-mesenchymal transition (EMT) or cancer stem cells) meta static dissemination regulation and chemo resistance are helpful.[54] Regarding targeted therapies, cancer cells having high-mesenchymal state emerged as an important method for both acquired and denovo resistance.[55,56] Constant cancer cells which are approved for going out from formal cytotoxic cure via a torpid state tumor demonstrated an undistinguishable selective reliance on the GPX4 pathway which has a great therapeutic strategy.[57,58] Hence, ferroptosis is studied as a possible therapeutic strategy which can also revert the resistant therapy in cancer strategy. Ferroptosis is a type which is more acknowledged than other cell programmed death which shows more immunogenicity. Few studies have explained that drug reposition of SASP and artesunate shows anti-tumor therapeutic effects by activating ferroptosis.[59,60]

Also, ferroptosis brings out a newly explained cell death and advances in the regression of drug-resistance and enhances the immune system of the host. Ongoing, researches on ferroptosis has an encouraging aspect in the cancer treatment. Still, ferroptosis did not achieve a formal recognition in clinical aspect due to the ramification of cancer cells including P53 and Ras-mutant. There is another question in the development of ferroptotic resistance which was shown in erastin treatment in Hela cells. Therefore, in future studies we need to find out the systemic responses and mechanism of interlink between distinct types of regulated cell death apart from ferroptosis sensitivity and resistance which would help us to achieve the complete possibility of cancer treatment by using FIT.

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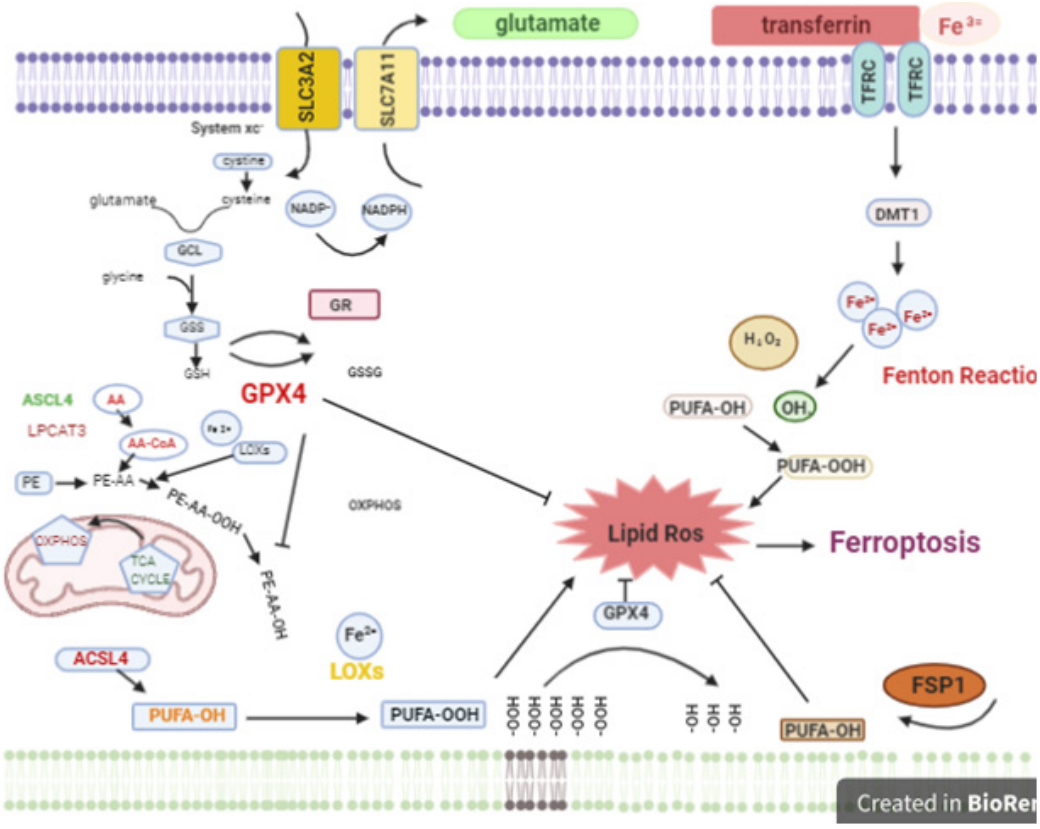

Figure 2 This is a pictorial representation of ferroptosis pathway. Ferroptosis follows abnormal progress of lipid reactive oxygen species (ROS) due to which the peroxidation (-OOH) of polyunsaturated fatty acids (PUFAs) occur. The main peroxidation target PUFAs namely arachidonic acid (AA) phosphatidylethanolamine (PE) lipid species within cellular membranes results in membrane destruction and shredding. Lipid peroxidation carried out by cytosolic redox active iron (Fe2+) moved into cells bound to transferrin via transferrin receptor (TFRC) endocytosis and endosomal release carry out by divalent metal transporter 1 (DMT1). Due to the existence of H2O2, Fe2+ catalyses hydroxyl radical (HO·) induce a Fenton reaction, which put in a radical lipid peroxidation chain reaction. Lipoxygenase (LOX) can also catalyse lipid peroxidation using Fe2+. As a required requirement for ferroptosis, Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidyl choline acyltransferase 3 (LPCAT3) induce the pool of AA-containing target lipids. Glutathione peroxidase 4 (GPX4), successively, hydrolyses lipid peroxides by converting them into their respective non-toxic lipid alcohols (-OH). GPX4 needs glutathione (GSH) as a cofactor which upon its oxidation (GSSG) by GPX4 is reduced to GSH by glutathione reductase (GR). GSH synthesis depends on glutamate cysteine ligase (GCL) and glutathione synthetase (GSS) as well as on intracellular cystine shuttled into the cell in exchange for glutamate mediated by system xc-(SLC3A2 and SCL7A11/xCT). Independently of GSH, ferroptosis suppressor protein 1 (FSP1) generates ubiquinol from ubiquinone which acts as a lipophilic radical trapping agent within membranes there by protecting from ferroptosis. Oxidative phosphorylation (OXPHOS) and the tricarboxylic acid (TCA)cycle have both been described to be needed for ferroptosis triggered by cystine-depletion or system xc-but not GPX4 inhibition.

Author contributions

Shreya S (SS) and Kanthesh BM (KBM) conceptualized the study. Shreya S (SS) and T. S. Gopenath (TSG) drafted the Manuscript. Parthiban R (PR), Prathibha Rajashekara S (PRS) and Kanthesh BM (KBM) helped with the Manuscript and Discussion.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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