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(Review Article)

Ferroptosis: A unique form of iron-dependent regulated cell death and its role in different diseases

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Abstract

Ferroptosis, a unique, non-apoptotic, iron-dependent, controlled cell death associated with excessive iron accumulation and phospholipid peroxidation. It causes a reduction in cell volume and an increased density of the mitochondrial membrane. This form of controlled cell death is genetically, biochemically, and morphologically unique from other cell deaths, such as apoptosis, uncontrolled necrosis, and necroptosis. Directly or indirectly, alteration of glutathione peroxidase by ferroptosis inducers, through various mechanisms, causes a loss of antioxidant potential and a build-up of lipid reactive oxygen species (ROS) in cells. Inhibition of glutathione peroxidase 4 (GPX-4), system Xc-cystine/glutathione antiporter, and arachidonoyl (AA) peroxidation induces ferroptosis in cells, which can be mediated by the mitochondrial VDAC3, p53 genes, and a variety of additional regulator genes such as HSPB1, CARS, and NFR2. Aside from these, a number of drugs like sorafenib, lanperisone, artemisinin, and sulfasalazine can induce ferroptosis. Recent research has linked ferroptosis to the pathophysiology of many diseases, including tumors, cancers, strokes, neurodegenerative, hepatic, kidney, and pulmonary diseases. In this article, we focused on the process of ferroptosis, its inducers and regulators, and its role in various diseases based on current evidence.

Keywords: Ferroptosis; Reactive oxygen species; Lipid peroxidation; Controlled cell death; Iron dependent cell death

1. Introduction

Cell death is an inevitable and crucial process of life that signals the end of a cell's life, whether in normal or pathological circumstances. Ferroptosis is a new kind of recently discovered cell death and is characterized by excess iron accumulation and phospholipid peroxidation[1]. Its characteristics are different than those of typical necrosis, like swelling of the cell by enlargement of cytoplasm and other organelles, followed by cell membrane rupture, and also different from conventional caspase-dependent apoptosis, for example, shrinkage of the cell, chromatin condensation, DNA fragmentation, and the development of apoptotic bodies[2–4].Mitochondrial shrinkage, along with disappearance or depletion of mitochondrial cristae and elevated membrane density, is the unique feature of ferroptosis and makes it different from other types of traditional cell death. Biochemically, due to lower intracellular glutathione (GSH), the activity of glutathione peroxidase 4 (GPX-4) is impaired, and it inhibits the GPX-4 mediated metabolism of lipid peroxides, resulting in the formation of ROS (reactive oxygen species) by ferrous ion (Fe^{2+}) mediated lipid oxidation, which causes ferroptosis[1,3,5].

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2. Discovery& history

Table 1 Depicts the progression of ferroptosis research over time

Year	Discovered theory	Reference
2003	Erastin, a novel compound identified by Dolma et al., can cause a new process of cell death.	6
2007	After Erastin, RSL3, another molecule that causes this kind of cell death, was found by Yagoda, N. et al., and can be attenuated by iron chelating agents.	4
2008	Yang, W. S. et al. verified the function of RSL3 in cell death and iron chelating agent-mediated inhibition of cell death in 2008.	3
2012 `	Dixon et al. found erastine-mediated cancer cell death with RAS mutation during their research and named it ferroptosis.	1
	In astrocytes, the transsulfuration process provides cysteine for glutathione biosynthesis.	7
2014	In in vitro models, like HD, PVL, and renal insufficiency, Skouta et al. discovered a potent inhibitor Ferrostatin (Fer-1) mediated cell death. This is the first time that the significance of ferroptosis has been emphasized.	8
	The studies of renal dysfunction in mice were mentioned in two research articles. The first included a mouse model of ferroptosis. And the non-cell-autonomous character of ferroptosis was initially established by Linkerman et al.	5,9
2015	Silencing of the Transferrin Receptor gene (TFR-1), blocked erastin-induced ferroptosis.	10
	By providing iron, heme oxygenase-1 can promote erastin-induced ferroptosis.	11
	The over expression of HSPB1 can significantly inhibits the process of ferroptosis.	12
	In the process of ferroptosis the role of glutamine metabolic pathway.	10
	p53 causes ferroptosis by suppressing the xc- system, which consists of two subunits, SLC7A11, and SLC3A2.	13,14
2016	The involvement of p53-SATI-ALOX15 pathway in the regulation of ferroptosis.	15
	NCOA4-mediated ferratin-associated autophagy can higher the quantity of unstable iron in cells, triggering ferroptosis.	16
	Regulation of pathway of lipid metabolism.	17,18
2017	Xie et al. revealed that p53 expression causes suppression of ferroptosis in colorectal cancer cells.	19
2018	In cancer cells, the p53-P21 pathway can repress the emergence of ferroptosis.	20
	Activation of GPX-4 can be utilized as a cytoprotective and anti-inflammatory treatment.	21
2019	GPX-4 is degraded by erastin.	22
	Ferroptosis has a key role in myocardial infraction, according to studies on heart transplantation and I/R damage.	23,24
	The FSPI-COQ10-NAD(P)H mechanism co-operates with glutathione and GPX-4 to inhibit the peroxidation of phospholipid and ferroptosis.	25,26
2020	Ionizing radiation-induced suppression of tumor in vivo is mediated by ferroptosis.	27
	The deficiency of ferritin H, present in the heart, triggers cardiomyopathy via ferroptosis mediated by Slc7a11.	28
2021	Increasing Nrf2 slowed the development of diabetic nephropathy via inhibiting ferroptosis.	29
	In human pancreatic cancer cells, the ferroptosis activator RSL3 can prevent MTOR activation and lead to GPX-4 protein breakdown.	30

	Dihydroorotate dehydrogenase (DHODH) has effects that are most noticeable in cancer cells with poor GPX-4 expression. It either reduces or increases ferroptosis brought on by GPX-4 inhibition.	31
2022	Expression of ferroptosis negative regulator genes (SLC7A11, GPX-4, and FTH1) is regulated by STAT3. Suppresion of STAT3 activity causes ferroptosis via inducing oxidative damage and iron accumulation in gastric cancer cells.	32

3. Morphological and biochemical features and core regulators

Table 2 Depicts the main morphological and biochemical features and core regulators of ferroptosis

Morphological features	Biochemical features	Core regulators		Reference
		Positive regulators	Negative regulators	
Condensed mitochondrial membrane densities; mitochondrial crista loss or absence; rupture of external mitochondrial membrane; normal nuclear size; and lack of chromatin condensation all influence mitochondria to shrink in size	Inhibition of system Xc-, which is made up of two components, SLC7A11 and SLC3A2, causes decrease in cystine absorption, resulting GPX-4 inhibition Iron and ROS buildup Activation of MAPKs	Ras p53 VDAC2/3 CARS TFR1 NOX	SLC7A11 NRF2 GPX-4 HSPB1	33–35

3.1. Inducer of ferroptosis: figure 1

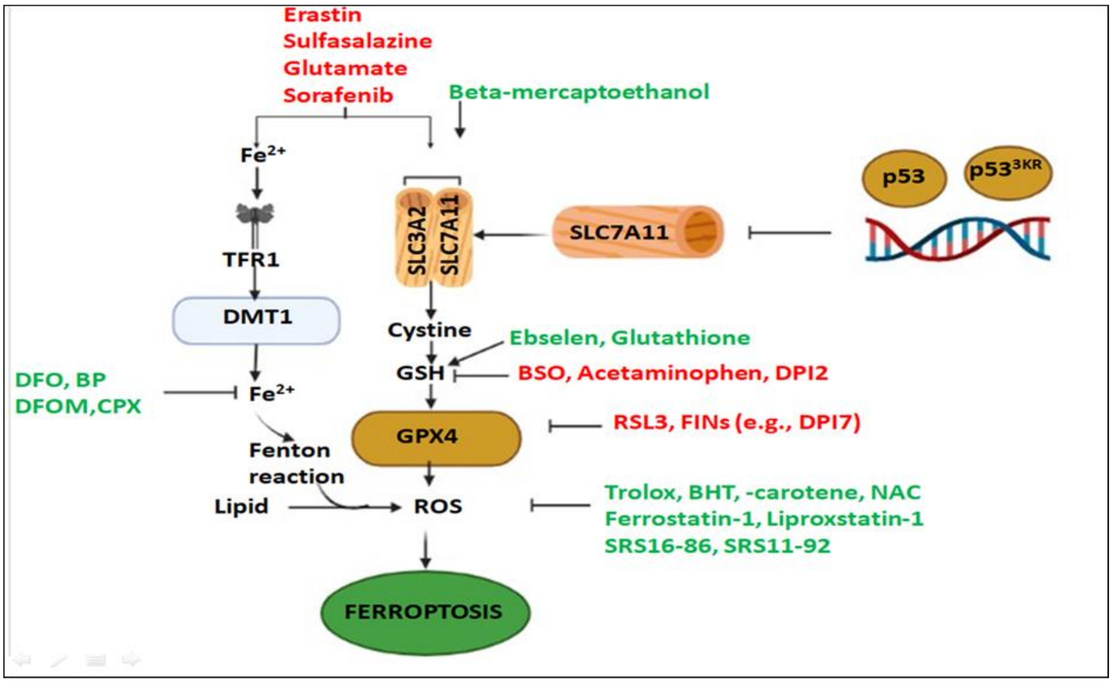

Figure 1 Core inducers of ferroptosis

3.1.1. Erastin

Iron chelators (deferoxamine) and antioxidants (like alpha tocopherol, butyalated hydroxyl toluene, and beta carotene) can prevent erastin from causing cell death. In the process of ferroptosis that is induced by erastin, ROS and iron dependent signalling are required[1,4]. Iron responsive element-binding protein 2 (IREB2), ATP synthase F0 complex subunit-3, ribosomal protein L8, citrate synthase, tetratricopeptide repeat domain 35, and andacyl-CoA synthetase family member 2(ACSF2) are among the six confidence genes[1]. In erastin-induced ferroptosis, the activation of RAF/MEK/ERK signalling is important. Erastin after binding with VDAC 2/3 in BJeLR cells leads to erasin resistance[4]. Erastin can inhibit system Xc- which is an antiporter of cystine/glutamine[1].

3.1.2. RSL3 and RSL5

They can induced ferroptosis. VDAC2/3 is required for RLS5-induced ferroptosis[3]. RSL3 binds with GPX-4 and inactivates GPX-4, which induces ROS production from lipid peroxidation[36].

3.1.3. Buthioninesulfoximine

It is an irreversibly inhibits the γ-glutamyl cysteine synthetase, in GSH synthesis it is the rate-limiting enzyme. As a result, buthioninesulfoximine can inhibit GSH synthesis with the decreasing activity of GPX-4 and increase the levels of ROS production. This process results in ferroptosis[36].

3.1.4. Acetaminophen

The metabolite of acetaminophen causes GSH depletion and increases the damage to the liver. Ferroptosis can be caused in mice hepatocytes, but not in HepG2 liver cancer cell lines[37].

3.1.5. FIN

Ferroptosis inducing compounds (FINs) that are a series of small molecules that were discovered by a larger screening process[38,39]. Reduced PC-OOH levels were shown in an LC-MS based GPX-4 assay, when any of the seven members of DPI family (DPI7, DPI10, DPI12, DPI13, DPI17, DPI18, and DPI19) were treated with cells. These FIN compounds (class II FINs), like RSL3, actively block GPX-4 activity without lowering GSH. Class I FINs, like DPI2, block GPX-4 by reducing GSH in the same manner that erastin and BSO do[36].

3.1.6. Lanperisone

Some study suggests that, through perturbation of voltage gated ion channels, lanperisone induces ROS generation but mechanism of it inducing ROS is not exactly known[40].

3.1.7. Sulfasalazine

Chronic inflammation in retina, gut and joints can be treated with the help of sulfasalazine. System Xc- antiporter can also be blocked by it[41].

3.1.8. Sorafenib

Ferroptosis is induced by sorafenib in hepatocellular carcinoma cells[42,43]. Oncogenes like p53, RAF, Ras, PIK3CA, are independent from sorafenib induced ferroptosis[44]. Gene expressions like NFR2 and RB can block sorafenib induced ferroptosis[42,45].

3.2. Signaling pathway of ferroptosis

3.2.1. Iron

Through Fenton Reaction excessive iron contributes by producing ROS in ferroptosis. . The transferrin receptor, which is distributed over the cell membrane, helps to enter the ferric ions ($Fe3+$) and then the ferric ions lie inside the endosome. Then one enzyme named ferrireductase coverts the ferric ions into ferrous ions ($Fe2+$) inside the endosome. Then another transporter named Divalent Metal Transporter (DMT-1)/SLC11A2 releases the ferrous ions from the endosome. The excessive iron is stored inside the ferritin. The export of iron is mediated by a membrane protein called SLC11A2, also called ferroptin. When ferroptosis occurs, the TFR-1 sensitivity increases, the activity of iron storage by the ferritin decreases, and then the amount of iron is overloaded, causing ferroptosis. For iron metabolism IREB2 is the master transcription factor. RNAi induces the expression of iron metabolism related genes and limited ferroptosis by the suppression of IREB2. Iron uptake is regulated by HSPB1 so, by inhibiting it ferroptosis can be induced (figure 2)[1,3].

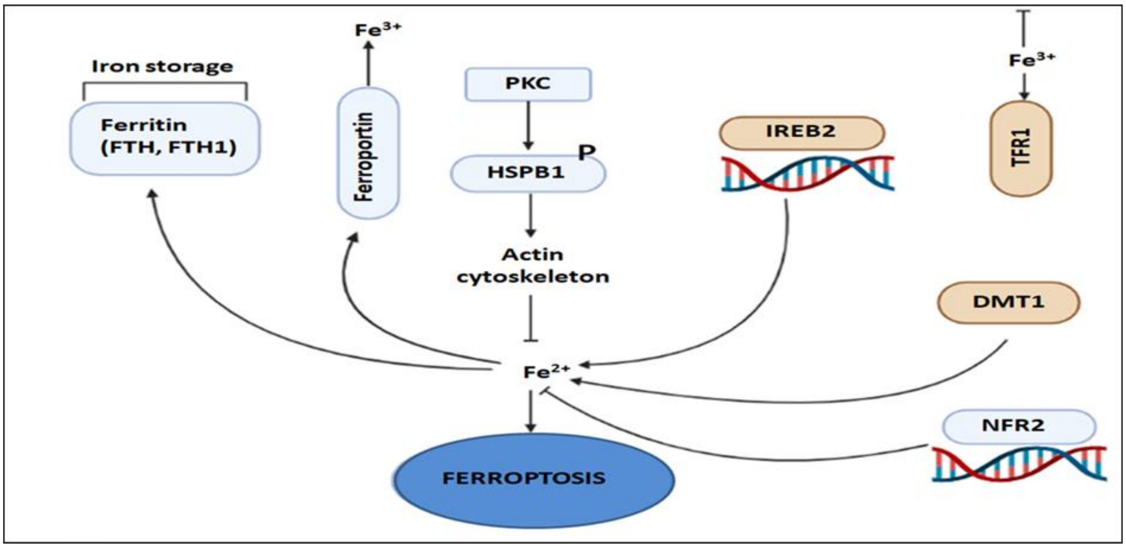

Figure 2 Roles of iron metabolism in ferroptosis

3.2.2. Reactive oxygen species (ROS)

In ferroptosis, the ROS may be induced by many sources. Not only the iron mediated fenton reaction but also the NADPH-dependent lipid peroxidation and inhibition of GSH are involved in ferroptosis. GPX-4 is inhibited by GSH depletion, which promotes ferroptosis by producing ROS. A specific lipid precursor is required for the process of ferroptosis that is produced from the metabolite of mitochondrial fatty acid. ACSF2 and CS function as the precursors for the metabolism of fatty acid in mitochondria, which are required in ferroptosis. If the ACSF2 and Cs are activated, that induces ferroptosis[1,36].The alpha keto glutamate is produced from glutamine, which produces the lipid metabolite that promotes ROS production and induces ferroptosis. Polyunsaturated fatty acids (PUFA) can react with ROS to induce lipid metabolism. There is the involvement of two genes, LPCAT3 and ACSL4, that promote RSL3 and DPI7, but not the erastin-induced ferroptosis (figure 3)[46].

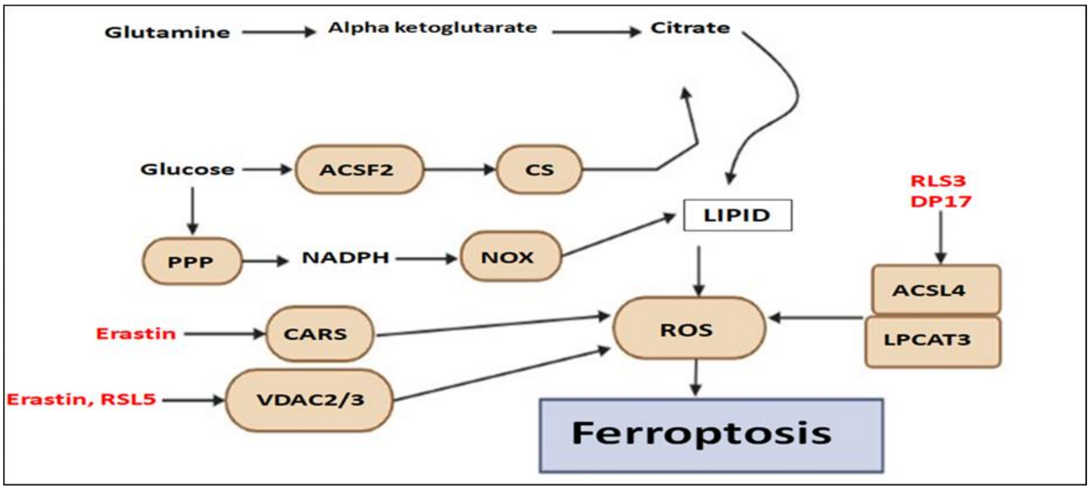

Figure 3 ROS mediated ferroptosis

3.2.3. Mitogen-activated protein kinase (MAPK)

MAPKs of mammalian family consists P38, ERK, and c-Jun NH2 terminal kinase (JNK). In Ras-mutated cancer cells, putting down Ras/Raf/MEK/ERK suppresses ferroptosis induced by erastin[4]. In Ras-mutated cancer cells, putting down Ras/Raf/MEK/ERK suppresses ferroptosis induced by erastin.4 In HL-60 cells, SB202190 (a p53 activator) and SP600125 (a JNK phosphorylation inhibitor) reduce erastin-induced cytotoxicity (figure 4)[47].

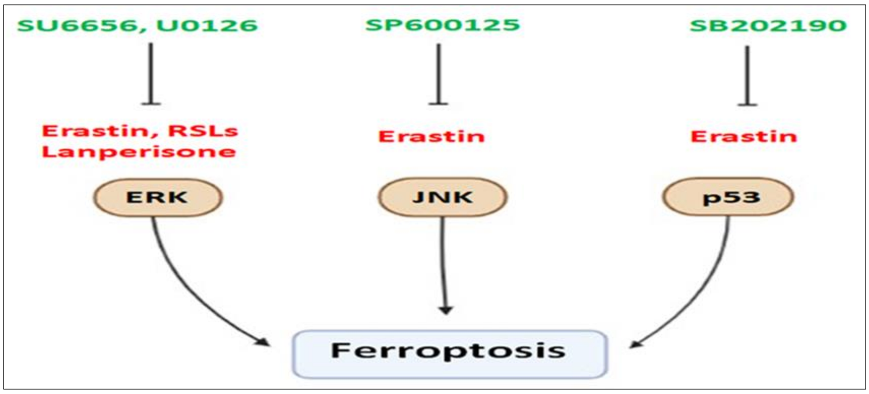

Figure 4 MAPK pathway in ferroptosis

3.3. Role of regulators in ferroptosis (table 2)

3.3.1. Positive regulators

VDAC2/3

Only the VDAC2/3, not the VDAC1, is involved in ferroptosis. So only by knocking out VDAC2/3 does the erastin-induced ferroptosis. Ferroptosis induced by erastin is much frequent in cells with a high amount of VDAC proteins[4]. In human liver cancer cells (e.g., HepG2), altering the connection between VDAC and tubulin, erastin can promote oxidative mitochondrial metabolism while limiting aerobic glycolysis, suggesting that energy metabolism and the cytoskeleton may play a role in ferroptosis modulation[48].

Ras

In Ras-mutant cells, which including N-Ras-mutant HT1080 cells, H-Ras-mutant engineered cells, and K-Ras-mutant Calu-1 cells, erastin promotes gene-selective mortality in those Ras-mutant cell[4]. Ferroptosis can be Ras dependent or Ras-independent. As example, artesunate induced pancreas cancer is a Ras dependent cell death manner, and leukaemia is a Ras independent cell death manner[47,49].

TFR1

Fe3+ is imported with the help of the transferrin receptor 1 (TFR1), and subsequently Fe3+ is stored in the endosome. This Fe3+ converts to Fe2+, which leads to ferroptosis. So the knockdown of TFR1 can inhibit iron-induced ferroptosis[10].

NOX

This protein family transfers electrons across cellular membranes to reduce the conversion of oxygen to superoxide. GKT137831, a NOX1/4 specific inhibitor, and diphenyleneiodonium, a conventional NOX inhibitor, both partially reduce erastin-induced ferroptosis in HT1080 cells[1].

p53

In certain cancer cells, the p53 gene has been found to be required for the process of ferroptosis. This p53 is responsible for inhibiting SLC7A11 expression, resulting in ferroptosis. This SLC7A11 is a system Xc-subunit. Ferroptosis induction is required for this p533kR's tumor suppressor activity[13].

CARS

cysteinyl-tRNA synthatase acts as a positive and potential regulator of ferroptosis. Thus, by suppressing this CARS, ferroptosis can be prevented[50].

3.3.2. Negative regulators

GPX-4

It helps in the conversation of oxidised glutathione from glutathione and reduces the concentration of lipid peroxidase by converting it to alcohol. As a result, the GPX-4 knockdown process causes ferroptosis in MEK, Iron, and ROS dependent manner. Some studies shows that overexpression of GPX-4 can create resistance to RSL3[36].GPX-4 degradation in several types of cancer cells can be caused by erastin, suggesting that the degradation of protein pathways is involved in ferroptosis[47].

System Xc

It consists of two subunits that are SLC7A11 and SLC7A2. So, by triggering the system Xc- erastin induced ferroptosis can be regulated. The anticancer effect of erastin can be enhanced by RNAi suppression of SLC7A11 expression, but over expression of this SLC7A11 via gene transfection reduces erastin-induced ferroptosis[1].

HSPB1

Heat shock factor-1 (HSF-1) induces HSPB1 expression after erastin treatments in human cancer cells.Erastin induced ferroptosis can be inhibited by the over expression of HSPB1[12].

NFR2

NFR2 has a role of ferroptosis inhibitor in HCC cell. Up regulation of NFR2 protein promotes the transcription of gene encoding antioxidants protein in ferroptosis[45].

3.3.3. Modulators of ferroptosis

Table 3 Depicts the name and functions of ferroptosis modulators

Gene	Product	Function	Reference
TFRC	Transferrin receptor	Ferric ions (Fe^{3+}) transport	3,10
ACSF2	Member of Acyl-coAsynthetase family	Metabolism of fatty acid	1
EMC2	ER membrane protein complex subunit-2	Not properly known, but may acts on protein folding mechanism inside the endoplasmic reticulum.	1
RPL8	Ribosomal protein L8	The components of the ribosomal large subunit that are involved in protein synthesis.	1
SLC7A11	Solute career family 7, member 11	Cystine/ glutamate antiporter	1
CS	Citrate subunit	Lipid metabolism	1
ATP5G3	ATP synthase, H+ transporting, mitrochondrial F0 complex, subunit C3(subunit-9)	Complex V of mitrochondrial F0 F1 ATPase; ATP synthesis	1
GPX-4	Glutathione peroxidise-4	Lipid repair	36
ACSL4	Long chain family member of Acytal Co-A synthatase	Lipid metabolism	46
LPCAT3	Lysophosphatidylcholineacyltransferase 3	Lipid metabolism	46
CARS, EPRS, HARS	Cysteinyl-tRNAsynthatase	Protein translation	50
SLC1A5	Solute carrier family-1, member-5	Glutamine transport	10
GSL2	Glutaminae-2	Glutaminolysis	10
HSPB1	Heat sock protein 1 (molecular weight 27 kDa)	Iron metabolism, folding of proteins	12
TP53	p53 Tumor suppressor protein	Tumor suppression , metabolic regulation	14
IREB2	Iron-responsive element binding protein 2	Iron metabolism's key transcription factor	1

3.4. Role of ferroptosis in various diseases: (figure 5)

3.4.1. Cancer

Pancreatic cancer

Eling et al. observed that ROS production can be induced by artesunate (ART) and initiates ferroptosis in pancreatic cells. Sulfasalazine, a ferroptosis inducer when given in a combination dose of phenylethylisothiocyanate (PEITC) and cotylenin A (CN-A) is an inducer of ferroptosis[49]. In some recent studies, it has shown that iperlongumine, CN-A, and sulfasalazine combinations are more effective in inducing ferroptosis in pancreatic cancer cell lines[51].

Hepatocellular carcinoma

For the treatment of higher level of HCC, sorafenib can be used. The loss of retinoblastoma protein in the development of liver cancer is very crucial. The retinoblastoma-negative status of HCC can promote ferroptosis studied by Louandre C et al after the exposure of sorafenib[43]. Sorafenib resistance can be developed by MT-1G through the inhibition of ferroptosis. Lipid peroxidation and GSH reduction can be enhanced by breaking down of MT-1G[52].

Gastric cancer

Hao et al. state that CDO1 is the key regulator for the ferroptosis in gastric cells. This CDO1 absorbs cystine and the GSH synthesis is restricted.As a result, inhibiting CDO1 restores GSH levels, preventing ROS formation and lowering lipid peroxidation levels, preventing ferroptosis[53].

Colorectal cancer

Xie et al. state that p53 suppresses Erastin-induced ferroptosis in colorectal cells by inhibiting dipeptidyl-peptidase-4 activity, which differs from the earlier mechanism of p53-induced ferroptosis in cancer cells. Accumulation of dipeptidyl-peptidase-4 inhibits loss of p53 and lipid peroxidation is promoted that causes ferroptosis[19]. Erastin and cisplatin (ferroptosis inducer) combination of both can increase the drug anti-tumor effect, found in another study. The ferroptosis has an important role in the therapy of anti-tumor[54].

Breast cancer

One of the most remarkable amino acids is cysteine. As a result, blocking cystine intake through the mechanism Xc- causes ferroptosis. The use of Fer-1 and DFO, on the other hand, prevents cell death[55]. Another study tells that xCT light chain of system Xc- similar to transmembrane protein MUC1-C enhances GSH level. Ferroptosis can be induced if MUC1-C/xCT complex activation is inhibited[56,57].

Lung cancer

NFS1 (iron sulfur cluster biosynthetic enzyme), is highly shown and the expression of iron sulfur cluster is maintained by it in highly differentiated lung adenocarcinomas. Only NFS1 cannot induced ferroptosis, it can only when a large amount of ROS is produced, then it can lead to ferroptosis. When erastin is introduced to lung cancer cell A549, it up-regulates and p53 gets activated, thereby transcriptionally activating its down-regulated gene, thereby the ROS accumulation and eventually ferroptosis, occur by inhibiting SLC7A11[58].

ccRCC/Clear cell renal cell carcinoma

Glutamine and cystine are necessary for GSH synthesis but ccRCC cells are extremely sensitive to the depletion of it. So, to prevent lipid peroxidation and cell death these cells depends on GSH/GPX pathway. Hence, tumor growth can be blocked if, GSH synthesis is inhibited in ccRCC that induces ferroptosis[59].

Ovarian cancer

ROS-dependent DNA damage and cell death happens due to ovarian cancer cells, when there is disclosure of it with the greater concentrations of ART, arrest in G2/M phase occur, which is sometimes responsible for ferroptosis[60]. Usual subtype of malignant ovarian tumor is high grade serous ovarian cancer. in the cell of it, there is interference in iron metabolism leading to increase in iron retention as well as iron uptake, increment in iron intake (TFR1 expression), reduction in iron efflux (FPN expression) and increment in ferritin happen. Hence extreme accumulation of iron in cells can happen due to above biological process leading to ferroptosis[61].

Melanoma

Ferroptosis happens because of the breaking down of the miR-137 regulator. It acts on the SLC1A5 transporter of melanoma cells, it was seen during the study of melanoma[62]. Mitochondrial complex-1 inhibition can increase the ROS level, causing ferroptosis found in another study[63].

3.4.2. Neurodegenerative disorder

There are lots of neurodegenerative disorders caused by the accumulation of iron in the central and peripheral nervous system. A neuro-degenerative disease (Alzheimer's) caused by cognitive impairment and iron accumulation in the hippocampus. Accumulation of iron leads to abnormalities in brain tissues and further leads to massive ROS production in brain cell damage the subcellular structure of brain cell[64].

3.4.3. Stroke

80% strokes are due to ischemic stroke, there is accumulation of iron in the basal ganglia, thalami, periventricular & subcortical white matter areas after hypoxic brain injury and severe ischemia[65]. Hemorrhagic stroke in brain cell namely N-acetylcystine blocks the heme-induced ferroptosis told in a study. This process occurs by neutralizing the toxic effect of a lipid, this toxic lipid is produced by arachidonate dependent ALOX-5 activity[66].

3.4.4. Traumatic brain injury

Iron deposition, iron metabolism disorder, decreased GPX activity, ROS accumulation and up regulation of genes related to ferroptosis occur due to evolution of TBI. Fer-1 (ferroptosis inhibitor) reduces the iron deposition, neuronal degeneration and injury and improves the recurrence of patients leading to TBI treatment targeting ferroptosis on experimental basis[67].

3.4.5. Acute kidney injury and I/R injury

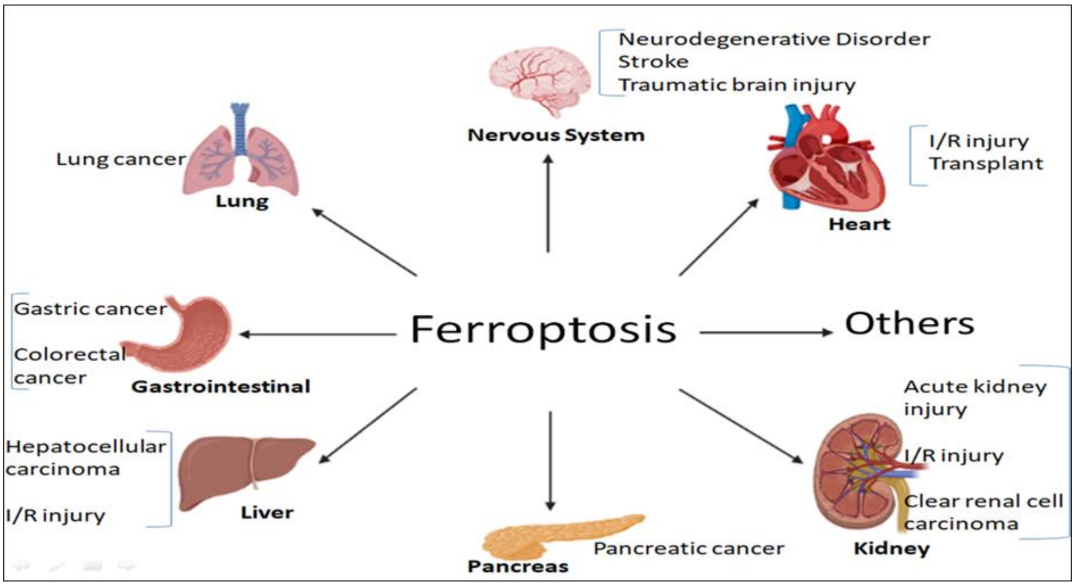

Figure 5 Role of ferroptosis in different diseases

The incidence and mortality were high in spontaneous AKI found in GPX-4 knockout mice[5]. In a study of Linkermann et.al., it was studied that in ischemia/reperfusion (I/R) injury and acute tubular necrosis in vivo, ferroptosis functions well, and showed that a new generation ferrostatin (a ferroptosis inhibitor), is protected against this injury[9]. In the Study of Gao et al. it found that inhibition of ferroptosis can be done by inhibiting glutamine metabolism in the treatment of damage tissue triggered by I/R injury is the isolated wild-type mice[10].

3.4.6. Pulmonary Diseases

Pulmonary infection

According to a research, lipoxygenase (pLoxA), released by *Pseudomonas aeruginosa,* may oxidize PUFA-PE, promote lipid peroxidation, and induce ferroptosis in bronchial epithelial cells of recipient[68].

COPD

Chronic cigarette smoke (CS) is a significant risk factor for COPD onset. A study found that smoking raises iron levels in lavage and raises ferritin levels in both lavage and serum from the lungs of rats with COPD[69]. Another study found that cigarette smoking promotes ferroptosis in lung epithelial cells by triggering NCOA4-mediated ferritinophagy. While GPX-4 knockdown exacerbates Smoking-induced COPD, iron restriction or use of iron cheaters significantly reduces cigarette smoking-induced COPD[70].

Pulmonary fibrosis

Increased ROS generation and GSH deficiency, both of which are closely linked to the ferroptotic process, are also important in the etiology of pulmonary fibrosis. Acute radiation-induced lung fibrosis (RILF) is associated with ferroptosis, and ROS build-up appears to be the key inducer of ferroptosis in this phase[71,72].

3.4.7. Asthma

In IL-13-cultured HAECs, inhibition of GPX-4 with RSL3 resulted in the build-up of excessive oxygenated polyunsaturated phosphatidylethanolamines. Polyunsaturated phosphatidylethanolamine binding protein 1 (PEBP1) inhibition in HAECs can reduce ferroptotic sensitivity. As a result, increasing GPX-4 at the start of an asthma attack may help to reduce ferroptosis and asthma symptoms[73]

4. Conclusion

In conclusion, ferroptosis' discovery has opened up a new platform in medical science, and its clinical importance in the incidence, development, and management of diseases has progressively emerged. Several compounds have recently been discovered that modulate ferroptosis by targeting iron metabolism and lipid peroxidation directly or indirectly. These ferroptosis regulators are also linked with other types of regulated cell death as well. To differentiate ferroptosis from other forms of regulated cell death, the most essential task in ferroptosis research is to discover the downstream signalling pathways of iron dependent free radicle metabolism. Further exploring the process of ferroptosis as well as its function in many diseases, as well as proposing effective and highly focused therapeutics, is important. This is also where ferroptosis research will go in the future.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors have no conflicts of interest regarding this review.

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