A Review on Ferroptosis an Emerging Form of Regulated Cell Death and Its Pharmacological Relevance

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ABSTRACT

Iron is an essential trace element involved in oxygen transport, energy metabolism, DNA synthesis, and enzymatic functions. However, excess intracellular ferrous iron (Fe^{2+}) can generate reactive oxygen species (ROS), leading to oxidative damage of cellular components. Ferroptosis is a unique iron-dependent form of regulated cell death characterized by excessive lipid peroxidation and disruption of cellular antioxidant defenses. Unlike apoptosis, it occurs without caspase activation or DNA fragmentation and is associated with iron overload, mitochondrial dysfunction, and impairment of the cysteine–glutathione–GPX4 pathway. Cells counteract ferroptosis through protective systems such as GPX4, FSP1–CoQ10, GCH1–BH4, and DHODH pathways.Due to its critical role in cancer progression and other diseases, ferroptosis has emerged as an important therapeutic target. Current research focuses on selectively inducing ferroptosis in cancer cells while minimizing damage to normal tissues by targeting key regulators such as GPX4, SLC7A11, and iron metabolism.

Keywords: Ferroptosis; Iron metabolism; Reactive oxygen species (ROS); Lipid peroxidation; GPX4; Cancer therapy

INTRODUCTION

Role of iron: Iron is an essential trace metal that is necessary for many biological processes, including oxygen transport, mitochondrial respiration, DNA synthesis, and enzymatic activities. Iron is necessary to maintain cellular balance, but it may also be a double-edged sword. Excess intracellular free iron, particularly in its ferrous ($Fe2^{+}$) state, can promote the generation of highly reactive oxygen species (ROS) through Fenton and Haber-Weiss processes. The tendency of these ROS to oxidatively damage lipids, proteins, and nucleic acids may ultimately endanger cell life. Iron metabolism needs to be strictly controlled for cells to live and function.[1] The increased attention in recent years to iron-dependent processes of cell death has led to the identification of ferroptosis, a unique type of regulated cell death.[2] Unlike other well-known Ferroptosis is characterized by the accumulation of iron-dependent lipid peroxides to lethal levels, in contrast to other forms of cell death such apoptosis, necrosis, and autophagy. The normal apoptotic features of apoptosis, including as caspase activation and DNA breakage, are absent in ferroptosis. Instead, it is brought on by oxidative stress and lipid peroxidation, which causes catastrophic membrane damage.

History: Ferroptosis was first described in 2012. The term "ferroptosis" was first used by Brent R. Stockwell, after research revealed that certain tiny chemicals, like elastin and RSL3, have the ability to trigger a non-apoptotic, iron-dependent mode of cellular death. Through mechanisms including the disruption of cellular redox balance and the weakening of antioxidant defences, these compounds were found to be catalysts for cell death. Since then, ferroptosis has gained recognition as an essential biological process with significant implications in both healthy and pathological settings.[3]

Key mechanism: A hallmark of ferroptosis is the disturbance of lipid metabolism, especially the oxidation of polyunsaturated fatty acids (PUFAs) that are integral components of cellular membranes. Due to their

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chemical structure, PUFAs are highly vulnerable to oxidative attack, leading to the formation of lipid peroxides and hydroperoxides. Under normal physiological conditions, cells employ efficient antioxidant defense mechanisms to prevent the excessive accumulation of these toxic lipid species. Among these protective systems, glutathione (GSH) and glutathione peroxidase 4 (GPX4) are of particular importance. GPX4 functions as a key antioxidant enzyme by reducing lipid hydroperoxides to non-toxic lipid alcohols, thereby maintaining membrane integrity and cellular viability.When intracellular GSH levels decline or GPX4 activity is impaired, lipid peroxides accumulate uncontrollably, promoting oxidative membrane damage and ultimately triggering ferroptotic cell death. Another critical regulator of this process is the cystine/glutamate antiporter, known as system Xc^-, which facilitates the uptake of cystine in exchange for intracellular glutamate. Once inside the cell, cystine is converted into cysteine, a precursor required for GSH biosynthesis. Inhibition of system Xc^- limits cysteine availability, reduces GSH production, and weakens cellular antioxidant capacity. As a result, cells become increasingly susceptible to oxidative injury and lipid peroxidation. Therefore, disruption of the system Xc^-–GSH–GPX4 signaling pathway is considered one of the central molecular events responsible for the initiation and progression of ferroptosis.

Aim and Objectives of Ferroptosis Study:

The primary objective of ferroptosis research is to gain a comprehensive understanding of the molecular pathways that regulate this unique form of cell death, with particular emphasis on iron metabolism, lipid peroxidation, and antioxidant defense mechanisms such as the glutathione (GSH)–glutathione peroxidase 4 (GPX4) system. Elucidating these mechanisms is essential for determining the role of ferroptosis in disease development and progression. Furthermore, a deeper understanding of ferroptotic signaling may facilitate the identification of novel therapeutic targets and support the development of innovative treatment strategies for conditions including cancer, neurodegenerative diseases, and ischemia–reperfusion injury.

Key Objectives:

Disease Therapy (Induction): The goal is to identify ferroptosis inducers (such as erastin and RSL3) that can trigger this specific mode of cell death in resistant cancerous cells (such as hepatocellular carcinoma, triple-negative breast cancer, and ovarian carcinoma).

Cytoprotection (Inhibition): To develop ferroptosis inhibitors, such as ferrostatin-1 and deferoxamine, to prevent excessive cell death in conditions including acute kidney injury, strokes, and neurological illnesses like Parkinson's and Alzheimer's.

Modulating Iron/Redox Balance: to prevent excessive lipid peroxides from being produced by the iron-driven Fenton reaction by controlling the labile iron pool (LIP) and limiting lipid peroxidation in cells.

Defining Signalling Pathways: To identify the regulatory networks that control ferroptosis sensitivity, including both GPX4-dependent and independent pathways (such FSP1/CoQ10).

Developing Biomarkers: To develop distinct and trustworthy markers (such oxidized phospholipids or particular protein changes) to detect ferroptosis in vivo for clinical assessment. Ferroptosis participates in immune surveillance and cell death during development and acts as a natural defence mechanism to suppress tumours (via p53).[17]

History And Overview: - The concept of ferroptosis emerged from studies investigating novel forms of regulated cell death. In 2003, Dolma et al. identified erastin, a small molecule capable of selectively killing RAS-mutant cancer cells through a mechanism distinct from apoptosis, as it lacked caspase activation and DNA fragmentation.[8] Subsequent studies demonstrated that RSL3 induced a similar form of cell death, which could be prevented by iron chelators. Based on these findings, Dixon et al. formally introduced the term ferroptosis in 2012.[2] Ferroptosis is characterized by unique morphological, biochemical, and genetic features. Morphologically, cells exhibit reduced mitochondrial size, increased membrane density, and loss of mitochondrial cristae, while the nucleus and plasma membrane remain largely unaffected. Biochemically, ferroptosis is associated with glutathione (GSH) depletion, inhibition of glutathione peroxidase 4 (GPX4),

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excessive lipid peroxidation, and iron-dependent oxidative damage. Key ferroptosis inducers include erastin, RSL3, FIN56, and FINO2, which promote cell death through disruption of antioxidant defenses and iron metabolism.[10] Several ferroptosis inhibitors, including ferrostatin-1 (Fer-1), liproxstatin-1, vitamin E, and iron chelators, have also been identified. These agents suppress ferroptosis by preventing lipid peroxide accumulation. The discovery of ferroptosis and its modulators has provided new insights into disease mechanisms and offers promising therapeutic opportunities for cancer, neurodegenerative disorders, and other pathological conditions.

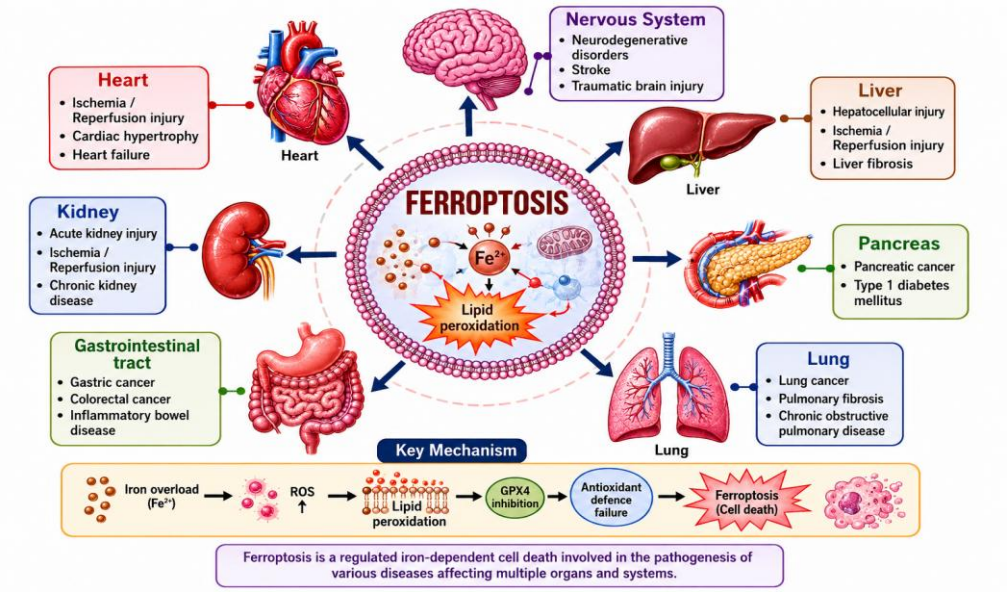

Figure No.01

Mechanism and Regulation of Ferroptosis

Promoting ferroptosis through the inhibition of system Xc-

System Xc^- is a membrane amino acid transporter composed of SLC7A11 and SLC3A2 subunits. It exchanges extracellular cystine with intracellular glutamate in a 1:1 ratio. Once inside the cell, cystine is converted to cysteine, a key precursor for glutathione (GSH) synthesis. GSH supports GPX4 activity, which protects cells from oxidative damage by eliminating reactive oxygen species (ROS). Inhibition of System Xc^- reduces cystine uptake, leading to GSH depletion, impaired GPX4 function, ROS accumulation, and ultimately ferroptosis. Furthermore, the tumor suppressor p53 can suppress SLC7A11 expression, thereby promoting ferroptosis through reduced antioxidant defense and increased lipid peroxidation. [11,12]

Induction of ferroptosis through the inhibition of GPX4:

GPX4 is a key antioxidant enzyme that plays a central role in preventing ferroptosis by reducing lipid hydroperoxides (L-OOH) to non-toxic lipid alcohols (L-OH) using glutathione (GSH) as a cofactor. Loss or inhibition of GPX4 activity leads to lipid peroxide accumulation, increased oxidative stress, and induction of ferroptosis. Studies have shown that elevated GPX4 expression protects cells from ferroptotic death, whereas reduced GPX4 levels increase susceptibility. Ferroptosis inducers such as RSL3, DPI7, and DPI10 directly inhibit GPX4, promoting reactive oxygen species (ROS) accumulation. GPX4 is a selenoprotein that requires selenocysteine for its activity. The mevalonate (MVA) pathway supports GPX4 synthesis by regulating selenocysteine tRNA maturation; therefore, disruption of this pathway can impair GPX4 function and trigger ferroptosis.

Ferroptosis that is influenced by mitochondrial VDACs:

Voltage-dependent anion channels (VDACs) are mitochondrial membrane proteins involved in the transport of ions and metabolites. They contribute to ferroptosis by regulating mitochondrial function. Erastin induces

ferroptosis through its interaction with VDACs, leading to mitochondrial dysfunction, increased reactive oxygen species (ROS) generation, and subsequent iron-dependent cell death. [16]

P53-Mediated ferroptosis:

The tumor suppressor protein p53 plays a complex role in ferroptosis regulation. It can promote ferroptosis by reducing cellular antioxidant defenses through downregulation of SLC7A11, thereby limiting cystine uptake, decreasing GPX4 activity, and enhancing reactive oxygen species (ROS) accumulation. The p53–SAT1–ALOX15 signaling pathway also contributes to lipid peroxidation and ferroptotic cell death. Conversely, p53 may inhibit ferroptosis in certain cell types through activation of p21 (CDKN1A), which helps maintain glutathione metabolism and cellular redox balance. Studies have shown that increased p53 expression can either enhance or suppress ferroptosis depending on the cellular context. Therefore, p53 acts as a dual regulator of ferroptosis, although the precise mechanisms remain incompletely understood. [18–20]

Role of ferroptosis suppressor protein 1:

Ferroptosis suppressor protein 1 (FSP1, formerly known as AIFM2) has emerged as an important regulator of ferroptosis. Initially recognized for its association with apoptosis, FSP1 was later identified as a potent inhibitor of ferroptotic cell death. Independent studies demonstrated that FSP1 protects cells from ferroptosis, even in the absence of GPX4 activity. Loss of FSP1 increases cellular sensitivity to ferroptosis inducers, whereas its restoration enhances cell survival. Mechanistically, FSP1 localizes to the plasma membrane and reduces coenzyme Q10 (CoQ10) using NAD(P)H, generating a powerful antioxidant system known as the FSP1–CoQ10–NAD(P)H pathway. This pathway prevents lipid peroxidation and functions independently of the GPX4–glutathione defense system. Elevated FSP1 expression has been associated with increased ferroptosis resistance in several cancer types, making FSP1 a promising therapeutic target and potential biomarker for ferroptosis-based cancer treatment. [21–23]

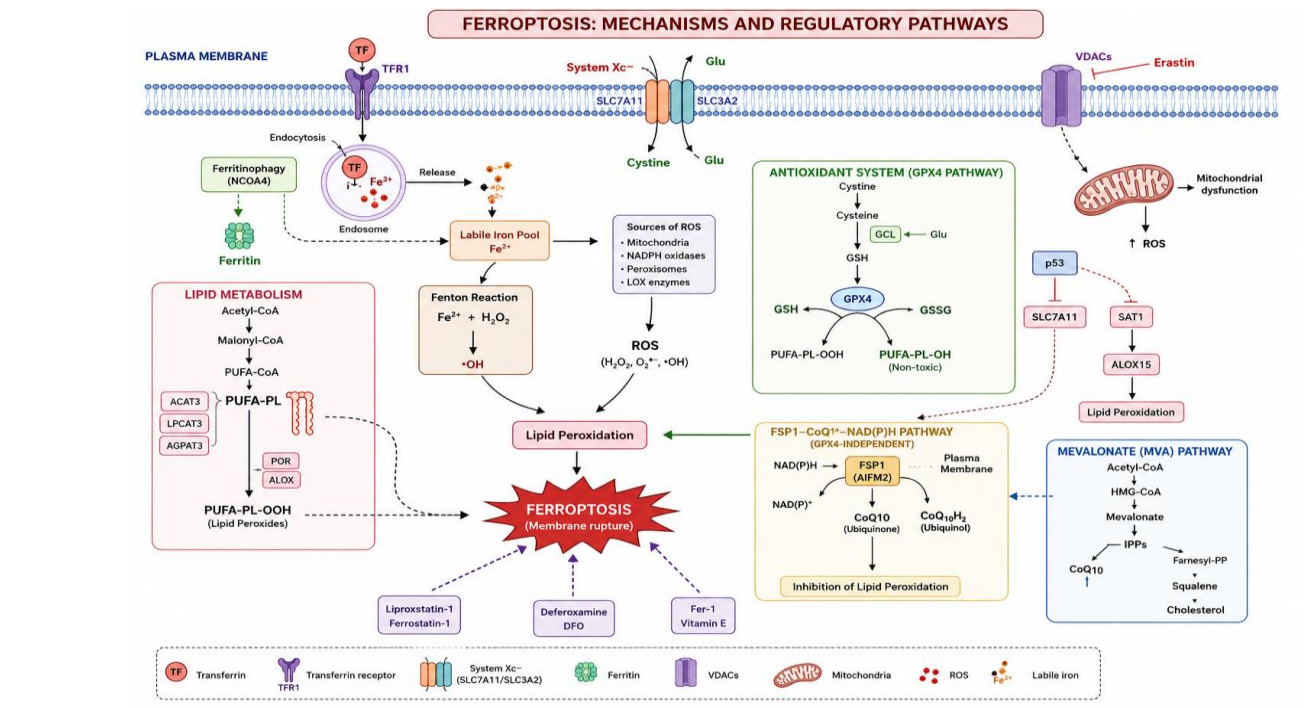

Figure No.2

Cellular Absorption, Transport, and Homeostasis

1. Dietary iron is mainly absorbed in the duodenum and proximal jejunum, where ferric iron (Fe^{3+}) is first reduced to ferrous iron (Fe^{2+}) or absorbed as heme-bound iron. [25,26]
2. After absorption, Fe^{2+} is transported from intestinal cells into the bloodstream through ferroportin (FPN) and binds to transferrin (Tf) for circulation. [27]

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3. Cellular iron uptake occurs via transferrin receptor 1 (TfR1)-mediated endocytosis, and DMT1 releases iron into the cytoplasm, forming the labile iron pool (LIP). [28]
4. Mitochondria obtain iron either directly from endosomes or from the LIP through transport proteins such as mitoferrin and SFXN1.
5. Excess intracellular iron is safely stored in ferritin, while ferritin degradation releases stored iron back into the LIP when required. [29,30]
6. The liver (hepatocytes) and spleen macrophages serve as major iron storage sites and contribute to iron export through ferroportin. [31]
7. Systemic iron homeostasis is regulated by the hepcidin–ferroportin axis, which controls dietary iron absorption, cellular iron release, and iron recycling from aged red blood cells.
8. Disruption of iron homeostasis can increase intracellular free iron levels, promote oxidative stress, and contribute to ferroptosis.

Physiological Functions and ROS Generation

1. Iron is an essential element involved in several biological processes, including oxygen transport, cellular energy generation, immune function, DNA synthesis, and the tricarboxylic acid (TCA) cycle.
2. Mitochondrial iron–sulfur clusters (ISCs) participate in electron transport reactions and contribute to the generation of endogenous reactive oxygen species (ROS). [32]
3. Under normal conditions, ROS levels are tightly regulated; however, excessive ROS production can cause oxidative damage to cellular lipids, proteins, and nucleic acids.
4. Iron promotes ROS formation through the Fenton reaction, highlighting the importance of maintaining proper intracellular iron balance. [33]
5. Disturbances in iron uptake, storage, utilization, or export can disrupt iron homeostasis and increase cellular vulnerability to ferroptosis.
6. Elevated intracellular iron levels, enhanced ferritin degradation, and accumulation of iron-derived metabolites can accelerate ROS generation and lipid peroxidation.
7. Excessive ROS and lipid peroxide accumulation ultimately trigger ferroptotic cell death, an iron-dependent form of regulated cell death.

The Mechanism of Ferroptosis Induction

1. Generation of reactive oxygen species (ROS) through the iron-dependent Fenton reaction is a key event in ferroptosis.
2. Superoxide radicals ($O_2^{\bullet -}$) are produced by NADPH oxidases (NOXs), cytochrome P450 enzymes, and the mitochondrial electron transport chain. [34]
3. Superoxide dismutase (SOD) converts superoxide radicals into hydrogen peroxide (H_2O_2).
4. Oxidation of heme-containing proteins by ROS releases Fe^{2+}, increasing the intracellular labile iron pool (LIP).
5. Excess Fe^{2+} reacts with H_2O_2 through the Fenton reaction, generating highly reactive hydroxyl radicals (•OH) that attack polyunsaturated fatty acids (PUFAs). [35]
6. This process initiates lipid peroxidation, leading to the formation of lipid radicals and lipid hydroperoxides (LOOH).
7. Iron-dependent enzymes, including lipoxygenases (LOXs), further catalyze the oxidation of PUFAs, amplifying lipid peroxide accumulation.
8. The combined action of LOX-mediated oxidation and the Fenton reaction promotes ferroptosis, although the exact iron threshold required to trigger this process remains unclear. [35]

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Cross-Talk with Other Metabolic Pathways

1. Iron plays an important role in regulating glucose, lipid, and amino acid metabolism. [36,37]
2. Excess iron can promote insulin resistance and impair insulin sensitivity, whereas iron deficiency may reduce glucose utilization while enhancing GLUT1-mediated glucose uptake. [36,37]
3. Iron deficiency disrupts lipid metabolism by reducing fatty acid oxidation and desaturation, increasing lipid synthesis, and lowering CPT-1 activity in the liver.
4. Iron overload suppresses hepatic PPARα expression, contributing to metabolic dysfunction. [38]
5. Polyunsaturated fatty acids (PUFAs) are susceptible to oxidation by iron-generated reactive species, leading to lipid peroxidation.
6. Several enzymes involved in amino acid metabolism, including prolyl-4-hydroxylase and cysteine dioxygenase, require iron as a cofactor, although their precise regulatory mechanisms remain incompletely understood. [39]

Pathways Promoting or Suppressing Ferroptosis

1. STEAP3 promotes the reduction of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), increasing the intracellular iron pool and facilitating Fenton reaction-mediated lipid peroxidation.
2. Ferritinophagy, the lysosomal degradation of ferritin, releases stored Fe^{2+}, thereby enhancing ferroptosis. [40]
3. Elevated cytoplasmic Fe^{2+} levels stimulate the expression of SFXN1, a mitochondrial iron transporter that increases mitochondrial iron accumulation, ROS generation, and ferroptotic cell death.
4. Apelin-13 promotes ferroptosis by enhancing ferritinophagy and mitochondrial iron transport through upregulation of NCOA4 and SFXN1. [41]

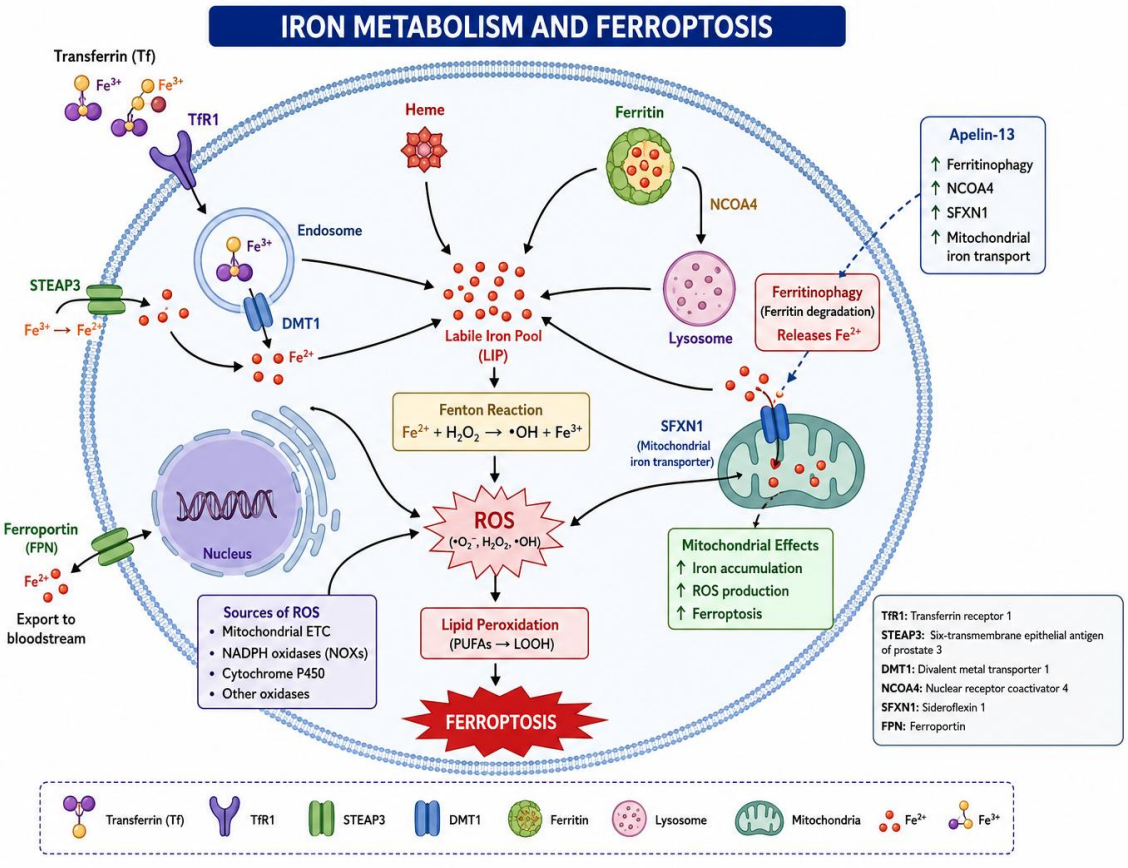

Figure No.3 Iron metabolism in ferroptosis

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Lipid peroxidation:

Lipid peroxidation is a central event in ferroptosis and involves the oxidative damage of membrane lipids, particularly polyunsaturated fatty acids (PUFAs). This process occurs through three sequential stages: initiation, propagation, and termination. During initiation, reactive oxygen species (ROS), such as hydroxyl radicals (•OH), abstract hydrogen atoms from lipids, generating lipid radicals (L•). In the propagation phase, these radicals react with oxygen to form lipid peroxyl radicals (LOO•), which further attack neighboring lipids and produce lipid hydroperoxides (LOOH), thereby sustaining a chain reaction. Termination occurs when antioxidants, including vitamin E, neutralize lipid radicals and halt further oxidation.The excessive accumulation of lipid peroxides is a hallmark of ferroptosis. Iron-dependent enzymes, particularly lipoxygenases (LOXs), and Fenton reaction-derived ROS promote PUFA oxidation and lipid peroxide formation. Under normal conditions, antioxidant defense systems such as the GPX4–glutathione axis and the FSP1–CoQ10 pathway prevent the buildup of toxic lipid peroxides. However, impairment of these protective mechanisms results in uncontrolled lipid peroxidation, membrane damage, and ferroptotic cell death.

Although lipid peroxidation and ferroptosis are closely linked, they are not identical processes. Lipid peroxidation is a general biochemical phenomenon that can occur under various physiological and pathological conditions, whereas ferroptosis is a distinct form of regulated cell death triggered by excessive iron-dependent lipid peroxide accumulation. Thus, ferroptosis represents a specific pathological outcome of dysregulated lipid peroxidation. [42–45]

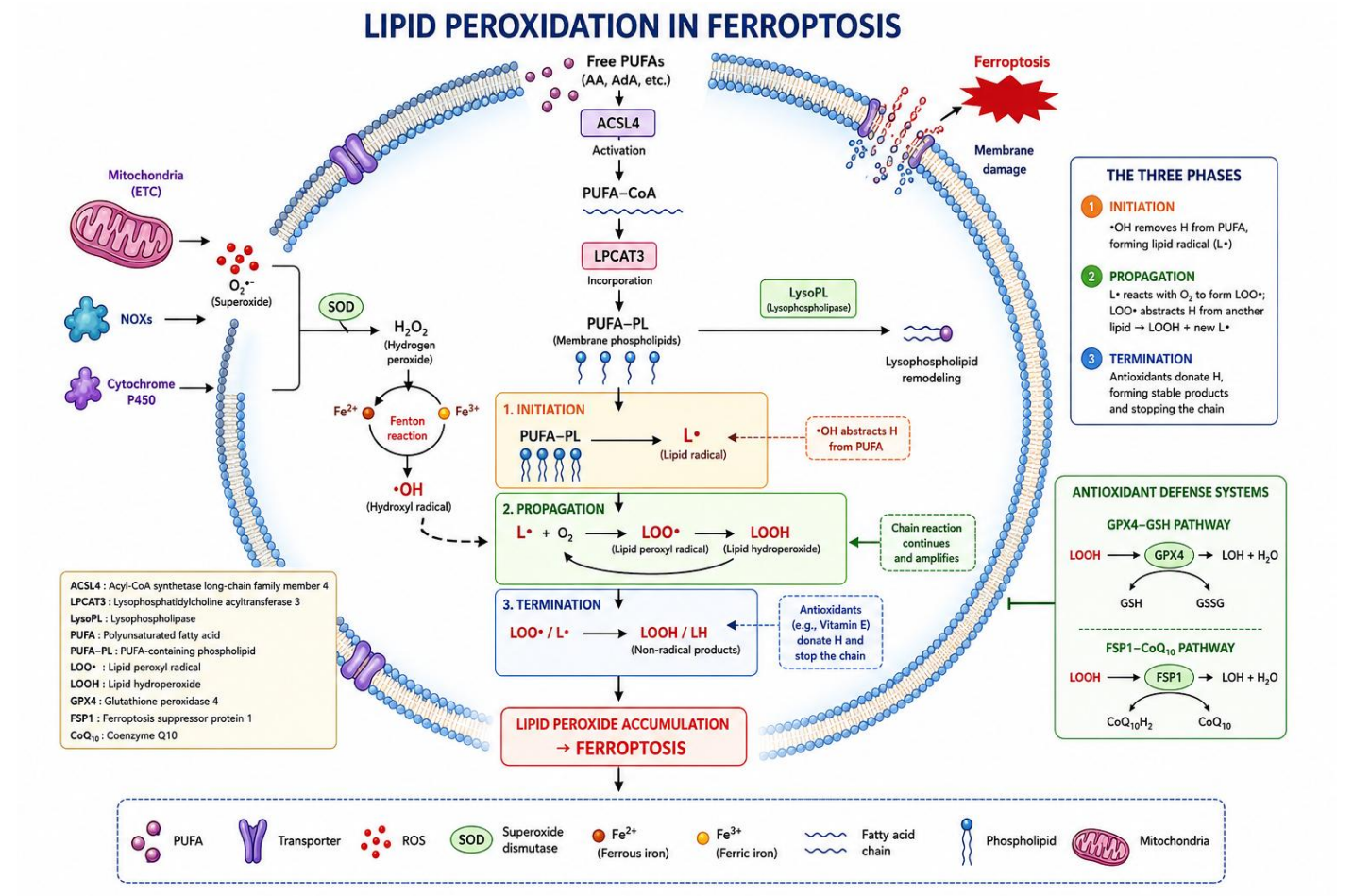

Figure No. 4

Significance of Ferroptosis in Diseases

Iron overload-related cell death, or ferroptosis, has a complicated role in illnesses like cancer (Chen et al., 2020a; Conrad et al., 2020; Tang et al., 2020). On the one hand, tumor development can be slowed by using

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specific tiny chemicals to induce ferroptosis. For example, when cyst(e)inase is administered to tumor in mice models of pancreatic cancer, the tumor exhibit typical ferroptotic symptoms such damaged mitochondria and an abundance of lipid droplets (Badgley et al., 2020). Polyunsaturated fatty acids (PUFAs) that promote lipid peroxidation may be supplied by these lipid droplets (Bai et al., 2019). Higher levels of lipid peroxidation in these tumor are supported by immunohistochemistry staining for 4-HNE (Badgley et al., 2020). Ferroptosis, however, may also have unexpected repercussions. DAMPs, which are molecules generated from dying cells, have the ability to depress the immune system, which in turn promotes the formation of tumor. For instance, lowering GPX4 in pancreatic cells or giving mice a diet high in iron can release nuclear DNA or mutant KRAS^G12D protein, which then stimulates macrophages in a way that promotes tumor growth (Dai et al., 2020a,b). Patients with pancreatic cancer who have higher KRAS^G12D levels in these macrophages have a lower chance of survival (Dai et al., 2020a). Together, these results demonstrate the dual nature of ferroptosis, which has the ability to both support and suppress tumor. This implies that the diagnosis and treatment of disorders involving ferroptosis damage may benefit from the monitoring of both intracellular and extracellular ferroptosis indicators.

Tumours and Ferroptosis

Pancreatic Cancer:

Eling and associates found that in pancreatic ductal adenocarcinoma cell lines, artesunate (ART) specifically raises ROS levels and causes ferroptosis. Similar to this, the combination of phenylethyl isothiocyanate (PEITC) and cotylenin A (CN-A) increases the production of ROS, which causes ferroptotic cell death and inhibits the growth of pancreatic cancer cells such MIAPaCa-2 and PANC-1. According to more recent research, a combination of piperlongumine (PL), CN-A, and sulfasalazine had an even more powerful effect, significantly increasing ferroptosis in these pancreatic cancer cell lines.[54]

Stomach/Gastric Cancer

According to Hao and associates, erastin causes ferroptosis in gastric cancer (GC) cells, and a crucial regulator is cysteine dioxygenase type 1 (CDO1). By competing for cysteine absorption, CDO1 inhibits the synthesis of glutathione (GSH) and increases ferroptosis. On the other hand, blocking CDO1 activity lowers the generation of reactive oxygen species (ROS) and lipid peroxidation, restores intracellular GSH levels, and eventually inhibits ferroptotic cell death.[55]

Lung Cancer

The iron-sulfur cluster biosynthesis enzyme NFS1 is abundantly expressed in highly differentiated lung adenocarcinomas, contributing to the maintenance of iron-sulfur cluster levels. NFS1 suppression causes iron depletion, which encourages ferroptotic cell death in situations of increased reactive oxygen species (ROS), even if NFS1 inhibition alone is insufficient to cause ferroptosis. Furthermore, research has demonstrated that the p53 tumor suppressor protein contributes to the induction of ferroptosis in lung cancer A549 cells. Erastin elevates and activates p53 in these cells, upregulating downstream target genes such bax and P21. Ferroptosis is the final outcome of this process, which also increases ROS buildup and reduces SLC7A11 activity.[56]

Breast Cancer

Triple-negative breast cancer (TNBC) accounts for 15–18% of cases, and breast cancer is still a leading cause of cancer-related death in women. Chemotherapy is the primary treatment for TNBC, which frequently has poor results due to the absence of effective targeted medicines. For TNBC cells to survive, cystine is essential. Ferroptosis results from reducing cystine uptake through inhibition of the system Xc^- transporter. However, substances like ferrostatin-1 (Fer-1) and deferoxamine (DFO) can stop this cell death. Furthermore, the transmembrane protein MUC1-C, which is abundantly expressed in TNBC, contributes to the preservation of glutathione (GSH) levels and redox equilibrium by acting similarly to the xCT subunit of system Xc^-. MUC1-C interacts with xCT to regulate GSH levels by forming a complex with xCT and CD44 variations (CD44v).

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Ferroptosis in TNBC cells can be induced by blocking the MUC1-C/xCT signaling pathway, which increases tumor cell death and decreases the cells' ability to self-renew.[57]

Ferroptosis and Neurological Diseases

Neurodegenerative Disorders

- Abnormal iron accumulation in the central and peripheral nervous systems promotes Fenton reactions, oxidative stress, and lipid peroxidation, contributing to neurodegeneration.
- Elevated iron levels are often accompanied by reduced glutathione (GSH) and GPX4 activity, increasing susceptibility to ferroptosis.
- In Alzheimer's disease (AD), excessive iron accumulation in the hippocampus enhances ROS production and neuronal damage. GPX4 deficiency has been linked to age-related neurodegeneration, suggesting that ferroptosis inhibition may provide therapeutic benefits.
- Parkinson's disease (PD) is characterized by iron accumulation in the substantia nigra and degeneration of dopaminergic neurons. Iron chelators such as deferoxamine (DFO) have shown neuroprotective effects by reducing oxidative stress. [58]
- In Huntington's disease (HD), iron overload, glutamate dysregulation, and decreased GSH and GPX activity contribute to ferroptosis. Ferroptosis inhibitors, including ferrostatin-1 (Fer-1), may protect neuronal cells.
- Amyotrophic lateral sclerosis (ALS) is associated with spinal cord iron accumulation, increased lipid peroxidation, and depletion of GSH, all of which promote neuronal injury.
- In Friedreich's ataxia, mitochondrial iron overload leads to elevated ROS and lipid peroxide levels, indicating a strong involvement of ferroptotic mechanisms.
- Periventricular leukomalacia (PVL) involves oligodendrocyte damage, and studies suggest that ferrostatin-1 can protect these cells by suppressing ferroptosis and restoring GSH levels.

Overall, growing evidence identifies ferroptosis as a key contributor to neurodegenerative disorders, making it a promising target for future therapeutic interventions. [58]

Traumatic Brain Injury

Iron buildup, altered iron metabolism, increased expression of ferroptosis-related genes, decreased GPX activity, and higher reactive oxygen species (ROS) are among the pathogenic alterations linked to the course of traumatic brain injury.[59] Ferrostatin-1 (Fer-1), a ferroptosis inhibitor, has been proven in studies to dramatically reduce iron deposition, minimize neuronal injury and degeneration, and enhance overall results. These results imply that ferroptosis targeting may be a promising treatment strategy for traumatic brain injury.

CONCLUSION

Ferroptosis is a distinct form of regulated cell death driven by iron-dependent lipid peroxidation. It is closely associated with iron metabolism, amino acid metabolism, and antioxidant defense systems, particularly the GPX4–GSH and FSP1–CoQ10 pathways. Increasing evidence highlights its involvement in various diseases, including cancer, neurodegenerative disorders, ischemia–reperfusion injury, and kidney diseases. While inhibition of ferroptosis may protect against tissue damage, its induction offers promising therapeutic opportunities in cancer treatment. Therefore, a deeper understanding of ferroptosis mechanisms is essential for developing effective and disease-specific therapeutic strategies.

Future Prospects

- Identification of reliable and specific ferroptosis biomarkers for early diagnosis and disease monitoring.
- Further investigation of key regulatory molecules such as GPX4, FSP1, NRF2, p53, and NADPH oxidases to better understand ferroptosis signaling pathways.
- Development of novel ferroptosis-inducing agents for cancer therapy and ferroptosis inhibitors for neurodegenerative and ischemic diseases.
- Exploration of targeted drug delivery systems, including nanoparticles, liposomes, and microspheres, to improve the efficacy and safety of ferroptosis-based therapies.
- Evaluation of ferroptosis-targeting drugs in large-scale preclinical and clinical studies to establish their therapeutic potential.
- Investigation of the interplay between ferroptosis and other regulated cell death pathways, such as cuproptosis, apoptosis, and pyroptosis, to identify new therapeutic targets.
- Application of precision medicine approaches to tailor ferroptosis-modulating therapies according to disease type, stage, and patient characteristics.
- Continued research on minimizing off-target effects and improving the long-term safety of ferroptosis-based interventions.

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