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Ferroptosis at the Crossroads of Redox Biology: Mechanisms, Regulators, and Therapeutic Opportunities

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ABSTRACT

Cellular death is a multifaceted process involving regulated (RCD) and accidental (ACD) mechanisms. While apoptosis has been extensively studied as a form of regulated cellular death, recent attention has shifted towards exploring non-apoptotic cell death pathways, particularly in the context of cancer treatment where resistance to apoptosis is common. Ferroptosis, a form of cell death dependent on iron and regulated by lipid peroxidation, has emerged as a novel mechanism distinct from apoptosis and necrosis. This review delves into the current understanding of ferroptosis, its regulatory processes, and its implications in various disease pathologies.

Ferroptosis is characterized by the accumulation of lipid peroxides and the involvement of labile iron, setting it apart from other forms of cell death. Dysregulation of lipid membrane integrity and overoxidation of polyunsaturated fatty acids are key features that contribute to membrane rupture and cell demise. Central to the orchestration of ferroptosis are regulatory proteins such as glutathione peroxidase 4 and iron-associated signaling pathways.

A critical interplay between reactive oxygen species (ROS) and ferroptosis dictates the balance between cellular damage and protection. ROS function as double-edged swords, serving as essential signaling molecules for various physiological processes while also posing a threat through oxidative damage to biomolecules. The intricate relationship between ROS, lipid peroxidation, and ferroptotic cell death underscores the importance of maintaining redox homeostasis for cell survival.

Several molecular players have been implicated in the regulation of ferroptosis, including the amino acid antiporter SLC7A11, glutathione peroxidase 4, and ferroptosis suppressor protein 1 (FSP1). These proteins play crucial roles in modulating cellular redox balance, lipid peroxidation, and susceptibility to ferroptotic stimuli. Understanding the interplay between these regulators provides insights into potential therapeutic targets for modulating ferroptosis in disease settings.

Moreover, metabolic pathways such as the trans-sulfuration pathway, nicotinamide adenine dinucleotide phosphate (NADPH) metabolism, and aldose reductase enzymes have been identified as key regulators influencing cellular sensitivity to ferroptosis. Targeting these pathways offers promising avenues for modulating ferroptotic cell death and mitigating oxidative damage in various disease states.

In conclusion, unraveling the intricate mechanisms of ferroptosis sheds light on novel avenues for therapeutic interventions targeting oxidative stress-related pathologies. By elucidating the molecular players and regulatory pathways governing ferroptotic cell death, researchers pave the way for innovative strategies aimed at modulating cellular redox balance and improving outcomes in disease states characterized by dysregulated cell death processes.

Keywords: oxidative stress, ferroptosis, cellular signaling, reactive oxygen species, lipid peroxidation, cellular death

INTRODUCTION

In the past years, numerous mechanisms of cellular death were detected and defined as regulated (RCD) or accidental (ACD). In contrast to ACD, RCD is modulated by multiple molecular processes and signalling pathways. Apoptosis is a very well-researched mechanism of RCD. It is mostly provoked by cysteine proteases activation [1,2]. Recently there has been growing interest in cellular death that does not involve apoptosis in context of cancer treatment, since one of the characteristics of malignancy is the absence of apoptosis. Ferroptosis is a form of cellular death which involves necrosis that relies upon iron and is induced by membrane injury controlled by lipid peroxidation (LPO). Toxic properties of iron and LPO were indicated in the beginning and the middle of the 20th century. Ferroptosis is essential for physiological processes in plantae and animalia [3]. Whereas this term was invented in 2012 following testing for micromolecule substance able to suppress the growing of Rat sarcoma virus-mutant malignant cells, the first hypothesis of ferroptosis could evolve from tumor cellular death caused by nutrient deficiency and oxytosis, which constitutes death of neurons susceptible to excitotoxic glutamate and suppression of aminoacid antiporter SLC7A-11/x-CT/system x-c-. A number of synthetic or organic agents and internal cellular proteins were demonstrated to control ferroptosis. In this review we are focusing on the available data on ferroptosis controlling processes and on its impact on development of different disorders [4,5].

FERROPTOTIC PROCESSES

Presently, the precise ferroptotic processes are still not fully explored, but there are some theories. Its process can be related to the lipid membrane pore creation, the same way a proteinaceous pore is found in pyroptotic and necroptotic processes. Overoxidation of PLs comprising PUFAs seems to be able to alter structure of membranes and elevate their penetrability, inducing ruptures in membranes as a reaction to deposition of lipid-reactive oxygen species (such as LOOHs) [6,7]. LOOHs can trigger synthesis of RASP, including malonic aldehydes and 4HNEs, that could inhibit activation of important cell proteins to stimulate ferroptosis. GSH peroxidase 4, iron and FSP-1 associated signaling pathways are major regulatory agents that were discovered in ferroptotic mechanism [8,9].

Interestingly, triggers of apoptotic and necrotic processes are not able to induce ferroptosis, which indicates that processes lying at its core are different from those of apoptotic and necrotic processes. Erastin, glutamate and other ferroptosis triggers can deplete glutathione and inhibit enzymatic function of glutathione peroxidase 4 by suppressing cystine import carried out by cystine/glutamate antiporter (CGA) system X_c^- [10-12]. Glutathione is a major inhibitor of ferroptosis and a nonenzymatic anti-oxidant. It exerts a cellular protective function against OS. Glutathione and glutathione disulfide typically shows the degree of OS. Glutathione peroxidase 4 belongs to the GSH peroxidase family, and thereby it uses glutathione to obtain electrons in order to transform LOOHs in membranes to fatty alcohols and H_2O [13]. LOOHs are not stable and can be disintegrated to reactive components such as malonic aldehydes, caproaldehyde, 4HNE and others, that are able to act as OS second messengers, as they have prolonged half-life and are capable of diffusion from the synthesis location. In this context, glutathione peroxidase 4 suppressants like RSL-3 are able to stimulate lipid reactive oxygen species overproduction and trigger ferroptosis [14,15]. CGA system X_c^- is importing cystine to the cytosol from outside the cell and exporting glutamate from the cell. Cystine can be transformed into glutathione, that is very important for reduction–oxidation balance in the cell since it may be used by glutathione peroxidase 4 as a co-factor to reduce LPO. Consequently, glutathione deficit and inhibition of glutathione peroxidase 4 activation with trigger of ferroptosis or with glutathione peroxidase 4 suppressant, e.g., RSL-3, stimulates overproduction of lipid reactive oxygen species which induces ferroptotic process [16,17].

Ferroptosis, a cellular death mechanism which relies on iron, may be stopped by iron chelators, but not by apoptosis or necrosis suppressants. Deposition of iron inside a cell plays a role in ferroptotic process. Hydroxyl radical ($^{\bullet}OH$) is one of the most reactive ones which may be synthesized via Fenton and Haber-Weiss reactions from H_2O_2 by catalyzing iron and copper. Iron binds transferring outside of the cell and is then imported to cytosol via TFR [18]. After that, inside the cell Fe^{3+} is transformed to Fe^{2+} by STEAP-3 and transported to endosome and then into a LIP by DMT-1. Overaccumulation of Fe^{2+} inside a cell provokes nonenzymatic lipid peroxidation via Fenton reaction. $^{\bullet}OH$ formed from that reaction extracts hydrogen from polyunsaturated fatty acids, creating $PL^{\bullet}$, a PL carbon-centered radical, and then adding oxygen to peroxyl radical to form PLOOH [19,20]. Then deposited LOOH is transformed into alkoxy radical $PL\text{-}O^{\bullet}$ while exposed to Fe^{2+}, that consequently undergoes a reaction with polyunsaturated fatty acids to trigger another LPO reaction. Moreover, iron takes part in peroxidation by LOXs, a family of enzymes catalyzing peroxidation polyunsaturated fatty acid peroxidation to synthesize LOO. Notably, lipoxygenase-mediated cell LOOHs and lipid peroxidation mediated by auto-oxidized peroxyl radicals can both facilitate ferroptotic processes. Hereby, deposition of iron inside cells is a fuse to provoke ferroptotic process [21].

Besides traditional GSH-based glutathione–glutathione peroxidase 4 axis, there was recently discovered an anti-ferroptotic pathway relying on ferroptosis suppressor protein 1. Bersuker, Doll and colleagues demonstrated that FSP-1, which had

earlier been found to be enhancing apoptotic processes, is an efficient agent against ferroptosis which defends cells against ferroptotic processes provoked by glutathione peroxidase 4 deletion [22,23]. FSP-1 undergoes myristoylation and recruitment to cell membrane, consequently catalyzing coenzyme Q_{10} reduction utilizing NADPH/NADH to synthesize coenzyme Q_{10} which acts as an anti-oxidant and a trap for radicals to inhibit lipid peroxidation, stopping ferroptosis. Thereby, multiple molecules, e.g., coenzyme Q_{10} and squalene synthesized from isoprenoid pathway also demonstrated possible involvement in ferroptotic protection [24,25]. Nonetheless, newer trials demonstrated another possible way of ferroptosis suppression for FSP-1, which does not rely on coenzyme Q_{10} synthesis, lipid peroxidation is modulated by FSP-1 via membrane restoration in an ESCRT3 dependent manner. Furthermore, aside from cellular tumor antigen p-53 involvement in apoptotic process, cell-division cycle and autophagy, available data indicates that it increases cellular sensitivity to ferroptosis by regulating reactive oxygen species and metabolic processes of cystine [26].

ROS: FRIEND OR ENEMY?

Free radicals constitute partly reduced molecules comprising O_2, also called reactive oxygen species. Superoxide is mostly synthesized by nicotinamide adenine dinucleotide phosphate oxidases, XAO, and Mt ETC. It is the source of the most part of reactive oxygen species inside cells. Via Fenton reaction, reactive oxygen species are converted by SOD to H_2O_2, that expresses very toxic $^{\bullet}OH$ while exposed to ferrous iron [26-29]. Via Haber-Weiss reaction, Fe^{3+} is reduced again by oxidation with peroxyl radical and O_2. OS induced by impaired balance of reactive oxygen species genesis rate. This leads to formation of free radicals which can damage proteins, fats and deoxyribonucleic acid. Reactive oxygen species may perform signaling function that is essential for multiple biophysiological mechanisms, such as growing proliferation, autophagocytosis, differentiation and cellular death [30]. Reactive oxygen species synthesis and clearance were closely investigated. Cells were observed during different steps of cellular life. Proliferation rate was significantly increased by hydrogen peroxide therapy (1-10 M). As Jurkat cells were in the presence of 50 M hydrogen peroxide, apoptotic process stimulation was poor. After 6 h, considerable changes in apoptosis were detected [31,32]. Conversely, cellular necrosis upon elevated OS was observed (100 M hydrogen peroxide). Interestingly, trials demonstrated that hydrogen peroxide generated in the intestine malignant cells can be of great importance in provoking cellular death to exert anticancer effect. Cellular anti-oxidant system is highly responsible for the dynamics and stability of reactive oxygen species balance [33]. In vivo, this system capacity for keeping this balance relies on sustenance of levels of H_2O_2 and NO synthesis and removal in range which averts excessive deposition of peroxonitrite or $^{\bullet}OH$. Anti-oxidants of internal origin comprise vitamins (A, C, E, CoQ_{10}), minerals (Se, Zn), metabolic products (bilirubin (BR), melatonin). Enzymes-anti-oxidants involve SOD, catalases, GSH peroxidase, GSH reductase (GR). OS may be induced by alterations in reduction–oxidation and anti-oxidant depletion, that may lead to oxidative injury [34].

ROS: TRIGGERS OF CELLULAR DAMAGE

Multiple compounds, such as deoxyribonucleic acid, proteins, and fats undergo interplay with reactive oxygen species. OS can induce numerous deoxyribonucleic acid lesions, such as base changes, AP sites, SSB and DSB in deoxyribonucleic acid. Srinivas and colleagues reported that 8-oxo-dG is the primary pathway of deoxyribonucleic acid modification. Such oxidative protein alterations as carbonylation and merox happen most often [35,36]. Oxidation decreases enzymatic capacity for binding and functioning. Aminoacids methionine and cysteine (Cys), which comprise sulphur, are vulnerable to OS damage. The two of them may undergo oxidation to generate sulphoxide and sulphur radical and disulphides. PUFAs are important PLs in plasma membranes [37,38]. They regulate CMF and membrane deformability. Oxygen free radicals cause damage to PUFAs thus inducing LPO. Genesis of radicals free of fats leads to synthesis of peroxidized-free radicals, that can target closely located PUFAs and cell membrane proteins, simultaneously inducing membrane LPO [39,40].

ROS AND FERROPTOSIS

The term ferroptosis means a new nonapoptotic cellular death which includes Fe and fats reactive oxygen compounds. Li and colleagues [41], Halliwell [42], Gutteridge and colleagues [43], Que and colleagues [44], Dixon and colleagues [45] reported that the main features of ferroptotic process are: polyunsaturated fatty acids-comprising cell membrane PLs oxidation, presence of reduction–oxidation active iron, and inability to restore LOOH. It was demonstrated that OS and cell anti-oxidant concentrations have major LPO regulation effect in ferroptotic process. This was induced by agents that are able to prevent LPO that relies on iron and by lipophilic anti-oxidants such as bioactive polyphenols, liproxstatin-1, vit E, and Fer-1. It was also induced by such medications as salazopyrin, erastin, and RSL-3. Multiple pathways in cell metabolism, e.g., Krebs cycle, ETC, metabolism of fats, and metabolism of aminoacids, produce considerable masses of reactive oxygen species which may provoke ferroptotic process [46,47].

Table 1. Functions of Reactive Oxygen Species (ROS)

Function	Description	Impact
Cellular Signaling	ROS play a crucial role in signaling pathways related to proliferation, differentiation, and autophagy	Essential for regulating various biophysical processes
Oxidative Stress (OS) Activation	Imbalance in ROS production and clearance leads to oxidative stress, causing cellular damage	Damage to proteins, DNA, and lipids, which can induce cell death
DNA Damage	ROS induce various DNA lesions, including base modifications, single-strand breaks (SSB), and double-strand breaks (DSB)	Contributes to genomic instability and mutagenesis
Protein Modification	Oxidation can lead to alterations in proteins, such as carbonylation, affecting their function	Reduces enzymatic activity and disrupts cellular functions
Lipid Peroxidation (LPO)	ROS target polyunsaturated fatty acids (PUFAs), causing membrane damage and altering membrane integrity	Disruption of cell membranes and potential necrotic cell death
Ferroptosis Trigger	ROS contribute to ferroptosis by promoting lipid damage in the presence of iron, leading to non-apoptotic cell death	Highlights a new pathway for cell death distinct from apoptosis and necrosis
Antioxidant Regulation	The cellular antioxidant system regulates ROS dynamics, utilizing vitamins and enzymes like SOD and catalases	Protects against oxidative injury and maintains redox homeostasis

FERROPTOTIC MECHANISMS

Ferroptotic process includes 2 major parts: lipid peroxides and Fe. Deposition of the former seems to induce ferroptosis, where Fe catalyzes or controls ferroptotic process. When exposed to GSH, toxic lipid peroxides are transformed into fatty alcohols by GSH peroxidase 4. By scavenging intrinsic lipid reactive oxygen species, GSH peroxidase 4 defends cells against ferroptotic activity, whereas suppression of GSH peroxidase 4 provokes ferroptosis. It can also be stimulated by reactive oxygen species synthesized by Fenton reaction, sped up by Fe [46,47].

Table 2. Mechanisms and Interactions in Ferroptosis Regulation

Mechanism/Protein	Function/Interaction	Impact on Ferroptosis
Ferroptotic Activators	RSL-3, Erastin	Suppress antioxidant systems, promoting ferroptosis
SLC7A11 (xCT/System Xc-)	Exchanges cystine for glutamate; crucial for glutathione synthesis	Suppression leads to decreased glutathione and increased ferroptosis
Glutathione Disulfide (GSSG)	Oxidized form of glutathione, converted back via GSR/GR	Depletion may promote ferroptotic processes
Glutamate-Cysteine Ligase (GCL)	Key enzyme in glutathione synthesis, regulated by nutrient availability	Inhibition increases susceptibility to ferroptosis
CDO-1	Converts cysteine to taurine, modulated by MYB	Involved in cysteine metabolism affecting cell survival
Glutathione Peroxidase 4 (GPX4)	Reduces lipid hydroperoxides to alcohol forms; influenced by selenium	Suppression triggers ferroptosis; crucial for cellular protection
Ferroptosis Suppressor Protein 1	Acts as an antioxidant independent of mitochondrial function	Inhibition can promote ferroptosis, while activity prevents it
Cystathionine-γ-lyase (CGL)	Linked to trans-sulfuration pathway, generating cysteine	Influences cysteine levels impacting ferroptosis susceptibility
NADP+H/NADPH	Key redox compound regulating oxidative stress; altered by enzymatic pathways	Low levels can enhance ferroptosis susceptibility
AKR1-C/D (Aldose Reductase)	Reduces lipid peroxides to fatty alcohols in resistant cells	Protects against ferroptosis by detoxifying lipid peroxides
Peroxiredoxins (Prx)	Redundant antioxidant system that reduces lipid hydroperoxides via hydrolysis	Suppresses ferroptotic processes in various cell types
Thioredoxin (TRX)	Essential in TRX antioxidant system; affects cellular redox status	Suppression can lead to increased susceptibility to ferroptosis
GTP Cyclohydrolase-1	Enzyme that regulates THB synthesis impacting neurotransmitter formation	Deficiency can be linked to ferroptosis-related disorders

GSH PEROXIDASE 4 FUNCTION AND FERROPTOSIS

System X_c^--glutathione-glutathione peroxidase 4 pathway is the typical ferroptosis regulation axis. GCL and GSS undergo catalyzation by glutathione. They generate cystine when system X_c^- exchanges glutamate for cystine in a one-to-one ratio. Elevated OS makes the majority of malignant cells susceptible to glutathione deficiency. That feature could be used in tumor treatments. Any cellular PL H_2O_2 undergoes reduction by glutathione peroxidase 4 to alcohols by glutathione activity [48,49]. Glutathione peroxidase 4 is a powerful reductase, and its suppression can induce ferroptotic process, whereas its excessive expression decreases reactive oxygen species concentrations and suppresses ferroptotic process. RSL-3 is a glutathione peroxidase 4 suppressant [50]. It induces cell ferroptosis by suppressing function of glutathione peroxidase 4. Fin-56 drains ubiquinol and glutathione peroxidase 4 and thus induces ferroptosis. Microelement Se was proved to be crucial for glutathione peroxidase 4 functioning. Glutamate cysteine ligase catalytic and regulation sub-units, glutamate cysteine synthase, and SLC7A-11 were proved to be critical for glutathione genesis and regulated by NFE2L2. NFE2L2 exerts a complex regulatory function of antiferroptotic reactions, as it regulates glutathione peroxidase 4 genesis and synthesis of other important anti-oxidant protection compounds [51,52].

IRON METABOLIC PROCESSES THAT TRIGGER FERROPTOSIS

LOX and CYPs are important enzymes that synthesize reactive oxygen species in ferroptotic process. Iron is necessary for their synthesis. Bia Fenton and Haber-Weiss reactions, iron metabolic mechanisms promote LPO. Iron supplements can drive cells to be more vulnerable to agents that suppress ferroptosis, such as erastin [53,54]. LIP is uncontrolled ferrous iron reduction–oxidation activity, which is found inside cells. By decreasing presence of iron in labile iron pool, iron metabolic suppressants and iron chelators decrease LPO. Multiple crucial proteins, such as Fe deposition proteins,

metabolic proteins and transport proteins, e.g., FTL, FTH-1, SLC40A-1, and BLVRA/B, have been proved to be also controlled transcriptionally by NFE2L2 [55,56].

Disintegration of haem into Fe^{2+}, biliverdin, and CO was stimulated by overactivation of haem-oxygenase 1 which was regulated by NFE2L2, elevating Fe concentrations in labile iron pool and contributing to ferroptosis. Hereby, haem-oxygenase 1 defense activity was explained by its anti-oxidant function, while its hazardous activity of overregulation was explained by elevated Fe^{2+} genesis which provoked peroxide catabolism modulated by Fenton reaction, while exposed to ferritin storage ability deficit. Moreover, by storing ferritin and trans-ferritin receptors, autophagy modulated by reactive oxygen species elevated cell Fe concentrations and induced ferroptotic process [57,58].

ANTIOXIDANT SYSTEM

Typical ferroptotic activators, such as RSL-3, erastin, also suppress anti-oxidant system, which is critical for elucidating network of various anti-oxidant proteins suppressing ferroptosis [2,3].

SLC7A11

Aminoacid antiporter SLC7A-11/xCT/system X_c^- consists of 2 main parts: L-chain SLC7A-11 and H-chain SLC3A-2. The two of them maintain genesis of glutathione, a major natural anti-oxidant, via a chain of reactions following swapping cystine for glutamate. Glutathione genesis relies on the presence of Cys, concentrations of sulphur aminoacid precursors, and function of GCL. Suppression of glutamate-cysteine ligase by BSO promotes ferroptotic process or increases cell vulnerability to ferroptotic triggers [59,60]. Likewise, SLC7A-11 suppression by erastin and similar agents or medications or glutamate drains glutathione and stimulates ferroptosis.

Reduced glutathione donates electrons and undergoes oxidation resulting in its conversion into glutathione disulphide. Glutathione restoration from glutathione disulphide is mediate by GSR/GR, an enzyme which utilizes nicotinamide adenine dinucleotide + hydrogen [61]. Erastin was first introduces as an activator of voltage-dependent anion-selective channel protein 2/3, which can promote Mt function impairment. Erastin can also upregulate the expression of SLC7A-11, hereby inducing activation of a feedback process regulating overconsumption of glutathione. SLC7A-11 function and expression is controlled by multiple factors, including BAP-1, TP-53, MUC-1, BECN-1, NRF2, that generate a network to regulate glutathione concentrations in ferroptotic process. Generally, SLC7A-11 pathway suppression is very important mechanism for promoting ferroptotic process [62,63].

CDO-1 is an enzyme which transforms Cys into taurine via catalysis of the Cys oxidation into sulphinic acid. Its expression modulated by MYB is able to stimulate death of malignant cells of the stomach provoked by erastin. This means that non-glutathione-dependent Cys metabolic processes could also be a part of ferroptotic regulation. Cystein may be utilized to generate coenzyme A through pantothenate pathway. Coenzyme A can suppress ferroptotic processes induced by SLC7A-11 suppression. Hereby, Cys metabolic processes can affect cellular proneness to ferroptotic processes [64,65].

GLUTATHIONE PEROXIDASE 4

Glutathione peroxidase 4 acts as a PL hydroperoxidase to decrease synthesis of PL hydroperoxides (AA/AdA-PE-OOH) to PL alcohol. Glutathione peroxidase 4 function and expression are regulated by Se and glutathione. When glutathione peroxidase 4 is generated, resulting polypeptide chain includes Se as amino acid selenocysteine, there Se takes place of the sulphur, and a UGA termination codon is re-coded by selenocysteine-transfer RNA and a SECIS inside glutathione peroxidase 4 messenger RNA [66]. Se is able to enhance antiferroptotic function of glutathione peroxidase 4 via Sec residue U-46. In transcription, glutathione peroxidase 4 overexpression by AP2γ and SP-1 caused by Se protects against intracranial haemorrhage associated with ferroptosis. Specificity protein 1 also targets ACSL-4, which results in ferroptotic intestinal ischemia-reperfusion injury. Hereby, specificity protein 1 can turn out to be involved in ferroptosis in more than one way [67,68].

In the catalysis of glutathione peroxidase 4, peroxide carries out oxidation of active selenol into selenic acid, with following reduction by glutathione to intermediate selenide disulphide. Then, glutathione peroxidase 4 undergoes activation by 2nd glutathione, expressing GSH disulphide. While glutathione peroxidase 4 is maturing, selenocysteine-transfer RNA is a major regulator that is upregulated by IPP. A number of micromolecule substances (such as RSL-3, Fin-56, $FINO_2$, ML-210, and ML-162) are able to suppress function of glutathione peroxidase 4, although, some of them are also able to trigger glutathione peroxidase 4 protein to degrade [69].

$FINO_2$ is not binding to glutathione peroxidase 4 or suppressing expression of glutathione peroxidase 4 directly. Mt LPO and oxidized ferrous iron synthesis caused by $FINO_2$ stimulate ferroptosis independently of arachidonate lipoxygenase. In contrast to other suppressants of glutathione peroxidase 4, ML-210 is a pro-drug which is transformed into active form

inside cells, where it forms alpha-nitroketoxime JKE-1674 that suppresses glutathione peroxidase 4 in a covalent manner [70]. Besides suppression of glutathione peroxidase 4, Fin-56 can also bind and activate FDFT1/SQS, thus averting ubiquinol synthesis. Hereby, KD of farnesyl-diphosphate farnesyltransferase 1 suppresses ferroptosis provoked by Fin-56 in HT-1080 cells. Also, KD of farnesyl-diphosphate farnesyltransferase 1 enhances ferroptotic processes provoked by ML-162^{-} and RSL-3 in squalene epoxidase-deficient ALK+ ALCL cells. These data suggest that squalene metabolic processes could take part in ferroptotic processes provoked by glutathione peroxidase 4 suppressants [71].

Precisely how glutathione peroxidase 4 is degraded in ferroptosis in yet to investigate. Acetyl-CoA carboxylase alpha stimulates degradation of glutathione peroxidase 4 triggered by Fin-56 in HT-1080 cells. Nonoxidized dopamine is a signaling molecule that suppresses degradation of glutathione peroxidase 4 triggered by erastin in malignant cells. Activation of HSPA-5 release averts degradation of glutathione peroxidase 4 triggered by erastin via genesis of HSPA-5–glutathione peroxidase 4 complexes [72]. Conversely, autophagy that is modulated by chaperones and relies on HSP-90 can stimulate degradation of glutathione peroxidase 4 triggered by erastin via recognition of KFERQ-like motifs (^{187}QVIEK^{191} and ^{124}NVKFD^{128}) in neurones. Hereby, cooperation of autophagy and UPS is required to stimulate glutathione peroxidase 4 to degrade [73,74].

Whereas suppression of glutathione peroxidase 4 is a major signal in ferroptosis, it can also happen independently of glutathione peroxidase 4. E.g., suppression of glutathione peroxidase 4 is not necessary for ferroptotic process mediated by TP-53, however, TP-53 suppresses expression of SLC7A-11. Depleted SLC7A-11 and glutathione peroxidase 4 significantly elevated cell resistance to ferroptosis triggered by insufficient Golgi function. P450 oxidoreductase also takes part in ferroptosis triggered by ML-210 independently of glutathione peroxidase 4. This evidence indicates the intricacy of ferroptotic processes utilizing various molecular mechanisms [75,76].

FERROPTOSIS SUPPRESSOR PROTEIN 1 (FSP1)

FSP-1 is a typical inductor of apoptosis in Mt. It was recently found to have anti-oxidant activity in ferroptotic process, independent of its Mt function. N-myristoylation is necessary to transfer FSP-1 from Mt to cellular membrane where it acts as a catalyst of restoration of non-Mt reduced ubiquinol utilizing nicotinamide adenine dinucleotide + hydrogen, hereby capturing LPO products independently of glutathione peroxidase 4 [77]. FSP-1 can suppress ferroptosis via activation of ESCRT3-dependent restoration of membrane rather than exhibit oxidoreductase activity. FSP-1 function in ferroptotic process is particularly suppressed by micromolecule agent named iFSP-1. Statins suppressing genesis of ubiquinol and glutathione peroxidase 4 can target mevalonate pathway. Statins were found to suppress selenoproteins synthesis, which makes them possibly able to promote ferroptosis. Idebenone is a hydrophilic ubiquinol analogue. It suppresses ferroptotic process triggered by Fin-56 or RSL-3, while stimulating apoptosis triggered by staurosporine [78,79].

CYSTATHIONINE-Γ-LYASE

Cystathionine participates in trans-sulphuration pathway. Cystathionine is decomposed in a CGL-dependent manner, which is another cysteine source. The trans-sulphuration pathway links Met (methionine) and glutathione synthesis. During Met cycle, Met generates SAM as a methyl donor, generating SAH. That is then transformed to aminoacid Hcy, that undergoes recycling to produce Met. Hcy has another pathway which generates cystathionine by cystathionine β-synthase and cysteine by cystathionine-γ-lyase [80]. Cysteine is utilized to synthesize glutathione by generating gamma-glutamylcysteine (GGC). Then it undergoes catalyzation by GCLC and suppressed by buthionine sulfoximine. CysRS1 is an enzyme that is charging transfer RNA^{Cys} with cysteine in cytosol. Silencing of this enzyme suppresses erastin-triggered ferroptosis related to overactivation of trans-sulphuration pathway by elevated cystathionine-β-synthase or PSAT-1 [81,82].

NICOTINAMIDE ADENINE DINUCLEOTIDE + HYDROGEN

Nicotinamide adenine dinucleotide + hydrogen is a major reduction compound. It is typically generated by PPP and it curbs ferroptosis-induced peroxidative injury. It can be generated via phosphorylation of nicotinamide adenine dinucleotide by nicotinamide adenine dinucleotide kinase. Silencing of nicotinamide adenine dinucleotide kinase triggers reduction of NADPH and stimulates ferroptosis caused by RSL-3, erastin and Fin-56 [83,84]. HDDC-3 is a cytosolic NADPH phosphatase which can trigger ferroptotic process upon excessive activation. Notably, medications suppressing PPP by 6AN or KD of G6PD and PHGDH partially avert ferroptotic processes triggered by erastin in Calu1 cells. Conversely, NADPH oxidases-mediated oxidation of nicotinamide adenine dinucleotide + hydrogen stimulates ferroptotic processes [85,86]. Hereby, alterations in NADP/NADP+hydrogen ratio can define the susceptibility of ferroptotic process. Cells that are resistant to ferroptosis can show elevated NADPH or decreased NADP/NADP+hydrogen ratio. Glutathione peroxidase 4, FSP-1, NADPH oxidase, P450 oxidoreductase and other regulators of ferroptotic process utilize NADP+hydrogen system to control ETC, which means that NADP+hydrogen could be a major player in ferroptotic reactions [87].

AKR1-C

AKR1-C and AKR1-D are subgroups of aldosterone reductase family 1. This is a superfamily of AKR enzymes associated with steroid metabolic processes. In malignant cells which are resistant to erastin, overexpression of AKR1-C averts ferroptosis by reduction of LOOHs to non-toxic fatty alcohols [88].

PEROXIREDOXIN

Peroxiredoxins (Prx) are a family of GPXs independent of Se which facilitate inhibition of ferroptotic process. Prx6 undergoes recruitment to peroxidized cellular membrane upon OS, then it carries out reduction and hydrolysis of Ox-sn2 fatty acyl or sn2 ester bond of OxPLs. Prx6 suppresses ferroptosis and genesis of lipid hydroperoxides triggered by RSL-3 or erastin via Ca^{2+}-independent phospholipase A2 function. Likewise, Prx5 suppresses deposition of reactive oxygen species triggered by erastin in Hep G2 cells. In addition, in corneal endothelium Prx1 suppresses ferroptotic process triggered by cumenehydroperoxide [89,90].

THIOREDOXIN (TRX)

TRX is a 12kDa oxidoreductase which is essential in TRX anti-oxidant system which comprises TRX, nicotinamide adenine dinucleotide + hydrogen, and TrxR. Ferroptocide quickly promotes ferroptosis-like cellular death in different malignant cells by suppressing enzyme function of TRX. However, it is still unclear if ferroptocide in fact promotes LPO. KO of TrxR1 suppresses ferroptosis triggered by ML-210 in malignant cells. Whereas these findings indicate the crucial role of TRX in inhibition of ferroptotic process, they do not indicate that TRX pathway activation is in fact required for restraining LPO [91].

GUANOSINE TRIPHOSPHATE CYCLOHYDROLASE-1

Guanosine triphosphate cyclohydrolase-1 is an enzyme that restrains rate of THB synthesis. THB is a co-factor for a number of essential enzymes participating in genesis of neurotransmitters and nitric oxide. Genesis of THB mediated by guanosine triphosphate cyclohydrolase-1 leads to fat remodeling and suppresses ferroptotic process by stopping 2 polyunsaturated fatty acyl tails from utilizing PLs. Dopamine was proved to suppress ferroptotic process triggered by erastin, while nitric oxide-mediated ferroptotic process is associated with tissue damage. Hereby, THB deficit can be important in development of ferroptosis-associated disorders [92,93].

CONCLUSION

As research on ferroptosis continues to unveil the intricate molecular pathways and regulatory mechanisms underlying this unique form of regulated cell death, it becomes increasingly evident that ferroptosis represents a crucial player in the landscape of cellular demise, distinct from conventional apoptotic and necrotic pathways. The interplay between lipid peroxidation, redox balance, and iron metabolism defines the vulnerability of cells to ferroptotic processes, highlighting the importance of maintaining homeostasis in these interconnected pathways.

Key players in the regulation of ferroptosis, such as glutathione peroxidase 4, SLC7A11, and ferroptosis suppressor protein 1, orchestrate a delicate balance between promoting cellular survival and triggering cell death in response to oxidative stress and lipid peroxidation. Understanding the dynamic interactions among these regulators provides insight into potential therapeutic targets for modulating ferroptosis in disease contexts characterized by dysregulated cell death.

The complex crosstalk between reactive oxygen species, lipid peroxidation, and cellular antioxidant systems underscores the intricate dance of protection and damage that defines the fate of cells undergoing ferroptosis. Targeting key metabolic pathways and molecular players involved in ferroptosis regulation opens up new avenues for therapeutic interventions aimed at modulating oxidative stress-related diseases and improving patient outcomes.

By untangling the web of signaling pathways, metabolic processes, and regulatory proteins associated with ferroptosis, researchers are paving the way for precision medicine approaches that harness the therapeutic potential of modulating cell death mechanisms to target specific pathologies. The growing body of knowledge on ferroptosis not only sheds light on the complexities of cellular demise but also offers opportunities for innovative therapeutic strategies that may revolutionize disease treatment paradigms.

In conclusion, the evolving understanding of ferroptosis as a unique form of regulated cell death with distinct regulatory mechanisms and implications in disease pathologies underscores the importance of continued research in this field. By elucidating the nuances of ferroptotic processes and identifying novel targets for intervention, the scientific community is poised to translate these discoveries into clinical applications that hold promise for improving patient outcomes and advancing precision medicine in the realm of oxidative stress-related disorders.

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