Trends in Biochemical Sciences

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Review

The metabolic code of ferroptosis: nutritional regulators of cell death

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Ferroptosis is a distinctive form of regulated cell death driven by iron-dependent phospholipid peroxidation. Its initiation and suppression are finely tuned by metabolic pathways, transcription factors, and nuclear receptors that control lipid peroxidation levels. Significantly, nutrients such as vitamins and trace elements play a pivotal role in this regulation, directly linking diet and nutrients to cellular fate. This review conveys the latest insights into the metabolic components that influence ferroptosis. We highlight how metabolic and transcriptional regulators and key nutrients, micronutrients, and metabolites orchestrate this process. Charting these interactions will be essential for developing new avenues for therapeutic interventions targeting ferroptosis in various diseases.

Highlights

Recent work has shown that nutrients (such as vitamins and trace elements) and metabolites can either suppress or promote lipid peroxidation and ferroptosis.

The trace elements iron and selenium have been shown to be essential for regulating ferroptosis.

Activation of nuclear receptors by their agonists (vitamins, lipids, bile acids, or hormones) can drive transcriptional programs associated with ferroptosis resistance.

Dietary components are important adjuvants in modulating ferroptosis-associated conditions.

Metabolic processes control ferroptosis susceptibility

Regulated cell death mechanisms are implicated in several diseases [1]. Degenerative diseases often involve the loss of critical cells, and the same disease may involve different cell death pathways. Conversely, abnormal cell populations can resist these death mechanisms in conditions such as cancer, fibrosis, and chronic inflammation. Traditionally, cell death has been categorized into two types: apoptosis, a regulated process, and necrosis, which was believed to occur accidentally and without regulation. However, research over the last two decades has revealed numerous non-apoptotic cell death processes, including necroptosis, pyroptosis, and ferroptosis, which are also tightly regulated [2].

Ferroptosis is a form of regulated cell death, distinct from apoptosis, necroptosis, and pyroptosis, which are typically triggered by signaling cascades. Its defining feature is iron-dependent **phospholipid peroxidation** (see Glossary), in which **polyunsaturated fatty acid (PUFA)** tails in phospholipids undergo oxidative damage [3–6]. Metabolic processes that alter the levels of iron or antioxidant elements critically influence susceptibility to ferroptotic cell death. Besides cellular **metabolism**, nutrients such as **vitamins** and **trace elements** significantly impact sensitivity to ferroptosis. This review first presents and discusses essential components of ferroptosis regulation, and then highlights novel discoveries linking metabolites, nutrients, and trace elements involved in regulating phospholipid peroxidation.

Pathways inducing ferroptosis

Over the past decade many discoveries have shed light on the mechanistic regulation of ferroptosis. In the following section we highlight key factors that promote lipid peroxidation and discuss metabolic pathways that modulate this process.

Iron-dependent oxidation of PUFA phospholipids

Lipid peroxidation in a biological context is catalyzed by iron, as iron chelators (e.g., deferoxamine and deferiprone) protect against ferroptosis [3,7]. However, the precise role of iron in ferroptosis execution remains partially unclear. The redox-active iron pool (free Fe^{2+}) can catalyze the formation of reactive oxygen species (ROS) [8], which promote peroxidation of PUFA tails in phospholipids (Figure 1). Thus,

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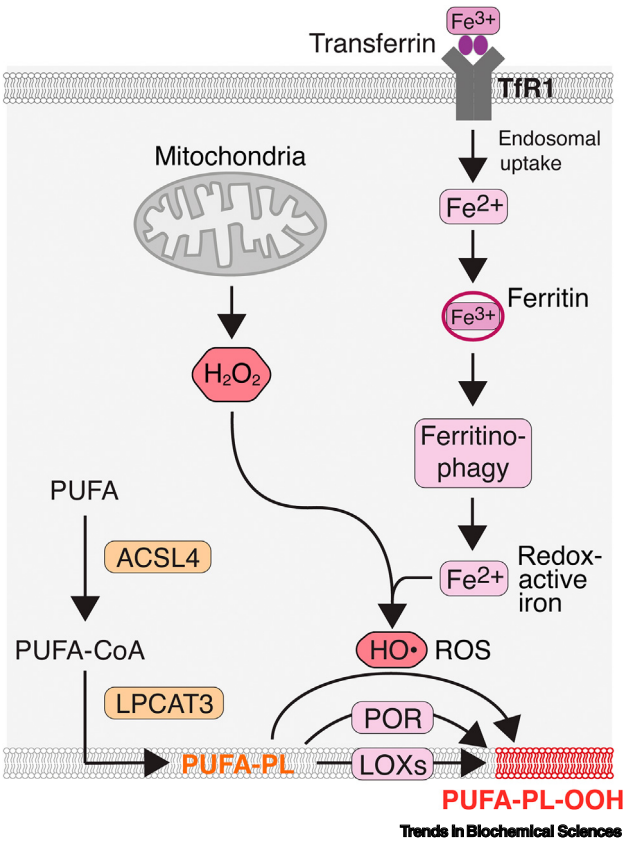

Figure 1. Pathways inducing ferroptosis. For a cell to undergo ferroptosis, two main conditions must be met: first, a pool of redox-active iron must be present, which is imported into the cell via endosomal uptake of the transferrin receptor (TfR1). In a non-toxic state, iron is bound to ferritin as Fe^{3+}, but can be released via ferritinophagy. Labile, redox-active iron (Fe^{2+}) together with H_2O_2 (e.g., from mitochondria) catalyzes the formation of reactive oxygen species (ROS) such as hydroxyl radicals (HO•), which in turn attack phospholipids in cellular membranes to induce lipid peroxidation. The second necessary condition is the presence of phospholipids with a polyunsaturated fatty acyl tail (PUFA-PL), which are more prone to radical attack. Subsequent formation of hydroperoxides (PUFA-PL-OOH) leads to membrane damage. The activation and incorporation of PUFA-PL is catalyzed by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). In addition to ROS-mediated lipid peroxidation, NADPH-cytochrome P450 reductase (POR) and lipoxygenases (LOXs) may catalyze the oxidation of PUFA-phospholipids.

mechanisms that regulate iron homeostasis at both systemic and cellular levels influence sensitivity to ferroptosis by affecting iron availability and compartmentalization [4].

Metabolic and signaling pathways that regulate iron trafficking, uptake, and utilization in cells are implicated in ferroptosis. For instance, once absorbed, iron is transported bound to the carrier protein transferrin (Tf) in plasma and delivered to all cell types. Tf-bound iron is imported into cells in a controlled manner through its receptor at the cell surface – transferrin receptor protein 1 (TfR1) – via a clathrin-mediated endocytosis process [8] (Figure 1). TfR1 appears to accumulate in ferroptotic cells and has recently been proposed as a marker for ferroptosis [9,10].

Iron storage in ferritin nanocages and iron export via ferroportin can prevent ferroptosis [8,11,12]. Conversely, pathways that increase the redox-active iron pool in the cytoplasm sensitize cells to ferroptosis. One of these pathways involves the degradation of ferritin via a nuclear receptor co-activator 4 (NCOA4)-mediated autophagy pathway known as **ferritinophagy** [13,14] (Figure 1). Heme degradation via heme oxygenase 1 (HO-1) also releases free Fe^{2+} and promotes lipid peroxidation [15]. Furthermore, iron-containing enzymes that promote lipid peroxidation include cytochrome P450 oxidoreductase (POR) and lipoxygenases (LOXs). Although these enzymes are not primary drivers of ferroptosis, they may contribute to the initiation and propagation of lipid peroxidation in certain contexts, for example by increasing the 'peroxide tone' [7,16,17] (Figure 1).

A growing body of evidence suggests that ferroptosis is implicated in the pathogenesis of iron-overload diseases and exacerbates tissue damage, particularly in the liver, heart, and pancreas

Glossary

Fenton reaction: the oxidation of organic substrates, catalyzed by iron in the form of Fe^{2+}. This reaction results in the conversion of hydrogen peroxide (H_2O_2) into a hydroxyl radical (HO•). This radical is highly reactive and can initiate lipid peroxidation when it encounters a lipid membrane.
Ferritinophagy: a type of autophagic process that facilitates the degradation of ferritin, leading to the release of redox-active iron (Fe^{2+}) into the cytoplasm.
Free radical: an atom or molecule that contains one or more unpaired electrons. An unpaired electron is one that occupies an atomic or molecular orbital by itself. Some free radicals act as oxidants and are relevant in the context of ferroptosis, such as radical superoxide ($O_2^{\bullet-}$), hydroxyl radical (OH•) and peroxyl radicals (ROO•). When a free radical reacts with an organic molecule, such as a polyunsaturated fatty acid in a membrane bilayer, it results in a new radical that initiates a chain reaction.
Metabolism: the sum of all chemical reactions that occur in a living organism to maintain life. It is crucial for growth, adaptation to environmental changes, and reproduction, and consists of two main processes: catabolism (the breakdown of macromolecules to obtain energy) and anabolism (the energy-requiring synthesis of macromolecules).
Monounsaturated fatty acid (MUFA): a fatty acid with a single double bond; MUFAs are less susceptible to oxidation than PUFAs.
Nuclear receptor: a class of receptors that, upon ligand binding, bind DNA response elements located in the promoter regions of target genes and thereby regulate downstream gene expression. Ligands of nuclear receptors can be vitamins, lipids, metabolites, or hormones, such as vitamin A, bile acids, and estrogen.
Phospholipid peroxidation: a complex free radical chain reaction where fatty acyl tails in phospholipids are oxidized by reactive radical species, leading to the formation of lipid hydroperoxides (LOOH) as primary products. LOOH species can in turn react with other biomolecules, causing oxidative damage. Additionally, these hydroperoxides serve as precursors to more harmful secondary products such as aldehydes (e.g., 4-hydroxy-2-

[18,19]. Understanding the connection between iron homeostasis and ferroptosis may provide new therapeutic strategies to mitigate tissue injury in pathological conditions.

Peroxidation of PUFA-phospholipids in membranes

The susceptibility of a cell to phospholipid peroxidation and ferroptosis depends on the composition of its lipid membrane [20]. PUFA tails in phospholipids (PLs) are particularly vulnerable to autoxidation because the C–H bonds at the bis-allylic positions are weak: for example, in C-7, C-10, and C-13 in arachidonic acid (AA, 20:4). Hydrogen atoms at these positions are preferentially abstracted by reactive species such as peroxyl radicals. By contrast, **monounsaturated fatty acid (MUFA)**-containing phospholipids, such as oleate (OA, 18:1), are more resistant to spontaneous oxidation [21]. Therefore, lipid remodeling of cellular membranes towards a higher MUFA-PL content protects cells from ferroptosis [22] (Figure 2, right; Box 1). PUFAs become potent drivers of ferroptosis once they are integrated into PLs. To be incorporated into PLs, free PUFAs must first be activated as acyl-coenzyme A (CoA) derivatives. This process is catalyzed by the enzyme acyl-CoA synthetase long-chain family member 4 (ACSL4). Activated PUFAs can be incorporated into PLs by lysophospholipid acyl transferases (e.g., lysophosphatidylcholine acyltransferase 3,

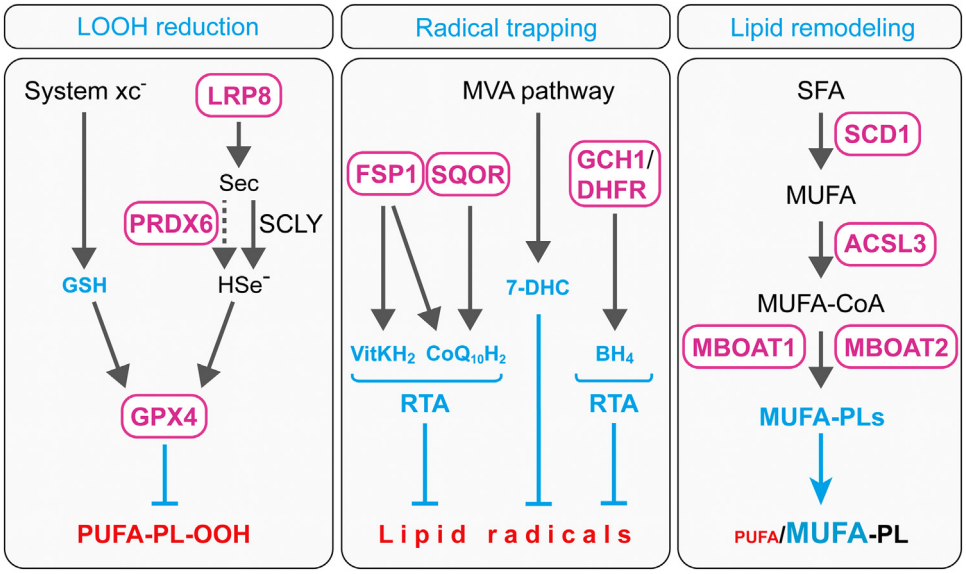

Figure 2. Pathways inhibiting ferroptosis. Several cellular mechanisms have been identified as defenses against iron-dependent lipid peroxidation and ferroptosis. Among the three main axes, the central enzyme is glutathione (GSH) peroxidase 4 (GPX4), which directly reduces phospholipid-hydroperoxides – polyunsaturated fatty acid (PUFA)-PL-OOH – in cellular membranes at the expense of reduced GSH. GSH is synthesized from cysteine, which is imported by system xc^-. For correct function, GPX4 needs a selenocysteine in its catalytic center, which is provided by selenium import via internalization of low-density-lipoprotein (LDL) receptor-related protein 8 (LRP8) and the actions of peroxiredoxin 6 (PRDX6). As a second line of anti-ferroptotic defense, the cell expresses enzymes that generate or recycle radical-trapping antioxidants (RTAs): the oxidoreductase ferroptosis suppressor protein 1 (FSP1) reduces ubiquinone and vitamin K to their respective RTA forms. Ubiquinol can also be produced by sulfide quinone oxidoreductase (SQOR). The RTA tetrahydrobiopterin (BH_4) is produced by GTP cyclohydrolase 1 (GCH1) or recycled from dihydrobiopterin (BH_2) by dihydrofolate reductase (DHFR). Further, the mevalonate (MVA) pathway, which provides building blocks for many essential cellular biomolecules, also synthesizes the anti-ferroptotic molecule 7-dehydrocholesterol (7-DHC). The third axis of defense against lipid peroxidation consists of lipid-remodeling enzymes such as stearoyl-CoA 9-desaturase (SCD1), acyl-CoA synthetase long-chain family member 3 (ACSL3), and membrane-bound O-acyl transferase 1 and 2 (MBOAT1/2), which synthesize and incorporate phospholipids with monounsaturated fatty acid tails (MUFA-PL) into cellular membranes. MUFA-PL-rich membranes are less prone to undergo radical-induced peroxidation and thereby are resistant to ferroptosis. Abbreviations: CoQ, coenzyme Q; SFA, saturated fatty acid; VitK, vitamin K.

nonenal, 4-HNE), which further exacerbate cellular damage.

Polyunsaturated fatty acid (PUFA): a fatty acid with more than one carbon–carbon double bond (C=C) within its hydrocarbon chain. When PUFAs are conjugated (alternating single and double bonds), they are highly reactive at the bis-allylic positions (carbons adjacent to the double bonds) and are more susceptible to oxidation. Common PUFAs are arachidonic acid (AA; 20:4, n-6), eicosapentaenoic acid (EPA; 20:5, n-3), and docosahexaenoic acid (DHA; 22:6, n-3).

Radical-trapping antioxidant (RTA): a compound that terminates a radical chain reaction by donating a hydrogen atom or an electron to the reactive radical species. RTAs act stoichiometrically and are consumed during the process, unless they are regenerated.

Trace elements: essential micronutrients required by organisms in precise quantities for proper physiological and biochemical function: examples are iron, copper, zinc, selenium, and iodine.

Vitamins: a group of organic compounds that are vital for normal development and metabolic functions in humans. Vitamins can be divided into fat-soluble (vitamins A, D, E, and K) and water-soluble (vitamin B and C). Since they mostly cannot be synthesized by cells, vitamins or their precursors are mostly obtained from the diet, and deficiencies can lead to health problems.

Box 1. Lipid remodeling to MUFA-rich PLs inhibits ferroptosis

The ACSL4–LPCAT3–PUFA axis regulates ferroptosis sensitivity. By contrast, generation of monounsaturated fatty acids (MUFAs), such as oleic acid or palmitoleic acid, and their incorporation into phospholipids renders cells resistant to ferroptosis (Figure 2 in the main text). Here, the plasma membrane is less prone to radical-induced peroxidation by replacement of oxidizable PUFAs, as MUFAs cannot be attacked by radicals due to the stronger hydrogen bond in the allylic position [103]. Necessary enzymes for this process are stearoyl coenzyme A desaturase 1 (SCD1), acyl-coenzyme A synthetase long-chain family member 3 (ACSL3), and membrane-bound O-acyltransferase domain-containing 1/2 (MBOAT1/2). SCD1 introduces double bonds in saturated fatty acids, converting them into MUFAs and thereby keeping an important balance in lipogenesis and metabolism. Dysregulation of SCD1 is associated with cancer development, metabolic diseases, and neurological disorders [104]. Studies have also shown that mammalian target of rapamycin complex 1 (mTORC1), a central regulator of metabolism, protects cells from ferroptosis by upregulating the protein synthesis of sterol-responsive element binding protein (SREBP1), which in turn acts as a transcription factor for SCD1 [105,106]. Besides its role in lipogenesis, mTORC1 enhances GPX4 protein expression to block ferroptosis [107]. By contrast, mTORC1 promotes cysteine use for protein synthesis at the expense of GSH, thereby sensitizing cells to ferroptosis [108].

ACSL3 catalyzes the conversion of free MUFAs to fatty acyl-CoA esters, which activates them for further processes, such as β-oxidation or lipid synthesis. Importantly, ACSL3 activity is important for ferroptosis inhibition via exogenous MUFAs [103]. As a last step of membrane remodeling, MBOAT 1 and 2 catalyze the transfer of MUFA-CoA to phospholipids, thereby enriching the cellular membrane with MUFA-phospholipids (Figure 2 in the main text) and competitively lowering the formation of PUFA-phospholipids [109]. MBOAT1 and 2 require the expression of SCD1 and ACSL3 to protect the cell against ferroptosis [109].

Interestingly, the expression of MBOAT1 and 2 is transcriptionally regulated by two different hormone nuclear receptors: MBOAT1 expression is regulated by estrogen through estrogen receptor (ER) signaling, whereas expression of MBOAT2 is regulated by dihydrotestosterone (DHT) through the androgen receptor (AR) [109] (Figure 3 in the main text). This sex-specific suppression of ferroptosis gives rise to potential therapies of sex-hormone-driven cancers, such as breast or prostate cancers [109,110]. Furthermore, the connection between estrogen signaling and ferroptosis suppression could shed light on the question of sex-specific disease prevalence (e.g., in cardiovascular diseases or kidney injury) [110].

LPCAT3) (Figure 1). At least in cell culture, ACSL4 plays a central role in determining sensitivity to ferroptosis by facilitating the enrichment of cellular membranes with PUFAs. It was the first identified pro-ferroptotic protein, and cells deficient in ACSL4 show decreased levels of PUFA-containing PLs and are characterized by a marked resistance to ferroptosis due to the absence of oxidizable substrates [23]. ACSL4 has a higher specificity for the substrates AA and adrenic acid (AdA, 22:4), and these species – esterified to phosphatidylethanolamine (PE) or phosphatidylcholine (PC) backbones – seem to be preferentially oxidized during ferroptosis. PUFAs can fragment into toxic by-products, disrupting plasma membrane permeability upon peroxidation. Recent evidence suggests that the accumulation of oxidatively truncated products in PLs leads to loss of membrane integrity and cell lysis during ferroptosis [24].

Pathways inhibiting ferroptosis

In this section we explore the cellular antioxidant networks that counteract lipid peroxidation, with a particular focus on glutathione (GSH) peroxidase 4 (GPX4), the master regulator of ferroptosis. We next discuss the metabolic pathways that support GPX4 function, including those that regulate the availability of selenium and GSH.

System x_c^-—(R)SH–GPX4 axis as the central gatekeeper of ferroptosis

The selenocysteine-containing protein GPX4, discovered by Ursini and coworkers in 1982, is the main enzyme responsible for the repair of peroxidized phospholipids and thus is central to the regulation of ferroptosis [25]. Insufficient GPX4 activity leads to the accumulation of lipid hydroperoxides [26,27]. GPX4 efficiently catalyzes the reduction of lipid hydroperoxides ($k = 10^7$–10^8 M^{-1} s^{-1}) in complex lipids such as PLs embedded in membranes. The reducing power supporting GPX4 activity is primarily provided by GSH, the most abundant low-molecular-weight (LMW) thiol in mammalian cells (1–10 mM). However, GPX4 can also use other LMW thiols, and even protein thiols, when GSH concentration becomes limiting [28]. This is particularly relevant because GSH-depleting

strategies have proved to be less efficient in inducing ferroptosis [29], suggesting that other metabolites or thiol-containing proteins may contribute to sustain GPX4 activity in the absence of GSH. However, the identity of these alternative substrates contributing to ferroptosis suppression remains unknown.

The first report on cell death induced by loss of GPX4 activity was provided by Imai and coworkers in 2003 [30]. The development of a conditional and inducible tissue-specific *gpx4* knockout mouse model by Conrad's laboratory was fundamental to demonstrating the relevance of GPX4 and ferroptosis in somatic tissues [31]. These early works were important to demonstrate that GPX4 is essential for early embryogenesis, also showing that it is constitutively expressed in most tissues, and plays an important role in maintaining homeostasis in various organs (including kidneys, liver, and brain). This enzyme is also a significant reason why selenium is essential for life, as protein levels and activity are directly linked to selenium availability [7,32]. Initial studies led by Stockwell identified that GPX4 and system x_c^- are the targets of the ferroptosis inducers RSL3 and erastin, respectively, establishing the cyst(e)ine–GSH–GPX4 axis as a central regulator of ferroptosis [29,33] (Figure 2, left). Cysteine serves as the critical substrate for the synthesis of GSH. In the process of GSH production, cysteine can enter cells via neutral amino acid transporters or in its oxidized form, cystine, through the system x_c^-. This system x_c^- is a transmembrane protein complex comprising SLC7A11 and SLC3A2, functioning as a cystine/glutamate antiporter. When the cystine uptake through system x_c^- is blocked, it leads to a depletion of both cysteine and GSH, thereby triggering ferroptosis [34].

Conversely, overexpression of the light chain of system x_c^- (SLC7A11) protects cells from lipid peroxidation [35]. SLC7A11 is considered a promising anticancer target; *Slc7a11*$^{-/-}$ mice do not display any major phenotype, and knockout in various tumor cell lines significantly reduced tumor growth [36–39]. In certain tissues, such as the liver, the trans-sulfuration pathway provides an alternative source of cysteine for the synthesis of GSH. This pathway can compensate for the inhibition or dysfunction of system x_c^-. In this process, methionine is converted into homocysteine, which is then transformed into cystathionine, ultimately resulting in the production of cysteine and bypassing the need for cystine and cysteine uptake [40]. Additionally, thiols can protect against lipid peroxidation in a GPX4-independent manner by increasing the production of thiolpersulfides, which can act as potent inhibitors of lipid peroxidation [41].

Another important feature associated with inhibition of system x_c^- is that it reduces thiol-assisted selenium uptake, which decreases the expression of selenoproteins such as GPX4 [42,43]. This makes cells more sensitive to ferroptosis. Increasing thiol availability, such as through treatment with N-acetylcysteine (NAC), can help decrease lipid peroxidation. Additionally, several thiol-containing compounds, including cysteine and β-mercaptoethanol, can indirectly inhibit ferroptosis by enhancing selenoprotein expression [42].

LRP8-selenocysteine–GPX4

While thiols play a supportive role in maintaining GPX4 activity, the bioavailability and cellular uptake of selenium are equally critical. In this context, the lipoprotein receptor-related protein 8 (LRP8 or ApoER2) emerges as a key regulator of selenium metabolism (Figure 2, left), influencing the efficiency of GPX4 translation through its role in selenocysteine uptake [44]. LRP8 acts as a surface receptor for selenoprotein P (SELENOP), which is rich in multiple selenocysteine (Sec) residues. When SELENOP binds to LRP8, the complex is internalized into the cell and subsequently degraded in the lysosome, leading to the release of Sec. Selenocysteine lyase (SCLY) is an enzyme necessary for the subsequent metabolism of selenocysteine and is responsible for converting selenocysteine to selenide (HSe^-), a critical step for the proper charging of tRNA with selenocysteine [6].

Recent studies have revealed that Sec can promote selenoprotein translation in the absence of SCLY in a PRDX6-dependent manner [45–47] (Figure 2, left), although the specifics of this newly identified pathway still require detailed characterization. Regardless of how Sec is metabolized, the loss of the upstream receptor LRP8 significantly reduces intracellular selenium levels, leading to decreased expression of selenocysteine-containing GPX4, ultimately sensitizing cells to ferroptotic death [48]. Notably, the inhibition of GPX4 expression results from ribosome stalling due to the lack of selenocysteine-charged tRNAs [48]. Interestingly, the mevalonate pathway plays a crucial role here, as it is required to stabilize the selenocysteine–tRNAs. Sec–tRNAs must undergo enzymatic isopentenylation, a process that depends on isopentenyl pyrophosphate (IPP), a product of the mevalonate pathway [49–51]. Targeting this pathway is a potential strategy to induce ferroptosis in *MYCN*-amplified neuroblastoma [44]. The specific dependency of *MYCN*-amplified neuroblastoma on the LRP8 uptake pathway stems from the low levels of system x_c^-, which ultimately decrease its capacity to take up other selenium sources. Hence, an *in vivo* mouse study revealed that LRP8 is a driving factor for neuroblastoma's initial growth and continuation [44]. Additionally, a recent study found that inhibiting selenoprotein translation reduces cancer progression and metastasis in melanoma [52]. These findings demonstrate a novel vulnerability of distinct cancer entities to selenium metabolism and a promising therapeutic avenue of 'indirectly' triggering ferroptosis in cancer since the direct inhibition of GPX4 could lead to fatal systemic consequences [7].

Trace elements, nutrients, and metabolites controlling ferroptosis

Pathways leading to induction or inhibition of ferroptotic cell death depend on the presence or absence of endogenous small molecules such as trace elements and metabolites. Here, iron as a trace element and GSH as an antioxidant are prominent examples to balance the cellular sensitivity towards lipid peroxidation-induced cell death. However, many more metabolites and nutrients have recently been discovered that shape the ferroptotic network.

Iron

Iron is essential for all forms of life because it is a component of electron-transfer proteins, which are necessary for oxygen storage and transport, cellular structures, and enzyme function [53]. As a result, iron deficiency and overload have severe consequences for cells and organisms, requiring strict regulation to maintain iron homeostasis. Upon iron uptake and release via ferritinophagy, Fe^{3+} is reduced to Fe^{2+}, contributing to the redox-active iron pool (Figure 1); this reactive species can promote the **Fenton reaction**, where it reacts with hydrogen peroxide and produces hydroxyl or hydroperoxyl radicals [4]. Hydroxyl radicals can initiate the peroxidation of PUFA phospholipids by generating lipid radicals. This process triggers a radical chain reaction that spreads oxidative damage to phospholipids, ultimately leading to ferroptotic cell death. Additionally, by managing the pool of redox-active iron in cells – such as through the use of iron chelators including deferoxamine – or by regulating the expression of iron-related proteins, the susceptibility of cells to ferroptotic death can be modulated [1]. However, a recent study unexpectedly showed that treatment with the iron chelator deferiprone could not improve Alzheimer's disease (AD) in patients, even though this neurodegenerative disease has been sparsely connected to ferroptotic cell death [54,55]. The treatment even accelerated the cognitive decline, hinting at a more complex role for iron and ferroptosis in AD [56].

Selenium

As previously discussed, selenium is a trace element that takes central stage in the regulation of ferroptosis [6,57]. Selenium is required to synthesize selenoproteins, such as GPX4 (Figure 2, left) or thioredoxin reductases (TXNRDs), which contain at least one selenocysteine in their amino acid sequence [49]. Since it is energetically very costly to incorporate selenocysteine instead of

cysteine into proteins, the question arises: why do selenocysteine-based redox processes exist instead of thiolate-based processes? Interestingly, it was shown that selenocysteine can withstand a higher 'oxidative pressure' from peroxide exposure, leading to irreversible oxidation. Therefore, selenocysteine-containing enzymes provide resistance to ferroptosis [58].

In addition to its role in the synthesis of selenocysteine, selenium has a selenoprotein-independent function in suppressing ferroptosis: the selenium metabolite selenide (HSe^-) was shown to reduce ubiquinone to ubiquinol, a potent antioxidant (see later) able to suppress lipid peroxidation. This reaction is catalyzed by sulfide quinone oxidoreductase (SQOR) [42] (Figure 2, middle).

GSH

GSH (γ-L-glutamyl-L-cysteinylglycine) is a tripeptide found in virtually all subcellular compartments in mammalian cells as one of the most important antioxidant molecules. It plays a critical role in detoxifying toxic electrophiles and heavy metals and is essential for the biogenesis of iron–sulfur clusters [59]. Its synthesis is restricted to the cytosol and occurs in two ATP-dependent reactions by consecutive actions of γ-glutamyl cysteine ligase (γ-GCL) and GSH synthase (GSS) [60]. Cysteine availability is the limiting factor in this process, which is controlled by the antiporter system x_c^- that imports cystine and exports glutamate [61] (Figure 2, left). GSH biosynthesis is inhibited by buthionine sulfoximine (BSO), an inhibitor of γ-GCL enzyme, leading to rapid depletion of GSH levels.

GSH serves as a substrate for various enzymes to reduce lipid hydroperoxides and control the redox state of cysteine residues in proteins. Here, GSH is oxidized to GSSG, which is then regenerated to GSH by an NADPH-dependent GSH reductase (GSR) [27]. GSH depletion can activate nuclear factor erythroid 2-related factor 2 (NRF2), a transcription factor that induces the expression of cellular antioxidant defense genes [62,63]. GSH is believed to protect against ferroptosis through multiple mechanisms. GSH supports the main system that counteracts lipid peroxidation: the GSH–GPX4 axis (Figure 2, left, and Figure 3). Additionally, GSH is used by other peroxidases to limit hydrogen peroxide availability. These systems prevent the reaction of hydrogen peroxide with iron and the subsequent generation of hydroxyl radicals that can initiate lipid peroxidation [64].

Hydropersulfides

Hydropersulfides (RSSHs) are recognized as effective **radical-trapping antioxidants (RTAs)** that can inhibit lipid peroxidation (Figure 3). These RSSH compounds, derived mainly from cysteine (CSSH) and GSH (GSSH), are produced in the body at steady-state micromolar concentrations. Compared with thiols (RSH), RSSH species are more nucleophilic and act as stronger agents for hydrogen transfer. They can directly reduce endogenously produced **free radicals**, leading to the formation of perthiyl radicals. These perthiyl radicals recombine with each other, promoting the termination of radical chain reactions. Due to their water-soluble characteristics, RSSH species may mitigate lipid peroxidation by reducing thiyl (GS•) or α-tocopherol/ubiquinone radicals present in the aqueous phase. Additionally, increased cellular uptake of cysteine provides the necessary sulfur for the biosynthesis of RSSH species, thereby safeguarding cells against ferroptosis independently of the GSH–GPX4 pathway [41,65].

Ubiquinone/CoQ_{10}

Ubiquinone or coenzyme Q_{10} (CoQ_{10}) is one of several metabolites known to regulate ferroptosis (Figure 3). It is a lipophilic metabolite present in cell membranes with a critical function in mitochondria, acting as an electron carrier. CoQ_{10} has a benzoquinone head group conjugated to a hydrophobic tail of ten (CoQ_{10}) repeats of the five-carbon isoprenoid unit. The mevalonate pathway provides the building blocks for its hydrophobic tail from the intermediate farnesyl

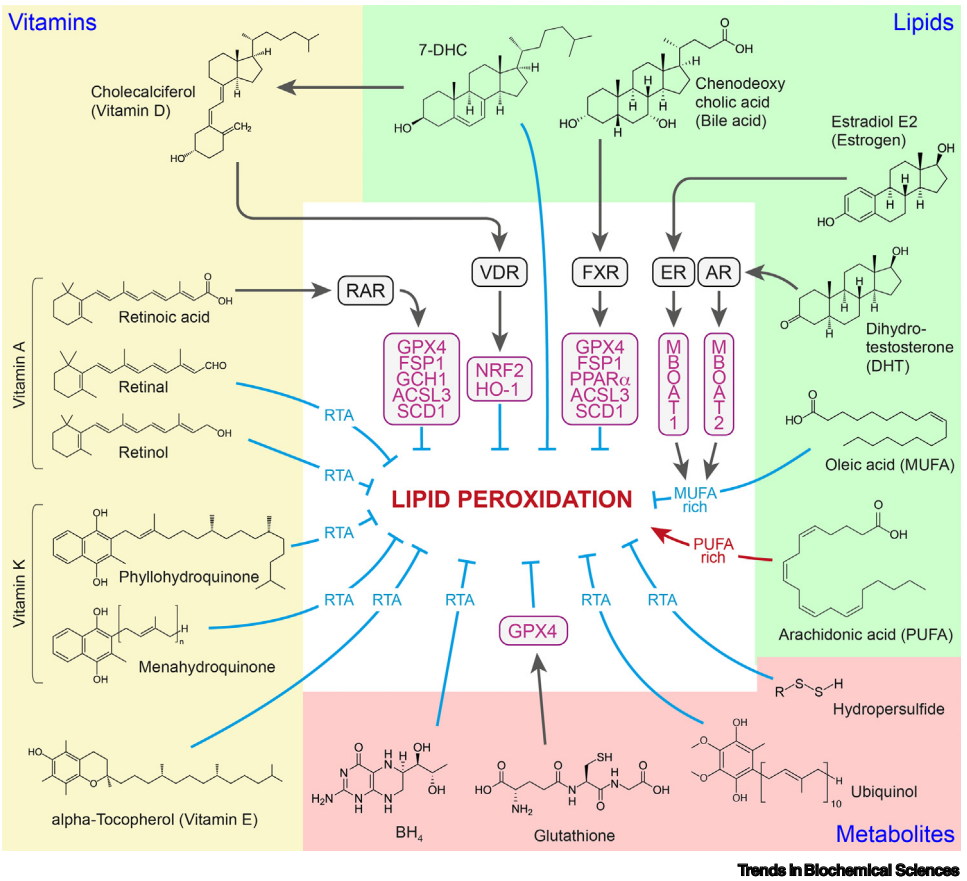

Figure 3. Nutrients, metabolites, and lipids modulating ferroptosis. Nutrients, including vitamins, lipids and metabolites, influence cellular susceptibility towards ferroptosis in two different ways: they are either radical-trapping antioxidants (RTAs) and block lipid peroxidation, or they bind to their respective nuclear receptors, which in turn transcriptionally regulate ferroptosis-modulating genes and enhance their transcription. Until now, vitamin A (all-trans retinoic acid), vitamin D3 (cholecalciferol), bile acids (chenodeoxycholic acid), estrogen (estradiol), and dihydrotestosterone (DHT) have been found to upregulate transcription of ferroptosis-suppressing genes via their nuclear receptors. By contrast, vitamin K (phyllohydroquinone and menahydroquinone), vitamin E (α-tocopherol), metabolites of vitamin A (retinol and retinal), 7-dehydrocholesterol (DHC), hydropersulfides, ubiquinol, GSH, and tetrahydrobiopterin (BH_4) have been classified as RTAs that directly suppress lipid peroxidation. Since many of these molecules are dietary, treatment of ferroptosis-related pathologies or tumors may be enhanced by adding either ferroptosis-suppressing nutrients – monounsaturated fatty acids (MUFAs), antioxidants, vitamins – or ferroptosis-inducing nutrients – iron, polyunsaturated fatty acids (PUFAs) – into a patient's diet. Abbreviations: AR, androgen receptor; ER, estrogen receptor; FXR, farnesoid X receptor; MBOAT, membrane-bound O-acyl transferase; RAR, retinoic acid receptor; VDR, vitamin D receptor.

pyrophosphate (FPP) and specific IPP molecules, whereas 4-hydroxybenzoate (4-HB) derived from tyrosine is the precursor of the quinone ring [66].

The benzoquinone head group of CoQ_{10} is the redox-active moiety, where it undergoes either one-electron reduction to form the semiquinone intermediate or two-electron reduction to generate ubiquinol ($CoQ_{10}H_2$), the fully reduced form. It has a central role in mitochondrial energy generation (oxidative phosphorylation, OXPHOS). Notably, the CoQ_{10} redox state influences the direction of the electron flow in the electron transport chain (ETC), with implications for mitochondrial ROS production [67]. CoQ_{10} can also be reduced by several other enzymes, acting as an electron hub and an important convergence point for multiple metabolic pathways [42,68,69]. Ubiquinol is a potent RTA (Figure 2, middle) protecting membranes from lipid peroxidation. Besides its presence in

mitochondria and other endomembranes, it is also available in the plasma membrane. The flavoprotein ferroptosis suppressor protein 1 (FSP1) (Figure 2, middle, and Box 2) is fundamental in regenerating the non-mitochondrial pool of CoQ_{10}, using NADP(H) as an electron donor. Also, the enzyme SQOR can regenerate ferroptosis-protecting ubiquinol from ubiquinone [42] (Figure 2, middle). Given the central role of ubiquinone in regulating membrane redox homeostasis, its depletion has been associated with an increase in ferroptosis sensitivity [70]. Currently, genetic defects of CoQ have been reported [71], and while most are associated with ETC dysfunction, it remains interesting to test whether some of the symptoms in these patients could be attributed to increased ferroptosis rates and ultimately ameliorated by ferroptosis inhibitors [72].

Tetrahydrobiopterin (BH_4)

BH_4 is a guanosine triphosphate (GTP)-derived metabolite that is produced *de novo* by the action of three enzymes: GTP-cyclohydrolase1 (GCH1), 6-pyruvoyl-tetrahydropterin synthase (PTS), and sepiapterin reductase (SPR). BH_4 has been reported to have an intrinsic antioxidant function, where its accumulation protects cells against ferroptosis [73,74] (Figure 2, middle, and Box 2). GCH1 is the rate-limiting enzyme in the biosynthesis of BH_4. Additionally, BH_4 can be produced by salvage and regeneration pathways [75]. Its best-known function is as a cofactor in amino acid catabolism, where it participates in critical oxidation reactions. Additionally, it facilitates the enzymatic conversion of phenylalanine, tyrosine, and tryptophan into precursors of monoamine neurotransmitters such as dopamine and serotonin [76].

BH_4 is an RTA (Figure 3) and can prevent lipid peroxidation. Supplementation with BH_4 or the oxidized form dihydrobiopterin (BH_2) potently protect against ferroptosis [73]. Upon oxidation, BH_4 can be regenerated from BH_2 by the dihydrofolate reductase (DHFR) using NADP(H) as a

Box 2. Key GPX4-independent ferroptosis gatekeepers

FSP1–ubiquinol–vitamin K axis

Ferroptosis suppressor protein 1 (FSP1), previously known as apoptosis-inducing factor mitochondria-associated 2 (AIFM2), is a GPX4-independent regulator of ferroptosis [97,98]. It is a flavin-dependent oxidoreductase enzyme that can use NADP(H) to reduce lipophilic radical-trapping molecules such as ubiquinone, vitamin K, and other quinone-containing substrates [82] (Figures 2 and 3 in the main text). Once in their reduced form, these molecules can prevent initiation/propagation of lipid peroxidation by 1-electron reduction of peroxyl radicals. FSP1 can compensate for the loss of GPX4 activity; FSP1-overexpressing cells are protected against pharmacological and genetic inhibition of GPX4 [97]. FSP1 localization to the plasma membrane is sufficient to provide resistance against ferroptosis, highlighting the central role of plasma membrane integrity in ferroptosis progression [98].

FSP1 positively correlates with the resistance of many cancer cell lines to GPX4 inhibitors. A first highly selective FSP1 inhibitor (iFSP1) has been developed [97], which turned out to be less suitable for *in vivo* use [70,99]. A next-generation inhibitor, icFSP1, was recently discovered which reaches a higher plasma concentration than iFSP1, thereby impairing tumor growth in mice [100]. In parallel, another on-target inhibitor of FSP1 inhibitor (FSEN1) has been generated with promising properties for *in vivo* studies, although its efficacy in mice has not yet been fully tested [101].

GCH1–DHFR–BH_4 axis

In addition to the xCT–GSH–GPX4 and FSP1–ubiquinol axes, a third enzyme has been discovered that protects against lipid peroxidation: GTP cyclohydrolase 1 (GCH1) is the rate-limiting enzyme for the biosynthesis of tetrahydrobiopterin (BH_4), a potent endogenous antioxidant that can act as an RTA (Figures 2 and 3 in the main text), thus, preventing peroxidation of PUFA-containing membrane phospholipids and ferroptosis [73]. Notably, the GCH1–DHFR–BH_4 axis acts independently of GSH–GPX4. Moreover, phospholipids that contain two PUFA-tails are selectively protected from peroxidation by BH_4 [102]. Upon oxidation by radicals, BH_4 can be regenerated from dihydrobiopterin (BH_2) by dihydrofolate reductase (DHFR), a well-established therapeutic target for suppressing tumor growth [74]. Besides the synthesis of antioxidants, the GCH1–DHFR–BH_4 axis inhibits ferroptotic cell death via an additional mechanism: increased levels of ubiquinone, another endogenous antioxidant, were observed in GCH1-overexpressing cells [73]. Notably, cellular BH_4 level could define cancer sensitivity towards ferroptotic cell death [74].

reducing substrate [74] (Figure 2, middle). Additionally, BH_4 availability might impact CoQ_{10} cellular levels [73], highlighting its broader role in modulating cellular redox balance.

Vitamin E

Vitamin E in the form of Trolox, a water-soluble analog, or the fat-soluble α-tocopherol (Figure 3) has been used as a ferroptosis inhibitor to block lipid peroxidation, acting as an RTA. The use of vitamin E has demonstrated that lipophilic antioxidants are able to suppress lipid peroxidation and protect cells from ferroptotic cell death [3]. Interestingly, as early as in the 1970s, long before the term ferroptosis was coined, researchers observed that cells dying in cysteine-free media could be fully rescued when α-tocopherol was added [77]. Physiologically, it has been shown that, among many other processes, neurodevelopment in zebrafish is dependent on vitamin E to reduce ROS-mediated lipid peroxidation [78,79]. Vitamin E deficiency in humans has been linked to a form of anemia characterized by the rupture of red blood cells. Curiously, the process of hemolysis, both *in vivo* and in blood banks, has been proposed to be driven by ferroptosis, with the fatty acid content of donors playing a determining role. This suggests that ferroptosis may be a pervasive factor throughout the lifespan of erythrocytes [80]. More severe forms of vitamin E deficiency, while rare, have also been associated with neurodegeneration and some forms of ataxia, supporting the fundamental role of this micronutrient in preventing ferroptosis *in vivo* [81].

Vitamin K

The reduced form of vitamin K (naphthoquinones such as phylloquinone and menaquinone) exhibits a potent anti-ferroptotic effect due to its RTA property [82] (Figure 3). Vitamin K is reduced by FSP1 in a similar way to ubiquinone (Figure 2, middle): phylloquinone and menaquinone are components of the ETC in plants and prokaryotes, whereas ubiquinone is used in eukaryotes, but FSP1 reduces all three at the expense of NAD(P)H. Because ferroptotic cell death has been shown to be an evolutionary commonality among different species, vitamin K is assumed to be an ancient physiological ferroptosis suppressor [82,83].

Vitamin A

Vitamin A inhibits ferroptosis via a dual mechanism: retinol, its primary dietary form, functions as an RTA [84,85]. It crosses the blood–brain barrier, and animal models show neuroprotective effects. Retinol is the storage and transport form of vitamin A. It can be converted into retinal by dehydrogenases and further irreversibly oxidized into retinoic acid (ATRA), a ligand that activates the retinoic acid receptor (RAR), a **nuclear receptor**, and thereby regulates gene expression of several development processes [86]. Recently, a study showed that ATRA activates RAR to upregulate the ferroptosis-suppressing genes GPX4, FSP1, GCH1, and ACSL3, ensuring correct neuron maturation and brain development [84]. Hence, unlike vitamins K and E, vitamin A has a dual mode of action: RTA activity and transcriptional control of ferroptosis (Figure 3).

Vitamin D

Vitamin D signaling has also been connected to ferroptosis inhibition: cisplatin-induced kidney injury in mice was attenuated by treatment with a vitamin D receptor (VDR) agonist, which led to reduced lipid peroxidation and enhanced GPX4 expression [87]. It has also been shown that the vitamin D receptor upregulates the NRF2–HO-1 axis, which protects hippocampal neurons of aging mice against ferroptosis and thereby reduces cognitive impairment [88]. Another study revealed that VDR activation promotes astrocyte reprogramming to neurons by reducing lipid peroxidation [89]. Notably, vitamin D3 (cholecalciferol) (Figure 3) is synthesized from 7-dehydrocholesterol (see next section), a cholesterol precursor with potent antioxidant activity that has been shown to protect membranes from lipid peroxidation [24].

7-dehydrocholesterol (7-DHC)

The mevalonate (MVA) pathway is integral to synthesizing cholesterol and non-sterol isoprenoids, which are crucial for cellular functions such as membrane integrity and protein prenylation. It starts with two molecules of acetyl-CoA and yields IPP and dimethylallyl pyrophosphate (DMAPP), which form the building blocks for over 30 000 biomolecules [90]. Two recent studies revealed that 7-DHC, a precursor of cholesterol, protects membrane phospholipids from damage by peroxyl radicals (Figure 2, middle, and Figure 3) and thereby confers survival on tumor cells [24,91]. By genetically or pharmacologically inhibiting 7-DHC reductase (DHCR7), the terminal enzyme in cholesterol biosynthesis, ferroptosis-driven tissue damage, such as hepatic ischemia–reperfusion injury (IRI) or acute liver failure, can be alleviated [92]. Notably, 7-DHC is also a precursor of vitamin D, adding an additional layer of anti-ferroptotic defense by 7-DHC.

Bile acids

A recent study revealed that activation of the nuclear receptor farnesoid X receptor (FXR) by bile acids (e.g., chenodeoxycholic acid, CDC) (Figure 3) or synthetic agonists (Turofexorate and Fexaramine) inhibits lipid peroxidation and ferroptosis [93]. FXR activation in cooperation with the retinoid X receptor (RXR) leads to the upregulation of several key genes involved in ferroptosis inhibition, including GPX4, FSP1, ACSL3, and peroxisome proliferator-activated receptor α (PPARα). Conversely, inhibiting or knocking out FXR sensitizes liver cells to ferroptotic cell death, further supporting the protective role of bile acids and FXR against ferroptosis. Importantly, these findings were validated using physiologically relevant cell models, such as *ex vivo* primary mouse hepatocytes and human induced pluripotent stem cell (iPSC)-derived hepatocytes [93]. Another study reported that FXR activation protects from cisplatin-induced acute kidney injury [94]. Together, bile acids may protect tissues with high exposure to toxins (liver, kidney, intestine) against ferroptosis by activating FXR. In line with this, a recent study showed that ferroptotic stress leads to liver aging, which is associated with metabolic dysfunction-associated steatotic liver disease (MASLD) [95]. Interestingly, bile acids and synthetic FXR agonists are beneficial in MASLD. Furthermore, production of bile acids by the microbiome may protect the intestine from ferroptotic events.

Concluding remarks

Ferroptosis, a unique form of regulated cell death, is driven primarily by iron-dependent phospholipid peroxidation and is tightly controlled by various metabolic pathways, transcription factors, and key enzymes such as GPX4 and ACSL4. Nutrients – particularly trace elements such as iron and selenium, as well as vitamins – play a pivotal role in determining cellular susceptibility to ferroptosis, linking dietary factors to cellular fate. The interplay between these metabolic and nutritional factors offers new insights into the underlying mechanisms of ferroptosis, with significant implications for disease treatment. By better understanding the molecular drivers of ferroptosis, such as lipid composition, redox balance, and nutrient availability, we can open new therapeutic avenues for conditions such as cancer, neurodegenerative diseases, and tissue injury, where ferroptosis plays a central role.

Despite significant advances in our understanding of ferroptosis, many questions remain (see Outstanding questions). The role of diet and nutrient supplementation in modulating ferroptosis is a promising area of exploration. Nutrients such as vitamin E, selenium, and iron have shown protective or promoting effects in different contexts, suggesting that dietary interventions could be attractive strategies to modulate ferroptosis susceptibility. Interestingly, regulation of ferroptosis by vitamin A, bile acids, estradiol, and vitamin D suggests that cells may sense levels of vitamins, hormones, and lipids through nuclear receptors to transcriptionally regulate ferroptosis gatekeepers. Such a mechanism may serve as a system for fine-tuning ferroptosis susceptibility.

Outstanding questions

Several nuclear receptors have been identified that control lipid peroxidation and ferroptosis. Do these receptors act as cellular sensors for vitamins, hormones, and lipids to fine-tune the regulation of ferroptosis?

Can dietary supplements (nutrients) be a treatment option for ferroptosis-related diseases? Which nutrients can be used to effectively modulate the response to ferroptosis efficiently without interfering with other critical cellular functions?

Can an iron- and PUFA-rich diet help enhance the efficacy of cancer drug treatment in ferroptosis-sensitive cancer? Conversely, can a diet rich in MUFAs and antioxidants reduce ferroptosis in degenerative diseases?

How do sex differences influence nutrient and metabolite availability, ultimately modulating sensitivity to ferroptosis?

Further studies will be needed to explore how specific diets or micronutrient supplementation can influence ferroptosis in various diseases, potentially offering non-invasive therapeutic options.

In therapeutic contexts, targeting ferroptosis holds the potential for treating diseases such as cancer, particularly in drug-resistant or ferroptosis-vulnerable cancer types. Developing specific ferroptosis modulators, such as GPX4 inhibitors or iron chelators, could offer new approaches for cancer therapy. Conversely, in conditions where ferroptosis contributes to unwanted organ damage – such as neurodegeneration, ischemia–reperfusion injury, or iron-overload diseases – ferroptosis inhibitors might provide protective benefits. Nonetheless, due to the pleiotropic effects that nutrients can have on tissue homeostasis, careful consideration is warranted, as recently highlighted by the failure of a clinical trial using an iron chelator in AD treatment. By fine-tuning the regulation of ferroptosis, future therapeutic strategies could potentially target a broad range of diseases more effectively.

As ferroptosis research enters the next phase to demonstrate clinical proof-of-concept [96], we posit that nutritional factors require considerable attention as they have a profound impact on ferroptosis-related processes. In future drug development strategies the adjuvant role of metabolites and nutrients and their interactions must be considered.

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Declaration of interests

J.T. and K.H. are inventors on a patent application involving ferroptosis (WO/2024/218322). The remaining authors declare no competing interests.

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