Ferroptosis in schizophrenia: Mechanisms and therapeutic potentials (Review)

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Abstract. Schizophrenia, a complex psychiatric disorder, presents with multifaceted symptoms and important challenges in treatment, primarily due to its pathophysiological complexity, which involves oxidative stress and aberrant iron metabolism. Recent insights into ferroptosis, a unique form of iron-dependent cell death characterized by lipid peroxidation and antioxidant system failures, open new avenues for understanding the neurobiological foundation of schizophrenia. The present review explores the interplay between ferroptosis and schizophrenia, emphasizing the potential contributions of disrupted iron homeostasis and oxidative mechanisms to the pathology and progression of this disease. The emerging evidence linking ferroptosis with the oxidative stress observed in schizophrenia provides a compelling narrative for re-evaluating current therapeutic strategies and exploring novel interventions targeting these molecular pathways, such as the glutathione peroxidase 4 pathway and the ferroptosis suppressor protein 1 pathway. By integrating recent advances in ferroptosis research, the current review highlights innovative therapeutic potentials, including N-acetylcysteine, selenium, omega-3 fatty acids and iron chelation therapy, which could address the limitations of existing treatments and improve clinical outcomes for individuals with schizophrenia.

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1. Introduction

Schizophrenia, a multifaceted psychiatric condition, affects ~287 per 100,000 individuals globally (1), presenting important challenges due to its diverse symptoms and effects on brain functionality. This disorder is characterized by three primary categories of symptoms: i) Positive symptoms, including hallucinations (predominantly auditory) and delusions (2,3); ii) negative symptoms, which comprise emotional numbness, apathy and social isolation (4,5); and iii) cognitive symptoms, which disrupt daily functioning by impairing memory, attention and executive skills (6). A total of >50% of patients with chronic schizophrenia experience at least one negative symptom (7). These symptoms do not tend to improve spontaneously throughout the progression of the disease and about one-third of patients demonstrate a poor response to the antipsychotics commonly used today, such as Chlorpromazine (8,9). The typical onset of schizophrenia varies by sex, with men usually developing the disorder between the ages of 18 and 25 years, whereas women tend to have a later onset, typically between 25 and 35 years (10). Schizophrenia evolves through various stages: i) The prodromal phase, marked by initial symptoms and a decline in brain function (11); ii) the acute phase, characterized by intense psychotic symptoms and significant functional degradation (12); and iii) the residual phase, during which some symptoms may abate but substantial functional difficulties persist (13,14). Treatment of schizophrenia involves both medications and psychosocial interventions (15). Medication includes primarily antipsychotic drugs that target dopamine receptors in the brain, which can alleviate positive symptoms, such as hallucination and delusions (16). Alongside medication, therapies like cognitive behavioral therapy aid the change of harmful thought patterns (17), while family-oriented interventions, such as psychoeducation and mutual support among families of schizophrenia patients, can notably enhance the patients' treatment satisfaction and adherence (18). Additional options such as electroconvulsive therapy may be used for severe cases (19). A comprehensive care approach, integrating these treatments, is crucial for the effective management of schizophrenia.

Ferroptosis is a distinct form of programmed cell death dependent on iron and characterized by the lethal accumulation of lipid peroxides (20). In contrast to other cell death mechanisms, such as apoptosis or necrosis, ferroptosis is predominantly caused by failure of the cellular antioxidant systems, particularly the enzyme glutathione peroxidase 4 (GPX4) (21,22). This enzyme normally detoxifies lipid peroxides by catalyzing the transformation of lipid hydroperoxides into harmless lipid alcohols, using glutathione (GSH) as a reducing agent. This action is crucial in maintaining the integrity of cellular membranes and preventing oxidative damage leading to ferroptosis (23). Researchers have also identified mechanisms of ferroptosis that do not depend on GPX4, and a major component of this GPX4-independent pathway is ferroptosis suppressor protein 1 (FSP1) (24). FSP1 uses NADPH to catalyze the reduction of coenzyme Q10 (CoQ10), a potent lipophilic antioxidant. This reduction is vital to prevent the accumulation of lipid peroxides (25). From a morphological perspective, cells undergoing ferroptosis demonstrate several distinctive alterations (26). Electron microscopy reveals that these cells typically have smaller mitochondria with denser membranes. Furthermore, the mitochondria often exhibit a loss of cristae and may show ruptures in their outer membranes (20,27,28). Changes in the cellular membrane, including increased density and notable damage, also occur, culminating in the disruption of cellular integrity and eventual death (29,30). This pathway of cell death is intricately connected to various metabolic functions within the cell, such as lipid metabolism, iron regulation and the management of reactive oxygen species (ROS), underscoring its important impact on cellular health and disease pathogenesis (31-33). Ferroptosis has been implicated in a range of diseases, such as cancer (34) and neurodegenerative conditions (35), where iron dysregulation and oxidative stress are prominent.

The interconnection between ferroptosis and schizophrenia is attracting considerable attention, triggered by the pervasive role of oxidative stress and anomalies in iron metabolism observed in schizophrenia (36,37). Oxidative stress, a well-documented aspect of schizophrenia, is linked to both the pathogenesis of the disorder and the degeneration of neural circuits (38). Ferroptosis, with its fundamental role in managing iron levels and oxidative responses (39), offers a compelling framework to explore how disruptions in these cellular mechanisms may contribute to the developmental and progressive phases of schizophrenia. Examining the biochemical processes underlying ferroptosis, such as iron accumulation, lipid peroxide formation and antioxidant system failures, in alignment with the pathophysiological traits of schizophrenia, could reveal potential contributions of ferroptosis to the onset and progression of this disorder. Additionally, insights into ferroptosis could lead to innovative therapeutic strategies, potentially addressing the limitations of current treatments by targeting the underlying cellular disturbances in schizophrenia.

2. Ferroptosis: Mechanisms and indicators

Iron metabolism and accumulation of iron. Iron is essential for various biological processes, including oxygen transport, DNA synthesis and electron transfer, due to its ability to exist in multiple oxidation states (40). The cellular uptake of iron is primarily facilitated through the binding of transferrin-bound iron to transferrin receptors, which internalize the iron into cells (41). Once inside the cells, iron is released from transferrin in acidic endosomes and then distributed into the labile iron pool (LIP), readily participating in critical cellular functions or being stored in ferritin (42,43). Most of the intracellular iron is sequestered in ferritin, where it is stored in a less reactive ferric iron state, helping to stabilize the balance with the volatile LIP (44). This storage mechanism is key, especially in the brain, where specific cells, such as oligodendrocytes, microglia and neurons, express ferritin (45-48), highlighting its role in preserving neural integrity and guarding against oxidative damage. Under conditions of stress or specific cellular signals, ferritin can undergo degradation via a process called ferritinophagy, typically facilitated by nuclear receptor coactivator 4 (NCOA4) (49). This degradation liberates iron back into the LIP, enhancing the availability of ferrous iron that can initiate the production of harmful lipid peroxides, thereby triggering the pathway of ferroptosis (50,51). The export of iron from cells is controlled by ferroportin, the sole known cellular iron exporter (52). The activity of ferroportin is stringently regulated by hepcidin, a hormone produced in the liver (53). Hepcidin binds to ferroportin, inducing its internalization and degradation, which diminishes iron export, and can result in an accumulation of intracellular iron if overexpressed or when mutations impede the function of ferroportin (50,54).

Propagation of lipid peroxidation. Lipid peroxidation is both a marker and mediator of ferroptosis (26). This biochemical process begins when ROS, particularly hydroxyl radicals (•OH), interact with the polyunsaturated fatty acids (PUFAs) in the phospholipid bilayer of cell membranes (55,56). Iron, through the Fenton reaction, catalyzes the conversion of hydrogen peroxide (H_2O_2) into •OH (57,58). These radicals are highly reactive and can abstract hydrogen atoms from the carbon atoms at the bis-allylic positions in PUFAs (59). This abstraction creates lipid radicals, initiating the lipid peroxidation chain reaction. Once initiated, the lipid radicals react with oxygen to form lipid peroxyl radicals, which are even more reactive (60). These radicals then abstract hydrogen from adjacent lipid molecules, propagating the chain reaction across the membrane, thereby spreading the oxidative damage extensively (61,62).

This chain reaction progresses until two lipid peroxyl radicals react, thus terminating the process. However, several reactive aldehydes, such as 4-hydroxynonenal (4-HNE) and malondialdehyde, are produced during this phase (63,64). These compounds can form adducts with DNA, proteins and other vital macromolecules, further impairing cellular functions (65-67). For instance, in the brain tissue of patients with Alzheimer's disease, the peroxidation product 4-HNE can bind covalently to critical neuronal mitochondrial, membrane and cytosolic proteins via Michael addition reactions. This binding results in functional impairments of important neuronal proteins, such as glyceraldehyde-3-phosphate dehydrogenase and α-enolase, leading to neuronal death and consequent cognitive decline (68). Moreover, lipid peroxidation involves feedback mechanisms that exacerbate damage. Released iron from damaged proteins or mitochondria can catalyze

additional Fenton reactions, perpetuating the cycle of ROS production and lipid peroxidation (69). This feedback loop is particularly harmful in environments with elevated iron levels or compromised antioxidant defenses.

In the neurological context of schizophrenia, the susceptibility of the brain to lipid peroxidation is important due to its high lipid content and metabolic activity, coupled with relatively low antioxidant protection (36,70,71). Schizophrenia may be exacerbated by anomalies in iron metabolism and antioxidant pathways, thereby increasing susceptibility to oxidative damage, which is linked to the cognitive and behavioral manifestations observed in schizophrenia (72,73).

Promotion and amplification mechanisms of ferroptosis. The intricate interplay of various cellular mechanisms contributes to the initiation and amplification of ferroptosis, particularly within the neural contexts relevant to schizophrenia. Mainly the NCOA4-, NADPH oxidase 4 (NOX4)-, activating transcription factor 3 (ATF3)-and p53-mediated mechanisms are crucial in modulating iron metabolism, lipid peroxidation and antioxidant defenses, thereby affecting the vulnerability to ferroptosis under physiological and pathological conditions (Fig. 1).

NCOA4-mediated promotion mechanism. NCOA4 is important in various cellular processes, surpassing its originally identified role as a coactivator for nuclear receptors, such as androgen and thyroid hormone receptors (74,75). By interacting with these receptors, NCOA4 promotes their transcriptional activities, aided by its ability to recruit additional transcriptional machinery (76). The functions of NCOA4 are attributed to its structural design, comprising an N-terminal domain that facilitates protein-protein interactions, a central coactivator domain essential for its coactivation role and a C-terminal domain crucial for the autophagic breakdown of ferritin (76-79).

NCOA4 has an essential function in iron metabolism, which is crucial for the proper maintenance of cellular iron balance (49,80,81). NCOA4 is highly expressed in critical organs involved in iron regulation, such as the liver, bone marrow and spleen (82,83). The involvement of NCOA4 in ferritinophagy underscores its capability to regulate iron storage and mobilization effectively (84). In conditions of iron sufficiency, NCOA4 is degraded to prevent excessive ferritinophagy, thereby avoiding iron overload that can exacerbate oxidative stress and cellular damage (79,85,86). Conversely, under conditions of iron deficiency or cellular stress, NCOA4 levels increase to promote ferritin degradation and maintain essential iron supply for metabolic processes (81,87,88). This regulatory mechanism ensures that ferritinophagy mediated by NCOA4 adapts to the cellular iron status and environmental cues, maintaining iron homeostasis and shielding cells from oxidative stress due to uncontrolled iron release.

NCOA4 is primarily regulated at the post-translational level, involving dual degradation pathways: Autophagy, particularly through its role in ferritinophagy (79,84), and proteasomal degradation, which is facilitated by the E3 ubiquitin-protein ligase HERC2 under iron-replete conditions (79). This degradation is further fine-tuned by ferritin levels. Knockout of ferritin heavy chain 1 (FTH1) has been demonstrated to reduce NCOA4 levels by increasing free iron, which activates the HERC2-mediated degradation of NCOA4 (79,89). Conversely, overexpression of FTH1 can lead to NCOA4 accumulation, indicating a protective sequestration from degradation pathways (89). This regulation can alter the interaction of NCOA4 with ferritin, potentially leading to its degradation and influencing the efficacy of ferritinophagy. Additionally, NCOA4 engages with autophagy components, such as microtubule-associated protein 1A/1B-light chain 3, which are integral to autophagosome assembly and the selective autophagic degradation of ferritin (49,90,91). This complex regulatory framework ensures that the activity of NCOA4 is finely adjusted according to the internal iron conditions, effectively responding to changes and protecting against iron-related oxidative stress.

NOX4-mediated promotion mechanism. The NOX enzyme family, encompassing seven isoforms (NOX1 to NOX5, DUOX1 and DUOX2), is pivotal for generating ROS, which are integral to cellular signaling, host defense and redox balance maintenance (92,93). Each isoform has specific tissue distributions, regulatory mechanisms and functional roles, thus contributing uniquely to cellular functions (94).

NOX4 is particularly notable within the NOX family for its intrinsic activity without the need for cytosolic subunits required by other isoforms, such as NOX1, NOX2 and NOX3 (95,96). This unique attribute of NOX4 allows it to maintain a consistent production of H_2O_2 rather than superoxide, which is more commonly produced by its counterparts (97-99). This ability to generate H_2O_2, which is capable of diffusing across membranes and acting as a signaling molecule, implies a role for NOX4 in cellular signaling and regulation (100).

In the context of ferroptosis, the involvement of NOX4 in the continuous production of H_2O_2 is critical. In the presence of free iron, H_2O_2 is converted into highly reactive •OH via the Fenton reaction (101-103). These radicals are potent inducers of lipid peroxidation, leading to the oxidative breakdown of PUFAs within cellular membranes, which is a hallmark of ferroptosis (104,105). Moreover, the activity of NOX4 further intersects with iron metabolism, thereby modulating the ferroptotic process (106). For example, NOX4 affects the expression of ferritin, thus controlling the availability of free iron necessary for lipid peroxidation, and influences the formation of iron-sulfur clusters essential for numerous cellular enzymes, including aconitase and mitochondrial respiratory chain complexes (107,108).

Pharmacological interventions through the use of NOX inhibitors, including diphenyleneiodonium and GKT137831, have demonstrated that inhibiting NOX4 can substantially reduce ROS levels and lipid peroxidation, and thus protect against ferroptosis (109,110). These findings are further corroborated by experimental models that show increased NOX4 activity under oxidative stress conditions, including treatment with RAS-selective lethal small molecule 3 (RSL3) or erastin, which have been shown to enhance lipid peroxidation and subsequent cell death (111,112). This highlights the crucial role of NOX4 not only in inducing cellular oxidative stress but also in regulating iron-dependent cell death, indicating its importance in both normal physiological and pathological conditions.

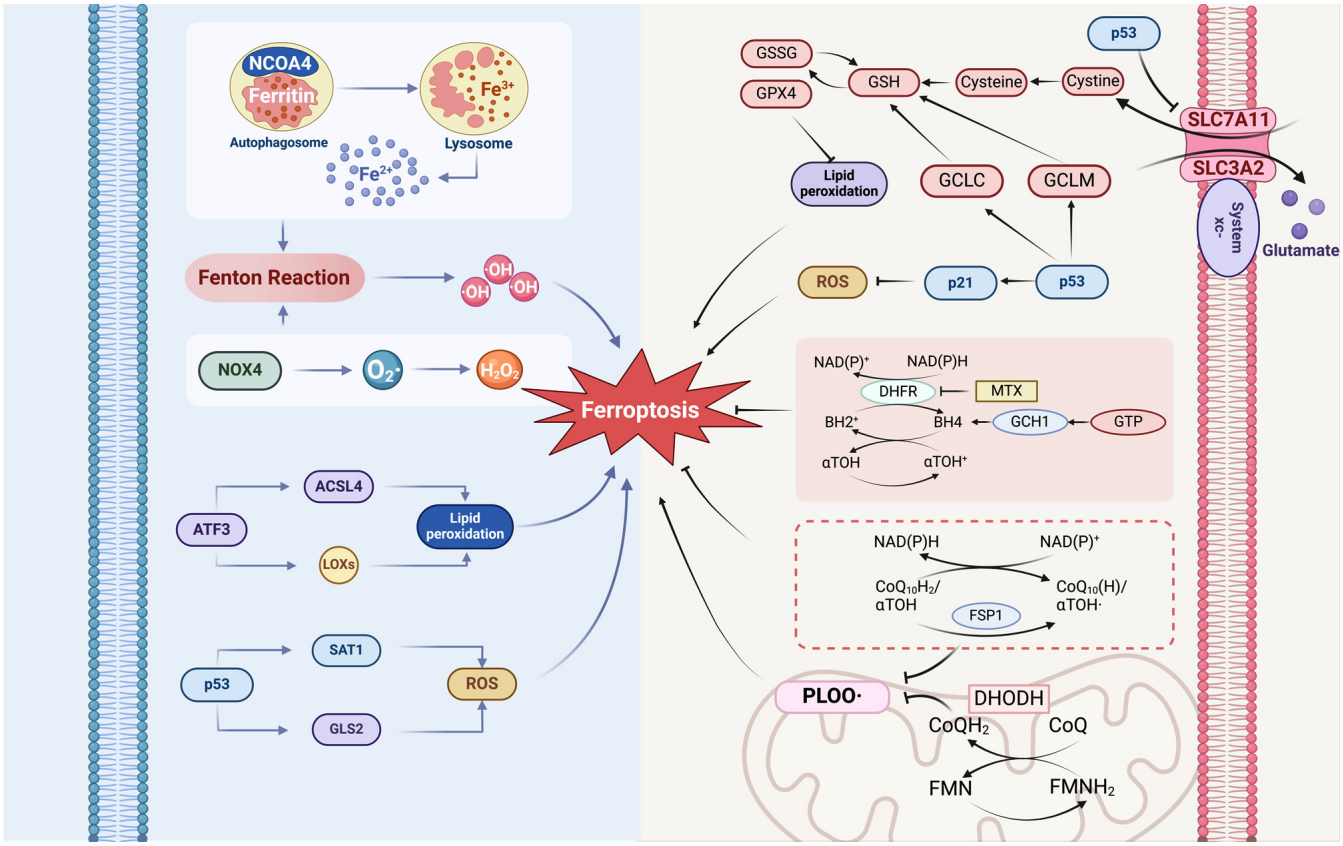

Figure 1. Major mechanisms that promote or inhibit ferroptosis. NCOA4 binds to ferritin and transports it to the autophagosome. The mature autophagosome then fuses with the lysosome, leading to the degradation of ferritin and the release of stored Fe^{2+}. NOX4 catalyzes the reduction of O_2 to H_2O_2. Fe^{2+} reacts with H_2O_2 in the Fenton reaction to produce •OH, which then promote ferroptosis. ATF3 enhances the expression of genes such as ACSL4 and LOXs, thereby promoting lipid peroxidation. System xc^-, a cystine/glutamate antiporter composed of the subunits SLC7A11 and SLC3A2, imports cystine into cells in exchange for the export of glutamate. Inside the cell, cystine is reduced to cysteine, which then participates in the synthesis of GSH. The enzyme GPX4 catalyzes the conversion of GSH into its oxidized form, GSSG, which inhibits ferroptosis. p53 upregulates the expression of SAT1 and GLS2, leading to the production of ROS and promoting ferroptosis. In addition, p53 facilitates ferroptosis by decreasing the expression of SLC7A11, which impairs cystine import and lowers GSH levels. p53 regulates ferroptosis in both directions. While it can promote ferroptosis, p53 also inhibits ferroptosis by increasing the expression of GCLC and GCLM, which are important for GSH synthesis. Additionally, p53 suppresses ferroptosis by promoting p21 expression, which functions as an antioxidant. DHODH is an enzyme in the mitochondria that converts dihydroorotate into orotate. This conversion also reduces CoQ to $CoQH_2$, which can inhibit the production of PLOO· that promote ferroptosis. FMN and its reduced form, $FMNH_2$, participate in the process by transferring electrons needed for these reactions. GCH1 converts GTP into BH4, which is then recycled back from its oxidized form, BH2, with the help of DHFR using NAD(P)H. BH4 and αTOH work together to prevent lipid peroxidation, effectively blocking ferroptosis. NCOA4, nuclear receptor coactivator 4; Fe^{2+}, ferrous iron; Fe^{3+}, ferric iron; NOX4, NADPH oxidase 4; H_2O_2, hydrogen peroxide; •OH, hydroxyl radicals; ATF3, activating transcription factor 3; ACSL4, acyl-CoA synthetase long chain family member 4; LOX lipoxygenase; SAT1, spermidine/spermine N1-acetyltransferase 1; GLS2, glutaminase 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; GSH, glutathione; GPX4, glutathione peroxidase 4; GSSG, glutathione disulfide; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier subunit; DHODH, dihydroorotate dehydrogenase; CoQ, coenzyme Q; PLOO·, peroxyl radicals; FMN, flavin mononucleotide; GCH1, GTP cyclohydrolase-1; BH4, tetrahydrobiopterin; BH2, dihydrobiopterin; MTX, Methotrexate; DHFR, dihydrofolate reductase; αTOH, α-tocopherol; FSP1, ferroptosis suppressor protein 1.

ATF3-mediated promotion mechanism. ATF3, part of the ATF/cAMP-response element-binding protein family, is recognized as a stress-induced transcription factor critically affecting ferroptosis (113). ATF3 participates in various aspects of ferroptosis, influencing iron metabolism and lipid processing, and modifying cellular antioxidant defense mechanisms (114-116).

Directly, ATF3 facilitates ferroptosis by regulating genes that play vital roles in iron management and the initiation of lipid peroxidation (115,117). ATF3 upregulates heme oxygenase 1 that is integral in controlling internal iron levels conducive to lipid peroxidation (118). Additionally, ATF3 regulates genes such as acyl-CoA synthetase long chain family member 4 and lipoxygenases, essential for producing and incorporating PUFAs into cellular membranes, which is a critical step in lipid peroxidation (119-121).

Indirectly, ATF3 undermines cellular antioxidant defense mechanisms and promotes ferroptosis by downregulating components of the GSH pathway and system xc^-, which safeguard cells against oxidative damage (113). Specifically, ATF3 reduces the expression of GPX4, which is crucial for converting lipid hydroperoxides into non-toxic compounds, thus promoting lipid peroxidation (115). Furthermore, the interactions of ATF3 with other stress-responsive transcription factors, such as NF-κB and p53, alter their regulatory activities, enhancing conditions that favor oxidative stress and ferroptosis (122-126). These interactions, especially with p53, may intensify pro-oxidant functions, thereby increasing the likelihood of ferroptosis under stress conditions (113,123).

p53-mediated bidirectional regulatory mechanism. The tumor suppressor protein p53 intricately regulates

cell fate through its dual role in promoting and inhibiting ferroptosis (127,128). p53 facilitates ferroptosis by diminishing antioxidant defenses and elevating oxidative stress. p53 suppresses the expression of solute carrier family 7 member 11 (SLC7A11), a critical component of the system xc^- cystine/glutamate antiporter necessary for cystine importation into cells (129). Cystine is transformed into cysteine, a precursor of GSH, which is crucial for detoxifying lipid peroxides (130). By lowering GSH levels, p53 increases the cellular vulnerability to oxidative stress and ferroptosis (129). Additionally, p53 increases the expression of spermidine/spermine N1-acetyltransferase 1 (SAT1), which leads to the acetylation of polyamines, thus reducing their antioxidant activity and elevating acetyl polyamine levels, which contribute to ROS production (128,131). Furthermore, p53 stimulates glutaminase 2 (GLS2) expression, enhancing the conversion of glutamine to glutamate, which increases ROS levels through the tricarboxylic acid cycle, thereby creating conditions conducive to ferroptosis (132,133).

Conversely, p53 also activates pathways that enhance the cellular antioxidant capabilities to counteract ferroptosis. p53 promotes CDKN1A gene transcription (coding for p21), which is known for regulating the cell cycle (134,135). However, p21 also affects the cellular antioxidant response, possibly by altering the stability and function of nuclear factor erythroid 2-related factor 2 (NRF2), which is a key regulator of antioxidant genes (136,137). This action enhances the cell ability to counteract oxidative stress and avert lipid peroxidation (138). p53 also promotes the expression of genes essential for synthesizing and recycling GSH, including glutamate-cysteine ligase modifier subunit (GCLM) and glutamate-cysteine ligase catalytic subunit (GCLC), as well as those involved in restoring oxidized GSH to its reduced state (139-141). These mechanisms demonstrate the comprehensive regulatory abilities of p53, enabling precise control over cell responses to stress signals, and switching between promoting and preventing ferroptosis depending on the cellular conditions.

Failure of cellular defense mechanisms. The disruption of cellular defense mechanisms against ferroptosis underscores the pathological processes observed in schizophrenia. Specifically, the GPX4-, FSP1-, dihydroorotate dehydrogenase (DHODH)- and GCH1-mediated mechanisms are crucial in safeguarding neural cells from oxidative stress and lipid peroxidation. The impairment of these defense mechanisms increases the susceptibility to ferroptosis, highlighting potential therapeutic targets (Fig. 1).

GPX4-mediated defense mechanism. GPX4 is a critical enzyme in mitigating oxidative stress by specifically targeting lipid peroxidation, which is a pivotal trigger of ferroptosis (22). GPX4 uses GSH as a reducing substrate to transform lipid hydroperoxides into lipid alcohols (142). This crucial reaction occurs at the active site of GPX4, distinguished by the presence of a selenocysteine residue that is vital for its activity (143). By limiting the accumulation of lipid peroxides, GPX4 contributes to maintaining the structural integrity of cellular membranes and preventing cell death (144).

GPX4 engages directly with lipid hydroperoxides found in cellular membranes or lipoproteins (144,145). By reducing the levels of these hydroperoxides, GPX4 inhibits the formation of more reactive and damaging lipid radicals, particularly protecting cells with membranes rich in PUFAs, which are highly susceptible to peroxidation (143,146). Furthermore, GPX4 extends its influence to regulate various signaling pathways that control cell proliferation and apoptosis, highlighting its broad functional implications beyond its antioxidant capabilities (144,147). GPX4 primarily regulates cell proliferation by inhibiting ferroptosis. Additionally, it acts as an anti-apoptotic factor by preventing the release of cytochrome C, inactivating caspase-3 and reducing hydroperoxide production, thus preventing mitochondrial apoptosis (144,147).

Ferroptosis is tightly linked to the disruption of cellular antioxidant defenses, notably through mechanisms impacting GPX4 (22). Central to this process are two primary factors: i) The depletion of GSH, which is critical for the antioxidant function of GPX4 (111); and ii) direct effects on GPX4, including oxidative damage to its structure, genetic alterations affecting its expression and functionality and the use of specific pharmacological inhibitors (148-150). Depletion of GSH due to intensified oxidative stress or the action of inhibitors significantly reduces the ability of GPX4 to counteract lipid peroxidation, leading to increased lipid peroxides and subsequent ferroptosis (151). Similarly, any direct disablement of GPX4 removes the critical barrier against lipid peroxidation, thereby inducing cell death via ferroptosis (149,150).

FSP1-mediated defense mechanism. Originally identified as apoptosis-inducing factor (AIF) mitochondria-associated 2 due to its resemblance to AIF, FSP1 has since been characterized through detailed studies as playing a crucial role in preventing ferroptosis rather than facilitating apoptosis (24,152). The FSP1 gene, located on human chromosome 10, encodes a protein comprising ~373 amino acids, including a flavin adenine dinucleotide (FAD)-binding motif critical for its enzymatic activity (153-155).

The enzymatic function of FSP1 is uniquely characterized by its ability to reduce CoQ10 to ubiquinol within the lipid bilayers of cell membranes via its FAD-binding domain (24,25). CoQ10, a lipid-soluble component of the electron transport chain that is prevalent in cellular membranes, serves as an electron carrier (156). The transformation of CoQ10 to ubiquinol by FSP1 markedly reinforces the cellular antioxidant capacity by providing ubiquinol (24,25), a powerful lipophilic antioxidant that captures lipid peroxyl radicals and prevents the peroxidation of PUFAs within the cell membranes (157).

Functioning independently from the traditional GSH-dependent antioxidant pathways, which are central to most cellular defense mechanisms against oxidative stress, FSP1 is instrumental in the inhibition of ferroptosis by directly limiting lipid peroxidation (24,25). The reduction of CoQ10 to ubiquinol not only impedes the onset but also the propagation of lipid peroxidation processes in the membranes (157,158). By neutralizing lipid peroxyl radicals produced when ROS interact with PUFAs, ubiquinol interrupts the lipid peroxidation chain reaction, thereby maintaining cellular integrity and function (159-161). This distinct role positions FSP1 as an essential, non-traditional regulator of ferroptosis.

DHODH-mediated defense mechanism. DHODH is an essential mitochondrial enzyme strategically positioned on

the outer surface of the inner mitochondrial membrane (162). DHODH comprises two distinct domains: An α/β barrel domain that extends into the mitochondrial matrix and a larger domain anchored to the membrane, which houses the binding sites for the substrate dihydroorotate and the coenzyme flavin mononucleotide (163-166). This structural arrangement is crucial as it enables the direct transfer of electrons from dihydroorotate to the mitochondrial respiratory chain, specifically to CoQ10 (167). This connection bridges the synthesis of pyrimidines with mitochondrial electron transport.

DHODH is central to the *de novo* pyrimidine synthesis pathway, catalyzing the conversion of dihydroorotate to orotate as a crucial step, which is the only reaction within this pathway involving a mitochondrial enzyme (168). This process is indispensable for the synthesis of nucleotides that are critical for cell proliferation and growth regulation (169,170).

Beyond its primary biochemical functions, DHODH impacts cellular redox homeostasis and the process of ferroptosis (171). The inhibition of DHODH by brequinar disrupts mitochondrial electron flow, resulting in an increase in ROS. This increase in ROS enhances lipid peroxidation, which is a critical marker of ferroptosis (171,172). Furthermore, the inhibition of DHODH also reduces the levels of vital antioxidants, such as GSH, which are necessary for counteracting lipid peroxides, thus rendering cells more prone to oxidative stress and lipid damage (173,174). Therefore, DHODH has emerged as a potential regulatory hub, where its inhibition may enhance ferroptotic cell death, offering a novel angle for therapeutic intervention, particularly in cancers such as pancreatic adenocarcinoma (175) and breast cancer (176), where certain cells show resistance to other forms of cell death (171,177).

GCH1-mediated defense mechanism. GTP cyclohydrolase-1 (GCH1) is the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH4), a critical cofactor necessary for various biochemical processes, including the synthesis of monoamine neurotransmitters and the regulation of nitric oxide levels (178,179). GCH1 catalyzes the conversion of GTP to formic acid and dihydroneopterin triphosphate, the initial and rate-limiting step in BH4 synthesis (180,181). Following this, BH4 can be recycled back from its oxidized form, dihydrobiopterin, with the help of dihydrofolate reductase using NAD(P)H (182,183). Structurally, GCH1 is organized into a homodecameric formation, comprising two pentameric rings aligned into a toroidal configuration, with each monomer possessing a catalytic domain essential for the activity of GCH1 (184).

Previous studies have identified a significant role for GCH1 in regulating oxidative stress and its potential influence on ferroptosis (185,186). As an antioxidant, BH4, the enzymatic product of GCH1, effectively neutralizes ROS and reactive nitrogen species (187,188). This function is pivotal in preventing the uncoupling of nitric oxide synthase, which can elevate oxidative stress by shifting the production from nitric oxide to superoxide (189). BH4, along with α-tocopherol, which exhibits similar activity, enhances antioxidant capacities when used together. This combination shows a synergistic effect, significantly improving protection against lipid peroxidation compared to their individual use, and effectively blocking ferroptosis (190). The ability of GCH1 to influence cellular resistance to oxidative stress conditions and ferroptosis has profound implications. Research indicates that elevating GCH1 expression or supplementing with BH4 can protect various cell types against ferroptosis by diminishing lipid peroxidation and oxidative stress (185,190). Conversely, a lack or inhibition of GCH1 increases the vulnerability to this type of cell death (185,191).

3. Evidence linking ferroptosis and schizophrenia

Animal studies. Studies using animal models have provided compelling evidence linking alterations in iron metabolism to schizophrenia-associated behaviors. In one investigation, male Sprague-Dawley rats subjected to social isolation, an environmental stressor known to affect mental health, demonstrated notable iron level discrepancies in the brain. Specifically, isolated rats showed increased iron levels in the prefrontal cortex and decreased levels in the hippocampus compared with their group-housed counterparts. These iron imbalances were associated with behavioral changes characteristic of schizophrenia, including increased anxiety, altered locomotor activity and impaired cognitive functions, suggesting that the altered distribution of iron in these brain regions may contribute to the development of schizophrenia-associated symptoms (192).

Further research indicates that iron imbalances at different life stages can have profound effects. Rats experiencing iron deficiency during the perinatal period exhibited enduring neurochemical and behavioral abnormalities in adulthood, which persisted even after rectifying the iron deficiency through supplementation (193). This points to the lasting impact of early-life iron deficiency on brain function and its potential to contribute to psychiatric disorders. Additionally, experiments that induced iron overload in the hippocampus and prefrontal cortex of male rats led to the development of schizophrenia-associated behaviors (37), suggesting that both an excess and a deficiency of iron could foster changes in the brain associated with schizophrenia.

Another innovative study involved transferring gut microbiota from patients with schizophrenia into germ-free mice. This transfer caused the mice to exhibit schizophrenia-associated behaviors, such as decreased social interaction and hyperactivity (increased total distance traveled and higher average speed in the Open-field test). Furthermore, a bioinformatics analysis comparing transcriptional changes between the brains of mice that received schizophrenia-associated fecal microbiota and those given a control (phosphate-buffered saline) highlighted notable overlaps in differentially expressed genes associated with critical brain areas and pathways, including those involved in ferroptosis (194).

Ferroptosis-related genes. Advances in genomic research have shed light on the involvement of ferroptosis-related genes in schizophrenia. A recent study specifically explored the differential expression of ferroptosis-related genes in schizophrenia by employing bioinformatics analysis to compare patient and control groups. Key among the identified genes are TP53, VEGFA and PTGS2 (195), which have been highlighted as potential markers for ferroptosis within the context of schizophrenia. These genes are implicated in the regulation of oxidative stress responses and cell survival (196-198),

and their altered expression in patients with schizophrenia indicates a potential disruption in cellular mechanisms that regulate oxidative stress and iron metabolism.

Building on these genetic insights, Lian *et al* (199) successfully developed a clinical diagnostic model based on ferroptosis-related hub genes, specifically DECR1, GJA1, EFN2L2, PSAT1, SLC7A11, SOX2 and YAP1. An effective clinical diagnostic model has been established based on these genes, enhancing the ability to diagnose and treat schizophrenia with a novel approach. Additionally, another study employing machine learning technology integrated various biological datasets to predict patterns of programmed cell death, including ferroptosis, in schizophrenia. This predictive model identified the ferroptosis-related genes ATG7 among the top 10 significant genes, underlining their importance in the progression of schizophrenia (200).

The impact of ancient viral elements on schizophrenia also presents a compelling avenue of research, particularly the role of the endogenous retrovirus group W member 1 (ERVW-1) retroviral element. This element has been shown to promote ferroptosis in neuronal cells by targeting and degrading key regulators, such as GPX4 and solute carrier family 3 member 2 (201). This contributes to increased iron levels and oxidative stress markers, decreased GSH levels and disrupted mitochondrial membrane potential, all of which are hallmarks of ferroptosis (202,203). Furthermore, the ERVW-1-induced effects could be reversed by the ferroptosis inhibitor ferrostatin-1 (201).

Iron dysregulation. In a case study of a patient initially diagnosed with Sydenham's chorea who later developed schizophrenia, autopsies revealed mineral accumulations, including predominantly iron, in the basal ganglia. These mineral deposits have been associated with disturbances in dopaminergic signaling, symptoms typical of schizophrenia and disorders characterized by irregular movements (204). In patients with schizophrenia, there was notably intense iron staining in the caudate nucleus compared with that in normal controls; however, it remains uncertain whether antipsychotic treatments induced this increase in iron staining (205). Further comprehensive autopsy analyses have indicated elevated iron concentrations in the prefrontal cortex, which is a critical area for cognitive processes, in patients with schizophrenia compared to matched controls (16.4 vs. 12.7 μmol/g). These iron levels were not associated with increased ferritin, which sequesters iron in a biologically inert form, thus suggesting the accumulation of potentially harmful free iron (37). Additionally, unlike in healthy individuals where iron accumulation increases with age, in patients with schizophrenia elevated iron levels were observed at a much younger age and remained stable across age, despite both groups having a similar age range at death (17-85 years for controls and 17-84 years for schizophrenia). And the difference in covariate-adjusted iron was substantial in the younger subcohort (age <35; 1.53 μmol/g) but marginal in the older subcohort (age ≥35 years; 0.46 μmol/g). This suggests that disruptions in iron regulation may be linked with developmental anomalies occurring early in the course of schizophrenia (37).

In the field of imaging studies, advanced techniques such as magnetic resonance spectroscopy and quantitative susceptibility mapping have provided a non-invasive method to examine the levels of brain iron in living patients with schizophrenia (206). Studies using these methods have shown that individuals with schizophrenia have distinct patterns of iron deposition. Particularly, increased iron levels have been documented in subcortical structures such as the thalamus and putamen, which are integral to dopaminergic pathways and are often implicated in schizophrenia (207,208). These imaging findings not only corroborate the autopsy studies regarding iron accumulation but also suggest that iron may modulate neurotransmitter systems directly involved in the symptomatology of schizophrenia (207).

Serological findings complement the neuropathological and imaging evidence of iron dysregulation in schizophrenia. Various studies have noted alterations in serum iron levels among patients with schizophrenia compared with healthy controls (209-211). Notably, lower serum $\log_{10}$ferritin:AST ratio levels and higher total serum iron have been observed in patients with schizophrenia (211), which may reflect an underlying imbalance in iron metabolism. These serological abnormalities are not isolated findings but are connected to broader physiological disruptions, including liver function, which is crucial in iron metabolism (209). Understanding these systemic changes is vital for developing targeted interventions that address the complex interplay between iron dysregulation and schizophrenia, potentially leading to more effective treatments for this disorder.

4. Therapeutic implications

N-acetylcysteine (NAC) supplementation. Decreased levels of antioxidant GSH in patients with schizophrenia have been well-documented and are considered a target for therapeutic intervention (212,213). NAC, as a precursor of GSH, plays a crucial role in attenuating oxidative stress and mitochondrial dysfunction (214), which are key contributors to the pathophysiology of schizophrenia. NAC has been shown to modulate neuroinflammatory pathways, protect against apoptosis and improve mitochondrial function (215). In GSH-deficient mouse models of schizophrenia, neurochemical changes were observed in the cortex, including elevated levels of glutamine, glutamate, N-acetylaspartate, myo-inositol, lactate, and alanine. NAC supplementation can effectively normalize these neurochemical changes during the development of the model mice, suggesting that NAC may play a therapeutic role in halting or mitigating the progression of schizophrenia (216).

Clinical trials have shown that NAC can markedly improve the symptoms of schizophrenia, particularly negative symptoms that are often less responsive to conventional antipsychotics (Table I) (217-226). For example, Berk *et al* (217) revealed notable improvements in negative symptoms as measured using the Positive and Negative Syndrome Scale in patients treated with NAC as an adjunct to their ongoing antipsychotic regimen. These clinical improvements were noted alongside enhancements in overall psychopathology scores, suggesting a broad therapeutic impact of NAC. In terms of cognitive improvements, NAC has been shown to exhibit a positive effect on cognitive functions in patients with schizophrenia. This includes enhancements in areas such as working memory

Table I. Clinical trials of NAC supplementation in the treatment of schizophrenia.

First author, year	Group	Age, years	Average duration of schizophrenia, years	Daily dosage of NAC or placebo	Treatment duration, weeks	Positive symptoms	Negative symptoms	Cognitive symptoms	(Refs.)
Berk, 2008	NAC (n=38); placebo (n=37)	NAC, 44.6±11.2; placebo, 46.6±13.8	Overall, 10.3	2.0 g	24	Not improved	Improved	/	(217)
Conus, 2018	NAC (n=32); placebo (n=31)	NAC, 26.1±6.1; placebo, 24.7±5.9	NAC, 2.3; placebo, 2.1	2.7 g	24	Not improved	Not improved	Improved	(218)
Rapado-Castro, 2017	NAC (n=27); placebo (n=31)	NAC, 38.6±12.2; placebo, 41.0±12.4	NAC, 8.6; placebo, 11.1	2.0 g	24	/	/	Improved	(219)
Sepehrmanesh, 2018	NAC (n=39); placebo (n=40)	NAC, 38.7±1.9; placebo, 39.4±2.2	NAC, 13.8; placebo, 17.0	1.2 g	12	Improved	Improved	Improved	(220)
Farokhnia, 2013	NAC (n=21); placebo (n=21)	NAC, 32.2±6.1; placebo, 33.4±7.0	NAC,6.9; placebo, 7.4	1.0 g during the first week, then 2.0 g	8	Not improved	Improved	/	(221)
Breier, 2018	NAC (n=30); placebo (n=30)	NAC, 22.2±4.2; placebo, 25.0±5.2	NAC, 1.3; placebo, 1.4	Started with 0.6 g and gradually increased to 3.6 g over the first 4 weeks	52	Not improved	Improved	Not improved	(222)
Medvedev, 2021	NAC (n=54); placebo (n=53)	18.0-65.0[a]	12.2	2.0 g	24	Improved	Improved	/	(223)
Rossell, 2016	NAC (n=84); placebo (n=84)	18.0-65.0[a]	Not provided	2.0 g	52	Not improved	Improved	Improved	(224)
Lavoie, 2008[c]	Cross-over design (n=11)	31.9±3.4[b]	9.4	2.0 g	8	Not improved	Not improved	Not improved; MMN improved	(225)
Carmeli, 2012[c]	Cross-over design (n=11)	31.9±3.4	9.4	2.0 g	8	Not improved	Not improved	Not improved; MPS improved	(226)

Data are presented as the mean ± SD unless differently indicated. Data are presented as [a]range and [b]mean ± SEM. NAC, N-acetylcysteine; MMN, mismatch negativity; MPS, multivariate phase synchronization; /, not applicable. [c]Based on the same clinical study.

and executive function (227). These cognitive improvements are vital, as they address core schizophrenia deficits that affect daily life and overall quality of life (228).

The therapeutic potential of NAC supplements is not limited to mitigating oxidative stress. For instance, NAC has been shown to exhibit neuroprotective effects by reducing pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, linked to schizophrenia. NAC also regulates glutamate levels through the cysteine-glutamate antiporter, influencing neurotransmitter pathways. These effects suggest that NAC may help prevent the progression of schizophrenia symptoms from prodromal stages to full-blown psychosis (229,230). Additionally, it may ameliorate side effects related to antipsychotic medications, such as akathisia and metabolic disturbances, thus improving patient adherence and overall quality of life (227,231). The safety and tolerability profile of NAC is also an advantage. It has been reported that NAC is generally well-tolerated by patients with minimal side effects. This aspect is crucial for long-term management strategies in schizophrenia, where treatments often continue for 1 to 5 years after the condition stabilizes (232).

Selenium supplementation. Given the role of oxidative stress in ferroptosis, treatments that reinforce the antioxidant defenses of the body, such as selenium, may help mitigate ferroptosis. Selenium, a vital trace element known for its antioxidant properties (233), has attracted interest in schizophrenia research due to the observed abnormalities in its levels among patients (234,235). Studies have shown that patients with schizophrenia typically have lower selenium concentrations in their bloodstream compared with healthy individuals (235,236). Additionally, a connection has been drawn between these depleted selenium levels and an increased risk of schizophrenia. Extensive epidemiological data from the European population have indicated an important association between lower selenium levels and increased schizophrenia prevalence (235). Selenium achieves its antioxidant effects primarily through selenoproteins, such as GPx and thioredoxin reductase, which reduce ROS and lipid hydroperoxides, thus protecting against oxidative stress. Moreover, these selenoproteins act as antioxidant enzymes that influence eicosanoid synthesis (lipid mediators involved in inflammatory responses), thereby affecting the balance between pro-inflammatory and anti-inflammatory eicosanoids and exerting an anti-inflammatory effect (237). This association highlights the role of selenium in combating oxidative stress and inflammation (238,239), factors that are believed to contribute to the onset and exacerbation of schizophrenia.

Clinical trials exploring the benefits of selenium supplementation for patients with schizophrenia have produced promising results. For example, it has been revealed that restoring selenium levels can lead to notable improvements in cognitive functions, such as memory, executive function and attention, which are frequently compromised in schizophrenia (240). Additionally, broader psychiatric improvements, including reductions in both positive and negative symptoms, have been observed, underscoring the wide-ranging benefits of correcting selenium deficiency (241). These outcomes suggest that selenium supplementation may be an effective adjunctive therapy in schizophrenia, capable of not only enhancing symptom management but also potentially addressing the underlying oxidative imbalances that contribute to disease progression.

PUFAs supplementation. While PUFAs are substrates for lipid peroxidation, their balanced intake can also modulate the composition and function of the cell membrane, affecting ferroptosis indirectly. Research into the effects of omega-3 fatty acids, particularly docosahexaenoic acid and eicosapentaenoic acid (EPA), reveals their potential to mitigate inflammatory processes and oxidative stress (242,243), which are pivotal in managing ferroptosis associated with schizophrenia.

Clinical studies and systematic reviews have indicated that supplementation with omega-3 fatty acids can ameliorate various psychopathological symptoms and metabolic disorders in patients with schizophrenia (244-247). For instance, a 12-week trial showed that omega-3 fatty acids supplementation significantly improved cognitive function and increased brain-derived neurotrophic factor (BDNF) levels, while reducing inflammatory markers such as IL-6, TNF-α and C-reactive protein (CRP) (244). Furthermore, omega-3 fatty acids have been reported to reduce the adverse effects of metabolic syndrome, conditions often exacerbated by antipsychotic medications, which typically promote weight gain and insulin resistance (244). Additionally, a review of 1,494 patients found significant improvements in general psychopathology and positive symptoms, particularly in severely ill patients receiving EPA at doses greater than 1 g/day, along with favorable effects on metabolic parameters such as serum triglycerides (247).

The incorporation of omega-3 fatty acids into cell membranes alters lipid profiles, changing the cellular vulnerability to lipid peroxidation that is central to ferroptosis (248,249). These fatty acids can decrease the production of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, while simultaneously enhancing the production of anti-inflammatory cytokines like IL-10 and IL-4 (250). The activation of inflammation can lead to ferroptosis (251), indicating that the anti-neuroinflammatory properties of omega-3 fatty acids may also contribute to reducing the levels of ferroptosis in neuronal cells (250,252,253). These capabilities suggest that omega-3 fatty acids could serve not only as supplementary treatments for symptom relief in schizophrenia but also as influential agents in modifying the fundamental mechanisms of the disease through the modulation of ferroptosis.

Iron chelation therapy. Iron chelation therapy offers a promising avenue for treating schizophrenia, given its efficacy in other neurological disorders, such as Parkinson's disease and Alzheimer's disease, where oxidative stress and iron dysregulation are implicated (254). Iron chelators, such as deferiprone, function by binding free iron in the body, thus mitigating the oxidative stress caused by excess iron (255). This is particularly important in the brain, where elevated iron levels can lead to the production of ROS, contributing to neuronal damage and neurodegeneration (256,257). Reducing iron-induced oxidative damage through chelation is an effective strategy in managing diseases such as Alzheimer's disease, Parkinson's disease and multiple

sclerosis, where iron chelators have been shown to effectively lower iron levels in brain regions associated with these conditions, thereby potentially slowing disease progression and improving neurological outcomes (254,258,259).

In schizophrenia, similar mechanisms of iron-induced oxidative stress could play a role in the pathophysiology of the disorder. The accumulation of iron in the brain not only enhances oxidative stress but also promotes ferroptosis. In a study involving seven psychiatric patients with iron overload evidenced by abnormal serum ferritin, transferrin saturation, or excessive urinary iron, treatment with iron chelators led to significant clinical improvements (260). Iron chelation could, therefore, offer dual benefits in schizophrenia treatment by reducing both oxidative stress and ferroptosis. This therapeutic approach may be particularly relevant for patients exhibiting elevated ferritin levels or other indicators of disturbed iron metabolism. However, further research is needed to systematically assess the efficacy of iron chelation in schizophrenia and to validate this approach as a viable treatment option.

5. Conclusion

Exploring ferroptosis in the context of schizophrenia represents a promising frontier in psychiatric research, offering new perspectives on the cellular and molecular mechanisms underlying this complex disorder. The association between iron dysregulation, oxidative stress and lipid peroxidation central to ferroptosis suggests that this form of cell death could be integral to the pathophysiology of schizophrenia. Understanding the intricate balance of iron metabolism and the oxidative stress response within neural circuits could reveal novel therapeutic targets, potentially revolutionizing the management of schizophrenia. Future research should focus on the validation of ferroptosis markers in clinical settings and the development of targeted therapies that modulate iron homeostasis and antioxidant systems. By integrating the mechanisms of ferroptosis with existing knowledge of schizophrenia, researchers can pave the way for innovative treatments that not only alleviate symptoms but also address fundamental pathological processes, ultimately enhancing patient outcomes and quality of life.

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Competing interests

The authors declare that they have no competing interests.

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