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Targeting the ferroptosis crosstalk: novel alternative strategies for the treatment of major depressive disorder

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ABSTRACT

Depression is a major contributor to poor global health and disability, with a recently increasing incidence. Although drug therapy is commonly used to treat depression, conventional antidepressant drugs have several disadvantages, including slow onset, low response rates and severe adverse effects. Therefore, developing effective therapies for depression remains challenging. Although various aetiological theories of depression exist, the underlying mechanisms of depression are complex, and further research is crucial. Moreover, oxidative stress (OS)-induced lipid peroxidation has been demonstrated to trigger ferroptosis. Both OS and ferroptosis are pivotal mechanisms implicated in the pathogenesis of neurological disorders, and investigation of the mediators involved in these processes has emerged as a prominent and active research direction. One previous study revealed that regulatory proteins involved in ferroptosis are implicated in the pathogenesis of depression, and antidepressant drugs could reverse depressive symptoms by inhibiting ferroptosis *in vivo*, suggesting an important role of ferroptosis in the pathogenesis of depression. Hence, our current comprehensive review offers an up-to-date perspective on the intricate mechanisms involved, specifically concerning ferroptosis and OS in the context of depression, along with promising prospects for using molecular mediators to target ferroptosis. We delineate the key targets of molecular mediators involved in OS and ferroptosis implicated in depression, most notably reactive oxygen species and iron overload. Considering the pivotal role of OS-induced ferroptosis in the pathogenesis of neurological disorders, delving deeper into the underlying subsequent mechanisms will contribute significantly to the identification of novel therapeutic targets for depression.

INTRODUCTION

Major depressive disorder (MDD) is a psychiatric disorder characterised by persistent low mood, loss of interest, cognitive impairment and loss of appetite, among other symptoms. In recent decades, the incidence of depression in adults has significantly increased due to accumulating pressure from life and work. Data from the National Health and Nutrition Examination Survey in the USA estimates approximately 8.1% of adults experience depression in a given 2-week period, with women (10.4%) almost twice as likely as men (5.5%) to be affected (online supplemental figure 1).[1] MDD affects 16.2% of adults during their lifetime, leading to substantial economic losses and posing a significant health burden on patients.[2] While drug therapy, such as amitriptyline, remains the preferred clinical treatment for MDD, traditional antidepressant drugs have several drawbacks, including slow onset, low response rate and severe adverse effects,[3–5] suggesting that other molecular mechanisms are involved in the progression of depression. Although the pathophysiology of MDD remains unknown, several underlying mechanisms have been reported.[6–8] Thus, further exploration of the pathogenesis of MDD and the development of novel potential drugs are necessary.

Previously, MDD was thought to be caused by brain-derived neurotrophic factor disorders and other neurotransmitter alterations[9–11]; however, recent studies have shown that inflammation and oxidative stress (OS) in the brain are highly related to depression.[12 13] OS is closely associated with various pathological mechanisms, including neuroinflammation and mitochondrial dysfunction, which are also strongly associated with depression.[14–16] Inflammation may augment the progression of depression, which further exacerbates inflammation and forms a co-activated state.[17 18] Additionally, inflammation and depression may share similar aetiological bases, such as OS.[19] OS is caused by the overproduction of reactive oxygen species (ROS) that cannot be eliminated by antioxidant defence systems. ROS homeostasis has a crucial role in regulating the cellular redox balance. Ding *et al* found that intracellular ROS causes dysfunction of the 5-hydroxytryptamine (5-HT) system in mouse

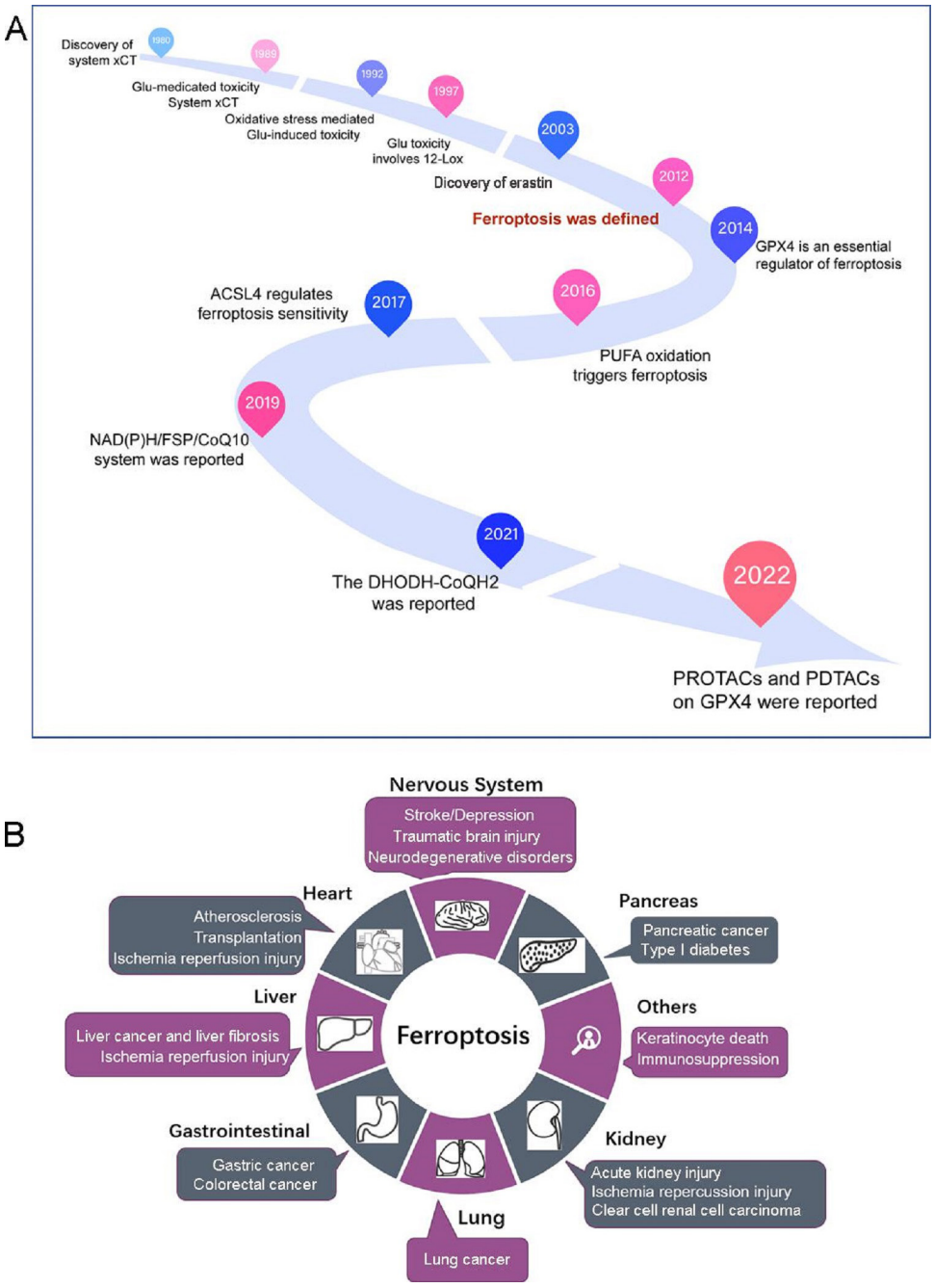

Figure 1 (A) Timeline of important affairs in ferroptosis discovery. (B) the role of ferroptosis in the pathological processes of different organs. ACSL4, acyl-CoA synthetase long-chain family member 4; CoQ10, coenzyme Q10; CoQH2, dihydroubiquione; DHODH, dihydroorotate dehydrogenase; FSP, ferroptosis suppressor protein; NADPH, nicotinamide adenine dinucleotide phosphate; PDTACs, photodegradation-targeting chimeras; PROTACs, proteolysis-targeting chimeras; PUFA, polyunsaturated fatty acid; xCT, cystine/glutamate antiporter.

brains by regulating tryptophan hydroxylase-2, eventually leading to depression-like behaviours.[20] Therefore, ROS accumulation associated with ferroptosis may have a significant role in the pathogenesis of MDD.

Ferroptosis was first reported in the 1980s by Bannai *et al*.[21] After over two decades of development, classical agonists of iron death, erastin and rat sarcoma (RAS)-selective lethal 3 (RSL3), were discovered in 2003 and 2008, respectively[22 23]; however, it was not until 2012 that Dixon *et al* identified iron-related death as a distinct form of cell death[24] (figure 1A). In the subsequent decade, research on iron death has gained momentum and has become a highly promising investigational domain. As shown in figure 1B, ferroptosis is responsible for many organ injuries and degenerative pathologies; therefore, inducing or inhibiting ferroptosis is of great significance for ameliorating related diseases.[25] Notably, Cao *et al* observed the activation of necroptosis and ferroptosis in a mouse model of chronic unpredictable mild stress-induced depression.[26] In addition, previous studies have

demonstrated that the nuclear factor erythroid 2-related factor 2 (NRF2)/haem oxygenase 1 (HO-1) signalling pathway and superoxide dismutase regulate ROS levels in the body, which is important for OS and inflammatory damage and is closely related to depression.[27 28] NRF2 is an important nuclear factor that regulates ferroptosis and has a vital role in the antioxidant, iron metabolism and lipid peroxidation pathways.[29] Wu *et al* reported that sulforaphane, an NRF2 activator, has an antidepressant effect in mice.[30] This suggests that targeting key proteins involved in ferroptosis may be a promising strategy for the treatment and prevention of MDD.

In the present review, we aim to highlight the precise molecular mechanisms of ferroptosis, the regulatory network of ferroptosis in depression and the potential of targeted therapies for treating depression. We also aim to summarise the current research hotspots and explore breakthroughs in drug treatment for depression. Finally, we discuss the focus and urgent issues related to ferroptosis in depression.

REGULATION OF THE FERROPTOSIS PATHWAY

Ferroptosis is an iron-dependent regulatory cell death pathway characterised by excessive oxidation of polyunsaturated fatty acids (PUFAs) and the accumulation of excess iron ions, which is associated with OS. Diseases of different organs, including traumatic brain injury, stroke, and neurodegenerative disorders, have been reported to be closely related to ferroptosis (figure 1B). Previous studies have confirmed that key proteins involved in ferroptosis are also involved in the development of depression, along with OS.[31] During the conversion of the PUFAs of phospholipids (PLs) into lipid peroxides, OS may stimulate neurons to produce active oxygen radicals and induce ferroptosis. Ferroptosis is a highly regulated process involving multiple metabolic changes (eg, iron and ROS metabolism) and complex signalling pathways that require several organelles. The detailed mechanisms of ferroptosis are summarised as follows.

Abnormal iron metabolism in the brain

Iron is a vital trace element that has a role in several biological processes, including inflammatory responses, OS, oxygen transport and cell metabolism.[32 33] In the brain, iron is involved in myelination, neurotransmitter synthesis and antioxidant function; however, inflammation and OS can disrupt the function of molecules involved in iron metabolism, leading to iron imbalance.

Figure 2A summarises the regulatory mechanisms of iron ion metabolism in cells. Iron ions (Fe^{3+}) enter the cytoplasm via transferrin channels by binding to transferrin. Inside the cell, Fe^{3+} is converted to ferrous ions (Fe^{2+}) by metalloreductases and participates in various physiological and biochemical processes, including ferroptosis. When iron storage becomes overloaded, excess Fe^{2+} is transported to the labile iron pool (LIP) via divalent metal transporter 1.[34] Bidirectional regulation of iron metabolism is facilitated by cellular proteins. Conversely, Fe^{3+} enters cells through the transferrin (TF)/transferrin receptor 1 (TFR-1) transport system, and upregulation of iron-related proteins can also cause intracellular iron overload. The nuclear receptor coactivator 4 (NOCA4) protein can release free iron from ferritin via ferritinophagy, and NRF2 gene-regulated HO-1 catalyses the degradation of haem to produce Fe^{2+}. Finally, excess iron leads to excessive ROS production via the Fenton reaction.[35] In contrast, heat shock protein family B (small) member 1 expression can inhibit the expression of TFR-1, reduce iron intake and control iron pool capacity. Free iron ions can be exported from cells by ferroportin and prominin2[36]; however, free iron can cause the Fenton reaction, generating ROS, including superoxide, hydrogen peroxide and hydroxyl radicals. Accumulated ROS can cause widespread damage, ultimately leading to the loss of cell function and cell death. Recent studies have shown that iron absorption, utilisation, recovery and storage are finely regulated by a series of iron transport-related proteins such as TFR1, ferritin light chain, ferritin heavy chain 1 (FTH1), NOCA4, ferroportin and divalent metal transporter 1.[37 38] Additionally, Daar *et al* reported that deferasirox provided a sustained reduction in LIP levels in heavily iron-overloaded patients, further reducing unregulated tissue iron loading and preventing end-organ damage.[39] Increased iron uptake and reduced iron storage may lead to an iron overload during ferroptosis.

Disturbances in ROS metabolism

Numerous studies have confirmed that lipid peroxidation is the driver of ferroptotic cell death.[40] High levels of ROS lead to the oxidation of cellular biomolecules, particularly biomembrane lipids, causing lipid peroxidation.[41] Figure 2B summarises the regulatory mechanisms of ROS metabolism in cells. Acyl-CoA synthetase long-chain family member 4 (ACSL4), a key regulator of fatty acid metabolism that facilitates the acylation of arachidonic acid, and lysophosphatidylcholine acyltransferase 3 (LPCAT3), an essential enzyme responsible for the reacylation of lysophospholipids within cell membranes, has emerged as crucial components of ferroptosis induced by RSL3 and erastin. Lipoxygenases (LOXs) primarily serve as catalysts for the synthesis of lipid hydroperoxides, generating double-oxygenated and triple-oxygenated (15-hydroperoxy)-diacylated phosphatidylethanolamine (PE) species, which are indicative of ferroptosis. Tocotrienols and tocopherols can suppress LOX activity, thereby exerting a preventive effect against ferroptosis. In addition, P53 may reduce ROS production by downregulating cyclo-oxygenase-2, nitric oxide synthase 2 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4.[42] Finally, voltage-dependent anion channels (VDACs) regulate mitochondrial ROS production.[43]

Cell membranes contain large amounts of PUFAs, which are primary targets for ROS attacks. PUFAs can be involved in the subsequent oxidation process as high-energy compounds, generating many lipid peroxidation

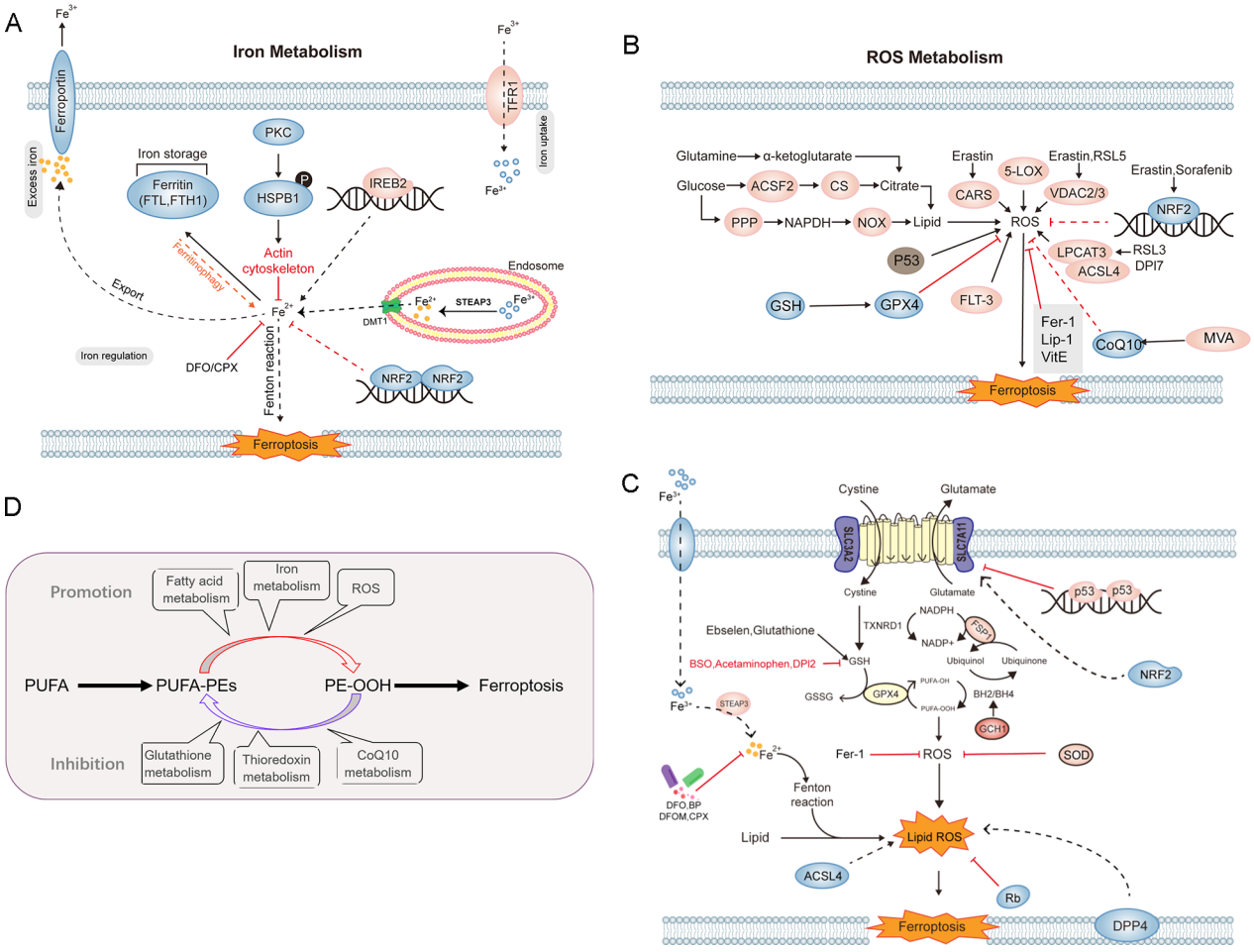

Figure 2 (A) Overview of intracellular iron metabolism. This schematic chart illustrates the processes involved in iron uptake, storage, regulation and output. The metabolism of iron is regulated by various factors, including transferrin, TRFC and ferritinophagy. Iron metabolism and its regulators contribute to lipid peroxidation and ferroptosis by increasing intracellular labile iron pool levels. (B) Overview of the intracellular modulation of ROS. This scheme depicts how ROS operates at the intersection of crucial signalling events. They work upstream and downstream of other signalling components, such as membranes, GPX4, FLT-3, ACSL4, CARS, CoQ10, 5-LOX and transcription factors. (C) Metabolic signalling pathways regulating ferroptosis. (D) Overview of ferroptosis modulation. This schematic illustrates that cystine import through the xCT system is essential for GSH synthesis and the proper function of GPX4. The activity of GPX4 prevents the accumulation of ROS. Ferroptosis is initiated through phospholipid peroxidation, which relies on ROS, PUFA-PL and transition metal iron as metabolic products. Intracellular and intercellular signalling events and environmental stimuli can all have a role in the progression of ferroptosis. 5-LOX, 5-lipoxygenase; ACSF2, acyl-coA synthetase Family family member 2; ACSL4, acyl-CoA synthetase long-chain family member 4; BH2, 7,8-dihydrobiopterin; BH4, tetrahydrobiopterin; CoQ10, coenzyme Q10; DFO, deferoxamine; DMT1, divalent metal transporter 1; DPP4, dipeptidyl peptidase 4; Fer-1, ferrostatin-1; FLT-3, fms-like tyrosine kinase 3; FSP1, ferroptosis suppressor protein-1; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; GCH1, GTP cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; HSPB1, heat shock protein beta 1; IREB2, iron responsive element binding protein 2; Lip-1, liproxstatin-1; NAPDH, nicotinamide adenine dinucleotide phosphate; NOX, nitrogen oxides; NRF2, nuclear factor erythroid 2-related factor 2; PKC, protein kinase C; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, Six-transmembrane epithelial antigen of the prostate 3; TFR1, transferrin receptor 1; VDAC2/3, voltage-dependent anion channel 2/3; xCT, cystine/glutamate antiporter.

intermediates and gradually accumulating in the cell membrane through the transport of LPCAT3. This causes a change in the cell membrane structure by altering the lipid composition, thereby inducing ferroptotic cell death. Furthermore, ROS accumulation within the cellular membrane requires the involvement of iron ions. The primary mechanism driving ferroptosis involves the catalytic activity of divalent iron or ester oxygenase, leading to heightened expression of unsaturated fatty acids on the cell membrane, ultimately causing lipid peroxidation and ensuing cellular demise.[44] Iron ions and ROS form cross-talk and mediate ferroptosis (figure 2C,D).

Dysregulation of the ferroptosis regulatory pathways

As research on ferroptosis has furthered, several regulatory pathways have been identified, including the cystine/glutamate antiporter (xCT)-glutathione (GSH)-glutathione peroxidase 4 (GPX4), NAD(P)H/ferroptosis

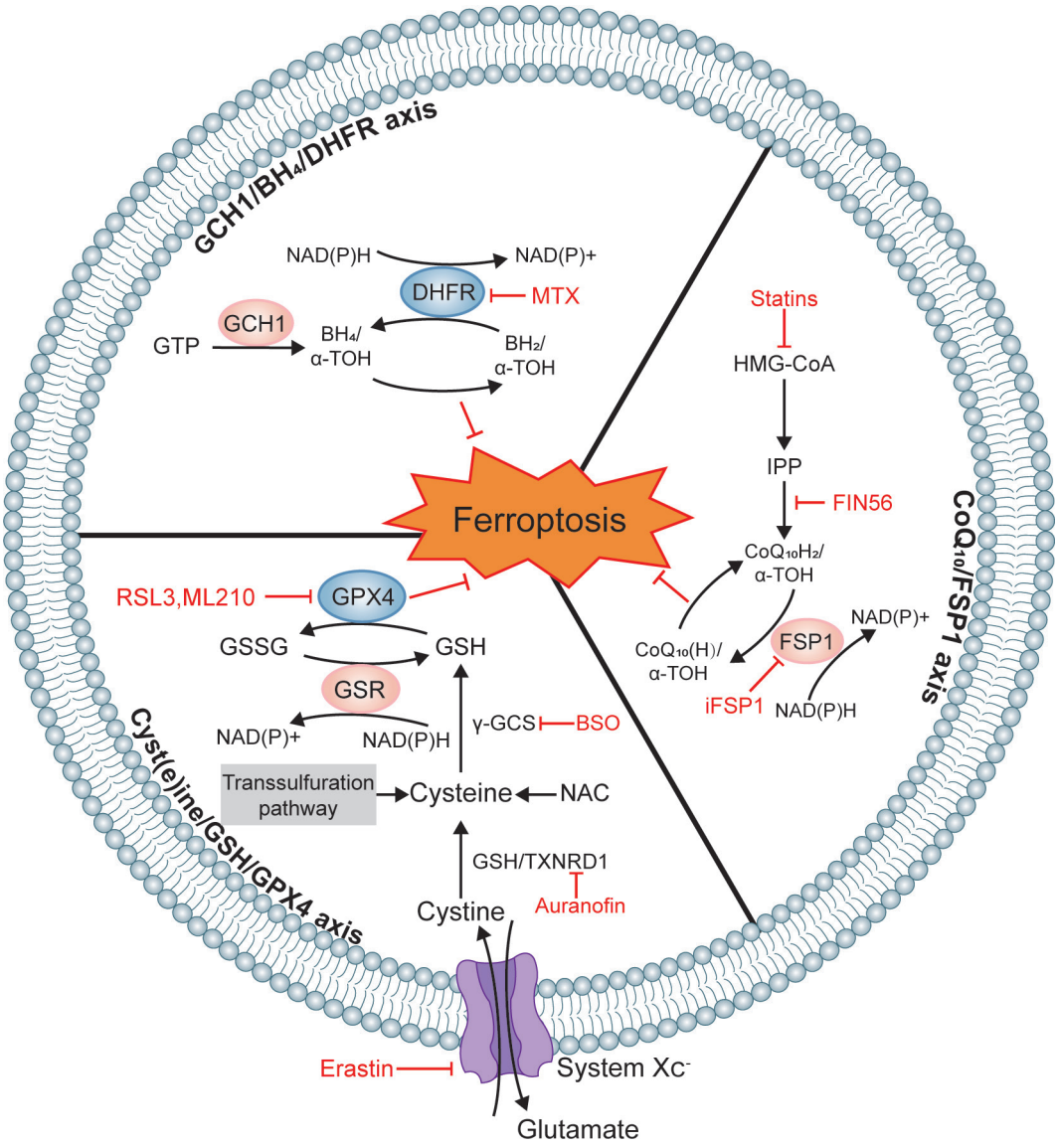

Figure 3 Ferroptosis regulation defence systems. This schematic chart illustrates the main control regulatory systems for ferroptosis, which include the xCT-GSH-GPX4, NAD(P)H/FSP1/CoQ10 and GCH1/BH4 pathways. The canonical axis for ferroptosis control involves the uptake of cystine via the cystine-glutamate antiporter, reducing cystine to cysteine through GSH. GSH is a crucial substrate of GPX4, thus preventing ferroptosis. The FSP1/CoQ10 system in ferroptosis has been identified in two independent genetic screens that fully protect against ferroptosis induced by pharmacological inhibition or genetic deletion of GPX4. Unlike GSH/GPX4, FSP1 prevents lipid peroxidation and associated ferroptosis via the reduction of ubiquinol/α-tocopherol on the level of lipid radicals. Researchers have recently identified a new pathway for regulating ferroptosis, which involves the GCH1/BH4/DHFR axis. BH4 is an effective free radical antioxidant that can be reduced by DHFR and inhibit lipid peroxidation. BH4 also has the potential to stimulate the production of CoQ10. BH4, tetrahydrobiopterin; CoQ10, coenzyme Q10; DHFR, dihydrofolate reductase; FSP1, ferroptosis suppressor protein 1; GCH1, GTP cyclohydrolase 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSR, glutathione-disulfide reductase; IPP, intracisternal a particle-promoted polypeptide; MTX, methotrexate; NAPDH, nicotinamide adenine dinucleotide phosphate; xCT, cystine/glutamate antiporter.

suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10), and guanosine triphosphate cyclohydrolase 1 (GCH1)/tetrahydrobiopterin (BH4) pathways. In the following sections, we discussed each of these three signalling pathways in detail (figure 3).

xCT-GSH-GPX4 regulatory pathway

The system xCT, a heterodimer transporter composed of solute carriers 7A11 and 3A2 proteins, was first discovered by Bannai *et al*.[45 46] This transporter is responsible for exchanging intracellular glutamate with extracellular cysteine across the cell membrane and is an essential substrate for GSH synthesis.[47] Inhibiting the xCT system consumes intracellular GSH, ultimately leading to cellular ferroptosis via ROS upregulation.[48] Notably, the xCT-GSH-GPX4 system is a crucial antioxidant system.

GPX4 is a selenocysteine-containing protein and peroxidase of GSH that catalyses the reduction of lipid peroxides, leading to the transition of GSH to glutathione

disulfide.[49 50] GPX4 has a critical role in inhibiting ferroptosis by reducing lipid peroxide toxicity and maintaining membrane lipid bilayer homeostasis. Therefore, targeting the GPX4 degradation pathway may be crucial for inhibiting ferroptosis in neurons and alleviating depressive symptoms.

NAD(P)H/FSP1/CoQ10 regulatory pathway

Bersuker *et al* found that FSP1 is a key component of the non-mitochondrial CoQ10 antioxidant system, which works in parallel with the canonical GSH-based GPX4 pathway to inhibit ferroptosis.[51] CoQ10 was first purified from bovine heart in 1956 and functions as an electron carrier in the electron transport chain. NAD(P)H serves as the electron source in this system, whereas FSP1 reduces the oxidised form of CoQ10, which acts as a lipophilic free radical-scavenging antioxidant in the plasma membrane.[51] Mechanistically, the ubiquinone outside the mitochondria is reduced from CoQ10 by FSP1, which can either directly capture lipid-free radicals or act as an antioxidant indirectly through the recovery of alpha-tocopherol; however, the detailed molecular mechanism of FSP1 action requires further investigation.

GCH1-BH4 regulatory pathway

GCH1 is another important regulator of ferroptosis and mediates the rate-limiting reactions in the BH4, a cofactor of aromatic amino acid hydroxylase and other enzymes, biosynthesis pathway. As shown in figure 3, BH4 is an antioxidant capable of trapping lipid peroxidation-free radicals. Importantly, GCH1 can selectively prevent the degradation of dihydroubiquione (CoQH2) and PL with two PUFA tails, and has a role in ferroptosis defence. Thus, the GCH1-BH4-PL axis may be a potential target for treating related diseases in clinical practice.

THE ROLE OF FERROPTOSIS IN THE PATHOLOGICAL MECHANISM OF DEPRESSION

Depressive symptoms are associated with hippocampal neuronal dysfunction and death.[52] Although previous studies have revealed that inhibition of ferroptosis has antidepressant functions, the regulatory mechanism of ferroptosis in MDD needs to be further understood. Since the target genes regulated by ferroptosis are involved in a variety of pathological processes, their roles in depression may also be multifaceted. Therefore, we summarised the potential mechanisms of ferroptosis and depression from the following aspects (figure 4).

The role of abnormal iron metabolism in depression

Iron in brain tissue mainly comes from serum iron transported through the cerebral microvasculature, and Fe^{3+} entering the brain tissue can be absorbed and used by neurons and glial cells.[53] Epidemiological and animal studies have indicated that many metal ions can cause emotional regulation disorders and insomnia.[54] For example, studies have shown that metal ions in serum increase the risk of depression and insomnia.[55] Iron in neurons and glial cells should be maintained at a certain level; excessive accumulation of iron leads to an increase in the LIP and ROS, which can cause neuronal damage.[56] The aetiology of depression is complex and determined by both genetic and environmental factors. A recent study demonstrated ferroptosis in the hippocampus of an MDD mouse model and indicated that the incidence of depression may be associated with ferroptosis-related pathways.[57] Free Fe^{2+} plays a significant role in catalysing the formation of oxygen free radicals in cells and initiating the chain reaction of lipid peroxidation by abstracting hydrogen from PUFA. The occurrence and development of depression are closely related to changes in the iron ion levels in the human body. Iron ions have a significant effect on the synthetic pathways of neurotransmitters, conduction of nervous impulses and functional regulation of receptors, which have crucial implications for memory, behaviour and cognitive function.[58]

The role of abnormal lipid metabolism in depression

Abnormal lipid metabolism has been extensively studied in patients with depression. Depressive symptoms were negatively correlated with high-density lipoprotein cholesterol levels.[59] Excessive lipid accumulation can increase ROS levels, which are crucial for neuronal growth under physiological conditions.[60] Previous studies have revealed that depression is accompanied by a reduction in antioxidant levels and an increase in ROS production.[61] Antidepressants have been found to protect neurons from OS damage by inhibiting the OS pathway and clearing ROS.[61] Clinical studies have shown that high lipid peroxidation increases the risk of treatment-resistant depression, whereas antidepressants, such as fluoxetine and citalopram, downregulate malondialdehyde (MDA) levels in patients with MDD[62] ; however, the potential regulatory mechanisms underlying the role of ROS in depression remains unclear. Next, we summarise the mechanisms regulating ROS in depression.

One previous study demonstrated that the downregulation of GSH levels and GPX4 expression may be potential mechanisms underlying the upregulation of MDA and ROS in depressed mice, further contributing to neuronal dysfunction and loss.[28] Mice exposed to chronic restraint stress showed iron ion accumulation and an imbalance in iron homeostasis. Autopsy findings in patients with MDD have shown that GSH levels and GPX4 expression in the anterior prefrontal cortex are significantly decreased.[28] These studies provide evidence for the presence of ferroptosis in depression and suggest that the modulation of ferroptosis may be a promising treatment. Edaravone upregulates the expression of Sirt1, NRF2, HO-1 and GPX4 in the hippocampus of depressed mice, and ameliorates depression-like behaviours.[28] Polydatin has been reported to alleviate chronic stress-induced depression-like behaviours by suppressing ROS levels and GPX expression.[63]

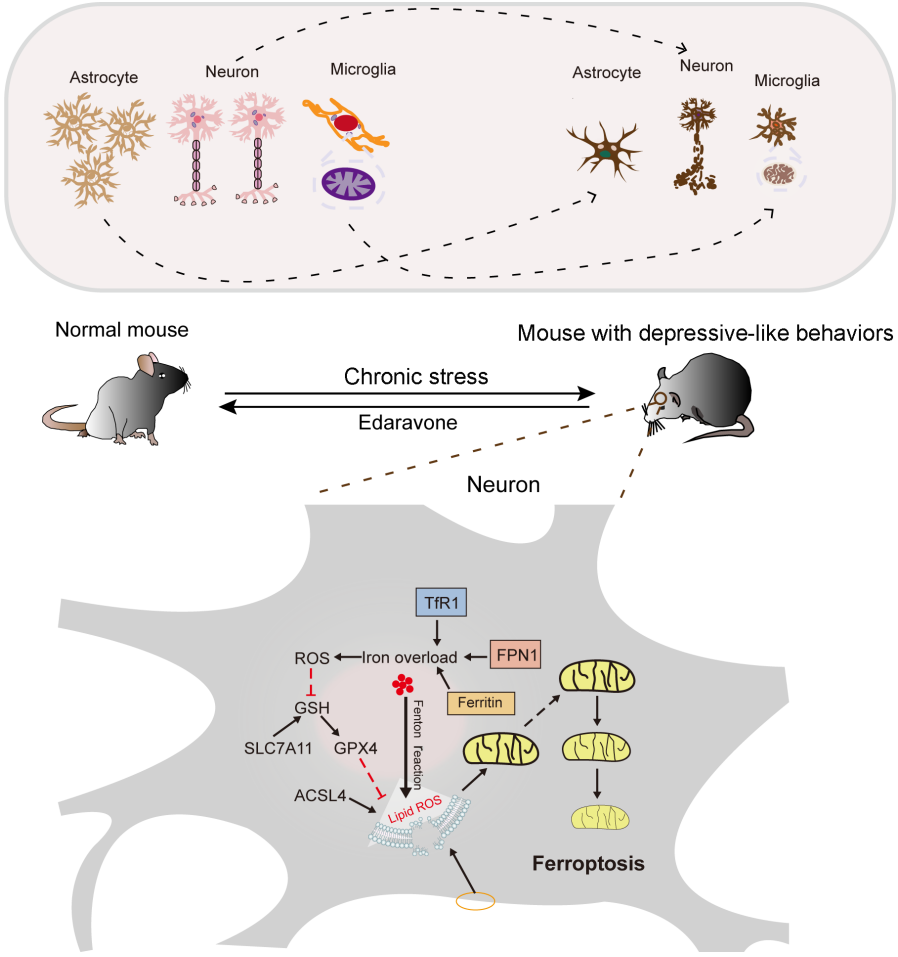

Figure 4 The potential role of ferroptosis in depression. The molecular mechanism of ferroptosis is involved in the progression of depression. Chronic stress can induce iron overload and the production of ROS in neurons. ACSL4, acyl-CoA synthetase long-chain family member 4; FPN1, ferroportin 1; GPX4, glutathione peroxidase 4; GSH, glutathione; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TFR1, transferrin receptor 1.

NRF2, an important antioxidant, expressed at low levels in the cortex and hippocampus, is a significant downstream target of Sirt1 and serves a crucial role in improving OS resistance. Previous studies have indicated that NRF2 knockout mice exhibited depression-like behaviour, and models of chronic unpredictable mild stress demonstrated decreased NRF2 expression in the rat hippocampus.[64 65] Accumulating evidence suggests a close link between the NRF2/HO-1 pathway and MDD, suggesting its crucial role in the treatment of depression.[66] Recent research has shown that polydatin inhibits chronic stress-induced depression-like behaviours by upregulating NRF2 expression.[63] The therapeutic effects of several antidepressants have been found to be strongly associated with NRF2.[67]

Another study showed significant changes in the expression of GPX4, FTH1, ACSL4 and total iron in the hippocampi of mice with depressive-like behaviours.[57] Xiaoyaosan and fluoxetine improve behavioural changes by regulating PE binding protein 1 (PEBP1)-GPX4-mediated ferroptosis.[57] Furthermore, PEBP1 increases the production of hydroperoxy-PE by forming a complex with 15 lipoxygenase (LO) 1 and 15LO2, which blocks GPX4 synthesis and leads to ferroptosis.[68] Additionally, reduced levels of zinc, CoQ10, vitamin C/E and GSH have been associated with low total antioxidant capacity in patients with MDD.[69]

TARGETING FERROPTOSIS TO TREAT DEPRESSION

Recently, several compounds that inhibit ferroptosis have been successfully approved for clinical use and have advanced to the late stages of clinical trials (online supplemental table 1). Currently, common inhibitors of ferroptosis target two key points in the ferroptosis pathway: iron overload and lipid peroxide accumulation. They primarily inhibit ferroptosis by reducing free Fe^{2+}, eliminating oxygen radicals and inhibiting lipid peroxidation. We further summarise the features of drugs that inhibit ferroptosis, either in clinical use or with strong translational potential, including iron chelators, radical-trapping antioxidants, natural compounds and other ferroptosis inhibitors (figure 5 and table 1).

Iron chelators

Iron chelators prevent the formation of highly reactive hydroxyl radicals by removing excess iron. To date, two

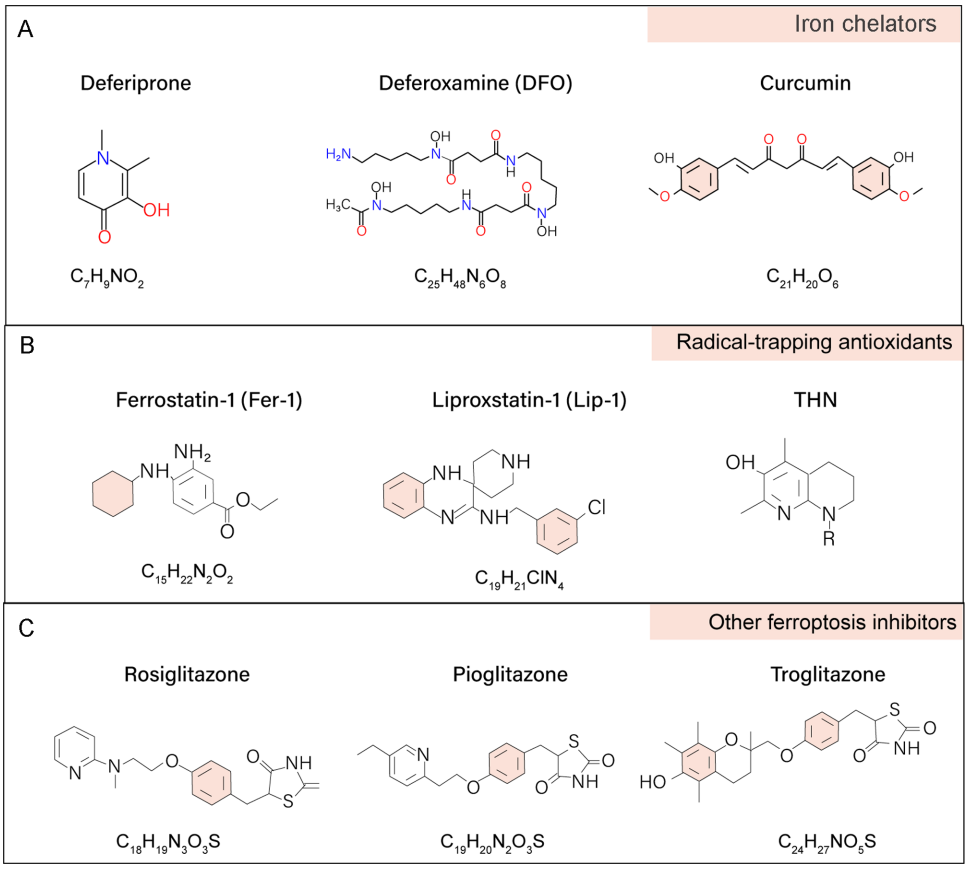

Figure 5 The structure of small molecule ferroptosis inhibitors. These inhibitors come in various forms, such as (A) iron chelators that hinder intracellular Fe^{2+}, (B) radical-trapping antioxidants that impede the role of reactive oxygen species (ROS) and (C) natural compounds that block the acyl-CoA synthetase long-chain family member 4 (ACSL4) protein. THN, tetrahydronaphthyridinols.

types of iron chelators have been reported. The first type, such as deferiprone, separates iron atoms from the cytoplasm, thereby blocking the process of ferroptosis. Preclinical studies have shown that iron chelation therapy can prevent ferroptosis in patients with intracerebral haemorrhage.[70] More recently, deferiprone has been used to prevent iron pathological processes in neurodegenerative diseases such as Parkinson's disease and Friedreich's

Table 1 Summary of ferroptosis inhibitors

Compound	CAS no.	Target	Mechanism	Ref. PMID
Deferiprone	30652-11-0	Iron	Reduces intracellular iron	22632970
Deferoxamine	138-14-7	Iron	Reduces intracellular iron	22632970
Curcumin	458-37-7	Iron; Keap1	Reduces iron accumulation and activates	30736288
			NRF2 signalling pathway	31034781
Ferrostatin-1	347174-05-4	Lipid ROS	Inhibits lipid peroxidation	31571665
Liproxstatin-1	950455-15-9	Lipid ROS	Inhibits lipid peroxidation	28386601
THN	18512-30-6	Lipid ROS	Reduces intracellular ROS	28386601
Rosiglitazone	122320-73-4	ACSL4	Suppresses the ACSL4 protein and reduces intracellular ROS	35038927
Pioglitazone	111025-46-8	ACSL4	Suppresses the ACSL4 protein and reduces intracellular ROS	35038927
Troglitazone	97322-87-7	ACSL4	Suppresses the ACSL4 protein and reduces intracellular ROS	27842070

ACSL4, acyl-CoA synthetase long chain family member 4; NRF2, nuclear factor erythroid 2-related factor 2; Ref, reference; ROS, reactive oxygen species; THN, tetrahydronaphthyridinols.

ataxia.[71] Deferoxamine is a natural product isolated from the soil bacterium *Streptomyces* and is the most widely used drug to inhibit lipid ROS-mediated ferroptosis; however, it is poorly absorbed and rapidly removed.[60] Therefore, improving the absorption and maintaining the metabolic stability of deferoxamine remain challenging. Additionally, curcumin acts as an iron chelator to reduce iron accumulation and prevent erastin-induced ferroptosis of pancreatic islet β-cells from islet cell tumours.[72]

Radical-trapping antioxidants

OS and antioxidant pathways are two important ways to regulate ROS levels, and lipophilic antioxidants (eg, liproxstatin (Lip)-1, ferrostatin (Fer)-1 and α-tocopherol) can inhibit ferroptosis when used appropriately.[73] Fer-1 is a specific inhibitor of ferroptosis discovered through high-throughput drug screening. It prevents elevated lipid ROS induced by erastin and RSL, but not by other oxidised compounds (eg, H_2O_2) or apoptotic inducers.[60] In addition, Fer-1 significantly upregulates the expression of GPX4 and NRF2 and reduces the accumulation of lipid ROS, thereby inhibiting ferroptosis.[74] Miotto *et al* found that Fer-1 could scavenge alkoxy radicals without being consumed and reduce intracellular unstable iron by binding to free Fe^{2+}.[75] Miotto *et al* proposed a cyclic mechanism in which Fer-1 catalyses the reduction of alkoxy radicals and Fe^{2+} increases the reduction of Fer-1 free radicals.

LIP-1 is a specific inhibitor of lipid ROS that can effectively inhibit ferroptosis without interfering with other classical types of cell death. Li *et al* found that LIP-1 can reduce ROS and alleviate radiation-induced pulmonary fibrosis by activating the NRF2 signalling pathway, providing a new therapeutic target for this disease.[76] Feng *et al* found that LIP-1 reduces mitochondrial ROS levels by downregulating VDAC1 expression and restoring GPX4 expression, thus exerting cardioprotective effects.[77]

α-Tocopherol performs its antioxidant capacity by destroying auto-oxidation chain reactions. The reaction rate of lipophilic tetrahydronaphthyridinols (THN) with peroxy radicals was almost 30 times that of α-tocopherol, and THN containing 12–15 carbon alkyl chains had the best inhibitory effect, even better than Fer-1 and Lip-1.[78]

Natural compounds inhibiting ferroptosis

Recently, several natural products have been shown to inhibit ferroptosis. Most of these products are polyphenols, which exert their effects through various mechanisms. Xie *et al* identified baicalein through natural compound screening and found that it inhibited erastin-induced ferroptosis in pancreatic cancer cells by inhibiting GSH depletion and GPX4 degradation.[79] Additionally, baicalein activated the NRF2 pathway and prevented erastin-induced NRF2 degradation. Gastrodin induces the expression of GPX4, FPN1 and ACSL4 through the NRF2-HO-1 signalling pathway and inhibits glutamate-induced ferroptosis in HT-22 cells.[80]

Other ferroptosis inhibitors

ACSL4 has a key role in the synthesis of long-chain PUFA-CoA by esterifying free fatty acids. Several studies have reported that rosiglitazone, pioglitazone and troglitazone can specifically inhibit ACSL4 but not other ACSL subtypes.[81] Although troglitazone has a low inhibitory effect on ACSL4, it may have inherent antioxidant activity because of its 6-chromogenoalkanol structure, which is the most protective thiazolidinedione.[82]

CONCLUSIONS

Recent literature suggests that OS and impaired antioxidant defence systems, induced by ROS production, have crucial roles in the pathogenesis of MDD. OS can induce or exacerbate a range of pathological processes, including ferroptosis. In this regard, we summarised the interaction network of iron ions and ROS, and several regulatory pathways (ie, xCT-GSH-GPX4, NAD(P)H/FSP1/CoQ10 and GCH1/BH4) involved in ferroptosis. Ferroptosis may be a key mechanism in the pathogenesis of depression; its inhibition could prevent damage to neurons and astrocytes and improve depressive symptoms. Currently, common inhibitors of ferroptosis mainly target two key aspects of the ferroptotic pathway: iron overload and lipid peroxide accumulation. Although various ferroptosis inhibitors have been discovered, the targets and potential applications of most of these compounds remain unknown. Therefore, it is necessary to further elucidate the mechanisms of these compounds and explore the possibility of drug combinations that will have a profound impact on their clinical applications in the future.

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REFERENCES

1 Brody DJ, Pratt LA, Hughes JP. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. *NCHS Data Brief* 2018:1–8.
2 Jung SJ, Shin A, Kang D. Menarche age, menopause age and other reproductive factors in association with post-menopausal onset depression: results from Health Examinees Study (HEXA). *J Affect Disord* 2015;187:127–35.
3 Guaiana G, Barbui C, Hotopf M. Amitriptyline for depression. *Cochrane Database Syst Rev* 2007:CD004186.
4 Baghai TC, Möller HJ, Rupprecht R. Recent progress in pharmacological and non-pharmacological treatment options of major depression. *Curr Pharm Des* 2006;12:503–15.
5 Levenberg K, Cordner ZA. Bipolar depression: a review of treatment options. *Gen Psychiatr* 2022;35:e100760.
6 Liu H, Wu X, Wang Y, *et al*. TNF-A, IL-6 and hsCRP in patients with melancholic, atypical and anxious depression: an antibody array analysis related to somatic symptoms. *Gen Psychiatr* 2022;35:e100844.
7 Wu J, Li J, Gaurav C, *et al*. CUMS and dexamethasone induce depression-like phenotypes in mice by differentially altering gut microbiota and triggering macroglia activation. *Gen Psychiatr* 2021;34:e100529.
8 Su YA, Si T. Progress and challenges in research of the mechanisms of anhedonia in major depressive disorder. *Gen Psychiatr* 2022;35:e100724.
9 Koo JW, Chaudhury D, Han M-H, *et al*. Role of mesolimbic brain-derived neurotrophic factor in depression. *Biol Psychiatry* 2019;86:738–48.
10 Lee B, Shin E, Song I, *et al*. Depression in adolescence and brain-derived neurotrophic factor. *Front Mol Neurosci* 2022;15:947192.
11 Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron* 2019;102:75–90.
12 Sakamoto S, Zhu X, Hasegawa Y, *et al*. Inflamed brain: targeting immune changes and inflammation for treatment of depression. *Psychiatry Clin Neurosci* 2021;75:304–11.
13 Tobe EH. Mitochondrial dysfunction, oxidative stress, and major depressive disorder. *Neuropsychiatr Dis Treat* 2013;9:567–73.
14 Won E, Na KS, Kim YK. Associations between melatonin, neuroinflammation, and brain alterations in depression. *Int J Mol Sci* 2021;23:305.
15 Li W, Ali T, He K, *et al*. Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. *Brain Behav Immun* 2021;92:10–24.
16 Morava E, Gardeitchik T, Kozicz T, *et al*. Depressive behaviour in children diagnosed with a mitochondrial disorder. *Mitochondrion* 2010;10:528–33.
17 Felger JC. Role of inflammation in depression and treatment implications. *Handb Exp Pharmacol* 2019;250:255–86.
18 Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. *Neuron* 2020;107:234–56.
19 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 2009;65:732–41.
20 Ding Q, Tian Y, Wang X, *et al*. Oxidative damage of tryptophan hydroxylase-2 mediated by peroxisomal superoxide anion radical in brains of mouse with depression. *J Am Chem Soc* 2020;142:20735–43.
21 Bannai S, Kitamura E. Transport interaction of L-cystine and L-glutamate in human diploid fibroblasts in culture. *J Biol Chem* 1980;255:2372–6.
22 Dolma S, Lessnick SL, Hahn WC, *et al*. Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells. *Cancer Cell* 2003;3:285–96.
23 Yang WS, Stockwell BR. Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells. *Chem Biol* 2008;15:234–45.
24 Dixon SJ. Ferroptosis: bug or feature. *Immunol Rev* 2017;277:150–7.
25 Jiang X, Stockwell BR, Conrad M. Ferroptosis: mechanisms, biology and role in disease. *Nat Rev Mol Cell Biol* 2021;22:266–82.
26 Cao H, Zuo C, Huang Y, *et al*. Hippocampal proteomic analysis reveals activation of necroptosis and ferroptosis in a mouse model of chronic unpredictable mild stress-induced depression. *Behav Brain Res* 2021;407:113261.
27 Seo Y-J, Lee K-T, Rho J-R, *et al*. Phorbaketal A, isolated from the marine sponge phorbas sp., exerts its anti-inflammatory effects via NF-KB inhibition and heme oxygenase-1 activation in lipopolysaccharide-stimulated macrophages. *Mar Drugs* 2015;13:7005–19.
28 Dang R, Wang M, Li X, *et al*. Edaravone ameliorates depressive and anxiety-like behaviors via Sirt1/Nrf2/HO-1/Gpx4 pathway. *J Neuroinflammation* 2022;19:41.
29 Song X, Long D. Nrf2 and ferroptosis: a new research direction for neurodegenerative diseases. *Front Neurosci* 2020;14:267.
30 Wu S, Gao Q, Zhao P, *et al*. Sulforaphane produces antidepressant- and anxiolytic-like effects in adult mice. *Behav Brain Res* 2016;301:55–62.
31 Zuo C, Cao H, Song Y, *et al*. Nrf2: an all-rounder in depression. *Redox Biol* 2022;58:102522.
32 Ward RJ, Zucca FA, Duyn JH, *et al*. The role of iron in brain ageing and neurodegenerative disorders. *Lancet Neurol* 2014;13:1045–60.
33 Poprac P, Jomova K, Simunkova M, *et al*. Targeting free radicals in oxidative stress-related human diseases. *Trends Pharmacol Sci* 2017;38:592–607.
34 Bradley R, Lakpa KL, Burd M, *et al*. Fetal alcohol spectrum disorder and iron homeostasis. *Nutrients* 2022;14:4223.
35 Louandre C, Ezzoukhry Z, Godin C, *et al*. Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib. *Int J Cancer* 2013;133:1732–42.
36 Wood MJ, Skoien R, Powell LW. The global burden of iron overload. *Hepatol Int* 2009;3:434–44.
37 Rouault TA. The role of iron regulatory proteins in mammalian iron homeostasis and disease. *Nat Chem Biol* 2006;2:406–14.
38 Jing X, Du T, Li T, *et al*. The detrimental effect of iron on OA chondrocytes: importance of pro-inflammatory cytokines induced iron influx and oxidative stress. *J Cell Mol Med* 2021;25:5671–80.
39 Daar S, Pathare A, Nick H, *et al*. Reduction in labile plasma iron during treatment with deferasirox, a once-daily oral iron chelator, in heavily iron-overloaded patients with beta-thalassaemia. *Eur J Haematol* 2009;82:454–7.
40 Wang K, Chen X-Z, Wang Y-H, *et al*. Emerging roles of ferroptosis in cardiovascular diseases. *Cell Death Discov* 2022;8:394.
41 Sánchez A, Calpena AC, Clares B. Evaluating the oxidative stress in inflammation: role of melatonin. *Int J Mol Sci* 2015;16:16981–7004.
42 Wang G, Wang J, Luo J, *et al*. Peg2000-DPSE-coated quercetin nanoparticles remarkably enhanced anticancer effects through induced programed cell death on C6 glioma cells. *J Biomed Mater Res A* 2013;101:3076–85.
43 Vu NT, Kim M, Stephenson DJ, *et al*. Ceramide kinase inhibition drives ferroptosis and sensitivity to cisplatin in mutant KRAS lung cancer by dysregulating VDAC-mediated mitochondria function. *Mol Cancer Res* 2022;20:1429–42.
44 Liu H, Li L. Ferroptosis in macrophage impairment in sepsis. *Appl Bionics Biomech* 2022;2022:5792866.
45 Tu H, Tang L-J, Luo X-J, *et al*. Insights into the novel function of system Xc- in regulated cell death. *Eur Rev Med Pharmacol Sci* 2021;25:1650–62.
46 Chen X, Kang R, Kroemer G, *et al*. Broadening horizons: the role of ferroptosis in cancer. *Nat Rev Clin Oncol* 2021;18:280–96.
47 Sahin M, Saxena A, Joost P, *et al*. Induction of Bcl-2 by functional regulation of G-protein coupled receptors protects from oxidative glutamate toxicity by increasing glutathione. *Free Radic Res* 2006;40:1113–23.
48 Hara KY, Kim S, Yoshida H, *et al*. Development of a glutathione production process from proteinaceous biomass resources using protease-displaying saccharomyces cerevisiae. *Appl Microbiol Biotechnol* 2012;93:1495–502.
49 Zhang Y, Swanda RV, Nie L, *et al*. mTORC1 couples cyst(e)ine availability with GPX4 protein synthesis and ferroptosis regulation. *Nat Commun* 2021;12:1589.
50 Ursini F, Maiorino M. Lipid peroxidation and ferroptosis: the role of GSH and GPX4. *Free Radic Biol Med* 2020;152:175–85.
51 Bersuker K, Hendricks JM, Li Z, *et al*. The CoQ oxidoreductase Fsp1 acts parallel to GPX4 to inhibit ferroptosis. *Nature* 2019;575:688–92.
52 Lee AL, Ogle WO, Sapolsky RM. Stress and depression: possible links to neuron death in the hippocampus. *Bipolar Disord* 2002;4:117–28.
53 Mills E, Dong X-P, Wang F, *et al*. Mechanisms of brain iron transport: insight into neurodegeneration and CNS disorders. *Future Med Chem* 2010;2:51–64.
54 Kim J, Wessling-Resnick M. Iron and mechanisms of emotional behavior. *J Nutr Biochem* 2014;25:1101–7.
55 Li Y, Wu F, Mu Q, *et al*. Metal ions in cerebrospinal fluid: associations with anxiety, depression, and insomnia among cigarette smokers. *CNS Neurosci Ther* 2022;28:2141–7.

56 Sabens Liedhegner EA, Gao XH, Mieyal JJ. Mechanisms of altered redox regulation in neurodegenerative diseases--focus on S--glutathionylation. *Antioxid Redox Signal* 2012;16:543–66.
57 Jiao H, Yang H, Yan Z, *et al*. Traditional Chinese formula xiaoyaosan alleviates depressive-like behavior in CUMS mice by regulating PEBP1-GPX4-mediated ferroptosis in the hippocampus. *Neuropsychiatr Dis Treat* 2021;17:1001–19.
58 Lien Y-C, Condon DE, Georgieff MK, *et al*. Dysregulation of neuronal genes by fetal-neonatal iron deficiency anemia is associated with altered DNA methylation in the rat hippocampus. *Nutrients* 2019;11:1191.
59 Chen CC, Lu FH, Wu JS, *et al*. Correlation between serum lipid concentrations and psychological distress. *Psychiatry Res* 2001;102:153–62.
60 Dixon SJ, Lemberg KM, Lamprecht MR, *et al*. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* 2012;149:1060–72.
61 Kagan VE, Mao G, Qu F, *et al*. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. *Nat Chem Biol* 2017;13:81–90.
62 Sowa-Kućma M, Styczeń K, Siwek M, *et al*. Lipid peroxidation and immune biomarkers are associated with major depression and its phenotypes, including treatment-resistant depression and melancholia. *Neurotoxicity Research* 2018;33:448–60.
63 Wang J, Men Y, Wang Z. Polydatin alleviates chronic stress-induced depressive and anxiety-like behaviors in a mouse model. *ACS Chem Neurosci* 2023;14:977–87.
64 Martín-de-Saavedra MD, Budni J, Cunha MP, *et al*. Nrf2 participates in depressive disorders through an anti-inflammatory mechanism. *Psychoneuroendocrinology* 2013;38:2010–22.
65 Liao D, Lv C, Cao L, *et al*. Curcumin attenuates chronic unpredictable mild stress-induced depressive-like behaviors via restoring changes in oxidative stress and the activation of Nrf2 signaling pathway in rats. *Oxid Med Cell Longev* 2020;2020:9268083.
66 Bian H, Wang G, Huang J, *et al*. Dihydrolipoic acid protects against lipopolysaccharide-induced behavioral deficits and neuroinflammation via regulation of Nrf2/HO-1/Nlrp3 signaling in rat. *J Neuroinflammation* 2020;17:166.
67 Ghosh S, Choudhury S, Chowdhury O, *et al*. Inflammation-induced behavioral changes is driven by alterations in Nrf2-dependent apoptosis and autophagy in mouse hippocampus: role of fluoxetine. *Cell Signal* 2020;68:109521.
68 Wenzel SE, Tyurina YY, Zhao J, *et al*. PEBP1 wardens ferroptosis by enabling lipoxygenase generation of lipid death signals. *Cell* 2017;171:628–41.
69 Yager S, Forlenza MJ, Miller GE. Depression and oxidative damage to lipids. *Psychoneuroendocrinology* 2010;35:1356–62.
70 Wan J, Ren H, Wang J. Iron toxicity, lipid peroxidation and ferroptosis after intracerebral haemorrhage. *Stroke Vasc Neurol* 2019;4:93–5.
71 Pandolfo M, Arpa J, Delatycki MB, *et al*. Deferiprone in friedreich ataxia: a 6-month randomized controlled trial. *Ann Neurol* 2014;76:509–21.
72 Kose T, Vera-Aviles M, Sharp PA, *et al*. Curcumin and (-)-epigallocatechin-3-gallate protect murine MIN6 pancreatic beta-cells against iron toxicity and erastin-induced ferroptosis. *Pharmaceuticals (Basel)* 2019;12:26.
73 Kajarabille N, Latunde-Dada GO. Programmed cell-death by ferroptosis: antioxidants as mitigators. *Int J Mol Sci* 2019;20:4968.
74 Chu J, Liu C-X, Song R, *et al*. Ferrostatin-1 protects HT-22 cells from oxidative toxicity. *Neural Regen Res* 2020;15:528–36.
75 Miotto G, Rossetto M, Di Paolo ML, *et al*. Insight into the mechanism of ferroptosis inhibition by ferrostatin-1. *Redox Biol* 2020;28:101328.
76 Li X, Duan L, Yuan S, *et al*. Ferroptosis inhibitor alleviates radiation-induced lung fibrosis (RILF) via down-regulation of TGF-B1. *J Inflamm* 2019;16:11.
77 Feng Y, Madungwe NB, Imam Aliagan AD, *et al*. Liproxstatin-1 protects the mouse myocardium against ischemia/reperfusion injury by decreasing VDAC1 levels and restoring GPX4 levels. *Biochem Biophys Res Commun* 2019;520:606–11.
78 Zilka O, Shah R, Li B, *et al*. On the mechanism of cytoprotection by ferrostatin-1 and liproxstatin-1 and the role of lipid peroxidation in ferroptotic cell death. *ACS Cent Sci* 2017;3:232–43.
79 Xie Y, Song X, Sun X, *et al*. Identification of baicalein as a ferroptosis inhibitor by natural product library screening. *Biochem Biophys Res Commun* 2016;473:775–80.
80 Jiang T, Cheng H, Su J, *et al*. Gastrodin protects against glutamate-induced Ferroptosis in HT-22 cells through Nrf2/HO-1 signaling pathway. *Toxicology in Vitro* 2020;62:S0887-2333(19)30658-7:104715.:.
81 Kim JH, Lewin TM, Coleman RA. Expression and characterization of recombinant rat Acyl-Coa Synthetases 1, 4, and 5. selective inhibition by Triacsin C and Thiazolidinediones. *The Journal of Biological Chemistry* 2001;276:24667–73.
82 Doll S, Proneth B, Tyurina YY, *et al*. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. *Nat Chem Biol* 2017;13:91–8.

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