Ferroptosis: A New Therapeutic Target for Depression Postprint

Authors: Du Shuqin, Qian Lifeng, Xiong Lie, Shi Hanqiang, Shi Yanbo, Shi Yanbo

Date: 2023-06-09T00:00:00+00:00

Abstract

Depression is a common affective mental disorder and constitutes the second largest health burden worldwide; however, its pathogenic mechanisms remain to be fully elucidated. Clinical treatment of depression predominantly relies on conventional pharmacotherapy, yet the suboptimal efficacy, pronounced therapeutic lag, and poorly tolerated adverse effects of current medications underscore the substantial clinical demand for effective and rapidly acting antidepressant agents. Ferroptosis, a recently identified modality of cell death, has been implicated in the pathological progression of various neurological disorders, including depression. Currently, some studies have shifted their focus to targeted inhibition of ferroptosis as an antidepressant therapeutic strategy, demonstrating promising efficacy. This article, based on the mechanistic interplay between depression and ferroptosis and integrating both clinical and preclinical research, summarizes the involvement of ferroptosis in depression pathogenesis and its therapeutic potential for the treatment of depression.

Full Text

Ferroptosis: A New Target for the Treatment of Depressive Disorder

DU Shuqin[1,2,3], QIAN Lifeng[4,5], XIONG Lie[1,2], SHI Hanqiang[1,2], SHI Yanbo[1,2*]

[1]Central Laboratory of Molecular Medicine Research Center, Zhejiang Chinese Medical University Affiliated Jiaxing TCM Hospital, Jiaxing 314001, China
[2]Jiaxing Key Laboratory of Diabetic Angiopathy Research, Jiaxing 314001, China
[3]School of Pharmacy, Zhejiang University of Technology, Hangzhou 310002, China

[4]Department of Rehabilitation, Zhejiang Chinese Medical University Affiliated Jiaxing TCM Hospital, Jiaxing 314001, China
[5]Jiaxing Key Laboratory of Cerebrovascular Disease Rehabilitation Research of Integrated Chinese and Western Medicine, Jiaxing 314001, China

Corresponding author: SHI Yanbo, Professor; E-mail: shiyanbocas@163.com

Abstract

Depressive disorder is a common affective mental disorder that currently represents the second largest health burden worldwide, yet its pathogenesis remains to be fully elucidated. Clinical treatment of depression primarily relies on Western medications; however, the unsatisfactory efficacy, significant therapeutic lag, and intolerable adverse effects of current drugs underscore the urgent clinical need for more effective and rapid-onset antidepressants. Ferroptosis, a novel form of cell death discovered in recent years, has been implicated in the pathogenesis of various neurological diseases, including depressive disorder. Some studies have begun exploring targeted inhibition of ferroptosis as an antidepressant strategy, yielding promising results. This review synthesizes clinical and preclinical evidence to examine the involvement of ferroptosis in depression pathogenesis and its therapeutic potential for depression treatment.

Keywords: Depressive Disorder; Ferroptosis; Iron overload; Mitochondria; Lipid peroxidation; Review

Funding: Zhejiang Provincial Traditional Chinese Medicine Health Science and Technology Plan Project (2021ZB283); Zhejiang Provincial Health Science and Technology Plan Project (2020PY029, 2023KY1227); Jiaxing Science and Technology Bureau Livelihood Science and Technology Innovation Special Project (2020AY30003); Key Project of Scientific Research Special Fund of Zhejiang Chinese Medical University Affiliated Hospital (2022FSYYZZ22)

1 Iron Deposition in the Central Nervous System (CNS) in Depression

Depression is a severe mental disorder that profoundly impairs psychosocial function and quality of life, characterized by persistent low mood, anhedonia, cognitive impairment, sleep disturbances, appetite loss, and suicidal ideation [1]. Reports indicate that nearly one in four women and one in six men will experience depression, with up to 65% of patients experiencing recurrent episodes [2]. The World Health Organization predicts that depression will become the leading cause of disability worldwide by 2030 [3]. Although the pathogenesis of depression remains incompletely understood, extensive clinical and preclinical studies have identified multiple factors that may contribute to its development (Table 1).

Iron is an essential trace metal element in organisms and the most abundant transition metal in the brain [4]. As a crucial cofactor, brain iron ions participate in various physiological processes including myelination, neurotransmitter synthesis, synaptic development, and energy production [5], playing a vital role in neural growth and conduction. Conversely, high iron levels lead to accumulation of toxic reactive oxygen species (ROS), interfering with mitochondrial function, disrupting DNA synthesis, and catalyzing dopamine (DA) oxidation to produce toxic quinone compounds [6], ultimately causing cell death and neurological disease. Ferroptosis, first described by Stockwell' s group in 2012, represents a novel cell death modality distinct from traditional programmed cell death, characterized by unique morphological, biochemical, and genetic features including mitochondrial morphological changes, iron deposition, and lipid ROS accumulation [7].

Recent studies have confirmed that ferroptosis is intimately linked to various neurological disorders including Alzheimer' s disease [8], Parkinson' s disease [9], and Huntington' s disease [10]. In both depressed patients and animal models, significant alterations in iron content and ferroptosis-related genes have been observed [11], suggesting that abnormal iron metabolism in the brain may represent a potential pathophysiological factor in depression. This review examines the intrinsic connections between depression and ferroptosis to provide valuable insights for depression prevention and treatment.

Trivalent iron ions (Fe^{3+}) entering the CNS first bind to transferrin (Tf) secreted in the choroid plexus and cerebrospinal fluid (CSF) [24], then cross the blood-brain barrier (BBB) via transferrin receptor 1 (TfR1) highly expressed on endothelial cells to enter brain parenchyma, where they are taken up by neurons [25]. Within cells, iron ions are converted to ferrous iron (Fe^{2+}) by metalloenzymes and released into the cytoplasm to participate in various physiological processes, while excess Fe^{2+} is stored as stable Fe^{3+} or exported via ferroportin (FPN) (Figure 1 [Figure 1: see original paper]). High Tf and TfR1 expression in the brain enhances neuronal iron uptake and increases susceptibility to ferroptosis [26].

As early as 1995, researchers found elevated plasma TfR1 expression in patients with psychiatric disorders, particularly schizophrenia and major depressive disorder (MDD), compared to healthy controls [27], suggesting that these patients may have increased iron uptake and deposition. Brain imaging studies in depressed patients have revealed iron deposition in the putamen and thalamic nuclei, with further research demonstrating that this brain iron deposition correlates with depression severity [28]. These findings align with Yao et al. [29], who proposed that brain iron deposition may be associated with depression and could serve as a biomarker for its pathophysiological mechanisms. Chang et al. [30] used two-dimensional electrophoresis (2-DE) combined with mass spectrometry to compare Tf and TfR1 levels between normal mice and chronic unpredictable mild stress (CUMS) mice, revealing significant upregulation of Tf and TfR1 expression in the liver, blood, and multiple brain regions of CUMS

mice. Another animal study confirmed elevated TfR1 expression in neurons of a depression mouse model and demonstrated that excess iron could exacerbate neuronal death [25]. Maaroufi et al. [31] found that rats treated with iron (3 mg/kg) exhibited impaired learning, motor skills, and emotional behaviors, which the authors attributed to significant iron deposition in the hippocampus and basal ganglia. These studies collectively demonstrate iron deposition in depressed patients and animal models, linking excess iron accumulation to depressive-like behaviors and suggesting that targeting iron deposition may represent a novel antidepressant strategy.

2 Ferroptosis in the CNS in Depression

Iron is indispensable for neuronal survival, influencing myelination, metabolism, and monoamine neurotransmitter synthesis by assisting in the production of tyrosine hydroxylase and tryptophan hydroxylase [32-33]. When iron deposition occurs in neurons, iron ions directly inhibit DA and 5-hydroxytryptamine (5-HT) synthesis by affecting the activity of these enzymes [34]. Although organisms possess physiological defense mechanisms against iron toxicity, iron can transfer electrons and generate harmful hydroxyl radicals through Fenton reactions, leading to DNA oxidation, lipid damage, and accelerated DA catabolism [11]. During this process, free iron catalyzes the production of peroxides from polyunsaturated fatty acids (PUFA) while promoting the release of inflammatory factors associated with arachidonic acid metabolism [35], triggering immune-inflammatory responses. These risk factors interact synergistically to impair brain motor and cognitive functions.

Glutathione peroxidase 4 (GPX4) is a crucial lipid membrane repair enzyme that reduces lipid hydroperoxides (PL-OOH) to non-toxic lipid alcohols (PL-OH) and water using two glutathione molecules as electron donors, thereby protecting cell membranes from free radical damage (Figure 1 [Figure 1: see original paper]). As a key regulator of ferroptosis, GPX4 deficiency increases susceptibility to oxidative stress-induced neuronal death [36]. Iron deposition has also been observed in patients with post-stroke depression [37] and multiple sclerosis-related depression [38]. Patients with more severe depressive symptoms exhibit lower serum ferritin (FTH) levels, while elevated serum FTH levels positively correlate with reduced depression rates. In rodent studies examining depression and iron, Cao et al. [39] used quantitative proteomics to compare hippocampal protein expression between CUMS mice and control mice. Among 4,046 quantified proteins, 47 were differentially expressed, with enrichment analysis indicating significant activation of neuronal necrosis and ferroptosis in CUMS mice, suggesting that inhibiting neuronal necrosis and ferroptosis may provide potential therapeutic targets for depression. Notably, some researchers found that moderate iron supplementation (12 mg/kg) significantly increased brain-derived neurotrophic factor (BDNF) expression and reduced immobility time in CUMS rats, while high-dose iron increased neuronal degeneration and loss —effects reversible by the iron chelator deferiprone [40]. Conversely, Uzungil

et al. [41] reported that deferiprone alleviated depressive-like behavior in serotonin transporter (5-HTT) knockout mice without significantly affecting brain iron levels. These studies confirm that targeting ferroptosis-related mechanisms can effectively alleviate depression, with recent research showing that another iron chelator, deferoxamine (DFO), significantly mitigates CUMS-induced damage [42], further underscoring the importance of ferroptosis-related mechanisms in depression treatment.

3 Depression and Mitochondrial Dysfunction in the CNS

Mitochondria are highly dynamic organelles that can alter their function and structure in response to environmental changes. Iron plays important roles in mitochondria, including heme biosynthesis, iron-sulfur cluster (ISC) assembly, and oxidative phosphorylation (OXPHOS) [43]. Mitochondrial iron deposition can contribute to depression by affecting mitochondrial function and structure. Under physiological conditions, mitochondrial iron homeostasis is tightly controlled by mitochondrial ferritin (FtMt), a nuclear-encoded mitochondrial iron storage protein that oxidizes Fe^{2+} to less redox-active Fe^{3+} [44], preventing free iron deposition. When iron deposition occurs in mitochondria, iron promotes mitochondrial ROS accumulation through Fenton reactions. Additionally, as a major regulator of OXPHOS, iron makes mitochondria the primary source of intracellular ROS due to physiological electron leakage during OXPHOS [43]. Multiple factors can cause mitochondrial ROS surge, damaging mitochondrial structure and ATP production capacity (Figure 1). Neurotransmitter synthesis and release, neuronal differentiation, and downstream pathway activation all require sufficient energy from mitochondria. Dysfunctional mitochondria may not only cause neurotransmission deficits but also impair neuroplasticity in depressed patients. Mitochondria also play critical roles in neurogenesis, neural stem cell proliferation, and differentiation into new neurons [45-46]. Furthermore, mitochondrial components (N-formyl peptides, cardiolipin, etc.) can promote inflammatory responses [47].

A meta-analysis evaluating eight oxidative stress markers in bipolar disorder (BD) patients reported increased lipid peroxidation, DNA/RNA damage, reduced mitochondrial electron transport chain protein levels, and elevated carbon monoxide (CO) markers [48]. Iwamoto et al. [49] performed DNA microarray analysis on postmortem brain samples from BD and MDD patients, revealing downregulation of multiple mitochondria-related genes in model groups compared to controls. Cataldo et al. [50] observed significantly shrunken mitochondria with reduced ATP production capacity in neurons of the prefrontal cortex from BD patients. In another study examining psychiatric comorbidities in subjects with mitochondrial cytopathies, 54% exhibited depressive symptoms and 17% showed BD [51]. Preclinical studies also confirmed mitochondrial impairment in rodent depression models. Yuan et al. [52] found significantly fewer mitochondria in prefrontal cortical and liver cells of CUMS rats, with swollen mitochondria showing disorganized or dissolved cristae, loose matrix, and vacuolar

degeneration. After antidepressant treatment, mitochondrial numbers increased markedly and morphological improvements were observed. Rezin et al. [53] observed inhibition of the mitochondrial respiratory chain in the cerebral cortex and cerebellum of rats exposed to chronic mild stress.

4 Antidepressant Drugs that Exert Effects by Inhibiting Ferroptosis

The antidepressant effects of certain drugs through ferroptosis inhibition further confirm the relationship between depression and ferroptosis. The mechanism of fluoxetine extends beyond 5-HT reuptake inhibition to include reducing iron deposition, regulating ferroptosis-related genes [3], promoting autophagosome formation, and enhancing clearance of damaged mitochondria [54]. The free radical scavenger edaravone ameliorates depressive- and anxiety-like behaviors in chronic social defeat stress mice by increasing expression of silent information regulator 1 (SIRT1), nuclear factor E2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1), and GPX4 [55]. Sodium hydrosulfide (NaHS) alleviates anxiety- and depressive-like behaviors in type 1 diabetes mellitus (T1DM) mice by reducing iron deposition and oxidative stress while increasing GPX4 and SLC7A11 expression [56]. Network pharmacology analysis revealed that 133 components of the traditional Chinese medicine formula Xiaoyaosan could regulate 43 ferroptosis-related genes in depression, with animal experiments confirming that Xiaoyaosan' s antidepressant effects may involve ferroptosis inhibition [3]. Ketamine [57] exhibits similar effects. The Chinese herbal monomers baicalin [58] and ginsenoside Rg1 [59] alleviate depression by improving mitochondrial dysfunction. Coenzyme Q10 (CoQ10), an essential cofactor in mitochondrial electron transport, enhances respiratory chain complex function, promotes mitochondrial bioenergetics, and exerts neuroprotective effects [60]. Recent studies suggest CoQ10 participates in ferroptosis regulation through the FSP1-CoQ10 pathway, with exogenous CoQ10 supplementation protecting membrane lipids from peroxidation and increasing cellular resistance to ferroptosis [61]. In neurological diseases, BD patients treated with CoQ10 showed decreased depression severity [62]. Recent research demonstrates that the mitochondria-targeted antioxidant Mito-TEMPO can rescue andrographolide-induced ferroptosis [63] and significantly improve lipopolysaccharide (LPS)-induced mitochondrial superoxide accumulation, increased mitochondrial membrane potential, and reduced ATP production, thereby alleviating depressive states in mice [21]. In summary, excessive iron deposition leads to reduced neurotransmitter synthesis, lipid peroxide accumulation, mitochondrial dysfunction, increased pro-inflammatory factor release, and damage to DNA and proteins with compromised antioxidant systems—collectively causing decreased neuroplasticity, delayed synaptic growth and development, impaired neural network conduction, and neurotoxicity that triggers depression.

5 Discussion and Outlook

Depression is a common, highly lethal, disabling, and recurrent mental disorder that poses a global mental health challenge. Despite advances in antidepressant research, treatment options remain limited and inadequate for many patients [64]. In addition to numerous side effects and long treatment courses, traditional antidepressants are ineffective in one-third of patients [1], and recovery may require multiple medications, suggesting that depression mechanisms may involve other targets and contributing factors that complicate treatment strategies. Over the past decade, many new targeted interventions have been developed and tested in clinical trials. This review focuses on research linking iron homeostasis imbalance and ferroptosis to depression, evaluating their potential value in depression diagnosis and treatment to stimulate further research in this field.

Due to its unique redox properties, iron serves as a cofactor for enzymes and structural proteins in numerous enzymatic reactions [65], playing important roles in multiple cellular biological processes. As a double-edged sword, both iron deficiency and excess can cause pathological damage. In depression, iron is essential for myelin production and maintenance, neuroplasticity, and synaptic development, and serves as a necessary cofactor for aromatic acid hydroxylases (key enzymes for DA, noradrenaline (NE), and 5-HT synthesis) [24]. Iron deficiency can thus cause delayed neural network conduction and neurotransmitter depletion, triggering depression, with literature reporting the promoting effect of iron deficiency in depression [66]. Conversely, excess iron can affect normal neural transmission, promote lipid peroxide generation, and disrupt redox systems while impairing mitochondrial function, driving depression progression. This review primarily focuses on the effects of excess iron in depression.

Ferroptosis, defined as iron-dependent accumulation of lipid peroxides, is a newly identified cell death modality. Extensive research has revealed its involvement in the pathophysiology of various neurological diseases. In depressed patients and animal models, iron deposition and altered ferroptosis-related genes have been observed [27,30]. These findings have spurred recent therapeutic research targeting iron metabolism disturbances in depression. Iron chelators such as deferiprone [41] and DFO [42] can improve behavioral and cognitive impairments in ferroptosis-induced depression models. The antidepressant efficacy of some drugs has also been linked to ferroptosis modulation, including the free radical scavenger edaravone [55], ketamine [57], fluoxetine, and the traditional Chinese medicine Xiaoyaosan [3]. Although current research on ferroptosis and antidepressant effects remains limited and primarily focused on animal studies, the promising results provide a foundation and confidence for future targeted therapies.

This review summarizes and discusses the potential involvement of ferroptosis in depression pathogenesis, demonstrating that iron deposition may participate in depression progression and that iron metabolism pathways represent poten-

tial therapeutic targets. Targeting ferroptosis in depression could significantly improve treatment efficacy; however, practical applications face numerous challenges. First, as a mental disorder with strong subjective components, depression research is complicated by variability in study subjects, duration, and living environments, increasing instability and complexity. Second, depression involves intricate neural network abnormalities, and brain iron homeostasis is precisely regulated by multiple factors, with different cells expressing distinct iron regulatory genes. Consequently, the causal relationship and mechanisms linking depression and ferroptosis remain unclear. Nevertheless, existing evidence demonstrates that iron deposition-induced ferroptosis plays an important role in depression development. Further investigation into depression-ferroptosis mechanisms will provide scientific basis for developing effective antidepressants. Finally, both iron deficiency and iron accumulation can promote depressive-like behaviors. Accurately balancing iron levels to meet physiological needs without inducing disease requires deeper understanding of depression-ferroptosis mechanisms.

Author Contributions: DU Shuqin conceived and designed the study, collected and organized research materials, and wrote the manuscript; QIAN Lifeng revised the manuscript and provided quality control; XIONG Lie and SHI Hanqiang edited and organized figures; SHI Yanbo revised the manuscript, provided quality control and final approval, and supervised the overall project.

Conflict of Interest: The authors declare no conflict of interest.

References

[1] ZUO C C, CAO H, SONG Y, et al. Nrf2: an all-rounder in depression[J]. Redox Biol, 2022, 58:102522. DOI:10.1016/j.redox.2022.102522.

[2] SLAVICH G M, IRWIN M R. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression[J]. Psychol Bull, 2014, 140(3):774-815. DOI:10.1037/a0035302.

[3] JIAO H Y, YANG H J, YAN Z Y, et al. Traditional Chinese formula Xiaoyaosan alleviates depressive-like behavior in CUMS mice by regulating PEBP1-GPX4-mediated ferroptosis in the Hippocampus[J]. Neuropsychiatr Dis Treat, 2021, 17:1001-1019. DOI:10.2147/NDT.S302443.

[4] WANG Y, GU C Y, EWING A G. Single-vesicle electrochemistry following repetitive stimulation reveals a mechanism for plasticity changes with iron deficiency[J]. Angew Chem Int Ed Engl, 2022, 61(20):e202200716. DOI:10.1002/anie.202200716.

[5] FERREIRA A, NEVES P, GOZZELINO R. Multilevel impacts of iron in the brain: the cross talk between neurophysiological mechanisms, cognition, and social behavior[J]. Pharmaceuticals (Basel), 2019, 12(3):126. DOI:10.3390/ph12030126.

[6] DUAN X X, XIE Y H, ZHU X F, et al. Quantitative susceptibility mapping

of brain iron deposition in patients with recurrent depression[J]. Psychiatry Investig, 2022, 19(8):668-675. DOI:10.30773/pi.2022.0110.

[7] DIXON S J, LEMBERG K M, LAMPRECHT M R, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death[J]. Cell, 2012, 149(5):1060-1072. DOI:10.1016/j.cell.2012.03.042.

[8] JAKARIA M, BELAIDI A A, BUSH A I, et al. Ferroptosis as a mechanism of neurodegeneration in Alzheimer' s disease[J]. J Neurochem, 2021, 159(5):804-825. DOI:10.1111/jnc.15519.

[9] MAHONEY-SÁNCHEZ L, BOUCHAOUI H, AYTON S, et al. Ferroptosis and its potential role in the physiopathology of Parkinson' s Disease[J]. Prog Neurobiol, 2021, 196:101890. DOI:10.1016/j.pneurobio.2020.101890.

[10] REICHERT C O, DE FREITAS F A, SAMPAIO-SILVA J, et al. Ferroptosis mechanisms involved in neurodegenerative diseases[J]. Int J Mol Sci, 2020, 21(22):8765. DOI:10.3390/ijms21228765.

[11] YAO S, ZHONG Y, XU Y H, et al. Quantitative susceptibility mapping reveals an association between brain iron load and depression severity[J]. Front Hum Neurosci, 2017, 11:442. DOI:10.3389/fnhum.2017.00442.

[12] SHAO X J, ZHU G. Associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorder[J]. Front Psychiatry, 2020, 11:381. DOI:10.3389/fpsyt.2020.00381.

[13] JIANG Y, ZOU D, LI Y M, et al. Monoamine neurotransmitters control basic emotions and affect major depressive disorders[J]. Pharmaceuticals (Basel), 2022, 15(10):1203. DOI:10.3390/ph15101203.

[14] VAVÁKOVÁ M, DURACKOVÁ Z, TREBATICKÁ J. Markers of oxidative stress and neuroprogression in depression disorder[J]. Oxid Med Cell Longev, 2015, 2015:898393. DOI:10.1155/2015/898393.

[15] MÉNARD C, HODES G E, RUSSO S J. Pathogenesis of depression: insights from human and rodent studies[J]. Neuroscience, 2016, 321:138-162. DOI:10.1016/j.neuroscience.2015.05.053.

[16] VOGELZANGS N, DUIVIS H E, BEEKMAN A T, et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation[J]. Transl Psychiatry, 2012, 2(2):e79. DOI:10.1038/tp.2012.8.

[17] KIECOLT-GLASER J K, DERRY H M, FAGUNDES C P. Inflammation: depression fans the flames and feasts on the heat[J]. Am J Psychiatry, 2015, 172(11):1075-1091. DOI:10.1176/appi.ajp.2015.15020152.

[18] BENEDETTI F, ZANARDI R, MAZZA M G. Antidepressant psychopharmacology: is inflammation a future target?[J]. Int Clin Psychopharmacol, 2022, 37(3):79-81. DOI:10.1097/yic.0000000000000403.

[19] SHARMA S, AKUNDI R S. Mitochondria: a connecting link in the major depressive disorder jigsaw[J]. Curr Neuropharmacol, 2019, 17(6):550-562. DOI:10.2174/1570159x16666180302120322.

[20] CASARIL A M, DANTZER R, BAS-ORTH C. Neuronal mitochondrial dysfunction and bioenergetic failure in inflammation-associated depression[J]. Front Neurosci, 2021, 15:725547. DOI:10.3389/fnins.2021.725547.

[21] CHEN W J, DU J K, HU X, et al. Protective effects of resveratrol on mitochondrial function in the hippocampus improves inflammation-induced depressive-like behavior[J]. Physiol Behav, 2017, 182:54-61. DOI:10.1016/j.physbeh.2017.09.024.

[22] HAN X K, GAO Y, YIN X, et al. The mechanism of electroacupuncture for depression on basic research: a systematic review[J]. Chin Med, 2021, 16(1):10. DOI:10.1186/s13020-020-00421-y.

[23] MIKULSKA J, JUSZCZYK G, GAWRONSKA-GRZYWACZ M, et al. HPA axis in the pathomechanism of depression and schizophrenia: new therapeutic strategies based on its participation[J]. Brain Sci, 2021, 11(10):1298. DOI:10.3390/brainsci11101298.

[24] BERTHOU C, ILIOU J P, BARBA D. Iron, neuro-bioavailability and depression[J]. eJHaem, 2022, 3(1):263-275. DOI:10.1002/jha2.321.

[25] LIANG S S, LU Y, LI Z X, et al. Iron aggravates the depressive phenotype of stressed mice by compromising the glymphatic system[J]. Neurosci Bull, 2020, 36(12):1542-1546. DOI:10.1007/s12264-020-00539-x.

[26] YU Y, YAN Y, NIU F L, et al. Ferroptosis: a cell death connecting oxidative stress, inflammation and cardiovascular diseases[J]. Cell Death Discov, 2021, 7(1):193. DOI:10.1038/s41420-021-00579-w.

[27] MAES M, MELTZER H Y, BUCKLEY P, et al. Plasma-soluble interleukin-2 and transferrin receptor in schizophrenia and major depression[J]. Eur Arch Psychiatry Clin Neurosci, 1995, 244(6):325-329. DOI:10.1007/BF02190412.

[28] ZHANG W H, ZHOU Y, LI Q Q, et al. Brain iron deposits in thalamus is an independent factor for depressive symptoms based on quantitative susceptibility mapping in an older adults community population[J]. Front Psychiatry, 2019, 10:734. DOI:10.3389/fpsyt.2019.00734.

[29] YAO S, ZHONG Y, XU Y H, et al. Quantitative susceptibility mapping reveals an association between brain iron load and depression severity[J]. Front Hum Neurosci, 2017, 11:442. DOI:10.3389/fnhum.2017.00442.

[30] CHANG X, MA M X, CHEN L P, et al. Identification and characterization of elevated expression of transferrin and its receptor TfR1 in mouse models of depression[J]. Brain Sci, 2022, 12(10):1267. DOI:10.3390/brainsci12101267.

[31] MAAROUFI K, AMMARI M, JELJELI M, et al. Impairment of emotional behavior and spatial learning in adult Wistar rats by ferrous sulfate[J]. Physiol

Behav, 2009, 96(2):343-349. DOI:10.1016/j.physbeh.2008.10.019.

[32] KIM J, WESSLING-RESNICK M. Iron and mechanisms of emotional behavior[J]. J Nutr Biochem, 2014, 25(11):1101-1107. DOI:10.1016/j.jnutbio.2014.07.003.

[33] YOUDIM M B H. Brain iron deficiency and excess; cognitive impairment and neurodegeneration with involvement of striatum and hippocampus[J]. Neurotox Res, 2008, 14(1):45-56. DOI:10.1007/BF03033574.

[34] MEISER J, WEINDL D, HILLER K. Complexity of dopamine metabolism[J]. Cell Commun Signal, 2013, 11(1):34. DOI:10.1186/1478-811X-11-34.

[35] YU Y, YAN Y, NIU F L, et al. Ferroptosis: a cell death connecting oxidative stress, inflammation and cardiovascular diseases[J]. Cell Death Discov, 2021, 7(1):193. DOI:10.1038/s41420-021-00579-w.

[36] YU M Y, GAI C C, LI Z, et al. Targeted exosome-encapsulated erastin induced ferroptosis in triple negative breast cancer cells[J]. Cancer Sci, 2019, 110(10):3173-3182. DOI:10.1111/cas.14181.

[37] ZHU L, HAN B, WANG L P, et al. The association between serum ferritin levels and post-stroke depression[J]. J Affect Disord, 2016, 190:98-102. DOI:10.1016/j.jad.2015.09.074.

[38] KNYSZYNSKA A, RADECKA A, ZABIELSKA P, et al. The role of iron metabolism in fatigue, depression, and quality of life in multiple sclerosis patients[J]. Int J Environ Res Public Health, 2020, 17(18):6818. DOI:10.3390/ijerph17186818.

[39] CAO H, ZUO C C, HUANG Y Q, et al. Hippocampal proteomic analysis reveals activation of necroptosis and ferroptosis in a mouse model of chronic unpredictable mild stress-induced depression[J]. Behav Brain Res, 2021, 407:113261. DOI:10.1016/j.bbr.2021.113261.

[40] MEHRPOUYA S, NAHAVANDI A, KHOJASTEH F, et al. Iron administration prevents BDNF decrease and depressive-like behavior following chronic stress[J]. Brain Res, 2015, 1596:79-87. DOI:10.1016/j.brainres.2014.10.057.

[41] UZUNGIL V, TRAN H, AITKEN C, et al. Novel antidepressant-like properties of the iron chelator deferiprone in a mouse model of depression[J]. Neurotherapeutics, 2022, 19(5):1662-1685. DOI:10.1007/s13311-022-01257-0.

[42] ZHANG W X, YU M Q, ZHANG Q Y, et al. DFO treatment protects against depression-like behaviors and cognitive impairment in CUMS mice[J]. Brain Res Bull, 2022, 187:75-84. DOI:10.1016/j.brainresbull.2022.06.016.

[43] HOROWITZ M P, GREENAMYRE J T. Mitochondrial iron metabolism and its role in neurodegeneration[J]. J Alzheimer' s Dis, 2010, 20(s2):S551-568. DOI:10.3233/jad-2010-100354.

[44] CAMPANELLA A, ROVELLI E, SANTAMBROGIO P, et al. Mitochondrial ferritin limits oxidative damage regulating mitochondrial iron availability: hypothesis for a protective role in Friedreich ataxia[J]. Hum Mol Genet, 2009, 18(1):1-11. DOI:10.1093/hmg/ddn308.

[45] ALLEN J, ROMAY-TALLON R, BRYMER K J, et al. Mitochondria and mood: mitochondrial dysfunction as a key player in the manifestation of depression[J]. Front Neurosci, 2018, 12:386. DOI:10.3389/fnins.2018.00386.

[46] GIMÉNEZ-PALOMO A, DODD S, ANMELLA G, et al. The role of mitochondria in mood disorders: from physiology to pathophysiology and to treatment[J]. Front Psychiatry, 2021, 12:546801. DOI:10.3389/fpsyt.2021.546801.

[47] DENG L Y, HE S S, GUO N Q, et al. Molecular mechanisms of ferroptosis and relevance to inflammation[J]. Inflamm Res, 2023, 72(2):281-299. DOI:10.1007/s00011-022-01672-1.

[48] NICOLE C, BROWN. An updated meta-analysis of oxidative stress markers in bipolar disorder[J]. Psychiatry Res, 2014, 218(1/2):61-68. DOI:10.1016/j.psychres.2014.04.005.

[49] IWAMOTO K, BUNDO M, KATO T. Altered expression of mitochondria-related genes in postmortem brains of patients with bipolar disorder or schizophrenia, as revealed by large-scale DNA microarray analysis[J]. Hum Mol Genet, 2005, 14(2):241-253. DOI:10.1093/hmg/ddi022.

[50] CATALDO A M, MCPHIE D L, LANGE N T, et al. Abnormalities in mitochondrial structure in cells from patients with bipolar disorder[J]. Am J Pathol, 2010, 177(2):575-585. DOI:10.2353/ajpath.2010.081068.

[51] FATTAL O, LINK J, QUINN K, et al. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies[J]. CNS Spectr, 2007, 12(6):429-438. DOI:10.1017/s1092852900015303.

[52] YUAN Qingjie, GUO Jianyou, WANG Jianwei, et al. Study on the mechanism of liver depression and spleen deficiency in depression and the intervention effect of Xingpi Jieyu Formula based on corticosterone-inflammatory response-mitochondria network[J]. China J Tradit Chin Med Pharm, 2017, 32(5):2241-2245. DOI:10.3969/j.issn.1673-7202.2014.12.22.

[53] REZIN G T, CARDOSO M R, GONÇALVES C L, et al. Inhibition of mitochondrial respiratory chain in brain of rats subjected to an experimental model of depression[J]. Neurochem Int, 2008, 53(6/7/8):395-400. DOI:10.1016/j.neuint.2008.09.012.

[54] SHU X D, SUN Y M, SUN X Y, et al. The effect of fluoxetine on astrocyte autophagy flux and injured mitochondria clearance in a mouse model of depression[J]. Cell Death Dis, 2019, 10(8):577. DOI:10.1038/s41419-019-1813-9.

[55] DANG R Z, WANG M Y, LI X H, et al. Edaravone ameliorates depressive

and anxiety-like behaviors via Sirt1/Nrf2/HO-1/Gpx4 pathway[J]. J Neuroinflammation, 2022, 19(1):41. DOI:10.1186/s12974-022-02400-6.

[56] WANG Y, WANG S W, XIN Y, et al. Hydrogen sulfide alleviates the anxiety-like and depressive-like behaviors of type 1 diabetic mice via inhibiting inflammation and ferroptosis[J]. Life Sci, 2021, 278:119551. DOI:10.1016/j.lfs.2021.119551.

[57] ZHANG M K, LYU D B, WANG F, et al. Ketamine may exert rapid antidepressant effects through modulation of neuroplasticity, autophagy, and ferroptosis in the habenular nucleus[J]. Neuroscience, 2022, 506:29-37. DOI:10.1016/j.neuroscience.2022.10.015.

[58] LU S F, LI C Y, JIN X H, et al. Baicalin improves energy levels in the prefrontal cortex of mice exposed to chronic unpredictable mild stress[J]. Heliyon, 2022, 8(12):e12083. DOI:10.1016/j.heliyon.2022.e12083.

[59] LI J N, GAO W, ZHAO Z H, et al. Ginsenoside Rg1 reduced microglial activation and mitochondrial dysfunction to alleviate depression-like behaviour via the GAS5/EZH2/SOCS3/NRF2 axis[J]. Mol Neurobiol, 2022, 59(5):2855-2873. DOI:10.1007/s12035-022-02740-7.

[60] PALLOTTI F, BERGAMINI C, LAMPERTI C, et al. The roles of coenzyme Q in disease: direct and indirect involvement in cellular functions[J]. Int J Mol Sci, 2021, 23(1):128. DOI:10.3390/ijms23010128.

[61] RIZZARDI N, LIPARULO I, ANTONELLI G, et al. Coenzyme Q10 phytosome formulation improves CoQ10 bioavailability and mitochondrial functionality in cultured cells[J]. Antioxidants (Basel), 2021, 10(6):927. DOI:10.3390/antiox10060927.

[62] FORESTER B P, HARPER D G, GEORGAKAS J, et al. Antidepressant effects of open label treatment with coenzyme Q10 in geriatric bipolar depression[J]. J Clin Psychopharmacol, 2015, 35(3):338-340. DOI:10.1097/JCP.0000000000000326.

[63] LI J Q, HUANG S Q, WANG Q, et al. Andrographolide promoted ferroptosis to repress the development of non-small cell lung cancer through activation of the mitochondrial dysfunction[J]. Phytomedicine, 2023, 109:154601. DOI:10.1016/j.phymed.2022.154601.

[64] TRIPATHI A, SCAINI G, BARICHELLO T, et al. Mitophagy in depression: Pathophysiology and treatment targets[J]. Mitochondrion, 2021, 61:1-10. DOI:10.1016/j.mito.2021.08.016.

[65] BATTAGLIA A M, CHIRILLO R, AVERSA I, et al. Ferroptosis and cancer: mitochondria meet the "iron maiden" cell death[J]. Cells, 2020, 9(6):1505. DOI:10.3390/cells9061505.

[66] HAMEED S, NASER I A, AL GHUSSEIN M A, et al. Is iron deficiency a risk factor for postpartum depression? A case-control study in

the Gaza Strip, Palestine[J]. Public Health Nutr, 2022, 25(6):1631-1638. DOI:10.1017/s1368980021003761.

(Received: March 23, 2023; Revised: May 29, 2023)

(Editor: WANG Shiyue)

Note: Figure translations are in progress. See original paper for figures.