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Nrf2: An all-rounder in depression

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ABSTRACT

The balance between oxidation and antioxidant is crucial for maintaining homeostasis. Once disrupted, it can lead to various pathological outcomes and diseases, such as depression. Oxidative stress can result in or aggravate a battery of pathological processes including mitochondrial dysfunction, neuroinflammation, autophagical disorder and ferroptosis, which have been found to be involved in the development of depression. Inhibition of oxidative stress and related pathological processes can help improve depression. In this regard, the nuclear factor erythroid 2-related factor 2 (Nrf2) in the antioxidant defense system may play a pivotal role. Nrf2 activation can not only regulate the expression of a series of antioxidant genes that reduce oxidative stress and its damages, but also directly regulate the genes related to the above pathological processes to combat the corresponding alterations. Therefore, targeting Nrf2 has great potential for the treatment of depression. Activation of Nrf2 has antidepressant effect, but the specific mechanism remains to be elucidated. This article reviews the key role of Nrf2 in depression, focusing on the possible mechanisms of Nrf2 regulating oxidative stress and related pathological processes in depression treatment. Meanwhile, we summarize some natural and synthetic compounds targeting Nrf2 in depression therapy. All the above may provide new insights into targeting Nrf2 for the treatment of depression and provide a broad basis for clinical transformation.

1. Introduction

Depression is a mental disorder characterized by persistent low mood, decreased interest, cognitive impairment, sleep disorders, decreased appetite and suicidal tendencies, which severely limits the patients' psychosocial function and quality of life [1]. With the increasing pressure of modern life and work, a growing number of people suffer from mental illness, with about 350 million depressed patients worldwide. The World Health Organization ranks depression as the third leading cause of the global burden of disease in the world [2]. People with depression also have a significantly increased risk of cardiovascular disease, stroke, autoimmune disease, diabetes and cancer and are less responsive to treatment for these conditions.

Currently, antidepressants are the mainstay of treatment for depression. The commonly used first-line antidepressants, including serotonin or norepinephrine reuptake inhibitors and monoamine oxidase inhibitor (MAOI), aligns well with the monoamine theory of depression. This hypothesis states that the underlying pathophysiology of depression is a decrease in the levels of 5-hydroxytryptamine (5-HT), norepinephrine, and/or dopamine in the central nervous system [3]. However, traditional antidepressants act slowly and have multiple side effects, with a third of patients failing to respond, indicating that other factors may be involved in the pathogenesis of depression [4]. Therefore, it is an urgent need to further investigate the pathophysiology of depression and explore novel targets.

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defences [5]. Abundant evidence suggests that oxidative stress plays a critical role in the pathophysiology of depression [6–8]. ROS/reactive nitrogen species

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Abbreviations

ARE	antioxidant response elements
AA	arachidonic acid
bZIP	basic-region leucine zipper
BDNF	brain-derived neurotrophic factor
BTB	bric-a-brac
β-TrCP	β-transducin repeat-containing protein
CREB	cAMP response element-binding protein
CBP	CREB-binding protein
CNC	Cap'n'collar
CK2	Casein kinase II
CAT	catalase
CSF	cerebrospinal fluid
CSDS	chronic social defeat stress
CUMS	chronic unpredictable mild stress
JNK	c-Jun N-terminal kinase
CRP	C-reactive protein
Cul3	Cullin 3
DAMPs	damage-associated molecular patterns
DMF	dimethyl fumarate
DGR	double glycine repeat
Drp1	dynamin-related protein 1
ETC	electron transport chain
ERK	extracellular regulated kinases
FTH1	ferritin heavy chain 1
FTL1	ferritin light chain 1
GCL	glutamate-cysteine ligase
GSH	glutathione
GPX	glutathione peroxidase
GR	glutathione reductase
GST	glutathione S-transferase
GSS	glutathione synthetase
GSK-3β	glycogen synthase kinase-3β
HO-1	heme oxygenase 1
IDO	indoleamine-pyrrole 2,3-dioxygenase
IL	interleukin
Keap1	Kelch-like ECH-associated protein 1
LIP	labile iron pools
LC3	light chain 3
LH	learned helplessness
L-OH	lipid alcohols
L-OOH	lipid hydroperoxides
LPS	lipopolysaccharide
MDD	major depressive disorder
MDA	malondialdehyde
mtDNA	mitochondrial DNA
mPFC	medial prefrontal cortex
MPTP	mitochondrial permeability transition pores
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
NQO1	NAD(P)H dehydrogenase quinone 1
NF-κB	nuclear factor-κB
Nrf2	nuclear factor erythroid 2-related factor 2
PRDX	peroxiredoxin
PPARγ	Peroxisome proliferator-activated receptor gamma
PGC-1α	peroxisome proliferator-activated receptor gamma coactivator alpha
PUFA	polyunsaturated fatty acids
PFC	prefrontal cortex
PKC	Protein kinase C
PKR	protein kinase R
PERK	PKR-like endoplasmic reticulum kinase
PINK1	PTEN-induced putative kinase 1
MAPK	p38 mitogen-activated protein kinases
RLS	reactive lipid species
RNS	reactive nitrogen species
ROS	reactive oxygen species
rTMS	Repetitive transcranial magnetic stimulation
RXRα	retinoic X receptor α
SSRIs	selective serotonin reuptake inhibitors
Sirt1	sirtuin-1
sMaf	small musculoaponeurotic fibrosarcoma
Srx1	sulfiredoxin 1
SOD	Superoxide dismutase
TRX	thioredoxin
TrxR	thioredoxin reductase
TFR1	Transferrin receptor 1
TSPO	translocator protein
TNF-α	tumor necrosis factor-α
ULK1	unc-51-like kinase 1
XO	xanthine oxidase
4-HNE	4-hydroxy-2-nonenal
5-HT	5-hydroxytryptamine
8-OHdG	8-OH 2-deoxyguanosine

(RNS) refer to free radicals (superoxide, hydroxyl radical) or nonradical molecules (hydrogen peroxide) and their derivatives [9]. Physiological levels of ROS/RNS are involved in many metabolic processes in the organism [6,7,10]. However, overproduction of ROS/RNS can cause extensive damages to DNA, proteins and lipids [11]. The brain is a major consumer of oxygen and is rich in oxidative lipids, making it more vulnerable to damage from oxidative stress. Oxidative stress markers, such as 8-OH 2-deoxyguanosine (8-OHdG) and F2-isoprostanes are found to be significantly increased in major depressive disorder (MDD) [8].

Oxidative stress is intimately linked to a variety of pathophysiological processes, including neuroinflammation, dysfunction of mitochondria and autophagical disorder. These pathological processes have also been found to be involved in depression. Oxidative stress and inflammation may mutually promote under pathological conditions and form a co-activation state [12]. Elevated levels of proinflammatory cytokines have been found both peripherally and centrally in patients with depression [13–15]. Activation of inflammatory pathways, such as nuclear factor-κB (NF-κB) signaling, are found in rodent models of depression [16]. Mitochondria, which are responsible for energy production, are the main source of ROS (mtROS) [17]. An increased level of mtROS has been found in depression, indicating mitochondrial dysfunction [18]. Damaged electron transport chain (ETC), ATP production and mitochondrial DNA have been reported in depressed patients [19]. Additionally, ROS can induce autophagy by mediating multiple signaling pathways [20]. Autophagy is a process that degrades cellular waste and maintains tissue homeostasis. Altered autophagy-related genes and signaling have been observed in patients with MDD and animal models of depression, indicating dysfunction of autophagy [21,22]. Recently, the role of ferroptosis in depression has received attention. Ferroptosis, which is first proposed in 2012, is an iron- and lipid peroxidation-dependent form of cell death [23]. By using quantitative proteomics, the study by our team identifies activation of ferroptosis in mice models of chronic unpredictable mild stress (CUMS)-induced depression [24].

The main way to combat oxidative stress in the body is the antioxidant defense system , in which the nuclear factor erythroid 2-related factor 2 (Nrf2) acts as a master regulator [11,25]. Nrf2 is a

transcription factor that can regulate a large number of antioxidant and cytoprotective genes [25,26]. By promoting the expression of these genes, Nrf2 is not only involved in the regulation of redox homeostasis, but also in the regulation of other processes, such as neuroinflammation, mitochondrial dysfunction, autophagical disorder and ferroptosis, making Nrf2 the hub for regulating these pathological processes. Dysregulation of the Nrf2 pathway may contribute to the development of a series of pathologies or diseases including psychiatric disorders and neurodegenerative diseases [26,27]. In fact, clinical and preclinical studies have demonstrated decreased expression of Nrf2 in the prefrontal cortex (PFC) of MDD patients and rodent models of depression [28,29]. Decreased protein levels of Nrf2 have been found in the postmortem brain from depressed patients compared with control subjects [30]. In the rodent models of depression, including learned helplessness (LH) paradigm and chronic social defeat stress (CSDS), the protein levels of Nrf2 in the medial prefrontal cortex (mPFC) and hippocampus are lower than those of control and LH/CSDS-resilient mice, which indicate that Nrf2 may contribute to stress resilience [31,32]. It is reported that Nrf2 knockout mice present depression-like phenotypes, which is associated with increased inflammation and decreased BDNF-TrkB signaling [29,33]. A large amount of studies suggest a crucial role of Nrf2 in the treatment of depression. The therapeutic effects of several antidepressants have been found to be strongly associated with Nrf2 [34,35]. Fluoxetine, a commonly-used SSRI, has anti-inflammatory and antioxidant properties in depression driven by alterations in Nrf2-dependent apoptosis and autophagy [34]. A new fast-acting antidepressant, (R)-ketamine, is shown to produce long-lasting antidepressant effects in Nrf2 KO mice via BDNF-TrkB activation [36]. Moreover, some Nrf2 activators, such as sulforaphane and dimethyl fumarate (DMF), exhibit significant antidepressant effects [37,38]. Therefore, targeting Nrf2 may represent a promising strategy for the treatment and prevention of depression.

In this review, we aim to highlight the critical role of Nrf2 in depression, in particular the possible mechanisms by which Nrf2 regulates related pathological processes that may be involved in the pathogenesis of depression, and further discuss natural and synthetic compounds that target Nrf2 in the treatment of depression.

2. The structure and regulation of Nrf2

Nrf2 , encoded by NFE2L2 gene, belongs to the Cap'n'collar (CNC) transcription factor family [39]. The Nrf2 protein is composed of 605 amino acids and contains seven highly conserved functional domains, named Nrf2-ECH homology 1 (Neh1)-Neh7 [39]. Neh1 has a basic-region leucine zipper (bZIP) motif which is required for combination with small musculoaponeurotic fibrosarcoma (sMaf) proteins and mediates Nrf2-antioxidant response elements (ARE) binding in the nucleus, thus promoting the transcription of various antioxidant enzymes [25]. Neh2 contains two motifs ETGE and DLG that are responsible for interaction with Kelch-like ECH-associated protein 1 (Keap1) and subsequent Keap1-dependent ubiquitination and proteasomal degradation of Nrf2 [40]. Neh3 modulates the activation of ARE-dependent genes by binding to the transcription coactivator, CHD6 [25]. Analogously, Neh4 and Neh5 can interact with cAMP response element-binding protein

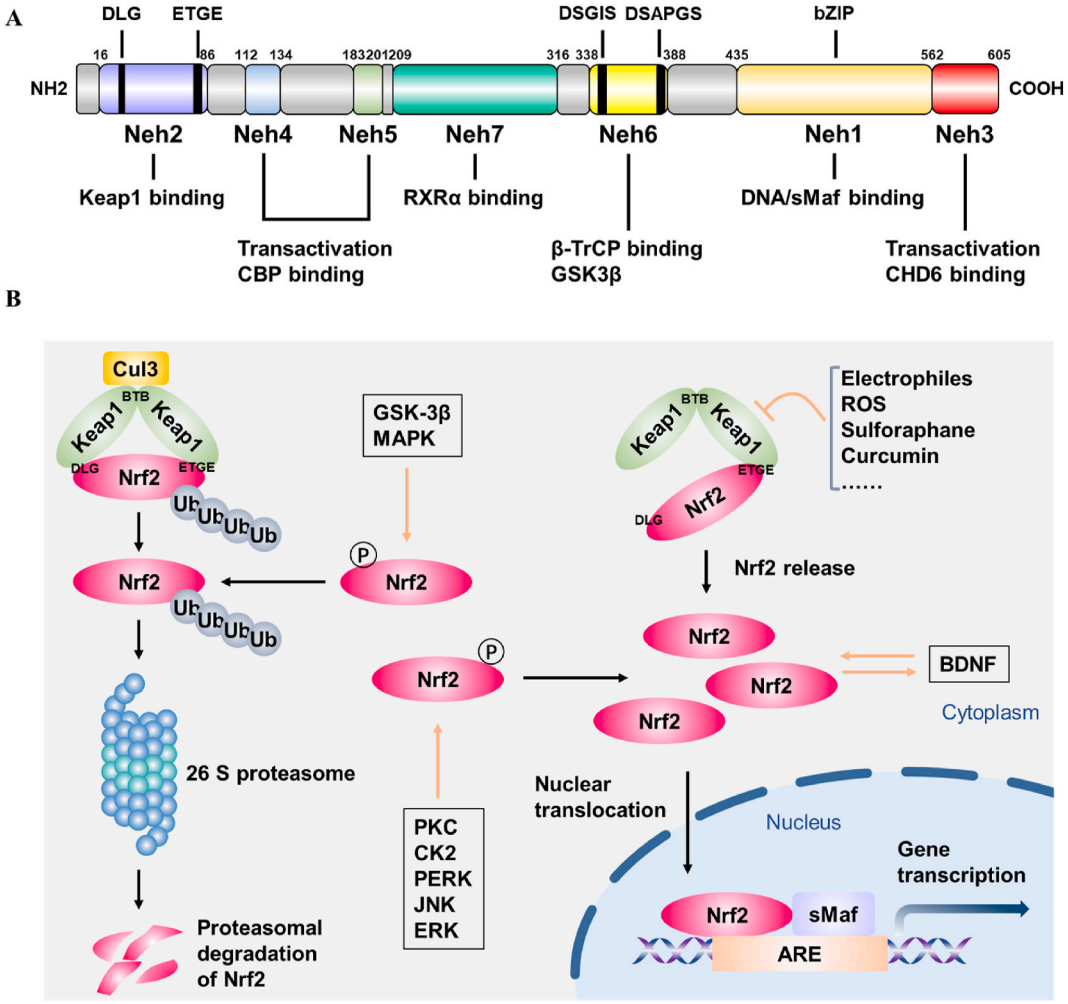

Fig. 1. The structure and regulation of Nrf2. (A) The fundamental structure of Nrf2. (B) Keap1 -dependent and -independent regulation of Nrf2.

(CREB)-binding protein (CBP) and facilitate transcription activation [41]. Neh6 has DSGIS and DSAPGS motifs that can bind with β-transducin repeat-containing protein (β-TrCP) and is involved in the keap1-independent degradation of Nrf2 [40]. Neh6 also mediates Nrf2 phosphorylation by glycogen synthase kinase-3β (GSK-3β) [42]. Neh7 is responsible for inhibition of Nrf2-ARE signaling pathway through binding to the retinoic X receptor α (RXRα) [43] (Fig. 1A).

The activity of the NRF2-ARE signaling pathway is mainly regulated by Keap1, a major negative regulator of Nrf2 [44]. Keap1 relies on the bric-a-brac (BTB) domain to form homodimer, which then binds to the ETGE and DLG motifs of Nrf2 [25]. Under physiological conditions, Keap1-Nrf2 combines with E3 ubiquitin ligase complex Cullin 3 (Cul3) via the Neh6 domain of Nrf2, leading to the ubiquitination and proteasomal degradation of Nrf2 by the 26 S proteasome [41]. Under stressed conditions such as ROS accumulation, the double glycine repeat (DGR) domain of Keap1 undergoes conformational changes and the DLG motif dissociates from Keap1. This process inhibits the ubiquitination and degradation of Nrf2 protein. Nrf2 is released and translocates into the nucleus where it binds to sMaf and ARE and further increases the transcriptional activation of a series of antioxidant enzymes [45]. Apart from the canonical Keap1-Nrf2 regulation, there exists Keap1-independent regulation of Nrf2. Several kinases can phosphorylate Nrf2 and regulate its activity. Protein kinase C (PKC), Casein kinase II (CK2), protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), c-Jun N-terminal kinase (JNK) and extracellular regulated kinases (ERK) phosphorylate Nrf2 and facilitate its translocation into the nucleus [46–49]. Furthermore, BDNF can act as a steady-state regulator of Nrf2 activity and promote the nuclear translocation of Nrf2 [50]. On the contrary, Nrf2 phosphorylation by GSK-3β and p38 mitogen-activated protein kinases (MAPK) promote its degradation [42,48]. In addition, BACH1 and Hrd1 play negative regulatory roles on Nrf2 and repress the transcription of NRF2 target genes [43,51] (Fig. 1B).

3. The role of Nrf2 in depression

Although studies have shown that activation of Nrf2 can play an antidepressant role, the specific mechanisms of Nrf2 regulation in depression has not been fully elucidated. Since the target genes regulated by Nrf2 are involved in multiple pathological processes, its role in depression may also be multifaceted. Consequently , the role of Nrf2 in regulating oxidative stress, neuroinflammation, autophagy and ferroptosis in depression will be discussed separately.

3.1. Nrf2 and oxidative stress in depression

Studies have confirmed the dysregulation of redox homeostasis in the pathophysiology of depression [52–54]. Meta-analyses also indicate increased oxidative stress production and impaired antioxidant defenses in depression [55]. ROS, including superoxide radicals, hydrogen peroxide, hydroxyl radicals and singlet oxygen, are byproducts of aerobic metabolism [10]. Normal physiological levels of ROS are essential in regulation of cellular functions, such as neurogenesis, neuronal activities and cellular signaling pathways [6,7,10]. However, high levels of ROS cause damage to lipids, proteins and DNA, a process known as oxidative stress, and ultimately lead to cell disruption and apoptosis [11,56]. The production of ROS also increases the secretion of inflammatory mediators [57]. Chronic psychological or physiological stress may increase generation of ROS [58]. Moreover, RNS, which refers to various nitric oxide–derived compounds, often act together with ROS to damage cells and exacerbate the deleterious effects [10]. The cause of oxidative stress in depression has not been elucidated. Stress-induced hyperfunction of the HPA-axis may increase blood cortisol level and accelerate ROS production [57]. Oxidative stress markers, F2-isoprostanes and 8-OHdG, increased in the plasma and urine of patients with depression [59–62]. The 8-OHdG is a derivative of deoxyguanosine and represents oxidative damage to DNA [59]. In addition to F2-isoprostanes, oxidative damage to lipids in depression is also indicated by increased concentration of malondialdehyde (MDA) [63]. MDA is a byproduct of polyunsaturated fatty acid peroxidation and an important feature of ferroptosis (see further). Elevated levels of xanthine oxidase (XO) and monoamine oxidase (MAO), enzymes involved in ROS production, have been detected in depressed patients and in postmortem depressed patients [9].

Under oxidative stress, the antioxidant defense system is activated to combat the cellular damage caused by ROS/RNS and maintain redox homeostasis [64,65]. Nrf2 is a major endogenous regulator of antioxidant defense [11]. When translocated into the nucleus, Nrf2 binds to ARE and induces the expression of a series of antioxidant enzymes [25]. These antioxidant enzymes involve multiple systems and are strongly linked to depression. The Nrf2 targets involved in the glutathione (GSH) system consist of GSH, glutamate-cysteine ligase (GCL), glutathione S-transferase (GST), glutathione synthetase (GSS), glutathione peroxidase (GPX) and glutathione reductase (GR) [66]. Decreased levels of GSH, GPX and GST Mu have been found in the post-mortem PFC from patients with MDD [67,68]. Reduced GSH level has also been observed in rodent brain exposed to chronic stress [69,70]. It is reported that administration of GSH centrally produces antidepressant-like effects in mice [71]. The thioredoxin (TRX)-based antioxidant system is another Nrf2-dependent system that maintains protein thiols in a reduced state [26]. This redoxin system contains TRX, peroxiredoxin (PRDX), thioredoxin reductase (TrxR) and sulfiredoxin 1 (Srx1). The level of TRX is significantly decreased in the brain of rats exposed to CUMS, which can be reversed by fluoxetine [72]. Studies have shown a reduced level of PRDX6 in the PFC of suicide victims and CUMS-induced rats [73]. In addition, the level of Srx1 is downregulated in depressed mice [74]. These results indicate that the TRX-PRDX system is compromised in depression. The expression of two antioxidant enzymes targeted by Nrf2, NAD(P)H dehydrogenase quinone 1 (NQO1) and heme oxygenase 1 (HO-1), is markedly decreased in rats under CUMS [75]. Administration of curcumin, an Nrf2 activator, can significantly increase the mRNA expression of NQO-1 and HO-1 and relieve depression-like state of rats [76]. Superoxide dismutase (SOD) and catalase (CAT) that belong to free radical scavengers are Nrf2 targets as well [66]. SOD breaks down the superoxide into oxygen molecules and H_2O_2, which is then scavenged by CAT to form water and oxygen [77]. Several studies have found lowered SOD activity in depressed patients [54,78]. Decreased SOD and CAT activities have also been found in the CUMS models [54]. The decreased activity of Nrf2 and changes of its regulated antioxidant enzyme profile indicate that Nrf2-mediated antioxidant stress defense was impaired in depression. In mice models of depression, Nrf2 translocation and activation of antioxidant enzymes can be prevented by the decreased levels of BDNF, leading to sustained oxidative stress [79]. Studies have demonstrated that various classes of antidepressants can lower the levels of oxidative stress and some antioxidants, especially Nrf2 activator, have potential antidepressant efficacy in depression [54,80,81].

ROS are mainly produced by mitochondria and accumulated ROS can in turn cause damage to mitochondria [82]. An increasing number of evidence indicates that there exists mitochondrial dysfunction in depression [83,84]. A series of mitochondrial disorders have been observed in patients with depression and animal models of depression [85]. For example, the levels of ATP production are lower in the brains and peripheral blood mononuclear cells of depressed patients compared to the controls [86,87]. Research from animals demonstrate the inhibition of oxidative phosphorylation and complexes I, III and IV of ETC as well as decreased ATP production [85,88]. Secondly, reduced activity of mitochondrial enzyme, damaged mitochondrial membrane potential, altered mitochondrial ultrastructure are found in mice with chronic mild stress-induce depression [88,89]. Increased amount of mtDNA deletions and mutations and decreased mtDNA copy number are detected in patients with depression [90,91]. These changes may result in reduced mitochondrial biogenesis and increased membrane permeability and mitochondrial ROS production, consequently, leading to impaired

neurogenesis and synaptic plasticity and elevated apoptosis [85].

Nrf2 is closely related to mitochondrial function. Decreased Nrf2 levels in depression may contribute to mitochondrial dysfunction as evidenced by studies demonstrating that impaired mitochondrial function is observed after Nrf2 knockout in vivo and in vitro [11,92]. Through multiple pathways, Nrf2 plays a protective role in mitochondrial structure and function. Nrf2 promotes mitochondrial biogenesis by regulating the expression of sirtuin-1/peroxisome proliferator-activated receptor gamma coactivator alpha (SIRT1/PGC-1α) [93,94]. Nrf2 activation can increase proteasomal activity which induces decreased dynamin-related protein 1 (Drp1) protein levels and ultimately result in mitochondrial hyperfusion [95]. Nrf2 also affects mitochondrial anti-apoptotic proteins Bcl-2 and Bcl-xL [96]. Downregulation of Bcl-2 and Bcl-xL can lead to increased mitochondrial permeability transition pores (MPTP), which perpetuates mitochondrial damage and loss of function [97].

3.2. Nrf2 and autophagy in depression

Autophagy is a process that removes cytosolic pathogens or damaged cell components to maintain cellular survival and homeostasis [98]. Macroautophagy, also known as autophagy, is the most studied form of autophagy [99]. Cytosolic materials are first enwrapped by autophagosome, a double-membrane vesicular structure. Then this complex fuses with lysosome to form autolysosome, where the cytosolic materials are degraded and recycled [100]. Under normal conditions, autophagy is beneficial and plays an important roles in promoting neuronal growth, differentiation and synaptic plasticity [101,102]. Whereas autophagy disorders can affect neuronal development and synaptic plasticity, induce accumulation of cellular wastes such as misfolded proteins and exacerbate redox imbalances and inflammatory responses, leading to cell dysfunction and death [103]. In fact, dysregulation of autophagy have been demonstrated in depression. Patients with MDD exhibit increased expression of autophagy genes like microtubule associated protein 1 light chain 3 (LC3), ATG12, and Beclin 1 in the peripheral blood mononuclear cells [21]. The mTOR signaling pathway which is associated with autophagy is comprised in the postmortem brains of MDD patients [104]. Reduced expression of autophagy markers and increased autophagosome accumulation have been found in the prefrontal cortex and hippocampus of depressed mice [105]. P62, a Ub-binding autophagy receptor, is shown to be increased in the PFC of mice exposed to CUMS [106]. Meanwhile, studies have found that antidepressants have an impact on autophagy. Classic antidepressants amitriptyline and fluoxetine can induce autophagic flux in the hippocampus, which can be abolished by inhibition of Beclin 1 [107,108]. mTOR-dependent signaling pathway and beclin pathway may mediate the regulation of autophagy by antidepressant drugs [103]. Non-pharmacological treatment such as electroconvulsive therapy has also been shown to enhance autophagy [109]. Moreover, interventions that promote autophagy are reported to have antidepressant effects, suggesting that targeting autophagy may be a promising strategy for treating depression [110].

There is a direct crosstalk between Nrf2 and autophagy due to the fact that Nrf2 can regulate the expression of autophagy genes. Nrf2 can induce the expression of autophagy-related genes, including Atg5, p62, LC3B and unc-51-like kinase 1 (ULK1) [111]. Nrf2 can induce the expression of Sestrin2, which can inhibit mTORC1 expression, thereby indirectly activating selective autophagy [112,113]. Nrf2 knockdown reduces autophagic flux whereas Nrf2 activation promotes autophagy, which is intimately related to changes of p62/SQSTM1 levels [45]. P62 can compete with Nrf2 in binding to Keap1, resulting in the release and nucleus translocation of Nrf2 [25,114]. Therefore, the mutual regulation of p62 and Nrf2 constitutes a positive feedback loop that is associated with cytoprotection.

Recently, another particular form of autophagy, mitophagy, has also been found to play an important role in depression [18,115]. Mitophagy is a method for mitochondria to achieve self-control and renewal. By removing damaged or redundant mitochondria through autophagy, mitophagy maintained the stability of mitochondrial number and energy metabolism [115]. Damage of mitochondrial DNA (mtDNA) has been reported in patients with MDD [18]. Mice treated with chronic mild stress exhibit damaged mitochondrial ultrastructure in the hippocampus, cortex and hypothalamus [18]. Recent evidence suggests that the upregulated levels of Mfn-2, short Opa-1 and Fis-1 in MDD patients, indicating increased mitochondrial fragments [116]. Besides, increased Pink-1 levels and decreased Parkin levels of MDD patients suggest impaired clearance of damaged mitochondria since PTEN-induced putative kinase 1 (PINK1)/Parkin pathway can specifically recognize defective mitochondria and regulate mitophagy [116]. Redundant mitochondrial fragments can lead to apoptosis under stress conditions through excess ROS production, impaired bioenergetics and dysfunction of endogenous respiration. Release of mitochondrial fragments especially mtDNA can act as damage-associated molecular patterns (DAMPs) and further induce inflammatory response via interacting with TLR9 and activating NF-κB and NLRP3 inflammasome [117,118].

Intriguingly, mitophagy is directly regulated by Nrf2. Functional sequence analysis demonstrated the presence of ARE in the PINK1 promoter, which is the binding site of NRF2 [119]. Activation of endogenous Nrf2 can induce an increase of Pink1 expression, while silencing Nrf2 reversed the upregulated Pink1 level triggered by Nrf2 inducer tBHQ [119]. On the other hand, p62 is also involved in mitophagy. P62 can interacts with ubiquitinated molecules on the autophagosome [120]. Studies have shown that p62 can mediate autophagy with or without dependence on the Pink1/Parkin pathway [121]. P62 knockdown thoroughly blocked the clearance of damaged mitochondria [122]. These observations point out the potential involvement of Nrf2 in controlling mitophagy and mitochondrial integrity through modulating Pink1 and p62.

3.3. Nrf2 and neuroinflammation in depression

Numerous studies have emphasized the strong link between depression and inflammation. Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) have been reported in the serum and cerebrospinal fluid (CSF) of patients with MDD [123]. Increased mRNA and protein levels of IL-1β, IL-6 and TNF-α have also been observed in the PFC of depressed individuals who died by suicide compared to controls [124]. Meanwhile, elevations of C-reactive protein (CRP), an acute-phase protein, and translocator protein (TSPO), a marker of neuroinflammation, have been found in patients with depression [125,126]. In animal studies, chronic stress can induce depression-like behaviors accompany with upregulation of pro-inflammatory cytokines levels. Administration of lipopolysaccharide (LPS) that activates the immune system and inflammatory responses can produce depressive-like behaviors in rodents [127]. Pro-inflammatory cytokines can also reduce brain serotonin through inducing indoleamine-pyrrole 2,3-dioxygenase (IDO), which metabolizes tryptophan [123]. Further evidence supporting the relationship of depression and inflammation come from the high comorbidity between depression and inflammation-related diseases, such as cancer, diabetes, cardiovascular diseases and inflammatory bowel disease [128,129].

Modulation of neuroinflammation may be one of the targets of antidepressant therapy. Classic antidepressants including selective serotonin reuptake inhibitors (SSRIs) have an impact on peripheral inflammation and can reduce inflammatory cytokines [130,131]. Several studies show that ketamine, a fast-acting antidepressant, also has immunomodulatory ability [128]. On the other hand, the antidepressant effects of anti-inflammatory agents have been studied. A meta-analysis comprised of 30 RCTs with 1610 participants suggest that anti-inflammatory agents, whether acting as adjunctive treatments or monotherapy, have significant antidepressant effects in comparison with placebo for patients with MDD [132].

The exact mechanisms by which inflammation plays a role in depression are not fully understood. Studies strongly indicate that microglia, the brain-resident immune cells, may play a central role in neuroinflammation of depression [133]. An increase of microglia activation has been found in both MDD patients and depressed animals [134,135]. Activated microglia are major source of inflammatory cytokines. It is assumed that the production of pro-inflammatory cytokines is mainly regulated by NF-κB signaling. NF-κB is an transcription factor belonging to Rel family and participates in regulating immune and inflammatory processes. Upon stress, IκBα is phosphorylated at serine residues and then becomes ubiquitinated and degraded. Subsequently NF-κB is phosphorylated by activated IκB and translocates into the nucleus, where it promotes the expression of its target genes, including IL-6, IL-1β, TNF-α, COX-2 and iNOS [125,136]. The pro-inflammatory cytokines in turn activate NF-κB and amplify inflammatory responses [137,138]. Antidepressants including SSRIs and SNRIs have been shown to alleviate the neuroinflammation through NF-κB inflammatory pathway and reducing cytokines in blood or tissue [139].

The finding that there exists a crosstalk between Nrf2 and NF-κB has established the anti-inflammatory role of Nrf2. Nrf2 can inhibit oxidative stress-mediated NF-κB activation through the mechanism of redox regulation. HO-1, one of the target genes of Nrf2, has been reported to inhibit NF-κB activity [140,141]. It is also shown that Nrf2 can restrain NF-κB-induced inflammatory response by competing with NF-κB to bind to CBP [39]. And NF-κB can in turn repress the transcriptional level of Nrf2 through this competition [142]. Nrf2-deficient mice have higher sensitivity to LPS-induced inflammation and enhanced levels of TNF-α and MMP-9 which are regulated by NF-κB, as well as depressive-like behaviors which can be reversed by the anti-inflammatory drug rofecoxib [33,143]. In addition, Nrf2 is reported to directly inhibit LPS-induced upregulation of proinflammatory cytokines, including IL-6 and IL-1β, through the ROS-independent transcriptional inhibition [144]. Studies also suggest that Nrf2 directly regulate certain anti-inflammatory mediators such as IL-17D and CD36 [145,146]. Several compounds that activate Nrf2 signaling have been shown to exert antidepressant effects via suppressing NF-κB signaling and lowering proinflammatory cytokines [45,147].

Recently, studies have found that Nrf2 inducers can activate the anti-inflammatory phenotype and inhibit the pro-inflammatory phenotype of microglia through regulating BDNF [50,148]. BDNF is a well-known neurotrophin that plays an important role in depression [149,150]. Emerging evidence suggest a close relationship between BDNF and neuroinflammation in depression [151]. Nrf2 KO mice showed decreased levels of BDNF-TrkB signaling and enhanced inflammation [29]. Activation of Nrf2 can transcriptionally activate BDNF through binding to the *bdnf* exon I promoter and decreasing transcriptional suppressors of BDNF (HDAC2, mSin3a, and MeCP2) [32]. BDNF can in turn activate the antioxidant defense mechanism by increasing the nuclear translocation of Nrf2 [50]. Hence, there seems to be a positive feedback loop between Nrf2 and BDNF in depression and the underlying mechanisms need further research.

3.4. Nrf2 and ferroptosis in depression

Ferroptosis is a novel form of regulated cell death characterized by iron-dependent lipid peroxidation which is distinct from other cell death processes in morphology and mechanism [152]. The classical pathologic processes of ferroptosis include excessive free iron, glutathione peroxidase 4 (GPX4) inactivation, and phospholipid oxidation of polyunsaturated fatty acids (PUFA) [23]. Excessive free iron acts as a critical initiator of ferroptosis although its precise role is unclear [153,154]. Ferroptosis can be inhibited by iron chelators such as deferoxamine and deferiprone [154,155]. GPX4 is a major negative regulator of ferroptosis. As a lipid repairing enzyme, GPX4 can transform the toxic lipid hydroperoxides (L-OOH) on the cell membrane into non-toxic lipid alcohols (L-OH) [154]. Deletion of GPX4 or inhibition of GPX4 expression can trigger ferroptosis [11,153–155]. The function of GPX4 requires GSH as a substrate, while GSH synthesis needs GCL and GSS and is regulated by the glutamate-cystine antiporter system xc- [152,154,155]. Inhibition of glutamate synthesis or XC - can induce ferroptosis as well [155]. Lipid peroxidation is the main characteristic of ferroptosis. The PUFA-containing phospholipids such as arachidonic acid (AA) and epinephrine are oxidized preferentially [156,157]. Lipid peroxidation alters the structure and function of the cell membrane, leading to cell dysfunction and extensive tissue damage. 4-hydroxy-2-nonenal (4-HNE) and MDA are reactive lipid species (RLS) generated by lipid peroxidation, which can initiate lipid peroxidation themselves.

Since it was defined in 2012, emerging evidence suggest that ferroptosis is involved in many diseases from cancer to a series of neurological diseases including stroke and AD [158,159]. Recent studies have shown a link between depression and ferroptosis. The study by our team using proteomics have found activation of ferroptosis in mice exposed to CUMS [24]. Further analysis demonstrates increased levels of MDA and ferritin light chain 1 (FTL1) and decreased levels of GPX4 and GSH in depressed mice which result in neuronal loss [24]. Mice exposed to chronic restraint stress exhibit iron homeostasis imbalance and iron accumulation [160]. Increased levels of lipid peroxidation have been repeatedly reported in patients with depression as evidenced by high levels of MDA and 4-HNE in the plasma [161,162]. High lipid peroxidation increases the risk of treatment-resistant depression [162]. Antidepressants including fluoxetine and citalopram can reduce MDA levels in depressed patients [163]. Post-mortem results of MDD patients showed decreased levels of GSH and GPX in the prefrontal cortex [67]. The single-nucleotide polymorphisms of GPX4 are found to be associated with the risk of depression [164]. As previously mentioned, the mitochondrial dysfunction observed in depression may also result from ferroptosis. Taken together, these studies provide evidence of ferroptosis existing in depression and regulating ferroptosis may be a promising treatment for depression.

Numerous studies indicate that Nrf2 can regulate ferroptosis through multiple aspects. Actually, almost all ferroptosis-related genes are directly or indirectly regulated by Nrf2. Nrf2 targets genes that are related to iron homeostasis such as HO-1, ferritin heavy chain 1 (FTH1), FTL, FPN1 (SLC40A1) and Transferrin receptor 1 (TFR1) [165–168]. FTH1 and FTL are two subunits of the cytosolic iron storage protein ferritin, which sequesters excess free iron and maintains labile iron pools (LIP) homeostasis [169]. FPN1 and TFR1 are responsible for exporting excess iron from cells and importing iron into cells respectively. NRF2 regulates genes involved in heme biosynthesis and transport and thus indirectly regulates iron metabolism [170]. The enzymes that are essential for GSH synthesis including GCLC, GCLM and GSS, as well as SLC7A11, an important subunit of xc-, all of which promotes the synthesis of GPX4 and further mediates suppression of ferroptosis, are targets of Nrf2 [171]. Moreover, Nrf2 is required for the basal expression of GPX4 [172]. Nrf2 also regulates a number of genes involved in lipid metabolism in ferroptosis. Peroxisome proliferator-activated receptor gamma (PPARγ), a major regulator of lipid metabolism, activates with Nrf2 mutually and initiates ferroptosis [171]. Although studies on Nrf2 regulation of ferroptosis in depression are very rare, a recent study have shown that edaravone, a free radical scavenger, can reduce oxidative stress and ferroptosis and alleviate depressive symptoms through the Sirt1/Nrf2/HO-1/Gpx4 pathway in chronic social defeat stress (CSDS) depression model [173].

4. Targeting Nrf2 to treat depression

Since Nrf2 activation can play a neuroprotective role by modulating a variety of pathological processes, many natural and synthetic compounds have been shown to activate the Nrf2 pathway and used to treat various neurological diseases, some of which have also been reported in the treatment of depression.

4.1. Natural NRF2 activators

Sulforaphane, an organosulfur compound isolated from Brassicaceae plants, is a potent natural NRF2 activator. Sulforaphane has been reported to increase Nrf2 expression and nuclear localization as well as interact with Cys151 residue of KEAP1 to inhibit Nrf2 degradation [174]. Several studies have evaluated the role of sulforaphane in depression. It is reported that sulforaphane exerts antidepressant- and anxiolytic-like activities and inhibits HPA axis and inflammatory response in chronic stress-induced depression models [37]. Another study have found that sulforaphane has both therapeutic and prophylactic effects on inflammation-related depression [175]. It is also found that sulforaphane can promote the binding of Nrf2 and BDNF in CSDS mice models, indicating that sulforaphane may confer stress resilience [32]. Moreover, sulforaphane has also been found to protect neurons via autophagy and promote mitochondrial biogenesis by activating Nrf2 [176].

Curcumin is naturally occurring polyphenolic compound derived from rhizomes of *Curcuma longa* and has anti-inflammatory and antioxidant properties [177]. Curcumin can also bind to Cys151 residue of KEAP1, leading to the Nrf2-ARE binding and an increase of HO-1 expression [178–180]. It is reported recently that curcumin can activate Nrf2 through PKCδ-mediated p62 phosphorylation at S351 [181]. Meta-analysis reveals that curcumin is effective in improving depressive and anxiety symptoms [182]. Curcumin exerts antidepressant and antioxidant effects in CUMS model of depression [183]. In a LPS-induced rat model of depression, curcumin is found to inhibit oxidative stress, inflammation and neuronal apoptosis [184].

Quercetin is a natural polyphenol flavonoid compound abundantly present in fruits and vegetables. Quercetin manifests potent free-radical scavenging activity and can reduce ROS levels [185]. In vitro, the administration of quercetin was able to promote Nrf2 nuclear translocation, upregulate the expression of GCLC and increase total GSH levels [186]. In mice subjected to CUMS, quercetin at 40 mg/kg relieves depressive-like behaviors and reverses the abnormalities of Nrf2, HO-1, SOD, GST, MDA and NO, indicating the antioxidant and anti-inflammatory role of quercetin [187].

Resveratrol is a naturally polyphenolic compound found in grapes, berries, and nuts. Studies have shown that resveratrol can alleviate cell oxidative damage by reducing MDA levels through activating Nrf2/HO-1 [188]. Anti-inflammatory and anti-apoptotic effects of resveratrol have also been reported in several studies [189–192]. Resveratrol is reported to alleviate depression-like symptoms and accompanied oxidative stress via reducing MDA and increasing SOD in rats exposed to CUMS. In addition, resveratrol can reduce the expression of NF-κB and pro-inflammatory cytokines in LPS-induced depression [193].

Melatonin , mainly produced by the pineal gland, is an endogenous neuro-hormone regulating circadian and seasonal rhythms. Numerous studies have shown that melatonin activates Nrf2 and its target phase-2 antioxidative enzymes including HO-1, NQO-1 and SOD [194]. It is shown that melatonin ameliorates LTP-induced depression-like behaviors in mice and suppress the production of mitochondrial and cytosolic ROS and NF-κB signaling through Sirt2/Nrf2 pathway [195]. Using the same depression model, another study have found that melatonin can exert pro-autophagy and anti-inflammatory effects [196].

Lycopene is an aliphatic hydrocarbon carotenoid extracted from tomatoes, watermelons and papayas. Lycopene has been reported to exert prophylactic and therapeutic effects in multiple neurological diseases including depression [197]. Lycopene can upregulate the expressions of HO-1 and NQO-1, and downregulate inflammatory cytokines IL-1β and TNF-α through activation of Nrf2 signaling and inactivation of NF-κB translocation [198]. Pretreatment of lycopene ameliorates LPS-induced depression-like behaviors, reduces the levels of IL-6 and TNF-α in the plasma and alleviates neuronal injury in the hippocampus [199]. In vitro, lycopene inhibits LPS-induced COX-2 expression through HO-1 activation in microglia [200]. However, the role of lycopene activating Nrf2 in depression needs more research.

4.2. Synthetic NRF2 activators

TBHQ is a synthetic phenolic antioxidant and commonly used as a food preservative. TBHQ activates Nrf2 through electrophilic modification of Keap1 [201]. Through inducing Nrf2, TBHQ activates enzymes of glutathione system such as GST, GCL, GSH-Px and GR and inhibits the NOX4 transcription, thereby decreasing the levels of ROS and MDA [202]. It has been shown that TBHQ ameliorates methamphetamine-induced depression-like behaviors, which is associated with reduced ROS and apoptosis levels resulted from activation of Nrf2/HO-1 and PI3K/AKT [203]. TBHQ is also found to promote autophagy in an Nrf2-dependent pathway in depressed mice [34]. Recently another study demonstrates that TBHQ alleviates LPS-induced depression-like behaviors by suppressing neuroinflammation in mice [204].

DMF is an Nrf2 activator approved by US Food and Drug Administration used for the treatment of relapsing multiple sclerosis. DMF has been found to promote Nrf2 transcription by modifying the Cys151 residue resides in the BTB domain of the Keap1 [205]. It is shown recently that DMF can also bind to the β-propeller domain (Keap1-DC) of Keap1 [206]. DMF was reported to mitigate CUMS induced anxiety- and depressive-like behaviors as well as neuinflammation through Nrf2 signaling [38]. DMF is also found to promote mitochondrial biogenesis in vitro and in vivo [207]. Recent study suggests that DMF can inhibit ferroptosis in chronic cerebral hypoperfusion model [208]. The multiple mechanisms of DMF in the treatment of depression need to be further investigated.

Edaravone is a free radical scavenger. Through activating Nrf2 pathway, edaravone plays a protective role in a variety of neurological diseases such as acute cerebral infarction, traumatic brain injury, amyotrophic lateral sclerosis and epilepsy [209–211]. Edaravone is found to have significant effects on corticosterone-, LPS-, and CRS-induced mice models of depression [212–214]. In a recent study, it is shown that edaravone ameliorates CSDS-induced depression and anxiety-related behaviors, prevents oxidative stress and mitochondrial damage as well as neuroinflammation and these effects can be abolished by Nrf2 and GPX4 inhibitor, indicating that Gpx4-mediated ferroptosis via Sirt1/Nrf2/HO-1 pathway may be involved [173].

TBE-31 and MCE-1 TBE-31 is a tricyclic compound containing two cyano enones, both of which can bind with cysteine residues of Keap1, making it a highly potent Nrf2 activator [215,216]. In an LPS-induced inflammatory model of depression, TBE-31 is found to significantly attenuate depression-like behaviors and decrease the serum level of TNF-α in mice [217].

In addition, some non-pharmacologic modulation have been found to exert beneficial effects by targeting Nrf2 pathway. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive and safe treatment for depression, but its underlying mechanism has not been fully elucidated. rTMS is proved to regulate synaptic plasticity, neurogenesis and inflammatory response in mice models of depression [218,219]. In the CUMS-induced rat depression model, rTMS increases Nrf2 nuclear translocation and reduces levels of inflammatory cytokines in the hippocampus [220]. Physical exercise is an effective intervention for depression but its mechanism is still unclear. Previous studies indicate that physical activity can improve depressive symptoms though regulating inflammation, oxidative stress and neuroplasticity [221]. Moreover, exercise has been shown to activate Nrf2 signaling in multiple tissues including brain in rodent models [222,223]. It is reasonable to speculate that Nrf2 activation may mediate the antidepressant effects of physical exercise, which still need further research.

5. Conclusion

A large amount of evidence indicate that oxidative stress and impaired antioxidant defense system induced by the production of ROS/

RNS play an important role in the pathogenesis of depression. Oxidative stress can lead to or aggravate a series of pathological processes including mitochondrial dysfunction, neuroinflammation, autophagical disorder and ferroptosis. Boosting antioxidant defenses has beneficial effects in the treatment of depression. NRF2 is a key endogenous regulator in the protection against oxidative stress. Activation of Nrf2 holds great promise in depression therapy. On the one hand, activation of Nrf2 promotes the transcription of antioxidant genes to combat oxidative stress. On the other hand, Nrf2 activation can affect the transcription of genes that directly regulate mitochondrial dysfunction, neuroinflammation, autophagical disorder and ferroptosis. Therefore, Nrf2 plays a neuroprotective role via regulating multiple pathways (Fig. 2). Targeting the Nrf2 pathway has shown exciting results in various depression models and in vitro experiments. However, since Nrf2 regulates multiple processes, the potential of Nrf2 activators in the treatment of depression needs to be further carefully investigated. Some natural and synthetic compounds acting as Nrf2 activators have shown significant antidepressant effects in preclinical experiments and have great potential for clinical translation. Although some fundamental questions remain to be addressed before these novel compounds targeting Nrf2 can be further used in clinical trials. Moreover, several non-pharmacological interventions such as rTMS and physical exercise have been shown to exert antidepressant effects by activating Nrf2 signaling.

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Declaration of competing interest

None.

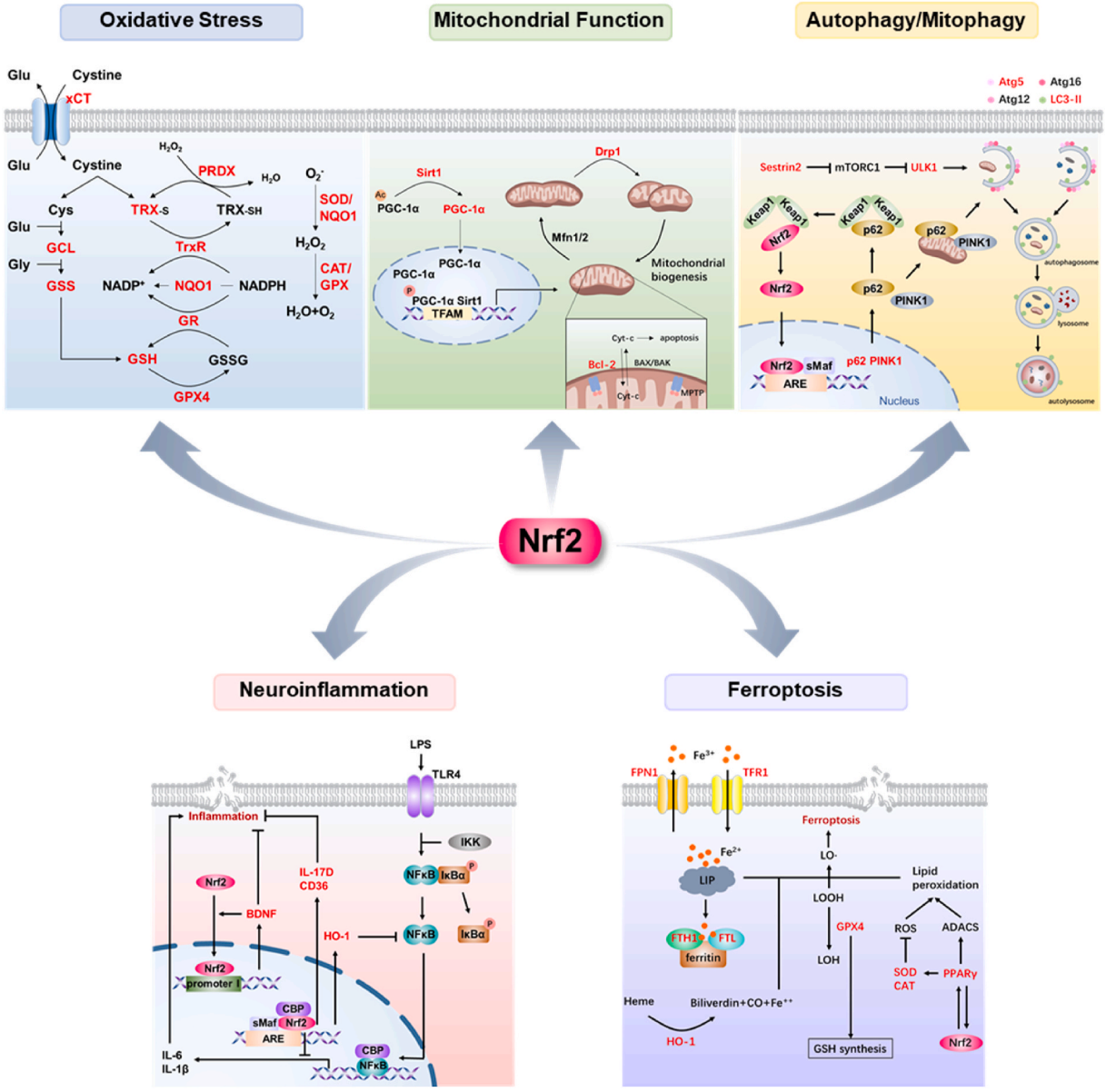

Fig. 2. Schematic representation of the multifaceted role of Nrf2 in depression. The target molecules of Nrf2 (marked in red) are invovled in oxidative stress, mitochondrial function, autophagy/mitophagy, neuroinflammation and ferroptosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Data availability

No data was used for the research described in the article.

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