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Review

Mitochondrial dysfunction: A fatal blow in depression

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ABSTRACT

Mitochondria maintain the normal physiological function of nerve cells by producing sufficient cellular energy and performing crucial roles in maintaining the metabolic balance through intracellular Ca^{2+} homeostasis, oxidative stress, and axonal development. Depression is a prevalent psychiatric disorder with an unclear pathophysiology. Damage to the hippocampal neurons is a key component of the plasticity regulation of synapses and plays a critical role in the mechanism of depression. There is evidence suggesting that mitochondrial dysfunction is associated with synaptic impairment. The maintenance of mitochondrial homeostasis includes quantitative maintenance and quality control of mitochondria. Mitochondrial biogenesis produces new and healthy mitochondria, and mitochondrial dynamics cooperates with mitophagy to remove damaged mitochondria. These processes maintain mitochondrial population stability and exert neuroprotective effects against early depression. In contrast, mitochondrial dysfunction is observed in various brain regions of patients with major depressive disorders. The accumulation of defective mitochondria accelerates cellular nerve dysfunction. In addition, impaired mitochondria aggravate alterations in the brain microenvironment, promoting neuroinflammation and energy depletion, thereby exacerbating the development of depression. This review summarizes the influence of mitochondrial dysfunction and the underlying molecular pathways on the pathogenesis of depression. Additionally, we discuss the maintenance of mitochondrial homeostasis as a potential therapeutic strategy for depression.

1. Introduction

Mitochondria generate sufficient energy for cellular metabolic stability and participate in an array of physiological processes, including cellular signaling, Ca^{2+} homeostasis, and apoptosis regulation. It is commonly acknowledged that the brain consumes approximately 20% of the available oxygen and energy, although it accounts for only 2% of the total body weight [1]. In line with their dependence on high-energy metabolic rates, neurons are particularly vulnerable to mitochondrial malfunction. Preclinical models of depression show altered expression of genes related to mitochondria, damage to mitochondrial membrane proteins and lipids, disruption of the electron transport chain, increased oxidative stress, neuroinflammation, and apoptosis. Most of these parameters can be altered in the brains of patients with depression. Currently, a new hypothesis of depression revolves around the impairment of neuroplasticity. Axonal and dendritic development, synaptogenesis, and the elimination of weak connections between neurons are examples of synaptic plasticity. Mitochondria play a significant role in neuroplasticity. According to a well-researched theory, numerous brain areas in individuals with depression exhibit structural and functional dysfunction because of poor neuroplasticity caused by mitochondrial stress [2]. Additionally, neurogenesis is thought to play a significant role in the physiological processes and recovery of the damaged brain. Several types of stress have been shown to impair neurogenesis and

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hippocampal cell proliferation in animal models [3,4]. Because more mitochondrial proteins and genomes are required for neural differentiation throughout neuronal development, mitochondrial biogenesis occurs at a higher rate [5,6]. As a typical consequence of mitochondrial oxidative phosphorylation (OXPHOS), mitochondrial reactive oxygen species (mtROS) also plays essential roles in cellular signaling and physiology. However, excessive accumulation of reactive oxygen species (ROS) can cause oxidation of proteins and lipids, which in turn causes apoptosis, necrosis, and inflammation. In depression, mitochondrial dysfunction has been associated with increased oxidative stress in both preclinical and clinical studies [7,8]. Therefore, maintenance of the number, morphology, and function of mitochondria, known as mitochondrial quality control (MQC), is indispensable for cell survival and functioning [9].

Major depressive disorder (MDD) is a severe psychological illness characterized by prolonged depressed mood, often accompanied by poor self-esteem, fatigue, anhedonia, and unprovoked discomfort [10]. Owing to its high morbidity and mortality rates, depression is a significant cause of disability globally, and owing to lost productivity, has a severe economic impact on society [11]. Selective serotonin reuptake inhibitors are routinely recommended as the first-line treatment for MDD. However, only about 50% of the patients experience improvement. Psychotherapy or repetitive transcranial magnetic stimulation is an excellent alternative treatment for patients who are unable to tolerate medication. However, such treatments can be addictive and may need to be repeated in treatment-resistant depression; these problems need to be urgently addressed. Considering the established roles of mitochondrial malfunction in depression, maintaining mitochondrial homeostasis is a promising therapeutic target. Numerous studies have focused on modulating mitochondrial dysfunction to screen for effective therapies. This review summarizes the interactions between depression and mitochondria to identify potential diagnostic biomarkers and prospective therapeutic avenues for depression.

2. Mitophagy and depression

Mitophagy is an early response for nerve cell protection, favoring adaptation to cell stress by clearing damaged and ageing mitochondria [12]. Mitophagy dysfunction can build-up impaired mitochondria resulting in an imbalance in homeostasis, nerve cell degeneration, and/or death, leading to depression. In a study conducted on subjects treated with fluoxetine to alleviate corticosterone-induced cell injury, fluoxetine attenuated cell death by increasing the clearance of damaged mitochondria, promoting astrocytic mitophagic flux, and reducing mtROS accumulation [13]. De Rudranil et al. [14] revealed that cold restraint stress, a stress-related mucosal disease model in rodents, induces severe gut mitochondrial dysfunction through excessive mitochondrial fission, concomitant with aberrant mitophagy, in the intestinal mucosa. Furthermore, insufficient activation of mitophagy leads to failure of MQC machinery and subsequent cascade activation of the caspase system during the later stages of stress, eventually resulting in NF-κB-mediated proinflammatory mucosal damage and Bax-dependent apoptosis. Researches have illustrated that G11–5 and fluoxetine can improve the depressive behaviors of the mice as demonstrated by fewer escape failures in the learned helplessness (LH) model and higher social interaction in the social defeat stress (SDS) model by protecting mitophagy and restoring retrograde axonal transport and neurotransmitter release [15,16].

2.1. The classic mitophagy pathway in depression

The PTEN-induced putative kinase 1 (PINK1)/Parkin system is the most extensively documented mitophagy mechanism. Under normal physiological conditions, Parkin is diffusely localized in the cytoplasm in a self-inhibitory manner. However, following mitochondrial damage, PINK1 undergoes rapid autophosphorylation and induces depolarized mitochondrial autophagy through a feed-forward mechanism involving Parkin activation [17,18]. Subsequently, the assembly of ubiquitin chains via the PINK1/Parkin pathway in damaged mitochondria initiates the recruitment and activation of mitophagy receptors, including optineurin, nuclear dot protein 52, SQSTM1/p62, and neighbor of BRCA1 gene 1. Recent studies have demonstrated that the absence of p62 is associated with elevated anxiety, depression, and hippocampal-dependent cognitive decline accompanied by mitochondrial dysfunction, which is evident in mice even at 2 months of age. Studies of neural tissue in 6-month-old p62-knockout mice have clearly revealed severe neuropathological lesions, including a notable drop in serum brain-derived neurotrophic factor (BDNF) levels and the total number of neurons [19,20]. Conversely, the overexpression of p62 in the hippocampus of p62-knockout mice can alleviate the resultant impairment of gross behavioral patterns, especially those related to anxiety and depression, and displays improved mitochondrial function [21]. During severe nutrient starvation, as a maintainer of mitochondrial equilibrium, AMP-activated kinase (AMPK) can promote mitophagy through activation of Unc-51–like autophagy-activating kinase 1 (ULK1), which is an initial kinase in the autophagy pathway, thus maintaining mitochondrial integrity and cell survival [22,23]. Depression significantly inhibits the activation of AMPK/ULK1 signaling, which in turn upregulates mTOR expression [24,25]. A study using a chronic unpredictable mild stress (CUMS) depression model revealed that the knockdown of miR-134–5p can regulate the AMPK/ULK1 pathway to substantially improve mitophagy in the hippocampus, thereby reducing mitochondrial damage and restoring the normal morphology of dendritic spines [26].

An increasing number of studies have focused on 18-kDa translocator protein (TSPO)-mediated mitophagy. The effectiveness of the MQC system is enhanced by TSPO's partnership of TSPO with VDAC1. Specifically, when the TSPO/VDAC1 ratio increases, it reduces mitochondrial coupling and promotes excessive ROS, thereby inhibiting downstream PINK1/Parkin-mediated mitophagy, subsequently limiting the recruitment of P62 and abolishing the aggregation of autophagosomes [27]. Recently, a growing body of evidence suggests that TSPO may be a key target for diagnosing or treating illnesses associated with stress. For example, teenage inpatients with a history of suicide attempts have lower platelet TSPO levels [28]. However, the information on the expression of TSPO in the brain is conflicting [29]. Interestingly, depression has been associated with higher TSPO expression in numerous positron emission tomography (PET) studies [30]. Moreover, according to recent genetic research, a greater frequency of genetic variation in TSPO, presumably affecting neurosteroid production, has been found in individuals with separation anxiety [31]. It has been shown that Wuling powder and 3-(3,4-methylenedioxy-5-trifluoromethyl phenyl)− 2E-propenoic acid isobutyl amide can improve the TSPO-mediated mitophagy to alleviate the depression-like behaviors in LH mice model [16,32].

2.2. The receptor-mediated mitophagy in depression

In addition to the PINK1/Parkin pathway that specifically induces mitophagy, different mitochondrial proteins and lipids function as mitophagy receptors to mediate basal mitophagy [33]. Previous studies have reported that receptor-mediated basic-level mitophagy occurs, especially in the brain with high-energy metabolism, which serves as an ongoing mitochondrial monitor in healthy settings or chronic illness conditions [34]. Interestingly, different modes of mitophagy can coexist in vivo and interact to regulate physiological and pathological changes. For example, BNIP3L/NIX mediated basal mitophagy interacts with the classical PINK/Parkin pathway to enhance mitophagy [35]. Recently, it has been reported that the mitochondrial and synaptic functions of hippocampal neurons are compromised by glucocorticoids, and the underlying mechanism involves the inhibition of NIX protein expression and NIX-mediated mitophagy. Further analysis demonstrates that basal

mitophagy generated by AMPK/PGC-1α/NIX signaling pathway is substantially more effective in controlling mitochondrial impairment and restoring mitochondrial function [36,37]. A recent study illustrated that the deficits in the BNIP3L/NIX-mediated mitophagy by TNF-α led to the accumulation of damaged mitochondria, which triggered synaptic defects and passive stress-coping behaviors [38]. In a steady state, BNIP3 is a stable outer mitochondrial membrane (OMM) protein that displays normal physiological function with very low levels of expression. However, in an irritable state, BNIP3 acts as an anti-stress factor to enhance transcription levels to counter deleterious effects in the mitochondria [39]. Tohda et al. previously revealed that antidepressants, such as imipramine, mianserin, and milnacipran, could elevate BNIP3 mRNA activity in vitro [40]. Animal research conducted using an LH model of depression showed that the transcriptional activity of the BNIP3 gene increases in response to stress stimulation, and the molecular mechanism may be responsible for the improvement of BNIP3-mediated mitophagy in depression by imipramine [39].

2.3. Sirtuins in depression

Sirtuins (SIRT1–7) belong to an evolutionarily conserved family and are predominantly involved in diverse cellular metabolic processes via nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylation of targeted proteins [41]. Accumulating evidence reveals that sirtuins can regulate mitophagy and mitochondrial biogenesis, which targets the activation of transcription factors FOXO1, FOXO3a, PPARγ, TFEB, and PGC-1α coactivator [42]. Sirtuins have various intracellular localization patterns that enable them to perform various functions. SIRT1, SIRT6, and SIRT7, which are mostly localized in the nucleus, regulate the expression of signaling proteins. SIRT2 is usually found in the cytoplasm, while SIRT2 is also a nuclear protein that modulates the cell cycle. SIRT3, SIRT4, and SIRT5 are mostly found in the mitochondria, where they control the metabolism of numerous mitochondrial proteins in response to stress [43].

It has been reported that SIRT1 can decrease in deacetylated PGC-1α and regulate the downstream molecule uncoupling protein-2 (UCP2) to induce depolarization of the mitochondrial membrane potential and reduction in mtROS, leading to mitophagy [44]. In the peripheral blood of patients with MDD, the expression of SIRT1 is significantly downregulated compared with that in healthy individuals and in remitted patients with MDD [45]. Additionally, a study discovered two loci on chromosome 10 that increased the risk of MDD, one adjacent to SIRT1 [46]. Recent research employing animal models of depression concluded that interruption of SIRT1 expression significantly contributes to depression-like actions. According to Abe-Higuchi et al., persistent stress causes decreased SIRT1 levels in the dentate gyrus, and pharmacological or genetic deletions of SIRT1 in the hippocampus [47]. Control of the FOXO1 pathway by SIRT1 can contribute to several mitophagy-related mechanisms, such as facilitating the formation of the ULK1 complex and elongation of the phagosome membrane. Physical activity plays a dominant role in ameliorating cognitive decline and mitigating synaptic dysfunction in Alzheimer's disease. Intrinsic physiological regulatory mechanisms enhance the PINK1/Parkin-mediated mitophagy pathway by altering the NAD^+/NADH ratio to upregulate the SIRT1-FOXO1/3 pathway [48]. Similar to SIRT1, SIRT3 exerts a neuroprotective effect by deacetylating FOXO3, thereby activating the SIRT3/FOXO3a axis to enhance the ubiquitination-dependent PINK1/-Parkin-mediated mitophagy pathway [49]. SIRT3 overexpression in cortical neurons significantly increased the phosphorylation of AMPK and lowered the phosphorylation of mTOR, leading to mitophagy [50]. A recent investigation demonstrated that honokiol, an extract from Magnolia bark, can induce mitophagy in the manner of SIRT3-dependence so as to alleviate mitochondrial dysfunction in hippocampal neurons, drastically reduce synaptic damage, and exhibit anti-Alzheimer's disease benefits [51]. Meanwhile, aging leads to SIRT4 activation that downregulates mitophagy to promote mitochondrial fusion [52]. Melatonin stimulates mitophagy and mitochondrial biogenesis by increasing the expression of SIRT6 and the AMPK/PGC-1α/AKT signaling pathway [53]. (Fig. 1).

3. Mitochondrial dynamics and depression

A tightly monitored balance between mitochondrial fusion and fission is essential for sustainable neuronal survival, axonal transport, and quality control [54]. Among the different metabolomic signatures observed in the ventral hippocampus between vulnerability and resilience to chronic stress, a study reported that vulnerable rats favored mitochondrial fusion to counteract the overproduction of reactive oxidative species, whereas resilient rats activated fission to ensure metabolic efficiency [55]. During times of significant metabolic stress, individual mitochondria integrate into a larger dynamic network of mitochondria that favors the exchange of metabolites, proteins, and mitochondrial DNA (mtDNA) to maintain mitochondrial stability and address urgent energy demands [56]. Mitochondrial fission involves the disintegration of larger mitochondrial networks into more compact structures. This mechanism, which is precisely regulated by the redistribution of mitochondria, later cooperates with mitophagy to eliminate harmful components of individual mitochondria, enabling the maintenance of an appropriate mitochondrial population to support adequate cellular respiration. In mammals, there are two different types of critical mitofusins in the mitochondrial membrane that execute the process of mitochondrial fusion: mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) embedded in the OMM, and optic atrophy 1 (OPA1) located in the inner mitochondrial membrane (IMM) [57]. Mfn2, a GTPase, is responsible for an array of processes including mitochondrial fusion, mitochondrial transportation, anchoring to the endoplasmic reticulum, and mitophagy [58]. Mfn1 interacts with OPA1 to facilitate IMM fusion [59]. When a fission event is triggered, dynamin-related protein 1 (Drp1) swiftly migrates from the cytosol to the OMM and binds to mitochondrial fission 1 protein (Fis1) at fission locations, where it loops around the mitochondria and develops larger oligomeric ring-like structures, eventually cutting off the mitochondrial membrane via GTP hydrolysis [60,61].

As neurons demand high and constant levels of mitochondrial metabolism to generate sufficient bioenergy, the cytoplasm contains many mitochondria distributed in axons, presynaptic terminals, and dendritic shafts, in case of any functional or morphological damage to the mitochondria [62]. In neurons, augmentation of mitochondrial fragmentation permits the redistribution of newly produced mitochondria to increase the density of dendritic spines and the abundance of dendritic mitochondria for sufficient ATP supply and Ca^{2+} buffering to distant regions [63,64]. Furthermore, any interruption in the fission of the IMM and OMM may diminish the voltage gradient and induce an unstable electrical potential, resulting in cellular malfunction. Alternatively, some findings clearly indicate that downregulation of mitochondrial fusion protein or overexpression of Drp1 to induce fission aggravates mitochondrial fragmentation associated with apoptotic stimuli, promotes cytochrome C (Cyt-C) releasing from the mitochondria into the cytoplasm, and activates apoptosis-related protein (Caspase-3), thereby inducing mitochondria-dependent neuronal apoptosis [65,66].

Once mitochondrial fission becomes stronger than fusion, massive mitochondrial fragmentation may cause brain damage [67]. Lptakalim, a novel K-ATP channel opener, exerts neuroprotective effects in depression by improving mitochondrial morphology and function to alleviate abnormal mitochondrial fission, thereby restoring synaptic energy supply and enhancing synaptic plasticity, depending on the mito-K-ATP channel in neurons [68]. Emerging data indicate that sinisan can reduce the risk of early life adversity-induced depression by upregulating the level of the mitochondrial fusion protein Mfn2 and decreasing the activities of mitochondrial fission proteins Drp1 and Fis1, resulting in increased ATP levels, decreased excessive mitochondrial division, and mitigated mitochondrial structural damage in the

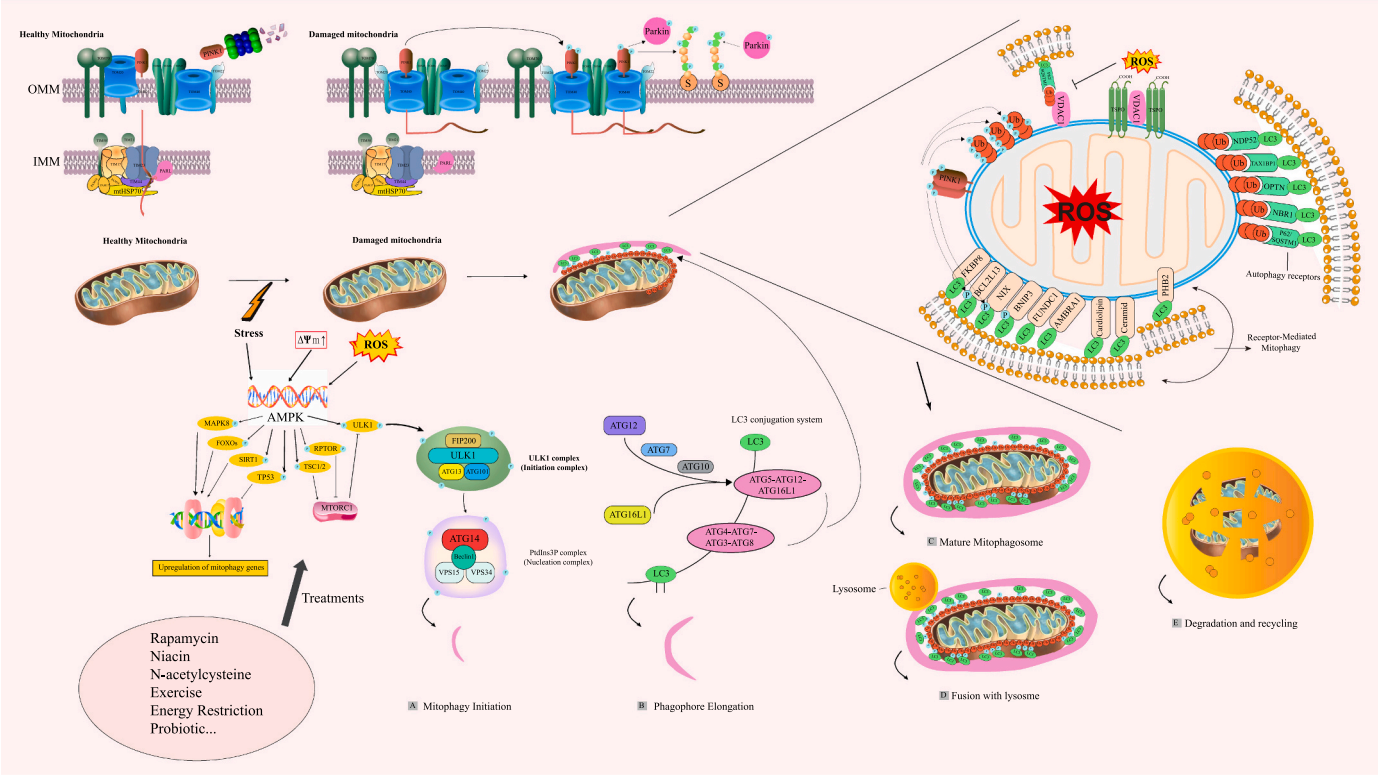

Fig. 1. : The role of mitophagy in depression. When healthy mitochondria are exposed to stress, ROS and other stimuli, mitochondria will undergo mitophagy to eliminate defective mitochondria involving the Ub-dependent PINK1/Parkin pathway and the Ub-independent receptor-mediated pathway. In damaged mitochondria, PINK1 is stabilized at the OMM and activates Parkin via a feed-forward mechanism of Parkin and ubiquitin phosphorylation (A). AMPK and MTORC1 mediate the formation of the initiation complex, which subsequently promotes nuclear complex formation (B, C). Parkin then assembles ubiquitin chains to recruit autophagy receptors on OMM, leading to the engulfment of defective mitochondria by autophagosomes known as mitophagosomes (D, E). Mitophagosomes fuse with the lysosomes for the degradation of damaged mitochondria and the recycling of certain mitochondrial components.

hippocampus [69]. Meanwhile, a study concerning comorbid depression with diabetes provides a similar insight into pathogenesis, its mechanistic investigations revealed that depression was favorably connected with the expression of Drp1/Fis1, and negatively correlated with the expression of mitochondrial fusion genes Mfn1, Mfn2, and OPA1 [70]. However, another study suggested that increased activation of mitochondrial fission by pDrp1 Ser616 is associated with PINK1-mediated MQC in resilient animals, potentially preventing the onset of major depressive abnormalities [55].

Mfn2, a transmembrane protein located in the OMM, mediates mitochondrial clustering and fusion to modulate dysfunctional mitochondria [71]. The deficiency of Mfn2 contributes to various critical malfunctions in physiological activities, including the build-up of mtROS and associated dysfunctions in mitochondrial bioenergetics [72]. An experimental study using viruses to overexpress Mfn2 in accumbens showed that it could ameliorate anxiety and depression-like behaviors through targeted medium spiny neuron mitochondrial structure and function [73]. Interestingly, intervention by Morinda officinalis oligosaccharides can significantly alleviate depression-like symptoms in hypertensive rats by downregulating the PI3K/Akt/mTOR signaling pathway, upregulating the expression of Mfn2, and triggering mitophagy in astrocytes, thereby eliminating toxic mitochondria to counteract oxidative stress and neurotoxicity [74]. One study demonstrated that CUMS decreased the expression of Mfn1 and Mfn2 in the cerebral cortex of depression-like rats, but not in rats subjected to exercise preconditioning [75]. Exposure to manganese triggers neuroinflammation by promoting the dysregulation of mitochondrial dynamics in astrocytes, which involves a reduction in mitochondrial bulk and a decrease in the expression of the Mfn2 protein [76]. Furthermore, DISC1 is a vital regulator of mitochondrial dynamics that governs the transportation, fusion, and regeneration of mitochondria in neuronal axons and dendrites [77]. Major mental disorders, including MDD and bipolar disorder, are associated with DISC1 mutations that affect mitochondrial dynamics and cause aberrant neural development [78]. (Fig. 2).

4. Mitochondrial biogenesis and depression

Mitochondrial biogenesis refers to the generation of new mitochondria to boost ATP production to meet metabolic demands under both physiological and pathological states. It is a highly complex phenomenon involving mtDNA replication, protein synthesis, and regulation by the concerted action of mitochondrial and nuclear genes [79,80]. The copy number of mtDNA, a marker of mitochondrial biosynthesis, has been evaluated in only a handful of individuals with mental illnesses: an elevated number of mtDNA copies in autism sufferers [81], low mtDNA copy numbers in bipolar disorder [82], and decreased mtDNA copy numbers in the leukocytes of depressed women over 60 years of age [83]. Greater mtDNA copy number is related to both childhood hardships and lifelong psychopathology. There are two primary routes that control mitochondrial biogenesis, SIRT1/PGC-1α axis and AMPK/PGC-1α axis. As an upstream regulator, AMPK directly stimulates PGC-1α via phosphorylation and indirectly modulates PGC-1α by SIRT1 activation in a NAD^+ -dependent manner. A recent study has revealed that suppressing SIRT1 gene has an inhibitory effect on both PGC-1α gene expression and mitochondrial density in the area of prelimbic prefrontal cortex(PFC). These findings offer critical confirmation for the hypothesis that mitochondrial malfunction may be a potential hazard in the onset of depression [84].

PGC-1α functions as an indispensable component of the transcriptional systems of the nuclear and mitochondrial genomes. PGC-1α

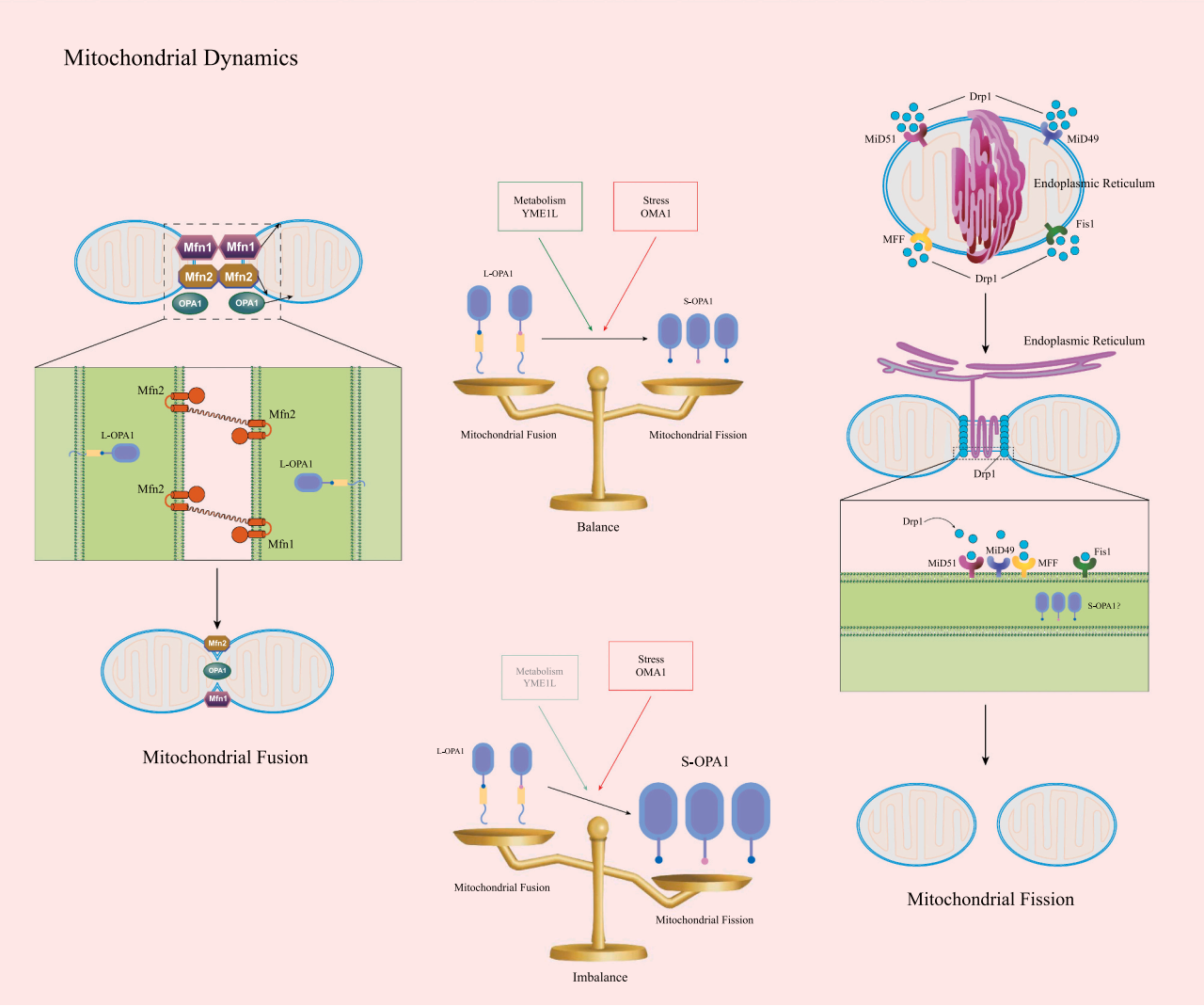

Fig. 2. : The role of mitochondrial dynamics in depression. The mitochondrial proteases OMA1 and YME1L respond to stress and metabolic stimuli respectively cleaving L-OPA1 forms into S-OPA1 forms. A reticulated, tubular network of mitochondria is maintained through balanced synthesis of L-OPA1 and S-OPA1. Under stress conditions, hyperactivated OMA1 excessively cleaves profusion L-OPA1 resulting in accumulation of S-OPA1 that appears to enhance fission events while disrupting the network structure. Mfn1 interacts with OPA1 specifically facilitating IMM fusion. Additionally, Mfn2, a GTPase, also promotes mitochondrial fusion processes. Upon triggering fission events, Drp1 swiftly migrates from the cytosol to OMM and binds to the mitochondrial fission 1 protein (Fis1) at the fission locations where it loops around the mitochondria and develops bigger oligomeric ring-like structures, eventually cutting off the mitochondrial membrane via GTP hydrolysis.

fosters the biosynthesis of mitochondria in the brain by integrating and coordinating the activity of multiple transcription factors, such as NRF1, NRF2, and UCP2 to meet energy demands for ischemic neurons [85]. A clinical investigation involving a sample of 974 Caucasians showed a surprising correlation between the PGC-1α gene and MDD, although this result could not be repeated after strict multiple comparisons and necessitated corrections [86]. Findings from the animal model of acute restraint stress indicated that higher levels of PGC-1α and NRF1 in rat hippocampus in response to stress compared with those in the control [87]. In contrast, a recent study demonstrated depression caused by prenatal stress associated with decreased mRNA levels of PGC-1α in the frontal cortex and hippocampus [88]. Several stress-related pathways targeting modulation of PGC-1α activity that attenuates mitochondrial dysfunction and affects mitochondrial biogenesis, have recently emerged as a promising therapy for multiple types of stress-related diseases [89]. Insulin-like growth factor 1 (IGF-1) can alleviate depression-like behaviors, and the abnormalities of mitochondrial biogenesis and dynamics by enhancing cAMP-response element binding protein (CREB)/PGC-1α pathway in high-fat diet mice [90]. Additionally, preliminary in vitro studies have revealed that paroxetine can promote mitochondrial biogenesis while increasing the expression of PGC-1α [91].

Interestingly, a growing body of evidences demonstrate that PGC-1α may participate in multiple pathological procedures associated with depression, including inflammation, energy metabolism, ROS, and neurogenesis [92]. Studies results show that compound 3 C can attenuate lipopolysaccharides (LPS) -induced depressive behaviors in mice and repair neurological dysfunction in ischemic rats via the AMPK/PGC-1α signaling pathway [93]. A recent investigation discovered that resveratrol had anti-inflammatory properties by controlling the polarization of M1/M2 microglial cells attributing to a PGC-1α-dependent manner. More importantly, PGC-1α alleviates NF-κB-induced neuroinflammation, thereby suppressing LPS-induced microglia polarization to the M1 phenotype and promoting microglia polarization to the M2 phenotype via coactivation of STAT6 and STAT3 [94]. Importantly, PGC-1α has been proposed to modulate mitochondrial antioxidant reactions as an adaptive strategy to ensure an adequate response to metabolic demands with high cellular energy and prevent cytotoxic

consequences of ROS build-up [95]. Activated PGC-1α provides neuroprotection against oxidative stress in hippocampal CA1 neurons subjected to transient ischemic injury. In particular, overexpression of the CaMKIV/PGC-1α pathway strengthens mitochondrial biogenesis and stimulates the expression of anti-mtROS-related enzymes, such as superoxide dismutase 2 (SOD2) and UCP2 [96]. Strikingly, PGC-1α can regulate the gene expression level of the mitochondrial SIRT3, a major mitochondria NAD^+-dependent deacetylase and a key element of the antioxidant framework, which can deacetylate and activate MnSOD to resist mtROS [89,97,98]. Additionally, in astrocytes, PGC-1α augments mitochondrial antioxidant capacity as well as decreases interleukin (IL) − 6 synthesis and release [99].

The generation of mtDNA and mitochondrial proteins is triggered by activation of the PGC-1α/NRF/TFAM axis, which ultimately results in the production of new healthy mitochondria [100]. NRF1, a nuclear transcription factor, modulates the expression of respiratory chain components and the initiation of mtDNA transcription, whereas TFAM, a mitochondrial transcription regulator, regulates the activation of mtDNA transcription and the number of mtDNA copies. A combined LPS/CUMS animal study demonstrated that stress can attenuate the expression of mtDNA and the pathway of PGC1-α/NRF1/TFAM to induce mitochondrial biogenesis. Treatment with fluoxetine and pentoxifylline can enhance the PGC1-α/NRF1/TFAM pathways to reverse energy metabolic reprogramming induced by TLR4 [101]. Similarly, metformin improves depression symptoms in old apoE4 mice probably by enhancing mtDNA replication and upregulating the mRNA expression levels involved in mitochondrial biogenesis (NRF1 and TFAM), antioxidant enzymes, and glucose metabolism regulators in the hippocampus [102]. A recent study demonstrated that electroacupuncture treatment ameliorated depression-like behaviors and cognitive dysfunction via CB1R dependent mitochondria biogenesis after experimental global cerebral ischemic stroke [103]. **(**Fig. 3**).**

5. Mitochondrial energy metabolism in depression

Neuroplasticity is inherently connected to mitochondria in the brain, which provide energy for important physiological processes involving dendritic reconstruction, neurotransmitter release, neurite extension, and neuronal differentiation [104]. In depression, the neurobiological hallmarks of the neurotrophic hypothesis are altered neuronal plasticity and neurogenesis, which can be significantly promoted by impaired OXPHOS and reduced mitochondrial ATP production [7]. Studies reported that the brain tissue from patients with MDD revealed lower levels of ATP than those from the healthy controls [105,106].

BDNF, a substance released by the nerve growth factor family, known as neurotrophins, controls neuronal survival, preserves neuronal function and synaptic plasticity, and promotes the synthesis and release of neurotransmitters [107]. BDNF plays a neuroprotective role by increasing the respiratory control index via the mitogen-activated protein kinase (MEK)/Bcl2 [108]. Therefore, suppression of the Bcl2-related signaling pathway reduces BDNF levels, which consequently affects mitochondrial function, resulting in the impairment of plasticity and initiation of apoptosis. In addition to manufacturing oxygen and nitrogen species for synaptic plasticity, mitochondria trigger caspases in dendrites to eliminate postsynaptic spines associated with chronic depression [109]. In line with mitochondrial function, BDNF enhances the utilization ratio of oxidation to enable neuronal plasticity. Antidepressant medication for 8 weeks resulted in a 48% increase in BDNF mRNA levels in participants [110]. Therefore, the alteration of BDNF in the plasma has been used as a measure of the therapeutic response for depression [111]. Multiple types of stress can lower BDNF levels in the limbic brain, but long-term treatment for depression improves BDNF expression [112].

CREB is a downstream protein of the BDNF pathway and has vital physiological relevance in fostering neurogenesis. This decreased activity of CREB may be related to the onset of depression; however, it can

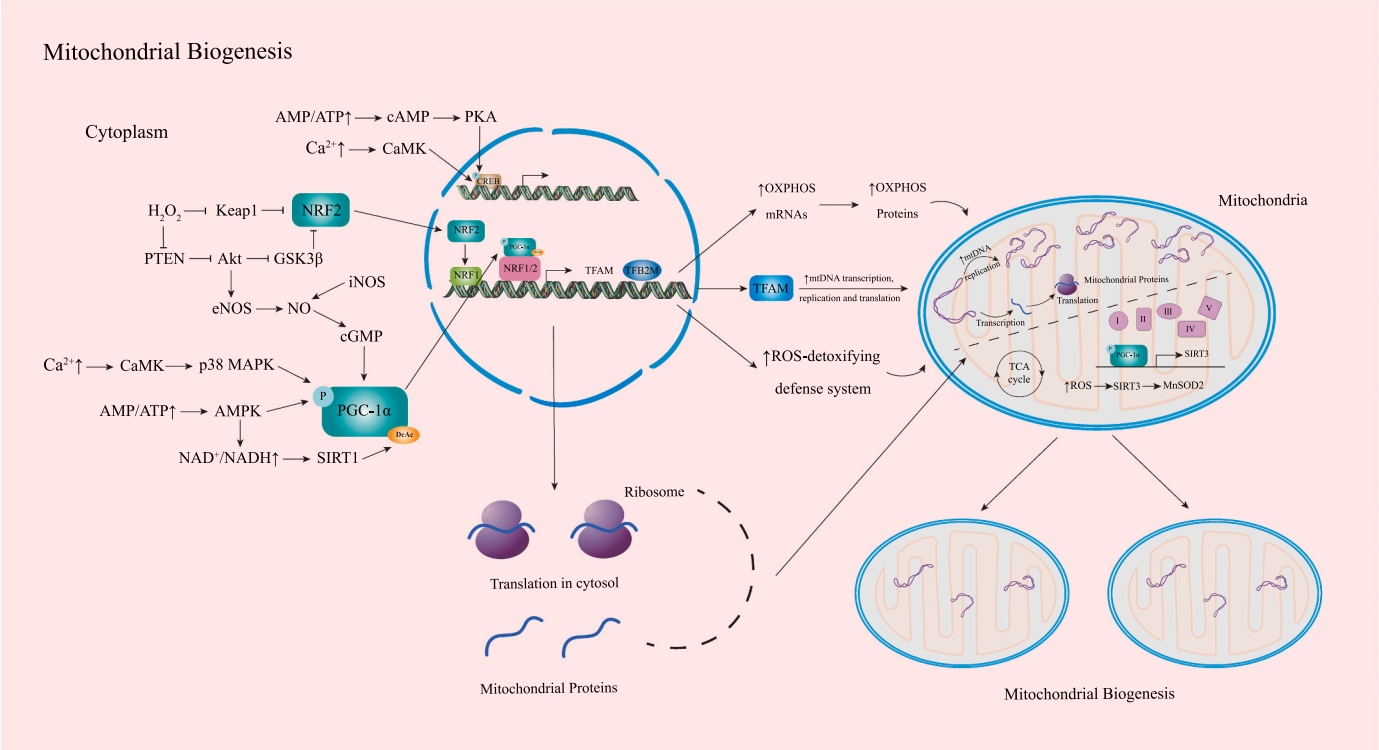

Fig. 3. : The role of mitochondrial biogenesis in depression. Two primary routes control mitochondrial biogenesis, respectively SIRT1/PGC-1α axis and AMPK/PGC-1α axis. As an upstream regulator, AMPK not only directly stimulates PGC-1α via phosphorylation, but also indirectly modulates PGC-1α by SIRT1 activation in a NAD^+ -dependent manner. NRF1 and NRF2, as nuclear transcription factors, regulate the expression of the respiratory chain components and the initiation of mtDNA transcription. Meanwhile, TFAM, as a mitochondria transcription regulator, regulates the activation of mtDNA transcription and the number of mtDNA copies.

be reversed by antidepressant administration [113]. A recent study indicated that mice treated with melittin exhibited depression-like behaviors, which are involved in the dysfunction of the mitochondrial OXPHOS system, oxidative stress injury, and synaptic plasticity dysfunction in the hippocampus via the BDNF/TrkB/CREB signaling pathway [114]. Associations between mitochondrial activity and antidepressant- and anxiolytic-like effects are supported by a study wherein mice underwent 6 weeks of voluntary running wheel exercise; this was explained by modulation of mitochondrial activities, elevated levels of BDNF and CREB, and potentiated expression of a variety of genes involved in energy metabolism [115]. Furthermore, it has been reported that pCREB and PGC-1α form a positive feedback loop with BDNF to further promote BDNF expression [116]. Physical exercise, an antidepressant intervention [117,118], has been shown in several studies to increase BDNF levels in the hippocampus through activation of PGC-1α and fibronectin type III domain-containing protein 5 (FNDC-5) [119,120]. Therefore, some studies have recently revealed a novel route in the brain as an option for ameliorating cognitive deficits and depression: enhanced PGC-1α synthesis contributes to an increase in neuronal FNDC5 levels and boosts the amount of BDNF in the brain [119].

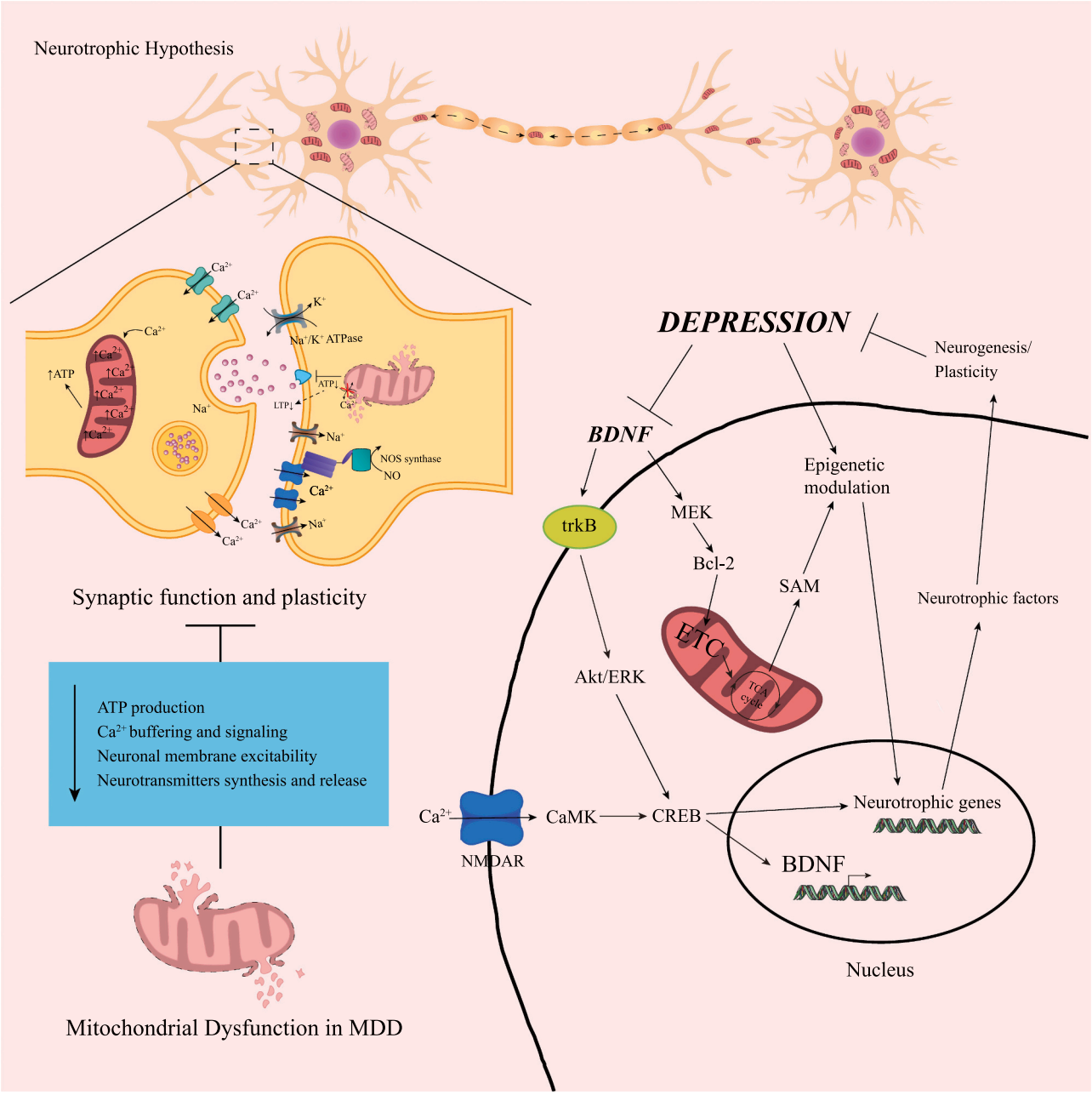

Fig. 4. : The neurotrophic hypothesis (synaptic plasticity) and mitochondria in depression. Mitochondria support synaptic plasticity in several ways, including ATP production, Ca^{2+} buffering/signaling, neurotransmitter synthesis/release, and the maintenance of membrane excitability. Mitochondria also produce oxygen and nitrogen required for synaptic plasticity and activate caspases in dendrites inducing the elimination of postsynaptic dendritic spines in long-term depression. Neuronal mitochondrial trafficking is largely interrupted in depression. In healthy neurons, mitochondria move from the cell body to axons, dendrites, and synapses by an anterograde mechanism, supplying ATP to nerve terminals. Mitochondria then travel back to the cell body from synapses through a retrograde mechanism. In depression neurons, these mechanisms are disrupted primarily due to defective or functionally inactive mitochondria. BDNF is of paramount importance in controlling neuronal survival, preserving neuronal function and synaptic plasticity, and promoting the synthesis and release of neurotransmitters. In depression, BDNF-related pathways can also affect neuronal plasticity in an epigenetic manner by reducing the supply of S-adenosylmethionine (SAM) from mitochondria.

FNDC-5, as a PGC-1α-dependent myokine, can be cleaved in muscle and brain and regulate the progress of the physiological activities in the form of irisin during exercise [121–124]. According to Wang and Pan, the peripheral supply of irisin to depressed animals effectively boosts energy levels and regulates metabolism to maintain neurological function on an even keel [125]. In addition, centrally targeted irisin treatment modulates neuroplasticity-related proteins in the hippocampus and mPFC to exert antidepressant effects [126]. Insulin-like growth factor II (IGF-II) is a hormone with universal neurotrophic and neuroprotective properties and is widely used as a therapeutic agent for disorders of the central nervous system (CNS) (e.g., neurodegenerative disorders and depression). IGF-II can restore normal levels of SYP and PSD-95 proteins and correct intracellular and extracellular secretion defects caused by CORT [127]. Given these considerations, IGF-II can restore neuronal mitochondrial homeostasis, which plays a vital role in calcium mobilization, energy metabolism, neurotransmitter release, neurogenesis, and apoptosis [128]. **(**Fig. 4**).**

6. Neuroinflammation and mitochondrial dysfunction in depression

Cumulative data support the existence of complex and dynamic interactions between mitochondrial dysfunction and neuroinflammation [129]. Damage-associated molecular patterns (DAMPs) from the mitochondria are identified by microglial immune receptors, which further exacerbate neuroinflammation. Activated glial cells release inflammatory factors that initiate intracellular cascades regulating mitochondrial metabolism and function. According to a clinical investigation, alterations in the protein levels of pathways connected to mitochondrial dynamics and mitophagy are linked to the intensity of depressive symptoms in MDD and may be influenced by the inflammatory status [130]. Low peripheral mtDNA copy numbers are associated with inflammation and disease severity degree during manic episodes of bipolar disorder [131]. Consequently, neuroinflammation and mitochondrial dysfunction constitute a positive feedback loop that accelerates the pathogenesis of depression [132].

Systemic inflammation caused by psychological agitation factors activates monocytes, which further aggravates the vulnerability of the intestinal environment to microbial infections and autoimmune diseases. These danger signals are not limited to the periphery, but may be disseminated to the brain via an array of immune-brain interaction routes that activate microglia [133]. Microglia-derived signaling molecules exert detrimental effects on physiological functions such as mitochondrial homeostasis in adjacent cells. Additionally, many studies have suggested that pathogenic microglia can transmit inflammatory signals to surrounding nerve cells by propagating mitochondrial fragments, which could obstruct ATP synthesis and decrease the mitochondrial inner membrane potential in neuronal cells [134]. Psychological stress promotes elevated extracellular ATP levels, prompts brain microglia to activate the NLRP3 inflammasome cascade through P2X7R, integrates stress-related signals, and ultimately stimulates the release of inflammatory cytokines [135]. A recent meta-analysis focused on genetics identified an association between the P2X7 gene and major depression [136]. In macrophages, Ca^{2+} influx and K^{+} efflux through P2X7 receptors result in a sustained decrease in mitochondrial membrane potential and an increase in mtROS generation prior to the formation of the NLRP3 inflammasome and apoptosis [137]. Several studies have shown that neuroinflammation, Ca^{2+} signaling, and mitochondrial dysfunction exhibit extensive crosstalk [138,139]. Proinflammatory molecules can stimulate the activation of voltage-sensitive L-type Ca^{2+} channels in neurons, resulting in an increase in intracellular Ca^{2+} concentration, which depolarizes the potential of the mitochondrial membrane and boosts ROS production, thus triggering cell death via the mitochondrial pathway [140–143]. Proinflammatory stimuli induce local mitochondrial dynamics, as evidenced by changes in mitochondrial division and fusion homeostasis in astrocytes, culminating in superabundant mitochondrial fission and debris [144]. Andre et al. reported a bidirectional relationship between mitochondrial dynamics and neuroinflammation. Specifically, the proinflammatory factor IL-1 induces an imbalance in mitochondrial fission/fusion in patients with AD, which contributes to synaptic loss and subsequent memory decline [145].

Importantly, injured mitochondria may induce inflammation on their own, leading to a vicious cycle. Once mitophagy is unable to clear seriously harmed mitochondria, DAMPs leak into the cytoplasm and external cell environments, such as mtDNA, ATP, Cyt-C, and cardiolipin, which induce sterile inflammation by interacting with toll-like receptor 9 (TLR9) and activate NF-kB and NLRP3 inflammasome, thereby initiating an immune response [146–148]. As noted in a small cohort of 29 adolescent patients with mood disorders, mitochondrial gene expression was positively correlated with NLRP3 inflammasome activation (with a positive correlation) [149]. Mitochondrial transfer can reduce LPS-induced neuroinflammation and activate proinflammatory microglia to treat depression [150]. Elevated mtROS are potent signal transducers that induce a shift in pro- and anti-inflammatory cytokine profiles [151]. Alterations in mitochondrial calcium metabolism, iron mismanagement, and increased ROS production have been linked to the activation of redox-sensitive inflammatory pathways [152,153]. A clinical study reported that elevated mtROS levels in T cells may be an early indicator of immune system dysfunction in otherwise healthy young adults with MDD [154]. ROS promotes the dissociation of thioredoxin-interacting protein (TXNIP) from thioredoxin, which then interacts with NLRP3 to activate the NLRP3 inflammasome [155]. Furthermore, in the CUMS-induced model of depression, UCP2-knockout rodents showed worsened depression-like behaviors, compromised neurogenesis, and increased NLRP3 inflammasome activity via elevation of ROS/TXNIP/NLRP3 signaling in astrocytes [156]. Another important mDAMP is Cyt-C, located in IMM and OMM, which functions to transfer electrons among the mitochondrial respiratory chain. TLR4 receptors and the C-Jun N-terminal kinase system in microglia can cooperate with mitochondrial Cyt-C to modify immune activities in the brain [157]. Furthermore, cascade activation of MAPK signaling molecules is central to an array of DAMP-mediated immune responses. Studies have suggested that dexmedetomidine inhibits LPS-induced neuroinflammation and apoptosis via the mitochondrial pathway by regulating p38 MAPK/c-Myc/CLIC4 [131]. (Fig. 5).

7. Treatments

7.1. Pharmacological methods

Coenzyme Q10 functions as a superoxide scavenger and overall mtROS level regulator to maintain mitochondrial homeostasis, which ameliorates lipid peroxidation in the IMM, plays a proactive role in the plasma membrane redox system, instigates uncoupling proteins, and promotes mitochondrial biogenesis. Protracted CoQ ingestion has proven useful for reversing metabolic dysfunction, and its effective mechanisms may involve active mitochondrial biogenesis and mitophagy in the blood-brain barrier and broader CNS [158,159]. Several reports have suggested that CoQ supplementation plays a constructive role in mitochondrial dynamics, bioenergetic supply, and antioxidant responses, which may be associated with a positive feedback loop between activated AMPK and increased transcription of CREB, SIRT1, and SIRT3 [160,161]. Previous evidence has suggested that CoQ ingestion boosts the accumulation of PPARs [162] and FOXO3a [163]. Moreover, a study reported that oral supplementation of CoQ10 could compensate for the deficiency of mitochondria and tissue CoQ10 in depression and exert neuroprotective effects via enhancing mitochondrial bioenergetics [164].

It has been claimed that **nicotinic acid (NAD)**, which is commonly provided as nicotinamide mononucleotide (NMN), benefits the cerebrovascular system, stimulates mitochondrial OXPHOS to preserve its stability, and lowers apoptosis [165]. Nicotinamide maintains a

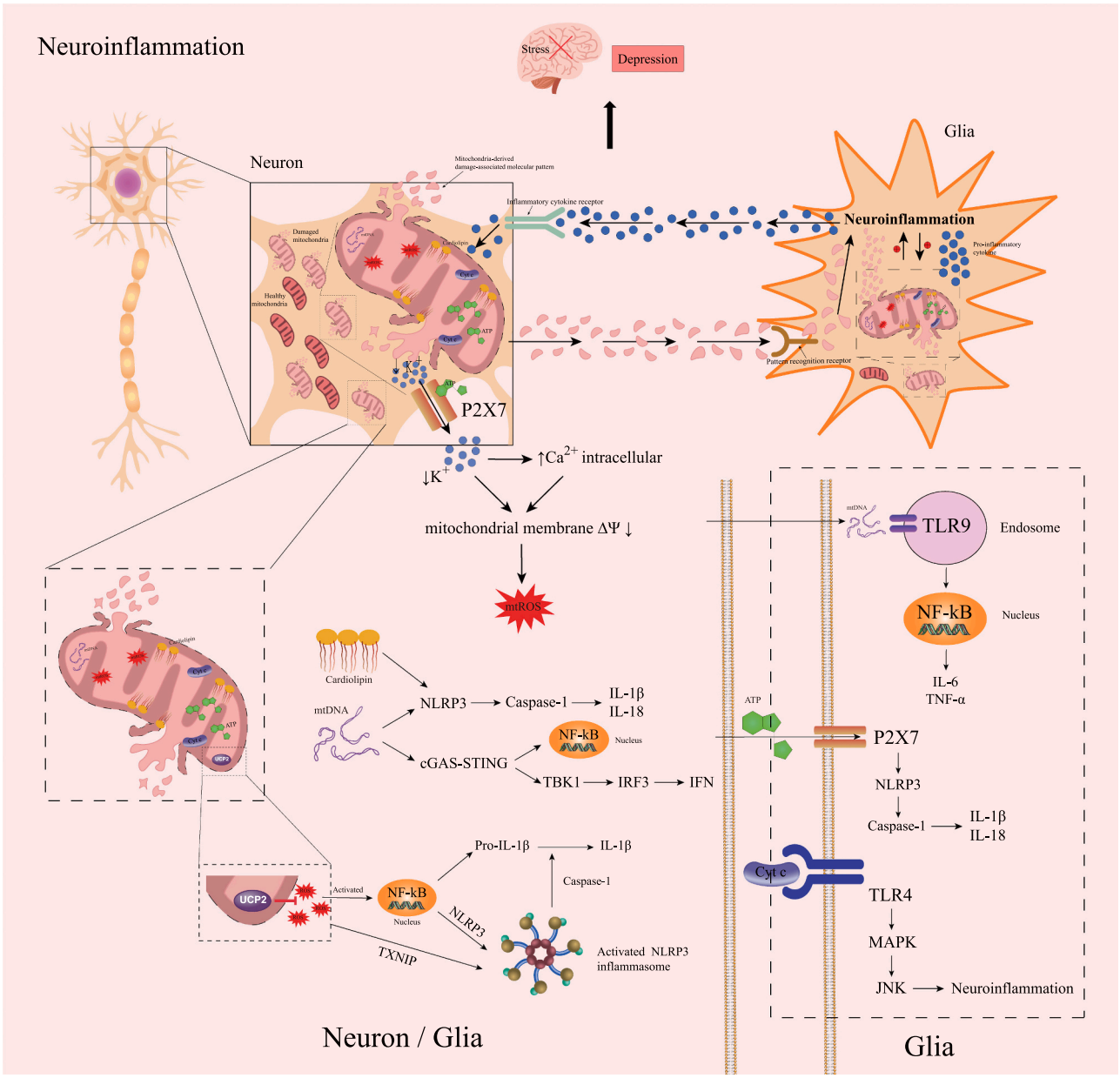

Fig. 5. The interaction between neuroinflammation and mitochondrial dysfunction in depression. Following exposure to external stimuli, the function of mitochondria in neurons or glia is impaired, leading to a decrease in mitochondrial membrane potential. Consequently, some molecules originally existing inside the mitochondria, such as mtDNA and cardiolipin, are released into the cytoplasm or extracellular space. These released molecules, known as DAMPs, interact with pattern recognition receptors on the glia to further exacerbate neuroinflammation. Additionally, activated glia release inflammatory factors that initiate intracellular cascades intensifying mitochondrial damage, thus establishing a vicious cycle of mitochondrial dysfunction and neuroinflammation. Mitochondrial dysfunction causes mtDNA to be released from glia cells into the cytoplasm where it is sensed by the cGAS-STING signaling pathway promoting expression of inflammatory factors. Moreover, mtDNA in the cytoplasm can activate NLRP3 inflammasome resulting in increased expression of IL-18 and IL-1β through caspase-1 activation. Then, psychological stress promotes elevated extracellular ATP and prompts brain microglia to activate NLRP3 inflammasome cascade through P2X7R, integrate stress-related signals, and ultimately stimulate the release of inflammatory cytokines.

constant level of ATP and boosts NAD^+ stores while simultaneously inhibiting PARP-1 activity. Because NAD^+ is a necessary co-substrate for the activity of most sirtuins, increasing NAD^+ levels can promote sirtuin-dependent mitochondrial biogenesis and function [166]. NMN stimulates SIRT3 activity to enhance mitochondrial bioenergetics, thereby attenuating CORT-induced depression-like behaviors [167].

One promising treatment for depression is **N-acetylcysteine (NAC)**, a forerunner of glutathione that stimulates neurogenesis, modifies the levels of glutamate and the response of unfolded proteins, mitigates neuroinflammation, central oxidative stress, and neuronal cell apoptosis [168], suppresses endoplasmic reticular stress, and improves cerebral mitochondrial function [169]. It has been reported NAC can also potentially exert prophylactic and therapeutic effects by activating the AMPK/PGC-1α axis contributing to increased mitochondrial biogenesis [170,171]. Several studies have revealed that these mechanisms are beneficial for relieving depressive and anxiety symptoms in psychiatric disorders [172]. Berk et al. demonstrated a satisfactory antidepressant effect of NAC in patients with more serious depression (MADRS score ≥25) in a 12-week randomized clinical experiment using an extremely persuasive sample (n = 269) [173]. Notably, the recognized advantages of NAC may be attributed in part to its capacity to function as an intermediary for 3-mercaptopyruvate, thereby boosting cysteine levels

and hydrogen sulfide in the mitochondria [174,175], which can then encourage mitophagy as a result of enhanced Parkin transcription and E3 ligase activity [176].

Melatonin, an endogenous neurohormone, is primarily produced by the pineal gland to regulate circadian and seasonal rhythms. It can also scavenge mitochondrial free radicals, maintain mitochondrial calcium homeostasis, increase the permeability of the blood-brain barrier, and upregulate the activity of mitochondrial SIRT3, thereby ameliorating neuroinflammation and glutamate-induced excitatory neurotoxicity. Unexpectedly, some studies have shown that oral melatonin treatment can reduce mitochondrial dysfunction by preserving a healthy balance of mitochondrial dynamics, maintaining mitochondrial morphology, and integrating them into cellular networks to improve the ATP utilization ratio [177–179]. Because of its substantial influence on neuronal function, survival, and neurotransmitter absorption, the mitochondrial melatonergic pathway is of special significance in astrocytes. For example, mood dysregulation is hypothesized to be induced by malfunction of the glial mitochondrial melanergic pathway [180]. Melatonin alleviated LPS-induced acute depression-like behaviors in mice, decreased mtROS generation, and inhibited microglial NLRP3 inflammasome activation via the SIRT2/NRF2 pathway [181]. Coincidentally, melatonin exerts a pro-autophagic effect by inhibiting neuroinflammation and attenuates depression [182].

Baicalin, a primary active flavonoid component of Scutellaria baicalensis Georgi, has various pharmacological properties, including antioxidant, anti-inflammatory, antiviral, anticancer, and antiapoptosis. Recently, its antidepression-like ability has been demonstrated in numerous animal models [183,184]. By enhancing mitochondrial structure and lowering the number of damaged mitochondria, baicalin dramatically performs mitochondrial protective functions. According to a previous study, baicalin has a neuroprotective function by modulating dysfunctional mitochondria during ischemia reperfusion [185]. Similarly, baicalin dramatically improves mitochondrial dysfunction, contributing to enhanced learning and memory functions, as well as synaptic plasticity in Alzheimer's disease mice [186]. In one study, corticosterone-induced depressive symptoms were reversed by baicalin because of decreased SGK1 expression in the hippocampus [184]. Another study indicated that baicalin ameliorates the basic mitophagy levels and promotes the axis of AMPK/PGC-1α/NIX to restore impaired mitochondria in the hippocampus, thereby exerting antidepressant effects in CUMS [36].

Resveratrol, a non-flavonoid polyphenolic molecule present in many plant species, such as grapes, berries, and nuts, has numerous neurological benefits. It diminishes nerve cell apoptosis, promotes hippocampal mitochondrial function, and suppresses neuroinflammation, and hence, is one of the most powerful anti-anxiety and antidepression agents [187,188]. A therapeutic study on adolescent social isolation has shown that resveratrol can ameliorate anxiety-like behaviors and social disorders in isolated female rats, alleviate stress-induced decreases in ATP levels in the nucleus accumbens, and modulate plasticity and mitochondrial function [189]. Another study in mice with LPS-induced depression found that resveratrol confers neuroprotection by interfering with the mitochondrial oxidative stress response and blocking apoptosis in the hippocampus [190]. Meanwhile, there are also indications that RSV therapy may offer neuroprotection in SAH animal models by activating the PGC-1α signaling pathway to improve mitochondrial biogenesis and mitigate mtDNA copy number [191]. Furthermore, the treatment of Alzheimer's disease animal models with resveratrol avoided cognitive impairment and reduced neurodegeneration in the hippocampus by reducing the acetylation of PGC-1α and p53. Specifically, resveratrol activates SIRT1 in neurons and deacetylates p53 to reduce FoxO- and p53-mediated neuronal death [192].

Quercetin, a naturally nontoxic flavonoid-type compound, has been reported to relieve CUMS-induced depression-like behaviors by promoting the FoxG1/CREB/BDNF signaling pathway to improve adult hippocampal neurogenesis [193] and reverse the impairment of antioxidant enzyme systems to modulate neuroinflammation and oxidative stress [194]. Quercetin, a mitochondrial protectant, substantially ameliorates methamphetamine-induced anxiety-like behaviors in vivo and in vitro by attenuating mitochondrial dysfunction and aberrant morphology, thus alleviating neuronal injury [195]. Similar to quercetin, **metformin** may also improve mitochondrial bioenergetics by modulating AMPK-associated signaling pathways to treat depression-like behaviors in methamphetamine withdrawn mice [196]. Metformin aids in the maintenance of healthy energy metabolism conditions and enhances mitochondrial biogenesis in the hippocampus of aged apoE4-target-replacement (TR) mice, thereby alleviating depression [102]. **MitoTEMPO,** a specific mitochondrial antioxidant, significantly ameliorates depression in rats [197] and alleviates stress-induced mucosal damage [14].

7.2. Nonpharmacological approaches

Mitochondrial transplantation can be used as an alternative treatment for depression. It is commonly acknowledged that mitochondria are large and difficult to introduce into cells. Numerous in vitro and in vivo studies have demonstrated that subcellular transporters such as tunnelling nanotubes and microvesicles can facilitate the natural shuttling of mitochondria between different cells, revealing novel cellular features in physiological and pathological contexts [198,199]. Intriguingly, studies reported that intravenous administration of mitochondria can protect rodents from depression behaviors brought on by LPS, boost neurogenesis and neural plasticity, and inhibit ROS accumulation and neuroinflammation in astrocyte and microglia [150]. Exogenous mitochondrial transplantation has been shown in a recent study to be beneficial in alleviating anxiety and depression and increasing the length and density of dendritic spines in the brains of aged rats undergoing CUMS. The intrinsic molecular mechanism involves regulation of the IDO/Kyn pathway and improvement of mitochondrial function in the PFC [200]. Multiple studies have demonstrated that intercellular mitochondrial transport is essential for maintaining normal body functions, substance metabolism, and neuronal survival. For instance, damaged mitochondria may be liberated by neurons and transported to astrocytes for regeneration and destruction [201]. Davis et al. first demonstrated that mitochondrial exchange within neurons and astrocytes is bidirectional [201]. In contrast, the donation of healthy mitochondria from astrocytes to injured neighboring neurons can promote the survival of nerve cells [202,203] and offer neurotrophic and metabolic support [204,205]. A highly authoritative study of transient focal cerebral ischemia in mice revealed that the release of astrocytic mitochondrial particles is mediated by a Ca^{2+}-dependent mechanism, and this neuroglial crosstalk may contribute to endogenous neuroprotective and neurorecovery mechanisms after stroke [202].

Ketogenic diet (KD) [206] is a diet rich in fat, moderate in protein, and low in carbohydrates. It dramatically alters the energy balance in the brain by switching the primary energy source from glucose to ketone bodies [207]. According to research conducted in animals, this mechanism may serve as a buffer in situations where glutamate is toxic, such as acute mood disorders [208]. Specifically, by allosterically altering the chloride reliance of transporters, ketones prevent the transit of glutamate into synaptic vesicles. In an investigation of depression therapy, rats on KD displayed less duration of immobility during the forced swimming test compared to rats on control diet, indicating that KD may have antidepressant characteristics [209]. A further study using repeated social defeat stress and LPS-induced depression models made similar inferences: the antidepressant therapeutic benefits of KD were achieved by the recovery of excitability among neurons and microglia in the lateral habenula [210]. Interestingly, it has been scientifically examined and systematically proven to correct mitochondrial malfunction, thereby reducing mood disorder symptoms [211]. The impact of KD on mitochondrial function appears to be correlated with epigenetic modifications involving mitochondrial function and mitochondrial

biogenesis. According to animal research, KD particularly enhances beta-hydroxybutyrate, which in turn improves the number of mitochondria and doubles mitochondrial electron transport chain proteins, thus boosting the number of proteins in the brain that regulate mitochondrial biogenesis [212,213]. In addition, a study demonstrated that KD enhances the bioenergetics of hippocampal mitochondria and behavioral cognition in healthy adult wild-type mice [214].

Calorie restriction (CR) is a 30–40% reduction in calorie consumption while maintaining adequate intake of proteins, vitamins, minerals, and water for optimal nutrition [215]. Additionally, a healthy fast may enhance daytime focus, sleep quality, and mood [216]. According to Hussin et al., fasting and calorie restriction substantially mitigate negative emotions such as tension, aggression, and disorientation, and promote a feeling of euphoria in older men [217]. Increased exposure to overfeeding and high-fat diets rich in saturated fatty acids induces a decline in mitochondrial numbers and increases mitochondrial oxidative stress. In contrast, caloric restriction can lead to an improvement in mitochondrial function by elevating transcriptional processes that intensify mitochondrial biogenesis, thus stimulating mitophagy [218], governing mitochondrial mass, strengthening mitochondrial efficiency, and activating ROS-scavenging mechanisms [219–221]. Through a mechanism involving the upregulation of SIRT3, SOD2, and PGC-1α, CR may also provide protection for mitochondria [222,223]. According to a study concerning the mechanism of a high-fat diet, research staff reported that IGF-1 could alleviate depression-like behaviors and mitochondrial malfunction via the CREB/PGC-1α pathway in these mice [224]. Moreover, it has recently been shown that rodents experience an antidepressant-like effect after 10 days of consuming fewer calories [225].

Physical exercise, an intervention that does not involve the use of pharmacological agents, has repeatedly been demonstrated to be valuable in the management of depression. Clinical trials have revealed that moderate-to high-intensity exercise can improve symptoms of depression in patients with MDD, and regular leisure activities can reduce an individual's risk of depression [226,227]. Notably, mitochondria form a link between exercise and neurogenesis [228]. Post-traumatic stress disorder has been shown to be mitigated by exercise because it increases the synthesis of BDNF, modifies mitochondrial function, and improves neuroplasticity in the hippocampus [229]. Based on depression-related experiments, physical exercise can partially alleviate depression by altering mitochondrial function [230,231]. In dexamethasone offspring, treadmill exercise ameliorated the development and progression of depression while enhancing mitochondrial health and decreasing corticosterone levels in the circulation [197]. Furthermore, running on a treadmill can mitigate perinatal hypoxia-induced antidepressant dysfunction in adults and promote hippocampal neuronal cell differentiation by modulating the mitochondrial AMPK pathway [232]. Muscle conditioning alters kynurenine metabolism to prevent stress-induced depression [233–235]. One study found that exercise increased PGC-1α expression in the hippocampus of depressed mice [236]. Mice overexpressing PGC-1α may be resistant to prolonged stress due of PGC-1α's effects on the kynurenine pathway [237].

8. Conclusions and outlook

Recent studies have confirmed that mitochondrial dysfunction plays a critical role in the etiology of depression. An imbalance in MQC directly induces depression; furthermore, mitochondrial disruption and other depression pathophysiologies such as inflammation, oxidative stress, the neurotrophic hypothesis, ferroptosis, and apoptotic pathways form reciprocal feedback loops that indirectly increase depression. MDD is a complex and heterogeneous mental ailment with an unknown etiology. As such, recovery is inconsistent between patients, which presents significant challenges in the diagnosis and treatment of the disease. Meanwhile, the intricate interactions across the pathways implicated in the pathogenesis of depression make it difficult to identify single actionable targets for the development of novel medications. In this review, given the commonality of numerous depression hypotheses, we have highlighted the contribution of mitochondria to multiple pathogeneses. It might be advantageous to target multiple pathways involved in the etiology of depression using a medication that focuses on regulating mitochondrial stability. Patients with MDD can benefit from therapeutically targeting mitochondria; however, mitochondrial function depends on patient age, sex, occupation, levels of activities, nutrition, and metabolic capability, all of which differ among patients. With further follow-up research, novel and effective mitochondria-targeting drugs will be combined with existing treatment methods to achieve individualized treatment.

Many scholars believe that there are inextricable links between mitochondrial dysfunction and inflammation in depression; however, so far, there has been little evidence of their mutual relationship with depression. The diversity, different neuronal localization, and contrasting functions of P2 receptors determine whether they play a positive or negative role in regulating neuroinflammation, thereby presenting therapeutic obstacles. P2X7 receptors participate in the development of inflammasomes that are associated with the onset of depression [238]. Chronically stressed mice display a deficiency in the release of ATP from astrocytes, which leads to a shortage of neuronal tone mediated by P2X2 receptors [239]. Additionally, polymorphism of P2X7 receptors increase susceptibility to mood disorders [240,241]. P2X4 receptors play a proinflammatory role by mediating the neurophagocytic activities of microglia during stroke and an antidepressant effect by promoting BDNF release during the post-ischemic recovery phase [242,243]. Therefore, further research should be conducted to investigate the involvement of inflammation and mitochondrial dysfunction in the pathogenesis of depression.

Recently, an increasing number of studies have focused on the pathogenesis of ferroptosis in depression. Mitochondria are the primary source of ROS and are required for the regulation of ferroptosis. The morphological features of ferroptosis include mitochondrial atrophy with increased mitochondrial membrane densities, a decrease in or disappearance of the mitochondrial crista, and rupture of the mitochondrial membrane. A recent study showed that energy stress modulation of AMPK/FOXO3 signaling inhibits mitochondria-associated ferroptosis [244]. Some studies have revealed that iron can induce the elevation of Ca^{2+}, which in turn initiates mitochondrial fragmentation [245–247]. The underlying molecular mechanism is that an increased concentration of exogenous Fe^{3+} in HT-22 cells of mice promotes mitochondrial fission through calcineurin-mediated dephosphorylation of Drp1 (Ser637) in hippocampal neurons [248]. Similarly, additional studies have shown that increased levels of Fe^{3+} can downregulate the expression of OPA1, leading to reduced mitochondrial fusion resulting in fragmented mitochondria [249,250]. However, there is limited literature on the regulation of ferroptosis by mitochondria from the perspective of depression. Therefore, more studies on ferroptosis are warranted to identify the appropriate pathways/targeted proteins associated with the mitochondria in patients with depression. In conclusion, by focusing on mitochondria, this review elucidates the pivotal role of mitochondria in the pathogenesis of depression, to further enhance the understanding of molecular processes of depression, which may lead to the discovery of new treatments to ameliorate symptoms in patients with MDD.

CRediT authorship contribution statement

Yu Song: Conceptualization, Investigation, Writing – original draft. **Huan Cao:** Writing – review & editing, Supervision. **Chengchao Zuo:** Visualization. **Zhongya Gu:** Writing – review & editing. **Yaqi Huang:** Writing – review & editing. **Jinfeng Miao:** Writing – review & editing. **Yufeng Fu:** Writing – review & editing. **Yu Guo:** Writing – review & editing. **Furong Wang:** Writing – review & editing, Conceptualization, Supervision, Project administration. **Yongsheng Jiang:** Writing –

review & editing, Conceptualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that there is not conflict of interest.

Data Availability

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

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