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Oxygen metabolism abnormality and Alzheimer's disease: An update

Guangdong Liu [a], Cui Yang [a], Xin Wang [a], Xi Chen [a], Yanjiang Wang [b], Weidong Le [a,c,*]

[a] Institute of Neurology, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, 610054, China
[b] Department of Neurology and Centre for Clinical Neuroscience, Daping Hospital, Third Military Medical University, Chongqing, 400042, China
[c] Liaoning Provincial Key Laboratory for Research on the Pathogenic Mechanisms of Neurological Diseases, The First Affiliated Hospital, Dalian Medical University, Dalian, 116021, China

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ABSTRACT

Oxygen metabolism abnormality plays a crucial role in the pathogenesis of Alzheimer's disease (AD) via several mechanisms, including hypoxia, oxidative stress, and mitochondrial dysfunction. Hypoxia condition usually results from living in a high-altitude habitat, cardiovascular and cerebrovascular diseases, and chronic obstructive sleep apnea. Chronic hypoxia has been identified as a significant risk factor for AD, showing an aggravation of various pathological components of AD, such as amyloid β-protein (Aβ) metabolism, tau phosphorylation, mitochondrial dysfunction, and neuroinflammation. It is known that hypoxia and excessive hyperoxia can both result in oxidative stress and mitochondrial dysfunction. Oxidative stress and mitochondrial dysfunction can increase Aβ and tau phosphorylation, and Aβ and tau proteins can lead to redox imbalance, thus forming a vicious cycle and exacerbating AD pathology. Hyperbaric oxygen therapy (HBOT) is a non-invasive intervention known for its capacity to significantly enhance cerebral oxygenation levels, which can significantly attenuate Aβ aggregation, tau phosphorylation, and neuroinflammation. However, further investigation is imperative to determine the optimal oxygen pressure, duration of exposure, and frequency of HBOT sessions. In this review, we explore the prospects of oxygen metabolism in AD, with the aim of enhancing our understanding of the underlying molecular mechanisms in AD. Current research aimed at attenuating abnormalities in oxygen metabolism holds promise for providing novel therapeutic approaches for AD.

1. Introduction

Dementia profoundly impairs memory and cognitive function. According to reports, the global population of dementia patients was around 55 million in 2019 and will be expected to reach 139 million in 2050 [1]. Alzheimer's Disease (AD) is the most common type of dementia, accounting for 60–70 % [2]. The main neuropathological features of AD are amyloid β-protein (Aβ), hyperphosphorylated tau, neuronal degeneration, and neuroinflammation [3,4]. Despite decades of efforts to develop candidate treatments targeting the core pathology of AD, the researchers still fail to generate promising results in clinical trials.

Oxygen is an essential molecule involved in biochemical reactions in living organisms. Above or below the threshold of optimal oxygen levels may lead to various pathological disorders of tissues and cells [5]. Both hypoxia and extreme hyperoxia can induce the generation of reactive oxygen species (ROS) [6,7]. Furthermore, the brain is highly dependent on oxygen supply and is susceptible to fluctuation in oxygen level [8]. The dysfunction of oxygen metabolism in AD primarily results in tissue hypoxia, oxidative stress, and mitochondrial dysfunction. Our previous studies have shown that hypoxia can promote AD progression [9]. Moreover, the brains of AD patients suffer more oxidative damage than healthy individuals, and increase the sensitivity to oxidative stress in Aβ-rich brain regions [10]. Mitochondria are complex organelles that produce energy, regulate metabolic function and calcium levels, and control apoptosis and ROS production [11]. Wang et al. observed that mitochondrial dysfunction occurs in the early stages of AD [12]. Thus, mitochondrial dysfunction is of great significance to AD. We place particular emphasis on the molecular mechanisms underlying recent discoveries related to oxygen metabolism abnormalities in association with AD, including hypoxia, oxidative stress, and mitochondrial dysfunction (Fig. 1). The molecular mechanism of oxygen metabolism can be involved in the disease progression of AD. This review may advance our understanding of the relationship between AD and oxygen

* Corresponding author. Institute of Neurology, Sichuan Provincial People's Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, 610054, China.
E-mail address: wdle@sibs.ac.cn (W. Le).

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metabolism, and may facilitate the therapeutic approach targeting oxygen metabolism abnormalities for the treatment of this devastating disease.

2. Oxygen metabolism and AD

Oxygen metabolism refers to the series of processes involved in the transfer, transport, and consumption of oxygen within an organism [13]. During the normal oxygen metabolism process, the majority of oxygen is involved in cellular respiration, converting it into adenosine triphosphate (ATP) to supply energy, while a minor portion is transformed into ROS [14]. In fact, ROS participate in cellular signal transduction, and an aberrant accumulation of ROS can contribute to many diseases [15]. Within the context of normal oxygen metabolism, a delicate equilibrium is upheld between the generation and clearance of ROS, thereby ensuring the function of the organism [16]. The mitochondrion is a critical organelle in oxygen metabolism, responsible for a significant portion of cellular oxygen consumption, influencing the redox potential and regulating the levels of ROS [17]. Oxygen metabolism is of paramount importance for the maintenance of normal physiological functions in cells and tissues.

Oxygen metabolism abnormality refers to deviations or dysregulations in the processes involving the transfer, transport, consumption, or handling of oxygen within cells or organisms. Oxygen metabolism abnormality primarily encompasses hypoxia, excessive accumulation of ROS, and mitochondrial dysfunction, all of which have the potential to lead to disruptions in physiological functions or the onset of diseases. Oxygen metabolism disorders result as secondary effects of several diseases, such as cerebrovascular disease, respiratory disease, and anemia. Cerebral hemodynamic disturbances can lead to oxygen metabolism disorder, which in turn leads to neuroinflammation, neuronal death, and amyloid aggregation [18,19]. Approximately 90 % of AD patients show cerebral hypoperfusion and amyloid angiopathy [20]. Nucera et al. showed that cerebral hypoperfusion and hypoxia in patients with ischemic stroke contribute to neurodegenerative processes [21]. Traumatic brain injury is a risk factor through hypoxic mechanisms contributing to AD pathology, including hyperphosphorylated tau and Aβ deposition [22,23]. Studies have revealed that patients with chronic obstructive sleep apnea (OSA) may show elevated serum levels of Aβ and phosphorylated tau and have a 58 % higher risk of developing AD compared to non-OSA individuals [24–26]. Ji et al. reported that high-altitude chronic hypoxia can lead to toxicity, culminating in neural injury and cognitive impairment [27]. Most AD patients suffer from anemia, which has been linked to declining cognitive abilities [28]. Compared with participants with clinically normal hemoglobin, anemic individuals had a 60 % increased risk of developing AD [29]. Many diseases are risk factors for AD, and oxygen metabolism abnormality is an important player in these diseases.

3. Hypoxia and AD

Hypoxia can induce cell death and neurodegeneration in AD. A sleep-disordered breathing mouse model has been reported to exhibit AD pathology, which may result from chronic hypoxia during sleep disruption [30]. Chronic intermittent hypoxia significantly enhances tau seeding and spreading, increases phosphorylated tau, and exacerbates memory and synaptic plasticity deficits in mice [31]. Han et al. showed that hypoxia promotes γ-secretase activity by inducing pyruvate kinase M2 (PKM2) expression, thereby exacerbating Aβ production and memory impairment [32]. Furthermore, chronic hypoxia promotes AD progression by inducing γ-secretase demethylation through downregulating DNA methyltransferase 3b [33]. Hypoxia also can result in abnormally increased expression of calcium channel proteins Orai1 and cyclin-dependent kinase 5 (CDK5), leading to tau hyperphosphorylation

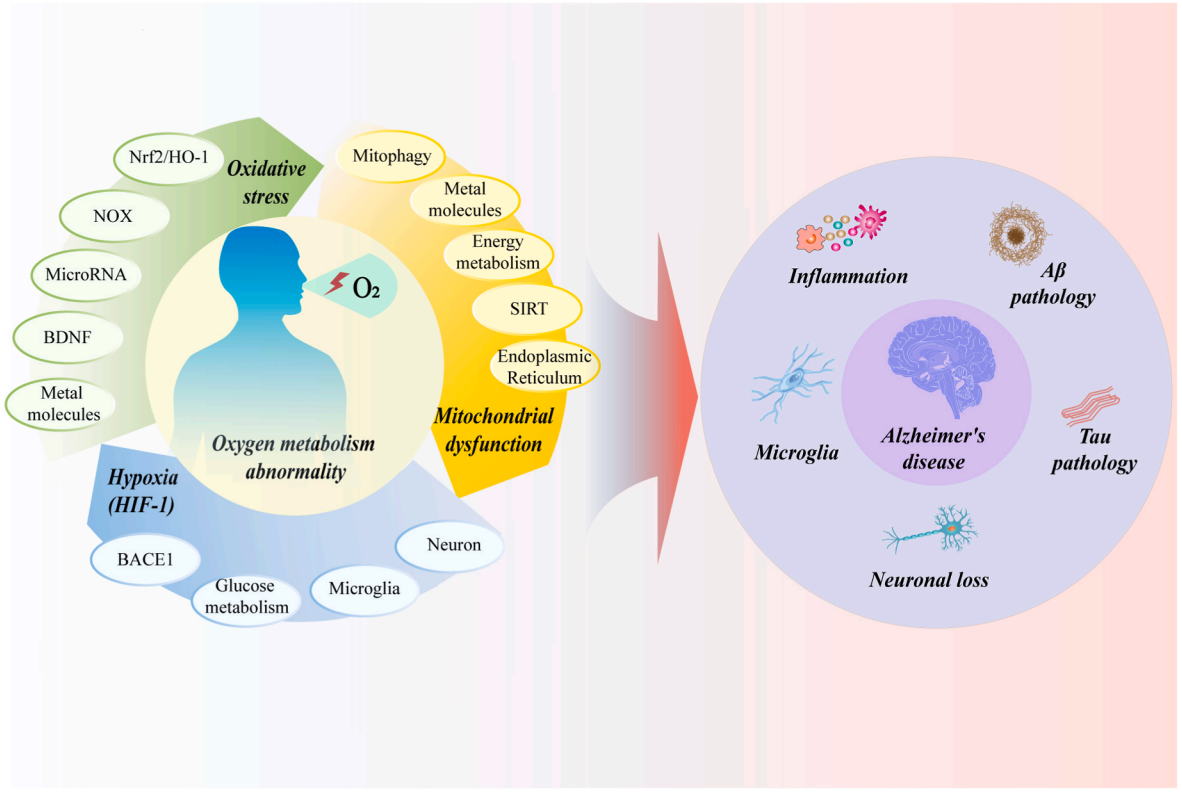

Fig. 1. Schematic representation of oxygen metabolism abnormality contributing to AD pathology. Oxygen metabolism abnormality is a significant risk factor for the pathogenesis and progression of AD. In recent years, hypoxia, oxidative stress, and mitochondrial dysfunction have been the most crucial parts of AD and oxygen metabolism research. Oxygen metabolism disturbance and AD pathology lead to the deterioration of AD together.

and inducing neuronal cell death [34]. Xie et al. found that hypoxia may increase exosomal Aβ levels [35]. Acute hypoxia increases APP, anterior pharynx-defective 1 (APH1), and CDK5 levels while promoting tau phosphorylation and inducing autophagy through mTOR signaling, thereby triggering mitochondrial dysfunction and neuroinflammation [36]. Moreover, moderate intermittent hypoxia has been suggested to have neuroprotective effects [37]. This protective effect may be associated with reduced IL-1β, IL-6, β-secretase, and Aβ levels [38]. The format, severity, duration, and frequency of hypoxia can affect the outcome of brain functions [39]. Thus, hypoxia may result in different biological processes. On the one hand, hypoxia can exaggerate AD pathology, such as Aβ, tau, and neuroinflammation. On the other hand, appropriate hypoxic exercise may protect neurons from degeneration.

Hypoxia can trigger microglial activation, causing neuroinflammation that may contribute to AD pathogenesis. Acute hypoxia activates M1 microglia and increases proinflammatory cytokines and chemokines [40]. Chronic intermittent hypoxia induces oxidative stress and inflammation, which lead to cognitive impairment and pathological brain aging [41,42]. March-Diaz et al. found that hypoxia impairs mitochondrial metabolism in microglia and enhances Aβ pathology [43]. Moreover, chronic hypoxia also drives astrocyte proliferation [44]. The blood-brain barrier (BBB) maintains the central nervous system microenvironment. BBB dysfunction can be induced by hypoxia, ischemia, and neurotoxic molecules. In addition, BBB dysfunction can lead to hypoxia and oxidative stress, which can exacerbate vascular and neurological impairment [45]. Hypoxia-induced disruption of barrier function in the neurovascular system leads to increased BBB permeability, which can lead to progressive synaptic and neuronal dysfunction [46,47]. Additionally, BBB dysfunction can impair Aβ clearance and cause tau hyperphosphorylation [48]. Therefore, hypoxia plays a complex role in neuronal disorders, and more studies are needed to explore it further.

3.1. HIF-1 and molecular pathways

HIF-1 is a highly conserved heterodimer, which acts as a transcription factor essential for mediating oxygen homeostasis [49]. HIF-1α is hydroxylated by oxygen-sensitive HIF prolyl hydroxylase enzymes. Hydroxylation triggers poly-ubiquitination of HIF-1α that was targeted by an E3 ubiquitin ligase-the von Hippel-Lindau protein complex for proteasomal degradation [50]. However, when oxygen demand exceeds supply, hydroxylation of HIF-1α is inhibited, and HIF-1 expression is switched on to promote adaptation to hypoxia [51]. HIF-1 can affect pathological changes in neurodegenerative diseases and serve as a potential target for drug research [52].

3.1.1. HIF-1 and β-site APP cleaving enzyme 1 (BACE1)

BACE1 overexpression can cause a sharp increase in Aβ. HIF-1 binds to the promoter region of BACE1 and activates BACE1 transcription, thereby increasing Aβ [53,54]. Additionally, the knockdown of HIF-1α can block the effects of hypoxia on the BACE1 [55]. Aβ treatment also significantly increased HIF-1α in microglia [56]. Hypoxia is known to induce BACE1 expression through the activation of HIF-1. However, silencing of HIF-1 inhibits the later upregulation of BACE1 mRNA and protein but not the early increase of BACE1 [57]. Guglielmotto et al. suggested that ROS is the main reason for the early upregulation of BACE1 after hypoxia, and the activation of HIF-1α is the reason for the later upregulation of BACE1 [58]. These findings suggest that HIF-1 increases Aβ accumulation by upregulating the expression of BACE1.

3.1.2. HIF-1 and glucose metabolism

Glucose metabolism is associated with mitochondrial dysfunction and oxidative stress in AD [59]. Numerous studies have demonstrated that low concentrations of Aβ are neuroprotective via the induction of HIF-1 expression, increase the rate of glycolysis, and reduce oxidative stress, while excessively high concentrations are toxic [60,61]. This finding is further supported by Zhang et al., who discovered that α-lipoic acid upregulates HIF-1α expression and restores glucose metabolism by promoting the brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B (TrkB) pathway [62]. The glucose transporter protein 1 (GLUT1) is a marker of angiogenesis and a target gene of HIF-1. Ollonen et al. observed that HIF-1 can increase vascularity formation by regulating GLUT1 expression to prevent Aβ accumulation [63]. In conclusion, HIF-1 may contribute to neuroprotective effects by modulating glucose metabolism in AD.

3.1.3. HIF-1 in microglia

The function of microglia is an important aspect of AD pathology. HIF-1α plays a role in microglial migration after spinal cord injury [64]. Zhao et al. also found that hypoxia induces cell death and autophagy in microglia by upregulating the expression of HIF-1α [65]. During chronic Aβ tolerance, microglial energy metabolism is inhibited through the mTOR/AKT/HIF–1α pathway [66]. Based on the above results, HIF-1α exacerbates microglial inflammation and inhibits phagocytosis.

3.1.4. HIF-1 in neurons

Neuronal loss is the main feature of AD. One of the mechanisms of Aβ neurotoxicity is cell cycle re-entry. Id1 and CDK5 can promote Aβ-induced neuronal cell cycle re-entry by acting on HIF-1 [67]. HIF-1 exacerbates neuronal death in a model of glutathione depletion-induced oxidative stress [68]. Neuregulin-1 (NRG1) inhibits HIF-1α accumulation to protect neurons from hypoxic injury [69]. However, a study showed that HIF-1 can suppress neuronal death induced by Aβ and ROS [70]. The effect of HIF-1 on neurons may be bidirectional due to the complexity of the mechanism of HIF-1.

Recent studies on AD have also identified several molecular mechanisms related to HIF-1. Hypoxia can increase HIF-1α expression, thereby degrading leucine carboxyl methyltransferase 1 (LCMT1) and reducing protein phosphatase 2A (PP2A) activity, ultimately promoting hyperphosphorylation of tau protein and impairing cognitive function [71]. Lu et al. reported that fibroblast growth factor 21 (FGF21) reduces Aβ-induced neuronal apoptosis, tau hyperphosphorylation, and oxidative stress, possibly by regulating the PP2A/MAPKs/HIF-1α pathway [72]. Presenilin-1 (Psen1) mutations cause familial AD, and Psen1 can reduce the degradation of the HIF-1α protein [73]. HIF-1 significantly increases the expression of the APH-1A, thereby increasing the expression of γ-secretase and Aβ [74].

HIF-1 affects Aβ aggregation, tau hyperphosphorylation, glucose metabolism, microglia, and neuron function through various molecular mechanisms (Fig. 2). The molecular mechanism of HIF-1 regulation is complicated, and the discovery of the HIF-1 regulation mechanism might be helpful for the understanding of AD pathogenesis. Apparently, the related mechanism of HIF-1 has potential value in improving pathological changes caused by hypoxia.

4. Oxidative stress and AD

ROS primarily originate from mitochondrial respiration and the synthesis of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) [75]. ROS can be categorized into free radical and non-free radical species [76]. The free radical species primarily comprise superoxide radical anion ($O_2^{\bullet-}$), hydroxyl radical (OH^-), peroxyl radical ($ROO^{\bullet}$), hydroperoxyl radical ($HO_2^{\bullet}$), and alkoxyl radical ($RO^{\bullet}$), and the non-free radical species mainly include singlet oxygen ($^1O_2$), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), and ozone (O_3) [77]. Elevated levels of ROS induce oxidative stress.

Oxidative stress is an important factor in the participation of AD. Hypoxia and extreme hyperoxia are both harmful to the brain, with hypoxia eliciting a greater augmentation in ROS production than hyperoxia [78]. NOX is the primary enzyme responsible for superoxide production. Chronic hypoxia can upregulate NOX in AD, potentially

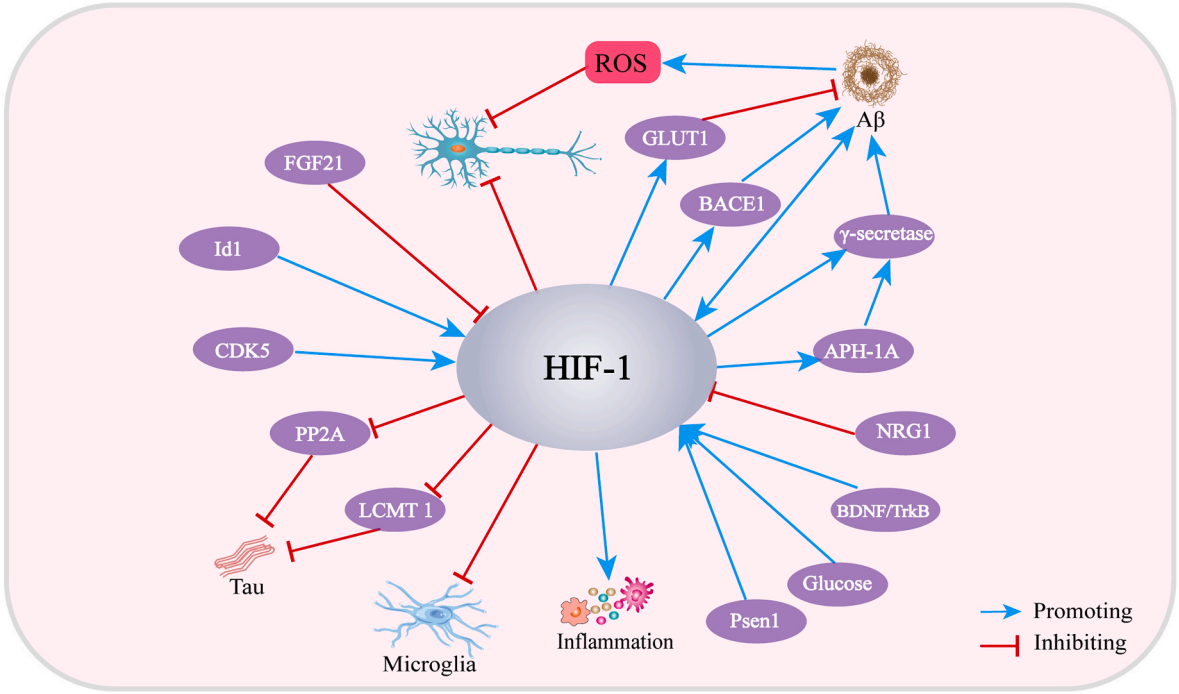

Fig. 2. Molecular Mechanisms of HIF-1 in AD. HIF-1 plays a crucial role in the normal maintenance of oxygen metabolism. Multiple molecular pathways of HIF-1 influence the pathological alterations in AD.

leading to an increase in $O_2^{\bullet-}$ [79]. Hypoxia exacerbates oxidative stress in APP/PS1 mice, possibly resulting in elevated levels of H_2O_2 and $ONOO^-$ [80]. Kaushal et al. also observed that hypoxia can induce oxidative stress in the brain of AD rat models, primarily likely leading to the production of H_2O_2 and $ONOO^-$ [81]. Extreme hyperoxia can increase $O_2^{\bullet-}$, $HO_2^{\bullet}$, and H_2O_2, subsequently causing neurodegeneration and impairments in learning and memory abilities [82,83]. Additionally, treating APP-transfected SH-SY5Y cells with high-level oxygen results in elevated levels of H_2O_2 and $ONOO^-$ [84]. In summary, both hypoxia and extreme hyperoxia can contribute to the elevation of ROS in AD.

Excessive ROS can impair mitochondrial function, which can further promote ROS generation, thereby promoting the progression of AD [85]. Numerous studies have revealed that oxidative stress and associated markers precede Aβ pathology [86,87]. Aβ produces H_2O_2, which can be converted into aggressive OH^-, and these ROS can cause early oxidative damage in AD [88]. Oxidative stress increases the activity and expression levels of γ-secretase and BACE1, thereby increasing Aβ production [89,90]. ROS can promote tau protein production, and the overexpression of tau protein can also promote oxidative stress in cells [91–93]. These findings indicate that Aβ and oxidative stress are mutually reinforcing, and the same is true for tau protein and oxidative stress.

4.1. Oxidative stress and nuclear factor E2-related factor-2 (Nrf2)/heme oxygenase-1 (HO-1)

Nrf2 is a regulator of oxidative stress that interferes with AD pathology, including Aβ and tau [94,95]. Nrf2 attenuates hippocampal damage induced by oxidative stress and neuroinflammation [96]. A study has demonstrated that Mitsugumin53 (MG53) reduces ROS production by activating the Nrf2 pathway [97]. Cheng et al. observed that overexpression of DJ-1 significantly increases Nrf2 expression in the nucleus, inhibiting oxidative stress and reducing Aβ deposition [98]. Zhao et al. found that activating adenosine monophosphate protein kinase (AMPK) can reduce the oxidative damage of neuronal cells [99]. Furthermore, the AMPK/Nrf2 signaling pathway can reduce ROS production and alleviate AD pathology [100]. Knockdown of myocyte enhancer factor 2C (MEF2C) increases the level of BACE1, enhances Aβ production and accumulation in the mouse cortex, and inhibits the Nrf2-antioxidant response element (ARE) to increase oxidative stress [101]. Nrf2 is mainly controlled by Kelch-like ECH-associated protein 1 (Keap1) [102]. Keap1-Nrf2 and AREs are fundamental defense mechanisms against oxidative stress [103,104]. Activation of Nrf2 can help restore cellular redox and mitochondrial functions [105].

Derivatives of heme can increase oxidative stress and exacerbate neurodegenerative disease progression [106]. Dysregulation of HO-1 expression is involved in neuroinflammation and neurodegeneration in AD [107]. HO-1 is an early target of oxidative modification. Increased oxidative stress in AD patients may elevate phosphorylation and protein expression of HO-1, facilitating its interaction with biliverdin reductase (BVR) [108]. Activation of HO/BVR is involved in adaptive stress response [109]. Therefore, the upregulation of HO-1 may exert beneficial effects by preventing oxidative stress.

The α7 nicotinic acetylcholine receptor (α7 nAchR) can reduce oxidative stress and Aβ-induced damage by activating the Nrf2/HO-1 pathway [110]. Interestingly, celecoxib further enhances Aβ-induced HO-1 expression by promoting the nuclear translocation of Nrf2 [111]. Cao et al. observed that antioxidative effects mediated by the Nrf2/Keap1/HO-1 pathway improve cognitive deficits and alleviate AD pathology [112]. In conclusion, the Nrf2/HO-1 system may prevent oxidative damage and mitigate the inflammation in the central nervous system, becoming a promising target for AD therapy.

4.2. NOX and oxidative stress

NOX is an enzyme complex consisting of five subunits that play diverse roles in cell development and proliferation. Oxidative stress regulated by NOX is an important pathogenesis of neurodegenerative diseases [113]. NOX4 is one of the main sources of ROS that promotes astrocyte ferroptosis by inducing lipid peroxidation [114]. Esteras et al. found that insoluble tau aggregates caused ROS production and cell death by activating NOX in a calcium-dependent manner [115]. Tao et al. revealed that overexpression of miR-204-3p can inhibit NOX4 expression, thereby reducing oxidative stress and Aβ levels [116].

Inhibition of receptors for advanced glycation end products (RAGE) downregulates the expression of NOX4, thereby upregulating Nrf2 and HO-1, which regulates inflammation and oxidative stress [117]. NOX2-mediated oxidative stress is a significant mechanism of Aβ-induced glucose hypometabolism [118]. Therefore, NOX4 and NOX2 can regulate oxidative stress in AD, and targeting NOX holds promising therapeutic potential for the treatment of AD.

4.3. MicroRNA and oxidative stress

MicroRNA (miRNA) is a small non-coding RNA that is a gene regulator in the physiological and pathological mechanisms [119]. MiRNAs are involved in maintaining nervous system function and integrity. MiR-204-3p is downregulated in AD mice and alleviates AD pathology by inhibiting NOX4 [116]. Meng et al. observed that the knockdown of circRNA AXL could inhibit phosphodiesterase 4A (PDE4A) by releasing miR-1306-5p, thereby attenuating Aβ-induced cytotoxicity, oxidative stress, and endoplasmic reticulum (ER) stress [120]. LncRNA H19, as a ceRNA, specifically binds miR-129 to regulate its expression. Silencing of H19 or elevation of miR-129 reduces oxidative stress and prevents mitochondrial dysfunction in Aβ-treated cells [121]. Duan et al. found that increased expression of miR-223-3p can specifically inhibit HDAC4, reduce Aβ-induced nerve damage, and inhibit apoptosis and oxidative stress [122]. The above studies demonstrate that miRNAs exert neuroprotective effects in AD by inhibiting oxidative stress, while some miRNAs can also promote oxidative stress. The overexpression of miR-1273g-3p can down-regulate mitochondria-related genes, thereby inducing oxidative stress and mitochondrial damage to enhance Aβ production [123]. The overexpression of miR-668-3p can negatively regulate oxidation resistance 1 (OXR1) expression, thereby activating p53-p21 signaling to promote Aβ-induced cell damage and oxidative stress [124]. Lei et al. found that NF-κB promotes oxidative stress in AD by inducing the inhibition of TIGAR caused by the upregulation of miR-146a-5p [125]. WT1-AS can inhibit miR-375 by inhibiting the expression of WT1, then promoting the expression of six homeobox 4 (SIX4), thereby protecting neurons from oxidative damage in AD [126]. Collectively, changes in miRNA expression can regulate AD pathology by modulating oxidative stress, and miRNAs have become attractive options for AD therapeutics.

4.4. BDNF and oxidative stress

BDNF is indispensable for neuronal survival and growth [127]. BDNF can reduce neuronal death and ameliorate cognitive impairments, exerting a protective effect on several key pathways in AD [128]. Protein kinase C (PKCε) activation attenuates oxidative stress to prevent microvascular damage during aging and AD [129]. Moreover, oxidative stress and Aβ can suppress PKCε, thereby inhibiting BDNF and MnSOD [130]. Aβ can increase neurotoxicity and oxidative stress by inhibiting BDNF and its receptor TrkB [131]. Li et al. reported that upregulating the BDNF-TrkB pathway can enhance synaptic plasticity in AD rodent models [132]. N-myc downstream-regulated gene 4 (NDRG4) overexpression attenuates Aβ-induced apoptosis, ROS release, and oxidative stress damage via BDNF-induced PI3K/AKT and MEK/ERK pathways [133]. Zhang et al. reported that the BDNF/TrkB/ERK/cAMP response element-binding (CREB) pathway can reduce MDA accumulation and exert antioxidant effects [134]. Additionally, the activation of the ERK/CREB/BDNF signaling pathway has been shown to ameliorate memory impairments in mice [135]. Yan et al. found that the activation of the BDNF/TrkB/CREB signaling pathway can exert neuroprotective effects in $A\beta_{1\text{-}42}$-induced mice [136]. Aβ can reduce BDNF by decreasing phosphorylated CREB protein [137,138]. Therefore, BDNF is associated with oxidative stress in AD and has potential therapeutic implications for AD.

4.5. Metal molecules and oxidative stress

Metal molecules are intimately involved in the regulation of oxidative stress in AD. An autopsy study revealed that the levels of copper, iron, and zinc in the brains of AD patients are 5.7, 2.8, and 3.1 times that of normal brains, respectively [139]. In AD, the interactions of metal molecules enhance the production of free radicals, and metal complexes can facilitate the aggregation of Aβ [140]. Aberrant copper distribution leads to redox-active copper complexes forming, catalyzing ROS generation in AD [141]. Cu^{2+}-catalyzed dityrosine crosslinking can lead to Aβ misfolding and stimulate the assembly of amyloid fibrils [142]. Additionally, the combination of Aβ and Cu^{2+} enhances ROS formation [143]. Aβ can bind to metal molecules such as Fe and Cu, thereby mediating the production of H_2O_2 and OH^- [144]. Iron can augment Aβ and tau, thereby promoting the progression of AD [145]. Moreover, iron ions can bind to Aβ and modify it to generate ROS, thereby inducing cellular damage [146]. Physiological levels of zinc can mitigate Aβ toxicity, but excessive zinc can interact with Aβ, leading to Aβ deposition and neuronal death [147]. Zinc significantly increases the levels of P-mTOR, P-p70S6K, and tau, and decreases Nrf2 and HO-1, which are involved in ROS generation [148]. Copper, iron, and zinc promote oxidative stress through multiple mechanisms in AD, thereby increasing Aβ aggregation and inducing neuronal death.

In addition to the above-mentioned aspects, numerous studies in recent years have investigated the molecular mechanisms underlying AD and oxidative stress (Table 1). Oxidative stress is considered a central factor in AD pathogenesis that links various hypotheses and mechanisms of AD. We summarized recent literature and found that Nrf2/HO-1, NOX, miRNA, BDNF, and metal molecules are all involved in oxidative stress in AD (Fig. 3). Collectively, these mechanisms may help to counteract AD damage caused by oxidative stress and discover underlying neuroprotective mechanisms.

5. Mitochondrial dysfunction and AD

Excessive ROS can induce mitochondrial DNA mutations, lipid peroxidation, and opening of mitochondrial membrane channels, thereby causing mitochondrial dysfunction [149]. Moreover, the opening of mitochondrial membrane channels leads to the collapse of mitochondrial membrane potential, increase in ROS, and disruption of mitochondrial permeability, ultimately resulting in mitochondrial damage [150]. Mitochondrial dysfunction is a severe adverse consequence of oxygen metabolism abnormality. Prolonged hyperoxia can result in mitochondrial dysfunction and excessive ROS formation [151]. Besides, chronic intermittent hypoxia also can induce mitochondrial dysfunction [152]. AD mice exhibit mitochondrial dynamics abnormalities, mitochondrial biogenesis defects, and reduced mitophagy [153]. Mitochondrial dysfunction can promote Aβ formation through multiple mechanisms, including promoting ROS generation, hindering mitochondrial fusion and biogenesis, and impairing mitochondrial respiratory capacity [154–156]. In addition, mitochondria-mediated oxidative stress promotes tau formation and accumulation [157]. Mitochondrial dysfunction can serve as a predictor and driver of AD pathology.

5.1. ER and mitochondrial dysfunction

ER stress triggers mitochondrial dysfunction, both implicated in AD pathology [158]. The mitochondria-associated ER membrane (MAM) is central to metabolic regulation and mitochondrial biology [159]. The functions of MAM include lipid synthesis, mitochondrial dynamics, ER stress, and Ca^{2+} delivery [160]. Mitofusin-2 (Mfn2), a member of MAM, is a protein that regulates mitochondrial fusion, connecting the ER to mitochondria, mutations of which lead to neurological disorders [161]. Che et al. reported that mitochondrial ROS can enhance Mfn2 S-glutathionylation, leading to mitochondrial dysfunction and neuronal necrosis [162]. β-Lactolin increases Mfn2 gene expression, thereby

Table 1
Supplementation of molecular mechanisms related to oxidative stress in AD.

Molecular	Mechanisms	Oxidative Stress (OS)	Function	References
↓ METTL3	↓ m6A modification	↑ OS	↑ Aβ-induced synaptic damage, cognitive impairment, and neuronal death	[237]
↓ Cx3cr1		↑ OS	↑ microglial dysfunction	[238]
HOCl		↑ OS		[239]
AKAP9 I2558 M mutation	↑ tau	↑ OS	↑ AD pathology	[240]
↓ STAT3		↓ OS	↓ Aβ	[241]
↓ DYRK1A	↓ p-Tau	↓ OS	↓ AD pathology	[242]
↑ PPARα	↑ CPT1C	↓ OS	↓ Aβ-induced deposition of AD marker proteins	[243]
↑ MKP1	↓ JNK pathway	↓ OS	↓ Aβ-induced apoptosis and neuroinflammation	[244]
↑ CART		↓ OS	↓ memory impairment	[245]
↑ FGF13	↑ PI3K/AKT/GSK-3β	↓ OS	↓ Aβ-associated neuronal damage	[246]
↑ Adenosine	↑ ERα pathway	↓ OS	↓ Aβ-induced brain injury	[247]
Rhein	↑ SIRT-1/PGC-1α	↓ OS	↓ Aβ, neuroinflammation, and cognitive impairment	[92]
↑ SIRT-1	↓ p21, ↓ MDA, ↑ SOD and GSH	↓ OS	↓ neuronal death	[248,249]

The content in the table is a supplement to the related mechanism of oxidative stress and AD in recent years. Abbreviations: METTL3, m6A methyltransferase like 3; HOCl, hypochlorous acid; AKAP9, a kinase anchoring protein 9; STAT3, signal transducer and activator of transcription 3; DYRK1A, dual-specificity tyrosine-phosphorylation regulated kinase 1A; PPARα, peroxisome proliferators-activated receptor alpha; CPT1C, carnitine palmitoyltransferase 1c; MKP1, mitogen-activated protein kinase phosphatase 1; JNK, c-Jun N-terminal kinase; CART, cocaine amphetamine regulated transcript; FGF13, fibroblast growth factor 13; ERα, estrogen receptor α; ↓, decrease; ↑, increase.

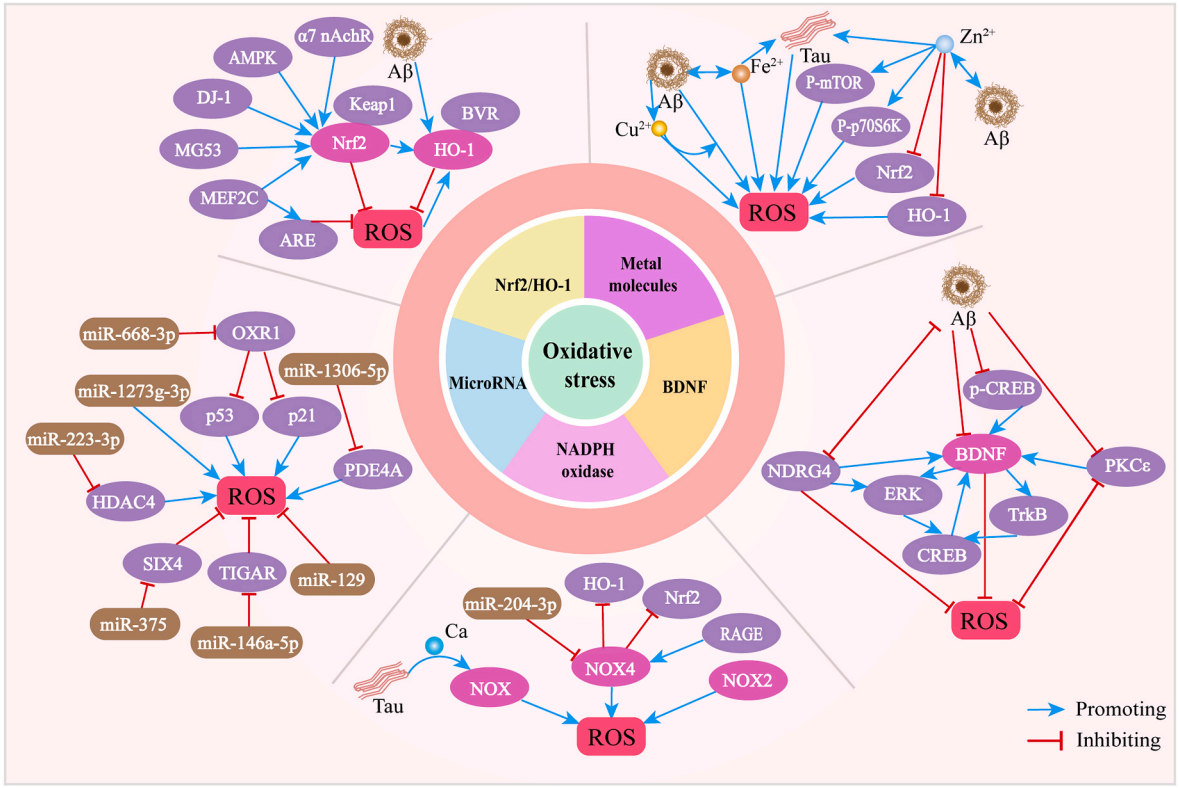

Fig. 3. Molecular mechanism of oxidative stress in AD. The diagram shows five major pathways through which oxidative stress plays a role in AD, including Nrf2/HO-1, NADPH oxidase, microRNA, BDNF, and Metal molecules. The figure also shows the molecular mechanisms associated with these five pathways.

attenuating mitochondrial damage and oxidative stress in Aβ-treated cells, ultimately inhibiting neuronal death [163]. Overexpression of PTEN-induced putative kinase 1 (PINK1) increases phosphorylation of Mfn2 and LC3-II and attenuates mitochondrial dysfunction in AD [164]. Lee et al. showed that peroxiredoxin five (Prx5) deficiency exacerbates ER-mediated mitochondrial fission and ER stress, thereby causing neuronal death [165]. In aging neurons, Aβ inhibits Ca^{2+} transfer from ER to mitochondria, increases ROS production, reduces mitochondrial potential, and promotes apoptosis [166]. Combining the above-mentioned AD-related findings indicates that ER and MAM's related mechanisms are central to oxygen metabolism abnormality and mitochondrial dysfunction.

5.2. Sirtuin (SIRT) and mitochondrial dysfunction

SIRT regulates the metabolic state of mammalian cells. SIRT is involved in the regulation of mitochondrial function, mitochondrial respiration, and ROS generation [167]. Aβ promotes microglia's mitochondrial dysfunction and cellular senescence by inhibiting the SIRT1/Nrf2 pathway [168]. SIRT1/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway can relieve Aβ-induced oxidative stress and promote mitochondrial biogenesis [92, 169]. Chen et al. found that SIRT1 significantly attenuates Aβ-induced NF-κB signaling, exerting neuroprotective effects [170]. The overexpression of SIRT1 can lead to a reduction in Aβ oligomers and

ameliorates oxidative stress [171,172]. Additionally, SIRT1 can reduce neurodegeneration in the hippocampus and enhance learning ability [173]. SIRT3 overexpression restores the expressions of ND2 and ND4 by inhibiting the activity of mitochondria that target p53, thus improving mitochondrial oxygen consumption [174]. Li et al. found that increased SIRT3 expression can enhance energy metabolism, alleviate oxidative stress, and restore Aβ-mediated mitochondrial dysfunction [175]. Moreover, SIRT3 can improve mitochondrial function and ATP production in ApoE4 mice [176]. SIRT regulates many processes in AD, such as APP processing, oxidative stress, and mitochondrial dysfunction [177]. In conclusion, SIRT1 and SIRT3 are involved in the regulation of mitochondria-related mechanisms, and the development of SIRT-related drugs has the potential to attenuate mitochondrial dysfunction in AD.

5.3. Energy metabolism affects mitochondrial function

The energy requirements of the brain account for 20 % of the total energy requirements, most of which are generated from glucose through oxidative phosphorylation in the mitochondria [178]. The rates of glucose uptake and utilization in the brain are both reduced in AD patients [179]. Furthermore, it is likely that brain energy metabolism impairment occurs prior to the clinical symptoms of AD [180]. ATP exerts neuroprotective effects by alleviating oxidative stress and mitochondrial damage [181]. ApoE4 interacts with mitochondria, reduces mitochondrial membrane potential, and causes mitochondrial fragmentation, which impairs energy production and contributes to AD pathology [182]. Park et al. represented that overexpression of NOX4 inhibits ATP production, thereby significantly increasing mitochondrial metabolic damage and promoting ferroptosis in AD astrocytes [114]. Low insulin-like growth factor 1 (IGF-1) expression significantly impairs ATP synthesis and mitochondrial function in astrocytes [183]. Energy metabolism, oxygen metabolism, and mitochondrial dysfunction are interrelated and participate in AD pathology. Research on the regulatory mechanism between energy metabolism and mitochondrial function will help to discover new treatments for AD and delay the progression of AD.

5.4. Metal molecules regulate mitochondrial function

Metals are crucial for enzyme activity and protein formation. Copper, iron, and zinc regulate various cofactors, molecular chaperones, and ion pumps, thereby ensuring the normal function of mitochondria [184]. Dysregulation of metal molecules in AD leads to disease progression and exacerbation of Aβ/tau protein abnormalities [185]. Copper can prevent the phosphorylation of CREB, thereby decreasing the expression of its downstream target protein BDNF, reducing the mitochondrial membrane potential, and affecting mitochondrial function [186]. Overloading of copper can induce mitochondrial dysfunction and increase ROS production, consequently resulting in impaired learning and memory abilities [187]. Chronic iron exposure can induce mitochondrial dysfunction and neuronal loss, thereby increasing the risk of developing AD [188]. However, AMPK can inhibit iron-induced mitochondrial damage [189]. Zinc can aggravate mitochondrial damage and promote liquid-liquid phase separation of tau protein [190]. Moreover, Zinc dysregulation can facilitate Aβ formation and oxidative stress [191]. Copper, zinc, and iron can enhance Aβ production and promote the aggregation of Aβ and tau [192]. In summary, metal molecule imbalance can lead to AD mitochondrial dysfunction.

5.5. Mitophagy

Mitophagy deficiency may constitute a significant factor in the pathology of AD [193,194]. The mechanism of mitophagy can be categorized into ubiquitin-dependent and non-ubiquitin-dependent processes [195]. Ubiquitin-dependent mitophagy is mainly related to the PINK1-parkin pathway [196]. Non-ubiquitin-dependent mitophagy primarily involves mitochondrial proteins serving as autophagic receptors, directing dysfunctional mitochondria for degradation within autophagosomes [197]. The accumulation of tau induces mitophagy deficiency by increasing membrane potential, while the upregulation of Parkin can mitigate tau-induced mitophagy deficiency [198]. Additionally, Parkin-induced mitophagy can clear intracellular Aβ, reduce oxidative stress, and ameliorate mitochondrial dysfunction, thereby reducing neuronal death [199]. PINK1 significantly attenuates oxidative stress and mitochondrial dysfunction and reduces Aβ levels by activating autophagy receptors (OPTN and NDP52) [200]. M2 microglia-derived exosomes restore the disrupted mitochondrial membrane potential and reduce mitochondrial and intracellular ROS accumulation by ameliorating PINK1/Parkin-mediated mitophagy [201]. Furthermore, PINK1/Parkin-mediated mitophagy can reduce Aβ-induced cell damage [202]. Zhao et al. showed that physical exercise reverses mitochondrial dysfunction through PINK1/Parkin-mediated mitophagy [203]. Collectively, PINK1/Parkin-mediated mitophagy can regulate mitochondrial function.

Mitochondrial dysfunction is an early pathological feature of AD [204]. In addition to the abovementioned aspects, numerous studies have explored the molecular mechanisms of AD and mitochondrial dysfunction (Table 2). ER, SIRT, energy metabolism, metal molecules, and mitophagy may all be involved in mitochondrial dysfunction in AD (Fig. 4). These mechanisms have reference value for in-depth research and treatment of AD.

Table 2
Supplementation of molecular mechanisms related to mitochondrial dysfunction in AD.

Molecular	Mechanisms	Mitochondrial dysfunction (MD)	Function	References
↓ ABAD		↓ Aβ-mediated MD	↑ cell viability, ↓ neuronal dysfunction	[250,251]
↑ BRIP1	↓ OS	↓ MD	↓ neuronal cell death	[252]
↑ DUSP6	↓ ERK1/2, ↓ OS	↓ MD	↓ Aβ-induced cytotoxicity	[253]
↑EP	↑ ROS/p38 MAP	↑ Aβ-induced MD	↑ synaptic injury, ↓ cognitive	[254]
↑ PITRM1	↑ Aβ clearance in mitochondria	↓ MD	↓ AD progression	[255]
↓ miR-204	↑TRPML1/ STAT3	↓ mitochondrial damage and autophagy	↓ AD progression	[256]
↑ ApoE4		↑ MD	↑ oxidative stress, ↓ synapses, and cognitive function	[257]
↑ GLP-1	↑ cAMP/PKA	↓ Aβ-induced mitochondrial ROS, mitochondrial membrane potential collapse, and mitochondrial fragmentation	↑ neuronal supportive ability	[258]

This table supplements the mitochondrial dysfunction and AD-related molecular mechanisms beyond the key points of the main text. Abbreviations: ABAD, amyloid-binding alcohol dehydrogenase; BRIP1, BRCA1 interacting protein C-terminal helicase 1; DUSP6, dual specificity phosphatase 6; EP, Endophilin A1; MAP, mitogen-activated protein; PITRM1, pitrilysin metallopeptidase 1; TRPML1, transient receptor potential mucolipin-1; STAT3, signal transducer and activator of transcription 3; GLP-1, glucagon-like peptide-1; PKA, protein kinase A; cAMP, cyclic adenosine 3′,5′-monophosphate; ↓, decrease; ↑, increase.

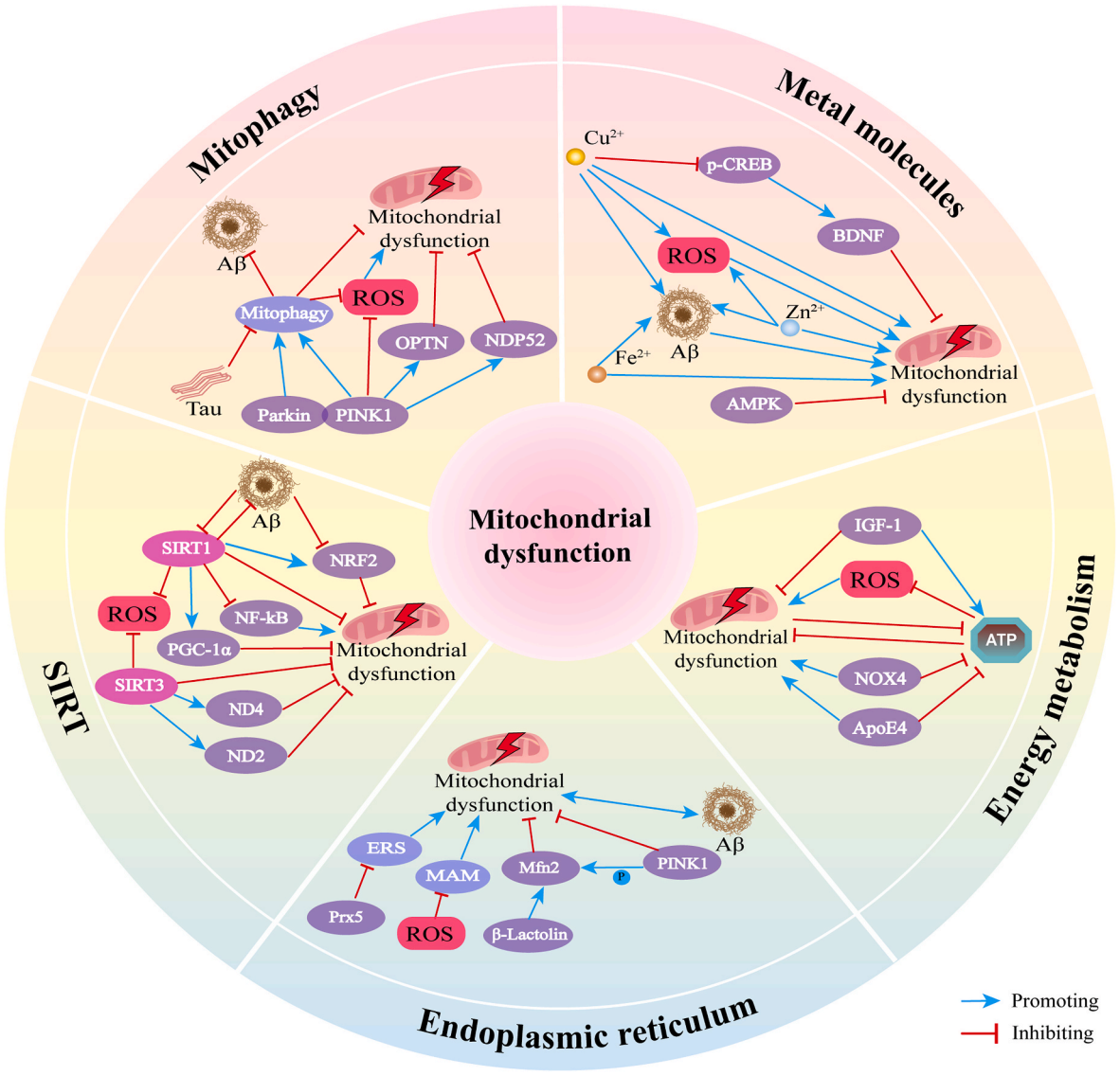

Fig. 4. Molecular mechanisms related to AD and mitochondrial dysfunction. The depicted diagram delineates the five cardinal pathways by which mitochondrial dysfunction exerts its influence in the context of AD. These pathways encompass the endoplasmic reticulum, SIRT, energy metabolism, metal moleculars, and mitophagy. Furthermore, the illustration elaborates on the precise molecular underpinnings associated with each of these enumerated pathways.

6. Oxygen metabolism and the treatment of AD

At present, various therapeutic interventions for AD used in clinical settings hardly achieve anticipated outcomes. Non-pharmacological treatments for AD patients comprise lifestyle modifications and standard care [205]. Drug treatment remains the mainstream approach. The first category encompasses drugs aimed at ameliorating cognitive symptoms, which include cholinesterase inhibitors (Donepezil and Rivastigmine) and glutamate receptor antagonists (Memantine) [206]. The second category comprises drugs intended to alleviate neuropsychiatric symptoms, which include selective serotonin reuptake inhibitors (Citalopram and Sertraline) and atypical antipsychotics (Olanzapine) [207]. The third category of drugs mainly delays the progression of AD and mainly targets Aβ aggregation, such as Aducanumab, Donanemab, and Lecanemab [208,209]. Leuco-methylthionium and methylthioninium are tau inhibitors with potential therapeutic value for AD [210,211]. Certainly, several emerging therapies have also been introduced. Stem cell therapy can replenish damaged neurons, thereby improving cognitive function in AD patients [212]. Neurostimulation techniques, as a novel therapeutic approach for AD, have undergone clinical trials, including deep brain stimulation, transcranial magnetic stimulation, and transcranial electrical stimulation [206]. AD is a multifactorial disease, and combination therapeutic approaches are more likely than individual therapies to have the desired effect.

Hyperbaric oxygen therapy (HBOT) is a potential strategy for treating AD by alleviating various pathological aspects [213]. HBOT ameliorates hypoxia in AD mice, reduces Aβ and tau, and attenuates neuroinflammation [214]. Shapira et al. also showed that HBOT attenuates vascular damage and Aβ in mouse models of AD and elderly patients [215]. HBOT for 20 days significantly improves cognitive function in AD patients [216]. Intermittent hypoxia-hyperoxia training can improve AD patients' cognitive function and slow AD development [217]. However, improper use of HBOT may also lead to excessive oxidative stress, which could result in tissue and cellular damage. Excessively high oxygen concentrations and prolonged exposure may also have harmful effects [218]. Further research is warranted to determine the optimal oxygen concentration and duration of treatment in HBOT. HIF-1 involves oxygen transport, glycolytic metabolism, angiogenesis, cell survival, and apoptosis. Hypoxia-inducible factor prolyl-4-hydroxylases (HIF PHDs) inhibitors exhibit neuroprotective

effects in neurons in AD and may serve as promising candidate drugs [219]. Activation of the HIF-1 signaling pathway and expression of its protective target genes may be attractive and feasible targets for preventing or alleviating AD pathology [220]. Ameliorating hypoxia and investigating hypoxia-related mechanisms could provide meaningful clinical benefits for treating AD.

The main therapeutic modalities against oxidative stress are to prevent the production of oxidants, inhibit redox signaling that causes inflammation or cell death, and increase antioxidant enzymes and their substrates [221]. Antioxidants are essential in fighting oxidative stress. Antioxidants are present in many foods, including lipoic acid, beta-carotene, vitamin C, and flavonoids [222]. Antioxidants are divided into direct antioxidants and indirect antioxidants. Direct antioxidants are short-lived and need to be replenished. Indirect antioxidants can activate the Nrf2 pathway, leading to the transcription of cytoprotective proteins that are not consumed and have a long half-life [223]. Nrf2 has been shown to regulate oxidative stress and neuroinflammation [224]. Significant progress has been made in the research of Nrf2 activators and drugs related to antioxidant mechanisms, which are considered potential pharmaceutical agents for enhancing antioxidant capacity and mitigating the progression of AD [225]. The development of NOX inhibitors also holds therapeutic promise for AD [226]. However, the specificity of NOX inhibitors remains a current challenge and requires further research [227]. Research on oxidative stress and its related mechanisms may hold promise for new therapeutic strategies for AD.

The treatment methods for mitochondrial dysfunction mainly include maintaining mitochondrial bioenergetic performance, improving mitochondrial dynamics, and enhancing mitochondrial health [228]. The Drp1 inhibitor Mdivi-1 can directly reduce mitochondrial fission and is a promising molecule for the treatment of AD [229]. M3 is a type of naphthalene monoimide. M3 can alleviate damage to mitochondrial structure and function, as well as inhibit inflammation, making it a candidate drug for AD [230]. Tannic acid binding to the glutathione peroxidase 4 (GPX4) activation site enhances its expression level, thereby restoring mitochondrial function in AD [231]. A study showed that Nano-Brake halts mitochondrial dysfunction cascades to attenuate neuropathology and rescue cognitive deficits in AD [232]. Mitochondrial dysfunction can directly damage neurons and synapses, and drugs targeting mitochondrial dysfunction may intervene and treat AD.

7. Conclusion

AD exhibits multiple features, among which Aβ deposition and hyperphosphorylated tau accumulation remain the main neuropathological criteria for AD diagnosis [233]. We summarize and analyze the mechanisms of hypoxia, oxidative stress, and mitochondrial dysfunction in oxygen metabolism in AD. Hypoxia and HIF-1 affect many pathological aspects of AD, including Aβ metabolism, tau phosphorylation, neuroinflammation, and oxidative stress [234]. Oxidative stress links the Aβ, tau protein, neuroinflammation, and metal ions in AD [235]. Mitochondria maintain the normal function of neurons and synapses, and mitochondrial dysfunction is an important pathological feature of AD [236]. We have systematically elucidated the relevant mechanisms of oxygen metabolism in AD, which may increase our understanding of the disease. Abnormal oxygen metabolism and AD pathology influence each other and jointly lead to the occurrence and progression of AD. However, the molecular mechanism of oxygen metabolism abnormality in AD is complex, and many mechanisms have not yet been elucidated. In-depth research on important molecular mechanisms related to oxygen metabolism may help discover new diagnostic and therapeutic targets for AD.

Currently, there is no effective treatment for AD. A variety of complex mechanisms jointly regulate the occurrence and development of AD. Therefore, an integrated approach may be required to ameliorate the multiple pathogenic mechanisms of AD in the future. The disorder of oxygen metabolism may be a bridge connecting different pathogenesis of AD, and it is also an inevitable process in these mechanisms. However, factors affecting oxygen metabolism are diverse, such as environmental factors and individual factors. There is still a need to explore further oxygen metabolism-related treatments to correct oxygen metabolism abnormalities in AD. The central role of oxygen metabolism in AD can provide a novel clue leading to the discovery of new anti-AD treatments.

Declaration of competing interest

The authors have declared that no competing interest exists.

Data availability

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

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