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Ageing and Neurodegenerative Diseases

Review

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Research progress on the role of PGC1α in mitochondrial dysfunction associated with Alzheimer's disease

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Abstract

The transcriptional coactivator Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC1α) holds significant importance in the regulation of mitochondrial function during the pathogenesis of Alzheimer's Disease (AD). PGC1α is highly expressed in the brain and has the ability to upregulate mitochondrial biogenesis. It modulates various metabolic pathways, such as the β-oxidation of fatty acids, which is important for generating ATP, and glycolysis, which supplies energy and protects against oxidative stress. The dysregulation of PGC1α can lead to alterations in energy metabolism in the brain, involving mitochondrial dysfunction and consequently decreasing cognitive function and neuronal pathologies. In the early stage of AD, the little amyloid-β protein (Aβ) induces the production of ROS, which upregulates the expression of PGC1α, resulting in increasing mitochondrial biogenesis, fatty acid oxidation and its mRNA expression. However, with the development of AD, a load of Aβ and neurofibrillary tangles ultimately lead to mitochondrial dysfunction, impaired mitochondrial respiration, reduced ATP production, and affect the behavioral brain function in AD. It provides a new idea for improvement or treatment of AD symptoms by activating PGC1α.

Keywords: AD, PGC1α, mitochondrial dysfunction, combinatorial therapy

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that deteriorates gradually with time. AD patients experience memory loss, decreased learning ability, and personality changes[1,2]. According to the annual report of Alzheimer's Disease International (ADI) in 2021, more than 55 million people suffer from AD and the annual expenditure related to this disease is over $1.3 trillion in the world[3]. AD places a substantial burden on both families and society, culminating in exceedingly high healthcare expenses. As human life expectancy continues to rise, AD is emerging as an inescapable public health concern in the aging society.

At present, the recognized pathology features of AD are senile plaques and neurofibrillary tangles (NFTs) formed by deposition of Aβ and hyperphosphorylation of tau protein, ultimately leading to loss of memory and behavior. However, almost all the drugs developed for these two pathological features have failed, the etiology of AD is still not fully understood, and new theoretical problems and treatment plans need to be solved urgently[4]. Studies have shown that the brain accounts for about 20% of the total energy consumption per day[5], even though its weight is only 2% of the normal adult body weight. As the "power plant" of life, the normal operation of mitochondria is important for maintaining a healthy nervous system. Mitochondrial dysfunction has also been gaining more and more attention in AD research. Mitochondrial dysfunction includes respiratory chain dysfunction caused by oxidative stress, loss of mitochondrial biosynthesis, mitochondrial dynamics defects, and mitochondrial gene (mtDNA) mutations[6]. PGC1α is a transcriptional coactivator that regulates cellular energy metabolism. It is highly expressed in brown adipose tissue, heart, skeletal muscle, liver, and brain[7]. PGC1α is also a key regulator of antioxidant responses in oxidative stress and an agonist of mitochondrial biosynthesis. Due to its antioxidant effect, PGC1α assumes a critical role in various neurological diseases[8]. The role of PGC1α in promoting mitochondrial synthesis has the potential to become a new therapeutic target for AD.

Firstly, we briefly discussed mitochondrial dysfunction in AD pathology. Secondly, the roles of PGC1α in neurons and glial cells were summarized, and then the transcriptional and protein modification process of PGC1α and its effects on neuronal mitochondria were summarized. Finally, we described the ways to intervene in neurodegenerative diseases with PGC1α, which is a new idea for AD treatment.

Mitochondrial related dysfunction and possible therapeutic targets in AD

The brain is an important organ for energy consumption, and the mitochondria are the main energy supply sites for neurons and glial cells in the brain. The normal mitochondrial function is very important for neurotransmitter transmission and other neural activities in neural cells[9], including mitochondrial biogenesis[10], fission-fusion homeostasis[11], mtDNA homeostasis[12], Ca^{2+} balance[13], membrane potential $\Delta\Psi m$[14], and so on. As early as 2004, Swerdlow proposed the mitochondrial dysfunction caused by oxidative stress in sporadic AD[15]. In addition, age is an important factor in the degradation of cellular mitochondrial function[16]. When mitochondrial function declines below a threshold, plaque deposition and NFTs will occur. Therefore, Aβ aggregation is an incidental phenomenon of AD pathological development, occurring later than the mitochondrial dysfunction[17]. If the rate of mitochondrial function decay is constant, the timing of disease onset is determined by the baseline level of mitochondrial function. Mitochondria exhibit a certain baseline level, and the prolonged preservation of mitochondrial function is associated with an increased susceptibility to age-related decay.

Mitochondrial biogenesis in AD

Mitochondrial biogenesis is crucial for regulating mitochondrial quantity, cellular turnover, response to cellular damage, and energy provision. The regulation of this process is governed by peroxisome

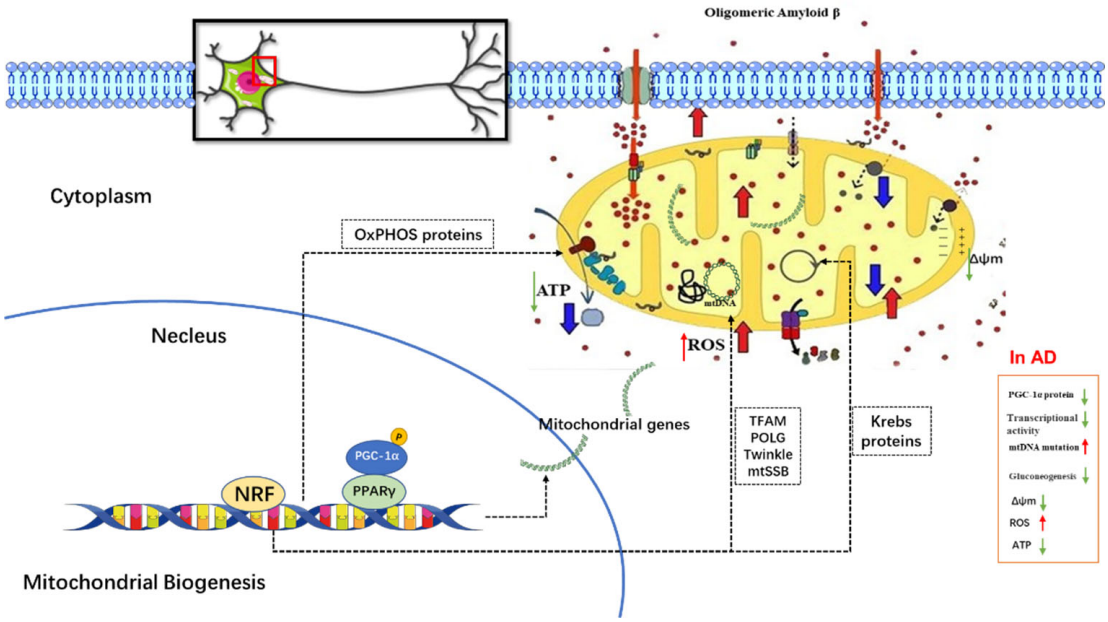

Figure 1. The role of PGC1α in the mitochondria of AD neurons, including effects on mitochondrial energy metabolism, biogenesis and ion homeostasis. mt: Mitochondrial; mtSSB: mitochondrial ssDNA-binding protein; NRF: nuclear respiratory factor; PGC1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; POLG: mitochondrial polymerase, polymerase-γ; PPARγ: the nuclear receptor peroxisome proliferator-activated receptor-γ; ROS: reactive oxygen species; TFAM: mitochondrial transcription factor A; Twinkle: twinkle helicase; ΔΨm: mitochondrial membrane potential.

proliferator-activated receptor (PPAR) and its coactivator, PGC1α[18], nuclear respiratory factors (NRF1, NRF2)[18-20], and mitochondrial transcription factor A (TFAM)[21] [Figure 1]. Assuming a vital function in maintaining energy balance and regulating metabolism, PGC1α is a pivotal regulator of mitochondrial biogenesis, with its activity subject to regulation by sirtuin 1 (SIRT1) or AMP-activated protein kinase (AMPK)[21]. Sirtuins (SIRT1-7) belong to the NAD-dependent histone deacetylase protein family[22], and SIRT1 deacetylates PGC1α and promotes nuclear transfer[23]. AMPK is a sensor of AMP/ATP ratio[24], and in low-energy states, AMPK promotes phosphorylation of PGC1α, which accelerates the regulation of glucose transport, fatty acid oxidation, and mitochondrial biogenesis[25] [Figure 2]. As a part of the mtDNA base excision repair process, TFAM controls mtDNA replication and transcription[26]. The expression of PGC1α, NRF1, NRF2, and TFAM in the hippocampus of AD is decreased significantly, suggesting abnormal mitochondrial biosynthesis in AD[27].

Mitochondrial oxidative stress in AD

Reactive oxygen species (ROS) are mainly produced in the mitochondria, including superoxide radicals (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-). In physiological circumstances, the organism meticulously regulates the concentration of ROS through endogenous antioxidant defense mechanisms, such as superoxide dismutase, catalase, and glutathione reductase. Elevated intracellular ROS levels can lead to oxidative stress, potentially causing cellular abnormalities. However, mitigating oxidative stress can be achieved by enhancing mitochondrial integrity and reducing the quantity of damaged mitochondria[23]. Interacting with antioxidant response elements (ARE), NRF2, a transcription factor, governs the expression of antioxidant genes[28]. In AD patients, there was a notable decrease in NRF2 expression within the nucleus of hippocampal neurons[29]. In APP/PS1 transgenic mice, NRF2-ARE activity gradually weakened with Aβ deposition, and NRF2 could also reduce Aβ accumulation by negatively regulating BACE1 and BACE1-AS[30]. In addition to its activation of NRF2, it is likely that the promotion of the autophagy adaptor protein NDP52 occurs and reduces the phosphorylation level of tau protein[31]. PGC1α regulates the expression of *NRF2* gene by increasing phosphorylation of GSK3β, thereby protecting against

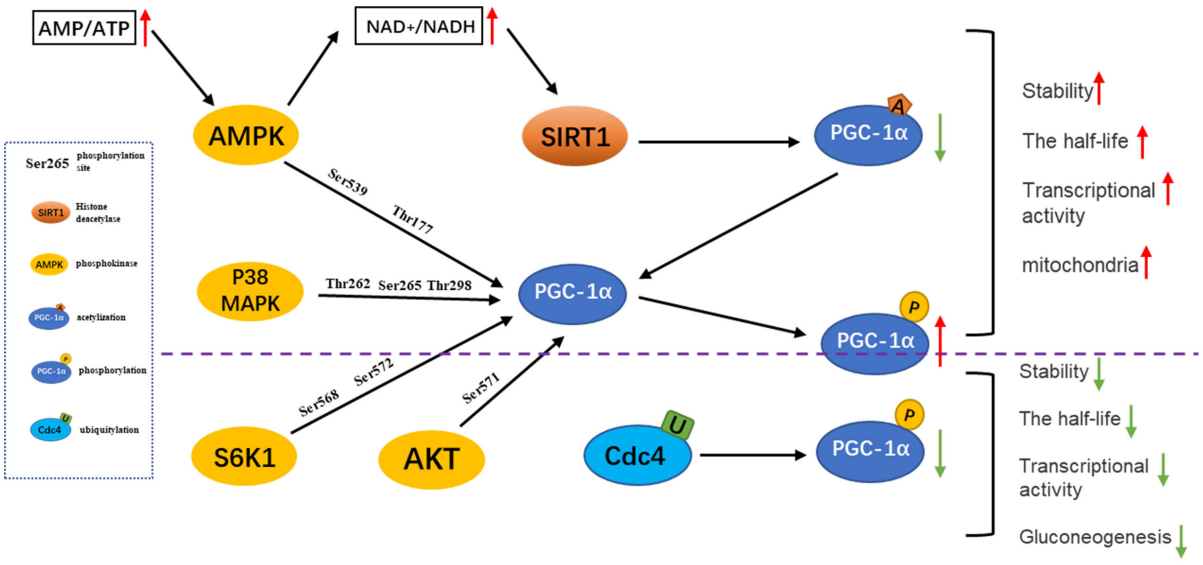

Figure 2. Partial transcriptional regulation and protein modification patterns of PGC1α. AKT: protein kinase B; AMP: adenosine 5′-monophosphate; AMPK: AMP-activated protein kinase; Cdc4: cell division control protein 4; NAD+: nicotinamide adenine dinucleotide; NADH: nicotinamide adenine dinucleotide; PGC1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; p38MAPK: p38 mitogen-activated protein kinase; SIRT1: sirtuin 1.

antioxidants[32], suggesting that the PGC1α/NRF2 pathway has potential therapeutic value.

Mitochondrial dynamics in AD

Mitochondrial dynamics is also known as fission-fusion equilibrium. Dynamically changing mitochondrial morphology affects energy synthesis and biological quality. In many neurodegenerative diseases, mitochondrial dynamics are impaired.

Mfn1, Mfn2, and Opa1 play essential roles in mitochondrial fusion, whereas Drp1 and Fis1 are involved in fission processes[27,33] [Figure 3A]. In frontal cortex of AD patients, the mRNA and protein levels of Drp1 and Fis1 were increased, while the expression of fusion genes *Mfn1*, *Mfn2*, and *OPA1* was significantly decreased, which suggests that mitochondrial fission and fusion imbalance are important neuronal dysfunction mechanisms[34]. Excessive mitochondrial fission caused by Drp1 interaction with Aβ and tau can lead to synaptic dysfunction and cognitive decline[35]. Oppositely, partial inhibition of Drp1 prevented the toxic effects of Aβ and tau, stabilized mitochondrial dynamics, and increased mitochondrial biogenesis and synaptic activity. Furthermore, DRP1 is associated with GSK3β, CDK5, and p53, but their associations in AD have not been fully elucidated[36].

Mitochondrial DNA mutation in AD

Mitochondrial DNA (mtDNA) contains 37 genes in total, 13 of which are associated with oxidative phosphorylation (OXPHOS)[37]. In most cases, the pathogenic variant is recessive. Mutations disrupt most OXPHOS before symptoms present. Unlike histone-protected nuclear DNA (nDNA), mtDNA is highly sensitive to mutagenesis and cytotoxic ROS, and its mutation rate is 10 times higher than that of nDNA[38]. Thus, abnormal products including NADH dehydrogenase, cytochrome C oxidase (COX), and faulty ATP synthase ultimately lead to more electron leakage and ROS production. This "vicious cycle" plays an important role in the aging process[39]. Studies on mitochondrial gene polymorphisms suggest that mitochondrial haplogroups may increase genetic susceptibility to AD independent of APOE4. Pathogenic

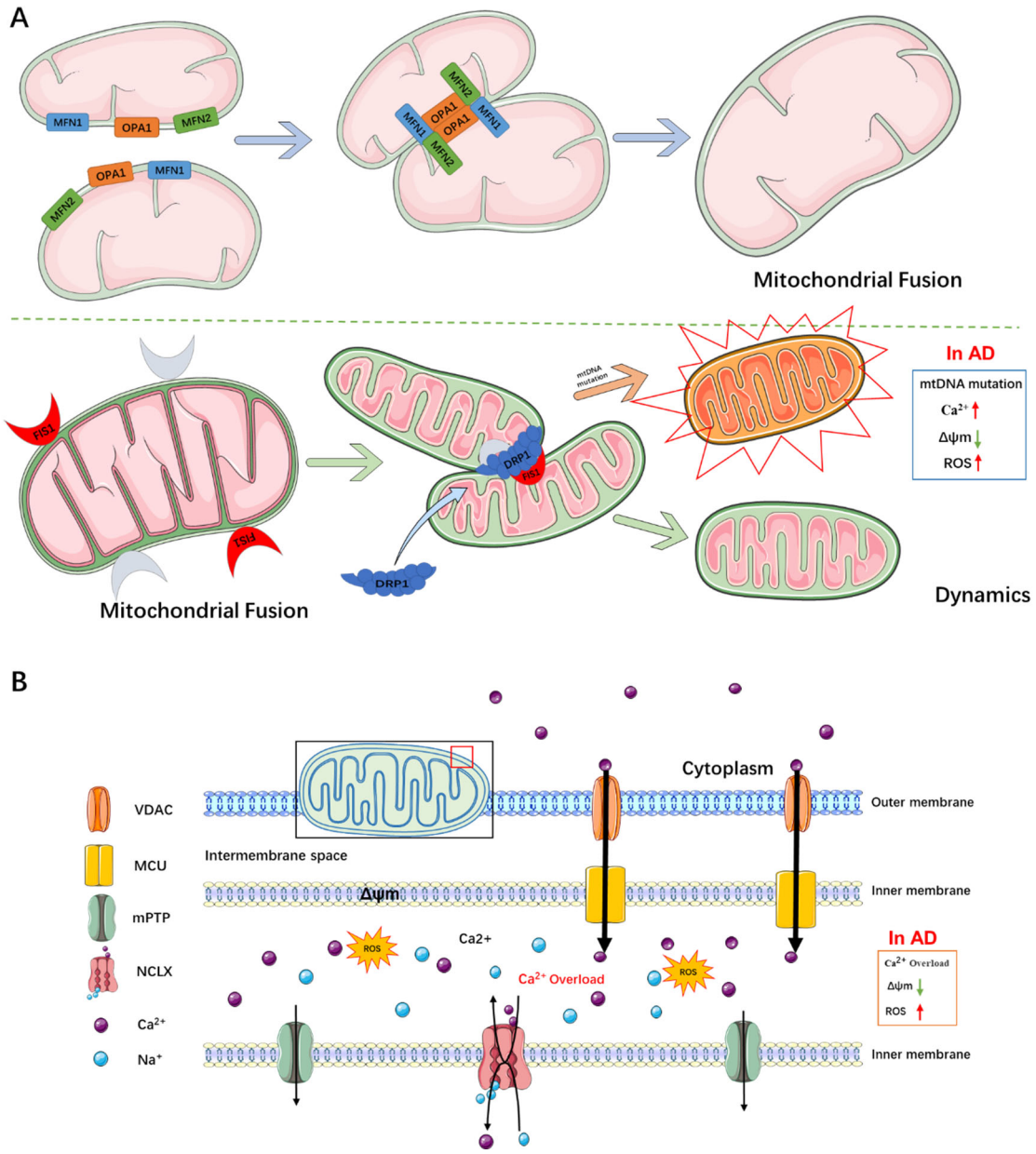

Figure 3. (A) Mitochondrial Fission-Fusion Patterns in AD; (B) Mitochondrial Ca^{2+} Homeostasis Patterns in AD. DRP1: Dynamin-related protein-1; FIS1: fission protein 1; MCU: mitochondrial calcium uniporter; MFN1: mitofusin1; MFN2: mitofusin2; mPTP: mitochondrial permeability transition pore; NCLX: mitochondrial $Na^+/Ca^{2+}/Li^+$ exchanger; OPA1: mitofusin1; ROS: reactive oxygen species; VDAC: voltage-dependent anion selective channel; ΔΨm: mitochondrial membrane potential.

mtDNA mutations coexist intracellularly with wild-type mtDNA, termed heteroplasmy[38]. Mitochondrial gene therapy strategies currently focus on lowering pathogenic mtDNA levels by increasing the ratio of wild-type mtDNA to mutant mtDNA. This can be achieved through the design of resistance gene sequences that bind and inhibit the replication of mutant mtDNA, or by using mitochondria-targeted nucleases such as peptide nucleic acids, restriction enzymes, and zinc finger nucleases to selectively degrade mutant mtDNA[39]. Although these methods have been validated in numerous animal models, many questions still persist. One such question pertains to the vector size, which might impede the passage of mtDNA through the inner mitochondrial membrane. Furthermore, achieving precise control over mtDNA degradation poses

challenges, particularly in neuronal cells characterized by elevated levels of mtDNA mutations.

Mitochondrial Ca^{2+} homeostasis in AD

The mitochondrial membrane potential (ΔΨm) is maintained by the OXPHOS proton pump (complexes I, III, and IV), which powers ATP production and ion transport (e.g., Ca^{2+}) [Figure 3B]. The level of ΔΨm is relatively stable and plays a key role in maintaining normal mitochondrial homeostasis. Zorova *et al.* found that when ΔΨm changes drastically or chronically, mitochondrial damage and cell death may be triggered[40]. Decreased levels of ΔΨm have been observed in many cellular and animal models of age-related diseases. Mitochondria coordinate with the endoplasmic reticulum (ER) to act on the buffering and regulation of Ca^{2+} in cells by sequestering or releasing ions into the cytoplasm, and mitochondrial Ca^{2+} homeostasis is critical for a variety of cellular functions. Driven by ΔΨm, mitochondrial ion channels such as voltage-dependent anion channel (VDAC) and mitochondrial calcium uniporter (MCU) are transported [Figure 3B]. Overloaded Ca^{2+} enters the mitochondrial matrix, which affects processes such as oxidative respiration, ATP production, mitochondrial dynamics, and so on[41]. Severe mitochondrial Ca^{2+} overload results in increased ROS production, ΔΨm dissipation, metabolic dysfunction, and induction of apoptosis or necrosis through the opening of mitochondrial permeability transition pore (mPTP). This influx of excess mitochondrial Ca^{2+} is harmful to neurons and has been associated with neurodegeneration and ischemia[42]. Therefore, modulating mitochondrial Ca^{2+} homeostasis may be an emerging therapeutic strategy for AD and other related degenerative neuropathies.

THE ROLE OF PGC1α IN NEURAL CELLS

PGC1α is involved in the metabolic process of neural cells

PGC1α is particularly abundant in brain regions such as the cerebral cortex, striatum, and substantia nigra (SN), but not in the hypothalamus[43]. PGC1α-deficient mice displayed spongiform lesions in the striatum, causing hyperactivity, muscle spasms, dystonia, and excessive startle responses. These behavioral disorders are associated with axonal degeneration in the central nervous system, and the molecular mechanism may involve disturbances in ROS metabolism and impaired energy homeostasis due to PGC1α deficiency[44]. In addition, PGC1α gene-deleted mice exhibited patchy micro-vacuolated areas in the cerebral cortex, with a slight increase in the number of astrocytes in the basal ganglia[45]. Some evidence suggests that activation or overexpression of PGC1α can be used to ameliorate neurological diseases, including AD, PD, and ALS, in cellular and rodent models[46]. The related mechanisms are mainly involved in the inhibition of mitochondrial dysfunction and oxidative stress[47]. The PGC1α also reduces the transcript level of APP cleaving enzyme (BACE1) in AD patients, thereby reducing Aβ deposition[48]. Therefore, to explore the function of the *PGC1α* gene in different brain regions and its potential therapeutic role is an urgent task.

PGC1α is involved in neuroinflammatory processes

Neuroinflammation is an inflammatory cascade primarily caused by activated microglia and astrocytes, including proinflammatory cytokines and chemokines, resulting in complex crosstalk between different types of cells in the CNS. It is a common pathological process in AD. Notably, microglia are CNS resident macrophages with functional plasticity of dual phenotype, proinflammatory M1 phenotype, and anti-inflammatory M2 phenotype. There is increasing evidence that microglia-mediated neuroinflammation is associated with AD progression[49]. PGC1α plays an important role in preventing neuroinflammation. 5-Aminoimidazole-4-carboxamide ribonucleoside (AICAR) activates AMPK to increase PGC1α expression, which inhibits LPS/Aβ-induced inflammation by suppressing proinflammatory cytokines such as iNOS and COX-2. AICAR also reduces ROS production and decreases astrocyte numbers[50]. PGC1α simultaneously inhibits M1 activation by inhibiting nuclear factor-κB (NF-κB) activity and enhances the polarization of microglia towards the M2 phenotype by activating the signal transducer and activator of the transcription (STAT) signaling pathway[51]. Sildenafil can activate PGC1α by inhibiting PDE5, increasing cGMP levels,

and PGC1α deacetylation. The mechanism may be that PGC1α inhibits the inflammatory response by inhibiting the production of ROS, upregulating the expression of anti-inflammatory related proteins and antioxidant enzymes, and inducing mitochondrial biogenesis[52].

Another strategy is to stimulate the PGC1α signaling pathway by activating PPAR to improve neuroinflammation. PPARγ has been shown to antagonize the activity of transcription factors and inhibit the transcription of proinflammatory cytokines, such as NF-κB and activator protein-1 (AP-1). In particular, PPARγ not only reduces proinflammatory cytokines but also enhances the expression of anti-inflammatory mediators, including IL-10 and methylenetetrahydrofolate reductase (MTHFR)[53]. Therefore, activation of the PGC1α signaling pathway helps to suppress neuroinflammation and promotes anti-inflammatory, thereby slowing the progression of AD.

Transcriptional regulation and protein modification of PGC1α in neural cells

PGC1α (also known as LEM6) is a 97-120 kDa member of the PGC1 protein family. According to NCBI, the human *PGC1α* gene is located at 4p15.2, and its DNA is about 67 kb in length, including 12 introns and 24 exons. There are many transcription factor binding sites upstream of the *PGC1α* gene transcription start site, such as AP-1, AP-2, CAAT/enhancer Binding Protein (C/EBP), MEF2, PPARresponse Element (PPRE), cAMP-responsive Element (CRE), and Insulin responsive Sequence (IRS), *etc.* PGC1α is involved in RNA processing and transcriptional co-activation together with multiple nuclear hormone receptors such as PPARγ, RAR, and TR. Human PGC1α protein is 798 amino acids (aa) in length. It contains an LxxLL nuclear receptor binding motif (aa 144-148, the LxxLL motif is a coactivator feature required for interaction with many types of other transcription factors and nuclear receptors), a PPAR-gamma interaction domain (aa 293-339), two NLSs and one RNA binding/processing region (aa 566-710). The activity of PGC1α is regulated by phosphorylation. AMPK can phosphorylate Thr178 and Ser539, promoting co-transcriptional activity. However, AKT-mediated phosphorylation of Ser571 downregulates the activity of PGC1α[54,55]. The latter effect is achieved by initialing Ser571 phosphorylation, followed by GCN5 binding and PGC1α acetylation, promoting the dissociation of PGC1α from target gene promoters[56].

The role of PGC1α in different neural cells and glial cells

Neural cells and glial cells in the brain mainly include neurons, astrocytes, oligodendrocytes, and microglia. PGC1α functions differently in the brain compared to that in peripheral tissues. Conditional knockout of the *PGC1α* gene in the CNS revealed its involvement in metabolic processes and related regulatory genes, including synaptotagmin 2 and complex protein 1 interneuron genes[57]. PGC1α overexpression protects neurons in culture from oxidative stressor-mediated death[58] and increases the formation and maintenance of dendritic spines in hippocampal neurons. Furthermore, conditional knockout of the *PGC1α* gene in adult mice resulted in the loss of dopaminergic neurons, accompanied by a decrease in dopamine in the striatum[59]. PGC1α is also expressed in astrocytes and functions to modulate neuroinflammation and oxidative stress[60]. In neurodegenerative disease, PGC1α can promote neuronal survival by affecting the activity of NFR2[61]. PGC1α expression is altered in neurodegenerative diseases such as ALS, HD, PD and multiple sclerosis[62,63], resulting in mitochondrial defects and elevated ROS levels[64,65]. In conclusion, PGC1α not only promotes mitochondrial biogenesis in neurons and glial cells but also participates in cellular immunity and inflammatory responses in glial cells.

PGC1α as a potential therapeutic target for AD

The decreased mRNA expression of PGC1α in the AD brain correlates with the pathological level of Aβ[66]. PGC1α is associated with reduced Aβ levels in AD pathology[67,68]. Furthermore, PGC1α proteins were reduced in the brains of APP/PS1 mouse models. In contrast, crossing Tg2576 mice with PGC1α-deficient mice or knocking down PGC1α in neuronal cells through siRNA transfection resulted in increased Aβ

levels[69]. ELISA results in double transgenic PGC1α and Tg19959 mice showed decreased Aβ40 expression but increased Aβ through Congo red staining[70]. In cells transfected with PGC1α siRNA, PPARγ-mediated PGC1α and BACE1 promoter activity was observed with the opposite results[71,72]. Reports indicate that PPARγ is a repressor of BACE1, and researchers found that the BACE1 promoter contains a PPRE domain[72,73]. However, other studies have indicated that PGC1α may promote BACE1 proteasome degradation by activating CF(Fbx2)-E3 ligase gene expression[71]. PGC1α contributes to the beneficial effects in AD through its impact on pathways other than BACE1[48,72], such as increasing α-secretase activity[48], or mediated by peroxisomal FoxO3a. However, other experimental studies in mouse hippocampal neurons suggest that PGC1 activation may affect BACE1 proteasomal degradation[71] in the absence of a promoter for PGC1α[73]. The mechanism of PGC1α reducing Aβ production is most likely by decreasing the expression of rate-limiting enzymes that produce Aβ.

Currently, treatments for AD do not directly focus on mitochondria. FDA-approved drugs for AD treatment include cholinesterase inhibitors (Donepezil, Neostigmine, and Galantamine) and N-methyl-D-aspartate receptor antagonists (Memantine). However, these drugs have only demonstrated modest clinical improvement[73]. Phase I clinical trials of anti-amyloid vaccines have failed due to multiple serious side effects[74]. In recent years, some encouraging results have been discovered in the field of β- and γ-secretase inhibitors[75]. However, there is still a lack of effective therapies to slow or stop AD progression.

Resveratrol is a polyphenolic compound, one of the main active components of wine, and can induce Sirt1 expression, increase AMPK activation, and activate PGC1α[76] [Figure 2]. Resveratrol reduces hippocampal degeneration and improves cognitive impairment in AD models by activating PGC1α, Sirt1, and AMPK signaling[77,78]. In vitro, resveratrol inhibits Aβ-induced apoptosis via Sirt1. Long-term intake of resveratrol reduces learning and memory impairment by activating AMPK and Sirt1, reducing amyloid and phosphorylated tau. In recent years, some clinical trials for mild to moderate AD have shown that resveratrol is safe and well-tolerated, and can cause a certain reduction in plasma and cerebrospinal fluid Aβ 40 levels[79,80]. However, there are also studies claiming that a certain dose of resveratrol can stabilize APP protein in an AMPK-proteasome signaling-dependent manner instead of increasing the production of Aβ[81], which poses a challenge for the study of resveratrol for AD treatment.

Nicotinamide Mononucleotide (NMN), the precursor of NAD[+], increases PGC1 levels through the NAD-dependent deacetylase Sirt1, and NAD levels are associated with reduced Aβ toxicity in experimental models of AD[82]. Pharmacological stimulation of PGC1α synthesis with nicotinamide riboside at 250 mg/kg/day for 3 months resulted in decreasing Aβ levels and attenuating cognitive impairment in Tg2576 mice, which were associated with decreased BACE1 expression[48].

Diammonium Glycyrrhizinate (DG), a component of glycyrrhizin, is considered a candidate compound for AD treatment. DG is known for its anti-inflammatory effects and has been shown to significantly upregulate the expression of PGC1α, thereby preventing oxidative stress, mitochondrial dysfunction, and further cognitive impairment[83]. However, Dumont *et al.* found that DG exacerbated Aβ and Tau deposition by causing overexpression of PGC1α. Furthermore, PGC1α overexpression not only leads to mitochondrial dysfunction and neuronal cell damage but also worsens behavioral hyperactivity[70]. Thus, maintaining a careful balance between PGC1α expression and function is crucial for achieving the benefits of DG and may assist in developing therapeutic strategies.

Bezafibrate is an activator of PGC1α and 3-methylglutaric acid (MGA) is a compound in 3-methylglutaric acid (MGTA) and 3-hydroxy-3-methylglutaric acid (HMGA) accumulated organic acids. MGA can impair

mitochondrial function and mitochondrial biogenesis by reducing the activity of succinate dehydrogenase and various respiratory chain complexes, the nuclear levels of PGC1α and NT-PGC1α, and the content of Sirt1 in cells. MGA further increased AMPKα1, leading to neuronal injury by reducing Akt and Synaptophysin content and ERK phosphorylation, as well as increasing active caspase3 and p38 and Tau phosphorylation. While Bezafibrate prevents MGA-induced toxic effects on mitochondrial function, redox homeostasis, and neuronal cell damage, implying that the compound could potentially be used in adjunctive therapy for MGTA and HMGA and other mitochondrial dysfunction[84].

The method of *PGC1α* gene intervention has been reported, which is injecting an adeno-associated virus (AAV) into the hippocampus of APP/PS1 mice to overexpress PGC1α. It promotes the increase of vitamin D receptor (VDR) expression and finally reduces the level of Aβ plaques[68]. Although there is substantial evidence that modulating PGC1α levels in the brain may be an effective approach, PGC1α overexpression may also have damaging effects on specific cell types, such as degeneration of dopaminergic neurons[85].

Exercise as a non-drug therapy against AD can induce the upregulation of PGC1α in skeletal muscle, stimulate the expression of FNDC5, and induce the transcription of BDNF by increasing the phosphorylation of PGC1α by AMPK[86]. Lin *et al.* showed that swimming exercise can stimulate the AMPK/SIRT1/PGC1α signaling pathway and inhibit the apoptosis and inflammation of hippocampal neurons in aged mice[87].

CONCLUSION AND PERSPECTIVES

In conclusion, improvement or treatment of AD symptoms by activating PGC1α offers hope for the cure of AD, either with drugs that increase the expression level of PGC1α (such as resveratrol or nicotinamide riboside) or with the activation of PGC1α-regulated transcription factors (e.g., PPAR agonists or AREs). However, it should still be used with caution, considering that overexpression of PGC1α may lead to deleterious effects. Future research on PGC1α-based therapies should also examine its effects on other pathological features (e.g., tau pathology, blood glucose, and skeletal muscle) present in the brain and throughout the body in AD. In addition, the effect of activating PGC1α on animal models of advanced aging and disease is also worth exploring. The potential research value in the future is that PGC1α can induce growth factor expression and maintain intracellular ion homeostasis (such as BDNF and mitochondrial Ca^{2+} homeostasis, *etc.*), which has neurogenesis-promoting, neuronal loss prevention, and potential anti-inflammatory effects.

DECLARATIONS

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Author contributions

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Coordinated the first draft: Lin HS, Huang XP
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All authors declared that there are no conflicts of interest.

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