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Invited Mini Review

Mitochondrial dysfunction and Alzheimer's disease: prospects for therapeutic intervention

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Alzheimer's disease (AD) is a multifactorial neurodegenerative disease and has become a major socioeconomic issue in many developed countries. Currently available therapeutic agents for AD provide only symptomatic treatments, mainly because the complete mechanism of the AD pathogenesis is still unclear. Although several different hypotheses have been proposed, mitochondrial dysfunction has gathered interest because of its profound effect on brain bioenergetics and neuronal survival in the pathophysiology of AD. Various therapeutic agents targeting the mitochondrial pathways associated with AD have been developed over the past decade. Although most of these agents are still early in the clinical development process, they are used to restore mitochondrial function, which provides an alternative therapeutic strategy that is likely to slow the progression of the disease. In this mini review, we will survey the AD-related mitochondrial pathways and their small-molecule modulators that have therapeutic potential. We will focus on recently reported examples, and also overview the current challenges and future perspectives of ongoing research. [BMB Reports 2020; 53(1): 47-55]

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder, characterized by the progressive loss of memory and neuronal degeneration. The prevalence of AD is high among aged individuals, and the incidence rate for AD increases exponentially after age 60. With the extended human average lifespan, AD is becoming an increasingly widespread health issue and tremendous research efforts have been made to design and develop novel drugs that can efficiently stop the progress of the disease (1). Given that aging is accompanied by a time-dependent progressive deterioration of multiple pathways in the cells, high energy-demanding organs such as the brain would greatly suffer from the age-dependent alteration in bioenergetics and redox homeostasis, leading to neuronal impairment and eventually to neurodegeneration. Notably, brain hypometabolism and oxidative stress are the prominent events in AD, which undoubtedly involve metabolic pathways and electron-transport systems in the mitochondria (2-4). Indeed, mitochondrial dysfunction is an early feature of AD and appears to play a significant role in its pathogenesis (4-6).

Mitochondria are multi-functional organelles responsible for a wide range of functions, including adenosine triphosphate (ATP) production, metabolism, and stress responses. Given the diverse roles of mitochondria, mitochondrial dysfunction has been linked to a variety of diseases, such as diabetes, cardiovascular disease, cancer, and neurodegenerative diseases. In particular, the central nervous system requires approximately 20% of the body's total basal oxygen consumption to support neuronal energy expenditure; therefore, neurons with impaired mitochondrial function suffer from ATP depletion, oxidative stress, and eventually cell death (7). Brain hypometabolism and increased oxidative stress were observed in brains from AD transgenic mice and AD patients even before the appearance of senile plaques and neurofibrillary tangle (NFT) (2, 4). These two main hallmark proteins of AD also have a direct effect on mitochondrial function, causing the impairment of mitochondrial membrane potential, the reduction of ATP production, and the acceleration of ROS generation in the brain (8, 9). Now many researchers have reached the hypothesis that restoring normal mitochondrial function may increase neuronal survival and potentially provide a therapeutic strategy to reverse the disease course of AD (10-14).

Currently available therapeutic agents approved for the treatment of AD provide only symptomatic relief, but AD therapies that can stop or slow the progression of the disease are urgently needed (15). In this context, compounds that can rescue dysfunctional mitochondria might generate a novel

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therapy for AD. To this end, compounds targeting the pathways associated with mitochondrial function have been developed over the past decades, and some of these compounds are currently in clinical trials for the treatment of AD. In this review, we will overview the AD-related mitochondrial dysfunction and potential therapeutic strategies that have been reported recently. We will also describe small-molecule functional modulators that target mitochondria (Table 1) and discuss their advantages and future challenges in the development of novel therapeutic agents for the treatment of AD.

MITOCHONDRIAL PROTEIN-QUALITY CONTROL

Healthy mitochondria maintain protein homeostasis by regulating protein folding, degradation, and fission and fusion processes to repair and remove damaged mitochondrial proteins, the overall processes of which are also termed protein-quality control (16). Mitochondrial dysfunction disrupts the protein-quality control processes, leading to the accumulation of the damaged and misfolded proteins inside mitochondria, eventually promoting the pathogenesis of various neurodegenerative diseases. The pathways and processes associated with protein-quality control are regulated at multiple levels, from proteolytic degradation at the molecular level to apoptosis at the cellular level; at the center of the stage, mitochondrial dynamics and mitochondrial protein degradation, also known as mitophagy, are critically involved (17). Whereas the eventual downstream effects of the defective mitochondrial quality control are the accumulation of neurotoxic, misfolded proteins associated with various neurodegenerative diseases, including AD, Parkinson's disease (PD), and Huntington's disease (HD) (18), in this section we will focus on the pathways and small-molecule modulators involved in the AD pathology.

Mitochondrial dynamics: Dynamin-related protein 1 (Drp1)

Mitochondria are highly dynamic organelles undergoing constant cycles of fusion and fission, forming the mitochondrial network, which is important for the control of the distribution, shape, and size of mitochondria, and also crucial for the regulation of cell-death pathways (19). The fine balance between the fusion and fission process is maintained by mitochondrial membrane proteins such as optic atrophy proteins (OPA) and mitofusins (MFN). Mutations in these proteins lead to a defective mitochondrial network, causing a slew of issues including impaired bioenergetics, disrupted protein-quality control, and mitochondrial proliferation (20). Many studies have indicated that the defective mitochondrial network is one of the major culprits in the pathogenesis of neurodegenerative diseases including Parkinson's disease and Alzheimer's Disease (20). Specifically, the mitochondrial fission protein, dynamin-related protein (Drp1), exacerbates AD pathogenesis by inducing excessive mitochondrial fragmentation and abnormal mitochondrial dynamics upon interacting with Aβ and tau proteins (21-23). Increased Drp1 activity also increases ROS production but abates ATP production, causing oxidative damage and synaptic dysfunction in AD neurons. Several studies also have found increased levels of Drp1 in postmortem AD brains as well as animal AD models (24-26), suggesting that the inhibition of Drp1 may generate therapeutic effects in AD.

Over the past decade, small-molecule Drp1 inhibitors have been developed and tested for their therapeutic efficacies in AD animal models. The most widely studied inhibitor, mdivi-1 is a quinazolinone-based cell-permeable Drp1 inhibitor which inhibited mitochondrial division in yeast and mammalian cells (27). More importantly, studies have found that the treatment with mdivi-1 demonstrated neuroprotective effects in transgenic AD mice by reducing excessive mitochondrial fragmentation (28, 29). In addition to mdivi-1, P110, a heptapeptide (DLLPRGT) derived from the sequences of Drp1, demonstrated similar protective effects by blocking mitochondrial fission and restoring ROS-induced mitochondrial dysfunction in neuronal cells (30, 31). Several research groups have developed small-molecule inhibitors with more potent Drp1 inhibitory effect by chemical library screening and structural optimization. Numadate *et al*. reported PAQ-22 (3-(4-chloro-3-methoxyphenyl)-2-thioxoquinazoline-4-one) (32); Mallat *et al*. identified two effective compounds containing the 1H-pyrrole-2-carboxamide scaffold (33). More recently, Kuruva *et al*. designed a novel Drp1 inhibitor named DDQ (diethyl (3,4-dihydroxyphenethylamino) (quinolin-4-yl)methylphosphonate), based on the molecular docking study of the Aβ and Drp1 protein complex. DDQ inhibited the Aβ and Drp1 interaction, reduced cellular levels of Aβ oligomers, and improved mitochondrial function in cell-based models of AD (34). Modulating the mitochondrial fusion and fission by using a small-molecule Drp1 inhibitor such as mdivi-1 is a novel strategy that can potentially generate a disease-modifying drug. However, considering that these inhibitors have been tested in only cells and a few selected animal models and a potential off-target effect was also reported (35), they may still have a long way to go before clinical development.

Mitophagy: PINK1 (PTEN-induced kinase 1)

PINK1 is a mitochondrial serine/threonine kinase located in the mitochondrial intermembrane space, and its association with early-onset PD is widely recognized (36). PINK1 detects damaged mitochondria, initiates mitophagy by recruiting cytosolic protein partner Parkin, and removes damaged mitochondria (37). Although PINK1 mutation is considered to be the hallmark of early-onset PD, several recent studies have found that PINK1 signaling is also associated with Alzheimer's disease (38, 39). According to the study reported by Du *et al*., PINK1 is downregulated in the brains of AD patients as well as in the transgenic mouse model, and restoring the PINK1 activity in the transgenic mice improved cognitive function

Table 1. Compounds targeting mitochondrial dysfunction in AD

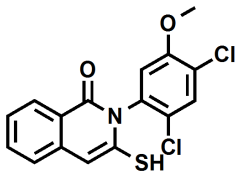
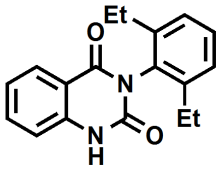
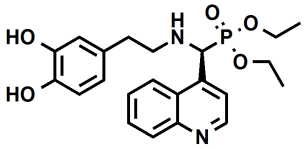
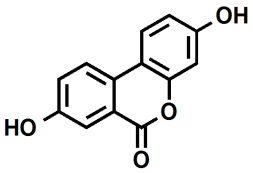
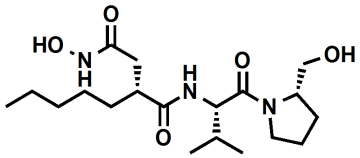
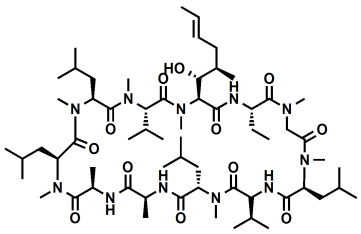
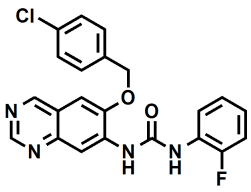
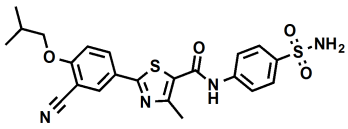
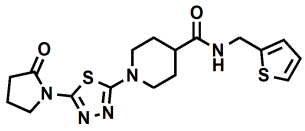
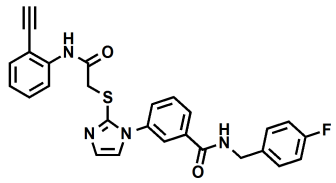
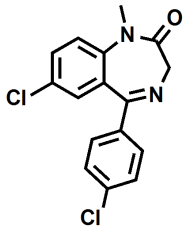
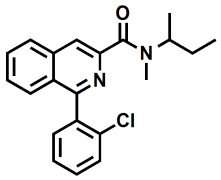
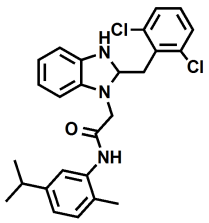
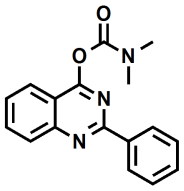
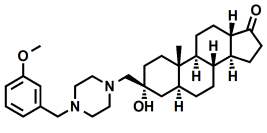
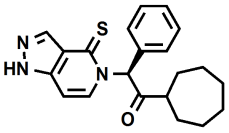
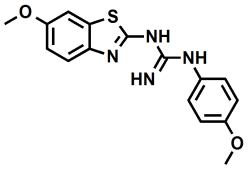
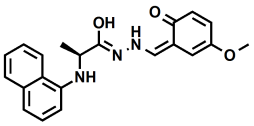
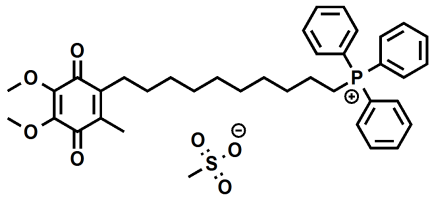
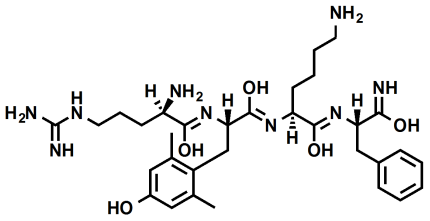
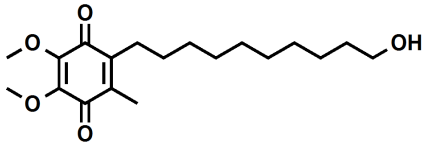
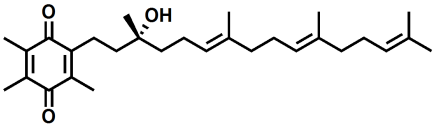
Structure	Mechanism (Molecular target)
 Mdivi-1  PAQ-22 (32)  DDQ (34)	Mitochondrial fission inhibitor (Drp1)
 Urolithin A (39)  Actinonin (39)	Mitophagy activator (PINK1)
 CsA  Compound 31 (50)	mPTP blocker (CypD)
 Compound 9 (51, 52)  Compound 7 (53)  Compound 29 (53)	
 Ro5-4864  PK11195  Compound 25 (62)  MGV-1 (63)	Neurosteroidogenesis (TSPO)
 Compound 1 (69)  AG18051 (70)  Compound 12 (72)  VC15 (73)	Neurosteroidogenesis (17β-HSD10)

Table 1. Continued

Structure	Mechanism (Molecular target)
 Mito Q (80)	Anti-oxidant
 Elamipretide	
 Idebenone	
 Vincerinone	

and lowered cerebral Aβ production in addition to restoring overall mitochondrial function (38). Fang *et al*. also found that mitochondrial dysfunction and defective mitophagy in the brains of AD patients; but more importantly, when they were treated with chemical inducers of mitophagy, urolithin A and actinonin, cognitive functions of transgenic AD mice and AD nematodes were improved by increasing PINK1 expression, whereas PINK1-deletion nematodes did not show such improvement (39). Urolithin A treatment reduced Aβ and phosphorylated tau proteins in the transgenic AD mice and AD nematodes. A recently completed phase I trial of urolithin A demonstrated a favorable safety profile and significant increases in mitochondrial biomarker genes (40), suggesting that mitophagy-related pathways can provide a promising drug target for neurodegenerative diseases including AD and PD. Currently several small-molecule PINK1 activators have been developed for the treatment of PD, but are still in the preclinical stage because of their poor bioavailability and issues with safety and brain penetration (41). These PINK1 activators are divided into two categories: direct activators that bind to the kinase domain of PINK1 (42, 43) and indirect activators that disrupt the mitochondrial membrane potential to initiate PINK1 activation (44). Urolithin A and actinonin were identified via chemical library screening, and they are likely to activate PINK1 via an indirect pathway, although their mechanisms have not been reported.

MITOCHONDRIAL PERMEABILITY TRANSITION PORE (mPTP)

The mitochondrial permeability transition pore (mPTP) is a multimeric protein complex located in the inner mitochondrial membrane, and the opening of the mPTP induces the loss of mitochondrial membrane potential and structural damage, leading to mitochondrial dysfunction (45). The mitochondrial cyclophilin D (CypD) is known to be the key component of the mPTP complex, playing a crucial role in the pathogenesis of AD (46-48). Specifically, elevated levels of CypD and Aβ-CypD complex were found in the cortical mitochondria of the transgenic AD mice, promoting the opening of the mPTP and exacerbating neuronal stress and mitochondrial dysfunction (48). Given that CypD is the only validated regulator of the mPTP (49), it has been hypothesized that the suppression of the CypD-mediated mPTP activation can be a novel therapeutic strategy for AD. To test the hypothesis, cyclosporin A (CsA), a well-known inhibitor of CypD, has been extensively studied to examine its potential therapeutic effect in AD. Although CsA inhibits the mPTP opening, CsA is not suitable for clinical application, since it is also an immunosuppressant and cannot penetrate the blood-brain barrier (BBB) effectively. Therefore, research efforts have focused on developing highly specific inhibitors with favorable pharmacokinetics. Elkamhawy *et al*. developed a library of quinazoline-based compounds that were modified from known cyclophilin A inhibitors, and these compounds demonstrated inhibitory activity against mPTP opening in cell-based assays (50). Valasani *et al*. reported CypD selective inhibitors, based on molecular docking studies and virtual screening, which also demonstrated the inhibitory effect against Aβ-induced mitochondrial dysfunction and cytotoxicity (51, 52). Park *et al*. reported an energy-based pharmacophore model by using the crystal structure of CypD-cyclosporine A (CsA) complex and performed virtual screening to identify novel non-peptidic small-molecule inhibitors of CypD (53). Although K_D values determined by surface plasmon resonance analysis indicated that these compounds were not as potent as CsA, it provides new

insights into the rational design of small-molecule CypD inhibitors for the treatment of AD.

NEUROSTEROIDOGENESIS

Neuroactive steroids are steroid-based molecules that can rapidly alter the neuronal excitability by interacting with neuronal receptors, such as the γ-amino-butyric type A (GABAA) receptor (54). Neuroactive steroids can be synthesized *de novo* inside neurons or from cholesterol transported into mitochondria. In recent years, neuroprotective and neurotrophic effect of neuroactive steroids have been reported, and growing evidence suggests that neuroactive steroids may offer therapeutic opportunities for neurodegenerative diseases including PD and AD (55). In particular, the mitochondrial translocator protein (TSPO) and 17β-hydroxysteroid dehydrogenase type 10 (17β-HSD10) have been studied because of their involvement in mitochondrial dysfunction as well as neurosteroidogenesis. In the following section, we will overview the AD pathogenesis associated with these two target proteins and known chemical ligands for potential therapeutic agents in AD.

TSPO (The translocator protein)

TSPO is a transmembrane protein located in the outer mitochondrial membrane (OMM). Although the exact role of TSPO still remains to be explained, many studies have suggested that TSPO is associated with the regulation of mitochondrial function, mainly through the cholesterol transport and neuroactive steroid hormone production (56). In AD, TSPO is believed to be linked to two distinct pathological pathways: first, the impaired cholesterol transport because of abnormal expression levels in the damaged neurons (57); second, the activation of the mitochondrial permeability transition pore (mPTP) (58), although the role of TSPO in the mPTP activation is now in question (59, 60). Given the regulatory role of TSPO in mitochondrial function and neurotrophic effects, many TSPO ligands have been developed over the past decade. Benzodiazepine compounds, Ro5-4864 and PK 11195, are the most widely used TSPO ligands. Ro5-4864 attenuated the development of AD pathology in the transgenic AD mice, and the combination therapy using Ro5-4864 and PK 11195 reduced Aβ levels in gonadectomized non-transgenic mice, supporting that TSPO is a potential treatment target for AD (61). More recently, Kim *et al*. reported a library of TSPO-targeted mitochondrial functional modulators for the treatment of AD (62). These compounds were able to restore mitochondrial function from Aβ-induced toxicity and improved cognitive function in transgenic AD mice. Monga *et al*. also identified two novel TSPO ligands, 2-Cl-MGV-1 and MGV-1, that can prevent LPS-induced activation of microglia. These ligands showed protective effects against ROS generation and exhibited potent anti-inflammatory activity relevant to the neuro-inflammatory diseases (63).

17β-hydroxysteroid dehydrogenase type 10 (17β-HSD10)

17β-HSD10, which was referred to as Aβ-binding alcohol dehydrogenase (ABAD), is a mitochondrial enzyme associated with the metabolism of steroid hormones. It plays crucial roles in neurosteroidogenesis and isoleucine degradation, and its genetic mutation has been implicated in delayed brain development and brain dysfunction (64). It is an essential enzyme for neuronal survival in a healthy brain, but many studies have also supported that 17β-HSD10 may be a therapeutic target as well as a potential biomarker for AD (65). In particular, increased levels of 17β-HSD10 were found in the brains of AD patients and transgenic AD mice (66); the interaction between Aβ and 17β-HSD10 appeared to promote ROS generation and to induce mitochondrial dysfunction (67). Although the exact mechanism of the specific interactions between Aβ and 17β-HSD10 has not been reported yet, research efforts have been made to develop small-molecule inhibitors targeting 17β-HSD10 for the treatment of AD (68). Steroid-based inhibitors demonstrated a highly selective but relatively weak inhibitory effect against the oxidation of allopregnanolone and estradiol (69). Non-steroidal compounds with fused pyrazole (70) and benzothiazole (71, 72) showed more potent activity with nanomolar to low micromolar IC_{50} values. Viswanath *et al*. reported small-molecule inhibitors based on the receptor-based pharmacophore modeling using the X-ray crystal structure of human 17β-HSD10 (73).

OXIDATIVE STRESS

Mitochondrial oxidative stress is an extensively studied pathological process, since the primary role of mitochondria is ATP production via aerobic cellular respiration. Mitochondria are the largest contributor of cellular reactive oxygen species (ROS), mostly generated by the respiratory chain complexes I and III as byproducts of oxidative phosphorylation (74). In healthy cells, natural antioxidant enzymes, such as superoxide dismutases, glutathione peroxidase, and catalase, swiftly act as scavengers to remove ROS; however, in the brains of AD patients, the catalytic activity of these enzymes is compromised, leading to the accumulation of ROS. An increased level of ROS is particularly detrimental in early-stage AD, during which oxidatively damaged proteins and DNA are produced, brain bioenergetics are impaired, and the structural and functional integrity of neuronal cells is severely altered (75, 76). Moreover, recent studies suggest that redox-active metals such as copper and zinc can promote Aβ aggregation and ROS generation depending on their oxidation states, further contributing to the progress of AD (77). Administration of exogeneous anti-oxidants is considered to be a promising strategy to block the ROS-induced damage and prevent further disease progression. Natural small-molecule anti-oxidants, including coenzyme Q (78) and vitamins C and E (79), were the first tested compounds among many other potential therapeutic anti-oxidants, although these naturally derived

molecules were not effective in clinical trials because they could not penetrate the BBB or localize into mitochondria. To improve mitochondrial localization, mitochondria-targeted antioxidants, such as mito Q (80) and mitoVit E (81), have been developed. These molecules contain coenzyme Q and vitamin E, but also have an additional triphenylphosphonium group, a lipophilic cation that can localize to the negatively charged mitochondrial membrane. Similarly, various peptidic anti-oxidants, including elamipretide, XJB peptides, and mito-glutathione, as well as coenzyme Q analogs idebenone and vincerinone, have been developed to improve cellular penetration and mitochondrial localization (82, 83). These compounds demonstrated excellent mitochondrial localization and anti-oxidant activity *in vitro*, and some were advanced to clinical trials for various mitochondrial diseases (84). Although these agents were mostly ineffective in clinical trials for AD, their proven anti-oxidant effects and favorable safety profile can be advantageous features for the development of preventive or combination therapy in the future.

CONCLUSION

In this mini review, we outlined the mitochondrial pathways that are directly associated with AD pathology and surveyed their small-molecule modulators for potential therapeutic applications. Compounds linked to mitochondrial quality control, such as division inhibitors and mitophagy activators, are relative newcomers in the field, demonstrating improved mitochondrial function and cognitive enhancement in animal models of AD. Although their clinical efficacy and safety must be examined, their mode of action is particularly intriguing, since these compounds can boost critical mitochondrial function in damaged cells. Another potential therapeutic strategy is the suppression of the mPTP to restore the structural and functional integrity of mitochondria in AD neurons. CypD is the most well-characterized component of the mPTP, and chemical modulation of CypD blocked the formation of the mPTP and restored mitochondrial function in animal models of AD. CypD has a highly conserved structure with other cyclophilins that are abundant and ubiquitous, thus specific modulation of the mitochondrial CypD is probably the key to the successful clinical development.

Compounds promoting neurosteroidogenesis and ROS-scavenging anti-oxidants have been extensively studied in many clinical studies as well as animal models because of their general protective effects against inflammation and oxidative stress. Interestingly, the protein structures and cellular locations of the potential targets involved in neurosteroidogenesis, TSPO and 17β-HSD10, have been recently elucidated, and new generations of chemical modulators have been introduced, which may enable to generate highly potent and selective therapeutic agents for AD in the near future. On the other hand, ROS scavengers have proven their anti-oxidant activity and safety, already being sold in the market or in the later stage of clinical trials. Recent developments in the ROS-scavenger studies are mostly focused on the targeted delivery of anti-oxidants to improve bioavailability and efficacy for various mitochondrial diseases. Mounting evidence suggests that mitochondrial function is associated with diverse diseases, including neurodegenerative diseases, metabolic disorders, and cancers; hence mitochondria-specific delivery of therapeutic agents can be an alternative to using existing drugs.

Identifying new therapeutic candidates for AD is still an enormously challenging task, because of the lack of reliable biomarkers, and the difficulties in clinical translation of animal models to human pathology, particularly given the long-term progression of the disease. In addition, tissue-specificity and brain penetration of the potential therapeutic agents pose another obstacle to overcome for effective AD therapy. Considering the multifactorial nature of AD, tackling a single target alone may not result in beneficial therapeutic outcomes, as we have seen in many previous clinical trials of AD. Compounds that can restore mitochondrial function not only have the potential to slow down the progress of the disease, but also can provide an additional therapeutic option in combination with currently available therapy.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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