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The emerging role of exercise in Alzheimer's disease: Focus on mitochondrial function

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ABSTRACT

Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by memory impairment and cognitive dysfunction, which eventually leads to the disability and mortality of older adults. Although the precise mechanisms by which age promotes the development of AD remains poorly understood, mitochondrial dysfunction plays a central role in the development of AD. Currently, there is no effective treatment for this debilitating disease. It is well accepted that exercise exerts neuroprotective effects by ameliorating mitochondrial dysfunction in the neurons of AD, which involves multiple mechanisms, including mitochondrial dynamics, biogenesis, mitophagy, transport, and signal transduction. In addition, exercise promotes mitochondria communication with other organelles in AD neurons, which should receive more attentions in the future.

1. Introduction

Alzheimer's disease (AD) is the leading cause of cognitive impairment in older individuals (aged 65 and above) and one of the key factors of disability and mortality in later life throughout the world(Jia et al., 2020; Jia et al., 2021b). AD is a progressively and incurably neurodegenerative disorder with cognitive dysfunction, memory decline, and behavioral disturbance(Dalal et al., 2024). Importantly, aging is the major risk factor for the development of AD, which includes two forms of early-onset familial and late-onset sporadic AD(Amakiri et al., 2019; Pradeepkiran and Reddy, 2020). In addition to the accumulation of β-amyloid (Aβ) and hyperphosphorylated microtubule-associated protein tau (p-Tau) with aging, multiple cellular changes are involved in the disease process, including mitochondrial abnormalities, microRNA deregulation, synaptic damage, iron overload, and glial/astrocyte activation(Dalal et al., 2024; Kim et al., 2024; Rajendran and Krishnan, 2024). Synaptic impairment and mitochondrial dysfunction are early cellular changes in the disease process of AD(Liu et al., 2020b; Oliver and Reddy, 2019; Pszczolowska et al., 2024). Tau and Aβ negatively impact neuronal cells by impairing energy supply and antioxidant responses, leading to mitochondrial and synaptic dysfunction(Misrani et al., 2021; Rawat et al., 2022).

Mitochondrial dysfunction plays a central role in aging and the development of AD(Jia et al., 2023; Kumar et al., 2021; Willemen et al., 2018). Neuronal activity is highly energy-dependent, and neurons are particularly sensitive to impaired mitochondrial function(Pszczolowska et al., 2024; Yip et al., 2021). Mitochondria produce energy through the process of oxidative phosphorylation (OXPHOS) and are also responsible for a range of important cellular processes, including Ca^{2+} homeostasis, iron-sulfur clustering, and apoptosis-related intracellular signaling in neurons(Zhang et al., 2022a). The proteins required for OXPHOS were both encoded by nuclear DNA and mitochondrial DNA (mtDNA) (Becker et al., 2022; Carter et al., 2022). Continuous mitochondrial-nuclear communication coordinates the production of OXPHOS complexes to maintain optimal mitochondrial function and energy homeostasis(Zhu et al., 2022). Erik et al. found that the abundance of mitochondrial mRNA was 160 times higher than that of nuclear-encoded OXPHOS mRNA, and the degradation rate was seven times faster than nuclear-encoded RNA by sequencing analysis of nucleus and mitochondrial genes (McShane et al., 2024). Moreover, compared with nuclear DNA, mtDNA is highly prone to genetic mutations induced by reactive oxygen species (ROS) due to a lack of chromatin structure(Ahn et al., 2016). Recent advances in single-cell multi-omics technology not only affords effective analysis of the heterogeneity of mtDNA deletion(Lareau et al., 2023), but also can reveal the specific molecular programs involved in signaling pathways of various types of cells in the brain at different pathological stages of AD (Murdock and Tsai, 2023). Single-cell multi-omics technology has also

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made it possible to clarify further and manipulate neuron-specific mitochondria-related molecular perturbations and signaling nodes that might bring new opportunities for the intervention and treatment of AD.

Mitochondrial dysfunction significantly decreases adenosine triphosphate (ATP) generation, induces Ca^{2+} imbalance, and leads to the production and accumulation of reactive oxygen species (ROS)(Misrani et al., 2021). Excessive mitochondria-derived ROS has been proven to accelerate aging and neurodegenerative disorders progression(Sun et al., 2020b). ROS inhibits phosphatase 2 A (PP2A) and activates glycogen synthase kinase (GSK) 3β to promote phosphorylated Tau and the formation of neurofibrillary tangles, which is a characteristic feature of AD pathogenesis(Misrani et al., 2021). Oxidative stress by AD further increases ROS production and accumulation, which causes oxidative damages of mitochondrial proteins, mtDNA, and phospholipids such as cardiolipin(Hsiao et al., 2013; Hu et al., 2021; Napso et al., 2022). The brain is particularly susceptible to oxidative damage due to its high oxygen consumption, high content of polyunsaturated fatty acids and redox transition metal ions accompanied by low antioxidant levels(Mu et al., 2021). Additionally, oxidative stress has been shown to increase Aβ production and accumulation by affecting the expression and processing of amyloid precursor protein (APP), while oxidative damage inhibits the clearance of Aβ in AD(Ganguly et al., 2017). Furthermore, a previous study showed that Aβ activated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to enhance ROS production and accumulation, which in turn further exacerbates mitochondrial dysfunction in both neurons and astrocytes(Abramov et al., 2004). More attention should be given to newly discovered role mitochondrial dysfunction in promoting inflammation, as recently demonstrated by study on lysocardiolipin acyltransferase 1 (ALCAT1), which promotes mitochondrial dysfunction by catalyzing the pathological remodeling of cardiolipin (CL). Upregulation of ALCAT1 by ROS caused excessive oxidative stress, mtDNA mutations, and mitochondrial dysfunction in mice with Parkinson's disease induced by 1-methyl-4-phenyl-1,2,4, 6-tetrahydropyridine, while ablation of ALCAT1 ameliorated neurotoxicity and neuronal degeneration by mitigating mitochondrial dysfunction and inhibiting α-synuclein oligomerization(Song et al., 2019). Therefore, it is speculated that ALCAT1 also plays a key role in the etiology of AD mice and might be a new target for the treatment of AD.

The role of exercise in the prevention and delay of AD has been widely studied(Liu et al., 2020b; Zhang et al., 2022b). Systematic review and meta-analysis studies demonstrated that regular exercise performed by older people not only reduced the risk of AD but also acted protectively by slowing down cognitive decline and AD progression (Lopez-Ortiz et al., 2023; Lopez-Ortiz et al., 2021). Regular exercise is conducive to mitigating age-related diseases and promoting brain health in individuals with advancing age in part by improving mitochondrial structure and function, including mitochondrial capacity, quality control (mitophagy), and mtDNA copy number(Clark-Matott et al., 2015; Jia et al., 2023; Liang et al., 2021). In support of a potential role of ALCAT1 in AD, exercise has been shown to downregulates ALCAT1 expression(Ren et al., 2022; Wu et al., 2020a). However, the molecular mechanisms by which exercise improves mitochondrial function in AD, including the role of ALCAT1, remain poorly understood. This review comprehensively summarizes the benefits of exercise and identifies the potential molecular mechanisms linking mitochondrial function to AD.

2. The past: what dilemma do mitochondria face in Alzheimer's disease?

2.1. Mitochondrial dynamics and biogenesis

Mitochondria are double membrane-bound organelles consisting of an inner membrane (IMM) and an outer membrane (OMM) that separate the matrix and the intermembrane space(Collier et al., 2023). Mitochondria are in a dynamic state within cells. After synthesizing ATP in the neuronal cell body, mitochondria travel along axons and dendrites to provide the necessary energy for synapses to support neural activity, including synapse formation and neurotransmitter release(Bastian et al., 2019). During axonal transport, mitochondria constantly undergo fission, fusion, and morphological changes that facilitate their movement between the cell bodies, axons, dendrites, and synapses(Manczak et al., 2016). Mitochondrial dynamics, the delicate balance between fission and fusion, is essential for the maintenance of mitochondrial function(Tsushima et al., 2018; Wei and Ruvkun, 2020). Mitochondrial fission is controlled by the evolutionarily conserved and dynamin-related large GTPases, namely dynamin-related protein 1 (DRP1) and fission protein 1 (IS1)(Moqbel et al., 2022). FIS1 is localized to the mitochondrial outer membrane, where it recruits DRP1 for translocation from the cytosol to the mitochondrial outer membrane to form a complex that initiates fission(Gao et al., 2022; Yu et al., 2021). Similarly, mitochondrial fusion is controlled by GTPase proteins, including mitofusin 1 and 2 (MFN1 and MFN2) on the outer membrane and optic atrophy 1 (OPA1) on the inner membrane(Donkervoort et al., 2019). Studies have demonstrated that excessive fission and impaired fusion disrupted mitochondrial dynamics and induced mitochondrial fragmentation in AD neurons(Ahmed et al., 2019; Han et al., 2021a). APP or Aβ induces the generation of ROS which promotes the interactions and complex formation between DRP1 and FIS1, leading to excessive mitochondria fragmentation. Excessive mitochondrial fragmentation impairs mitochondrial ATP transport to the synapse, ultimately resulting in synaptic dysfunction in AD neurons(Ahmed et al., 2019; Baek et al., 2017; Kang et al., 2020). Accordingly, p-Tau has been shown to impair mitochondrial (fission/fusion) dynamics, which is required for mitochondrial quality control process, leading to defective axonal transport(Klein et al., 2021). It has been reported that ALCAT1 also played an important role in mitochondrial dynamics, catalyzing the pathological remodeling of CL to promote mitochondrial dysfunction in age-related and neurodegenerative diseases(Li et al., 2012). Overexpression of ALCAT1 increases oxidative stress and inhibits mitochondrial fusion, inducing mitochondrial fragmentation, whereas ablation of ALCAT1 reverses mitochondrial fusion defects and fragmentation by increasing MFN2 expression(Li et al., 2012). Likewise, dafaglitapin (Dafa), an inhibitor of ALCAT1, significantly restored mitochondrial dynamics through inhibition of DRP1 and calmodulin-dependent protein kinase II (CaMKII) signaling(Jia et al., 2021a). However, further studies are required to demonstrate whether inhibition of ALCAT1 attenuates the pathogenesis of AD by improving mitochondrial dynamics and function in AD.

Mitochondrial biogenesis is a complex process that involves the synthesis, import,incorporation of proteins and lipids, and mtDNA replication(Andres et al., 2017; Yazdani et al., 2019). It is in this process that an organism generates new functional mitochondria to increase mitochondrial abundance and ATP production in response to the cell energy demands. Peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) plays an essential role in regulating mitochondrial biogenesis and co-activating nuclear respiratory factors (NRF) 1 and 2, which is conducive to the transcription of mitochondrial transcription regulator A (TFAM)(Ibrahim et al., 2023; Jia et al., 2023). Mitochondrial regulatory factors enter mitochondria to initiate mtDNA replication and transcription and further promote mitochondrial biogenesis when cellular energy demands exceed mitochondrial ATP production(Pirooznia et al., 2020; Townsend et al., 2020). Strikingly, it has been found that ablation of ALCAT1 reversed mtDNA depletion and promoted mtDNA biogenesis by increasing mtDNA copy number and fidelity(Li et al., 2012). In support of a key role of mtDNA depletion in the pathogenesis of AD, recent studies have shown that the mRNA and protein levels of mitochondrial biogenesis-related genes PGC-1α, NRFs and TFAM were reduced in postmortem brain tissue of AD patients, AD cell models, APP transgenic mice and Tau transgenic mice(Kandimalla et al., 2016; Manczak et al., 2016; Manczak et al., 2018). Likewise, PGC-1α was decreased in the cortex of AD patients, while exogenous

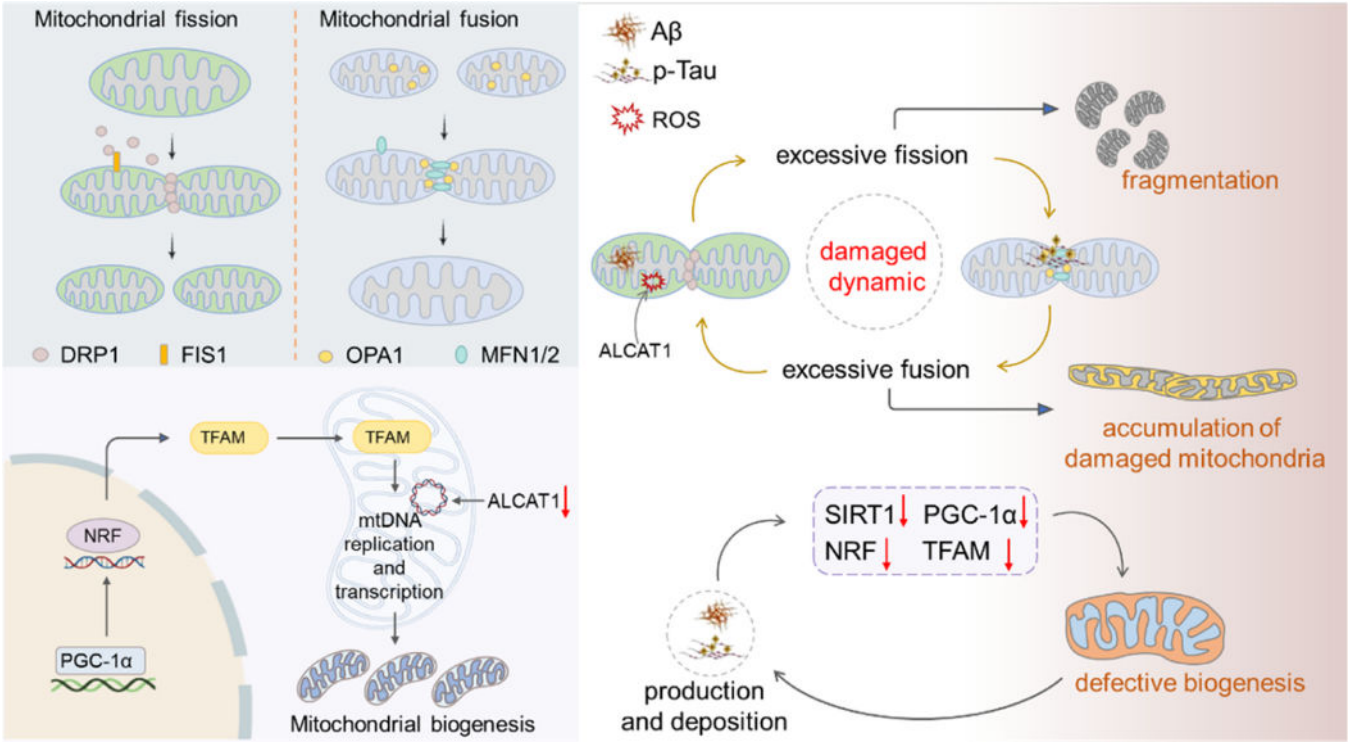

Fig. 1. Mitochondrial dynamics and biogenesis are impaired by Aβ and p-Tau in neurons of Alzheimer's disease. Mitochondrial dynamics are maintained through the balance of fission and fusion that is damaged by p-Tau, Aβ, and Aβ-induced ROS, which is conducive to excessive mitochondria fragmentation and accumulation of damaged mitochondria. Aβ and p-Tau inhibit mitochondria biogenesis-related signaling to hinder mtDNA replication and transcription, which is exacerbated by ALCAT1 in response to ROS, thereby leading to defective biogenesis. ALCAT1: lysocardiolipin acyltransferase 1; Aβ: β-amyloid; ROS: reactive oxygen species; p-Tau: hyperphosphorylated microtubule-associated protein tau; DRP1: dynamin-related protein 1; FIS1: fission protein 1; MFN1/2: mitofusin 1 and 2; mtDNA: mitochondrial DNA; NRF: nuclear respiratory factors; OPA1: optic atrophy 1; PGC-1α: peroxisome proliferator-activated receptor γ coactivator (PPARγ)-1α; SIRT1: sirtuin-1; TFAM: mitochondrial transcription factor A.

expression of PGC-1α inhibited Aβ plaque formation(Katsouri et al., 2011). Additional evidence suggests that sirtuin-1(SIRT1) promotes mitochondrial biogenesis via deacetylation of PGC-1α(Wang et al., 2018). A study has found that SIRT1 deacetylase activity was reduced, and Aβ production was increased in APP/PS1 double-transgenic mice with specific SIRT1 knockout(Liang et al., 2021). Tau acetylation inhibits its polyubiquitination and degradation, further promoting Tau accumulation in neurons(Grinberg et al., 2013). Moreover, evidence suggests that activation of SIRT1 enhances Tau ubiquitination and inhibits Tau accumulation by SIRT1-mediated deacetylation(Min et al., 2010). In summary, the impairment of mitochondrial dynamics and biogenesis caused by Aβ and p-Tau are important mechanisms underlying neuronal dysfunction and loss in AD. (Fig. 1)

2.2. Mitophagy

The mitochondria content in neurons is regulated by the balance of mitochondrial biogenesis and degradation(Vo et al., 2019). Mitophagy is a process wherein damaged or dysfunctional mitochondria are selectively degraded and cleared by autophagic machinery, a key process for mitochondrial quality control and homeostasis. Mitophagy is also essential for maintaining neuronal homeostasis and function(Sun et al., 2021). Mitophagy is initiated by the formation of a spherical and double-membrane structure known as the autophagosome. It fuses with lysosomes to form autolysosomes, in which damaged mitochondrial components are degraded and recycled by lysosomal hydrolases(Hwang et al., 2022a). This process is primarily regulated by the phosphatase and tensin homolog (PTEN)-induced putative kinase protein 1 (PINK1)/Parkin-dependent and ubiquitin-independent mechanisms(Pan et al., 2022; Yang et al., 2022a). Upon mitochondrial damage, PINK1 is stabilized on the OMM by the depolarization of mitochondrial membrane potential (ΔΨ m), where it activates the ubiquitin ligase parkin and ubiquitinates OMM proteins to promote the autophagic clearance of damaged mitochondria(Patoli et al., 2020; Yang et al., 2020). A decrease in PINK1 expression level is associated with the pathology of AD, as demonstrated by a recent study that PINK1 and Parkin were significantly reduced in hippocampal tissues of (APP/PS1/Tau) 3xTg AD mice, which is associated with impaired mitophagy capacity (Xie et al., 2022). Likewise, PINK1 expression is reduced in AD brain and Aβ-rich-model APP mice, while overexpression of PINK1 attenuates the accumulation of Aβ(Du et al., 2017). Addtionally, Tau also plays a role in defective mitophagy in AD. Tau directly impaired mitophagy by sequestering Parkin in the cytosol and disrupting the recruitment (Cummins et al., 2019). Consequently, overexpression of Tau and APP impairs ΔΨ m, reduces PINK1 accumulation and Parkin recruitment, and ultimately causes defective ubiquitination and mitophagy impairment in the brain(Grimm et al., 2016). Thereby, stimulation of mitophagy has been shown to improve memory in mice by reducing the phosphorylation of Tau protein through inhibition of p-Tau sites (Fang et al., 2019). Strikingly, inhibition of ALCAT1 effectively improved mitophagy by stimulating Parkin expression and promoting Parkin association with mitochondria in neurons[28].

Microglia are the innate immune cells in the brain that play a complex role in AD by clearing Aβ plagues. Microglia are mostly clustered around Aβ plaques to facilitate extracellular Aβ clearance in APP/PS1 mice(Krauthausen et al., 2015). Activation of microglia has been shown to be a prominent feature of AD. Mitochondrial dysfunction and defective mitophagy significantly impaired the Aβ-clearing capacity of microglia(Fang et al., 2019), whereas stimulation of mitophagy dramatically enhanced microglial phagocytosis and the clearance of Aβ plaques in APP/PS1 mice (Xie et al., 2022). Emerging evidence suggest M2 microglia-derived exosomes are potentially important for AD

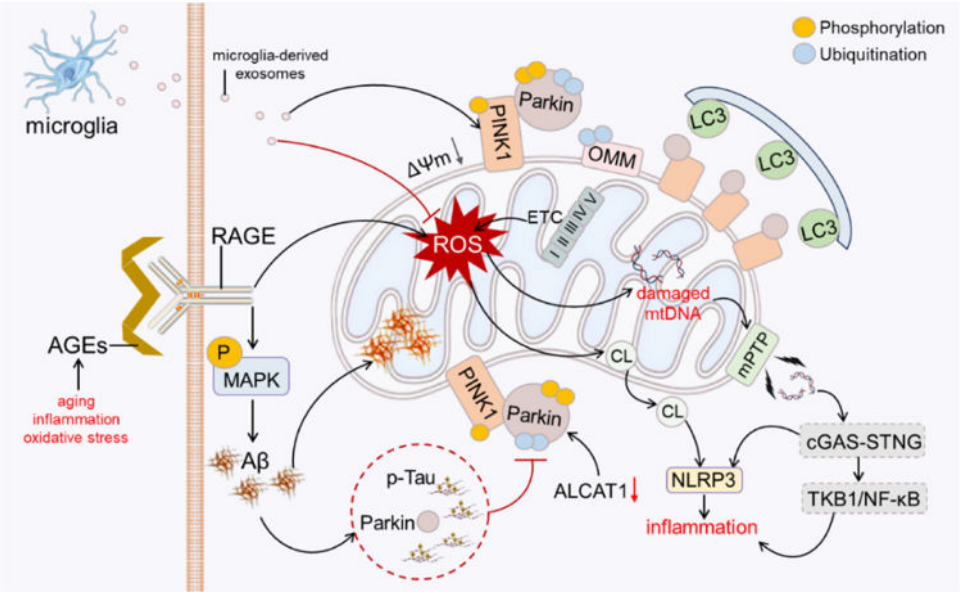

Fig. 2. Defective mitophagy is occurred in neurons of Alzheimer's disease. Tau directly impairs mitophagy by sequestering Parkin in the cytosol and damaging the recruitment. AGEs bind to their receptor RAGEs to induce oxidative stress and active MAPK, and further damage mitophagy. AGE: advanced glycation end-product; ALCAT1: lysocardiolipin acyltransferase 1; Aβ: β-amyloid; cGAS: cyclic GMP-AMP synthase; CL: cardiolipin; ETC: electron transport chain; RAGE: AGE receptor; ROS: reactive oxygen species; LC3: light chain 3; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; NLRP3: NLR pyrin domain containing 3; OMM: mitochondrial outer membrane; PINK1: putative kinase protein 1; p-Tau: hyperphosphorylated microtubule-associated protein tau; STING: cyclic GMP-AMP receptor stimulator of interferon genes; TKB1: tank binding kinase 1; ΔΨ m: mitochondrial membrane potential.

treatment in part by restoring ΔΨ m, reducing ROS production, and improving PINK1/Parkin-mediated mitophagy, leading to reduced Aβ plaque deposition and Aβ oligomer expression, and ultimately exerting neuroprotection in cultured hippocampal neurons and APP/PS1 mice(Li et al., 2022b). It is also worth noting that microglial Piezo1, a mechanosensitive protein known as mechanosensory ion channel, senses the stiffness stimuli of AD fibrils and subsequently induces Ca^{2+} influx, microglial clustering and phagocytosis, thereby resulting in the clearance of Aβ plaques(Hu et al., 2023). Moreover, Piezo1 has been reported to improve mitochondrial functionby promoting cyclic adenosine monophosphate (cAMP) signaling(Jiang et al., 2023; Li et al., 2022c). Activation of Piezo1 increases mitochondrial OXPHOS and enhances mitochondrial respiration and glycolysis, resulting in the production of ATP(Jiang et al., 2023; Li et al., 2022c). Terefore, Piezo1 might represent a potential therapeutic target for AD.

However, studies have reported that the increase in complex I caused the reverse transfer of the electron transport chain (ETC), thereby making mitochondria switch from producing ATP to producing superoxide. The switch is conducive to the production of mitochondrial ROS, which mediates neuroinflammation by activating microglia(Mills et al., 2016; Peruzzotti-Jametti et al., 2024). ROS produced by mitochondrial ETC and NADPH oxidase (NOX) would cause mtDNA damage because mtDNA lacks protective histones and complex DNA repair mechanisms (Bhattacharya et al., 2022). Due to defective mitophagy, damaged mtDNA is released into the cytoplasm through mitochondrial permeability transition pore (mPTP), which would trigger inflammation via tank binding kinase 1 (TBK1)/nuclear factor-κB (NF-κB) pathway and NLR pyrin domain containing 3 (NLRP3) signaling, both activated by the cyclic GMP-AMP synthase (cGAS)-cyclic GMP-AMP receptor stimulator of interferon genes (STING) axis(Lin et al., 2022; Zhang et al., 2022c). Moreover, mitochondria-derived damage-related molecules, including ROS, mtDNA and cytochrome c, were recognized by microglia and judged as harmful molecules, activating immune mechanisms and exacerbating neuroinflammation in neurodegenerative diseases(Lin et al., 2022). Furthermore, CL, a signature phospholipid of in mitochondria, is exposed to the mitochondrial surface in response oxidative damage of its double bonds by ROS, which serves as the platform for the assembly and activation of the NLRP3 inflammasomes(Lin et al., 2022). Inhibition of ALCAT1 has been shown to effectively alleviate pathological remodeling of CL and oxidative stress, attenuation of NRLP3 activation, and mitochondrial dysfunction(Hao et al., 2024; Li et al., 2010), which might thus exert neuroprotective effects. ROS also plays a critical role in stress-induced mitophagy(Wu et al., 2020b). Advanced glycation end-products (AGEs) have been reported to increase the synthesis of ROS and induce mitophagy(Lee et al., 2022a). AGEs are produced by the post-translational modification of proteins via non-enzymatic glycation, lipids, and nucleic acids(Qrareya et al., 2022), while the formation of AGEs is accelerated by inflammation, oxidative stress, and aging(Li et al., 2020). Interaction of AGEs with the receptor of AGEs (RAGE) increases oxidative stress and inflammation, induces defective mitophagy, and results in neuronal damage(Xing et al., 2013). Moreover, Aβ binding to RAGE promotes synaptic dysfunction via the activation of mitogen-activated protein kinase (MAPK) phosphorylation and leads to further Aβ deposition in mitochondria through increased Aβ influx(Ripoli et al., 2014). Increased Aβ causes the excessive phosphorylation and release of Tau in neurons, which is necessary for Tau deposition and Aβ-induced mitochondrial dysfunction(Berger et al., 2022; Mattsson-Carlgren et al., 2020). In summary, defective mitophagy is presumably one of the important pathways for pathological changes in AD neurons (Fig. 2). Therefore, newly discovered regulators, such as ALCAT1 and Piezo1, might exert enormous potential for improving mitochondrial dysfunction in AD, especially those associated with mitophagy.

2.3. Mitochondrial transport and signal transduction

2.3.1. Mitochondrial transport in neurons

Mitochondria are not anchored nor moved randomly in neurons. The proper distribution of mitochondria in neurons is regulated by the mitochondrial transport system in response to the changes in the physiological environment in axons and synapses(Benoy et al., 2018; Misrani et al., 2021). Mitochondrial transport is essential for supplying ATP to axons, maintenance of synaptic function, Ca2+ homeostasis, mitochondrial quality control(Vevea and Chapman, 2023). Healthy

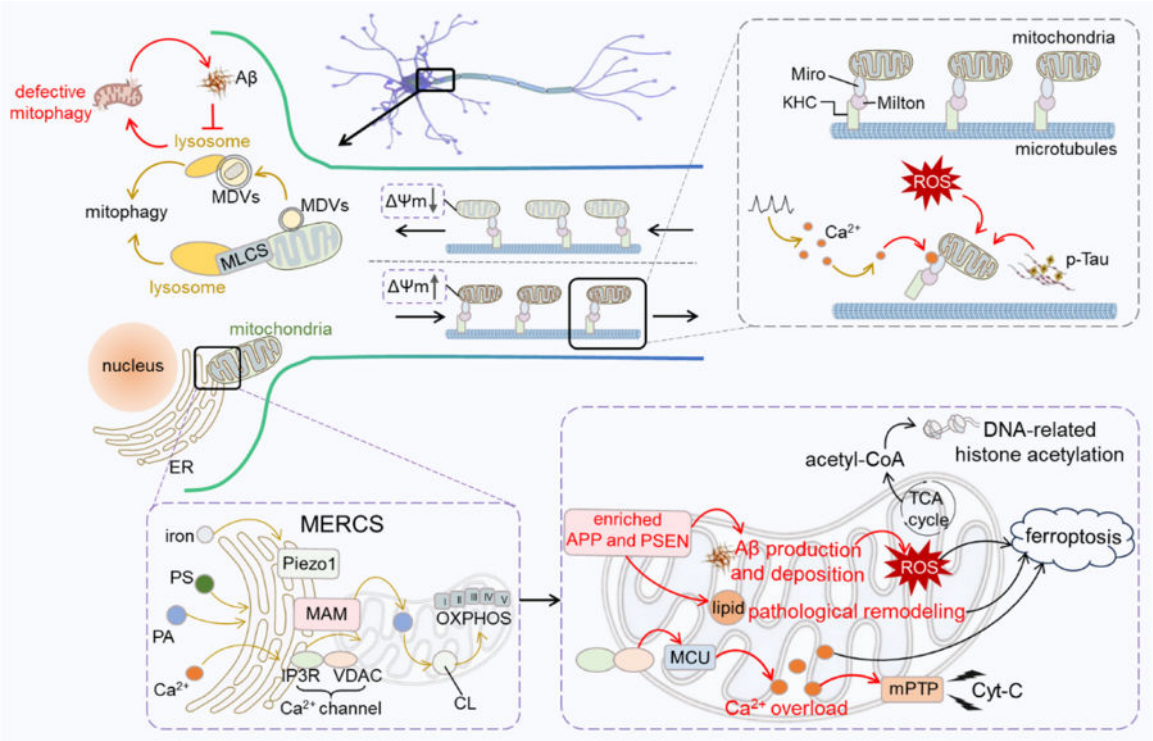

Fig. 3. Mitochondrial transport and signal transduction are damaged in neurons of Alzheimer's disease. Excessive mitochondria-ER contacts cause Ca^{2+} overload and Aβ production in mitochondria, which is contribute to mitochondrial dysfunction. Ca^{2+} overload, ROS and p-Tau damage mitochondria-microtubules transports. Aβ inhibits lysosome function and MDVs to induce defective mitophagy. These disorders can lead to neuronal structure and function impairment. Aβ: β-amyloid; CL: cardiolipin; ER: endoplasmic reticulum; IP3R: inositol 1, 4, 5-trisphosphate receptor; KHC: kinesin heavy chain; MAM: mitochondria-associated endoplasmic reticulum membrane; MCU: mitochondrial calcium uniporter; MDVs: mitochondria-derived vesicles; MERCS: mitochondria-ER contact site; MLCS: mitochondria-lysosome contact site; mPTP: mitochondrial permeability transition pore; OXPHOS: oxidative phosphorylation; PA: phosphatidic acid; PS: phosphatidylserine; p-Tau: hyperphosphorylated microtubule-associated protein tau; ROS: reactive oxygen species; TCA: tricarboxylic acid; VDAC: voltage-dependent anion-selective channel; ΔΨ m: mitochondrial membrane potential.

mitochondria are recruited to distal regions with high energy demand, whereas damaged mitochondria are returned to the neuronal body for repair or degradation(Jiang et al., 2015). In neurons, anterograde transport is mediated by kinesin on microtubules that are responsible for the long-distance transport of mitochondria, while retrograde transport is mediated by dynein(Van Steenbergen et al., 2022). The Milton/Miro complex serves as an adaptor that links kinesin to the mitochondria and is required for the axonal transport of mitochondria(Canty et al., 2023). Milton binds to the kinesin heavy chain (KHC), which in turn binds Miro to OMM to initiate the recruitment of mitochondria to microtubules (Fenton et al., 2021). It is worth noting that the conformation of the KHC/Milton/Miro complex is also affected by various cellular signals, including changes in synaptic Ca^{2+} concentration, the elevation of ROS, neuronal glucose metabolism, and ATP levels, thereby mediating the attachment and dissociation of mitochondria and microtubules, and ultimately determining the transport and positioning of mitochondria (Pekkurnaz and Wang, 2022; Zaninello et al., 2022). A study has shown that in AD, the p-Tau protein disrupted mitochondrial transport, which caused the accumulation of neurotoxins(Kang et al., 2022). Furthermore, Aβ is a critical factor in mediating AD. Deposition of Aβ in AD neurons has been implicated in mitochondrial dysfunction(Beck et al., 2016; Mastroeni et al., 2017). Aβ disrupts the electron-transport chain and results in ROS generation(Liang et al., 2019), which abolishes mitochondrial axonal transport by increasing the level of Ca^{2+}(Choi et al., 2017). The binding of Ca^{2+} to the two EF-hand domains of Miro changes the conformation of the KHC/Milton/Miro complex, promotes the dissociation of mitochondria from microtubules, and ultimately leads to mitochondrial arrest(Saotome et al., 2008; Woolums et al., 2020).

2.3.2. *Signal transduction of mitochondria*

Mitochondria are vital bioenergy organelles that not only synthesize ATP but also play an important role in transmitting cellular signals in neurons(Collier et al., 2023; Picard and Shirihai, 2022). Mitochondria form membrane contact sites (MCSs) with other organelles in neurons, including the endoplasmic reticulum (ER) and lysosomes, to facilitate the exchange of irons, metabolites, and lipids between organelles (Andersen et al., 2020; Sotomayor-Flores et al., 2020). As a critical structure in neurons, the ER plays an irreplaceable role in Ca^{2+} homeostasis, protein folding and assembly, and lipid synthesis(McNally et al., 2022; O'Hare et al., 2022). Mitochondria-ER contact sites (MERCSs) are particularly important and are widely involved in neurodegeneration(Van Lent et al., 2021). Mitochondria are precisely connected to the ER through mitochondria-associated endoplasmic reticulum membranes (MAMs)(Wang et al., 2020b). MAMs are enriched in enzymes involved in lipid metabolism, such as phosphatidylserine synthase (PSS) and phosphatidylserine decarboxylase (PSD), as well as phospholipids(Saneto and Perez, 2022). Phosphatidylserine (PS) synthesized by PSS is transferred from the ER to mitochondria via MERCSs, where it is converted to phosphatidylethanolamine (PE) by the decarboxylation of PSD(Tatsuta et al., 2014). Part of the mitochondria-produced PE is then transferred back to the ER and further methylated to phosphatidylcholine (PC) or depleted in other cell compartments(Renne et al., 2022). Phosphatidic acid (PA) produced by the ER is transported to mitochondria for the synthesis of specific lipid CL, which is required for mitochondrial membrane structure, OXPHOS, and mtDNA biogenesis(Grevengoed et al., 2015; Li et al., 2012). The complex transfer of phospholipids is dependent on MERCSs. Moreover, MERCSs also play a pivotal role in Ca^{2+} exchange between the ER and mitochondria(Hirabayahi et al., 2017), and interacts with the

Table 1
Exercise-exerted neuroprotective effects reduce the risk of Alzheimer's disease.

Model	Exercise	Exerkines	Biological effects	Refs
APP/PS1 mice	12-week treadmill exercise	PGC−1α/TFAM ↑ PINK1 ↑ Parkin ↑ LC3 ↑	Enhances mitochondrial biogenesis and mitophagy Increases synaptogenesis in hippocampal neurons Reduces Aβ production and deposition	(Zhao et al., 2020)
APP/PS1 mice	12-week treadmill exercise	PINK1 ↑ Parkin ↑ LC3 ↑ SIRT1 ↑ FOXO 1/3 ↓ ATP↑ Complex I, IV ↑	Enhances mitochondrial function Reduces the accumulation of Aβ plaques Improves learning and memory ability	(Zhao et al., 2023)
APP/PS1 mice	12-week treadmill exercise	VDAC ↓ Complex IV ↑	Mitigates Aβ deposition and the opening of mPTP Improves OXPHOS Attenuates errors of working memory and reference memory	(Mu et al., 2019)
APP/PS1 mice	8-week treadmill exercise	SIRT−1/PGC−1α ↑	Reduces Aβ deposition Alleviates neuronal damage and cognitive decline	(Shi et al., 2023)
APP/PS1 mice	5-month voluntary wheel-running exercise	AMPK ↑ LC3 ↑ TFEB ↑ Rab7 ↑ Rab9 ↑	Reduces Aβ accumulation and p-Tau Enhances lysosomal biogenesis and function Increases the colocalization of lysosomes with Aβ Activates vesicle trafficking Improves cognitive function	(Wang et al., 2022)
APP/PS1/ Tau mice	3-month voluntary wheel-running exercise	PGC1α ↑ p-CREB/CREB ↑ BDNF ↑	Enhances neuroprotection and plasticity Improves behavioral and cognitive responses	(Garcia-Mesa et al., 2014)
Aβ peptide oligomers-injected rats	4-week maternal swimming training during Pregnancy	α-KGDH ↑ Complex IV ↑ MFN1 ↑DRP1 ↓ Synaptophysin ↑	Promotes mitochondrial energy metabolism Increases number of functional mitochondria and mitochondrial membrane potential in the prefrontal cortex and hippocampus Alleviates impairments of recognition, learning and memory	(Klein et al., 2019)
NSE/APP mice	4-week treadmill exercise	SIRT−1/PGC−1α ↑	Decreased APP processing and Aβ production Ameliorates spatial learning and memory dysfunction	(Koo et al., 2017)
Aged mice With cognitive disorders	5-week resistance exercise	PGC−1α/BDNF/Akt/ GSK−3β ↑ MFN1/2 ↑	Increases mitochondrial biogenesis and mitophagy Reverses mitochondrial dynamics Promotes ER-mitochondria contact Ameliorates synaptic deficit, neuroinflammation, and cognitive impairment	(Liu et al., 2022)
Rats	12-week treadmill or voluntary wheel-running exercise	Complex I and V ↑ PGC1α ↑ TFAM ↑ MFN1/2 ↑DRP1 ↓ LC3II ↑PINK1 ↑	Increases the tolerance to Ca^{2+} Promotes mitochondrial biogenesis, mitophagy and dynamics Improves mitochondrial respiratory function Enhances cognitive function	(Marques-Aleixo et al., 2015)

Akt: protein kinase B; APP: amyloid precursor protein; AMPK: adenosine monophosphate-activated protein kinase; Aβ: β-amyloid; α-KGDH: α-ketoglutarate dehydrogenase; BDNF: brain-derived neurotrophic factor; DRP1: dynamin-related protein 1; FIS1: fission protein 1; GSK-3β: glycogen synthase kinase-3β; HIIT: high-intensity interval training; PGC-1α: peroxisome proliferator activated receptor γ coactivator (PPARγ)-1α; LC3: light chain 3; MFN1/2: mitofusin 1 and 2; NSE: neuron-specific enolase; OXPHOS: oxidative phosphorylation; PINK1: putative kinase protein 1; PS1 (PSEN1): presenilin-1; SIRT-1: sirtuin-1; Rab7/9: GTP-bound Ras-related protein; TFAM: mitochondrial transcription factor A; TFEB: transcription factor EB: VDAC: voltage-dependent anion-selective channel

voltage-dependent anion-selective channel (VDAC) in the OMM to form a Ca^{2+} channel(Wu et al., 2019). Ca^{2+} is then transported to the mitochondrial matrix through the mitochondrial calcium uniporter (MCU) located in the IMM(Liu et al., 2020a). However, excessive Ca^{2+} influx triggers the mitochondrial permeability transition pore (mPTP), causing the release of cytochrome *c* and apoptosis(Liu et al., 2022). Furthermore, MAMs regulate ferroptosis (an iron-dependent form of regulated cell death induced by excessive accumulation of lipid peroxides) through Ca^{2+} transport and lipid remodeling, while IP3R/VDAC complex provides a dissemination platform for ferroptosis signal transduction(Zhang et al., 2024). Piezo1 channel, which is localized on the ER membrane, is identified as a key iron transporter that mediates iron overload and Ca^{2+} influx, disturbing iron metabolism and exacerbating ROS production and lipid peroxidation, thereby leading to ferroptosis(Guo et al., 2021; Hirata et al., 2023; Xiang et al., 2024). Although it has not been reported whether Piezo1 is involved in the mitochondria-ER communication to regulate ferroptosis in AD, Piezo1 appears to be closely related to MAMs. In contrast, ALCAT1 has been shown to be localized at MAM and plays a critical role in the pathogenesis of Parkinson's disease(Song et al., 2019). In addition, MAMs may also be involved in amyloidogenesis. Aβ-related proteins such as amyloid protein precursor (APP), presenilin-1 (PSEN1), and PSEN2 have all been reported to be enriched in the MAMs(Zhao et al., 2022). Aβ enters the mitochondria through the translocase of OMM and further leads to progressive Aβ deposition in AD neurons(Eimer et al., 2018; Reddy and Beal, 2008; Zhao et al., 2022).

The mitochondria-lysosome contact sites (MLCSs) are a dynamically regulated process that is critical for degrading and clearing damaged mitochondria as well as transferring of lysosomal Ca^{2+} into mitochondria(Peng et al., 2020; Yan et al., 2020). GTP-bound Ras-related protein Rab7 promotes the formation of MLCSs, whereas the untethering is controlled by Rab7-GTP hydrolysis driven by FIS1 and Rab7 GTPase-activating protein (Rab7-GAP, TBC1D15)(Kim et al., 2021; Wong et al., 2022; Wong et al., 2019). Importantly, it has been reported that mitochondrial fission occurred at MLCSs, while MERCSs were also observed at mitochondrial fission sites(Cheng et al., 2021; Paradis et al., 2022). In addition to MLCSs, there is another degradation mechanism in which misfolded or oxidized proteins of mitochondria are delivered to lysosomes by mitochondria-derived vesicles (MDVs) budded off from damaged mitochondria(Hsu et al., 2018; Todkar et al., 2021). Aβ production induces lysosomal malfunction, which leads to defective degradation and clearance of damaged mitochondria, Aβ accumulation, and neuronal dysfunction. Whereas lysosomal enhancement restores mitochidrial function by promoting elimination of damaged mitochondria and alleviating synaptic damage in AD neurons(Han et al., 2021b).

The abnormality of mitochondrial energy metabolism is closely associated with the development of AD. The tricarboxylic acid (TCA) cycle is the most widely used mitochondrial metabolic pathway and also plays a critical role in biosynthesis, in which TCA cycle intermediates regulate cell metabolism and signal transduction by entering and leaving the cycle(Xu et al., 2016). Citrate exported from mitochondria is

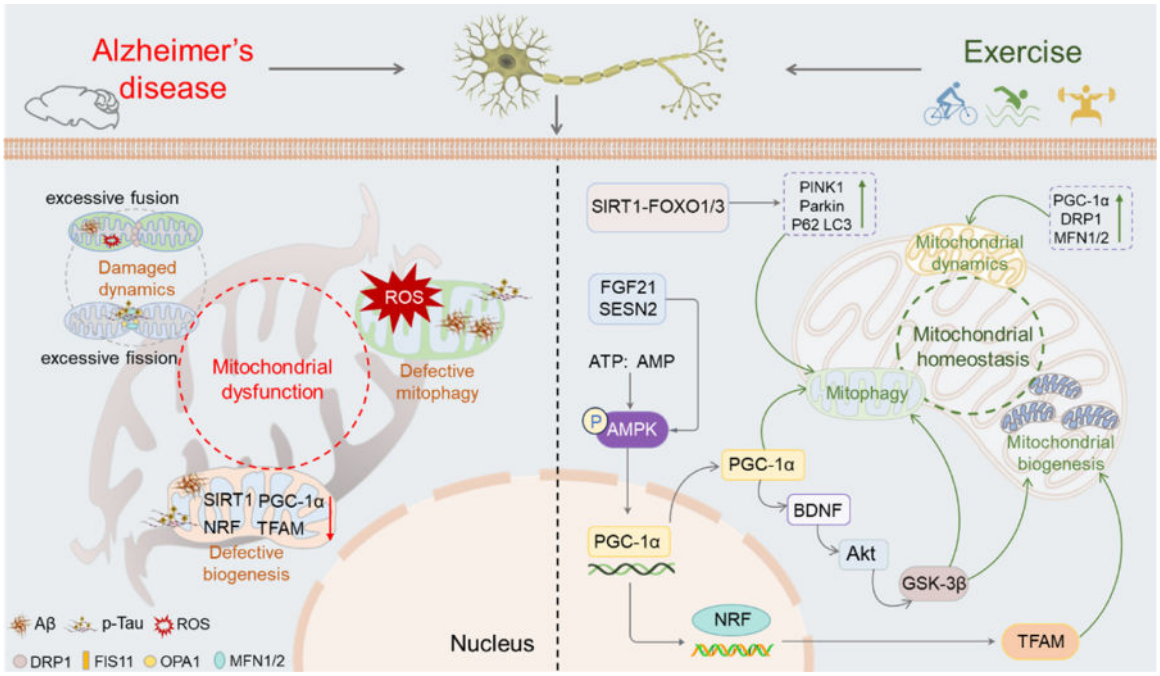

Fig. 4. Exercise mediates mitochondrial homeostasis by improving mitophagy, and mitochondrial biogenesis and dynamics. Defective mitophagy and biogenesis, and damaged dynamics of mitochondria are caused by Aβ and p-Tau in Alzheimer's disease. Exercise induces exerkines and activates related signaling pathways to attenuate mitochondrial dysfunction in neurons. Aβ: β-amyloid; Akt: protein kinase B; AMP: adenosine monophosphate; AMPK: adenosine monophosphate-activated protein kinase; ATP: adenosine triphosphate; BDNF: brain-derived neurotrophic factor; DRP1: dynamin-related protein 1; FIS1: fission protein 1; FGF21: fibroblast growth factor 21; FOXO: forkhead box protein O; GSK-3β: glycogen synthase kinase-3β; LC3: light chain 3; MFN1/2: mitofusin 1 and 2; NRF: nuclear respiratory factors; OPA1: optic atrophy 1; PGC-1α: peroxisome proliferator activated receptor γ coactivator (PPARγ)-1α; PINK1: putative kinase protein 1; p-Tau: hyperphosphorylated microtubule-associated protein tau; SESN2: sestrin2; SIRT1: sirtuin-1; ROS: reactive oxygen species; TFAM: mitochondrial transcription factor A.

converted to acetyl-CoA, which is used for nuclear DNA-related histone acetylation(Madiraju et al., 2009). A study has revealed that increased acetyl-CoA levels in senescence-accelerated prone mice exerted neuroprotection and delayed age-related cognitive decline by enhancing acetylation of histone H3 lysine 9 (H3K9), a site associated with memory (Currais et al., 2019). Mitochondrial transport and signal transduction, which are essential in supporting neuronal growth and activity and maintaining neuronal function, are disrupted in AD neurons (Fig. 3). It is critical to explore how to protect mitochondrial transport and signal transduction as a potential treatment for AD.

3. The present: what exercise can do from mitochondria to Alzheimer's disease?

Evidence suggests that mitochondrial dysfunction is involved in AD and other neurodegenerative diseases(Luo et al., 2022; Yang et al., 2022b). Aging significantly increases the production and accumulation of Aβ and p-Tau, as well as their interaction with the mitochondrial fission protein DRP1, leading to excessive mitochondrial fragmentation and impair mitochondrial dynamics, resulting in defective mitochondrial transport to synapses, synaptic damage, and neuronal degeneration in AD neurons(Baek et al., 2017; Dowding et al., 2014; Kshirsagar et al., 2022; Nakanishi et al., 2013). Studies have shown that exercise reduced the risk of AD and improved memory-associated events by inducing exerkines (Liu et al., 2020b; Wang et al., 2020a) (Table 1), which were released from many different organs and tissues in response to exercise and exerted their effects via autocrine, paracrine, or endocrine pathway (Chow et al., 2022; Heo et al., 2023).

3.1. Exercise mediates mitochondrial homeostasis

Mitochondria undergo active fission, fusion, biogenesis and mitophagy, and contact with other organelles(Fischer et al., 2018; Pekkurnaz and Wang, 2022). Mitochondrial biogenesis occurs in response to meet the high energy demand of neurons(Fenton et al., 2021), whereas the impairment of mitochondrial biogenesis and decreased PGC-1α expression were observed in AD neurons(Cen et al., 2020). Exercise-induced mitochondrial biogenesis results from a complex interplay of multiple signaling pathways that respond to metabolic and stress in neurons(Hwang et al., 2022b). PGC-1αregulates a range of neuronal adaptive responses related to mitochondrial biogenesis and mitophagy, while TFAM is a key nuclear-encoded factor that controls mtDNA packing, replication and transcription in neurons(Liu et al., 2022; Wen et al., 2019). In APP/PS1 transgenic mice, a 12-week treadmill exercise significantly upregulated the expressions of PGC-1α and TFAM and increased ATP levels to mitochondrial biogenesis against AD-related mitochondrial dysfunction(Zhao et al., 2020). During exercise, ATP is continuously synthesized and catabolized into ADP and finally into AMP, which binds to the γ subunit of the heterotrimeric AMPK, causing AMPK conformational changes and phosphorylation (Cao et al., 2022; Xu et al., 2020). AMPK activation increases the phosphorylation of PGC-1α, further stimulating mitochondrial biogenesis(Xu et al., 2020). A study demonstrated that activation of AMPK upregulated the PGC-1α/NRFs/TAFM pathway and promoted mitochondrial biogenesis in response to exercise(Jia et al., 2023). Moreover, stress-induced protein sestrin2 (SESN2) can effectively prevent age-related diseases, including diabetes and neurodegenerative disease, by activating multiple signaling pathways(Sun et al., 2020a). It has been reported that SESN2 silencing inhibited the activation of the AMPK/PGC-1α pathway, thereby inhibiting mitochondrial biogenesis and ultimately aggravating neurological deficits and neuronal damage in rats with ischemia/reperfusion injury(Li et al., 2016). Studies have demonstrated that both aerobic and resistance exercise effectively improved mitochondrial function and mitophagy, as well as ameliorated prefrontal lobe injury and dysfunction by activating SESN2/AMPK signaling(Feng et al., 2023; Liu et al., 2021b). However, it is unclear

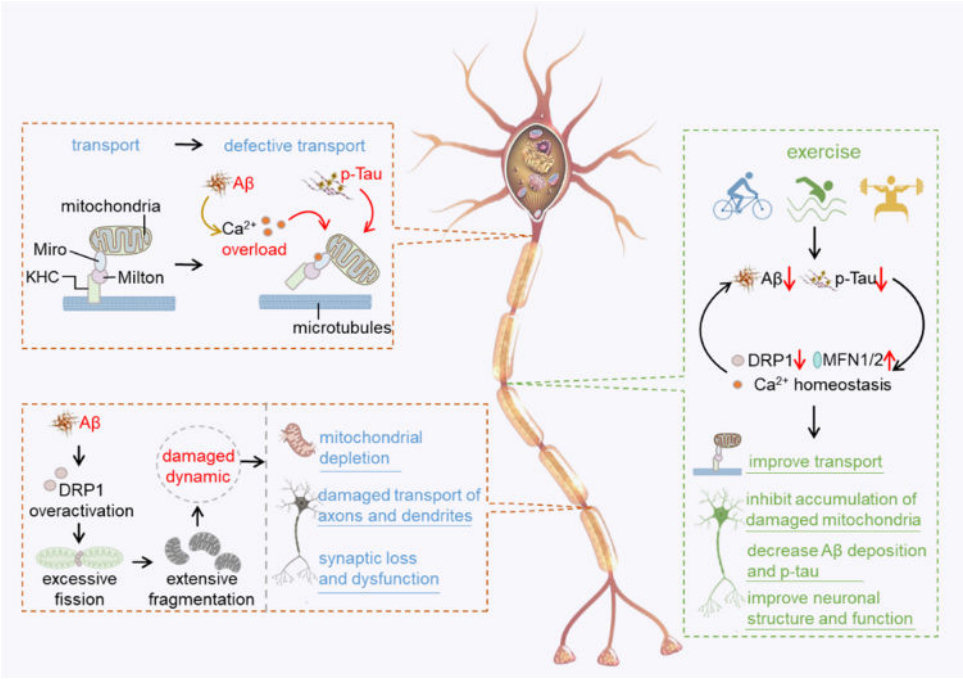

Fig. 5. Exercise enhances mitochondrial transport to improve neuronal structure and function in Alzheimer's disease. Imbalance of mitochondrial dynamics and Ca^{2+} overload caused by Aβ and p-Tau impairs mitochondrial transport, which is conducive to synaptic dysfunction and loss. Exercise reduces the levels of Aβ and p-Tau and improves mitochondrial dynamics for enhancing transport, what is essential for alleviating accumulation of damaged mitochondria and supplying the energy needs of neurons. Aβ: β-amyloid; DRP1: dynamin-related protein 1; FIS1: fission protein 1; KHC: KHC: kinesin heavy chain; MFN1/2: mitofusin 1 and 2; p-Tau: hyperphosphorylated microtubule-associated protein tau.

whether exercise exerts neuroprotective effects by acting on mitochondria via SESN2 in the AD model.

Interestingly, in addition to mitochondrial biogenesis, exercise-induced PGC-1α also plays an essential role in mitophagy(Liu et al., 2021a). Resistance exercise activates hippocampal PGC-1α/brain-derived neurotrophic factor (BDNF)/protein kinase B (Akt)/glycogen synthase kinase-3β (GSK-3β) signaling to improve mitophagy, which contributes to mitochondrial biogenesis and synaptic plasticity in aged mice(Liu et al., 2022). It is worth noting that in human dopaminergic neurons, PGC-1α and mitochondrial function are enhanced by fibroblast growth factor 21(FGF21), which can cross the blood-brain barrier (BBB) and bind to β-klotho to promote remyelination and neuronal survival(Ren et al., 2021). Meanwhile, FGF21 can also activate AMPK and its downstream via FGF receptor 1 (FGFR1)/β-klotho(Cheng et al., 2020). It is speculated that FGF21 could play an important role in promoting mitochondrial function in AD neurons. Moreover, PINK1 is essential for orchestrating the Parkin-dependent mitophagy. Among the different mitophagy pathways, the PINK1/Parkin-dependent mechanism is the focus of current AD research(Li et al., 2022a). PINK1 is recruited to damaged mitochondria and induces the phosphorylation of Parkin, which links to LC3 to initiate mitophagy(Pan et al., 2022). It is reported that treadmill exercise significantly increased mitophagy-related proteins PINK1, Parkin, LC3II and P62 and enhanced mitophagy activity, thereby alleviating mitochondrial dysfunction induced by Aβ, and ultimately restoring synaptic function and the ability of learning and memory(Zhao et al., 2020). Another study also reported that in APP/PS1 mice, a 12-week treadmill exercise effectively reduced the accumulation of Aβ plaques and improved learning and memory ability by increasing mitophagy via the PINK1/Parkin pathway, which was enhanced by SIRT1-forkhead box protein O (FOXO) 1/3 axis in the hippocampus(Zhao et al., 2023).

Mitochondria go through periodical cycles of fusion and fission, which plays a critical role in repairing damaged or dysfunctional through mitophagy(Corrado et al., 2020). Mitochondrial fission and fusion is also required promote axonal transport and meet the synaptic energy demands(Fenton et al., 2021). Mitochondrial fission is mainly controlled by DRP1 and FIS1, whereas fusion is regulated by MFN1 and MFN2(Fan et al., 2022). A 10-week swimming training program has been shown to enhance mitochondrial fission and fusion by increasing the levels of PGC-1α, DRP1, and MFN1/2 in the hippocampus, which is conducive to maintaining mitochondrial dynamics and cognitive function in aged mice(Luo et al., 2017). Moreover, DRP1 expression is also increased in the cortex of aged mice in response to treadmill training(Liu et al., 2022). Another study reported that treadmill training caused a decrease of DRP1 and an increase in MFN1/2 in the brain cortex (Marques-Aleixo et al., 2015). Mitochondrial fusion and division events are dynamic and balanced. Excessive activation of DRP1 induces abnormal mitochondrial fission, which breaks the balance between fusion and fission, causing mitochondrial dysfunction. Exercise could restore mitochondrial homeostasis by maintaining mitochondrial dynamics, mediating biogenesis, and enhancing mitophagy, thereby exerting effective neuroprotection in AD (Fig. 4).

Furthermore, as mentioned before, ALCAT1 plays a pivotal role in regulating mitochondrial dynamics and function(Hao et al., 2024; Song et al., 2019). Previous studies have shown that exercise could effectively down-regulate the expression of ALCAT1 to alleviate impairments induced by oxidative stress in various tissues such as kidney and skeletal muscle(Ren et al., 2022; Wu et al., 2020a). Although it has not been reported whether exercise regulates the level of ALCAT1 in the brain, exercise-regulated ALCAT1 deserves further investigation in AD.

3.2. Exercise participates in mitochondrial transport and signal transduction

Mitochondria are transported to specific neuronal compartments, such as axons and dendrites, to support neuronal growth and activity (Lee et al., 2022c). Neuronal activity increases synaptic Ca^{2+} influx, which leads to the dissociation of mitochondria from microtubules. Mitochondria are anchored and involved in synaptic signals and homeostasis(Gutnick et al., 2019; Vaccaro et al., 2017). A study reported

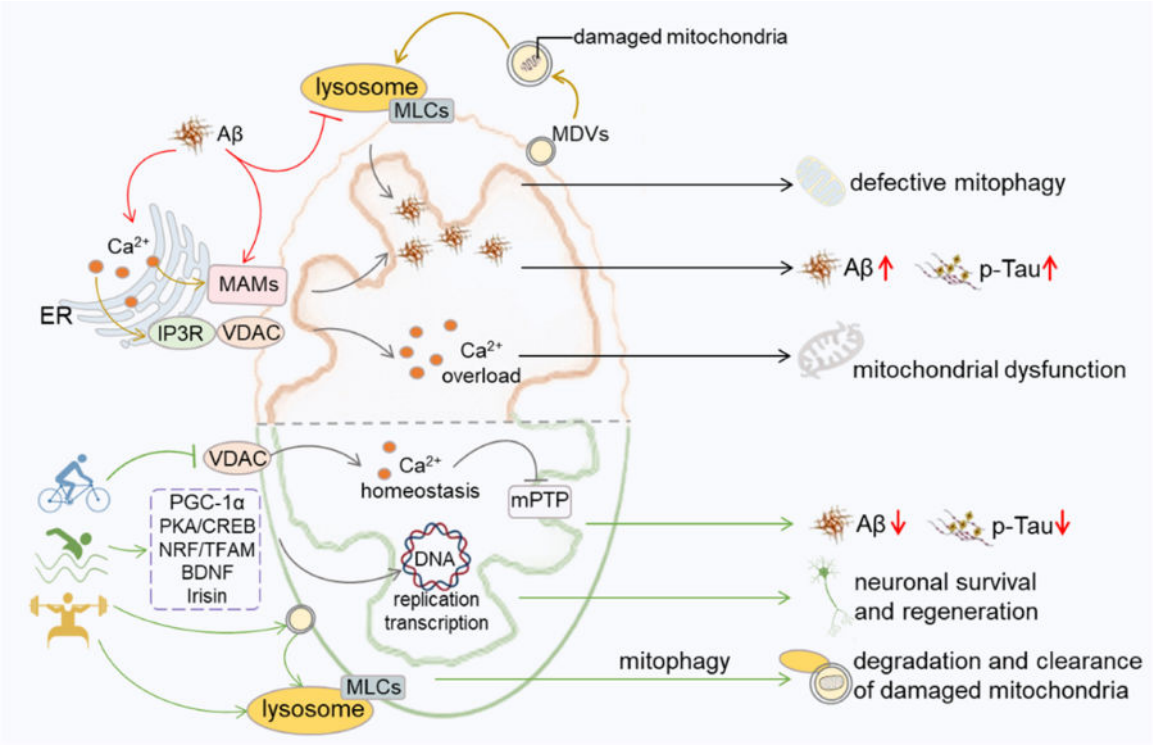

Fig. 6. Exercise participates mitochondrial signal transduction by inducing exerkines. Mitochondria transmit cellular signals by contacting with other organelles such as ER and lysosomes in neurons, which are hindered by Aβ and p-Tau in Alzheimer's disease. Exercise increases exerkines levels, inhibits related channels, promotes vesicle transport, improves mitochondrial signal transduction, and ultimately ameliorates mitochondrial dysfunction and neuronal damage. Aβ: β-amyloid; BDNF: brain-derived neurotrophic factor; CREB: cAMP response element-binding protein; ER: endoplasmic reticulum; IP3R: inositol 1, 4, 5-trisphosphate receptor; KHC: kinesin heavy chain; MAM: mitochondria-associated endoplasmic reticulum membrane; MDVs: mitochondria-derived vesicles; MERCs: mitochondria-ER contact site; MLCs: mitochondria-lysosome contact site; mPTP: mitochondrial permeability transition pore; PA: phosphatidic acid; PGC-1α: peroxisome proliferator activated receptor γ coactivator (PPARγ)-1α; PKA: cyclic adenosine monophosphate (cAMP)-dependent protein kinase; p-Tau: hyperphosphorylated microtubule-associated protein tau; VDAC: voltage-dependent anion-selective channel.

that mitochondrial transport was undermined by the hyperphosphorylation of Tau and Aβ-induced Ca^{2+} overload, while the reduction of Tau alleviated Aβ-induced impairment of axonal transport (Calvo-Rodriguez and Bacskai, 2021). Many studies have proven that exercise can effectively decrease the levels of Aβ and Tau(Koo et al., 2017; Shi et al., 2023; Wang et al., 2022). Importantly, in AD, the interaction between DRP1 and Aβ is conducive to excessive activation of DRP1 (Zhang et al., 2020), while extensive fragmentation induced by excessive DRP1 and abnormal distribution would disturb mitochondrial fission-fusion dynamics, further impairing mitochondrial transport, leading to mitochondrial depletion of axons and dendrites, and subsequently, synaptic loss(Wang et al., 2021). A study demonstrated that treadmill running exercise significantly reduced the DRP1 level in brain tissues(Marques-Aleixo et al., 2015). Moreover, mitochondrial transport includes bidirectional trafficking in the anterograde (providing ATP supply and Ca^{2+} buffering capacity) and retrograde (degrading and recycling damaged mitochondria) directions (Jiang et al., 2015). Mitochondria with high ΔΨ m are conducive to moving in the anterograde direction, while mitochondria with low ΔΨ m move in the retrograde direction(Cai et al., 2012). It has been proven that both treadmill training and free-wheel voluntary running alleviate Ca^{2+} overload and maintain Ca^{2+} homeostasis(Marques-Aleixo et al., 2015). Maternal exercise during pregnancy inhibits excessive fission by increasing MFN1 and reducing DRP1. Meanwhile, ΔΨ m and mitochondrial respiration were improved in adult offspring Aβ-injected rats by maternal exercise during pregnancy(Klein et al., 2019). All of the above factors have beneficial effects on improving mitochondrial transport, inhibiting damaged mitochondria accumulation, decreasing Aβ deposition and p-Tau, and resulting in improvement of neuronal structure and function. (Fig. 5)

Mitochondrial signaling in neurons are mediated by a complex network. Mitochondria transmit cellular signals by contacting other organelles, such as ER and lysosomes, via MCSs in neurons(Andersen et al., 2020; Collier et al., 2023; Picard and Shirihai, 2022; Soto-mayor-Flores et al., 2020). Mitochondria are precisely connected to the ER through MAMs to exchange signals(McNally et al., 2022; O'Hare et al., 2022; Wang et al., 2020b). In AD, however, MAMs-mediated essential cellular events, including Ca^{2+} transport from the ER to mitochondria, glucose metabolism, and lipid synthesis and transport, are impaired(Calvo-Rodriguez and Bacskai, 2021). ER-mitochondrial Ca^{2+} transfer is critical for maintaining neuronal Ca^{2+} homeostasis, since excessive release of Ca^{2+} from the ER cause mitochondrial Ca^{2+} overload and stress-associated mitochondrial dysfunction (Calvo-Rodriguez and Bacskai, 2021). MAM-related proteins are increased by Aβ, which increases MAM activity and ER-mitochondria connectivity and leads to excessive Ca^{2+} influx and accumulation into mitochondria(Area-Gomez et al., 2018). It has demonstrated that a 12-week treadmill exercise reduced the levels of MAM-related protein VDAC and Ca^{2+}-induced mPTP opening in APP/PS1 mice, resulting in improved ER-mitochondria communication and mitochondrial function (Mu et al., 2019). A study revealed that PGC-1α transmitted mitochondrial biogenesis signaling by regulating VDAC and mediated mitochondrial biogenesis via cAMP-dependent protein kinase (PKA)/cAMP response element-binding protein (CREB) signaling and NRF/TFAM pathway in hippocampal neurons of 3xTg-AD mice(Singulani et al., 2020). It has been confirmed that exercise significantly actives PGC-1α-associated signaling to improve mitochondrial function in neurons of AD mice, including SIRT1, BDNF, and Irisin(Garcia-Mesa

et al., 2014; Koo et al., 2017; Shi et al., 2023; Zhao et al., 2020). Thus, PGC-1α is an important factor that mediates exercise to participate in mitochondrial signal transduction.

In addition, the lysosome is critical for degrading and clearing damaged mitochondria in neurons. The deficiency of the autophagy-lysosomal pathway exhibits neurodegeneration in AD(Martini-Stoica et al., 2016). In addition to direct contact via MLCSs, damaged mitochondria are degraded and cleared by lysosomes through MDVs transfer (Hsu et al., 2018; Todkar et al., 2021). However, Aβ production leads to lysosomal malfunction, defective degradation and clearance of damaged mitochondria, and causes further Aβ accumulation(Cenini et al., 2014). A study has shown that a 5-month running wheel training significantly enhanced lysosomal function and vesicle trafficking, reduced the accumulation of Aβ and the level of p-Tau in the prefrontal cortex and hippocampus, and ultimately improved the cognitive function in APP/PS1 mice(Wang et al., 2022). (Fig. 6)

3.3. *Exercise improves mitochondria-nuclear communication*

In addition to the functional status of mitochondria themselves, mitochondrial function is also mediated by nuclear-mitochondria communication signals dependent on PGC-1α, NRF, and TFAM (Mohanraj et al., 2019; Wang et al., 2014). The proteins required for OXPHOS were both encoded by nuclear DNA and mtDNA(Becker et al., 2022; Carter et al., 2022). Continuous mitochondrial-nuclear communication coordinates the expression, translation, and assembly of the OXPHOS complexes encoded by the mitochondrial and nuclear genomes to maintain optimal mitochondrial function(Zhu et al., 2022).In AD, Aβ and p-Tau synergistically inhibit the activity of the OXPHOS complex and further decrease mitochondrial activity, leading to the impairment of mitochondrial-nuclear communication(Lee et al., 2022b). Studies have demonstrated that a reduction in glucose metabolism and mitochondrial complex I-V was observed in AD brain(Demarest et al., 2020; Marano et al., 2014), which is closely linked to Tau deposition(Pascoal et al., 2019). A study has found that eight weeks of combined aerobic and resistance training significantly increased ETC complex V activity in the brain of mice with cerebellar neurodegeneration caused by apoptosis-inducing factor deficiency(Fernandez-de la Torre et al., 2020). It has also been reported that a four-week treadmill running upregulated the levels of PGC-1α, NRF, and TFAM, increased complex I, improved OXPHOS activity, and ultimately exerted a neuroprotective effect in the dopaminergic system in mice with Parkinson's disease(Fernandes Ferreira et al., 2020). In summary, exercise could be used to regulate mitochondrial and nuclear genomes, improve OXPHOS activity, maintain nuclear-mitochondria intercommunication, enhance mitochondrial function, and promote neuroprotection in AD.

The metabolites released by the TCA cycle of mitochondria, such as succinate and citrate, transduce epigenetic modification signals by regulating DNA methylation or demethylation and histone acetylation (Fu et al., 2019). For example, acetyl-CoA produced by citrate acts as a second messenger to transmit mitochondrial signals to the nucleus, which provides an acetyl group for histone acetylation(Li et al., 2018; Sun et al., 2022). Tau contains cysteine residues in the microtubule-binding domain, which facilitates the lysine acetylation of Tau and interacts with the phosphorylation (Prifti et al., 2022). Increasing acetyl-CoA promotes Tau auto-acetylation on lysine and further causes Tau aggregation and neurofibrillary tangles (NFTs) formation in the frontal-cortex tissues and primary hippocampal neurons in AD mice(Cohen et al., 2013). Moreover, Tau increases the level of acetyl-CoA, reduces histone deacetylase 6 (HDAC6) activity, and results in long-term neurotoxicity(Tseng et al., 2021). HDAC6 is a unique isoenzyme with two deacetylase domains(Cao et al., 2018),whereas Tau binds to HDAC6 and inhibits its activity(Sohn et al., 2016), thereby increasing the lysine acetylation of Tau. It has been reported that a 12-week treadmill running significantly reduced the expression of acetyl-CoA carboxylase, a catalytic enzyme of acetyl coenzyme A, in

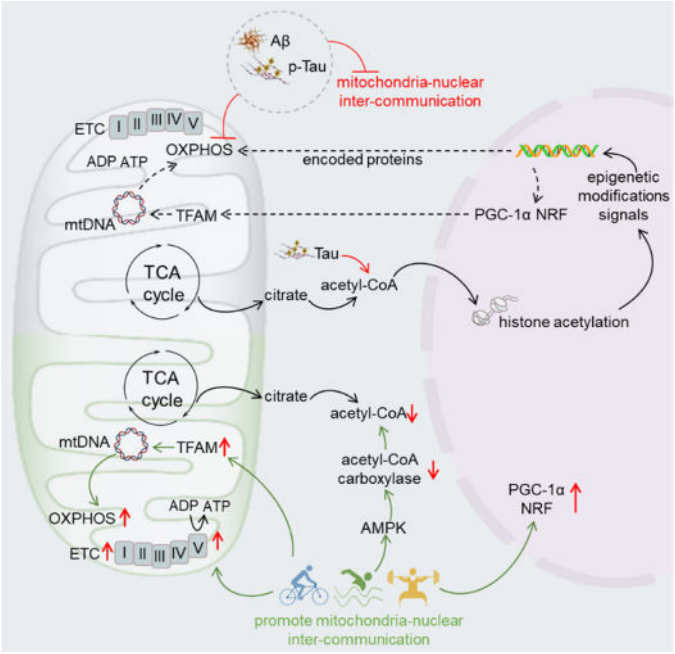

Fig. 7. Exercise revers the mitochondria-nuclear communication impaired in Alzheimer's disease. Mitochondria-nuclear communication is essential for mitochondrial function. Aβ and p-Tau inhibit the communication by impairing oxidative phosphorylation and TCA cycle. However, exercise reverse it through inducing exerkines, promoting mitochondria-nuclear communication, and ultimately improving mitochondrial function. ADP: adenosine diphosphate; ATP: adenosine triphosphate; Aβ: β-amyloid; ETC: electron transport chain; mtDNA: mitochondrial DNA; NRF: nuclear respiratory factors; OXPHOS: oxidative phosphorylation; PGC-1α: peroxisome proliferator activated receptor γ coactivator (PPARγ)-1α; TCA: tricarboxylic acid; TFAM: mitochondrial transcription factor A.

mice fed a high fat-high sugar diet(St Aubin et al., 2022). Another study has also demonstrated that swimming training remarkably decreased the level of acetyl-CoA carboxylase in rats fed with a high fat diet, partially via AMPK signaling(Bai et al., 2023). Although there is no direct evidence that exercise regulates the level of acetyl-CoA and mediates histone acetylation in AD, exercise-induced change s in acetyl-CoA carboxylase imply that exercise has therapeutic potential. (Fig. 7)

4. The future: what do we need to do?

Mitochondrial dysfunction plays a central role in the development of AD. Impaired mitochondrial dynamics, biogenesis, and mitophagy in AD neurons are associated with oxidative stress and neuroinflammation. The newly discovered regulators, such as ALCAT1 and Piezo1, have been proven to influence mitochondrial function. In particular, ALCAT1 effectively mediates oxidative stress and pathological remodeling of CL, which would prompt mitochondrial dysfunction and neuroinflammation in neurodegenerative diseases, where CL exits in mitochondria and is indispensable for mitochondrial function. Therefore, inhibition of ALCAT1 is particularly important for preventing and treating AD. Both exercise and Dafa (a powerful inhibitor of ALCAT1) show remarkable inhibitory effects on ALCAT1 and could effectively alleviate oxidative stress, inflammation,and mitochondrial dysfunction. However, the neuroprotective effects of Dafa and exercise on inhibiting ALCAT1 remain unclear and deserve further study. Furthermore, advanced technologies such as single-cell sequencing and single-cell omics could be used to screen and identify molecular targets related to mitochondrial heath and further explore the link between mitochondrial dysfunction and AD, which is the key to deciphering the pathogenesis and

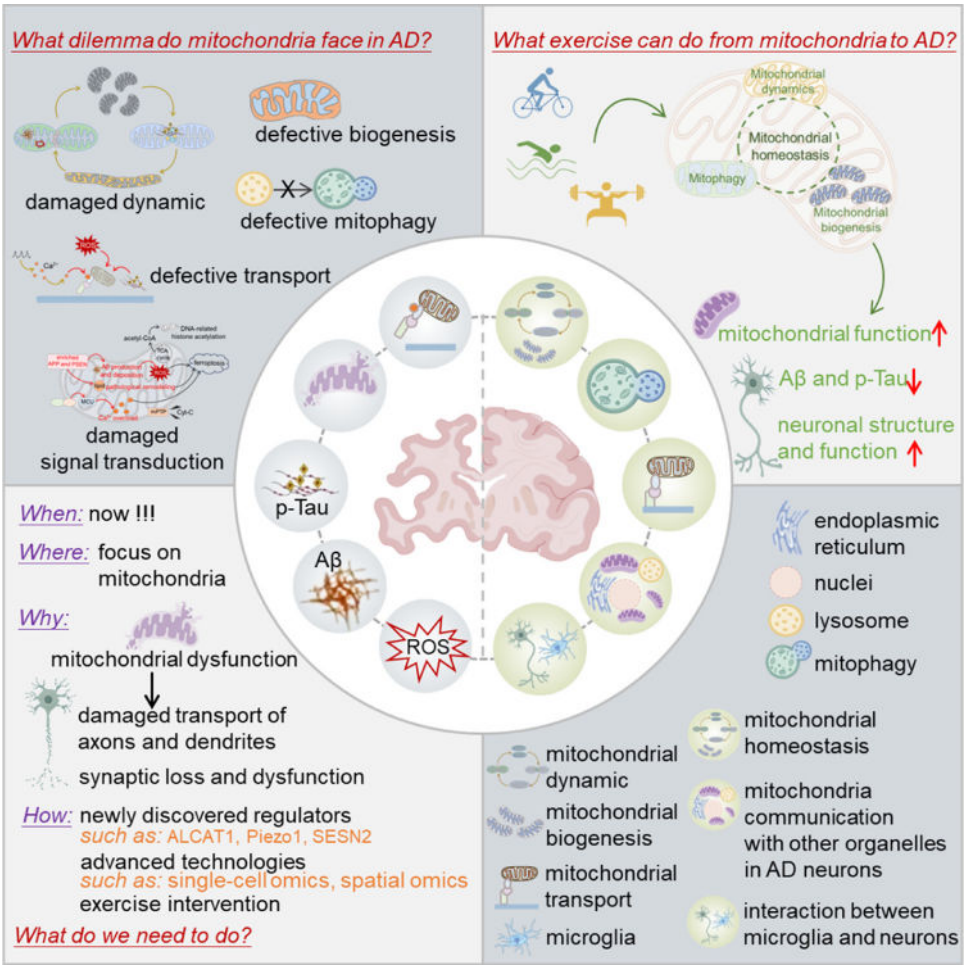

Fig. 8. The emerging role of exercise in Alzheimer's disease: Focus on mitochondrial function. ALCAT1: lysocardiolipin acyltransferase 1; Aβ: β-amyloid; ROS: reactive oxygen species; p-Tau: hyperphosphorylated microtubule-associated protein tau; SESN2: sestrin2.

intervention targets of AD.

Moreover, defects in mitochondrial transport and signal transduction not only cause damage to neuronal structure and function, but also promote the further development of AD. Exercise has been proven to reduce the likelihood of risk and mitigate the neuronal impairment of AD by improving mitochondrial function via exerkines-mediated complex mechanisms involving adjustment of mitochondrial homeostasis and participation in mitochondrial transport and signal transduction. Although the notion that exercise promotes mitochondrial-nuclear communication to regulate epigenetic signaling in AD neurons has not been fully confirmed, existing evidence shows that exercise has great potential for ameliorating neuronal damage in AD, particularly from the perspective between mitochondria-nuclear communication and epigenetics. Furthermore, exercise promotes mitochondria communication with other organelles in AD neurons, which should receive more attention in the future (Fig. 8).

Declaration of Competing Interest

The authors have no financial or proprietary interests in any material discussed in this article. No conflict different exists in the submission of this manuscript, and manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that this work has not been published previously and not under consideration for publication elsewhere, in whole or in part.

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Author contributions

Conceptualization and Writing-original draft (Lili Feng and Zhenjun Tian); Writing-review & editing (Bowen Li, Su Sean Yong, Xu Wen, and Zhenjun Tian)

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