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Review

The Role of Microglia with Mitochondrial Dysfunction and Its Therapeutic Prospects in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD), a primary cause of dementia, is rapidly emerging as one of the most financially taxing, lethal, and burdensome diseases of the 21st century. Increasing evidence suggests that microglia-mediated neuroinflammation plays a key role in both the initiation and progression of AD. Recently, emerging evidence has demonstrated mitochondrial dysfunction, particular in microglia where precedes neuroinflammation in AD. Multiple signaling pathways are implicated in this process and pharmaceutical interventions are potentially involved in AD treatment. In this review, advance over the last five years in the signaling pathways and pharmaceutical interventions are summarized and it is proposed that targeting the signaling pathways in microglia with mitochondrial dysfunction could represent a novel direction for AD treatment.

Keywords: Alzheimer's disease; microglia; mitochondria; microglia with mitochondrial dysfunction

1. Background

Alzheimer's disease (AD) is an ambient neurodegenerative disorder distinguished by memory deficits and diverse mental impairments. It manifests in a variety of cellular alterations such as dysregulation of microRNAs, activation of glial cells and astrocytes, hormonal imbalances, impaired mitophagy and synaptic deterioration, as well as the accumulation of intracellular neurofibrillary tangles (NFTs), extracellular β-amyloid (Aβ) plaques and phosphorylated tau (P-tau) [1]. Once considered a rare condition, AD now ranks among the top eight major global health concerns [2]. In 2006, the global prevalence of AD stood at 26.6 million; this figure is expected to quadruple by 2050, affecting approximately one in 85 individuals worldwide [3]. Rather than being a mere secondary response to the formation of senile plaques and neurofibrillary tangles, neuroinflammation in AD contributes significantly, if not more, to the disease pathogenesis [3].

AD is characterized as a dual-proteinopathy disorder, exhibiting a spatially selective distribution of diffuse neuritic Aβ plaques within the brain parenchyma [4,5]. Initially, these plaques are intracytoplasmic but later become extracellular, accompanied by neurofibrillary tangles, synaptic degeneration, neuronal loss and gliosis [6–9].

The etiology of AD continues to be a controversial topic and is not fully understood [10–12]. Current models suggest that the accumulation of neurotoxic Aβ species at synapses triggers a cascade of events, including microglial activation, ionic imbalances, neurotransmitter dysregulation, mitochondrial dysfunction, oxidative stress and hyperphosphorylation of tau protein, leading to tangle formation [12–23]. Tau-mediated mechanisms exacerbate synaptic and neuronal impairments, culminating in cortical dysfunction [24].

Microglia, as the resident macrophages of the central nervous system (CNS), are crucial for maintaining CNS homeostasis. They have been implicated in AD pathology and participate in phagocytosis, removal of pathogenic molecules and modulate neuroinflammatory responses [25–29]. Activation of microglia is a critical element in the pathogenesis of AD [30]. Robust experimental data suggest a role for activated microglia in Aβ and p-Tau-mediated neuronal dysfunction during AD pathogenesis [30,31]. These immune functions are energy-intensive and regulated by mitochondrial activity [28]. Mitochondria are ubiquitous organelles, essential to nearly all eukaryotic cells [32,33]. They are primarily responsible for adenosine triphosphate (ATP) production, the principal cellular energy molecule [34].

Mitochondria play an important role in oxidative stress, cell survival, calcium homeostasis and energy metabolism [35]. Mitochondrial dysfunction is considered to be directly involved in the death of autonomic neurons [35]. AD has been thought to be a metabolic disease [28,35–37]. Although glial mitochondria are more metabolically flexible than neurons, they also play a critical role in the function of the CNS and have specific metabolic and mitochondrial characteristics to support their functional

diversity [28,35,38]. Several studies have identified a range of mitochondrial dysfunctions in microglia and other brain cells, including age-related accumulation of mitochondrial DNA (mtDNA) mutations, structural remodeling, overproduction of mitochondrial reactive oxygen species (ROS), changed mitocondrial membrane potential, reduced ATP levels, disruptions in the electron transport chain, and elevated mitochondrial fragmentation, resulting in defective mitophagy [1,31,39–44]. These mitochondrial dysfunctions contribute to the onset of AD. Further research has revealed drugs targeting various signaling pathways related to mitochondrial energy metabolism, dynamics, biogenesis, and autophagy.

This review outlines recent advancements in understanding the relationship between microglial mitochondrial dysfunction and AD. It also summarizes the signaling pathways involved and pharmaceutical interventions targeting these pathways over the past five years. Lastly, we introduce a novel perspective for targeting specific signaling pathways as a therapeutic approach for AD.

2. Mitochondrial Dysfunction in Microglia

2.1 Physiological Function of Microglia and Its Roles in Brain Inflammation

Serving as the resident macrophages of the CNS, microglia maintain CNS homeostasis; they are also implicated in AD pathology [25,45]. Upon exposure to pathogenic or damage signals, microglia rapidly activate to acquire different phenotypes exerting either neuroprotection or neurotoxicity [46]. As brain resident innate immune cells - microglia - sculpt neural circuitry and coordinate copious and numerous neurodevelopmental requirements [47].

Microglia, acting as effector cells in the brain's innate immune system, exhibit an adaptability to perform various specialized functions in AD, including phagocytosis and elimination of harmful clusters of Aβ and tau proteins that contribute to neurodegeneration. These immunological processes necessitate substantial energy resources, which are controlled by mitochondria. Furthermore, microglia exhibit metabolic flexibility, capable of utilizing both glycolysis and oxidative phosphorylation and reprogram their mitochondrial function to meet their energy needs when activated by inflammation [28]. Myeloid Triggering receptor expressed on myeloid cells 2 (TREM2) is a regulatory factor that adapts to mitochondrial metabolism and is only expressed in microglia. Recent studies have shown that TREM2 is involved in multiple microglial activities, including calcium mobilization, phagocytosis, cytokine production, energy metabolism and immune response regulation. TREM2 is highly expressed in the brains of AD patients. Modulation of TREM2-mechanistic target of rapamycin (mTOR) signaling increases microglial phagocytosis in AD [48]. Increasing evidence suggests that TREM2 maybe involved in regulating microglial polarization of the anti-inflammatory Macrophages (MΦs) type 2 (M2) phenotype through multiple signaling pathways, including the Toll-like receptor 4 (TLR4)-mediated pathway, Phosphatidlinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. In the field of neurodegenerative diseases, TREM2 has been observed to reduce the accumulation of lactate dehydrogenase (LD) in aging microglia. At the same time, studies have shown that TREM2 restores microglia homeostasis through the TREM2-Apolipoprotein E (APOE)-mediated pathway, possibly by regulating key transcription factors such as transforming growth factor β (TGF-β) that are homologous to microglia [49]. APOE is a glycoprotein involved in the regulation of lipid metabolism and is widely expressed in astrocytes, microglia, vascular parietal cells and choroid plexus cells in the central nervous system [50]. APOE is a polymorphic gene with three common alleles: ϵ2, ϵ3, and ϵ4. Although the most common allele, APOE ϵ3 (APOE3), is not associated with the disease, APOE ϵ4 (APOE4) is the largest known genetic risk factor for late-onset AD. APOE4 is involved in AD pathogenesis by affecting microglial reactivity, synaptic integrity and plasticity, lipid transport, cerebrovascular integrity and function, and glucose metabolism, some of which are independent of Aβ-associated pathways [51]. Under pathological conditions and injury, APOE is found to be sharply upregulated in activated microglia and stressed neurons. Investigators have found that the TREM2-APOE pathway plays a key role in microglial phenotypic change from a homeostatic to a neurodegenerative phenotype.

Microglia express glycolysis and oxidation and in the absence of glucose, they are metabolically flexible and have the capacity to quickly adapt to consume glutamine as an alternative metabolic fuel. Glutamine hydrolysis supports the maintenance of motor and damage sensing functions of microglia processes in insulin-induced hypoglycemia in blood glucose or *in vivo* in acute brain sections. This metabolic adaptation sustains mitochondrial function and is regulated through mTOR-dependent signaling. This plasticity allows microglia to maintain their critical monitoring and phagocytosis roles even after disruption of neural energy homeostasis [52,53]. Glucose deprivation may sensitize microglia to release inflammatory mediators and major microglia functions in survival and inflammation, which probably result in psychiatric comorbidities of ischemia, diabetes, and/or metabolic disorders [54]. Microglia also undergo a transition from a resting phenotype to a reactive phenotype, known as disease-associated microglia. There is a common misconception that M1, the glycolytic type, and M2 are dependent on the oxidative phosphorylation phenotype. The glucose uptake of microglia is mainly promoted by glucose transporter type 1 (GLUT1), especially within inflammatory environments [55].

Microglia continuously monitor the brain parenchyma to detect changes in neuronal activity and homeostatic pro-

cesses to maintain normal brain function. Metabolic pathways participating in microglial activity adapt and promote cell phenotypes. While mitochondrial oxidative phosphorylation is efficient in the production of ATP, microglia produce ATP faster and produce intermediates for cytokine production and cell growth. In macrophages, pro-inflammatory stimulation induces a metabolic transition from oxidative phosphorylation to glycolysis, a phenomenon similar to the Warburg effect in tumor cells. Alterations in metabolic function allow macrophages to respond appropriately to changing environments and much evidence suggests that, similar to macrophages, microglia are able to variably adapt to the energy matrix. Neuroinflammation frequently manifests in various neurodegenerative disorders and metabolic reprogramming of microglia has been found in neurodegenerative diseases [56].

2.2 Physiological Function of Microglia

Mitochondria serve as the primary energy-generating organelles in human cells. The genetic blueprint for mitochondria, mitochondrial DNA (mtDNA) is a circular, double-stranded molecule comprising 16,569 nucleotides. It encodes 13 messenger RNAs, 2 ribosomal RNAs and 22 transfer RNAs [57].

Proteins transcribed from mitochondrial messenger RNAs form essential subunits of the oxidative phosphorylation complexes I to V except complex II. These complexes play a key role in mitochondrial oxidative phosphorylation, influencing electron transfer and ATP generation [58,59]. The principal sites for oxidative phosphorylation and ATP generation are mitochondria, mitochondria supply about 95% of the energy needed for cellular functions [60]. Under hypoxic conditions, cells rely solely on glycolysis for ATP production, which leads to the conversion of pyruvate into lactic acid. In aerobic conditions, glycolysis produces pyruvate that enters the tricarboxylic acid (TCA) cycle, also known as the citric acid or Krebs cycle, facilitating mitochondrial ATP synthesis [61].

Mitochondria generate circulating metabolites from the TCA cycle that influence cellular fate and function. TCA cycle metabolites have traditionally been regarded as by-products of cellular metabolism. These metabolites are crucial for the biosynthesis of macromolecules, including nucleotides, proteins and lipids. While fundamental to cellular homeostasis, these processes occur rapidly. It has been recognized that metabolites in the TCA cycle are also involved in controlling chromatin modification, DNA methylation and change of function post-translational protein modification [62].

Mitochondrial morphology exhibits significant variations across different cell types and tissues and swiftly responds to external stimuli and metabolic signals such as nutritional status. The structure of mitochondria, characterized by continuous fission and fusion of their inner and outer membranes, has been intensively studied for its functional implications. Unregulated fission leads to mitochondrial disruption, commonly linked with metabolic dysfunction and disease. Controlled fusion produces stable mitochondrial networks, which counteract metabolic damage, maintain cellular integrity, and inhibit autophagy [63]. Mitochondrial morphology undergoes constant alterations through a dynamic interplay of fusion, fission and cytoskeletal trafficking. The balance between fission and fusion rates determines both the extent to which mitochondria form closed networks and their length. Moreover, these rates are controlled by mitochondrial metabolism, harmful conditions and their cellular environment. Fusion and fission are significant for mitochondrial redistribution, growth, and maintaining a robust mitochondrial network. Moreover, fission and fusion process of mitochondria exert a significant role in disease-associated procedures, including mitochondrial apoptosis and autophagy.

Three members of the Dynamin family play an important role in fission and fusion mechanisms [64]. As dynamic organelles, mitochondria can fuse and divide. These continuous and simultaneous processes are mediated by nuclear DNA-coding proteins, which act upon the mitochondrial membrane. The balance of fission and fusion dictates mitochondrial morphology, adapting to the metabolic demands of the cell. Additionally, these two processes are essential for optimizing mitochondrial bioenergetic and functional capabilities [65]. Maintaining a healthy network of interconnected mitochondria is crucial for ensuring the proper positioning of mitochondria towards high-energy-demanding neurons, as well as safeguarding neurons by minimizing oxidative stress. To achieve these objectives, it is imperative to achieve an equilibrium between mitochondrial fusion and fission processes [66].

2.3 Microglia with Mitochondrial Dysfunction in Alzheimer's Disease

Implications can be observed in conditions like AD and cerebral ischemia/reperfusion, where microglial mtDNA undergoes mutations or deletions [67,68]. Recent research has reported a correlation between levels of microglial mtDNA deletions in distinct brain regions with varying pathological susceptibilities to AD and their corresponding disease stages [69]. Once taken up by nearby microglia, mtDNA will binds to cyclic guanosine 5′-monophos-phate-adenosine monophosphate (GMP-AMP) synthase (cGAS) protein and activates the cGAS-Sting cytoplasmic DNA recognition pathway, thereby increasing the expression of interferon-beta (IFN-β) [67]. Additionally, after treated by mtDNA, the human microglia will produce large amounts of ROS, activate the nuclear factor-κB (NF-κB) signaling pathway, synthesize excessive pro-inflammatory cytokines, aggravate the inflammatory microenvironment and lead to cell death and tissue damage [70]. Therefore, the release of damage-associated molecular patterns is increased and more microglia are activated, triggering a feed-forward cycle of neuroinflammation [71].

Table 1. Mitochondrial associated biological process changes occurred in the pathological and physiological environments in microglial.

Biological process	Physiological environment	Physiological environment
OXPHOS	Main way of generating energy	Complex I, III, IV activity decreased; ROS increased
Glycolysis	It produces almost no energy	Fast energy supply in response to inflammation or stress
TCA cycle	Normal	PDH, 2OGDH, glutamate, glutamine, GABA, and NAA decreased
Mitochondrial fusion	Normal	Tomm40, Opa1, Mfn1, Mfn2 decreased
Mitochondrial fission	Normal	Drp1, Fis1 increased
PGC-1α/TFAM	Normal	TFAM, Nrf1, Nrf2, and PGC-1α decreased
Mitophagy	Normal	PINK, Pakin, LC3 decreased

TCA, Trica rboxylic acid; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; PDH, Pyruvate dehydrogenase; 2OGDH, 2-oxoglutarate dehydrogenase; GABA, Gamma-aminobutyric acid; NAA, N-acetyl-aspartate; Tomm40, Translocase of outer mitochondrial membrane 40; Opa1, Optic atrophy 1; Mfn1, mitofusin-1; Mfn2, mitofusin-2; Drp1, dynamin related protein 1; Fis1, mitochondrial fission 1 protein; TFAM, mitochondrial transcription factor A; Nrf1, Nuclear respiratory factor 1; Nrf2, Nuclear respiratory factor 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PINK, PTEN-induced kinase 1; PTEN, Phosphatase and tensin homolog; LC3, microtubule-associated proteins light chain 3.

These observation suggest that microglial mtDNA abnormalities contribute to glial activation and deposition of pathogenic material deposition in AD.

Accumulating *in vitro* and *in vivo* evidence suggests that metabolic impairments in the CNS contribute to both microglial activation and cell death, exacerbating pathology in neurodegenerative diseases [72]. Oxidative stress and reactive oxygen species generation are pivotal mechanisms in this process [72,73]. Microglia are attacked by oxidative stress, and reactive oxygen species, leading to mitochondrial dysfunction. Microglia with mitochondrial dysfunction increase mitochondrial damage, increase the release of inflammatory factors into the extracellular space and overproduce ROS. These pathological changes further increase the inflammatory response of microglia. Considerable proteomic analyses of AD brains and cerebrospinal fluid have demonstrated elevated levels of proteins linked to glucose metabolism, coinciding with early-stage microglial activation [74]. Upon inflammatory stimulation, microglia shift their metabolic pathway to less efficient glycolysis, potentially undermining their metabolic efficiency and phagocytic capability, ultimately leading to microglial dysfunction and Aβ accumulation [75,76]. Analogous observations have been reported in murine models [45]. Additionally, it has been observed by the current authors that a spatial correlation exists between aerobic glycolysis in cognitively normal young adults and Aβ deposition in individuals with both dementia of the Alzheimer's type and cognitively normal participants with elevated Aβ levels [77].

An increasing body of literature highlights the significant role of mitochondrial fusion/fission imbalance in microglia-mediated neuroinflammation in AD. Evidence has demonstrated that activated microglia in AD mouse models exhibit mitochondrial damage due to dysregulated mitochondrial dynamics [78]. In neurodegenerative conditions, neuronal debris is believed to initiate glial-mediated neuroinflammation, contributing to further neuronal loss. Notably, this phenomenon has been specifically observed in microglia. The ratio of damaged to functional mitochondria released from microglia and the resultant neuronal damage, are both regulated by Fis1-mediated mitochondrial fragmentation within these glial cells [79].

Recent studies have suggested that defective mitophagy might play a role in the development of AD. Further research has shown that mitophagy is impaired in the hippocampi of patients with AD, as well as in induced pluripotent stem cell-derived human neurons and animal models of the disease [80].

3. Signaling Pathways that Regulate Microglia with Mitochondrial Dysfunction in AD

Mitochondrial dysfunction can trigger diverse signaling pathways, leading to the metabolic reprogramming of glial cells and exacerbate pathogenic events related to AD [81]. Signaling pathways associated with mitochondrial dysfunction in microglia are showed in Fig. 1 and Table 1.

Mitochondrial energy metabolism encompasses multiple processes, including oxidative phosphorylation, the TCA cycle and glycolysis. Mitochondria serve as the primary site for oxidative phosphorylation, where the electron transport chain synthesizes ATP. This chain is mainly composed of Complexes I to V, located in the inner mitochondrial membrane [82]. Glycolysis comprises ten reactions that are divided into two phases: ATP investment and ATP payoff. These reactions take place in the cytosol [82]. The mitochondrial matrix is responsible for the production of the TCA cycle, which consists of eight enzymatic steps that consume and regenerate citrate [62]. The researchers observed a decline in mitochondrial complex I, III, and IV activity in AD models or the brains of AD patients. Furthermore, levels of TCA cyclically derived metabolites (glutamate, Gamma-aminobutyric acid (GABA), N-acetyl-aspartate (NAA), and glutamine) were

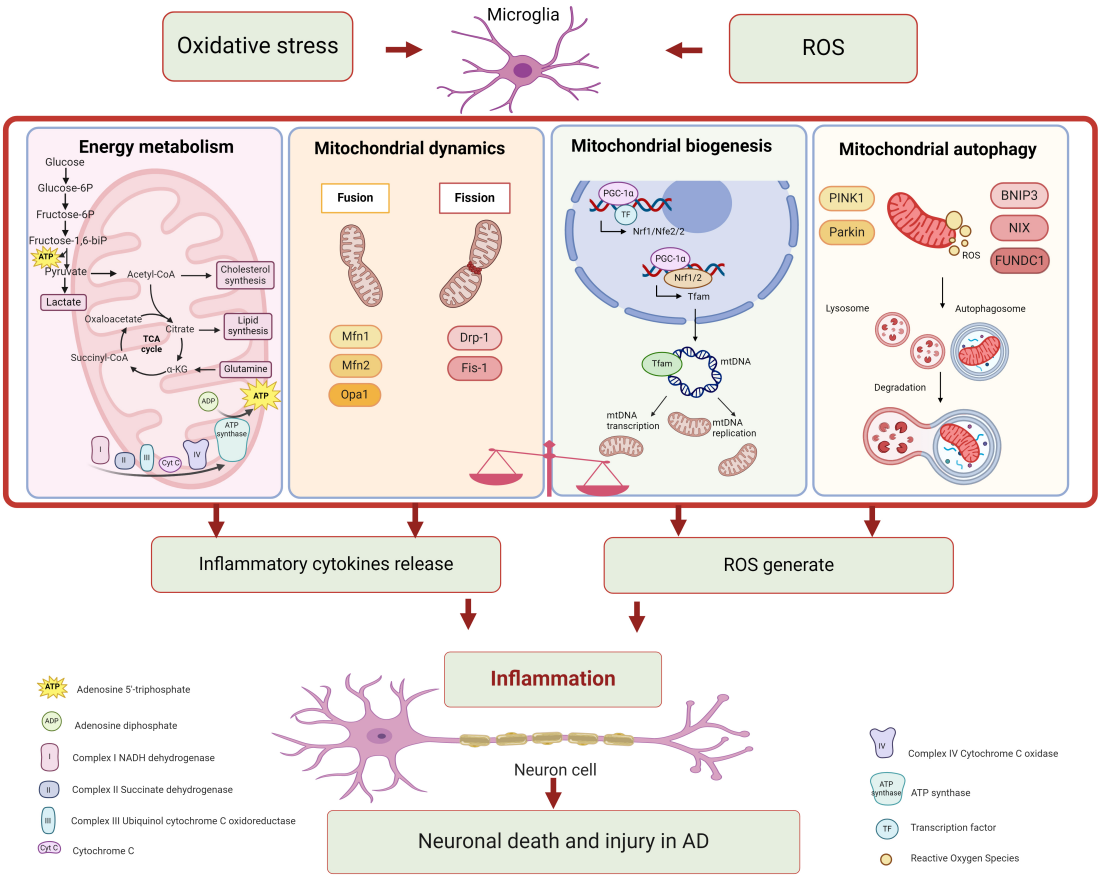

Fig. 1. Mitochondrial dysfunction in microglia associated with Alzheimer's disease. Mitochondria perform multiple roles, including energy metabolism, mitochondrial dynamics, mitochondrial biogenesis, and mitochondrial autophagy. Each function participates in various signaling pathways. Microglia with mitochondrial dysfunction significantly contribute to neuroinflammation in Alzheimer's disease. Figure was made by biorender (https://www.biorender.com/). ROS, reactive oxygen species; ATP, denosine triphosphate; Acetyl-CoA, acetyl coenzyme A; TCA, tricarboxylic acid cycle; α-KG, α-ketoglutarate; CytC, Cytochrome C; ADP, Adenosine diphosphate; Mfn1, mitofusin-1; Mfn2, mitofusin-2; Opa1, Optic atrophy 1; Drp-1, dynamin related protein 1; Fis-1, mitochondrial fission 1 protein; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; TF, Transcription factor; Nrf1/2, Nuclear respiratory factor 1/2; Nfe, nuclear factor ets-like; TFAM, mitochondrial transcription factor A; mtDNA, mitochondrial DNA; PINK, PTEN-induced kinase 1; PTEN, Phosphatase and tensin homolog; BNIP3, BCL2/adenovirus E1B interacting protein 3; BCL2, B-cell lymphoma 2; FUNDC1, FUN14 domain containing 1; AD, Alzheimer's disease; NADH, Nicotinamide adenine dinucleotide; NIX, NIP3-like protein X.

found to be significantly reduced in the AD model, which correlates with the pathology of AD [83]. Dysfunction in the energy metabolism of mitochondria and metabolic reprogramming in microglia have a strong association with AD [84].

Mitochondria are active organelles that exist dynamically in networks. They are constantly brought together and then separated by a process of fusion and fission. A previous study has revealed elevated expression of the mitochondrial fission genes mitochondrial fission 1 protein (Fis1) and dynamin related protein 1 (Drp1), alongside decreased expression of mitochondrial fusion genes Translocase of outer mitochondrial membrane 40 (Tomm40), Optic atrophy 1 (Opa1), mitofusin-1 (Mfn1) and mitofusin-2 (Mfn2) [85]. Research indicates that an imbalance in mitochondrial fusion and fission significantly contributes to microglia-mediated neuroinflammation in AD [84].

Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), is a controller of the generation of mitochondria. The activation of PGC-1α (either through phosphorylation or deacetylation) initiates this pathway, cascading into the stimulation of a set of important transcription factors located in the nucleus, specifically the nuclear respiratory factors Nuclear respiratory factor-1 (NRF-1), Nuclear respiratory factor-2 (NRF-2), along with estrogen-associated receptor-α. This leads to augmented expression of mitochondrial transcription factor A (TFAM), responsible for both the transcription and replication of mtDNA [86]. Investigation has revealed that the levels of TFAM protein in the hippocampus of individuals with AD

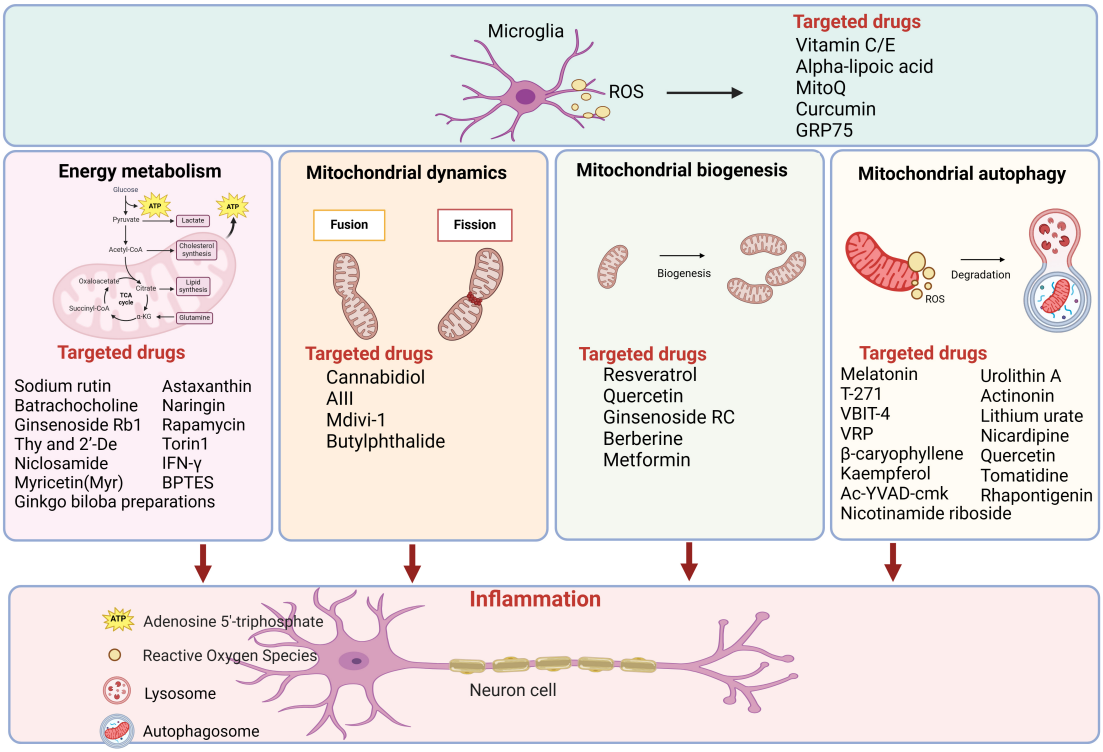

Fig. 2. Drugs categorized by mitochondrial energy metabolism, mitochondrial biogenesis and mitochondrial autophagy for AD therapy. More than 40 candidate molecules were showed in the figure, which have demonstrated promising results in preclinical AD models. Figure was made by biorender (https://www.biorender.com/). ROS, reactive oxygen species; GRP75, glucose-regulated protein 75; ATP, denosine triphosphate; acetyl-CoA, acetyl coenzyme A; IFN-γ, Interferon-γ; BPTES, bis-2-(5-phenylacetamido-1, 3, 4-thiadiazol-2-yl) ethyl sulfide; AD, Alzheimer's disease; mitoQ, mitoquinone; VBIT, voltage-dependent anion channel oligomerization inhibitor; VRP, virus-like replicon particle; Ac-YVAD-cmk, acetyl-tyrosyl-valyl-alanyl-aspartyl-chloromethylketone.

are diminished by half, with a concurrent decrease in the levels of NRF-1, NRF-2 and PGC-1α. These findings indicate a disruption in mitochondrial biosynthesis within the AD's brain [87].

The signaling pathway that regulates mitophagy is the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1)/Parkin axis. In depolarized and damaged mitochondria, PINK1 accumulates on the outer membrane of the mitochondria and enlists the E3-ubiquitin ligase Parkin [88,89]. Parkin contributes to the removal of damaged mitochondria by ubiquitinating proteins in the outer mitochondrial membrane, which include Mfn1, Mfn2, and voltage-dependent anion channel 1 (VDAC1) [82]. Investigation has observed that levels of PINK1, microtubule-associated proteins light chain 3 (LC3), and Lon protease 1 (LONP1) were up-regulated in animal models and the brains of AD patients. Emerging evidence suggests that mitochondrial autophagy, or mitophagy, takes part in the inflammatory responses and phagocytic activities of microglia [80,90].

4. Future Perspectives

In neurodegenerative diseases, mitochondrial dysfunction often precedes the accumulation of toxic proteins, establishing a vicious cycle of deteriorating cellular conditions. Consequently, mitochondria have become prime targets for the development of novel therapeutics in neurodegenerative diseases.

Here, a summary of literature from the past five years is complied into Table 2 (Ref. [91–125]) and Fig. 2, more than 40 candidate molecules were categorized by different drug targets. It shows the treatment of AD by drugs is targeting mitochondrial energy metabolism, mitochondrial homeostasis, mitochondrial biogenesis and mitochondrial autophagy. Encouragingly, some drugs have already entered clinical trials. Rapamycin, targeting mitochondrial energy metabolism, was in phase 2 clinical trials. And metformin, a small molecule targeting mitochondrial biosynthesis, was in phase 3 clinical trials. Perhaps in the near future, these candidate molecules are expected to become effective drugs for the treatment of AD.

Recent studies have demonstrated promising results in preclinical AD models. Some of these drugs have also been used in healthy or AD patients at various stages of clinical trials. However, there are many challenges between preclinical success and clinical application. Initially, it must be determined whether drugs are safe and whether they cause serious adverse reactions. Subsequently, do all drug candidates cross the blood-brain barrier? If not, can nanotechnol-

Table 2. Pharmacological agents targeting pathways that regulate mitochondrial dysfunction in microglia.

Targets	Drugs	Mechanisms	References
	Vitamin E, Vitamin C, Alpha-lipoic acid, MitoQ, Curcumin, Astaxanthin, Ginkgo biloba preparations	Reduce superoxide radicals and scavenge hydrogen peroxide	[91–94]
Energy metab-olism	Sodium rutin	Enhances the level of mitochondrial oxidative phosphorylation	[95]
	Batrachocholine	Improves mitochondrial ATP metabolism and modifying antioxidant proteins	[96]
	Ginsenoside Rb1	Inhibition of mitochondrial complex I activity	[97,98]
	Interferon-γ (IFN-γ)	Boosts glycolytic metabolism	[99]
	Thy and 2'-De	Increase ATP production and inhibited glycolysis	[100]
	Naringin	Reduces oxidative damage	[101]
	Rapamycin, Torin1 and Niclosamide	Downregulation of the mTORC1 pathway	[102]
	Myricetin (Myr)	Inhibits P38 MAPK pathway activation	[103]
	BPTES	Glutaminase inhibitor	[104]
	Mesenchymal stem/stromal cells (MSCs)	Secret neuroprotective and anti-inflammatory factors to promote the survival of neurons and transfer functional mitochondria and miRNAs to boost their bioenergetic profile as well as improve microglial clearance of accumulated protein aggregates	[105]
	GRP75	Improves mitochondrial function and decrease oxidative stress	[106]
Mitochondrial dynamics	Mdivi-1	Repairs mitochondrial breakage and distribution defects	[107]
	Butylphthalide	Balances the mitochondrial dynamics	[108]
	AIII	An inhibitor of JAK2	[109]
	Cannabidiol	Increases the expression of Mfn2	[110]
Mitochondrial biogenesis	Resveratrol	Sirtuin proteins activator	[111]
	Quercetin	Promotes PGC-1α to regulate mitochondrial homeostasis	[112]
	Ginsenoside RC	Activates the SIRT1-pgC1α pathway	[113]
	Berberine	AMPK activator	[114]
	Metformin	Enhances the transcriptional activity of mitochondrial biogenesis factor Nrf-2 and thus upregulating the expression of peroxidase GPx7	[115]
Mitochondrial autophagy	Melatonin	Improves mitochondrial-lysosomal fusion	[116]
	β-caryophyllene	Increases the expression of PINK1, Parkin and Beclin-1	[117]
	Lithium urate, Tomatidine, Rhapontigenin, Urolithin A, Actinonin, Nicotinamide riboside, T-271	Mitophagy enhancers	[118–120]
	Ac-YVAD-cmk	Caspase-1 inhibitor	[121]
	VBIT-4	VDAC1 inhibitor	[122]
	VRP, Nicardipine	Ca^{2+} blockage, and regulation of Ca^{2+}-dependent genes	[123,124]
	Quercetin	Inhibition of mtROS-mediated NLRP3 inflammasome activation in microglia through promoting mitophagy	[125]

ATP, denosine triphosphate; mitoQ, mitoquinone; mTORC1, mammalian target of rapamycin complex 1; MAPK, mitogen-activated protein kinase; BPTES, bis-2-(5-phenylacetamido-1, 3, 4-thiadiazol-2-yl) ethyl sulfide; GRP75, glucose-regulated protein 75; Mdivi-1, Mitochondrial division inhibitor-1; JAK2, Janus kinase-2; Mfn2, mitofusin 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; SIRT1-pgC1α, silent information regulator factor 2-related enzyme 1- peroxisome proliferator-activated receptor gamma coactivator 1; AMPK, AMP-activated protein kinase; Nrf-2, Nuclear respiratory factor 2; GPx7, Glutathione peroxidase 7; PINK1, PTEN induced putative kinase 1; VDAC1, voltage-dependent anion channel 1; mtROS, mitochondrial reactive oxygen species; NOD, nucleotide-binding oligomerization domain; LRR, leucine-rich repeat; NLRP3, (NOD-, LRR- and pyrin domain-containing 3); miRNAs, micro-ribonucleic acids.

ogy be employed as a vehicle to help the drug translocate? Further, can these drugs target the mitochondria that reach microglia and are there an off-target effects? Is a guide-RNA required for localization? Can the bioavailability of these drugs following entry through the blood-brain barrier reach an effective concentration? Finally, do these drugs have an effect on nerve cells other than microglia? These issues still need to be addressed. Further study of the mechanisms of microglia mitochondrial dysfunction in AD is required to provide ideas and directions for such clinical research.

5. Conclusion

In this article, the role of mitochondrial dysfunction in microglia in AD is reviewed and the preclinical drugs targeting mitochondria for AD in the past five years are summarized. It is proposed that mitochondria may be a potential target for AD treatment and the preclinical drugs targeting mitochondria for AD in the past five years are summarized. However, there is still a long path from preclinical research to clinical application and further research on mechanisms of mitochondrial dysfunction in microglia are needed.

Author Contributions

XZ, and FZ and YX formulated the original idea and modified the manuscript. YL and TL organized documents, wrote the manuscript and designed and draw the figures and tables. CL, TC and WY prepared the tables and figures and helped with paper revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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