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Review

Research Progress of the AMPK/PINK1/Parkin Pathway in Alzheimer's Disease Mechanism and Therapeutic Potential

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by β-amyloid (Aβ) plaque deposition, tau pathology, and mitochondrial dysfunction. Recent studies have found that the AMP-activated protein kinase (AMPK)/PTEN-induced kinase 1 (PINK1)/Parkin pathway plays a key role in the pathogenesis of AD by regulating energy metabolism, mitophagy, and neuroinflammation. As a core regulator of energy metabolism, AMPK enhances the efficiency of mitochondrial autophagy by phosphorylating PINK1, while inhibiting β-site amyloid precursor protein cleaving enzyme (BACE1) and reducing Aβ production. The PINK1/Parkin pathway selectively clears damaged mitochondria and alleviates oxidative stress and neuronal damage. This article systematically reviews the molecular mechanism of the AMPK/PINK1/Parkin pathway and its multi-target regulatory role in AD, and discusses the therapeutic strategies based on this pathway, to provide new directions for AD drug development.

Keywords: Alzheimer's disease; AMPK; PINK1; Parkin; mitophagy; tau protein; β-amyloid

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia worldwide, with clinical manifestations such as memory loss and cognitive dysfunction [1] and pathological features such as deposition of β-amyloid plaques (Aβ), formation of neurofibrillary tangles (NFTs) resulting from abnormal phosphorylation of tau protein, and mitochondrial dysfunction [2]. NFTs are considered histopathological markers of several neurodegenerative diseases, including AD [3]. Based on Eugen Macovschi's theory of biological structure, the pathogenesis of AD is related to cell senescence and brain atrophy due to the reduction of biological structures [4]. Although the pathological mechanisms of AD have not been fully elucidated, the accumulation of damaged mitochondria resulting from mitochondrial autophagy deficiency disorder is considered an important drivers of disease progression. Mitochondria are the energy centers of the double-layer membrane structure, which play an important role in the regulation of cell metabolism, bioenergetics, proliferation, and death. Their integrity is affected by various external and internal stimuli, such as oxidative stress, exposure to harmful substances, and aging [5]. Mitochondrial dysfunction leads to reduced production capacity and the release of reactive oxygen species (ROS), which in turn leads to inflammatory damage to neurons [6]. Mitophagy maintains cellular energy homeostasis and reduces ROS production by selectively removing dysfunctional mitochondria. The AMPK/PINK1/Parkin pathway integrates energy metabolism regulation and mitochondrial quality control and has gained importance for AD treatment. This article focuses on the molecular mechanisms, pathological effects, and therapeutic potential of this pathway, aiming to provide a theoretical basis for targeted intervention strategies.

2. Molecular Mechanisms of AMPK/PINK1/Parkin

2.1 AMPK: The Core Regulator of Energy Metabolism

Adenosine monophosphate-activated protein kinase (AMPK) is a heterotrimeric complex composed of three subunits: α, β, and γ, and is the core regulator of cellular energy metabolism. The α subunit contains a catalytic domain and is responsible for kinase activity; the β subunit mainly plays a link-up role; the γ subunit contains multiple CBS domains and can bind AMP, ADP, and ATP. As a sensor of cellular energy, it is activated when cellular energy is insufficient (e.g., elevated AMP/ATP ratio) and promotes fission through phosphorylation of mitochondrial fission factor, thereby promoting the clearance of damaged mitochondria [7], alleviating ATP depletion in AD, promoting energy production (e.g., promoting lipolysis and glycolysis), and inhibiting energy-expending processes (e.g., inhibiting protein and fat synthesis). In addition, it increases the kinase activity of Unc-51-like autophagy activating kinase 1 (ULK1) and regulates mitophagy, which is a key protein in initiating autophagy, by phosphorylating multiple sites on ULK proteins in the ULK1 complex, such as Ser317 and Ser777 [8]. ULK1 further promotes PINK1/Parkin-dependent mitophagy.

2.2 Pink1/Parkin: Executor of Mitophagy

PINK1, a mitochondria-localized serine/threonine protein kinase, also known as Parkinson disease 6 (PARK6), contains a mitochondrial targeting sequence at its N-terminus; the middle section has a kinase structure with kinase activity; the C-terminus contains a conserved region whose function is not yet fully understood. PINK1 is located on the outer mitochondrial membrane and plays a role in protecting cells from mitochondrial stress, acting as a probe for mitochondrial damage. Usually, PINK1 enters the mitochondria through the outer mitochondrial membrane and is subsequently cleaved by mitochondrial proteases and degraded in the mitochondrial matrix. However, when the mitochondrial membrane potential is disturbed (because of mitochondrial damage), the transport and cleavage of PINK1 is blocked, resulting in its accumulation and Ub molecules phosphorylation on the outer mitochondrial membrane [9]. The Ub molecule can interact with the Really Interesting New Gene 1 (RING1) structure in Parkin to activate Parkin, acting as a receptor molecule for Parkin recruitment. It is transferred from the cytosol to the mitochondria. This promotes the ubiquitination of mitochondrial outer membrane proteins and the activation of the ubiquitin proteasome system. In addition, studies have shown that PINK1 can also directly recruit autophagosomes and initiate weaker mitophagy [10].

The *Parkin* gene, also known as Parkinson Disease 2, Autosomal Recessive Juvenile (PARK2), is located at 6q26 on chromosome 6 [11,12]. It comprises an N-terminal ubiquitin-like domain (UBL), a C-terminal RING1-IBR-RING2 domain, and a RING0 domain, and is part of the interring ring domain family of ubiquitin ligases [13]. The UBL domain can interact with other proteins to regulate the activity and localization of Parkin. The RING1-In Between Really Interesting New Gene fingers (IBR)-Really Interesting New Gene 2 (RING2) domain constitutes the E3 ubiquitin ligase activity center of Parkin and catalyzes the ubiquitination of substrate proteins. Following PINK1 activation, phosphorylated Parkin is selectively recruited to the surface of damaged mitochondria, where it attaches to substrate proteins in the outer mitochondrial membrane through its E3 ubiquitin ligase, forming ubiquitin chains that ubiquitinate outer mitochondrial membrane proteins [14]. These ubiquitinated substrate proteins recruit autophagy-related proteins (e.g., P26, Nuclear Dot Protein 52 kDa (NDP52)) to mediate mitochondrial coating by autophagosomes, which in turn initiates mitophagy and ultimately degrades damaged mitochondria.

2.3 Interaction Between AMPK and PINK1/Parkin

Beyond its role in mitochondrial fission and ULK1 activation, AMPK critically intersects with the PINK1/Parkin pathway to orchestrate mitochondrial quality control and cell survival. AMPK directly phosphorylates PINK1 serine residues, stabilizing the kinase and enhancing its activity to initiate Parkin-mediated mitophagy [9]. This AMPK-PINK1 axis facilitates an "energy stress-induced mitochondrial repair" mechanism for targeted removal of damaged organelles. Under energy deprivation, AMPK and PINK1/Parkin function synergistically to eliminate dysfunctional mitochondria, thereby preserving cellular energy homeostasis.

As can be seen in Fig. 1, AMPK further amplifies PINK1/Parkin signaling indirectly through mammalian Target Of Rapamycin Complex 1 (mTORC1) inhibition [15]. By phosphorylating Tuberous Sclerosis Complex 2 (TSC2) and activating the Tuberous Sclerosis Complex 1 (TSC1)/TSC2 complex, AMPK suppresses mTORC1 activity. This relieves mTORC1-mediated repression of autophagy initiation and concurrently activates the transcription factor Transcription Factor EB (TFEB). Nuclear TFEB upregulates autophagy- and lysosome-related genes, enhancing cellular clearance capacity. Critically, targeted activation of the AMPK-PINK1 node addresses the dual AD pathologies of bioenergetic failure and impaired mitochondrial clearance, offering a potentially safer alternative to multi-target therapeutics.

3. Role of the AMPK/PINK1/PARKIN Pathway in AD

In the brains of patients with AD, mitochondrial dysfunction leads to the accumulation of damaged mitochondria, which cannot produce energy normally and also release large amounts of ROS, further exacerbating oxidative stress and neuronal damage. Fig. 2 shows the relationship between AMPK/PINK1/Parkin pathway and AD pathology. Activation of the AMPK/PINK1/Parkin pathway can promote mitophagy, remove damaged mitochondria in time, reduce ROS production, and thus protect neurons from oxidative stress damage. In mouse models of AD, activation of the AMPK/PINK1/Parkin pathway could significantly increase the level of mitophagy, improve mitochondrial function, and alleviate cognitive impairment.

3.1 Regulation of $A\beta$ Metabolism and Tau Pathology

AMPK mainly regulates $A\beta$ metabolism through two mechanisms One of them is to inhibit β-site amyloid precursor protein cleaving enzyme (BACE1) activity and reduce $A\beta$ production after activation [16]. In AD cell models (e.g., $A\beta$-treated neurons) and Amyloid Precursor Protein/Presenilin 1 (*APP/PS1*) transgenic mice, a significant correlation was noted between the decrease of AMPK activity and the up-regulation of BACE1 and the increase of $A\beta$ production. The second mechanism of AMPK regulating $A\beta$ metabolism is to enhance autophagy and promote the clearance of $A\beta$, offering a dual protection of "reduced production + enhanced clearance". The PINK1/Parkin pathway mitigates $A\beta$ toxicity and neuronal damage by clearing mitochondria damaged by $A\beta$ accumulation.

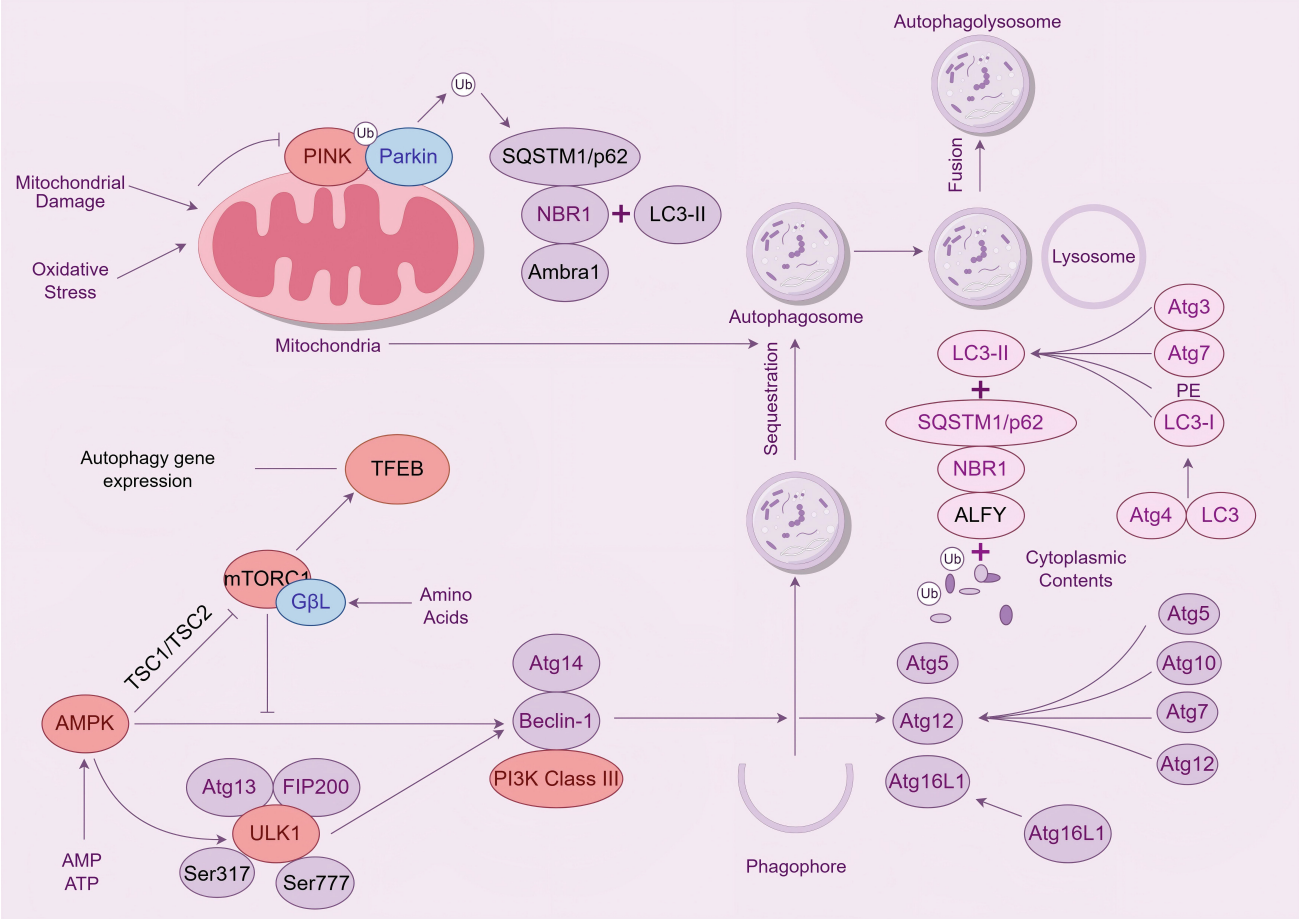

Fig. 1. AMPK/PINK1/Parkin signaling pathway. Legend: The diagram shows the regulation of mitophagy. When mitochondria are damaged by oxidative stress, PINK1 and Parkin are activated, initiating the process of mitophagy. Simultaneously, the mTORC1 signaling pathway can sense nutrient signals such as amino acids and inhibit the expression of autophagic genes. The AMPK signaling pathway, on the other hand, is activated when energy is insufficient, promoting the formation of autophagy-related protein complexes. Autophagy-related proteins, such as members of the Atg family, play an important role in the formation of autophagosomes, and LC3 is processed to form LC3-II, which binds to proteins such as SQSTM1/p62 and participates in the encapsulation of mitochondria and other substances by autophagosomes. Autophagosomes fuse with lysosomes to form autophagolysosomes, which degrade mitochondria. AMPK, AMP-activated protein kinas; PINK1, PTEN-induced kinase 1; LC3, Microtubule - associated protein 1 light chain 3; SQSTM1, Sequestosome 1; TFEB, Transcription Factor EB; ALFY, Autophagy-linked FYVE protein; NBR1, NBR1 autophagy cargo receptor; TSC1, TSC complex subunit 1; ULK1, unc-51 like autophagy activating kinase 1.

AMPK reduces tau hyperphosphorylation by inhibiting Glycogen Synthase Kinase-3β (GSK-3β) and activating Protein Phosphatase 2A (PP2A), inhibits the formation of NFTs, activates the autophagic pathway, promotes aberrant tau degradation, and reduces tau aggregation [17]. PINK1/Parkin pathway defect exacerbates tau protein-mediated mitochondrial dysfunction, promotes autophagy, and attenuates the toxicity of tau protein arising from aberrant phosphorylation.

3.2 Alleviation of Neuroinflammation and Oxidative Stress

AMPK inhibits the interference of the Nuclear Factor kappa-light-chain-enhancer of Activated B cells (NF-κB) signaling pathway [18], reduces the expression and release of inflammatory factors, such as tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β), and alleviates neuroinflammation. Experiments have shown that 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) (an AMPK agonist) reduces the levels of the inflammatory cytokine IL-1β and inhibits the transfer of NF-κB p65 in activated macrophages induced by Complete Freund's Adjuvant (CFA) [19]. Inhibition of the NF-κB pathway in microglia can mitigate tau-mediated learning and memory deficits and increase the levels of neuronal tau inclusion bodies, while promoting microglial polarization toward the anti-inflammatory M2 phenotype and alleviating neuroinflammation [20]. Recent studies have found that AMPK activation can also improve the glycolytic capacity of astrocytes, restore lactate supply, and maintain neuronal energy metabolism [21]. PINK1/Parkin reduces the inflammatory

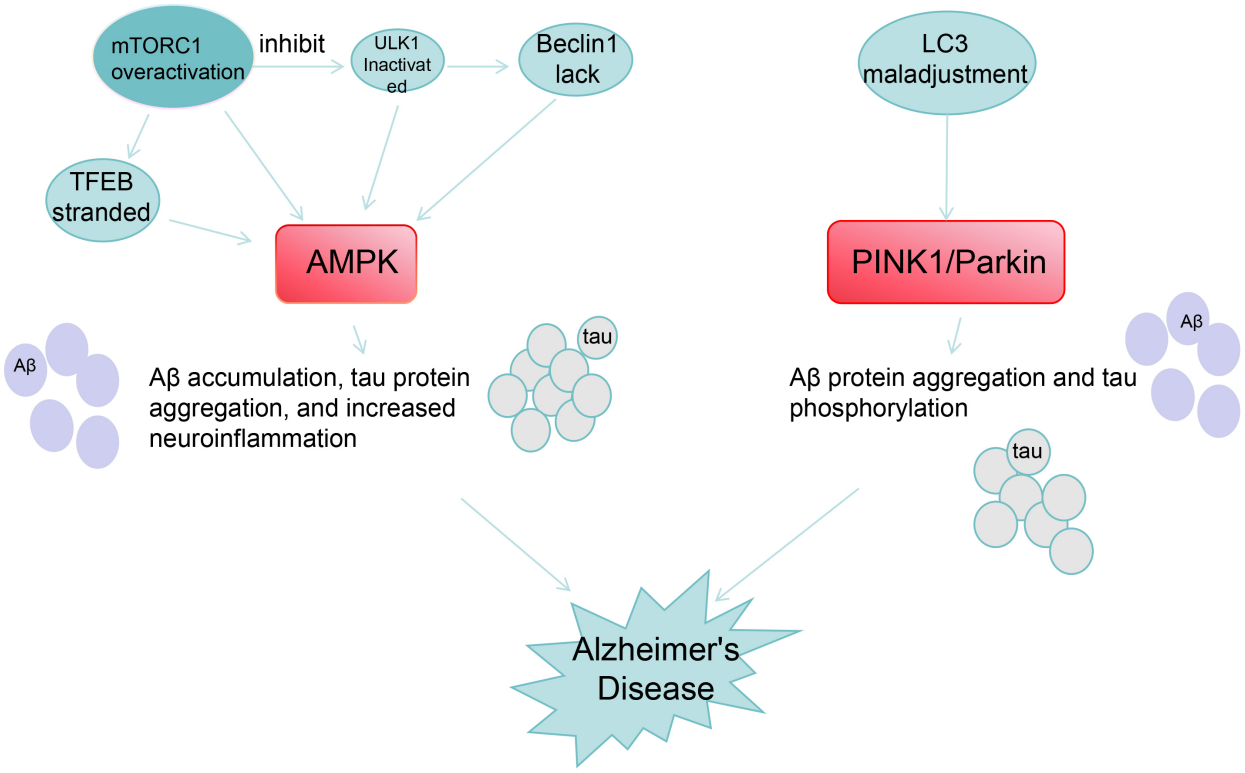

Fig. 2. Relationship between AMPK/PINK1/Parkin and AD pathological processes. Legend: This diagram shows the molecular mechanisms of two pathways associated with the pathogenesis of AD: AMPK pathway: Overactivation of mTORC1 inhibits ULK, leading to Beclin1 deficiency and TFEB retention, acting on AMPK to triggers Aβ accumulation, tau protein aggregation, and increased neuroinflammation, thereby promoting the development of AD. PINK1/Parkin pathway: LC3 dysregulation affects PINK1/Parkin, triggers Aβ protein aggregation and tau protein phosphorylation, and promotes the development of AD. AD, Alzheimer's disease; Aβ, β-amyloid.

response resulting from mitochondrial damage by removing damaged mitochondria. In addition, AMPK activates PPARγ coactivator 1α (PGC-1α) and promotes mitochondrial biosynthesis and antioxidant enzyme expression [22]. By regulating the balance of mitochondrial division/fusion proteins (e.g., Mitofusin 1 (MFN1) and Dynamin-Related Protein 1 (DRP1)), Aβ-induced mitochondrial fragmentation and calcium overload are reduced, thereby protecting neurons from oxidative damage [23].

4. Potential Treatment Strategies

Since the occurrence of neurological diseases such as AD is closely related to mitophagy dysfunction, the regulation of mitophagy may have a beneficial effect on the treatment of such diseases. Fig. 3 below is a timeline of studies on the treatment of AD through the AMPK/PINK1/Parkin pathway, which can be traced back to as early as 2004.

4.1 Pharmacological Interventions

AMPK can simultaneously regulate Aβ production, tau pathology, mitochondrial function, and energy metabolism, potentially acting as "one drug target with multiple effects" [16]. Metformin (MET) is a common oral antidiabetic medication that can lower blood sugar through several mechanisms. Among the glycemic-lowering mechanisms regulated by MET, the regulatory mechanism centered on AMPK plays an important role not only in diabetes mellitus but also in AD [24]. Lu *et al.* [25] demonstrated that MET activates insulin-degrading enzyme (IDE) to ameliorate Aβ-induced pathology in *APP/PS1* mice. MET treatment enhanced the autophagy pathway and reduced the levels of oxidative stress (malondialdehyde and superoxide dismutase) and neuroinflammation (IL-1β and Interleukin-6 (IL-6)) markers. Furthermore, MET significantly lowered brain Aβ levels, promoted Aβ elimination, and reduced Aβ deposition. Mechanistically, MET did not affect the enzyme activity or *mRNA* expression levels of Aβ-generating secretases (ADAM metallopeptidase domain 10 (ADAM10), BACE1, and PS1) and Aβ-related transporters (Low-Density Lipoprotein Receptor-Related Protein 1 (LRP1) and Receptor for Advanced Glycation End products (RAGE)). However, it significantly increased the protein levels of phosphorylated AMPK and IDE in the brain. The activation of the AMPK pathway represents a potential mechanism underlying MET's beneficial effects in this AD model. MET has also been shown to in-

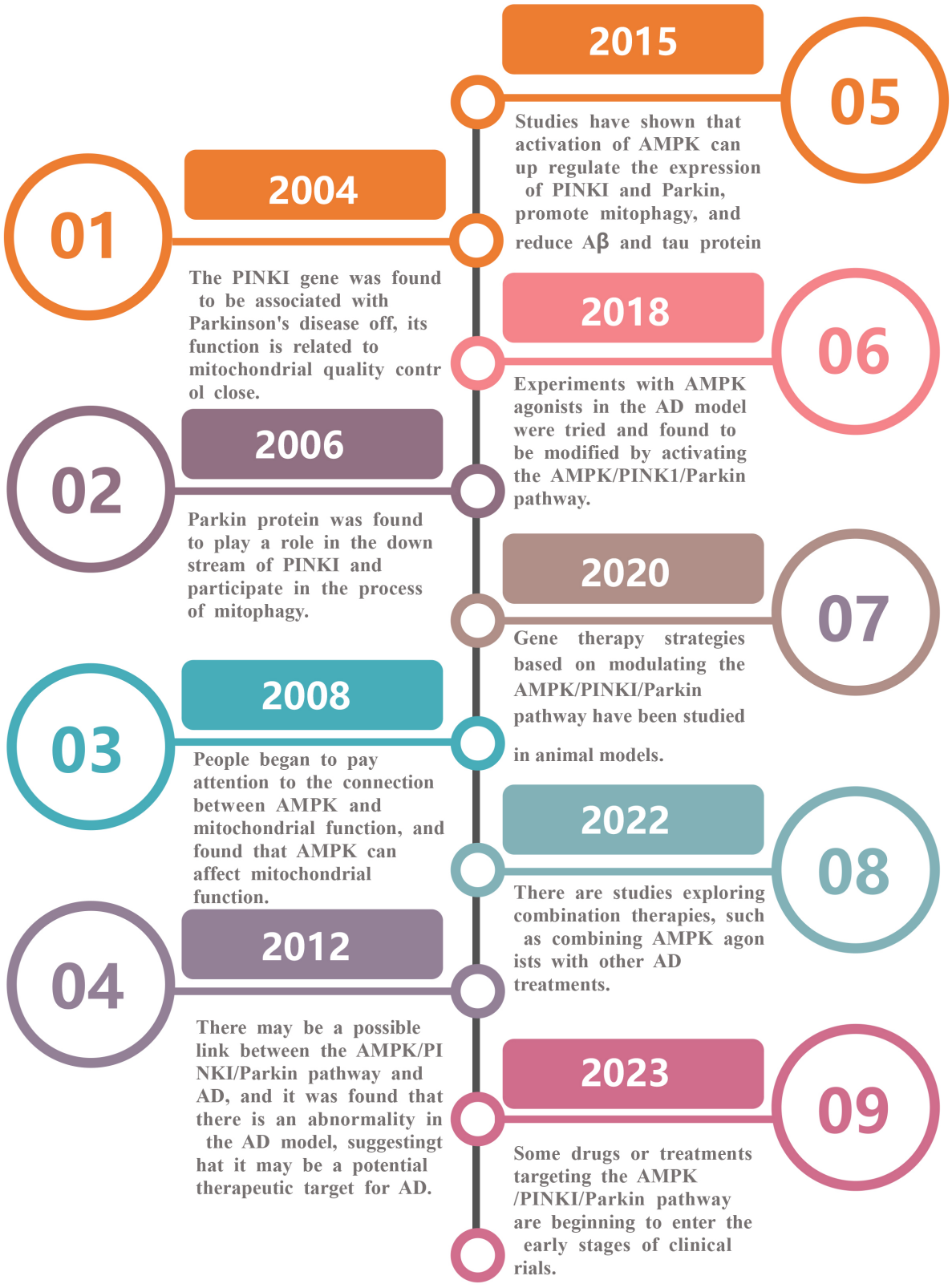

Fig. 3. Timeline of studies on the role of AMPK/PINK1/Parkin pathway for the treatment of AD. Legend: This is a timeline of the progress of research on the AMPK/PINK1/Parkin pathway, from the discovery of the role of *PINK1* gene in Parkinson's disease (2004) to the elucidation of the role of various proteins in the pathway, exploring the connection with mitochondria and AD, conducting animal model studies, and attempting combination therapy, until the progress of drugs or therapies to the early stage of clinical trials can be achieved (2023).

Table 1. Metformin, AICAR, MTK-458 clinical study phase, treatment window and safety analysis.

Drugs	Clinical research phase	Treatment window	Safety analysis	References
Metformin	Phase II/III	In the prenatal period or the stage of mild cognitive impairment (aMCI).	Common gastrointestinal reactions (diarrhea, nausea in 10% of patients).	Luchsinger *et al*. [34]
			Very rare lactic acidosis.	Tahmi and Luchsinger [35]
			Rare vitamin B_{12} deficiency.	
AICAR	Preclinical stage	No human data: early intervention may theoretically be effective.	No human safety data; Overactivation of AMPK can be detrimental (e.g., neuronal damage).	Hu *et al*. [18]
MTK-458	Preclinical stage	No human data.	No human safety data; To be evaluated before a clinical trial.	Hertz *et al*. [33]

AMPK, Adenosine monophosphate-activated protein kinase; AICAR, 5-Aminoimidazole-4-carboxamide ribonucleotide.

crease the transcriptional levels of AMPK's target B-cell lymphoma 2 (Bcl-2) and cAMP response element-binding protein (CREB) thereby enhancing AMPK expression [26]. AMPK also mediates neuroprotection through signaling pathways involving γ coactivator-1 α (PGC1α), nitrogen response factor 1 (NRF-1), and transcription factor A mitochondria (Tfam). MET can rescue the expression levels of PGC1α, NRF1, and *Tfam* genes in human neural stem cells, thereby regulating the role of AMPK in neuroprotection and improving AD. Phase III clinical trials have shown that MET can reduce the level of Aβ42 in the cerebrospinal fluid of patients with AD. However, the metabolic side effects of long-term use of MET should be carefully assessed.

Cell experiments have shown that the AMPK agonist AICAR can increase the expression of *pAMPK* and *pULK1* in *APP* transgenic cell line 20E2, regulate the expression of division- and fusion-related proteins, and improve mitophagy and mitochondrial dynamics abnormalities resulting from APP gene transfection [27]. Although specific AMPK agonists are yet to be developed, the use of AMPK activators to promote mitophagy and ameliorate AD may be a feasible treatment option in the future.

Aβ and tau oligomers are reported to activate indoleamine-2,3-dioxygenase 1 (IDO1) in astrocytes [28]. In astrocytes overproduction of kynurenine resulting from IDO1 activation inhibits glycolysis, which is essential for providing energy to neurons. Minhas *et al*. [21] found that inhibition of kynurenine production by blocking IDO1 restored glycolysis and lactate production in astrocytes. Therefore, IDO1 inhibitors (such as Epacadostat), which were originally used in cancer treatment, can also be used to improve cognitive function and have entered phase I clinical trials.

4.2 Pink1/Parkin Enhancers

PINK1/Parkin enhancers mainly include natural compounds (e.g., urolithin A [29]) and small molecule compounds (e.g., trehalose), which can improve mitophagy and alleviate pathological features of neurodegenerative diseases by activating the PINK1/Parkin pathway. For example, MTK-458 can directly stimulate PINK1 and accelerate mitochondrial degradation and has entered phase I clinical trials. Kinetin (a molecule known to modulate splicing) [30] acts as a kinase modulator that activates Cdc2-like kinase 1 (CLK1). This activation phosphorylates arginine-serine-rich domains within splicing factors, leading to enhanced Parkin activity and subsequently enabling efficient recognition of damaged mitochondria. Some protein kinases such as casein kinase 2 (CK2), which can phosphorylate PINK1 and regulate its stability and activity, also regulate this pathway. The cytokinin kinetin N^6-furfuryladenine, an adenosine-derived plant hormone, enhances PINK1 autoactivation, promotes Parkin recruitment to depolarized mitochondria, and blocks mitochondrial motility in axons [31]. Experimental studies have found that rapamycin, an mTOR inhibitor, can also activate mitophagy, enhance the downstream PINK1/Parkin pathway, reduce neuronal loss, and improve cognitive impairment [15].

4.3 Gene and Cell Therapy

Overexpression of the gene encoding *α-synuclein* is the cause of AD inheritance. A study by Shiba-Fukushima *et al*. [32] showed that when the Tyrosine Hydroxylase-Gal4 (*TH-Gal4*) transgene drives α-synuclein and *PINK1* gene expression, overexpression of the *PINK1* gene in both genes can prolong lifespan. Therefore, overexpression of PINK1 and Parkin through gene editing or viral vectors is a strategy to improve AD treatment. Induced Pluripotent Stem Cell (IPSC) technology can also be used to verify the efficacy and mechanism of drugs with patient-derived neurons; Regulation of circadian clock genes (e.g., *BMAL1*) enhances nighttime activation of the AMPK/PINK1 pathway and promotes Aβ clearance. Gene editing techniques, such as Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR associated protein 9 (*CRISPR-Cas9*), can be used to edit the *PINK1/Parkin* gene to correct possible gene defects or enhance its expression to restore mitophagy. At present, most of these strategies are in the basic research stage.

Through the comparison of the three drugs in Table 1 [18,33–35], we can see that metformin, in AD-related trials, has mainly targeted patients with mild cognitive impairment (prodromal stage), and its phase II pilot study showed a positive effect on memory; the latest MAP trial is an adaptive design phase II/III study. AICAR is currently only an experimental AMPK activator, with no trials conducted so far on humans with AD; MTK-458, a PINK1 activator, is still in preclinical research for treatment of neurodegenerative diseases. The above content is mainly based on public clinical trial registrations and research reports, and no reports indicate that AICAR or MTK-458 have undergone human trials targeting AD.

4.4 Combination Therapy

A combination of AMPK activators (e.g., AICAR) and PINK1/Parkin activators (e.g., MTK-458 [33]) have been investigated in animal and cell model experiments. AICAR can increase the intracellular AMP/ATP ratio, activate AMPK, and promote energy metabolism and autophagy initiation. MTK-458 can directly stimulate PINK1 and accelerate mitochondrial degradation. The combination of the two can improve the overall energy status of cells on the one hand, enhance mitophagy on the other hand, and effectively remove the accumulation of misfolded proteins and damaged mitochondria in the AD model, reduce neurotoxicity, and improve neuronal function. Gene therapy can also be used in combination with drugs to overexpress the PINK1 or Parkin genes and generate AMPK activators. The combination of the two can reduce the formation of Aβ and improve synaptic function and cognitive behavior. Some nutritional supplements, such as antioxidants (coenzyme Q10, vitamin E, etc.) and mitochondrial biosynthesis promoters (resveratrol [36], etc.), can also be used in the treatment of AD and can comprehensively improve mitochondrial function.

4.5 Clinical Translational Challenges

The AMPK/PINK1/Parkin pathway is intertwined with multiple other signaling pathways to form a complex regulatory network. Therefore, strategies to avoid affecting other normal physiological functions while leveraging the regulation of this pathway in AD treatment are necessary. Overactivation of AMPK may interfere with pathways such as mTOR and inhibit synaptic protein synthesis. Moreover, most AMPK activators (e.g., AICAR) have poor blood-brain barrier penetration. Excessive inhibition of BACE1 can affect physiological processes such as myelination. The therapeutic effect in AD is phase-dependent, with early targeting of the AMPK-PINK1 axis preventing mitochondrial injury. However, mitochondrial damage may be irreversible at later stages and requires Aβ clearance therapy [14]. Awareness of drug side effects is important to prevent higher levels of mitochondrial autophagy from promoting cancer growth [37].

5. Conclusions and Prospects

With the aging of the global population, maintaining g healthy life expectancy has gradually become important, especially in older adults with degenerative mental illnesses such as AD. The AMPK/PINK1/Parkin pathway plays an important neuroprotective role in AD by regulating mitophagy, energy metabolism, and neuroinflammation. Therefore, it has great potential for the treatment of neurodegenerative diseases. AMPK enhances PINK1/Parkin-mediated mitophagy by directly regulating PINK1 and activating ULK1, thereby alleviating Aβ deposition, tau protein pathology, and neuronal damage. Future studies should further elucidate the structure of the AMPK-PINK1 complex to guide allosteric drug design. Other areas for future research include developing a brain-targeted delivery system to improve drug center permeability, exploring the interaction and regulatory network of AMPK and PINK1/Parkin pathways in AD, and designing specific AMPK agonists or AMPK-PINK1 dual-targeted agonists. Developing individualized treatment (e.g., based on alkylphenol ethoxylates (APEO) genotype) based on patient classification and verifying the efficacy and safety of combination therapy in advanced models are avenues for further exploration.

Author Contributions

YJ and GL are responsible for the conception and design of articles, collection and collation of research materials, and drafting the manuscript. YJ and GL are responsible for the revision of the manuscript, quality control and review of the manuscript, and overall supervision and management. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both 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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