# 线粒体功能障碍在阿尔茨海默病发病中的作用和机制研究进展

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**摘要**: 阿尔茨海默病 (Alzheimer's disease, AD) 是一种复杂的神经退行性疾病, 病理机制尚未完全明了。近年来, 线粒体功能障碍被认为是AD的重要病理特征之一。作为细胞内能量代谢中枢, 线粒体在生理状态下通过三羧酸循环和氧化磷酸化维持三磷酸腺苷稳态, 并参与重要生理过程。然而在AD病理状态下, 线粒体功能发生显著改变, 表现为生物能量代谢失衡、线粒体自噬障碍、动力学异常 (包括过度分裂和融合缺陷) 以及线粒体活性氧过量产生等特征性改变。此外, 线粒体与内质网的异常相互作用破坏了细胞稳态, 进而通过加剧AD病理过程, 显著加速神经元退行性病变。本文系统综述了AD的核心病理特征, 重点解析线粒体生理功能及其在AD病理进程中的动态变化规律。最后, 本文总结了调控线粒体功能的抗AD治疗策略, 包括小分子药物、天然产物, 为AD的治疗提供了新的思路和可能的解决方案。

**关键词**: 阿尔茨海默病; 线粒体功能障碍; 线粒体融合; 线粒体分裂; 线粒体自噬; 氧化应激

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# Research progress on the role and mechanisms of mitochondrial dysfunction in the pathogenesis of Alzheimer's disease

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**Abstract**: Alzheimer's disease (AD) is a complex neurodegenerative disorder, and its pathological mechanisms are not yet fully understood. In recent years, mitochondrial dysfunction has been recognized as one of the important pathological features of AD. As the central hub of intracellular energy metabolism, mitochondria maintain ATP homeostasis through the tricarboxylic acid cycle and oxidative phosphorylation under physiological conditions, and they are involved in important physiological processes. However, under the pathological state of AD, mitochondrial function undergoes statistically significant changes, characterized by bioenergetic metabolism imbalance, impaired mitophagy, abnormal dynamics (including excessive fission and fusion defects), and excessive production of mitochondrial reactive oxygen species. Moreover, abnormal interactions between mitochondria and the endoplasmic reticulum disrupt cellular homeostasis, thereby significantly accelerating neuronal degeneration by exacerbating the pathological processes of AD. This article systematically reviews the core pathological features of AD, focusing on the physiological functions of mitochondria and their dynamic changes during the pathological progression of AD. Finally, this article summarizes the anti-AD therapeutic strategies that regulate mitochondrial function, including small molecule drugs and natural products, providing new ideas and potential solutions for the

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treatment of AD.

**Key words**: Alzheimer's disease; mitochondrial dysfunction; mitochondrial fusion; mitochondrial fission; mitophagy; oxidative stress

阿尔茨海默病 (Alzheimer's disease, AD) 是一种进行性神经退行性疾病, 也是最常见的痴呆症类型, 其特征在于逐渐加重的认知功能障碍和记忆丧失。大多数AD为散发型, 约占95%, 发病原因复杂; 少数为家族遗传型, 仅占5%, 相关基因有载脂蛋白E基因*ε*4等位基因 (apolipoprotein E gene *ε*4 allele, *APOE ε4*)、淀粉样前体蛋白 (amyloid precursor protein, *APP*)、早老素1 (presenilin 1 gene, *PSEN1*)、早老素2 (presenilin 2 gene, *PSEN2*)、补体成分Clq相关蛋白基因 (complement component Clq-related protein gene, *CLU*) 等, 尤其是*APOE ε4*等位基因, 会影响*β*-淀粉样蛋白 (amyloid-beta protein, A*β*) 的代谢和清除, 使携带者面临更高的发病风险[1,2]。《中国阿尔茨海默病报告2024》显示, 我国目前AD及其他痴呆患病人数高达1 699万例, 约占全球总数的30%, 患病率、死亡率均显著高于全球平均水平[3]。由于早期筛查不足、规范化诊疗率低, 且尚未出现能够逆转病程的有效药物, 我国AD防治工作正面临早期识别难、有效干预少、疾病负担重的三重挑战。进一步研究AD的发病机制, 研发新型药物至关重要。近年来的研究表明, 线粒体功能障碍在AD的发生发展中起着重要作用。下文作者具体综述AD中线粒体功能障碍的研究进展。

## 1 AD的病理机制

AD的发病机制涉及遗传因素、环境影响及个体的生活方式等多种交织的因素, 极为复杂且仍未完全明确[4]。

### 1.1 *β*-淀粉样蛋白的异常积累

A*β*是通过*β*-分泌酶 (*β*-secretase) 与*γ*-分泌酶 (*γ*-secretase) 复合物先后切割APP而产生的, 这一过程受到磷脂酰肌醇结合蛋白等分子调控[5,6]。作为AD的核心病理特征之一, A*β*在AD早期即通过多泡体途径在神经元内异常聚集, 引发突触结构改变, 这一病理现象早于经典淀粉样斑块的形成[7]。不同聚集形态的A*β*呈现阶梯式神经毒性: 可溶性A*β*寡聚体通过激活*N*-甲基-*D*-天冬氨酸受体 (*N*-methyl-*D*-aspartate receptor, NMDAR) 引起钙超载, 并诱导线粒体膜通透性转换孔开放, 直接导致神经元凋亡; 而纤维状A*β*则通过结合小胶质细胞表面的髓样细胞触发受体2 (triggering receptor expressed on myeloid cells 2, TREM2), 激活NLR家族含pyrin结构域蛋白3 (NLR family pyrin domain containing 3, NLRP3) 炎症小体, 驱动慢性神经炎症[8,9]。更具病理意义的是, A*β*通过激活糖原合成酶激酶-3*β* (glycogen synthase kinase-3 beta, GSK-3*β*) 等激酶促进微管相关蛋白Tau过度磷酸化, 同时抑制泛素化修饰依赖的蛋白酶体降解途径, 双重机制导致微管结合功能丧失的Tau蛋白异常聚集, 形成级联损伤轴, 引发神经元毒性、炎症反应、干扰蛋白清除系统及血管损伤, 共同构成神经退行性病变的病理基础[10,11]。

### 1.2 Tau蛋白的过度磷酸化

AD的另一重要病理特征是磷酸化Tau蛋白 (phosphorylated Tau protein, p-Tau) 错误折叠后在神经元内异常积累并逐渐聚集, 最终形成神经原纤维缠结 (neurofibrillary tangles, NFTs)[12,13]。这会进一步影响细胞运输和神经元信号传递, 并诱导微管解体破坏细胞骨架, 最终导致神经元死亡和认知衰退[14]。在过表达Tau的转基因AD小鼠海马体中, 三磷酸腺苷 (adenosine triphosphate, ATP) 水平下降约30%, 说明p-Tau引发线粒体能量代谢损伤[15,16]; 过度磷酸化的Tau还会干扰线粒体轴突运输, 使其无法向突触分布; p-Tau通过调控动力相关蛋白1 (dynamin-related protein 1, Drp1) 等线粒体分裂蛋白, 显著增加线粒体碎片化比例, 减少线粒体长度[17]。此外, p-Tau抑制核因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2) 介导的抗氧化系统的应答能力, 使活性氧(reactive oxygen species, ROS) 产生增加, 形成氧化损伤的正反馈环路[18]。蓝斑核区域的p-Tau可能导致L型钙通道过度激活, 引发线粒体钙超载和膜电位崩溃, 共同造成线粒体损伤[19]。研究人员利用JC-1荧光染料和钙绿荧光探针检测线粒体功能的同时, 发现在AD发病过程中线粒体功能障碍与p-Tau蛋白异常之间的关联。鉴于p-Tau病理在AD中的核心作用, 脑内p-Tau蛋白聚集的PET显像已被纳入AD主要诊断指南。

### 1.3 氧化应激

氧化应激在AD病理机制中发挥核心作用, 其本质是ROS和活性氮 (reactive nitrogen species, RNS) 的生成与抗氧化防御系统 (如超氧化物歧化酶、谷胱甘肽过氧化物酶) 之间的失衡[20,21]。在AD患者中, 金属离子蓄积、线粒体功能障碍及A*β*与p-Tau等病理蛋白的相互作用导致ROS过量产生, 超出抗氧化系统的清除能力, 引发神经元脂质过氧化、蛋白质和核酸损

伤[22,23]。这种氧化失衡通过调控APP的处理过程和分泌酶的活性, 不仅直接促进A$\beta$异常聚集形成淀粉样斑块, 还通过激活Tau蛋白过度磷酸化驱动NFTs的形成[24,25]。同时, 氧化应激还会降低线粒体膜电位, 触发自噬异常及钙离子超载, 进一步损害线粒体能量代谢功能, 导致ATP合成减少和电子传递链泄漏, 形成ROS恶性循环[26,27]。此外, 金属离子超载与*APOE ε4*等风险因子可协同放大线粒体损伤, 促进A$\beta$途径的发展, 并直接参与Tau蛋白的磷酸化和NFTs的形成[28,29]。

### 1.4 其他

神经炎症在AD发病机制中同样至关重要, 其与A$\beta$的异常沉积共同推动了Tau蛋白在脑内的扩散, 不仅引发神经元损伤, 还会进一步加剧疾病进展和认知功能衰退[30,31]。小胶质细胞和星形胶质细胞在A$\beta$斑块刺激下异常激活, 释放肿瘤坏死因子-$\alpha$ (tumor necrosis factor-alpha, TNF-$\alpha$)、白细胞介素-1$\beta$ (interleukin-1$\beta$, IL-1$\beta$) 等促炎因子, 这种炎症反应初期作为防御机制, 促进斑块清除, 但长期慢性炎症状态, 最终导致神经损伤[32,33]。

研究表明, AD患者的认知功能损伤与血脑屏障破坏、脑血流变化和脑微血管病变密切相关[34]。神经血管不仅为大脑提供氧气和营养物质, 还参与调节脑血流、维持血脑屏障的完整性, 并支持神经元的正常功能[35]。在AD病程中, 脑血流减少和血脑屏障破坏作为早期病理特征, 其发生与血管老化导致的慢性脑灌注不足密切相关。这一过程不仅直接引发神经元损伤并阻碍A$\beta$清除, 还会通过血脑屏障渗漏促使外周炎症因子入脑, 与中枢神经炎症产生协同效应, 进一步加剧认知功能损伤[36,37]。

近年来, 越来越多的证据表明, 线粒体作为能量代谢核心调控者, 与A$\beta$沉积、p-Tau及氧化应激形成恶性循环, 其动态失衡导致的ATP生成障碍、钙稳态失调及ROS增加, 正成为AD病理级联反应的关键推动力[38]。

## 2 线粒体动力学的生理意义

线粒体是由双层膜结构包裹的细胞器, 其外膜与内膜共同形成封闭的腔体, 为电子传递链提供了功能分区的基础[39]。线粒体外膜由两层紧密贴合的脂质膜组成, 表面呈现多边形的脊状突起结构, 与下方膜系统共同构成表膜, 这种特殊构型可能与其物质交换和机械支撑功能相关[40]。内膜的折叠形成许多嵴, 显著增加线粒体表面积, 为细胞能量代谢提供高效场所, 支持生理活动所需能量[41]。线粒体DNA (mitochondrial DNA, mtDNA), 编码13个蛋白质、22个转运RNA和2个核糖体RNA。mtDNA的完整性对线粒体功能至关重要, 损伤可能导致疾病。在健康细胞中, mtDNA通过修复、降解和线粒体分裂与融合等机制维持稳定性[42]。

线粒体作为细胞能量代谢的核心场所, 主要负责ATP的生物合成[43]。线粒体通过动力学调控机制, 即线粒体持续进行的融合和分裂过程, 不仅维持其自身的形态、功能和分布平衡, 还在细胞代谢调控和信号转导中发挥重要作用, 进而确保细胞正常生理功能的实现 (图1)[44]。

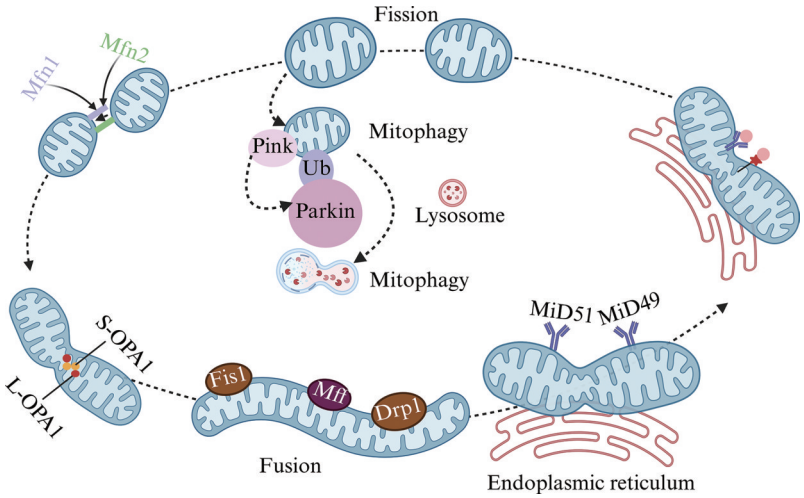



**Figure 1** Schematic illustration of the dynamics of mitochondria. Mitochondrial processes include fission, fusion, and division. The primary factors involved in mitochondrial fusion are OPA1, Mfn1, and Mfn2. These proteins bind to the inner and outer mitochondrial membranes (IMM and OMM). Mitochondrial fission is primarily mediated by Drp1. This protein binds to the OMM and forms a ring-like structure that facilitates the division of the mitochondrion into two separate entities. Mitochondrial degradation involves the process of phagocytosis, where the PINK/parkin complex directs damaged mitochondria to lysosomes for breakdown. Drp1: Dynamin-related protein 1; Mfn1/2: Mitofusin-1/2; S-OPA1: Short form optic atrophy 1; L-OPA1: Long form optic atrophy 1; Fis1: Protein fission 1; Mff: Mitochondrial fission factor; PINK: PTEN induced kinase 1; MiD49/51: Mitochondrial dynamics protein of 49/51 kDa

### 2.1 线粒体动力学

**2.1.1 线粒体融合** 线粒体融合是指两个线粒体通过外膜和内膜的相互连接形成更大线粒体的动态过程。通过介导受损线粒体间的成分混合与功能互补, 有效补偿线粒体功能缺陷, 显著提升线粒体网络的功能完整性。该过程还可通过清除功能障碍的线粒体, 避免其异常积累引发的细胞损伤, 同时允许健康线粒体代偿性接管受损线粒体的功能模块, 从而维持细胞能量代谢稳态[45,46]。线粒体融合分为外膜融合和内膜融合两个独立步骤, 外膜融合由线粒体外膜上的线粒体融合蛋白1/2 (mitofusin-1/2, Mfn1/2) 介导, 而内膜融合依赖于视神经萎缩蛋白1 (optic atrophy 1, OPA1)。这两种蛋白通过相互作用及磷酸化修饰调控融合速率和效率[47]。

Mfn1是一种线粒体外膜跨膜鸟苷三磷酸酶 (guanosine triphosphatase, GTPase), 属于线粒体融合蛋白家族核心成员, 在能量代谢活跃的组织中高表达[48]。Mfn2作为GTPase动力蛋白, 通过构象变化直接介导线粒体外膜融合: 其N端GTPase结构域为水解GTP提供能量, C端跨膜结构域锚定线粒体外膜并诱导膜曲率变化, 最终形成融合孔道完成膜结构整合, 并通过协调线粒体网络形态维持mtDNA均质化分布和代谢底物交换[49,50]。此外, *Mfn2*基因还介导内质网−线粒体接触位点 (mitochondria-endoplasmic reticulum contact sites, MERCs), 该基因通过选择性剪接产生两种功能特异性亚型: 内质网型线粒体融合蛋白2 (ER mitofusin 2, ERMIN2) 和内质网型线粒体融合蛋白2衔接因子 (ER mitofusin 2 tether, ERMIT2)。其中, ERMIT2直接定位于MERCs, 参与内质网与线粒体的衔接, 通过调控内质网形态间接影响线粒体形态[51]。胆汁酸可作为Mfn2的内源性配体。胆汁酸淤积时, 可促进线粒体与内质网的锚定, 导致线粒体内钙超载, 进而激活NLRP3炎症小体并诱发细胞焦亡。与此相反, 在生理低浓度下, 胆汁酸促进线粒体融合, 导致氧化磷酸化增强, 从而加强浸润巨噬细胞介导的细菌吞噬清除[52]。上述机制共同表明: Mfn2不仅是稳定线粒体形态的关键执行者, 更是整合代谢信号、细胞器互作和程序性死亡调控的多功能分子平台。

OPA1在细胞中有多种异构体, 主要为长型视神经萎缩蛋白1 (long form OPA1, L-OPA1) 和短型视神经萎缩蛋白1 (short form OPA1, S-OPA1)。L-OPA1通过蛋白水解生成S-OPA1, 后者虽缺乏跨膜结构域, 但保留GTPase结构域, L-OPA1启动膜重塑, 而S-OPA1则驱动膜的弯曲和融合, 二者协同维持线粒体网络的动态平衡和功能[53]。研究表明, L-OPA1通过与外膜融合蛋白Mfn1/2的协同介导内膜融合及损伤修复, 并确保线粒体基质成分 (如mtDNA、代谢中间体) 的均匀分布, 从而避免功能碎片化[54]。此外, OPA1通过维持嵴连接处的紧密构象, 一方面限制细胞色素C的异常泄漏以抑制凋亡[55], 另一方面通过优化电子传递链超复合体的空间排布, 显著提升氧化磷酸化效率及ATP合成能力[56]。

线粒体融合在应对细胞应激、维持能量代谢平衡和减少凋亡中至关重要, 帮助细胞适应压力并促进能量合理分配, 确保细胞的正常功能和生存[57]。线粒体融合参与细胞信号传导, 特别是在细胞响应环境变化如炎症或分化时, 通过调整膜电位和蛋白质组成, 影响其他信号蛋白的活性[58]。线粒体融合在免疫反应调控中扮演重要角色, 如在巨噬细胞中, 线粒体融合可调控其从促炎状态向抗炎状态的表型转换, 并通过抑制线粒体碎片化来调节免疫反应的强度与类型[59]。

**2.1.2 线粒体分裂** 线粒体分裂是一个高度调控的生物学过程, 指的是线粒体通过特定的蛋白质实现物理分裂形成两个或多个较小的线粒体的过程[60]。线粒体分裂过程通过显著改变其形态, 直接参与细胞应激的适应性调控, 从而增强细胞的应激适应能力[60]。线粒体分裂的启动常由细胞应激信号 (如氧化应激或能量失衡) 驱动[61]。Drp1作为线粒体分裂的核心效应蛋白, 其活性受到双重调控机制的精密控制。一方面, Drp1通过线粒体外膜上的线粒体分裂蛋白1 (mitochondrial fission protein 1, Fis1)、线粒体分裂因子 (mitochondrial fission factor, Mff)、线粒体动力学蛋白49/51 (mitochondrial dynamics protein of 49/51 kDa, MiD49/51) 等适配膜锚定蛋白形成的受体复合物实现空间定位调控。这些锚定蛋白为Drp1提供特异性结合位点, 驱动其从胞质向线粒体外膜的募集过程[62,63]。另一方面, Drp1的活性受到翻译后修饰的动态调节, 由细胞周期蛋白依赖性激酶1/蛋白激酶C$\delta$ (cyclin-dependent kinase 1/protein kinase C delta, Cdk1/PKC$\delta$) 介导616位丝氨酸的磷酸化修饰可增强其线粒体靶向能力, 而由钙调磷酸酶介导的637位丝氨酸的去磷酸化则通过构象改变激活GTPase活性, 共同完成分裂过程的能量驱动[60,64]。这种双层次调控系统使Drp1能够响应氧化应激、能量代谢异常等细胞信号, 通过协调线粒体分裂频率维持线粒体网络动态平衡, 在清除受损线粒体、调控氧化磷酸化效率、分配子细胞线粒体等关键生物学过程中发挥核心作用[65-67]。

**2.1.3 线粒体自噬** 线粒体自噬是一种选择性自噬过程, 通过PTEN诱导激酶1 (PTEN-induced kinase 1, PINK1)/Parkin RBR E3泛素蛋白连接酶 (Parkin RBR

E3 ubiquitin protein ligase, Parkin) 依赖的泛素化途径和泛素非依赖途径清除受损或多余线粒体。在经典PINK1/Parkin通路中, 受损线粒体膜电位丧失, 导致PINK1在线粒体外膜稳定积累, 进而激活E3泛素连接酶Parkin, 催化线粒体外膜蛋白的K48位泛素化, 电压依赖性阴离子通道 (voltage-dependent anion channel, VDAC)、募集核点蛋白52 (nuclear dot protein 52 kDa, NDP52)、视神经蛋白 (optineurin, OPTN) 等自噬受体, 最终通过微管相关蛋白1A/1B轻链3 (microtubule-associated protein 1a/1b light chain 3, LC3) 介导的自噬体–溶酶体途径完成降解[68,69]。而泛素非依赖途径则通过Bcl-2相互作用蛋白3 (Bcl-2 interacting protein 3, BNIP3)、Bcl-2相互作用蛋白3类似物 (Bcl-2 interacting protein 3-like, NIX) 等蛋白直接结合LC3, 或通过OPTN识别线粒体膜电位去极化等损伤信号启动自噬清除, 不依赖泛素化修饰。该过程可以通过以下3种方式来维持细胞的稳态: 第一, 清除功能失调的线粒体, 防止产生过量的ROS; 第二, 可以维持健康的线粒体网络, 保障ATP供应与钙离子稳态; 第三, 可以选择性清除突变mtDNA, 防止炎症小体异常激活[70]。线粒体自噬功能失衡与神经退行性疾病 (如帕金森病中*PARK2/PARK6*突变) 密切相关, 已成为疾病机制研究和靶向治疗的重要方向。

### 2.2 线粒体功能障碍在AD发病中的作用和机制

越来越多的证据表明, 线粒体功能障碍作为AD的关键特征, 其严重程度随疾病进展显著加剧。在早发型AD患者的大脑中, 线粒体ROS水平显著升高, 而ATP的生成量明显减少, 线粒体膜电位降低, mtDNA拷贝数及完整性显著下降。此外, LC3-II等线粒体自噬标志物的表达也出现异常, 线粒体呼吸链复合体的活性显著降低[70]。这些线粒体指标的异常变化, 进一步加剧了神经元能量代谢紊乱与氧化应激损伤, 成为早发型AD病理进程中的关键因素。家族遗传型AD是早发型AD的一个子类型。其中, *PSEN1*突变会导致线粒体动力学失衡, 显著影响线粒体的分裂与融合, 进而导致线粒体碎片化, 这种变化损害了轴突的运输, 并造成能量供应的不均衡, 从而加剧神经元的损伤[71]。不同的*PSEN1*突变位点对疾病的影响程度各不相同[72]。携带*APOE ε4*基因的个体, 其线粒体压力显著增加, 且该基因水解产生的神经毒性C末端片段与线粒体复合物III和IV相互作用, 降低了呼吸复合物的活性, 导致能量生成受阻和氧化应激增加, 从而对神经元造成损伤[73]。而线粒体在散发型AD中的作用和机制也十分复杂 (图2), 其病理作用可通过多维度机制共同驱动AD的进程。

**2.2.1 线粒体生物能量代谢异常** 葡萄糖是神经元获得能量的必需底物, 健康大脑消耗的葡萄糖超过全身消耗总量的20%[74]。在生理状态下, 能量代谢酶系统高效协调运作, 维持神经元电活动、突触可塑性及离子稳态[75]。早期AD患者脑内线粒体数量减少, 并发生嵴断裂、膜电位降低等线粒体结构改变, 关键代谢酶活性下降, 葡萄糖代谢显著降低[76]。此外, 研究者通过荧光素酶发光法来研究线粒体呼吸功能, 该方法直接反映线粒体通过氧化磷酸化产生能量的能力, 是评估线粒体呼吸功能的关键指标[77,78]。葡萄糖代谢障碍可导致还原型烟酰胺腺嘌呤二核苷酸/还原型黄素腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide/flavin adenine dinucleotide, NADH/$FADH_2$) 生成减少, 造成电

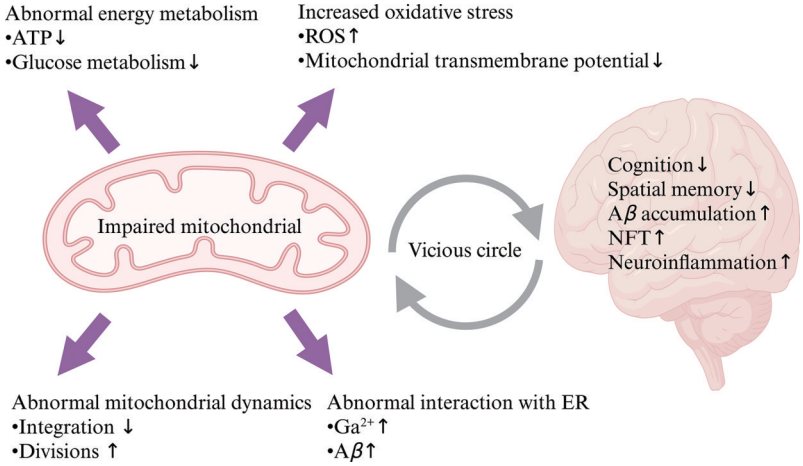



**Figure 2** Mitochondrial dysfunction plays a critical role in the pathological mechanisms of AD. The interplay of mitochondrial bioenergetic metabolism, increased oxidative stress, altered mitochondrial dynamics, and interactions with the endoplasmic reticulum contributes to the development of AD. AD: Alzheimer's disease; ATP: Adenosine triphosphate; ROS: Reactive oxygen species; A$\beta$: Amyloid-beta protein; NFT: Neurofibrillary tangles

子传递链功能损害及ROS爆发。这一代谢紊乱在AD模型中出现极早, APP/PS1小鼠在4月龄时 (Aβ斑块尚未形成) 已出现线粒体复合体IV活性下降40%, ATP/ADP比值降低35%[79]。此时, 神经细胞仍可通过其他代谢途径或线粒体的代偿机制来维持基本的能量需求和正常的功能, 但线粒体的能量代谢效率下降[80]。进入AD中晚期阶段, 线粒体功能的障碍呈现出不可逆的恶化趋势, 海马体的复合体I和IV活性在AD进展期显著受损, 膜电位先增高后下降, ATP水平较早期降低40%[81]。此外, 过氧化物酶体增殖物激活受体γ共激活因子1α (peroxisome proliferator-activated receptor-γ coactivator 1α, *PGC-1α*) 等线粒体生物合成相关基因的表达减少, 导致能量供应的崩溃[82]。同时, 小胶质细胞可能因炎症活化而更易出现线粒体膜电位去极化, 而星形胶质细胞则可能通过糖酵解代偿来维持膜电位的相对稳定[83]。随着疾病进展, 持续的电子传递链功能障碍诱发神经元凋亡, 并通过影响突触线粒体钙缓冲能力, 导致神经网络稳定性下降[84]。脑细胞对葡萄糖的利用能力持续减弱, 能量代谢紊乱引发突触传递效率下降, 尤其损害海马体等脑区的长时程增强效应, 导致神经元功能障碍和细胞死亡, 影响认知功能和日常生活[85,86]。

**2.2.2 线粒体氧化应激增强** 在APP/PS1小鼠的早期轻度认知障碍阶段, 海马体线粒体耗氧量增加, ROS水平开始上升, 但未达损伤的阈值, 主要由线粒体膜电位异常和电子传递链泄漏驱动, 随着病程进入AD的中晚期, 可溶性Aβ寡聚体可以直接抑制细胞色素C氧化酶 (cytochrome c oxidase, CcO) 活性并破坏线粒体膜通透性, 二者协同导致超氧阴离子泄漏和促氧化物质外流, 引发ROS爆发性增长, 形成推动AD进展的恶性循环[87,88]。研究者可以使用线粒体靶向超氧化物荧光探针, 该探针可特异性进入线粒体, 被超氧化物氧化后产生荧光信号, 通过荧光显微镜或酶标仪定量检测荧光强度, 信号强度与线粒体内ROS呈正相关[89]。通过上述方法可精准量化线粒体内ROS水平, 为揭示其病理作用奠定基础。研究表明, ROS过度积累可导致氧化损伤, 与多种疾病模型中的细胞死亡呈正相关性。升高的线粒体ROS通过激活p38丝裂原活化蛋白激酶 (p38 mitogen-activated protein kinase, p38 MAPK), 导致突触密度显著降低[90]。其也能通过破坏运输相关分子机制、干扰能量供应和离子平衡影响轴突运输, 进而导致神经元能量代谢失衡、神经递质传递异常及异常物质积累产生细胞毒性, 最终导致认知功能下降[91,92]。研究还表明, 不同脑区对氧化应激的反应存在差异, 如前额叶皮层因高代谢需求导致线粒体密度更高, 电子传递链活性更强, 在Aβ刺激下更易发生ROS泄漏, 使其对氧化应激更为敏感[88]。这些差异不仅影响脑区的能量代谢, 还可能在神经退行性疾病的进展中发挥关键作用[93]。

**2.2.3 线粒体动力学异常** 线粒体动力学的改变是AD进展的重要因素之一[94]。研究者可通过透射电镜观察线粒体形态变化, 并结合荧光蛋白 (如GFP、mCherry) 标记分裂融合相关蛋白, 实时追踪线粒体动力学标志蛋白在细胞器上的定位及表达水平, 反映动力学的变化[95]。研究表明, Aβ生成增加、Tau蛋白病理性积累, 一方面会使Drp1等线粒体分裂蛋白活性增强; 另一方面, 二者与Drp1蛋白互作异常, 共同驱动线粒体动力学失衡, 表现为融合过程显著抑制与分裂过程过度激活, 导致线粒体膜完整性破坏、能量代谢障碍, 最终引发神经元功能异常, 加速AD病程进展[96,97]。此外, 线粒体过度分裂又促使Aβ和Tau蛋白异常聚集, 导致钙稳态失衡, mtDNA损伤和氧化应激加剧, 引起线粒体形态改变, 造成突触局部能量代谢衰竭和抗氧化防御系统崩溃, 最终突触萎缩及神经递质释放减少, 推动神经元网络功能的进行性退化, 进一步加重了AD的病理进程[98,99]。

在AD小鼠中, 额叶和顶叶皮层神经元的线粒体裂变尤为显著, 可能与其高代谢需求相关。海马体、顶叶等脑区因对线粒体功能依赖性强, 也易受到线粒体动力学异常的影响[83]。不同类型的神经细胞也表现出不同的线粒体动力学特点。小胶质细胞在促炎活化状态可通过激活Drp1磷酸化促进线粒体过度分裂; 同时促炎信号抑制自噬相关蛋白表达, 过度p-Tau蛋白和Aβ的毒性作用也使PINK1、Parkin、LC3-II等线粒体自噬相关蛋白的表达水平显著降低, 导致受损线粒体清除障碍, 形成“分裂–自噬抑制”的恶性循环[100]。而星形胶质细胞则可能通过保留融合蛋白和代偿性糖酵解来维持线粒体网络的完整性[101]。

在AD早期, 尽管细胞能够通过其他途径维持一定的自噬水平来清除代谢废物, 但这一水平尚不足以高效地清除受损线粒体, 导致其清除效率降低。然而, 到了AD的中晚期阶段, 自噬清除能力则严重受损, 表现为自噬体与溶酶体的融合障碍以及线粒体自噬效率的显著下降, 导致功能缺陷的线粒体大量积累, 进一步加重细胞的损伤和功能障碍, 从而促进AD的加重和病情的恶化[102]。研究者通过荧光蛋白 (如mCherry-GFP-LC3) 标记自噬体, 结合溶酶体红色荧光探针染色标记溶酶体, 通过共定位分析评估自噬体–溶酶体融合效率; 通过免疫电镜观察自噬体与溶酶体的超微结构, 或利用线粒体靶向荧光探针追踪线粒体, 可进一步

揭示AD中自噬功能的动态变化与线粒体分裂蛋白激活效应的关联性[103]。

**2.2.4 线粒体与内质网相互作用异常** 在生理状态下, 内质网与线粒体通过钙离子精准传递、脂质双向交换及融合与分裂协同调控机制, 动态维持细胞能量代谢和膜系统稳态[104]。在AD中, 线粒体呈现“串珠状”形态, 与内质网膜的接触位点显著增多。异常的MERCs会促进$\gamma$-分泌酶活性增高, 加速A$\beta$生成, 同时激活钙失调激活激酶 (如GSK-3$\beta$), 导致Tau过度磷酸化。这会触发未折叠蛋白反应 (unfolded protein response, UPR) 信号通路持续激活, 从而加剧A$\beta$和p-Tau病理, 引发钙信号紊乱、能量代谢障碍及氧化应激, 最终导致细胞凋亡与神经元死亡。其中, 线粒体与内质网相互作用异常会显著加速神经元的退行性病变, 进而影响整个神经系统的功能和健康[105,106]。

AD中异常的MERCs通过多种分子机制驱动病理进展, 其中1,4,5-三磷酸肌醇受体–葡萄糖调节蛋白75-电压依赖性阴离子通道1 (inositol 1,4,5-trisphosphate receptor-glucose-regulated protein 75-voltage-dependent anion channel 1, IP3R-GRP75-VDAC1) 复合物作为关键连接结构, 其失调扮演着核心角色[107]。GRP75的表达或功能缺陷会削弱内质网–线粒体的物理连接, 导致钙信号传递效率降低。IP3R与VDAC1的解偶联则直接阻断钙从内质网向线粒体的定向运输, 导致内质网钙释放失控, 胞质钙浓度异常升高; 同时, 线粒体因钙摄取减少导致排出机制代偿性激活, 若代偿不足则加剧胞质钙蓄积[108]。在AD中, A$\beta$寡聚体会直接结合IP3R, 增强其钙释放的活性, 并通过GRP75-VDAC1促进线粒体的钙摄取, 从而引发神经元的凋亡。此外, A$\beta$还会降低线粒体钠/钙交换器的表达, 抑制线粒体的钙排出, 加剧钙的过载, 同时破坏内质网与线粒体的接触位点, 导致局部钙的异常[109]。这种钙超载与线粒体功能损伤又会进一步破坏MERCs结构, 持续驱动神经元退行性病变。

**2.2.5 线粒体基因组紊乱** mtDNA是一种独特而重要的遗传物质, 主要存在于细胞内的线粒体中[110]。mtDNA由于缺乏蛋白保护且修复机制有限, 对ROS攻击高度敏感。这种易损性使其在氧化磷酸化过程中特别容易产生8-氧鸟嘌呤等氧化性损伤产物, 这些损伤会干扰mtDNA的复制和修复机制, 导致碱基损伤、链断裂和拷贝数变化, 最终导致能量代谢紊乱, 引起细胞死亡[111]。研究发现, AD患者外周血中游离线粒体DNA (circulating free-mtDNA, cf-mtDNA) 水平显著降低, 与认知功能下降正相关, 可作为AD的生物标志物[112]。在AD患者中, mtDNA的突变频率显著高于健康对照组。早期mtDNA突变引发线粒体功能障碍, 影响细胞能量代谢, 增加氧化应激, 促进AD的A$\beta$蛋白和Tau蛋白聚集[113]。mtDNA突变导致神经元功能障碍和死亡, 从而引发AD和帕金森病等疾病[114]。在AD转基因小鼠中还检测到mtDNA甲基化, 表观遗传学变化影响神经元健康, 进而加速疾病进程[115]。mtDNA的改变不仅能影响神经炎症、细胞凋亡、能量代谢紊乱, 还通过复杂机制与多种信号通路相互作用, 加剧神经元损伤和功能障碍, 导致认知能力和记忆力下降。

综上, 线粒体生物能量代谢紊乱表现为ATP生成减少、电子传递链复合体活性降低及线粒体膜电位下降, 直接削弱神经元能量供应, 加剧突触功能障碍和认知衰退。其一, 线粒体氧化应激增强导致ROS过度积累, 引发脂质过氧化、蛋白质和DNA氧化损伤, 并与A$\beta$、Tau病理形成恶性循环, 加速神经元凋亡; 其二, 线粒体动力学失衡 (分裂/融合异常) 促使线粒体碎片化、分布异常及自噬清除障碍, 进而导致突触区域线粒体功能储备不足; 其三, 线粒体–内质网相互作用失调通过钙稳态失衡、线粒体相关内质网膜功能异常及未折叠蛋白反应激活, 诱发内质网应激与线粒体钙离子过量, 进一步放大细胞损伤; 最后, 线粒体基因组稳态紊乱导致氧化磷酸化系统受损, 形成不可逆的功能代偿失败。上述机制相互交织, 共同构成AD中线粒体级联损伤网络, 这一病理网络的发现提示靶向线粒体多维度调控 (如能量代谢重塑、抗氧化干预、动力学平衡恢复等) 或为AD治疗提供突破性策略。

## 3 调控AD线粒体动态失衡的小分子和天然产物

近年来, 基于线粒体功能障碍的干预策略为AD治疗开辟了全新方向。通过协同改善线粒体的能量代谢、氧化还原稳态及细胞器相互作用等, 能有效缓解AD病理进程中的线粒体动态失衡, 为延缓疾病进展提供了新的解决方案。

### 3.1 小分子化合物

小分子药物在AD治疗中通过改善线粒体功能、抑制氧化应激和促进神经元生存等机制发挥作用。亲环素D (cyclophilin D, CypD) 是线粒体基质中的一种关键酶, 参与线粒体通透性转换孔的形成, 可以改善线粒体动力[116]。依布硒啉 (ebselen) 是一种安全且可透过血脑屏障的化合物, 能保护细胞免受氧化应激的损害[117]。CypD-ebselen作为一种新型的CypD抑制剂, 通过抑制钙离子超载和ROS生成, 阻断A$\beta$寡聚体诱导的线粒体损伤–氧化应激恶性循环, 减轻Tau蛋白磷酸化, 发挥神经保护作用, 改善AD患者的线粒体功能受损导致的细胞凋亡和神经元损伤[118]。CypD-ebselen通过抑制线粒体通透性转换孔开放干扰钙信号传导,

在神经保护领域极具潜力, 但长期使用可能影响肝脏、心脏等高代谢器官的功能[118]。有研究显示, 线粒体分裂抑制剂-1 (mitochondrial division inhibitor 1, Mdivi-1) 可以抑制 Drp1, 进而改善线粒体动力学, 并且联合使用线粒体靶向抗氧化剂能够显著降低突变型细胞中的 $A\beta_{1\text{-}40}$ 和 $A\beta_{1\text{-}42}$ 水平, 改善线粒体功能和线粒体分裂水平, 在心血管疾病和神经损伤治疗方面具备显著价值[119]。UMI-77 作为髓系细胞白血病 1 (myeloid cell leukemia-1, MCL-1) 小分子抑制剂, 通过解除 MCL-1 对 LC3A 的抑制, 促进自噬体与受损线粒体的结合, 从而增强线粒体自噬清除效率。在 APP/PS1 小鼠中, UMI-77 通过靶向 MCL-1 蛋白并诱导线粒体自噬, 减少 A$\beta$ 斑块和神经炎症, 恢复线粒体形态。通过 Morris 水迷宫测试发现, UMI-77 显著恢复学习和记忆能力[120]。米托蒽醌甲磺酸盐 (mitoquinonemesylate, MitoQ) 是一种可穿透血脑屏障的线粒体靶向抗氧化剂, 尽管其在帕金森病治疗的 II 期临床试验中因未能显示疾病修饰作用而失败[121], 但其在 AD 模型小鼠中仍展现出治疗潜力。MitoQ 通过将 $H_2O_2$ 转化为 $H_2O$ 和 $O_2$、降低 ROS 水平和模拟内源性辅酶 Q (coenzyme Q, CoQ) 的活性来改善线粒体功能和维护正常的氧化还原状态, 进而抑制神经元的凋亡过程, 改善记忆, 减少 A$\beta$ 积累与 Tau 过度磷酸化, 并增强神经突起生长[122]。烟酰胺腺嘌呤二核苷酸 (nicotinamide adenine dinucleotide, $NAD^+$) 是人体细胞中的一种关键辅酶, 对细胞的核心代谢至关重要。在功能上, $NAD^+$ 可通过调节 SIRT1-PGC-1$\alpha$ 信号通路来促进线粒体自噬, 清除受损的线粒体, 从而恢复细胞功能。鉴于 $NAD^+$ 的这些关键作用, 通过设计其前体药物来提升体内的生物利用度和浓度, 已成为一种极具前景的治疗策略。$NAD^+$ 前体烟酰胺核苷 (nicotinamide riboside chloride, NR) 对 APP/PS1 小鼠进行为期 5 个月的干预研究发现, NR 可升高脑组织 $NAD^+$ 水平, 下调促炎细胞因子表达, 并增强自噬功能。这一过程中, NR 通过促进 A$\beta$ 蛋白清除和受损线粒体降解, 减少 A$\beta$ 诱导的 ROS 和线粒体损伤, 进而修复神经元结构与功能, 最终改善 APP/PS1 小鼠认知能力和突触可塑性[123]。在针对肾脏疾病的临床试验中, 志愿者出现严重的潮红反应, 推测可能在 AD 长期治疗过程中也容易导致患者不耐受, 从而限制其临床应用[123]。

这类小分子药物在临床开发中因靶点清晰、机制明确, 便于制定针对性开发策略, 拥有清晰的临床应用方向, 为 AD 的治疗提供了新的思路, 尤其是可以通过改善线粒体功能来减缓疾病的进展, 在神经退行性疾病、代谢性疾病等领域展现出广阔的转化前景。

### 3.2 天然产物

天然产物可以通过多种机制改善线粒体功能, 从而延缓神经退行性疾病的进程。有研究发现, 天麻的主要生物活性成分之一天麻素 (gastrodin, GAS) 对 $A\beta_{1\text{-}42}$ 诱导的原代神经元细胞神经毒性具有神经保护作用, 可能通过激活 PINK1/PARK2 通路促进线粒体自噬, 改善线粒体的功能和数量, 保护神经元[124]。天麻素可改善线粒体能量代谢, 增强神经元抗损伤能力, 安全性相对较高[125]。白芍苷 (paeoniflorin) 可通过降低分裂蛋白 Drp1 的水平, 上调 Mfn1、Mfn2 和 OPA1 的表达以改善线粒体功能, 并调节线粒体膜电位, 减轻氧化应激[126]。值得注意的是, 白芍苷在类风湿性关节炎 III 期临床试验中引起胃肠道紊乱, 提示其在 AD 治疗中可能存在类似风险[127]。天然产物如槲皮素、黄连素、丹参酮 II A 等能够促进线粒体的融合, 稳定线粒体动力学, 从而改善线粒体的功能[128,129]。马钱苷 (loganin) 是一种来源于山茱萸的环烯醚萜苷, 在 3×Tg-AD 小鼠模型中可恢复线粒体动力学和调节线粒体自噬, 减少 A$\beta$ 积累并改善学习和记忆缺陷[130]。也有研究表明, 三七皂苷 (notoginsenoside) 通过激活线粒体自噬减少 AD 小鼠脑内 A$\beta$ 斑块沉积并改善记忆障碍, 在体外通过促进 Parkin 蛋白向线粒体的非 PINK1 依赖性招募, 增强线粒体自噬以清除受损线粒体并提高 A$\beta$ 损伤的 PC12 细胞存活率, 改善了 AD 的病理过程[131]。三七皂苷在临床已被用于治疗急性心肌梗死和心力衰竭, 长期大量使用可能影响凝血功能, 因此也有可能增加 AD 患者的出血风险[132]。尿石素 A (urolithin A, UA) 是一种由肠道菌群代谢植物化合物产生的天然产物, 可以通过改善线粒体功能、溶酶体功能, 激活线粒体自噬, 减轻 mtDNA 的损伤和神经炎症, 显著改善 AD 小鼠的学习、记忆和嗅觉功能[133], 但缺少毒性、代谢研究。

综上所述, 在 AD 线粒体动态失衡的干预策略中, 小分子化合物 (表 1[118-120,122,123]) 与天然产物 (表 2[124,126,130,131,133]) 是两大研究热点。相较于靶点明确的小分子药物, 天麻素、白芍苷等天然产物展现出独特的优势。它们不仅能作用于线粒体, 更能发挥多通路、多靶点的协同效应。这种综合调控模式为治疗 AD 等复杂疾病提供了宝贵的新思路, 但同时也意味着其机制更为复杂, 有赖于多学科交叉研究的进一步探索。

## 4 总结

AD 的病理机制与线粒体功能障碍存在密切联系。在早发型 AD 中, mtDNA 突变频率显著升高, 直接破坏细胞能量稳态并触发病理循环。在散发型 AD 中, 线粒体功能异常与核心病理形成恶性循环[134,135]。

**Table 1** Targeted mitochondrial therapy strategies based on small molecule compounds for the treatment of AD. mAPP: Transgenic mouse line expresses a mutated human APP (hAPP: K670N/M671L and V717F) under the control of the platelet-derived growth factor promoter; 5×FAD: Five-fold familial Alzheimer's disease transgenic mice; APP/PS1: APPswe/PS1dE9 double transgenic mice; 3×Tg-AD: Triple-transgenic Alzheimer's disease mice

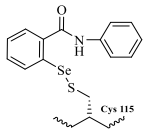
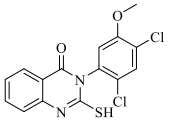
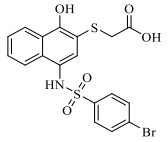
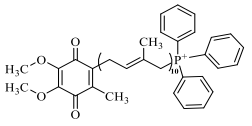
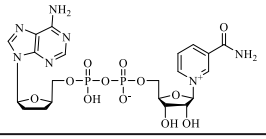
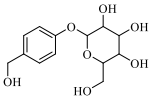
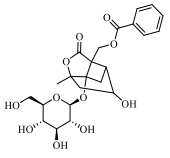
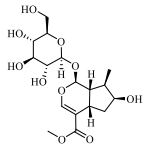
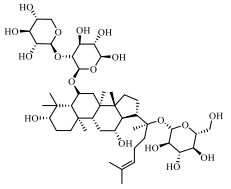
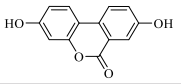
| Name | Chemical name | Structure | Mechanism | Model | Reference |
|---|---|---|---|---|---|
| CypD-ebselen | 2-(((2-Ethylbutyl)thio)selanyl)-*N*-phenylbenzamide |  | Inhibit calcium overload in mitochondria | mAPP, 5×FAD | [118] |
| Mdivi-1 | 3-(2,4-Dichloro-5-methoxyphenyl)-2-sulfanylidene-2,3-dihydroquinazolin-4(1*H*)-one |  | Inhibit Drp1 | APP/PS1 | [119] |
| UMI-77 | (3*R*,4*S*)-3-((1*H*-Pyrrolo[2,3-b] pyridin-5-yl) oxy)-4-(4-chlorophenyl) piperidine-1-carboxylic acid methyl ester |  | Mitochondrial autophagy activator | APP/PS1 | [120] |
| MitoQ | [10-(3,4-Dimethoxy-2-methyl-5,6-dioxo-1, 4-cyclohexadienyl) decyl] triphenylphosphonium bromide |  | Antioxidant | 3×Tg-AD | [122] |
| $NAD^+$ | Nicotinamide adenine dinucleotide |  | Increase $NAD^+$ levels | APP/PS1 | [123] |

**Table 2** Targeted mitochondrial therapy strategies based on natural products for the treatment of AD. SIRT1: Sirtuin 1; PGC-1*α*: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

| Name | Source | Structure | Mechanism | Model | Reference |
|---|---|---|---|---|---|
| Gastrodin | *Gastrodia elata* |  | Active SIRT1 and PGC-1*α* protein expression in the hippocampus | C57BL/6 mice with hippocampal stereotactic injection of A*β* | [124] |
| White peony glycoside | *Paeonia lactiflora* Pall |  | Reduce the level of split proteins and increase the level of fusion proteins | APP/PS1 | [126] |
| Loganin | *Cornus officinalis* |  | Promote mitochondrial autophagy | 3×Tg-AD, SH-SY5Y | [130] |
| Panax notoginseng saponins | *Panax notoginseng* |  | Promote mitochondrial autophagy | A*β*-induced PC12 cells | [131] |
| Urolithin A | Ellagic acid |  | Restore mitochondrial autophagy and lysosomal function | APP/PS1, 3×Tg-AD | [133] |

但线粒体功能障碍并非AD的单一诱因或结果, 而是与核心病理机制形成动态反馈环路 (图3), 共同驱动疾病进展。

然而, 在将线粒体靶向策略从基础研究推向临床

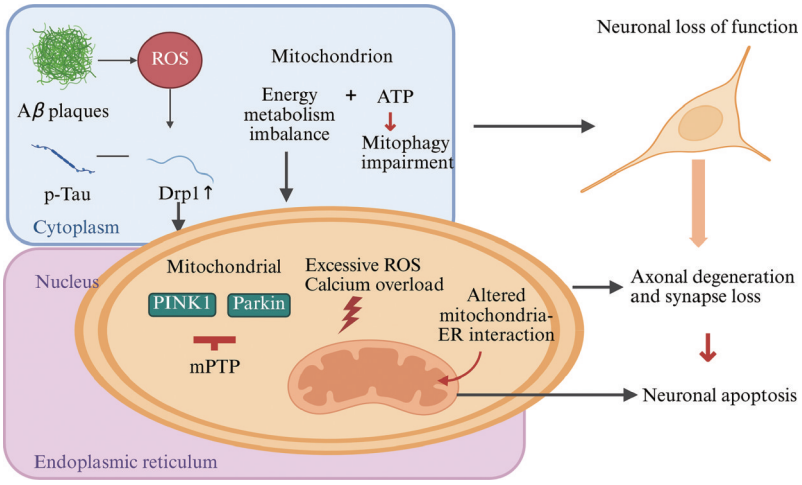



**Figure 3** The relationship between mitochondrial dysfunction and other core pathological mechanisms in AD. In AD, A$\beta$ plaques and p-Tau proteins induce energy metabolism disorders and mitochondrial autophagy impairment by promoting the generation of ROS and upregulating the mitochondrial fission protein Drp1, further leading to the accumulation of ROS within mitochondria, calcium overload, abnormal mitochondrial endoplasmic reticulum interactions, and abnormal opening of the mPTP, ultimately inducing neuronal dysfunction, axonal degeneration, synaptic loss, and neuronal apoptosis. p-Tau: Phosphorylated tau protein; ER: Endoplasmic reticulum; mPTP: Mitochondrial permeability transition pore

应用的过程中, 面临着诸多关键挑战。当前发现的线粒体靶向药物多为极性化合物, 血脑屏障通透能力不强, 导致其在中枢神经系统内的有效浓度不足, 无法充分作用于病变神经元的线粒体。同时, 细胞器靶向效率较低, 线粒体基质中的药物易被溶酶体降解, 难以实现对线粒体功能障碍的精准干预。此外, 现有AD转基因小鼠模型的淀粉样斑块特征早于神经元死亡, 无法模拟人类慢性病程中的异质性及线粒体动态损伤过程, 使得基于此类模型的研究成果难以有效外推至临床[136]。未来可通过开发脂质体等新型递送技术提升药物入脑和靶向能力, 运用多组学及人源类器官平台优化靶点研究, 多学科融合有望攻克转化难题, 为AD治疗带来希望[137]。

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