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衰老与阿尔茨海默病的系统性关联:从共性机制到多靶点干预

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摘 要:随着人口老龄化加速,阿尔茨海默病(Alzheimer's disease,AD)的疾病负担日益加重。目前靶向Aβ的疗法带来的认知改善有限,提示AD防治亟需探索突破单一靶点的新策略。衰老是AD最核心的风险因素,也是患者认知功能下降的重要促进因素,其通过从分子、细胞到系统层面的渐进性功能衰退,构成AD发生发展的生物学基础。基于衰老与AD在多层次上的复杂性、系统性关联,我们提出未来防治应演进为"病理事件干预-系统性年轻化-神经保护和脑网络重塑"的协同整合模式。这一多靶点、动态调整的策略,为突破当前治疗瓶颈、实现AD有效防控与促进健康老龄化提供了理论依据与新的研究方向。

关键词:衰老;阿尔茨海默病;年轻化;神经保护;脑网络重塑
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Systemic association between aging and Alzheimer′s disease: From shared mechanisms to multi-target interventions

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Abstract: With the accelerating trend of population aging, the burden of Alzheimer′s disease (AD) continues to rise. Current disease-modifying therapies that target β-amyloid (Aβ) have demonstrated clear biological efficacy in clearing cerebral Aβ plaques; however, their ability to delay overall cognitive decline remains limited, and the clinical benefits have not yet reached the anticipated threshold. This discrepancy underscores the urgent need to develop systemic prevention and treatment paradigms that transcend single-target approaches and enable multi-level intervention. Aging, the predominant risk factor for AD, drives

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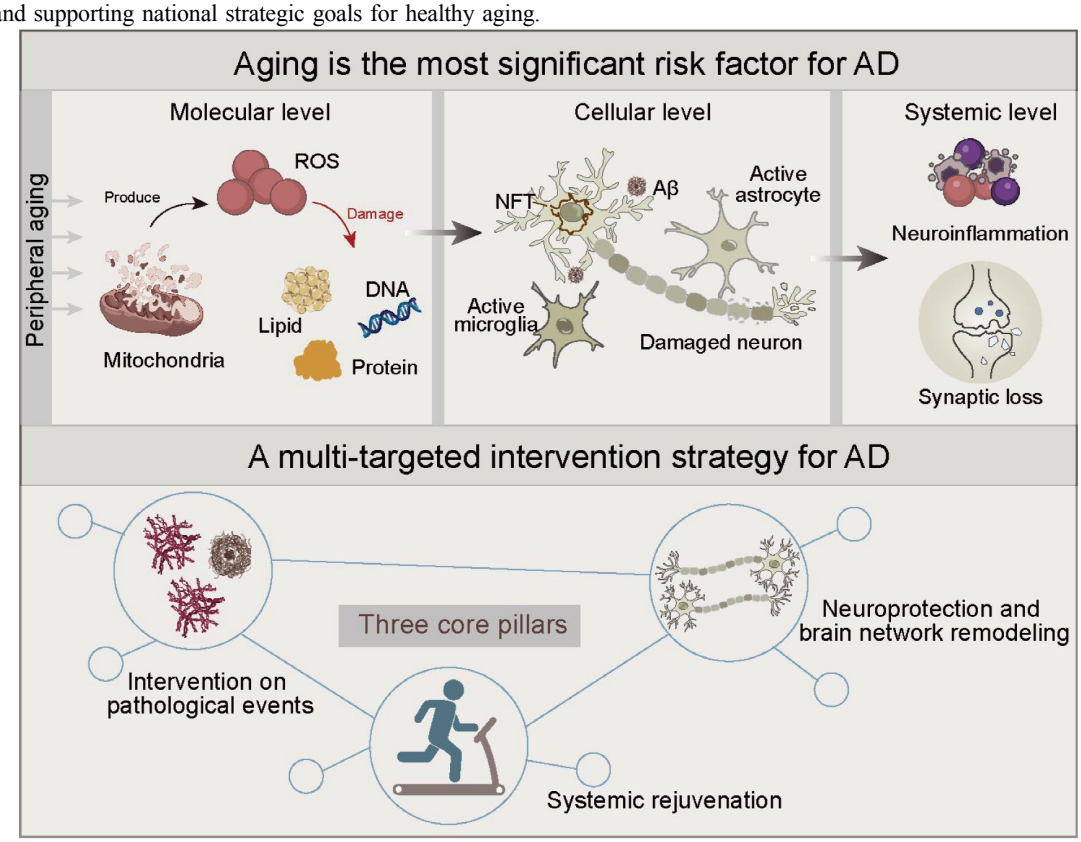
disease initiation and progression through multi-layered mechanisms, including disruption of molecular homeostasis, cellular functional decline, and systemic regulatory dysregulation. Collectively, these age-dependent changes establish a permissive microenvironment that substantially lowers the threshold for neurodegeneration. Within the brain, aging drives a cascade of interrelated pathological processes, including elevated oxidative stress, aberrant activation of microglia and astrocytes, and sustained neuroinflammation. Critically, it also directly promotes abnormal aggregation of pathogenic proteins. The brain is not an anatomically isolated organ; rather, its structural integrity, functional homeostasis, and adaptive plasticity are dynamically regulated by systemic signaling networks emanating from peripheral organs. Peripheral aging further accelerates brain aging through the “body–brain axis” interaction network: age-related deterioration of the cardiovascular system and skeletal muscle directly elevates the biological age of the brain. Furthermore, peripheral aging disrupts central Aβ metabolic homeostasis—not only by increasing Aβ production (driven in part by platelet hyperactivation and gut dysbiosis) but also by impairing Aβ clearance mechanisms, particularly those mediated by the liver and kidney. In addition, systemic comorbidities such as obesity and hypertension further aggravate AD-related neuropathology and heighten disease susceptibility. Given the complex and multi-layered interplay between aging and AD, this review advocates for a paradigm shift in future preventive and therapeutic strategies toward an integrative and coordinated framework. This framework comprises three core pillars: intervention on pathological events (clearing pathological proteins and blocking associated cascades), systemic rejuvenation (ameliorating comorbid factors and decelerating the aging background), and neuroprotection and brain network remodeling (enhancing neuronal resilience and rebuilding brain networks). This multi-pronged strategy simultaneously addresses the upstream aging drivers and the downstream pathological consequences. Such a multimodal, dynamically adjustable approach not only provides a solid theoretical foundation and a translational pathway for overcoming existing therapeutic bottlenecks, but also establishes a scientific basis and practical direction for achieving comprehensive life-course prevention and control, precision management of AD, and supporting national strategic goals for healthy aging.



Key words: aging; Alzheimer′s disease; rejuvenation; neuroprotection; brain network remodeling

1 引言

根据《中国老龄发展报告(2025)》，我国65岁及以上人口占比已达15.6%，标志着社会正式进入中度老龄化阶段。基于此，发病率最高的神经退行性疾病——阿尔茨海默病(Alzheimer’s disease，AD)的防治已成为日益紧迫的公共卫生挑战。我国AD的患病率、发病率和死亡率均持续高于全球平均水平，其中2021年数据表明，国内AD患者约1 699万例，占全球总患病人数的29.8%[1]，给社会和家庭带来沉重的照护压力和经济负担。为应对这一严峻形

势,国家卫生健康委于2025年1月联合15个部门印发《应对老年期痴呆国家行动计划:2024—2030》。因此,探索高效、可推广的AD防治策略,已成为积极应对全球和我国人口老龄化中亟待解决的重大科学问题。

AD以进行性全面认知功能衰退为主要临床表现,其典型神经病理特征包括β-淀粉样蛋白(amyloid-β,Aβ)在细胞外沉积形成的老年斑和过度磷酸化tau蛋白在细胞内聚集形成的神经纤维缠结[2]。近年来,AD的治疗策略实现了从对症治疗向疾病修饰治疗转变,其中靶向Aβ的免疫治疗取得重要进展,可将脑内Aβ沉积水平降低至正常范围。目前已有2种抗体药物在我国获批临床使用[3,4],近期,特朗替尼单体(trontinemab)的Ⅲ期临床试验正在积极开展,其具有高效穿透血脑屏障的能力,可加速Aβ的清除。然而,即使实现Aβ的有效清除,患者的临床认知改善也十分有限,仅表现为认知下降速度延缓27%~29%[5,6],提示除Aβ病理外,尚有其他关键机制参与AD的疾病进程。

衰老是AD的最重要的风险因素,随着年龄增加,AD的患病率显著上升。衰老不仅是AD发生的背景条件,还可促进多种系统性共病的发展,例如心血管事件、肥胖和糖尿病等。我国流行病学调查表明,60~69岁、70~79岁、80岁及以上人群的AD患病率分别为3.2%、6.2%和14.3%[7],呈现明显的年龄依赖性增长趋势。生理学衰老是不可逆的自然过程,持续推动AD的发生发展。随着高通量单细胞组学技术及大规模数据分析方法的快速发展,系统解析衰老与AD的分子特征及其交互作用机制,为超越传统Aβ靶点、发掘新型干预策略提供了关键的理论基础。与此同时,抗衰老研究领域的前沿进展正使针对衰老本身来防治AD从理论走向实践。通过干预衰老的共性机制以延缓甚至部分逆转AD的病理进程,不仅有望显著延长个体的健康寿命,更将为全面提升生活质量开辟全新的治疗范式。

2 衰老是AD的核心驱动力:从中枢到系统的多维失衡

在衰老进程中,机体的内稳态维持和适应性应答能力进行性衰退,导致炎症、氧化损伤、病理蛋白积累等有害生物过程逐渐加剧。当外界刺激超出代偿范围,或受损的应答系统无法有效纠正刺激所引发的紊乱时,机体将发生不可逆的功能失调,最终表现为以Aβ异常沉积、广泛神经元丢失和认知崩塌为特征的AD病理结局[8,9]。接着我们从大脑衰老、外周衰老及衰老相关系统性共病三个层面,系统阐述衰老促进AD发生发展的多维作用机制(图1)。

2.1 中枢衰老:AD病理的多维驱动和协同恶化

大脑衰老使AD风险增加3.1倍,而维持大脑年轻状态可使AD风险降低74%[10]。大脑衰老涉及分子、细胞、神经回路、组织以及脑功能的多维度与多层次退行性变化,这些变化与AD共享一系列核心生物学机制,包括蛋白质稳态失衡、氧化应激、干细胞耗竭、异常神经网络兴奋性以及神经炎症等,且在AD进程中表现得更为显著[11]。

大脑衰老通过加剧非特异病理事件间接推动AD发生。一方面,衰老大脑中氧化应激水平升高,活性氧(reactive oxygen species,ROS)生成增加,对细胞组分如DNA、蛋白质和脂质造成广泛氧化损伤[12]。氧化应激作为AD的核心致病节点,连接Aβ级联反应、tau蛋白病理、神经生长因子以及金属离子紊乱等多种假说,整合多重病理信号,最终导致神经元死亡[13]。另一方面,慢性低度炎症(又名“炎症性衰老”)特征突出,表现为小胶质细胞和星形胶质细胞的持续性异常活化[14]。随年龄增长,小胶质细胞在形态、分布、迁移及应答能力上均发生改变,且呈现出促炎的M1型增多而保护性的M2型减少[15-17];同时,星形胶质细胞向神经毒性的A1型转化[18]。上述细胞亚型的失衡导致促炎因子、趋化因子及活性氧大量释放,持续加剧神经炎症、神经元功能障碍和突触丢失[19]。此外,脑内出现衰老特征的细胞类型同样也表现出AD相关改变,这些衰老细胞及其分泌的衰老相关分泌表型(senescence associated secretory phenotype,SASP)随年龄累积,进一步推动神经退行性变[20]。

大脑衰老直接引起AD特异性病理改变。神经元中负责淀粉样前体蛋白(amyloid precursor protein,APP)剪切加工的β-和α-分泌酶活性在衰老过程中上调,促进Aβ生成[21]。而小胶质细胞作为清除病理物质和细胞碎片的主要效应细胞,其清除功能在衰老过程中显著减弱[22]。此外,衰老导致血脑屏障通透性增加,而类淋巴系统的运输和清除功能逐渐减弱,进一步阻碍了Aβ及其他毒性代谢物质的外排[23,24]。这种生成增加和清除减少的双重作

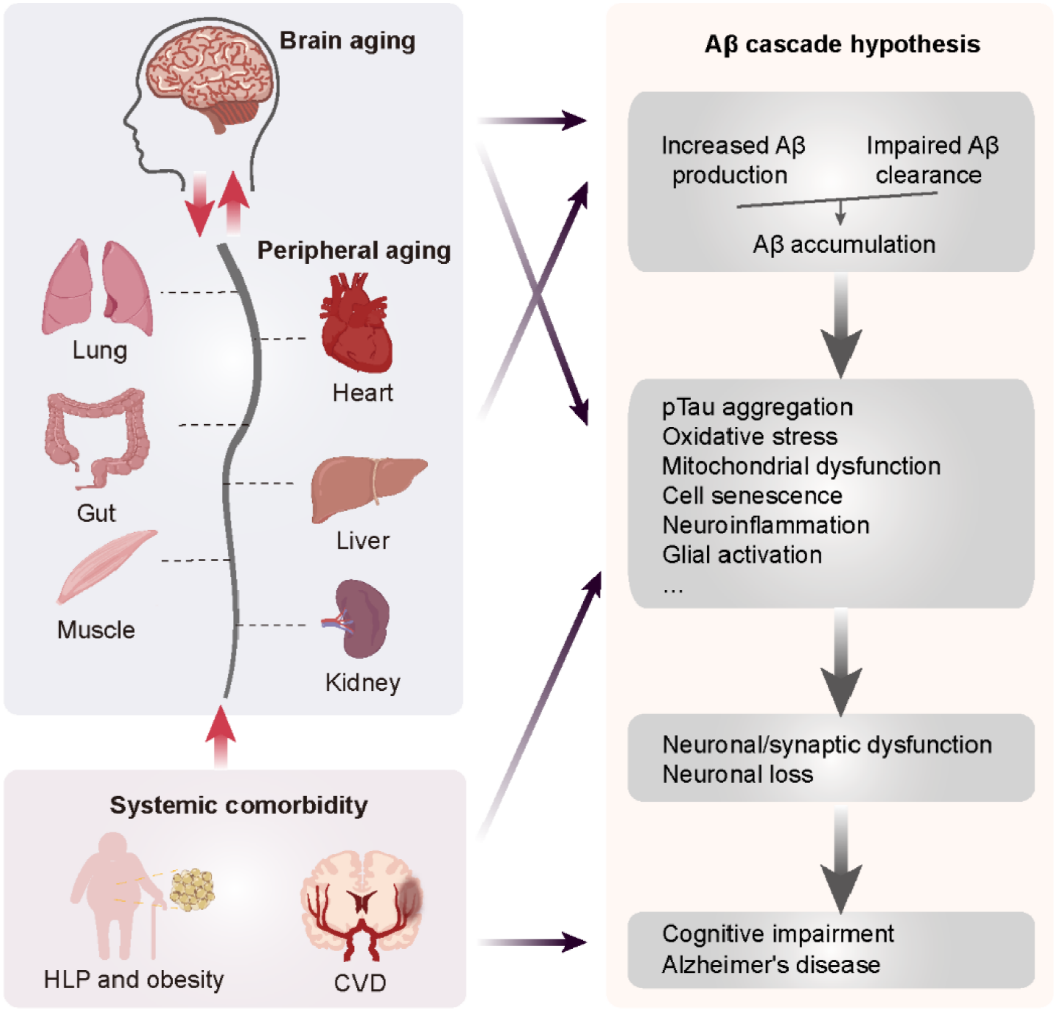


图1　衰老促进AD发生发展的多维机制

脑衰老加剧氧化应激、神经炎症等非特异性病理事件并直接促进病理蛋白的异常聚集。外周衰老则通过“体-脑轴”交互网络影响大脑衰老进程并破坏脑内Aβ代谢平衡。系统性共病进一步恶化AD病理改变并放大疾病易感性。HLP，高脂血症；CVD，脑血管疾病；pTau，磷酸化tau。

Figure 1　Multi-dimensional mechanism of aging promoting the development of AD

Brain aging exacerbates nonspecific pathological processes, including oxidative stress and neuroinflammation, and directly facilitates the abnormal aggregation of pathogenic proteins. Peripheral aging influences brain aging through the ″body-brain axis″ interaction network and disrupts central Aβ metabolic homeostasis. Systemic comorbidities further aggravate AD-related neuropathology and increase disease susceptibility. HLP, Hyperlipoproteinemia; CVD, Cerebrovascular disease; pTau, phosphorylated tau.

用促使错误折叠蛋白（Aβ和tau蛋白过度磷酸化）和其他神经毒性物质在脑内加速累积，直接驱动AD病理进程。

2.2　外周衰老：体-脑轴交互网络对AD病理的系统性调控

大脑并非孤立运作，它与外周器官共同构成一个复杂的“体-脑轴”交互网络，以维持机体整体功能稳态。越来越多研究表明，外周器官的衰老不仅加速大脑整体老化，还直接参与AD的病理进程[25]。这一发现揭示了衰老和AD机制的复杂性，提示需从系统生物学视角重新审视“体-脑轴”在疾病调控中的作用。

外周器官衰老可通过加速大脑衰老间接影响AD。基于英国生物银行（UK Biobank）数据的研究表明，通过评估多个器官系统的生物学年龄（biological age，BA），心血管系统的BA对大脑BA的影响最为显著，每增加1岁，大脑BA相应增加约27天；肺BA每增加1岁，大脑BA增加约25天；肌肉BA每增加1岁，大脑BA增加约13天[26]。这提示维持外周器官的健康状态对于延缓大脑衰老、降低AD风险

具有全局意义。

外周器官衰老直接恶化AD特异性病理，核心在于破坏Aβ的“外周-中枢”平衡。血源性Aβ可进入大脑，导致稳态失衡并引发AD相关病理变化[27]。循环中约90%的Aβ来源于血小板[28]，衰老导致的血小板过度激活会释放更多Aβ入血，从而促进脑内沉积和认知损害[29-31]。此外，衰老相关的微生物菌群失调导致细菌淀粉样蛋白和脂多糖(lipopolysaccharide，LPS)等毒性代谢产物增加[32]。前者可能以朊病毒样方式诱导Aβ聚集[33]，后者可损害Aβ通过血脑屏障的转运[34]。同时，衰老还会引起嗜黏蛋白阿克曼氏菌等有益共生菌的丰度下降，使其所分泌的、具有神经保护作用的短链脂肪酸减少，进而削弱该菌原本具备的改善脂质代谢与降低脑内Aβ斑块负荷的生理功能[35]。在外周清除方面，肝脏承担约60%的循环Aβ清除工作[36]，但衰老导致肝细胞低密度脂蛋白受体相关蛋白1表达水平降低，清除能力受损[37,38]。同时，肝脏中可溶性环氧水解酶活性增强，导致大脑中14,15-环氧二十碳三烯酸水平下降。该物质可通过直接结合Aβ抑制其沉积，并增强小胶质细胞的吞噬功能来发挥保护作用[39]。肾脏也是介导外周Aβ清除的关键器官，在慢性肾脏病患者以及单侧肾切除动物模型中，其循环和脑内Aβ水平显著升高，并伴随认知衰退[40,41]。

大脑衰老不仅表现为中枢神经系统功能的退化，还可通过神经、内分泌及免疫等多种途径向外周器官与组织传递衰老相关信号，进而系统性地驱动机体的整体衰老进程。研究表明，衰老早期即出现的下丘脑微炎症状态，能够显著影响全身能量代谢平衡，降低胰岛素敏感性及葡萄糖耐量，并通过激活肾素-血管紧张素系统引发血压调控失调；且下丘脑中核因子κB(NF-κB)通路的异常激活，已被证实可诱发全身性衰老表型，是构成衰老信号自上而下传递的关键机制之一[42]。此外，衰老相关的小胶质细胞会持续释放多种炎症因子，进而激活脑内皮细胞，促进外周T细胞向脑实质浸润，这可能是大脑向外周传递免疫衰老信号的重要环节[43]。这些发现共同揭示了大脑与外周组织在衰老过程中的双向交互作用。在衰老背景下，此类交互往往趋于恶化，形成正反馈的恶性循环，共同加剧全身性炎症反应及其他衰老相关病理事件，从而为AD的发生发展提供一个系统性的促病变微环境。

2.3 系统性共病：AD风险窗口

衰老常伴随一系列代谢性与血管性共病。高脂肪饮食和肥胖已被广泛证实可加重AD病理进程[44,45]。流行病学研究表明，中年时期中心型肥胖可使痴呆风险最高增加3.6倍[46]，其潜在机制可能涉及全身炎症反应的激活，进而加剧星形胶质细胞增生、小胶质细胞活化、神经炎症以及Aβ病理[47,48]。高血压不仅可通过诱发动脉粥样硬化和卒中等脑血管病变间接增加AD风险，还可直接促进慢性神经炎症、氧化应激和病理性蛋白聚集，从而加速AD的病理进展[49]。

综上所述，衰老通过中枢与外周的多层面机制，共同构成了AD发生与发展的系统性驱动因素。在大脑层面，衰老所伴随的氧化应激增强、神经炎症慢性化、神经胶质细胞异常激活及神经元功能进行性减退等一系列非特异性病理事件，为AD的发病提供了易感微环境，从而间接推动疾病进程。另一方面，大脑衰老会直接扰乱Aβ的代谢平衡，导致其生成增加而清除效率下降，引发病理蛋白的异常沉积，并启动下游的级联病理反应，直接加速AD特征性病理进程。

在外周层面，全身性衰老通过复杂的“体-脑轴”交互网络，一方面加剧大脑的衰老状态，间接促进AD；另一方面，外周来源的炎症因子、代谢产物等亦可跨越血脑屏障，干扰脑内Aβ代谢稳态，直接加剧AD病理。此外，衰老相关的系统性共病会进一步恶化AD的神经病理改变，提高个体的疾病易感性，显著增加AD的发病风险。

3 AD病理事件干预-系统性年轻化-神经保护和脑网络重塑的多重干预策略

3.1 AD病理事件干预

即使Aβ已被成功清除，tau病理、神经炎症及线粒体功能障碍等AD核心病理环节仍是改善临床症状的关键干预靶点。Tau蛋白的异常聚集和扩散与AD患者认知衰退的程度高度相关，因此，针对其翻译后修饰、细胞骨架功能障碍和蛋白清除途径缺陷等方面的干预成为重点，相关研究正从多维度探索调控tau病理的策略[50]。例如，口服OGA抑制剂(BIIB113)可通过增加tau蛋白的O-乙酰葡糖胺糖基化修饰并抑制其聚集，从而减缓tau病理进展，其Ⅰ期临床试验已证实具有良好的安全性、耐受性

和靶点结合率[51]。反义寡核苷酸疗法(BIIB080)通过靶向MAPT,在转录水平减少tau蛋白合成,在轻度AD患者的Ⅰ期临床研究中显著降低脑脊液中tau的生物标志物水平和与认知下降相关的tau-PET信号[52]。上述疗法对认知功能的潜在获益正在评估中。此外,tau蛋白的免疫治疗在动物模型中表现出一定疗效,然而多项临床试验未能显著改善患者的临床结局,提示需要进一步明确最佳治疗时机和更具特异性的靶标[53]。

神经炎症是驱动AD进展的核心机制之一。目前,许多调节炎症通路的药物在AD动物模型中表现出良好疗效,其临床转化价值正在被评估[54]。线粒体功能障碍和氧化应激形成恶性循环,共同加剧Aβ沉积与神经元丢失。研究表明,通过药物或基因干预手段改善线粒体动力学与运输、线粒体自噬以及线粒体基因组稳定性,可以有效减轻AD模型中的氧化损伤、Aβ负荷以及认知缺陷[55],部分靶向该通路的药物已在临床试验中取得积极效果[56]。但需考虑到大分子药物(如抗体)和许多小分子化合物难以高效穿透血脑屏障,且无法精准靶向病变细胞,这导致系统给药后中枢有效浓度不足,或为达到疗效而引发外周副作用。

3.2　靶向衰老的系统性干预策略

鉴于目前尚无任何单一药物或疗法能够实现对人类衰老进程的全面干预,采取多层次、多系统的整合性策略已成为核心共识。未来的干预方向需着眼于在分子、细胞、器官/系统和个体等多个维度上协同作用,通过同时调控同一通路或不同层面中的多个关键靶点,系统性地延缓,甚至部分逆转衰老相关的特征性病理改变与进行性功能衰退,从而有效预防或推迟AD的发生,为实现健康老龄化提供可行路径。

靶向调控衰老核心通路与选择性清除衰老细胞在抗衰老药物研发中极具前景。雷帕霉素作为哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1,mTORC1)的特异性抑制剂,被多项研究证实可延长小鼠寿命,其机制涉及影响蛋白质翻译、促进自噬、改善免疫衰老以及恢复干细胞的自我更新能力[57]。一项为期12个月的临床试验初步验证了低剂量间歇性雷帕霉素在成年人中的安全性及对部分健康指标的改善[58],正在进行评估其在AD患者中的疗效的Ⅱ期临床试验。Sirtuin 1(SIRT1)通过去乙酰化修饰蛋白底物,发挥减轻氧化应激和炎症、增强自噬活性等生物学功能[59]。SIRT1过表达可延长小鼠寿命并改善衰老相关表型[60],在AD模型中表现出抑制Aβ生成、减轻神经炎症并防止神经元凋亡的多重保护效应[61]。其小分子激活剂可降低老年人群的胆固醇和甘油三酯水平[62],并具有降低AD患者脑脊液中炎症因子,诱导适应性免疫应答的潜力[63]。此外,Senolytics能够选择性清除衰老细胞及其分泌的SASP,延缓或减轻组织功能紊乱。在衰老小鼠中清除衰老细胞可部分逆转衰老相关的功能衰退,并使其中位生存期延长35%[64]。在AD小鼠模型中,该疗法能够有效降低Aβ负荷及促炎因子水平,显著改善认知功能[65],且其在AD患者中具有良好的安全性、可行性和耐受性,相关Ⅱ期临床试验正在开展,以评估其对认知功能的改善效果[66]。

在衰老干预研究中,“年轻化”是指通过干预措施,使机体在多层面呈现与衰老逆转相关的积极变化。这些变化既包括炎症减轻、SASP缓解、表观遗传时钟回调等分子与细胞层面的病理事件改善,也涵盖认知功能与机体活动能力等系统功能的提升。其中,免疫衰老作为全身性衰老的核心驱动力之一,已成为实现系统性年轻化的关键靶点。研究发现,将年轻骨髓移植至老年小鼠,不仅能够有效维持突触连接并改善认知功能[67],还能使其最长寿命延长30%[68]。近期研究进一步揭示,移植年轻AD小鼠的骨髓干细胞,可逆转与衰老相关的差异表达基因的表达模式,恢复单核细胞的吞噬功能,并显著缓解认知障碍[69]。相比于复杂的骨髓移植,肠道菌群年轻化是一种更可行的替代策略。将年轻小鼠的肠道菌群移植至老年宿主,可有效逆转免疫衰老和神经炎症,改善海马神经发生、行为表现及认知功能[70,71]。而在AD模型小鼠中移植健康肠道菌群,能显著减轻Aβ沉积、神经纤维缠结及胶质细胞过度活化,并恢复认知功能[72,73]。此外,移植年轻造血干细胞不仅能在系统层面重塑衰老机体的免疫功能,降低表观遗传年龄,还能在运动能力、肌肉功能及神经系统等方面诱导广泛的年轻化效应,并显著延长寿命[74]。在AD模型中,该策略还能通过替换大脑内功能失调的小胶质细胞,减少Aβ沉积及营养不良性神经突起的形成[75]。

优化生活方式是最易行且有效的预防和治疗策

略,规律作息、饮食管理及体育锻炼等非药物干预,可有效延缓衰老进程,并直接或间接改善AD病理。规律且充足的睡眠有助于清除脑内代谢废物,使BA减少达4.1 年[76]。健康饮食策略,例如间歇性进食、热量限制(calorie restriction,CR),不仅可延长果蝇寿命,还可通过激活昼夜节律调控的自噬途径,延缓多组织器官中衰老标志物的累积[77]。在早衰小鼠模型中,CR可将其寿命延长三倍,并使神经元数量增加50%,同时改善运动功能[78]。CR可延缓健康成年人的衰老速度达2%~3%[79],并使BA降低0.4年[80]。规律体育锻炼,尤其是有氧运动,可逆转衰老相关的大脑体积萎缩及功能衰退[81,82],其机制包括抑制炎症相关通路[83],改善氧化还原平衡和胰岛素敏感性,以及优化全身代谢功能[84]。运动诱导分泌的肌因子也可调控细胞存活、神经发生、神经炎症、蛋白质稳态、氧化应激及蛋白质修饰等过程,产生广泛的神经保护与修复效应[85,86]。上述生活方式显示出强大的疾病预防与治疗潜力。规律的体育锻炼和均衡饮食,可使痴呆风险降低约32%[87]。调节昼夜节律可激活与胰岛素信号转导和线粒体功能相关的时钟基因表达,从而缓解Aβ病理[88]。间歇性进食可减轻AD模型中Aβ负荷,并改善海马转录组[89];CR通过诱导自噬也可减少Aβ沉积和tau蛋白过度磷酸化,并增强认知功能[90]。临床研究也证实,有氧运动有助于改善AD患者的功能独立性、身体功能、认知能力和神经精神症状[91]。然而,在实施上述干预措施时,需高度重视长期治疗依从性与精准化、个体化管理策略的协同推进。鉴于老年群体存在认知储备下降的情况,其固有行为模式的重塑尤为困难;同时,个体在病理机制、临床表型及进展速度等方面具有高度异质性,干预方案亦须据此动态优化与适时调整。

3.3 神经保护和脑网络重塑

直接增强神经元对病理损伤抵抗力的药物是AD治疗的重要方向。靶向兴奋性毒性通路的药物研发较为成熟。例如,非竞争性N-甲基-D-天冬氨酸(NMDA)受体拮抗剂美金刚已获临床批准,其通过调节谷氨酸能信号,减轻由受体过度激活引发的钙离子内流及神经元损伤,是目前兼具症状改善与潜在神经保护作用的常用药物之一[92]。针对氧化应激这一核心致病环节,依达拉奉作为一种氧自由基清除剂备受关注。临床前研究表明,该药物不仅在体外可抑制Aβ聚集及其神经毒性,在AD小鼠体内也可有效降低Aβ负荷和tau磷酸化水平,挽救神经元和树突的丢失,减轻神经炎症和氧化应激,最终预防或阻止认知衰退[93]。基于此开发的新型药物的生物学利用率进一步提高,其在体外和AD动物模型中表现出良好的神经保护效应,显著改善病理和行为缺陷[94]。目前,相关药物的多中心Ⅱ期临床试验正在进行中。线粒体功能作为神经保护的另一个关键靶点,相关药物如二美苯旨在维持细胞能量稳态与钙缓冲能力。一项Ⅱ期临床试验表明,二美苯对轻中度AD患者的认知功能、行为症状及整体临床病程进展表现出一定的改善趋势[95]。此外,多靶点天然产物亦为重要研究方向。包括多酚、维生素、欧米伽-3脂肪酸在内的多种天然化合物,因兼具抗炎、抗氧化、抗凋亡及调控神经可塑性等多重保护作用,并能通过不同机制抑制异常蛋白聚集,目前正被用于治疗AD的临床探索之中[96]。

细胞移植旨在通过补充或替换受损细胞来逆转衰老与神经退行性改变。将年轻小鼠的肌肉干细胞/祖细胞移植至早衰模型小鼠体内,可诱导肌肉组织年轻化并延长寿命[97]。此外,巨噬细胞通过清除髓鞘碎片促进髓鞘再生,并有效逆转因年龄增长导致的少突胶质细胞去分化现象[98]。在AD背景下,单核细胞富集能够增强脑内单核细胞的浸润能力,从而促进Aβ的吞噬清除[99]。干细胞来源的细胞外囊泡(extracellular vesicles,EVs)因其较低的免疫原性和较高的安全性,被视为更具临床可行性的替代策略。脂肪间充质干细胞和脐带间充质干细胞来源的EVs能够显著改善多种衰老表型,延缓老年小鼠的衰老进程[100,101]。年轻小鼠血浆中提取的EVs可增强线粒体功能,恢复多器官的蛋白质组、代谢及生理机能,使其中位寿命延长12.4%[102]。此外,神经干细胞来源的EVs可抑制神经炎症,并改善AD小鼠的病理特征和行为表现[103]。然而,Senolytics、骨髓移植和细胞移植等策略,在临床转化过程中,仍面临一系列严峻的安全问题与伦理挑战。在临床安全性层面,包括免疫排斥反应与移植物抗宿主病风险、长期免疫抑制所继发的感染、细胞疗法潜在的成瘤性。伦理层面的挑战同样突出,此类干预往往需在衰老个体或疾病早期患者中开展长期试验,其风险-获益比的评估极为复杂,高昂的治疗成本可能加剧医疗资源分配不公。这些多

维度挑战的解决,是相关策略从概念走向临床实践的前提。

认知功能源于广泛大脑网络中的动态相互作用,而认知训练可增强默认模式网络内部的连接性[104],并特异性激活额下回和楔前叶等关键脑区。其中楔前叶的激活与认知改善直接相关,而额下回则通过其与楔前叶的功能耦合间接发挥作用,共同促进健康衰老[105]。一项为期6个月的临床试验表明,长期、多领域的认知训练可以改善轻度认知障碍患者的大脑功能连接,并提升其认知水平[106]。非侵入性神经调控技术为实现脑网络重塑提供了物理工具。在动物实验中,40 Hz的声光联合刺激和振动触觉刺激能够诱导皮层神经活动,缓解神经元退行性变,保护突触蛋白并增强突触功能[107,108]。初步临床试验表明,40 Hz的声光刺激能增强AD患者脑内的神经活动和默认模式网络的功能连接[109]。经颅磁刺激则通过增强不同脑区间的功能性连接,调控大脑重叠系统(在不同认知任务或静息状态下多个功能网络共享的脑区)的功能和重建,促进AD患者认知功能的恢复[110]。本文对上述临床试验进行了总结(表1)。

3.4　多维度联合干预

基于衰老和AD复杂的系统性特征,单一维度的干预均难以彻底遏制疾病进展。因此,整合"病理靶向、抗衰老和神经保护/脑网络重塑"等多维度干预措施,是取得突破性疗效的必然方向(图2)。短期临床试验已初步验证了联合干预的可行性。例如,结合饮食、运动和睡眠的综合性干预使表观遗传年龄平均逆转3.2年,并改善代谢指标[111],为系统性延缓生物衰老提供了直接证据。在AD治疗领域,旨在探索协同效应的多项联合临床试验正在积极开展,如联合重复经颅磁刺激与认知训练[112],或结合40 Hz声光刺激与认知训练、有氧运动。目前仍缺乏将AD病理靶向药物、系统性年轻

表1　抗衰老和AD防治的临床试验

Table 1　Clinical trials on anti-aging and AD prevention and treatment

分类	药物/干预措施	临床试验注册号	阶段	研究人群	结果
靶向AD核心病理事件	BIIB113	NCT05195008	Ⅰ期	健康参与者	耐受性好,靶点结合率高
	BIIB080	NCT03186989	Ⅰ期	轻度AD患者	Tau生物标志物降低
	西瑞奈单抗	NCT03828747	Ⅱ期	中度AD患者	血浆GFAP浓度增加
系统性年轻化干预	雷帕霉素	NCT04488601	Ⅱ期	健康老年人	改善女性瘦组织质量和疼痛
	雷帕霉素	NCT04629495	Ⅱ期	MCI和早期AD患者	-
	SRT2104	NCT00964340	Ⅰ期	健康老年人	安全性良好,改善脂质代谢
	白藜芦醇	NCT01504854	Ⅱ期	轻中度AD患者	降低脑脊液MMP9,调节神经炎症
	达沙替尼 + 槲皮素	NCT04063124	Ⅰ期、Ⅱ期	早期AD患者	衰老相关细胞因子和趋化因子呈下降趋势
神经保护和脑网络重塑	依达拉奉	CTR20253688	Ⅱ期	早期AD患者	-
	二美苯	NCT00377715	Ⅱ期	轻中度AD患者	安全和耐受良好,并显著改善临床病程
	姜黄素	NCT01001637	-	AD患者	-
	维生素B6、B12、叶酸	NCT00056225	Ⅲ期	AD患者	不能减缓轻中度AD患者的认知衰退
	多巴胺能治疗	NCT03250741	Ⅱ期	AD患者	减轻额叶认知功能障碍相关症状,延缓日常活动受损
	肌酸	NCT05383833	-	AD患者	适度的骨骼肌益处
	欧米伽-3脂肪酸	NCT00440050	Ⅲ期	轻中度AD患者	未减缓轻中度AD患者的认知和功能衰退速度
	40 Hz声光刺激和认知训练	NCT06595511	-	AD患者	-
	有氧运动和认知训练	NCT03313895	-	MCI患者	-
	重复经颅磁刺激和认知训练	NCT01504958		轻中度AD患者	可能改善认知状态
	多领域认知训练	NCT03883308	-	MCI患者	改善认知功能,延缓结构性脑衰退

注:MCI,轻度认知障碍;MMP9,基质金属蛋白酶9;-表示临床试验尚未明确分期,或相关研究结果尚未公开发表。

Note: MCI, mild cognitive impairment; MMP9, matrix metallopeptidase 9; - indicates that the clinical trial has not yet been clearly staged, or the relevant research results have not been published yet.

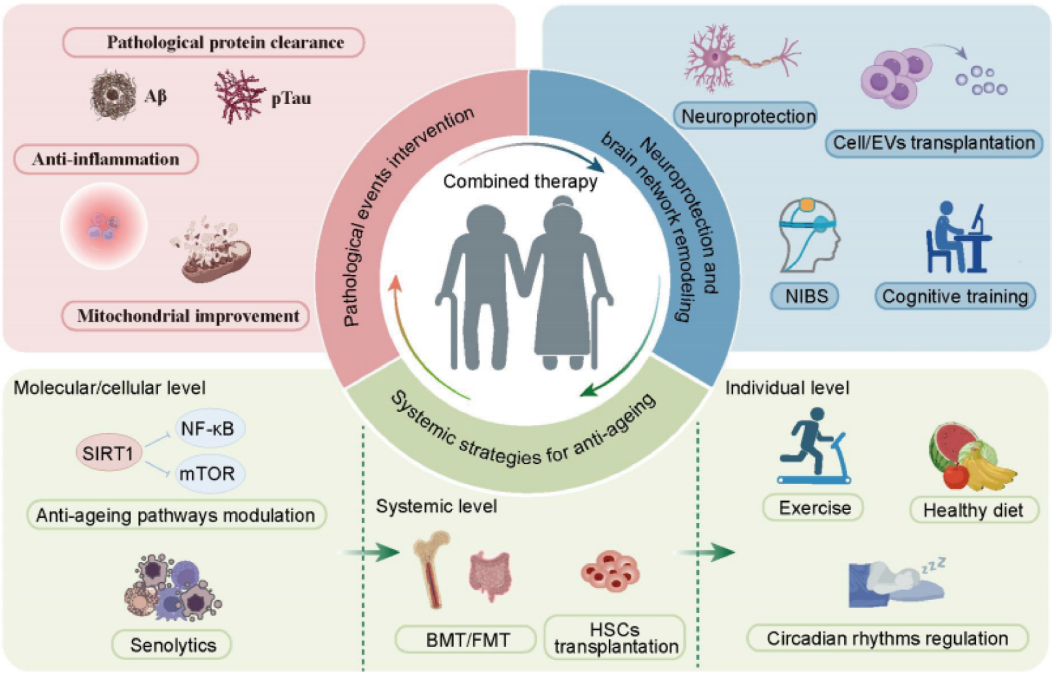


图2 AD的多重维度干预策略

注：pTau，磷酸化tau；SIRT1，Sirtuin1；NF-κB，核因子κB；mTOR，哺乳动物雷帕霉素靶蛋白；BMT，骨髓移植；FMT，肠菌移植；HSCs，造血干细胞；NIBS，无创脑刺激；EVs，细胞外囊泡。

Figure 2 An integrated AD intervention strategy

Note: pTau, phosphorylated tau; SIRT1, sirtuin1; NF-κB, nuclear factor kappa-B; mTOR, mammalian target of rapamycin; BMT, bone marrow transplantation; FMT, fecal microbiota transplantation; HSCs, hematopoietic stem cells; NIBS, noninvasive brain stimulation; EVs, extracellular vesicles.

化策略、神经保护和脑网络重塑机制融合的基础研究和临床试验，亟需进一步推进跨层次、多靶点的综合干预体系构建。

4 展望

衰老是AD最核心的风险因素，其通过分子、细胞和系统层面的渐进性功能衰退，构成了AD病理启动和加速的基础背景。因此，AD干预策略的设计必须超越单一病理靶点的局限，将系统性年轻化干预纳入整体框架。随着衰老生物学机制的系统解析及抗衰老干预策略的多维度拓展，靶向衰老已成为极具潜力的前沿防治方向，其最终目标不仅在于延缓疾病临床症状的出现，更在于延长健康寿命并全面提升生活质量。

面对国内老龄化的严峻现实，AD的防治重心需要从“疾病治疗”转向“衰老管理”，其核心是从“被动应对认知损伤”转向“主动管理衰老进程”。这强调要在中年人群中有计划地实施一级预防，推广抗衰老生活方式，例如规律运动、健康饮食、认知刺激。这些策略有望延缓甚至阻断AD病理事件的启动，增强大脑认知储备，从公共卫生层面降低群体的发病风险，实现疾病的早期防控。为客观、精准地评估系统性干预措施所实现的“年轻化”程度，亟需建立一套新型的多维度、动态生物标志物评估体系。该体系应超越传统单一或孤立的指标，整合来自不同器官系统与生理层面的互补信息，以全面捕捉机体衰老逆转的复杂生物学状态。须涵盖以下核心维度：多器官表观遗传年龄、炎症因子谱、代谢组学特征、微生物组特征等，为抗衰老及AD预防的临床疗效评估及个性化方案优化提供至关重要的客观量化工具。

通过对衰老与AD系统性关联的深入解析，未来防治策略需逐步演进为“AD核心病理事件干预（去除病理蛋白、阻断级联反应）、系统性年轻化（改善共病因素，延缓衰老背景）、神经保护和重塑（增强神经抵抗能力，重建神经网络）”的协同整合策略，最终实现AD的有效防治与健康老龄化。在这一动态框架中，针对AD疾病谱中的不同阶段——临床前期、

轻度认知障碍期及痴呆期，实施具有阶段特异性的“三元策略”至关重要。该策略强调，须依据各阶段核心的病理生理学特征与临床需求，动态调整不同干预方式的优先次序与组合模式。在临床前阶段，策略应优先侧重于风险预警与一级预防，结合Aβ清除药物；进入轻度认知障碍期，则需转变为持续优化机体整体状态，启动病理清除并辅以神经保护；至痴呆期，治疗重点应在于症状管理、脑网络重塑、功能维持及并发症防控。这种基于疾病阶段的序贯性、组合式干预布局，有望为实现精准的AD全程管理提供理论框架与实践路径。

此外，鉴于AD病因的多维异质性与病理的跨系统交互特性，构建跨学科整合研究平台至关重要。这一平台应深度融合老年医学、神经病学、代谢病学、康复医学的核心视角，并积极整合数字医疗技术，以形成覆盖疾病预防、诊断、治疗与管理的全链条协同研究体系。通过该平台，各学科知识与方法可实现衔接与互补，不仅能系统验证“衰老-AD”整合干预框架的科学性与可行性，更能通过优化干预组合实现早期风险预警与远程智能管理，从而最大化治疗协同效应，有效降低整体医疗成本与因单一或不当干预带来的不良反应风险，最终推动研究成果向临床实践与公共卫生策略的转化。尽管在机制研究、临床转化与方案优化方面仍面临诸多挑战，但这一系统性的治疗理念为攻克AD提供了全新的路径与战略方向。

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