XXXX DOI:

动脉粥样硬化相关脑血管损害与阿尔茨海默病关系的研究进展

高 强[1],吕丽芳[2]

(1.黑龙江中医药大学基础医学院,哈尔滨 150040;2.哈尔滨医科大学基础医学院,哈尔滨 150081)

【摘 要】动脉粥样硬化(atherosclerosis,AS)相关脑血管损害是连接血管病变与阿尔茨海默病(Alzheimer's disease,AD)的重要环节。临床队列、影像学和病理学研究提示,颈动脉内膜中层厚度增加、颈动脉斑块、Willis环AS、动脉僵硬和脑低灌注等改变,与认知下降、痴呆风险及AD相关病理负荷有关。其潜在机制包括β-淀粉样蛋白(amyloid-β,Aβ)生成与清除失衡、微管相关蛋白Tau(microtubule-associated protein tau,Tau)异常、脂质代谢紊乱、载脂蛋白E(apolipoprotein E,APOE)ε4相关易感性、血脑屏障(blood-brain barrier,BBB)和神经血管单元(neurovascular unit,NVU)功能障碍、慢性炎症及氧化应激等。现有证据支持将血压、血脂和血糖等血管危险因素管理及生活方式干预用于认知下降风险管理;APOE ε4携带状态可反映AD遗传易感性,并与AS相关血管风险有关,但其单独用于临床AS风险识别或与血管风险指标联合预测AD风险的价值仍需验证;针对Aβ/Tau、炎症和Aβ跨BBB转运等靶点的策略仍以临床前或早期探索为主。本文从关联证据、潜在共同机制和风险识别与干预启示三个方面综述AS相关脑血管损害与AD的关系,并区分不同结局和证据层级,以避免过度解释现有研究结果。

【关键词】动脉粥样硬化;脑血管损害;阿尔茨海默病;神经血管单元;认知下降

【中图分类号】R543.5;R741.02 【文献标志码】A

Research progress on the relationship between atherosclerosis-related cerebrovascular injury and Alzheimer's disease

Gao Qiang[1],*Lü Lifang*[2]

(*1.School of Basic Medical Science,Heilongjiang University of Chinese Medicine;*

2.School of Basic Medical Science,Harbin Medical University)

【**Abstract**】Atherosclerosis (AS)-related cerebrovascular injury is an important link between vascular lesions and Alzheimer's disease (AD). Clinical cohort, imaging, and pathological studies suggest that increased carotid intima-media thickness, carotid plaques, AS of the circle of Willis, arterial stiffness, and cerebral hypoperfusion are associated with cognitive decline, risk of dementia, and AD-related pathological burden. Potential mechanisms include an imbalance between β-amyloid production and clearance, microtubule-associated protein tau abnormalities, lipid dysregulation, apolipoprotein E ε4-related susceptibility, blood-brain barrier and neurovascular unit dysfunction, chronic inflammation, and oxidative stress. Current evidence supports the application of vascular risk factor management, such as blood pressure, blood lipids, and blood glucose, as well as lifestyle interventions for the management of the risk of cognitive decline. Apolipoprotein E ε4 carrier status may reflect genetic susceptibility to AD and is associated with AS-related vascular risk; however, its value in clinical identification of the risk of AS when used alone or in prediction of the risk of AD when used in combination with vascular risk indicators still needs to be validated. Strategies targeting β-amyloid/microtubule-associated protein tau, inflammation, and β-amyloid transport across the blood-brain barrier are still mainly preclinical or in early exploration. This article reviews the relationship between AS-related cerebrovascular injury and AD from three aspects: evidence of association, potential common mechanisms, and implications for risk identification and intervention, and distinguishes different outcomes and levels of evidence to avoid overinterpretation of existing findings.

【**Key words**】atherosclerosis; cerebrovascular injury; Alzheimer's disease; neurovascular unit; cognitive decline

作者介绍:高强,Email:gaoqiangphysiology@hrbmu.edu.cn,研究方向:海马神经损伤与衰老研究。

通信作者:吕丽芳,Email:102466@hrbmu.edu.cn。

基金项目:黑龙江省教育厅资助项目(编号:2023-KYYWF-0251);黑龙江省自然科学基金资助项目(编号:LH2024H019);国家自然科学基金资助项目(编号:82370279)。

阿尔茨海默病(Alzheimer's disease,AD)是老年期痴呆最常见的病因,临床上主要表现为进行性记忆减退、认知功能障碍及行为异常[1]。其典型病理特征包括β-淀粉样蛋白(amyloid-β,Aβ)异常沉积形成老年斑,以及微管相关蛋白Tau(microtubule-associated protein tau,Tau)异常磷酸化形成神经原纤维缠结[2]。除Aβ和Tau病理外,神经炎症、氧化应激、线粒体功能障碍、突触损伤,以及血脑屏障(blood-brain barrier,BBB)和神经血管单元(neurovascular unit,NVU)功能障碍等多种病理过程也参与AD的发生发展[2-3]。上述病理改变可进一步导致神经元功能受损及神经元丢失,最终引起相关脑区萎缩及神经网络功能障碍[2-3]。因此,除中枢蛋白异常沉积外,血管功能异常、脂质代谢紊乱和慢性炎症等全身性因素,以及脑低灌注等局部脑血管改变,也可能参与AD的病理进程[4]。

动脉粥样硬化(atherosclerosis,AS)是以脂质沉积、慢性炎症和血管壁重构为特征的慢性血管病变,也是多种心脑血管疾病的重要病理基础[5-6]。其发生通常始于内皮功能障碍,低密度脂蛋白(low-density lipoprotein,LDL)进入内膜并被氧化修饰,诱导单核细胞募集、巨噬细胞吞噬和泡沫细胞形成,放大炎症反应[5]。随着病变进展,平滑肌细胞迁移、表型转换和基质沉积共同参与斑块形成。斑块进展可导致血管狭窄和灌注不足,而不稳定斑块破裂则可触发血小板聚集和血栓形成,进而引起心脑血管事件[7-8]。

AS累及颈动脉、颅内大动脉或脑微循环时,可致颈动脉内膜中层增厚、颈动脉斑块、Willis环AS、动脉僵硬、脑血流反应性下降及慢性脑低灌注等血管损害。这些改变可能通过降低脑灌注、破坏BBB/NVU稳态、干扰Aβ转运和改变炎性微环境而影响AD相关病理过程。流行病学、影像学与病理学研究提示,AS相关脑血管损害与AD及其病理存在关联。但认知下降、轻度认知障碍和痴呆均不是AD的特异性临床表现。因此,现有证据应被视为二者存在多层面关联的线索,而非单一因果关系的直接证明[2-3]。

尽管上述联系已逐渐受到关注,既往综述仍多从炎症、脂质代谢异常或血管危险因素等角度分别讨论AS与AD的关系,较少围绕AS相关脑血管损害这一核心环节进行系统整合[9]。为此,本文以叙述性综述的方式,重点梳理AS相关脑血管损害与AD的关联证据、前者可能影响AD相关病理过程的机制、以及AS相关风险管理对AD防控的启示。本文同时区分AD相关病理类型、不同临床认知结局及不同证据层级,避免将观察性关联解释为因果关系,或将非AD特异性认知结局归因于AD。

1 AS相关脑血管损害与AD的关联证据

流行病学证据提示,AS病变负荷与认知下降及AD风险存在关联。颈动脉内膜中层厚度增加、颈动脉斑块和动脉僵硬常被用作AS病变负荷或血管老化的替代指标,相关研究显示其与记忆、执行功能和总体认知表现下降相关[10]。多个血管危险因素聚集时,AD发生风险亦可能增加[11]。但此类证据多来自观察性研究,易受年龄、教育水平、糖尿病、高血压、高脂血症和其他共病的影响,宜解释为风险关联而非直接因果关系。

病理和影像学研究进一步显示,血管异常与AD相关病理负荷存在关联。尸检研究显示,Willis环AS程度与Aβ沉积和神经原纤维缠结负荷相关[12]。影像学研究提示,脑血流反应性下降、脑低灌注和动脉僵硬可能与Aβ沉积及AD易损脑区皮层萎缩相关[13-14]。这些发现提示血管功能障碍可能与Aβ清除受损及神经退行性改变相关,但尚不能确定三者的先后关系和因果方向。

需要强调的是,AD和血管性认知损害并非同一疾病。AS相关脑血管损害既可能通过脑低灌注、脑内微环境紊乱和Aβ清除受损影响AD相关病理过程,也可能通过独立的血管性脑损伤降低认知储备。后续研究应结合AD生物标志物、脑血管影像和纵向认知评估,区分AD相关认知损害与血管性认知损害的相对作用及发生时序。

2 AS相关脑血管损害与AD的潜在共同机制

2.1 Aβ/Tau病理与血管损害的相互影响

Aβ代谢失衡是连接AS相关脑血管损害与AD的重要候选机制。慢性脑低灌注和缺氧可激活缺氧相关信号,促进β-位点淀粉样前体蛋白裂解酶1(β-site amyloid precursor protein cleaving enzyme 1,BACE1)表达,促进淀粉样前体蛋白(amyloid precursor protein,APP)裂解并增加Aβ生成[15]。同时,AS相关血管损害可破坏血脑屏障转运功能,使低密度脂蛋白受体相关蛋白1(low-density lipoprotein receptor-related protein 1,LRP1)介导的Aβ外排减少,并增强晚期糖基化终末产物受体(receptor for advanced glycation end products,RAGE)介导的Aβ入脑,从而加重Aβ清除障碍[16-17]。

Tau蛋白异常同样可能受到血管病变影响。脑缺血、脑低灌注和炎性微环境可促进Tau过度磷酸化;血管平滑肌细胞功能异常亦可能参与Tau相关神经炎症反应[18-19]。Tau还可通过多聚谷氨酰胺结合蛋白1(polyglutamine binding protein 1,PQBP1)-环状GMP-AMP合成酶(cyclic GMP-AMP synthase,cGAS)-干扰素基因刺激因子(stimulator of interferon genes,STING)通路激活小胶质细胞并加重神经炎症[20]。因此,Aβ、Tau和血管损害可能相互促进,但相关证据仍以临床前机制研究和观察性研究为主。

2.2 脂质代谢、载脂蛋白E ε4与遗传易感性

脂质代谢异常是AS发生发展的核心因素,也与AD相关病理和认知结局相关。临床研究显示,AD患者可伴有血脂异常、颈动脉内膜中层厚度增加及斑块形成增多[21];动物研究亦提示,高脂或高胆固醇饮食可同时诱发主动脉AS、脑Aβ沉积和学习记忆损害[22]。机制上,高胆固醇血症可通过内皮损伤、LDL氧化、炎症激活和泡沫细胞形成加速斑块进展,同时脑内胆固醇失衡可增强BACE1与APP相互作用并促进Aβ生成[23-26]。载脂蛋白E(apolipoprotein E,APOE)ε4

等位基因是AD的重要遗传风险因素，也与AS和血管性认知损害风险相关[27]。APOE ε4可影响外周脂质代谢、BBB完整性、脑内脂质转运和Aβ清除，因而可能同时影响AS相关血管损害和AD病理涉及的多条通路[28-31]。不过，脂质指标、APOE ε4携带状态与AD风险或认知下降之间的关系受年龄、降脂治疗、血管共病和研究设计等多种因素影响，不宜简化为单一的线性因果关系。

2.3　脑低灌注、BBB/NVU损伤与Aβ清除障碍

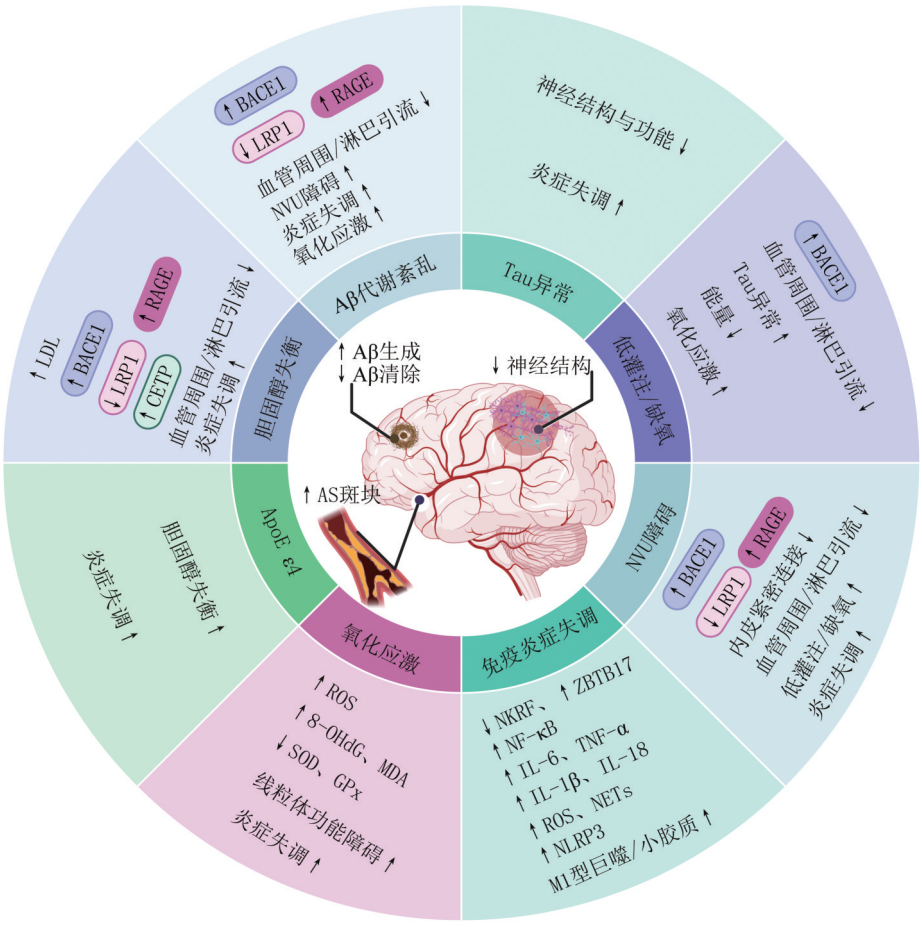
AS相关动脉狭窄、动脉僵硬和内皮功能障碍可导致慢性脑低灌注，是血管病变影响AD病理的重要环节。尸检研究显示，Willis环AS程度与散发性AD病理负荷相关。结合脑灌注研究，这一关联提示持续脑低灌注可能参与Aβ沉积、Tau异常的形成和神经元能量代谢障碍[32]。动物研究显示，高脂饮食诱导的AS可加剧AD模型中的神经退行性改变，并与慢性血小板激活和脑灌注异常相关[33-34]。

NVU由神经元、胶质细胞、内皮细胞、周细胞、平滑肌细胞和细胞外基质共同组成，负责维持脑血流调节、BBB完整性和脑内微环境稳态[35]。AD相关病理状态下，紧密连接破坏、周细胞退变、星形胶质细胞水通道蛋白4极性异常和小胶质细胞过度激活均可加重NVU功能障碍[35-36]。AS相关血管损伤进一步影响内皮功能、血管壁结构和脑血流调节能力，可能使BBB/NVU损伤、Aβ清除障碍和低灌注相互促进[37-38]。

2.4　慢性炎症、氧化应激与线粒体损伤

慢性低度炎症是AS和AD共享的重要病理背景。AS引起的系统性炎症可破坏BBB并促进外周炎症因子进入中枢神经系统，激活小胶质细胞和星形胶质细胞，释放白细胞介素-6、肿瘤坏死因子-α等促炎介质，从而加重神经炎症和NVU损伤[39-40]。转录组学和基因互作网络研究提示，两病共有的部分分子网络与核因子κB（nuclear factor-κB，NF-κB）信号和免疫清除功能障碍有关[41-42]。

氧化应激与炎症、Aβ代谢异常和线粒体功能障碍相互作用。在AS中，氧化LDL可促进巨噬细胞和泡沫细胞产生大量活性氧（reactive oxygen species，ROS），加速斑块炎症和进展[43-47]；在AD中，Aβ可激活小胶质细胞产生ROS，并促进Aβ聚集和Tau蛋白磷酸化[48-49]。线粒体功能障碍既可加重血管内皮损伤和脂质代谢稳态失衡，也可导致神经元能量代谢障碍、突触功能受损和铁死亡相关改变[50-51]。综上，AS相关脑血管损害与AD的潜在共同机制涉及Aβ/Tau病理、脂质代谢与APOE ε4相关易感性、脑低灌注与BBB/NVU功能障碍、炎症免疫失调、氧化应激及线粒体损伤。上述通路相互交织，其中炎症-氧化应激-线粒体损伤构成AS相关脑血管损害与AD病理相互影响的重要机制群（图1）。



注：本图采用Adobe Illustrator绘制；↑，升高、增强或促进；↓，降低、减弱或抑制

图1　动脉粥样硬化相关脑血管损害与阿尔茨海默病共同病理机制

3 AS相关脑血管损害的风险管理及对AD防控的启示

3.1 AS相关血管危险因素管理

与尚处于临床前阶段的机制靶向策略相比，血压、血糖和血脂管理具有较多临床研究依据。降压、控糖和降脂有助于控制AS相关血管损伤，并可能通过改善脑灌注、内皮功能和代谢稳态降低认知下降风险[52-56]。SPRINT-MIND等研究提示，强化降压与轻度认知障碍（mild cognitive impairment，MCI）风险下降相关，但其对AD特异性病理、痴呆转化和长期认知结局的影响仍需明确[55-56]。

降脂治疗是AS防治的重要组成部分，也被用于探索血脂管理与痴呆或AD风险之间的关系。观察性研究和荟萃分析提示，他汀类药物使用可能与痴呆或AD发生风险降低相关[57-60]，其潜在机制可能涉及改善脂质代谢、抑制炎症和氧化应激，以及影响Aβ生成与Tau蛋白磷酸化[61-63]。但不同研究在用药时间、药物类型、APOE状态和结局定义方面差异较大，目前不宜将降脂治疗直接视作AD治疗策略。

3.2 生活方式干预与高危人群识别

生活方式干预可作为AS相关脑血管损害和认知下降风险管理的基础措施。地中海饮食、终止高血压膳食疗法（dietary approaches to stop hypertension，DASH）、规律运动、改善睡眠和戒烟限酒等措施，有助于改善血管功能、血脂谱、炎症状态和神经可塑性，并与维持认知功能或降低痴呆风险相关[64-72]。这类证据支持长期风险管理，但不能证明某一生活方式可单独逆转AD病理进程。

APOE ε4同时与AD遗传易感性和AS相关血管风险有关，但两方面证据的强度和临床含义不同。APOE ε4是AD的重要遗传易感因素。与非携带者相比，ε4携带者的AD风险较高，且纯合者通常高于杂合者，但其效应受年龄、性别和族群等因素影响[73-74]。对于AS，近年系统综述和荟萃分析提示，APOE ε4与颈动脉粥样硬化风险升高相关，且纯合者关联更明显[75]。然而，不同研究结果并不一致，1项人群队列研究未发现ε4与颈动脉内膜中层厚度或斑块显著相关[76]。因此，研究中可按ε4非携带、杂合和纯合状态进行分组，并探索不同基因型人群的干预反应差异，但其单独用于临床AS风险识别的价值仍需验证。临床解释时应结合年龄、家族史、血脂状态、其他血管危险因素及AD生物标志物，不能仅凭APOE ε4阳性诊断AD、识别AS与AD双重高危人群或决定治疗。

3.3 临床前机制靶点与转化边界

炎症是AS与AD共同涉及的病理过程之一，因此抗炎和免疫调节是临床前研究方向之一。动物实验显示，通窍活血汤可能通过下调抵抗素、抑制炎症反应并减少靶器官脂质摄取，减轻动物模型主动脉斑块与脑内Aβ病理负荷[77]。在ApoE$^{-/-}$小鼠中，β-羟基丁酸可减轻动脉斑块与Aβ沉积。其机制可能涉及抑制NOD样受体热蛋白结构域相关蛋白3（NLR family pyrin domain containing 3，NLRP3）炎症小体，降低白细胞介素1β（interleukin-1β，IL-1β）和白细胞介素18（interleukin-18，IL-18）水平，并通过羟基羧酸受体2（hydroxycarboxylic acid receptor 2，HCA2）调节巨噬细胞表型[78-79]。在同时呈现AS与AD相关病理的兔模型中，蜂王浆活性成分10-羟基-2-癸烯酸（10-hydroxy-2-decenoic acid，10-HDA）与斑块负荷下降及Tau蛋白异常减轻相关。其作用可能涉及上调三磷酸腺苷结合盒转运体G1（ATP-binding cassette transporter G1，ABCG1）以促进胆固醇逆向转运，并调节糖原合成酶激酶3β（glycogen synthase kinase 3β，GSK-3β）磷酸化、载脂蛋白E及胆固醇24S-羟化酶（cholesterol 24-hydroxylase，CYP46）[80]。在炎性脑病小鼠模型中，抑制中性粒细胞胞外诱捕网（neutrophil extracellular traps，NETs）形成可减轻神经炎症和BBB损伤[81]。在AD小鼠模型中，给予体外扩增的人源调节性T细胞（regulatory T cell，Treg）可抑制神经炎症并减轻Aβ病理负荷[82]。在AD和AS小鼠模型中，靶向NLRP3炎症小体[83-84]和髓样细胞触发受体2（triggering receptor expressed on myeloid cells 2，TREM2）通路[85-86]，分别与Aβ清除改善和斑块稳定性提高相关。过氧化物酶体增殖物激活受体γ（peroxisome proliferator-activated receptor γ，PPARγ）激动剂具有调节血脂、抗炎和增加胰岛素敏感性的作用，有研究报告了其对AD相关认知结局和AS相关病理负荷的改善[87-88]。因此，抗炎及免疫调节策略在临床前研究中显示出一定潜力，但其临床转化价值仍需更多高质量研究加以验证。

Aβ沉积与Tau蛋白异常磷酸化是AD的核心病理标志，也是在AS与AD关系研究中的候选干预靶点。现有抗Aβ治疗在疗效、安全性和适用人群方面仍有局限。西洛他唑除用于预防心血管事件外，在临床前研究中与脑血管Aβ沉积减少及认知功能改善相关，但尚无充分证据证实其能够改善临床认知结局[89]。BACE1抑制剂可减少脑内Aβ生成，目前主要处于机制研究和药物开发阶段[90]。RAGE抑制剂（如azeliragon）在临床前研究中与脑内Aβ斑块负荷和炎症水平下降、内皮屏障保护相关[91]；LRP1靶向调控则可能促进Aβ外排，并影响糖脂代谢和心血管功能[92-93]。间充质同源盒2（mesenchyme homeobox 2，MEOX2）与心肌素（myocardin，MYOCD）等转录因子可能是潜在调控靶点，并可能通过影响血管重构和脑血流，参与AS与AD相关病理过程[94]。多数靶向Aβ/Tau及相关转运策略仍处于机制研究或临床前验证阶段，现有证据不足以支持其临床应用。

表1按证据来源和临床可用性将相关策略分为3个层级。血管危险因素控制和生活方式干预具有较多临床依据。APOE ε4携带状态主要用于评估AD遗传易感性，并可作为研究分组变量；血管风险及AS相关血管表型应单独评估，二者联合预测AD风险的效能尚待验证。其余机制靶向策略多处于临床前阶段，尚不能作为临床推荐方案。相关研究还需同时评价AS相关脑血管指标、AD生物标志物和认知结局，避免仅凭单一机制指标的改善推断临床获益（表1）。

表1 AS相关脑血管损害与AD风险识别及干预启示的证据分层概述

干预层级	干预策略	代表性措施/药物	可能作用机制	证据来源
临床基础管理	血管危险因素控制	降压、控糖、降脂等综合管理	降低血管损伤，改善脑灌注和代谢稳态，降低认知下降风险和痴呆发生风险	前瞻性队列/随机对照试验/Meta分析[52-56]
临床基础管理	降脂管理	他汀类药物	改善脂质代谢，抑制炎症与氧化应激，并可能影响Aβ生成及Tau磷酸化	流行病学研究/观察性研究/部分临床前研究[57-63]
临床基础管理	生活方式干预	地中海饮食、DASH饮食、体育锻炼、改善睡眠、戒烟限酒	改善脂质代谢，减轻炎症与氧化应激，维持血管功能和神经可塑性	前瞻性队列/Meta分析/部分干预研究[64-72]
风险分层研究	遗传易感性与血管风险评估	APOE ε4携带状态；血管危险因素及AS相关血管表型的另行评估	用于研究分组和综合风险解释；单独用于临床AS风险识别及联合预测AD风险的效能尚待验证	遗传筛查研究/系统综述与Meta分析/人群队列研究[73-76]
临床前探索	抗炎干预	通窍活血汤	下调抵抗素，抑制炎症反应和靶器官脂质摄取，可能同步影响主动脉斑块与脑内Aβ病理	基础研究/动物实验[77]
临床前探索	抗炎及代谢调节	β-羟基丁酸	抑制NLRP3炎症小体，降低IL-1β和IL-18水平，作用于羟基羧酸受体2并调节巨噬细胞表型，从而减轻神经炎症	动物实验[78-79]
临床前探索	抗炎及代谢调节	蜂王浆活性成分10-HDA	降低LDL，上调三磷酸腺苷结合盒转运体G1以促进胆固醇逆转运，调节糖原合成酶激酶3β磷酸化、载脂蛋白E和胆固醇24S-羟化酶	动物实验/转化研究[80]
临床前探索	抗炎及免疫调节	抑制NETs、增强Treg功能	调节免疫微环境，平衡炎症反应与免疫清除	机制研究/动物实验[81-82]
临床前探索	抗炎及免疫调节	MCC950	抑制NLRP3炎症小体，减轻Aβ负荷及斑块炎症	动物实验[83-84]
临床前探索	抗炎及免疫调节	TREM2激动剂	增强小胶质吞噬功能，并与学习记忆改善及斑块稳定性提高相关	动物实验/临床前研究[85-86]
临床前探索	抗炎与代谢调节	PPARγ激动剂（罗格列酮、吡格列酮）	调脂、抗炎、改善胰岛素敏感性并抑制氧化应激	机制研究/部分临床与临床前证据[87-88]
临床前探索	Aβ/Tau相关靶向调控	抗血小板相关药理干预（如西洛他唑）	可能降低脑血管Aβ负荷，并兼具血管保护作用	临床前研究/部分临床探索[89]
临床前探索	Aβ/Tau相关靶向调控	BACE1抑制剂	抑制Aβ生成	临床前研究/部分临床探索[90]
临床前探索	Aβ转运调控	RAGE抑制剂（如azeliragon）	减少Aβ入脑，减轻炎症反应并保护内皮屏障	临床前研究/部分临床探索[91]
临床前探索	Aβ转运调控	LRP1靶向调节剂	促进Aβ外排，改善糖脂代谢及血管功能	机制研究/临床前研究[92-93]
临床前探索	血管-神经调控靶点	MEOX2、MYOCD等基因调控	调节血管重塑、脑血流及神经血管稳态	机制研究/动物实验[94]

4 小结与展望

现有证据提示，AS相关脑血管损害与AD及其病理改变存在关联。颈动脉斑块、动脉僵硬、Willis环AS和慢性脑低灌注可能影响脑灌注、BBB/NVU稳态及Aβ清除，加重AD相关神经退行性病理改变。临床上，这些血管损害既可能参与AD相关认知表现，也可能参与非AD所致的认知下降或血管性认知损害。两者的潜在共同机制涉及Aβ/Tau病理、脂质代谢和APOE ε4相关易感性，以及脑低灌注、BBB/NVU损伤、慢性炎症和氧化应激。

目前研究仍存在一些局限。不同研究对AD、MCI、痴呆、认知下降和血管性认知损害的结局定义并不一致。相关证据主要来自非干预性研究，包括横断面研究、队列研究，以及基于影像学或尸检病理资料的关联分析。这些研究可识别AS相关脑血管损害与AD相关指标之间的统计关联，但难以充分排除混杂因素，亦不能单独确定因果方向。多数临床前靶点尚未经过以AD生物标志物变化和认知功能结局为终点的高质量临床验证。因此，AS相关脑血管损害更适合作为AD风险和病理进展的关联因素，以及后续干预研究的候选切入点，而非单一的明确病因。

后续研究可在前瞻性队列中同步评估AS相关脑血管损害、AD生物标志物、APOE基因型和纵向认知功能变化，并分别按血管危险因素聚集程度和客观血管损害程度进行分层。血管危险因素可按高血压、糖尿病、心脏病和吸烟的聚集个数分为0、1、2和≥3项，血管损害可分为无明确损害、亚临床AS或血管老化表型及明确的脑血管损害。各层应比较AD生物标志物和纵向认知结局，并检验血管危险因素聚集程度或血管损害严重程度与这些结局之间是否存在剂量-反应关系。在此基础上，再通过干预研究检验改善AS相关脑血管损害能否延缓AD相关病理进展或AD相关认知下降。

利益冲突 所有作者声明不存在利益冲突

作者贡献声明 高强：收集文献、论文撰写；吕丽芳：论文设计与修改

参 考 文 献

[1] Alzheimer's Disease International. World Alzheimer Report 2019：

Attitudes to dementia[EB/OL]. (2019-09-20) [2026-04-15]. https://www.alzint.org/u/WorldAlzheimerReport2019.pdf.

[2] Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease[J]. Alzheimers Dement, 2018, 14(4): 535-562.

[3] Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup[J]. Alzheimers Dement, 2024, 20(8): 5143-5169.

[4] Sweeney MD, Montagne A, Sagare AP, et al. Vascular dysfunction-The disregarded partner of Alzheimer's disease[J]. Alzheimers Dement, 2019, 15(1): 158-167.

[5] Libby P, Buring JE, Badimon L, et al. Atherosclerosis[J]. Nat Rev Dis Primers, 2019, 5: 56.

[6] World Health Organization. Cardiovascular diseases[EB/OL]. (2025-07-31) [2026-04-15]. https://www. who. int/health-topics/cardiovascular-diseases.

[7] Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis[J]. Circ Res, 2016, 118(4): 692-702.

[8] Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture[J]. Circ Res, 2014, 114(12): 1852-1866.

[9] Vataja E, Ratti G, Safa A, et al. Exploring the intersection of atherosclerosis and Alzheimer's disease: the role of inflammation and complement activation[J]. Inflamm Res, 2025, 74(1): 102.

[10] Xie BJ, Shi XR, Xing Y, et al. Association between atherosclerosis and Alzheimer's disease: A systematic review and meta-analysis[J]. Brain Behav, 2020, 10(4): e01601.

[11] Luchsinger JA, Reitz C, Honig LS, et al. Aggregation of vascular risk factors and risk of incident Alzheimer disease[J]. Neurology, 2005, 65(4): 545-551.

[12] Yarchoan M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias[J]. Brain, 2012, 135(Pt 12): 3749-3756.

[13] Høilund-Carlsen PF, Revheim ME, Alavi A. Alzheimer's disease at a crossroad: time to part from amyloid to more promising aspects-atherosclerosis for a start[J]. J Alzheimers Dis, 2022, 88(2): 455-458.

[14] Cardenas VA, Reed B, Chao LL, et al. Associations among vascular risk factors, carotid atherosclerosis, and cortical volume and thickness in older adults[J]. Stroke, 2012, 43(11): 2865-2870.

[15] Kaufman CS, Morris JK, Vidoni ED, et al. Apolipoprotein E4 moderates the association between vascular risk factors and brain pathology[J]. Alzheimer Dis Assoc Disord, 2021, 35(3): 223-229.

[16] Zhou R, Chen LL, Yang H, et al. Effect of high cholesterol regulation of LRP1 and RAGE on aβ transport across the blood-brain barrier in Alzheimer's disease[J]. Curr Alzheimer Res, 2021, 18(5): 428-442.

[17] Khowdiary MM, Al-Kuraishy HM, Al-Gareeb AI, et al. The peripheral amyloid-β nexus: connecting Alzheimer's disease with atherosclerosis through shared pathophysiological mechanisms[J]. Neuromolecular Med, 2025, 27(1): 20.

[18] Dong SY, Maniar S, Manole MD, et al. Cerebral hypoperfusion and other shared brain pathologies in ischemic stroke and Alzheimer's disease[J]. Transl Stroke Res, 2018, 9(3): 238-250.

[19] Aguilar-Pineda JA, Vera-Lopez KJ, Shrivastava P, et al. Vascular smooth muscle cell dysfunction contribute to neuroinflammation and Tau hyperphosphorylation in Alzheimer disease[J]. iScience, 2021, 24(9): 102993.

[20] Jin MH, Shiwaku H, Tanaka H, et al. Tau activates microglia *via* the PQBP1-cGAS-STING pathway to promote brain inflammation[J]. Nat Commun, 2021, 12(1): 6565.

[21] 周汝娟,何龙锦,汪小荣,等. 阿尔茨海默病与血脂代谢异常、颈动脉粥样硬化的相关性研究[J]. 实用临床医药杂志, 2016, 20(23): 149-151.

Zhou RJ, He LJ, Wang XR, et al. Correlation between Alzheimer's disease and dyslipidemia and carotid atherosclerosis[J]. J Clin Med Pract, 2016, 20(23): 149-151.

[22] Li L, Cao DF, Garber DW, et al. Association of aortic atherosclerosis with cerebral beta-amyloidosis and learning deficits in a mouse model of Alzheimer's disease[J]. Am J Pathol, 2003, 163(6): 2155-2164.

[23] Capitini C, Bigi A, Parenti N, et al. APP and Bace1: Differential effect of cholesterol enrichment on processing and plasma membrane mobility[J]. iScience, 2023, 26(5): 106611.

[24] Yang N, Lin K, Zhang J, et al. Amelioration of cholesterol rich diet-induced impaired cognition in AD transgenic mice by an LXR agonist TO901317 is associated with the activation of the LXR-β-RXR-α-ABCA1 transmembrane transport system and improving the composition of lipid raft[J]. Exp Aging Res, 2023, 49(3): 214-225.

[25] Wu MG, Zhai YY, Liang XY, et al. Connecting the dots between hypercholesterolemia and Alzheimer's disease: a potential mechanism based on 27-hydroxycholesterol[J]. Front Neurosci, 2022, 16: 842814.

[26] 张云莎,郭茂娟,李虎虎,等. Aβ的外周清除与阿尔茨海默病[J]. 现代生物医学进展, 2016, 16(22): 4398-4400.

Zhang YS, Guo MJ, Li HH, et al. Peripherocial clearance of amyloid-beta in Alzheimer's disease[J]. Prog Mod Biomed, 2016, 16(22): 4398-4400.

[27] Duong MT, Nasrallah IM, Wolk DA, et al. Cholesterol, atherosclerosis, and APOE in vascular contributions to cognitive impairment and dementia (VCID): potential mechanisms and therapy[J]. Front Aging Neurosci, 2021, 13: 647990.

[28] Pawlik J, Wrześniok D. Cholesteryl ester transfer protein: the physiological and molecular characteristics in the pathogenesis of atherosclerosis and Alzheimer's disease[J]. Postepy Hig Med Dosw, 2019, 73: 387-396.

[29] Li Q, Huang P, He QC, et al. Association between the CETP polymorphisms and the risk of Alzheimer's disease, carotid atherosclerosis, longevity, and the efficacy of statin therapy[J]. Neurobiol Aging, 2014, 35(6): 1513.e13-1513.e23.

[30] Li H, Dhanasekaran P, Alexander ET, et al. Molecular mechanisms responsible for the differential effects of apoE3 and apoE4 on plasma lipoprotein-cholesterol levels[J]. Arterioscler Thromb Vasc Biol, 2013, 33(4): 687-693.

[31] Zhang XY, Chen CY, Liu Y. Navigating the metabolic maze: anomalies in fatty acid and cholesterol processes in Alzheimer's astrocytes[J]. Alzheimers Res Ther, 2024, 16(1): 63.

[32] Kalback W, Esh C, Castaño EM, et al. Atherosclerosis, vascular amyloidosis and brain hypoperfusion in the pathogenesis of sporadic Alzheimer's disease[J]. Neurol Res, 2004, 26(5): 525-539.

[33] Wang M, Lv JY, Huang XS, et al. High-fat diet-induced atherosclerosis promotes neurodegeneration in the triple transgenic (3 × Tg) mouse model of Alzheimer's disease associated with chronic platelet activation[J]. Alzheimers Res Ther, 2021, 13(1): 144.

[34] Gupta A, Iadecola C. Impaired Aβ clearance: a potential link between atherosclerosis and Alzheimer's disease[J]. Front Aging Neurosci, 2015, 7: 115.

[35] Soto-Rojas LO, Pacheco-Herrero M, Martínez-Gómez PA, et al. The neurovascular unit dysfunction in Alzheimer's disease[J]. Int J Mol Sci, 2021, 22(4): 2022.

[36] He JT, Zhao X, Xu L, et al. Vascular risk factors and Alzheimer's disease: blood-brain barrier disruption, metabolic syndromes, and molecular links[J]. J Alzheimers Dis, 2020, 73(1): 39-58.

[37] 李 清, 刘录山. 动脉粥样硬化与阿尔茨海默病相关性研究进展[J]. 湘南学院学报(医学版), 2018, 20(1): 67-70.
Li Q, Liu LS. Research progress on the correlation between atherosclerosis and Alzheimer's disease[J]. J Xiangnan Univ Med Sci, 2018, 20(1): 67-70.

[38] Tarumi T, Zhang R. Cerebral hemodynamics of the aging brain: risk of Alzheimer disease and benefit of aerobic exercise[J]. Front Physiol, 2014, 5: 6.

[39] Stahr N, Galkina EV. Immune response at the crossroads of atherosclerosis and Alzheimer's disease[J]. Front Cardiovasc Med, 2022, 9: 870144.

[40] Olsen I, Singhrao SK, Potempa J. Citrullination as a plausible link to periodontitis, rheumatoid arthritis, atherosclerosis and Alzheimer's disease[J]. J Oral Microbiol, 2018, 10(1): 1487742.

[41] Zhang D, Chen KY, Shan LS. Meta-analysis and transcriptomic analysis reveal that NKRF and ZBTB17 regulate the NF-κB signaling pathway, contributing to the shared molecular mechanisms of Alzheimer's disease and atherosclerosis[J]. CNS Neurosci Ther, 2024, 30(5): e14683.

[42] An WH, Zhou JJ, Qiu ZQ, et al. Identification of crosstalk genes and immune characteristics between Alzheimer's disease and atherosclerosis[J]. Front Immunol, 2024, 15: 1443464.

[43] Cynn E, Li DY, O'Reilly ME, et al. Human macrophage long intergenic noncoding RNA, *SIMALR*, suppresses inflammatory macrophage apoptosis *via* NTN1 (netrin-1) [J]. Arterioscler Thromb Vasc Biol, 2023, 43(2): 286-299.

[44] Dover M, Moseley T, Biskaduros A, et al. Polyunsaturated fatty acids mend macrophage transcriptome, glycome, and phenotype in the patients with neurodegenerative diseases, including Alzheimer's disease [J]. J Alzheimers Dis, 2023, 91(1): 245-261.

[45] John A, Reddy PH. Synaptic basis of Alzheimer's disease: Focus on synaptic amyloid beta, P-tau and mitochondria[J]. Ageing Res Rev, 2021, 65: 101208.

[46] Liang T, Zhang Y, Wu SY, et al. The role of NLRP3 inflammasome in Alzheimer's disease and potential therapeutic targets[J]. Front Pharmacol, 2022, 13: 845185.

[47] Blagov AV, Markin AM, Bogatyreva AI, et al. The role of macrophages in the pathogenesis of atherosclerosis[J]. Cells, 2023, 12(4): 522.

[48] Dias D, Socodato R. Beyond amyloid and tau: the critical role of microglia in Alzheimer's disease therapeutics[J]. Biomedicines, 2025, 13(2): 279.

[49] Chang YT, Chang WN, Tsai NW, et al. The roles of biomarkers of oxidative stress and antioxidant in Alzheimer's disease: a systematic review[J]. Biomed Res Int, 2014, 2014: 182303.

[50] Xu MW, Wang WJ, Cheng JP, et al. Effects of mitochondrial dysfunction on cellular function: Role in atherosclerosis[J]. Biomed Pharmacother, 2024, 174: 116587.

[51] Zhao D, Yang KL, Guo H, et al. Mechanisms of ferroptosis in Alzheimer's disease and therapeutic effects of natural plant products: A review[J]. Biomed Pharmacother, 2023, 164: 114312.

[52] Peters R, Xu Y, Fitzgerald O, et al. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis[J]. Eur Heart J, 2022, 43(48): 4980-4990.

[53] Lourida I, Hannon E, Littlejohns TJ, et al. Association of lifestyle and genetic risk with incidence of dementia[J]. JAMA, 2019, 322(5): 430-437.

[54] Li J, Wang YJ, Zhang M, et al. Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease[J]. Neurology, 2011, 76(17): 1485-1491.

[55] SPRINT Research Group, Lewis CE, Fine LJ, et al. Final report of a trial of intensive versus standard blood-pressure control[J]. N Engl J Med, 2021, 384(20): 1921-1930.

[56] Dolui S, Detre JA, Gaussoin SA, et al. Association of intensive vs standard blood pressure control with cerebral blood flow: secondary analysis of the SPRINT MIND randomized clinical trial[J]. JAMA Neurol, 2022, 79(4): 380-389.

[57] Du Y, Yu ZJ, Li CY, et al. The role of statins in dementia or Alzheimer's disease incidence: a systematic review and meta-analysis of cohort studies[J]. Front Pharmacol, 2025, 16: 1473796.

[58] Walter J, van Echten-Deckert G. Cross-talk of membrane lipids and Alzheimer-related proteins[J]. Mol Neurodegener, 2013, 8: 34.

[59] Olmastroni E, Molari G, De Beni N, et al. Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies[J]. Eur J Prev Cardiol, 2022, 29(5): 804-814.

[60] Jamshidnejad-Tosaramandani T, Kashanian S, Al-Sabri MH, et al. Statins and cognition: Modifying factors and possible underlying mechanisms[J]. Front Aging Neurosci, 2022, 14: 968039.

[61] Reiss AB, Voloshyna I. Regulation of cerebral cholesterol metabolism in Alzheimer disease[J]. J Investig Med, 2012, 60(3): 576-582.

[62] Song GH, Liu J, Zhao ZM, et al. Simvastatin reduces atherogenesis and promotes the expression of hepatic genes associated with reverse cholesterol transport in apoE-knockout mice fed high-fat diet[J]. Lipids Health Dis, 2011, 10: 8.

[63] Degrush E, Shazeeb MS, Drachman D, et al. Cumulative effect of simvastatin, L-arginine, and tetrahydrobiopterin on cerebral blood flow and cognitive function in Alzheimer's disease[J]. Alzheimers Res Ther, 2022, 14(1): 134.

[64] Fekete M, Varga P, Ungvari Z, et al. The role of the Mediterranean diet in reducing the risk of cognitive impairement, dementia, and Alzheimer's disease: a meta-analysis[J]. GeroScience, 2025, 47(3): 3111-3130.

[65] Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of

cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts[J]. N Engl J Med, 2018, 378(25): e34.

[66] Zhang XQ, Li Q, Cong WQ, et al. Effect of physical activity on risk of Alzheimer's disease: A systematic review and meta-analysis of twenty-nine prospective cohort studies[J]. Ageing Res Rev, 2023, 92: 102127.

[67] Wang YY, Wu HJ, Sun J, et al. Effect of exercise on carotid artery intima-media thickness in adults: a systematic review and meta-analysis[J]. J Phys Act Health, 2022, 19(12): 855-867.

[68] Hörder H, Johansson L, Guo XX, et al. Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women [J]. Neurology, 2018, 90(15): e1298-e1305.

[69] Lutsey PL, Misialek JR, Mosley TH, et al. Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study[J]. Alzheimers Dement, 2018, 14(2): 157-166.

[70] Lutsey PL, Norby FL, Gottesman RF, et al. Sleep apnea, sleep duration and brain MRI markers of cerebral vascular disease and Alzheimer's disease: the atherosclerosis risk in communities study (ARIC)[J]. PLoS One, 2016, 11(7): e0158758.

[71] Ji WG, Sun J, Hu ZH, et al. Resveratrol protects against atherosclerosis by downregulating the PI3K/AKT/mTOR signaling pathway in atherosclerosis model mice[J]. Exp Ther Med, 2022, 23(6): 414.

[72] Zarezadeh M, Mahmoudinezhad M, Faghfouri AH, et al. Alcohol consumption in relation to cognitive dysfunction and dementia: A systematic review and dose-response meta-analysis of comparative longitudinal studies[J]. Ageing Res Rev, 2024, 100: 102419.

[73] Nicolas G, Zaréa A, Lacour M, et al. Assessment of Mendelian and risk-factor genes in Alzheimer disease: A prospective nationwide clinical utility study and recommendations for genetic screening[J]. Genet Med, 2024, 26(5): 101082.

[74] Williams T, Borchelt DR, Chakrabarty P. Therapeutic approaches targeting Apolipoprotein E function in Alzheimer's disease[J]. Mol Neurodegener, 2020, 15(1): 8.

[75] Culleton S, Niu M, Alexander M, et al. Extracranial carotid artery atherosclerotic plaque and APOE polymorphisms: a systematic review and meta-analysis[J]. Front Cardiovasc Med, 2023, 10: 1155916.

[76] Pitchika A, Markus MRP, Schipf S, et al. Effects of Apolipoprotein E polymorphism on carotid intima-media thickness, incident myocardial infarction and incident stroke[J]. Sci Rep, 2022, 12(1): 5142.

[77] Ha E, Kim M, Chun J, et al. Tongqiaohuoxue hinders development and progression of atherosclerosis: a possible role in Alzheimer's disease[J]. Biology, 2020, 9(11): 363.

[78] Krishnan M, Hwang JS, Kim M, et al. β-hydroxybutyrate impedes the progression of Alzheimer's disease and atherosclerosis in ApoE-deficient mice[J]. Nutrients, 2020, 12(2): 471.

[79] Yang L, Zhang XJ, Wang Q. Effects and mechanisms of SGLT2 inhibitors on the NLRP3 inflammasome, with a focus on atherosclerosis [J]. Front Endocrinol, 2022, 13: 992937.

[80] 潘永明. 蜂王浆对高胆固醇饮食致兔动脉粥样硬化和阿尔茨海默病的影响及其机制[D]. 杭州: 浙江大学, 2019.

Pan YM. Effects and mechanisms of royal jelly on atherosclerosis and Alzheimer's diseases in rabbits induced by high cholesterol diet[D]. Hangzhou: Zhejiang University, 2019.

[81] Yue JH, Mo LJ, Zeng GT, et al. Inhibition of neutrophil extracellular traps alleviates blood-brain barrier disruption and cognitive dysfunction *via* Wnt3/β-catenin/TCF_4 signaling in sepsis-associated encephalopathy[J]. J Neuroinflammation, 2025, 22(1): 87.

[82] Faridar A, Vasquez M, Thome AD, et al. *Ex vivo* expanded human regulatory T cells modify neuroinflammation in a preclinical model of Alzheimer's disease[J]. Acta Neuropathol Commun, 2022, 10(1): 144.

[83] Dempsey C, Rubio Araiz A, Bryson KJ, et al. Inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice[J]. Brain Behav Immun, 2017, 61: 306-316.

[84] van der Heijden T, Kritikou E, Venema W, et al. NLRP3 inflammasome inhibition by MCC950 reduces atherosclerotic lesion development in apolipoprotein E-deficient mice-brief report[J]. Arterioscler Thromb Vasc Biol, 2017, 37(8): 1457-1461.

[85] Zhao P, Xu YZ, Jiang LL, et al. A tetravalent TREM2 agonistic antibody reduced amyloid pathology in a mouse model of Alzheimer's disease[J]. Sci Transl Med, 2022, 14(661): eabq0095.

[86] Piollet M, Porsch F, Rizzo G, et al. TREM2 protects from atherosclerosis by limiting necrotic core formation[J]. Nat Cardiovasc Res, 2024, 3(3): 269-282.

[87] Yin LQ, Wang LH, Shi ZH, et al. The role of peroxisome proliferator-activated receptor gamma and atherosclerosis: post-translational modification and selective modulators[J]. Front Physiol, 2022, 13: 826811.

[88] Alhowail A, Alsikhan R, Alsaud M, et al. Protective effects of pioglitazone on cognitive impairment and the underlying mechanisms: a review of literature[J]. Drug Des Devel Ther, 2022, 16: 2919-2931.

[89] Yakushiji Y, Kawamoto K, Uchihashi K, et al. Low-dose phosphodiesterase III inhibitor reduces the vascular amyloid burden in amyloid-β protein precursor transgenic mice[J]. Int J Mol Sci, 2020, 21(7): 2295.

[90] Campagna J, Jagodzinska B, Wi D, et al. Discovery of an APP-selective BACE1 inhibitor for Alzheimer's disease[J]. Neurotherapeutics, 2025, 22(5): e00610.

[91] Reddy VP, Aryal P, Soni P. RAGE inhibitors in neurodegenerative diseases[J]. Biomedicines, 2023, 11(4): 1131.

[92] Sagare AP, Deane R, Zlokovic BV. Low-density lipoprotein receptor-related protein 1: a physiological Aβ homeostatic mechanism with multiple therapeutic opportunities[J]. Pharmacol Ther, 2012, 136 (1): 94-105.

[93] Actis Dato V, Chiabrando GA. The role of low-density lipoprotein receptor-related protein 1 in lipid metabolism, glucose homeostasis and inflammation[J]. Int J Mol Sci, 2018, 19(6): 1780.

[94] Sagare AP, Bell RD, Zlokovic BV. Neurovascular defects and faulty amyloid-β vascular clearance in Alzheimer's disease[J]. J Alzheimers Dis, 2013, 33(Suppl 1): S87-S100.

(收稿: 2026-05-06; 修回: 2026-07-21; 录用: 2026-08-20)

(责任编辑: 曾 玲)

本文引用格式:

高强, 吕丽芳. 动脉粥样硬化相关脑血管损害与阿尔茨海默病关系的研究进展[J]. 重庆医科大学学报, XXXX, XX(XX): 1-8.