马驰远,王新志,刘向哲,等. 小胶质细胞胞葬在阿尔茨海默病中的作用研究进展 [J]. 中国比较医学杂志, 2024, 34(11): 163-168.
Ma CY, Wang XZ, Liu XZ, et al. Research progress on the role of microglia efferocytosis in Alzheimer's disease [J]. Chin J Comp Med, 2024, 34(11): 163-168.
doi: 10.3969/j.issn.1671-7856.2024.11.020

小胶质细胞胞葬在阿尔茨海默病中的作用研究进展

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【摘要】 小胶质细胞胞葬作用是指小胶质细胞吞噬受损和死亡细胞的过程,具有抗炎和促损伤修复的作用。最新研究表明,小胶质细胞胞葬在阿尔茨海默病(Alzheimer's disease,AD)病理过程中发挥重要作用,可能是治疗 AD 的新靶标。因此本文综述了小胶质细胞胞葬与 AD 病理机制的关系以及胞葬相关分子作为 AD 治疗靶标的潜力,以期为 AD 的治疗提供新思路和新方法。

【关键词】 小胶质细胞;胞葬;阿尔茨海默病;认知障碍;神经炎症
【中图分类号】 R-33 **【文献标识码】** A **【文章编号】** 1671-7856 (2024) 11-0163-06

Research progress on the role of microglia efferocytosis in Alzheimer's disease

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【Abstract】 Microglia efferocytosis, the process by which microglia phagocytose damaged and dead cells, has anti-inflammatory and pro-damage repair effects. Recent studies have shown that microglia efferocytosis plays a crucial role in the pathogenesis of Alzheimer's disease (AD) and may be a novel therapeutic target for AD. This paper reviews the relationship between microglia efferocytosis and AD pathogenesis and the potential of using efferocytosis-related molecules as therapeutic targets for AD. The aim of this review is to provide new ideas and approaches for the treatment of AD.

【Keywords】 microglia; efferocytosis; Alzheimer's disease; cognitive impairment; neuroinflammation
Conflicts of Interest: The authors declare no conflict of interest.

[基金项目]中医药传承与创新"百千万"人才工程(岐黄工程)-国家中医药领军人才支持计划(国中医药人教发[2018]12 号);河南省中医药传承与创新人才工程(仲景工程)中医药学科领军人才(豫卫中医函[2021]8 号);河南省科技攻关项目(242102311277);国家资助博士后研究人员计划(GZC20240442);河南省自然科学基金(232300420271);河南省中医药科学研究专项(2022JDZX116)。

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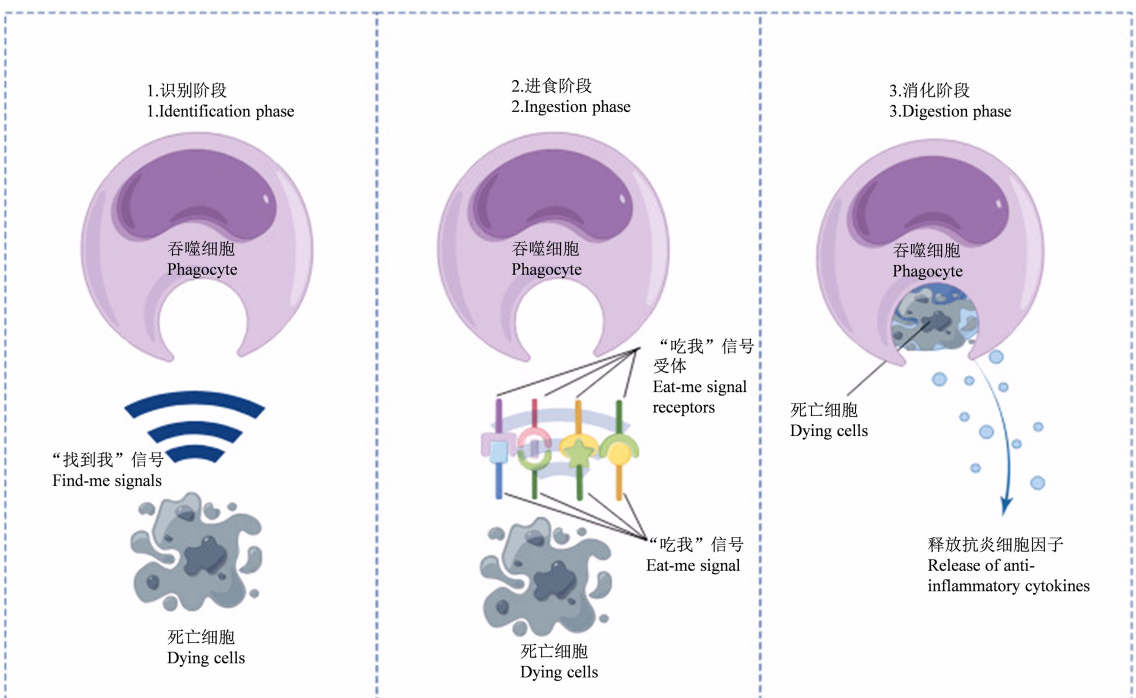
阿尔茨海默病(Alzheimer's disease,AD)是一种以认知障碍为主要症状的老年神经退行性疾病,以细胞外 β-淀粉样蛋白(amyloid-β,Aβ)斑块和细胞内微管蛋白形成的神经纤维缠结为主要病理特征[1-2]。随着人口老龄化进程的加快,AD 病例数量呈指数级增长,给患者家庭和社会带来了巨大负担[3]。由于 AD 的病理机制尚不明确,仍未找到有效改善 AD 后期认知障碍的方法,且临床上用于治疗 AD 的一线药物易导致诸多不良反应[4-5]。因此,进一步探索 AD 的病理机制并寻找新的干预靶点是医学领域面临的重大挑战,同时也是当前人类社会的迫切需要。

小胶质细胞作为中枢神经系统的"专职"吞噬细胞[6-7],是 AD 病理过程的关键参与者[8-9]。活化的小胶质细胞表现为两种功能相反的表型,M1 促炎表型释放炎症介质并诱导炎症和神经毒性,而 M2 抗炎表型通过发挥吞噬和抗炎作用保护神经细胞[10-11]。小胶质细胞吞噬作用的一个重要功能就是通过胞葬作用清除死亡细胞[12],以防止细胞继发性坏死和细胞内容物释放引起的炎症反应[13-14]。近年来,越来越多的研究表明小胶质细胞胞葬(microglial efferocytosis,ME)在 AD 病理过程中发挥重要作用,因此从胞葬的角度探讨 AD 的发生发展过程有助于进一步阐明 AD 的病理机制,并为临床治疗提供新思路。

1 胞葬概述

胞葬是指巨噬细胞吞噬受损和死亡细胞的过程[15-16]。与吞噬细胞对病原体的吞噬作用不同,胞葬不仅是一种碎片清理机制,还具有抗炎作用,对于维持组织稳态和促进损伤修复具有重要意义[13-14,17]。这是由于人体每天大约有超过 3000 亿个细胞死亡[18],巨噬细胞通过胞葬作用迅速清除这些死亡细胞,能有效防止死亡细胞及其释放的细胞内损伤相关分子模式(damage associated molecular patterns,DAMPs)引起机体免疫反应[14]。

胞葬过程大致可分为 3 个关键阶段(图 1):(1)识别阶段,凋亡细胞通过释放可溶性介质发出"发现我(find-me)"信号,以募集吞噬细胞;与此同时,这些可溶性介质能调节吞噬细胞的细胞骨架,并上



注:1. 识别阶段:吞噬细胞识别死亡细胞释放的"find-me"信号;2. 进食阶段:吞噬细胞识别死亡细胞释放的"eat-me"信号;3. 消化阶段:吞噬细胞消化死亡细胞的同时释放抗炎介质。

图 1 胞葬的 3 个关键阶段(由 Figdraw 绘制)

Note. 1. Identification phase, Phagocytes recognise the "find-me" signal released by dying cells. 2. Ingestion phase, Phagocytes recognise the "eat-me" signal released by dying cells. 3. Digestion phase, Phagocytes digest dying cells, releasing anti-inflammatory mediators.

Figure 1 Three key stages of efferocytosis(By Figdraw)

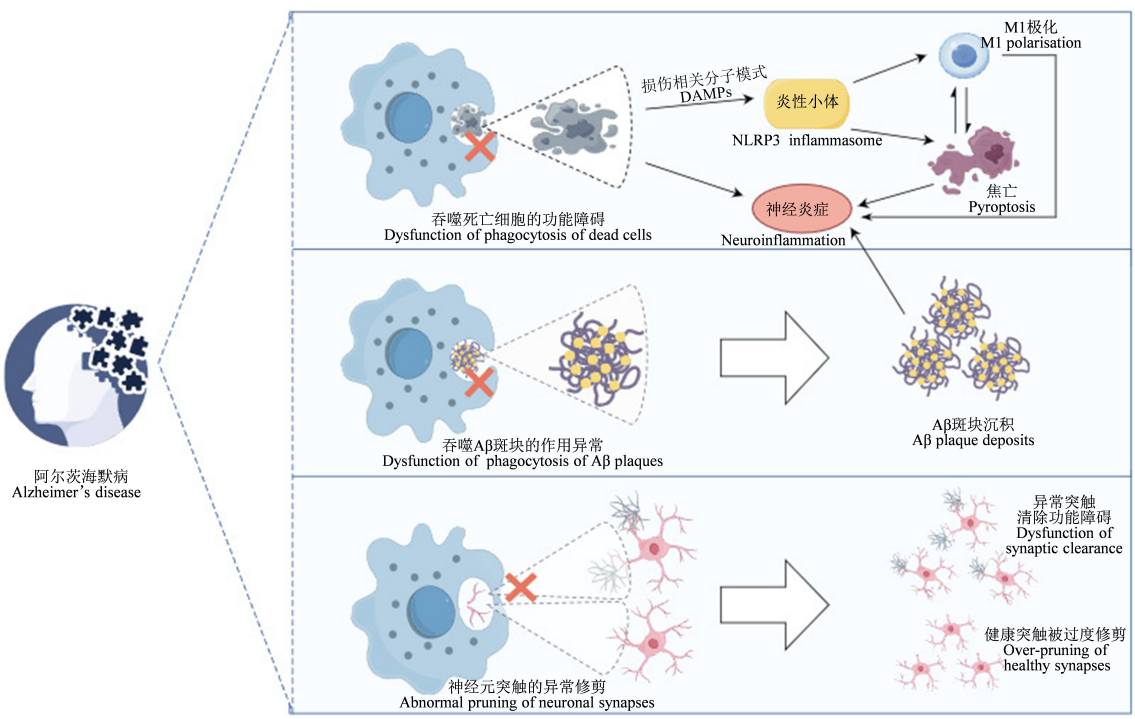
调吞噬受体和激活胞葬信号，为进食和消化阶段做准备[19]。(2)进食阶段，死亡细胞表面暴露的磷脂酰丝氨酸(phosphatidylserine，PS)等释放“吃我(eat-me)”信号，被吞噬细胞上的 T 细胞免疫球蛋白及黏蛋白结构域蛋白 4(T cell Ig and mucin domain，TIM-4)、脑组织特异性血管生成抑制因子 1(brain-specific angiogenesis inhibitor 1，BAI1)等受体识别，从而触发吞噬信号，引起细胞骨架的相应变化[14]。同时，活跃健康的细胞通过释放白细胞分化抗原 47(cluster of differentiation 47，CD47)、分化抗原 31(cluster of differentiation 31，CD31)等“别吃我(do not eat-me)”信号，以避免被巨噬细胞吞噬[20]。(3)消化阶段：死亡细胞被吞噬细胞识别和吞噬后，细胞碎片等凋亡物质会极大增加巨噬细胞免疫代谢压力，因此吞噬细胞通过加强胆固醇代谢和促进前列腺素 E2(prostaglandin E2，PGE2)、转化生长因子-β(transforming growth factor-β，TGF-β)、白细胞介素-10(interleukin，IL-10)等抗炎介质释放[7,14,21]增强对细胞内容物的降解作用。在胞葬的各阶段中，凋亡细胞和吞噬细胞通过细胞间通讯作用协同清除凋亡细胞，以促进炎症消退和组织修复[14]。

2　ME 功能障碍和 AD

2.1　ME 失调导致 AD 神经炎症

在 AD 的病理过程中，持续的神经炎症会导致突触异常修剪或丢失，造成认知能力损害[11]。同时，神经炎症还会引起小胶质细胞 M2 极化和吞噬功能被抑制，并促进促炎细胞因子释放，最终进一步加剧神经炎症[22-23]，造成神经元和突触损失[11,24-25]。在这一复杂的病理过程中，小胶质细胞是重要的触发者和参与者，其在不同阶段、不同激活状态下对 AD 的进展具有不同的影响[11,24]。

ME 通过清除死亡细胞促进小胶质细胞向 M2 抗炎表型极化，从而释放抗炎细胞因子、营养因子等，发挥抗炎作用，加速组织修复[15,20,26]，是促进炎症消退的重要机制[15,27]。ME 功能障碍会造成大量受损和死亡细胞在组织中积累，这些细胞碎片本身能作为内源性因子刺激免疫系统，能促进炎症反应；另外，未清除的死亡细胞释放大量 DAMPs 以及核蛋白(如 HMGB1)[14]，DAMPs 通过激活 NLRP3 炎症体[28]造成小胶质细胞 M1 极化/焦亡恶性循环，进一步加剧炎症反应(图 2)，导致脑稳态失调和



注：ME 功能障碍通过导致神经炎症、Aβ 斑块沉积和神经元突触异常修剪，参与 AD 的病理机制。

图 2　ME 功能障碍与 AD 病理机制密切相关(由 Figdraw 绘制)

Note. ME dysfunction is involved in the pathomechanism of AD by causing neuroinflammation, Aβ plaque deposition and abnormal pruning of neuronal synapses.

Figure 2　ME dysfunction is closely related to the pathological mechanism of AD(By Figdraw)

神经变性[29]。因此,ME 是 AD 神经炎症的潜在治疗靶点。

2.2 ME 功能障碍导致 Aβ 斑块沉积

髓样细胞触发受体 2(triggering receptor on myeloid cells 2,TREM2)是一种先天性免疫受体,其表达水平与神经炎症和 AD 发病风险密切相关[30-32]。TREM2 能促进小胶质细胞发挥吞噬功能,在胞葬中发挥关键作用[33-35]。有研究表明,TREM2 的水平降低会损害小胶质细胞对 Aβ 的吞噬作用,从而导致 Aβ 沉积和神经炎症[24,36],诱导 APP/PS1 小鼠的认知功能障碍[24](图 2)。而增强 TREM2 信号传导可以恢复小胶质细胞/巨噬细胞的吞噬能力[35],促进 Aβ 的清除,减少神经炎症[24,37]。

此外,ME 功能障碍后,神经炎症也能促使 Aβ 斑块的沉积和 tau 蛋白的异常过度磷酸化,进而抑制小胶质细胞的免疫吞噬作用,不仅加重 Aβ 斑块和 tau 蛋白聚集,更进一步加重神经炎症,导致 Aβ 斑块沉积和神经炎症的恶性循环,最终造成认知能力损害[11]。

2.3 ME 功能障碍导致突触的异常修剪

ME 的另一个重要作用是修剪不活跃神经元的突触[38]以优化神经回路和神经网络的工作效率[13]。ME 功能障碍可引起健康突触的过度修剪和异常突触清除功能障碍(图 2),这是 AD 的重要病理特征[13,39]。有研究表明,这种突触修剪机制同样由死亡细胞发出的“find me”[40]、“eat-me”[41]和“do not eat-me”[38]信号介导[13],表明 ME 在 AD 认知障碍中发挥重要作用。

3 靶向 ME 治疗 AD 的潜在靶点

3.1 靶向“识别阶段”

磷酸鞘氨醇(sphingosine-1-phosphate,S1P)是由凋亡细胞释放的“find-me”信号,与 Aβ 沉积、过度 tau 磷酸化水平呈负相关性,可作为 AD 治疗的靶点[3]。CX3CR1 在小胶质细胞中高度表达,其配体 CX3CL1 由神经元表达[42],具有神经保护和神经营养作用;CX3CR1/CX3CL1 信号通过介导小胶质细胞和神经元通讯调节 ME 对突触的修剪作用[43],在 AD 病理机制中发挥重要作用,也可作为“识别阶段”的治疗靶点。另外,在细胞凋亡的早期阶段,三磷酸腺苷(ATP)和三磷酸尿苷(UTP)释放后向吞噬细胞上的 P2Y2 受体发送信号,并引导巨噬细胞迁移,因此 P2Y2 受体能通过促进胞葬发挥保护作用[14,44]。在 AD 中,P2Y2 能刺激 $A\beta_{1-42}$ 的降解和摄取[45],并参与调节小胶质细胞对死亡神经元的清除。

3.2 靶向“进食阶段”

磷脂酰丝氨酸(phosphatidylserine,PS)是促进突触修剪的“eat-me”信号分子,通常在凋亡或损伤细胞的树突上表达[41,43]。TREM2 是小胶质细胞上的细胞表面受体,能促进突触修剪。TREM2 可以通过识别并靶向消除 PS 调控突触的修剪[43],因此可作为靶向“进食阶段”的治疗靶点。CD31 又称血小板内皮细胞黏附分子 1(platelet endothelial cell adhesion molecule 1,PECAM1),是一种“do not eat-me”信号分子,通过调控 APOE4 参与 AD 的发病机制[46];CD47 也是一种“do not eat-me”信号分子,在 AD 海马中的表达水平显著升高,且与磷酸化 tau 蛋白共表达[47],因此 CD31 和 CD47 也可作为靶向“进食阶段”的治疗靶点。此外,细胞外信号调节激酶 5(extracellular signal regulated kinase,ERK5)能同时增加“eat-me”和“find-me”信号分子的表达,并能促进 M2 极化[48],因此是 AD 等神经退行性疾病的潜在治疗靶点。

3.3 靶向“消化阶段”

死亡细胞被吞噬细胞识别和吞噬后,吞噬细胞主要通过加强胆固醇代谢和促进抗炎介质释放加快对细胞内容物的降解作用。胆固醇转运蛋白 ATP 结合盒转运子 A1(ATP-binding cassette transporter A1,ABCA1)是在胞葬后期“消化阶段”中起重要作用的蛋白,能促进胆固醇流出,并受 BAI1/ELMO1/Rac1 途径的调控[7,14]。此外,ABCA1 与 ANXA1、MEGF10、GULP1 等分子之间也存在反馈轴[49]。已有研究表明,过表达 ABCA1 有利于维持 AD 胆固醇稳态和外周动脉血管的正常功能,保持血脑屏障的完整性,并最终防止 AD[50]。因此,ABCA1、BAI1/ELMO1/Rac1 途径以及 ANXA1、MEGF10、GULP1 是靶向“消化阶段”治疗 AD 的潜在靶标。

4 展望

由于 AD 的病理机制尚不明确,目前仍未找到安全高效的治疗方法[51-52],AD 已成为全球范围内亟待解决的医疗难题。近年来,随着国内外对胞葬分子机制的深入研究,为 AD 的治疗提供了许多新思路。因此,本文综述了 ME 的 3 个关键阶段、ME

与 AD 病理机制的关系以及 ME 识别阶段、进食阶段和消化阶段的相关分子作为 AD 治疗靶标的潜力。在今后的研究中,应继续以 ME 为切入点,深入研究 AD 的病理机制和干预靶点,以发掘治疗 AD 的新方法和新靶标。

参考文献:

[1] JUCKER M, WALKER L C. Alzheimer's disease: From immunotherapy to immunoprevention [J]. Cell, 2023, 186(20): 4260-4270.

[2] GUSTAVSSON A, NORTON N, FAST T, et al. Global estimates on the number of persons across the Alzheimer's disease continuum [J]. Alzheimers Dement, 2023, 19(2): 658-670.

[3] CUSTODIA A, ROMAUS-SANJURJO D, ARAMBURU-NÚÑEZ M, et al. Ceramide/sphingosine 1-phosphate axis as a key target for diagnosis and treatment in Alzheimer's disease and other neurodegenerative diseases [J]. Int J Mol Sci, 2022, 23(15): 8082.

[4] REARDON S. FDA approves Alzheimer's drug lecanemab amid safety concerns [J]. Nature, 2023, 613(7943): 227-228.

[5] VAN DYCK C H, SWANSON C J, AISEN P, et al. Lecanemab in early Alzheimer's disease [J]. N Engl J Med, 2023, 388(1): 9-21.

[6] MÁRQUEZ-ROPERO M, BENITO E, PLAZA-ZABALA A, et al. Microglial corpse clearance: lessons from macrophages [J]. Front Immunol, 2020, 11: 506.

[7] MORIOKA S, MAUERÖDER C, RAVICHANDRAN K S. Living on the edge: efferocytosis at the interface of homeostasis and pathology [J]. Immunity, 2019, 50(5): 1149-1162.

[8] SARLUS H, HENEKA M T. Microglia in Alzheimer's disease [J]. J Clin Invest, 2017, 127(9): 3240-3249.

[9] LEPIARZ-RABA I, GBADAMOSI I, FLOREA R, et al. Metabolic regulation of microglial phagocytosis: Implications for Alzheimer's disease therapeutics [J]. Transl Neurodegener, 2023, 12(1): 48.

[10] GUO S, WANG H, YIN Y. Microglia polarization from M1 to M2 in neurodegenerative diseases [J]. Front Aging Neurosci, 2022, 14: 815347.

[11] LENG F, EDISON P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? [J]. Nat Rev Neurol, 2021, 17(3): 157-172.

[12] HALL-ROBERTS H, DANIEL E D, JAMES W S, et al. *In vitro* quantitative imaging assay for phagocytosis of dead neuroblastoma cells by iPSC-Macrophages [J]. J Vis Exp, 2021, 168: e62217.

[13] ROMERO-MOLINA C, GARRETTI F, ANDREWS S J, et al. Microglial efferocytosis: Diving into the Alzheimer's disease gene pool [J]. Neuron, 2022, 110(21): 3513-3533.

[14] POON I K H, RAVICHANDRAN K S. Targeting efferocytosis in inflammaging [J]. Annu Rev Pharmacol Toxicol, 2024, 64: 339-357.

[15] ZHANG G, LI Q, TAO W, et al. Sigma-1 receptor-regulated efferocytosis by infiltrating circulating macrophages/microglial cells protects against neuronal impairments and promotes functional recovery in cerebral ischemic stroke [J]. Theranostics, 2023, 13(2): 543-559.

[16] RAZI S, YAGHMOORIAN KHOJINI J, KARGARIJAM F, et al. Macrophage efferocytosis in health and disease [J]. Cell Biochem Funct, 2023, 41(2): 152-165.

[17] SHI H, MOORE M P, WANG X, et al. Efferocytosis in liver disease [J]. JHEP Rep, 2024, 6(1): 100960.

[18] MA L, CHEN C, LIU D, et al. Apoptotic extracellular vesicles are metabolized regulators nurturing the skin and hair [J]. Bioact Mater, 2023, 19: 626-641.

[19] MEHROTRA P, RAVICHANDRAN K S. Drugging the efferocytosis process: concepts and opportunities [J]. Nat Rev Drug Discov, 2022, 21(8): 601-620.

[20] BOADA-ROMERO E, MARTINEZ J, HECKMANN B L, et al. The clearance of dead cells by efferocytosis [J]. Nat Rev Mol Cell Biol, 2020, 21(7): 398-414.

[21] MORIOKA S, PERRY J S A, RAYMOND M H, et al. Efferocytosis induces a novel SLC program to promote glucose uptake and lactate release [J]. Nature, 2018, 563(7733): 714-718.

[22] HUANG Y, LI X, LUO G, et al. Pyroptosis as a candidate therapeutic target for Alzheimer's disease [J]. Front Aging Neurosci, 2022, 14: 996646.

[23] ZHAO R. Exercise mimetics: a novel strategy to combat neuroinflammation and Alzheimer's disease [J]. J Neuroinflammation, 2024, 21(1): 40.

[24] AL-GHRAIYBAH N F, WANG J, ALKHALIFA A E, et al. Glial cell-mediated neuroinflammation in Alzheimer's disease [J]. Int J Mol Sci, 2022, 23(18): 10572.

[25] MEGUR A, BALTRIUKIENĖ D, BUKELSKIENĖ V, et al. The microbiota-gut-brain axis and Alzheimer's disease: neuroinflammation is to blame? [J]. Nutrients, 2020, 13(1): 37.

[26] NAKAHASHI-ODA C, FUJIYAMA S, NAKAZAWA Y, et al. CD300a blockade enhances efferocytosis by infiltrating myeloid cells and ameliorates neuronal deficit after ischemic stroke [J]. Sci Immunol, 2021, 6(64): eabe7915.

[27] DORAN A C, YURDAGUL A Jr, TABAS I. Efferocytosis in health and disease [J]. Nat Rev Immunol, 2020, 20(4): 254-267.

[28] YANG Y, WANG H, KOUADIR M, et al. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors [J]. Cell Death Dis, 2019, 10(2): 128.

[29] ZHAO J, ZHANG W, WU T, et al. Efferocytosis in the central nervous system [J]. Front Cell Dev Biol, 2021, 9: 773344.

[30] POPESCU A S, BUTLER C A, ALLENDORF D H, et al. Alzheimer's disease-associated R47H TREM2 increases, but wild-type TREM2 decreases, microglial phagocytosis of

synaptosomes and neuronal loss [J]. Glia, 2023, 71(4): 974-990.

[31] DECZKOWSKA A, WEINER A, AMIT I. The physiology, pathology, and potential therapeutic applications of the TREM2 signaling pathway [J]. Cell, 2020, 181(6): 1207-1217.

[32] KONISHI H, KIYAMA H. Non-pathological roles of microglial TREM2/DAP12: TREM2/DAP12 regulates the physiological functions of microglia from development to aging [J]. Neurochem Int, 2020, 141: 104878.

[33] ZHAO Y, WU X, LI X, et al. TREM2 is a receptor for β-amyloid that mediates microglial function [J]. Neuron, 2018, 97(5): 1023-1031.

[34] WANG X, HE Q, ZHOU C, et al. Prolonged hypernutrition impairs TREM2-dependent efferocytosis to license chronic liver inflammation and NASH development [J]. Immunity, 2023, 56(1): 58-77.

[35] HU M, LIN Y, MEN X, et al. High-salt diet downregulates TREM2 expression and blunts efferocytosis of macrophages after acute ischemic stroke [J]. J Neuroinflammation, 2021, 18(1): 90.

[36] WANG Y, LIN Y, WANG L, et al. TREM2 ameliorates neuroinflammatory response and cognitive impairment *via* PI3K/AKT/FoxO3a signaling pathway in Alzheimer's disease mice [J]. Aging, 2020, 12(20): 20862-20879.

[37] EWERS M, BIECHELE G, SUÁREZ-CALVET M, et al. Higher CSF sTREM2 and microglia activation are associated with slower rates of β-amyloid accumulation [J]. EMBO Mol Med, 2020, 12(9): e12308.

[38] FAUST T E, GUNNER G, SCHAFER D P. Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS [J]. Nat Rev Neurosci, 2021, 22(11): 657-673.

[39] GRIFFITHS J, GRANT S G N. Synapse pathology in Alzheimer's disease [J]. Semin Cell Dev Biol, 2023, 139: 13-23.

[40] NONAKA S, NAKANISHI H. Microglial clearance of focal apoptotic synapses [J]. Neurosci Lett, 2019, 707: 134317.

[41] SCOTT-HEWITT N, PERRUCCI F, MORINI R, et al. Local externalization of phosphatidylserine mediates developmental synaptic pruning by microglia [J]. EMBO J, 2020, 39(16): e105380.

[42] BIVONA G, IEMMOLO M, GHERSI G. CX3CL1 pathway as a molecular target for treatment strategies in Alzheimer's disease [J]. Int J Mol Sci, 2023, 24(9): 8230.

[43] CORNELL J, SALINAS S, HUANG H Y, et al. Microglia regulation of synaptic plasticity and learning and memory [J]. Neural Regen Res, 2022, 17(4): 705-716.

[44] HONG J, HONG S G, LEE J, et al. Exercise training ameliorates cerebrovascular dysfunction in a murine model of Alzheimer's disease: role of the P2Y2 receptor and endoplasmic reticulum stress [J]. Am J Physiol Heart Circ Physiol, 2020, 318(6): H1559-H1569.

[45] MERIGHI S, POLONI T E, TERRAZZAN A, et al. Alzheimer and purinergic signaling: just a matter of inflammation? [J]. Cells, 2021, 10(5): 1267.

[46] ZHANG Z, GAN Q, HAN J, et al. CD31 as a probable responding and gate-keeping protein of the blood-brain barrier and the risk of Alzheimer's disease [J]. J Cereb Blood Flow Metab, 2023, 43(7): 1027-1041.

[47] PHONGPREECHA T, GAJERA C R, LIU C C, et al. Single-synapse analyses of Alzheimer's disease implicate pathologic tau, DJ1, CD47, and ApoE [J]. Sci Adv, 2021, 7(51): eabk0473.

[48] HEO K S, CUSHMAN H J, AKAIKE M, et al. ERK5 activation in macrophages promotes efferocytosis and inhibits atherosclerosis [J]. Circulation, 2014, 130(2): 180-191.

[49] CHEN W, LI L, WANG J, et al. The ABCA1-efferocytosis axis: a new strategy to protect against atherosclerosis [J]. Clin Chim Acta, 2021, 518: 1-8.

[50] LEWANDOWSKI C T, LAHAM M S, THATCHER G R J. Remembering your A, B, C's: Alzheimer's disease and ABCA1 [J]. Acta Pharm Sin B, 2022, 12(3): 995-1018.

[51] YU Y, LV J, MA D, et al. Microglial ApoD-induced NLRC4 inflammasome activation promotes Alzheimer's disease progression [EB/OL]. [2024-03-23]. https://onlinelibrary.wiley.com/doi/10.1002/ame2.12361.

[52] 魏玉婷, 朱田田, 苏明莉, 等. D-半乳糖法制备 AD 动物模型的分类总结与初步评价 [J]. 中国实验动物学报, 2022, 30(6): 846-856.
WEI Y T, ZHU T T, SU M L, et al. Classification and research progress on animal models of Alzheimer's disease prepared by D-galactose [J]. Acta Lab Anim Sci Sin, 2022, 30(6): 846-856.

〔收稿日期〕2024-05-06