

综述

外周免疫细胞在阿尔茨海默病中的作用及机制研究进展：聚焦肠道菌群

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[摘要] 阿尔茨海默病(AD)是常见的老年神经退行性病变, 日益增加的证据显示外周免疫细胞参与AD的发生发展。肠道菌群失调和外周免疫细胞异常均在AD早期发生; 肠道菌群可通过肠-脑轴以及对外周免疫细胞的调节作用等机制, 对中枢神经系统产生影响。靶向肠道菌群和免疫细胞的AD治疗方法日益受到重视。本文综述肠道菌群对外周免疫细胞的调节作用和机制, 及其在AD发生发展中作用的相关研究进展, 以期为AD预防、诊断和治疗的相关研究提供新思路。

[关键词] 阿尔茨海默病; 免疫细胞; 肠道菌群; 血脑屏障**Research progress on the roles and mechanisms of peripheral immune cells in Alzheimer's disease: focus on the gut microbiota**Chen Ya-Ting^{1,2,3}, Chen Qing-Cheng^{1,2,3}, Hu Li^{2,4}, Liu Zhou^{1,2,3*}¹Department of Neurology, ²Institute of Neurology, the Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524001, China³Guangdong Key Laboratory of Age-Related Cardiac and Cerebral Diseases, Zhanjiang, Guangdong 524001, China⁴Department of Histology and Embryology, Guangdong Medical University, Zhanjiang, Guangdong 524023, China

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[Abstract] Alzheimer's disease (AD) is a common neurodegenerative disease in the elderly. Increasing evidence shows that peripheral immune cells are involved in the occurrence and development of AD. Both gut microbiota dysbiosis and abnormalities of peripheral immune cells occur in the early stage of AD. The gut microbiota can influence the central nervous system through mechanisms such as the gut-brain axis and the regulatory effects on peripheral immune cells. AD treatment methods targeting the gut microbiota and immune cells have been receiving increasing attention. This review summarizes the regulatory effects and mechanisms of the gut microbiota on peripheral immune cells, as well as the research progress on the gut microbiota's roles in the occurrence and development of AD, aiming to provide new ideas for relevant research on the prevention, diagnosis, and treatment of AD.

[Key words] Alzheimer's disease; immune cells; gut microbiota; blood-brain barrier

阿尔茨海默病(Alzheimer's disease, AD)是表现为进行性认知功能障碍和行为损害的神经退行性疾病^[1]; 其主要病理特征为 β 淀粉样蛋白(amyloid-beta, A β)沉积和Tau蛋白异常磷酸化, 同时伴神经元丢失和突触功能障碍^[1-5]。AD是老年痴呆的常见病因。预

计到2050年, 全球老年痴呆患者数量将超过1亿^[6-7]。AD的病因和发病机制尚未阐明, 目前有A β 级联假说、神经炎症假说、胆碱能假说等^[8]。近年研究显示, AD患者和AD小鼠模型均呈现免疫细胞的改变, 提示免疫细胞可能在AD发生和发展中发挥重要

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作用。

肠道菌群是定居在机体胃肠道中的所有微生物群落的集合,包括细菌、真菌、病毒等^[9]。肠道菌群可调节肠道黏膜免疫细胞^[10-11],参与黏膜免疫和全身免疫^[12]。肠道和中枢神经系统(central nervous system, CNS)可通过神经、内分泌、体液、代谢和免疫等多种通信途径相互作用,即“肠-脑轴”(gut-brain axis, GBA)。多项研究显示,AD发病早期即存在肠道菌群失调^[13-16]。本文综述近年来肠道菌群对外周免疫细胞的调节及其在AD发生发展中作用的相关研究进展,以期为AD预防、诊断和治疗的相关研究提供新思路。

1 外周免疫细胞在AD中的作用

外周免疫细胞可能通过肠-脑轴对CNS的发育或功能产生影响,肠道菌群产生的短链脂肪酸(short-chain fatty acids, SCFAs)、神经递质等小分子物质通过血液循环进入大脑,或对免疫细胞产生作用,刺激后者产生细胞因子进而影响大脑(图1)。

1.1 T细胞 T细胞可分为辅助性T细胞[CD4⁺T细胞,包括辅助性T细胞17(T helper cell 17, Th17)和调节性T细胞(regulatory T cells, Tregs)等]、细胞毒性T细胞(CD8⁺T细胞)和 $\gamma\delta$ T细胞等。研究显示,AD患者Tregs比例下降且白细胞介素-10(IL-10)分泌减少^[17-18],提示Tregs介导的免疫耐受机制失衡,Tregs可能具有保护作用。AD小鼠模型相关研究显示,Tregs耗竭可加剧小胶质细胞增生、炎症反应、免疫细胞浸润,导致认知缺陷恶化^[19]。通过设计工程化特异性针对A β 的T细胞受体(T cell receptor, TCR),可赋予Tregs对A β 抗原的特异性。移植A β 特异性Tregs可减轻5xFAD小鼠(一种携带有5个家族性基因突变的APP/PS1转基因小鼠模型)的AD病理特征,改善其学习和记忆能力^[20-21]。

在AD中,Th17与Tregs之间的平衡可能被破坏。AD动物模型的相关研究显示,A β 可促使循环和脑脊液(cerebrospinal fluid, CSF)中IL-17A水平升高,Th17极化^[22],血脑屏障(blood-brain barrier, BBB)破坏,使Th17更易渗入大脑实质^[23]。Th17还可通过IL-17A激活凋亡途径诱导神经元退变^[24-25],影响小胶质细胞和星形胶质细胞的活化状态,间接影响A β 斑块清除^[26-27]。有研究显示,AD患者血清、大脑和CSF中IL-17A水平升高^[25-27],但也有研究报告AD患者的IL-17A水平降低^[28]。Th17和IL-17A在AD发病机制中的作用可能与中性粒细胞相关^[26]。

在生理状态下, $\gamma\delta$ T细胞可调节短期记忆^[29];而在AD的病理过程中, $\gamma\delta$ T细胞可借助自身 $\gamma\delta$ T细胞受体($\gamma\delta$ TCR),释放细胞毒性分子,激活小胶质

细胞和星形胶质细胞,减少A β 在大脑中的积累^[30-31],发挥类似“清道夫”的作用,有助于维持认知功能。有趣的是, $\gamma\delta$ T细胞也可分泌大量IL-17A这种促炎细胞因子^[32]。此外,AD患者可能具有独特的 $\gamma\delta$ T克隆,后者具有作为生物标志物的潜在用途^[33]。

1.2 B细胞 B细胞是适应性免疫系统的关键组成,主要负责产生抗体以对抗外来病原体。根据产生的抗体类型和细胞因子,B细胞可划分为B-1和B-2两个亚型^[34]。文献^[35]报道,在疾病状态下,B细胞可通过受损的BBB进入CNS。激活小胶质细胞和星形胶质细胞,促使促炎因子上调^[36]。

有临床研究显示,遗忘型轻度认知障碍(aMCI)患者的后扣带皮质中A β 沉积程度与B细胞数量呈正相关^[37]。相较于轻度AD患者,中重度AD患者唾液IgA水平降低^[38],提示病理状态下循环活化的B细胞向CNS的浸润可能与AD发病有关;对小鼠的研究显示AD进展需要B细胞参与^[35,39]。与健康对照组和轻度AD受试者相比,中重度AD患者B细胞亚群重塑,CD19⁺B细胞减少,幼稚B细胞(IgD⁺CD27)显著减少,而双阴性(IgG⁺IgD⁺CD27)记忆B细胞增加,并且相关促炎趋化因子表达增高,B细胞的数量和趋化因子受体的表达与AD严重程度相关^[40]。研究显示,MyD88是Toll样受体(Toll-like receptors, TLRs)信号通路中的关键蛋白,MyD88信号增强在B细胞增殖和激活中起重要作用^[41]。选择性破坏TLRs—MyD88相互作用可抑制炎症反应并减轻AD的病理严重程度^[42]。

对AD转基因小鼠模型进行治疗性耗竭B细胞可延缓AD进展,靶向B细胞可能对控制AD进展有益^[39]。B细胞可产生抗A β 抗体,一项临床研究显示,相较于健康对照者,AD患者中产生针对A β_{42} 原纤维抗体的B细胞数量较多^[43]。对Rag-5xFAD小鼠[该模型由5xFAD小鼠与Rag2^{-/-}/Il2r γ ^{-/-}双敲除背景小鼠杂交,缺乏T细胞、B细胞和自然杀伤(NK)细胞]的研究显示,该动物模型中A β 沉积显著增加,而补充IgG可缓解A β 沉积^[44]。可见,B细胞在AD中的作用较为复杂,尚需要更多的研究与探索。

1.3 单核/巨噬细胞 单核/巨噬细胞广泛分布于全身,被称为单核/巨噬细胞系统。巨噬细胞可分为两个表型:M1型(即经典活化状态)和M2型(即替代活化状态)^[45]。研究显示,M2型巨噬细胞对病原体、死亡细胞及A β 斑块具有积极响应能力^[46]。在AD中,A β 沉积可激活小胶质细胞和星形胶质细胞中的核因子- κ B(NF- κ B)信号通路,引发炎症反应^[47]。当存在慢性炎症时,AD患者外周血单核/巨噬细胞向大脑迁移增多,可识别和吞噬A β 斑块^[48];部分药物如姜

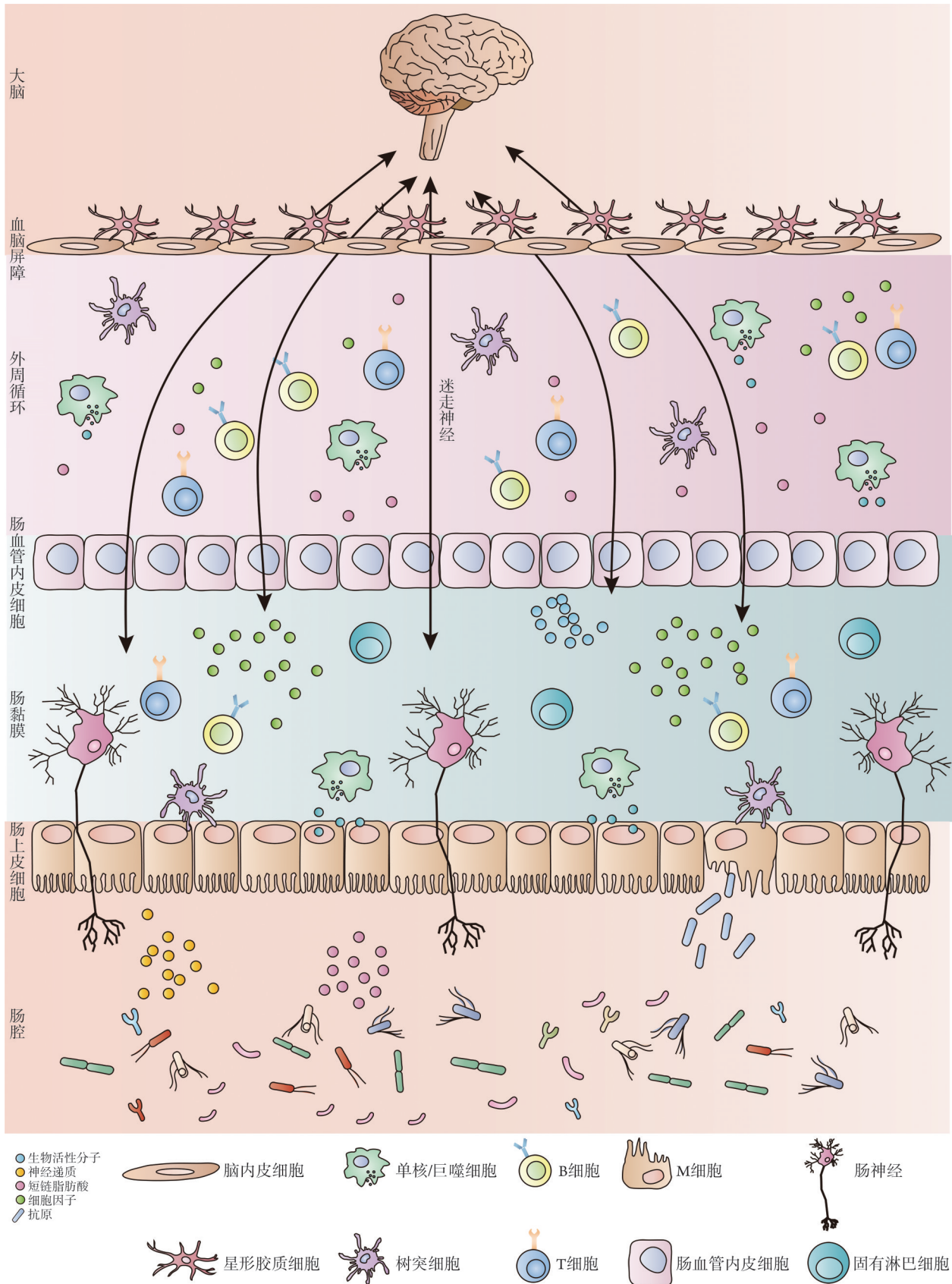


图1 外周免疫细胞和肠-脑轴之间关系示意图

Fig.1 A diagram of the correlation of peripheral immune cells and the gut-brain axis

黄素可通过缓解氧化应激，增强AD和轻度认知障碍(MCI)患者巨噬细胞对Aβ斑块的吞噬能力^[49]，缓解

Aβ在脑内的沉积。Baruch等^[50]发现，阻断程序性死亡蛋白-1(PD-1)后，5×FAD小鼠可在CNS病理部位

招募单核/巨噬细胞, 促进A β 斑块的清除。因此, 开发针对巨噬细胞的治疗, 以增强A β 斑块的清除或抑制神经炎症, 可能是AD治疗研究的一个方向。

1.4 树突细胞(DCs) 树突细胞是一种专职抗原呈递细胞, 具有连接先天性免疫和适应性免疫的独特能力^[51]。以往研究显示, DCs减少与AD的严重程度呈负相关^[52], 且外周DCs可在AD动物的大脑中被招募, 参与A β 斑块的清除^[53], 有助于缓解AD进展。近年研究显示, DCs也可通过免疫调节和增强炎症反应影响AD的进展, 如DCs对A β 的加工可启动Th1激活^[54]; 从AD患者分离的DCs可持续产生促炎分子细胞间黏附分子-1(ICAM-1), 导致Th1极化, 进而引发AD患者的炎症事件^[55]。脑细胞外Tau蛋白和A β 可通过淋巴通路 and CSF 引流至颈深部淋巴结^[56], 进一步被DCs处理和呈递, 激活T细胞^[57], 致使外周的炎症反应发生。

1.5 天然淋巴细胞(innate lymphoid cells, ILCs) ILCs是一类具有适应性免疫功能的固有免疫细胞, 包括ILC1、ILC2、ILC3和ILCreg亚群。在生理条件下, ILCs可存在于脉络丛和脑膜中, 而脑实质几乎不含ILCs; 但在神经炎症和CNS感染等病理条件下, ILCs会渗入脑实质。ILC2被证实与衰老相关, 可能具有保护作用^[58]。在AD的背景下, ILC2数量减少, 且残存的功能受到破坏, 丧失神经保护作用^[58], 甚至表达多种促炎因子^[59]。此外, ILC3亚群定位于肠上皮的孤立淋巴滤泡(ILFs)或固有层中, 其中肠固有层中的CXCR6⁺NCR⁺ILC3s是IL-22的主要来源^[60]。研究发现, IL-22可影响A β 代谢和Tau蛋白缠结^[61], 具有潜在神经保护和抗炎作用, 可能成为AD治疗的潜在靶点。近年来发现的AD患者和动物模型中免疫细胞的改变, 见表1^[17-18,37-40,43-44,48,50,53,55,58-59,62-68]。

表1 阿尔茨海默病(AD)患者和AD动物免疫细胞的变化

Tab.1 Alteration of the immune cells in Alzheimer's disease (AD) patients and animals

细胞类型	患者/动物模型	免疫细胞的改变	文献
T细胞	AD患者	外周血源性的CD8 ⁺ T细胞浸润	[62-63]
		Tregs减少、IL-10水平降低	[17-18]
		Th17增多	[64]
B细胞	AD患者	A β 原纤维抗体减少, 外周血中B细胞增多	[43]
	中重度AD患者	唾液IgA水平降低	[38]
	重度AD患者	双阴性(IgG ⁺ IgD ⁻ CD27 ⁻)记忆B细胞增加, 促炎趋化因子表达增加	[40]
	遗忘型轻度认知障碍患者	皮质中A β 沉积增多与记忆性B细胞数量呈正相关	[37]
	Rag-5xfAD小鼠	缺乏B细胞导致A β 沉积显著增加	[44]
	AD小鼠模型	B细胞增多, B细胞的积累与疾病进展相关	[39]
单核/巨噬细胞	AD患者	T和B淋巴细胞增多, IL-2、GM-CSF、TNF- α 和IL-17水平增高	[65]
	AD患者	外周血的单核/巨噬细胞迁移至大脑	[48,66]
	AD和轻度认知障碍患者	M1型巨噬细胞标志物增多, M2型巨噬细胞标志物减少	[67]
树突细胞(DCs)	SxFAD小鼠	阻断PD-1后, 中枢神经系统病理部位招募单核/巨噬细胞, 帮助A β 斑块清除	[50]
	AD患者	DCs水平与AD严重程度呈负相关	[68]
天然淋巴细胞(ILC)	AD患者	DCs中促炎分子ICAM-1持续产生, 导致Th1极化, 引发炎症事件	[55]
	AD动物	DCs在大脑中被招募, 参与A β 斑块清除	[53]
天然淋巴细胞(ILC)	AD患者/动物	ILC2数量降低, 功能破坏, 促炎基因表达上调	[58-59]

Tregs. 调节性T细胞; Th. 辅助性T细胞; A β . β 淀粉样蛋白; GM-CSF. 粒细胞-巨噬细胞集落刺激因子; TNF- α . 肿瘤坏死因子- α ; IL. 白细胞介素; PD-1. 程序性死亡蛋白-1; ICAM-1. 细胞间黏附分子-1

2 肠道菌群对外周免疫细胞的调节作用

2.1 对T细胞的影响 肠道菌群对T细胞的作用是一个动态和复杂的过程, 在健康和疾病中都扮演着重要角色。Th17与Tregs比例失衡是慢性炎症发生的关键因素之一^[69]。多种共生菌包括双歧杆菌、脆弱拟杆菌、罗伊氏乳杆菌、大肠杆菌、埃希菌、阿克曼菌及链球菌等不同类型的菌株, 可通过调节全

反式视黄酸和STAT3通路减少Th17数量^[70-71], 降低IL-17水平^[72], 减少神经元凋亡; 或调节Th17和Tregs的数量和比例^[73], 上调IL-10和转化生长因子- β (TGF- β)水平^[72], 发挥抗炎作用。例如, 在无菌(germ free, GF)小鼠中定植特定混合的上述菌株, 可塑造富含TGF- β 的微环境, 诱导肠道中Foxp3⁺Tregs提高免疫活性进而抑制炎症反应^[74]。另有研究显示, 肠菌代谢产物SCFAs可通过抑制组蛋白去乙酰化酶

(HDAC), 促进 CD4⁺ T 细胞产生 IL-22^[75], 以及抑制 $\gamma\delta$ T 细胞产生 IL-17^[76]。提示肠道菌群可通过多种途径对 T 细胞产生不同影响。

2.2 对 B 细胞的影响 AD 患者的肠道菌群组成发生显著变化, 表现为促炎细菌增加, 抗炎细菌减少。菌群失调可增加肠上皮屏障的通透性, 引起多种促炎细胞因子(如 IL-1 β 、IL-6、TNF- α)、微生物代谢物(如 SCFAs)和有毒物质[如脂多糖(LPS)]释放入血, 影响全身的免疫反应, 包括 B 细胞激活和抗体产生。近年来研究提示, 老年小鼠中由于嗜黏蛋白阿克曼菌减少, 肠道完整性破坏, 导致细菌产物(如 LPS)渗漏, CCR2⁺单核细胞被激活, 促使 B1 细胞向 4BL 细胞转化, IgA 分泌减少^[77]; B1 细胞在保护黏膜表面抵御病原体入侵和感染方面扮演着重要角色。LPS 可被宿主 B 细胞 TLRs 选择性识别^[78], 诱导产生 TLRs 配体, 并通过 MyD88 传递的信号改变 B 细胞的反应^[79-80]。纠正失调的肠道菌群则可能恢复异常的 B 细胞抗体分泌, 如节丝状细菌(SFB)可促使肠道内淋巴组织中 B 细胞分化增殖并分泌 IgA^[81], 脆弱拟杆菌也

可促进肠道中 IgA 水平升高^[82]。因此, 寻找更多可能的调节 B 细胞的有益共生菌, 有望成为 AD 的一个新疗法。

2.3 对单核/巨噬细胞的影响 研究显示, AD 患者肠道厚壁菌门数量显著减少, 而厚壁菌门是丁酸盐的主要生产者^[83]; 丁酸盐可抑制 NF- κ B 活化和 γ 干扰素(IFN- γ)信号进而发挥抗炎作用^[84-85]。在 AD 背景下, 巨噬细胞通过表面 TLR4 受体识别 LPS, 并由此转变为 M1 表型释放炎症因子, 参与炎症反应^[13,86-87]。可见, 菌群失调可导致巨噬细胞清除 A β 斑块和抗炎过程障碍, 加重 AD 相关病理变化^[88]。近期研究还提示, 肠道菌群与血管周围和肌层的巨噬细胞存在密切联系^[89-90], 它们可形成紧密的解剖屏障, 防止细菌易位并紧急修复血管^[91]; 肌层巨噬细胞还可通过 β_2 -肾上腺素能受体(β_2 -AR)信号上调神经保护因子, 并借助精氨酸酶 1 多胺轴介导神经元保护机制^[92]。近年来研究报道的、可引起免疫细胞改变的肠道微生物类别总结见表 2^[13,73-74,77,79,81,86-87,93-97]。

表 2 常见肠道微生物类别引起的免疫细胞变化

Tab.2 Alteration of the immune cells induced by common intestinal microorganism

免疫细胞	肠道菌类别	免疫细胞的变化	参考文献
T 细胞	双歧杆菌、脆弱拟杆菌、罗伊乳杆菌、大肠杆菌、埃希菌、阿克曼菌和链球菌等	Th17 和 Tregs 数量和比例改变	[73]
	梭菌属(<i>Clostridium</i>)	Tregs、IL-10 增高	[74]
B 细胞	化脓性链球菌	导致 B-1 细胞库的发育发生显著变化	[79]
	嗜黏蛋白阿克曼菌	可能使 B-1 细胞减少	[77]
	节丝状细菌(SFB)	促使肠道淋巴组织派氏结中 B-2 细胞增多, 并分泌 IgA	[81]
	大肠杆菌和双歧杆菌	CD27 ⁺ 记忆 B 细胞增多	[93-94]
	梭状芽胞杆菌 UCG-014	分泌 IL-10 的 B 细胞增多, 促炎细胞因子(如 IL-1 β 、IL-6、TNF- α)增高	[95]
	瘤胃球菌属	免疫球蛋白结合蛋白(IbpA 和 IbpB)激活 B 细胞, IgA 增高, 肠道中游离 IgA 增高	[96]
单核/巨噬细胞	厚壁菌门	M1 型巨噬细胞释放 IL-1 β 、TNF- α 等促炎因子参与炎症反应	[13,86-87,97]

Tregs. 调节性 T 细胞; Th. 辅助性 T 细胞; IL. 白细胞介素; TNF- α . 肿瘤坏死因子- α

3 基于外周免疫细胞的 AD 治疗策略

近年来, 免疫细胞在 AD 发病机制中的作用受到关注, 特别是它们在 A β 清除和神经炎症调节中的作用。一方面, 通过补充抗体或补充产生相应抗体的 B 细胞, 有助于 AD 动物中 A β 斑块的清除^[44]; 另一方面, 通过 B220/CD20 抗体中和耗竭 B 细胞, 可导致海马区 IgG 水平降低和抗炎小胶质细胞数量增加^[39,98-99], 缓解神经炎症; 提示 B 细胞在 AD 治疗中可发挥多重作用。体外研究显示, 治疗剂量的美金刚可诱导人外周血 CD4⁺ T 细胞耗竭, 可能因此缓解

AD 病理改变^[100]。移植 A β 特异性 Tregs 和抑制 C3⁺A1 样反应能抑制有害的小胶质细胞或星形胶质细胞, 促进其有益功能^[101], 减少 APP/PS1 小鼠中 A β 沉积, 减轻神经炎症^[102]。研究发现, NK 细胞在老年人和老年小鼠大脑齿状回中优先积累, 提示衰老可能增加大脑中的 NK 细胞, 而使用针对 NK1.1 抗原的单克隆抗体耗竭 NK 细胞则可促进神经生长和减轻炎症, 改善 AD 小鼠的认知功能^[103]。文献[63]报道, 抑制 TGF- β 信号可将 M2 型巨噬细胞招募到脑内 A β 沉积部位, 有助于清除脑内 A β 斑块, 修复行为障碍。

免疫细胞在 AD 治疗中展现出巨大潜力, 但仍然

存在很多未知, 未来需要进一步探索这些细胞的具体作用机制。近年来靶向外周免疫细胞治疗AD的基

础研究或临床试验总结见表3^[39,44,63,98-103]。

表3 靶向外周免疫细胞的阿尔茨海默病(AD)治疗

Tab.3 Targeting peripheral immune cells for Alzheimer's disease (AD)

免疫细胞	治疗方法	治疗效果	治疗机制	参考文献
B细胞	补充产生IgG的B细胞或IgG	Rag-5×fAD小鼠脑内A β 沉积减少	恢复B细胞数量和功能, 以及IgG介导免疫途径, 促进A β 清除, 减轻神经炎症, 缓解AD进展	[44]
	B细胞耗竭	AD动物脑内A β 沉积减少, 改善认知功能	B细胞被B220/CD20抗体中和, 缓解大脑中IgG沉积和增加抗炎小胶质细胞, 促进A β 斑块清除, 缓解AD病理过程	[39,98-99]
CD4 ⁺ T细胞	CD4 ⁺ T细胞耗竭	改善AD患者异常的免疫病理	治疗剂量美金刚通过阻断Kv1.3通道而诱导CD4 ⁺ T细胞耗竭	[100]
Tregs	移植A β 特异性Tregs	改善AD动物模型的神经毒性和神经退行性变	Tregs抑制有害的小胶质细胞和星形胶质细胞, 减轻神经炎症反应	[101]
	激活Tregs	APP/PS1小鼠中的认知功能和神经炎症得到改善	增强外周和CNS中抗炎和Tregs激活, 减少A β 斑块沉积, 增加小胶质细胞激活, 减轻神经炎症	[102]
NK细胞	NK细胞耗竭	减轻炎症, 改善AD小鼠的认知功能	使用NK1.1抗原的单克隆抗体耗竭NK细胞, 促进神经发生, 减轻炎症	[103]
单核/巨噬细胞	M2型巨噬细胞	APP/PS1小鼠脑内A β 减少, 行为障碍得到修复	阻断先天免疫细胞中TGF- β 和下游Smad2/3信号(TGF- β -Smad2/3)可显著减少脑内淀粉样蛋白负荷	[63]

Tregs. 调节性T细胞; A β . β 淀粉样蛋白; CNS. 中枢神经系统; NK. 自然杀伤; TGF- β . 转化生长因子- β

4 总结与展望

本文总结了近年来发现的外周免疫细胞在AD中的作用, 特别是肠道菌群对免疫细胞的调节在AD发生发展中的重要作用, 以及相关治疗策略的探索, 为理解AD发病机制、寻找新的治疗途径提供新视角。尽管面临挑战, 但这一领域的进展为AD的预防、诊断和治疗提供了新希望。

受到肠道菌群调节的外周免疫细胞可能在AD早期阶段即发生变化, 但目前大规模研究尚少, 需要更多的临床和基础研究来探究外周免疫细胞具体的改变及其分子机制, 以促进AD早期诊断生物标志物的开发。例如, 通过粪便样本或外周循环免疫细胞来检测这些肠菌或免疫细胞标志物, 可减少侵入性操作并使常规体检中纳入AD早期筛查成为可能。此外, 结合其他已知的AD风险因素(如遗传因素、生活方式等), 可建立更为精准的预测模型。通过追踪健康人群中肠道菌群或外周免疫细胞的动态变化, 识别可预示AD发生的早期变化。还可将外周免疫细胞数据与基因组学、代谢组学等其他组学数据结合, 提高筛选标志物的可靠性; 通过大规模临床试验来验证这些潜在标志物的实际诊断价值, 评估这些标志物在不同人群中的诊断敏感度和特异性, 确保其在实际应用中的可靠性和有效性。这一领域的进一步研究将有助于提高AD的早期发现, 为患者提供更早期的干预和治疗机会, 进而改善患者的生活质量。

由于AD的发病机制复杂, 单一治疗手段往往难以取得满意效果; 而基于外周免疫细胞的个体化治疗策略可能是未来AD治疗的重要方向。通过评估患者外周免疫细胞的功能状态, 选择适当的免疫调节治疗策略, 结合患者的遗传背景及肠道菌群的表型, 如APOE基因型、肠菌丰度, 可制定更加精准的肠菌-免疫干预策略。随着基因编辑技术的不断发展, 未来还可能通过基因疗法直接干预肠道菌群的组成和功能。随着研究深入和技术进步, 有理由相信这一领域将为AD患者带来更加有效和个性化的治疗方案。

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