

·综述·

T淋巴细胞与阿尔茨海默病相关性的研究进展

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摘要 阿尔茨海默病(AD)是一种中枢神经系统退行性疾病。神经炎症是影响AD进展的关键因素,研究显示AD患者脑实质内存在外周T淋巴细胞及其亚群的浸润,提示外周免疫细胞可通过血脑屏障并介导和参与中枢神经炎症的调节,影响AD病程进展。本文将阐述T淋巴细胞及其亚群与AD疾病发展之间的相关性和研究进展,并概述AD的主要治疗药物与炎症相关性。
关键词 阿尔茨海默病;T淋巴细胞;亚群;研究进展
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Research Progress on the Correlation between T Lymphocytes and Alzheimer's Disease LIU Yanmei¹, MENG XinLing². 1. The Fourth Clinical Medical College of Xinjiang Medical University, Xinjiang Urumchi 830000, China; 2. Department of neurology, Affiliated Hospital of Traditional Chinese Medicine of Xinjiang Medical University, Xinjiang Urumchi 830000, China
Abstract Alzheimer's disease (AD) is a neurodegenerative disease. Neuroinflammation is a key factor affecting the progression of AD. In recent years, a number of studies have identified the infiltration of peripheral T lymphocytes and their subsets in the brain parenchyma of AD patients, which confirmed that peripheral immune cells can cross the blood-brain barrier and participate in the regulation of central neuroinflammation, affecting the progression of AD. In this review, we will describe the research progress on the correlation between T lymphocytes, their subsets and the development of AD, and summarize the correlation between inflammation and the main therapeutic drugs for AD.
Keywords Alzheimer's disease; T lymphocytes; subset; research progress

1 AD概述

阿尔茨海默病(Alzheimer disease, AD)是一种中枢神经系统退行性疾病,以进行性认知功能下降及行为改变为主要表现^[1]。根据2020年发布的一项全国性的横断面研究结果显示,中国60岁及以上的痴呆患者约有1507万,其中AD患者约为983万,是目前老年痴呆的主要类型^[2]。《2022年中国阿尔茨海默病报告》统计结果显示,随着中国人口老龄化程度的加深,AD的发病率和死亡率逐步上升,目前AD已成为中国城乡居民的第5大死因^[3]。但AD在我国的诊断和治疗率仍然较低,积极寻找影响AD发生发展的相关因素,并对其尽早进行防治尤为重要。

2 T淋巴细胞与AD

AD所公认的病理学特征是淀粉样蛋白 β (amyloid β , A β)的细胞外沉积、Tau蛋白的细胞内聚集引起神经原纤维缠结(neurofibrillary tangles, NFTs)和神经变性。然而,AD发病的具体发病机制目前仍不明确,其中神经炎症持续存在被认为是驱使疾病发展的关键因素。当中枢神经系统(central nervous system, CNS)内固有的小胶质细胞和星形胶质细胞被疾病蛋白激活,可通过产生炎症和神经毒性因子导致神经损伤^[4]。近年来已有研究证明

AD患者CNS神经炎症与T淋巴细胞(T lymphocyte)(下简称T细胞)浸润增加相关,并在小鼠模型和患者的尸检样本中发现其浸润部位靠近A β 沉积物,证实T细胞及其亚群可通过AD患者的受损的血脑屏障(Blood-Brain Barrier, BBB)渗透CNS从而介导神经炎症,影响AD的病理学改变及认知损伤^[5,6]。然而,T细胞分类复杂且各亚群参与AD发展的机制及变化程度不同^[7],因其功能主要取决CD4⁺、CD8⁺和调节性T细胞,故对此3类进行逐一论述。

2.1 CD4⁺T细胞

AD患者存在外周免疫功能障碍,CD4⁺亦可通过BBB从外周渗透CNS与脑内神经胶质细胞相互作用而影响神经元活性^[8]。近年Machhi等^[9]在APP-PS1小鼠实验研究中发现CD4⁺可加速AD的病程进展,主要印证了其亚型A β -Th1和A β -Th17的自身反应性效应T细胞(Teffs)均可通过下调周围神经系统和CNS内Treg细胞的作用,促进AD的病理学改变发生,同时伴随小胶质细胞激活升高和神经炎症加剧,迫使记忆障碍加剧。此外,CD4⁺T细胞的主要亚型Th1、Th17和Th2参与AD机制亦有区别。

2.1.1 Th1 Th1分泌的细胞因子干扰素- γ (interferon- γ , IFN- γ)可活化巨噬细胞以增强细胞介导的抗

感染免疫,早期 Browne 等^[10]的实验研究证实,IFN- γ 在大脑中的有限表达有利于T细胞浸润到CNS,并与小胶质细胞形成免疫突触,而渗入大脑的T细胞亦可产生IFN- γ 促进小胶质细胞激活增加、A β 沉积和认知功能受损。同时,在5XFAD小鼠的脑室内注射A β -Th1细胞后,也促进了IFN- γ 和趋化因子CXCL9、CXCL10和CXCL11的表达^[11];与实验结果相一致的是,在AD患者及轻度认知障碍(mild cognitive impairment, MCI)受试者的脑脊液中检测到IFN- γ 诱导的CXCL10浓度明显增加,并与简易精神状态量表评分呈正相关^[12]。除此以外,IFN- γ 等炎症因子还可抑制人脑血管平滑肌的强直收缩力加重AD患者的微出血,炎症细胞因子产生的自身调节紊乱可导致脑灌注受损,并导致AD患者微出血和A β 清除失调,使患者的认知受损更为严重^[13],这也提示了在AD疾病进展中的微出血。

2.1.2 Th17 Th17是研究最多的CD4 Th亚群之一,目前已有研究表示AD患者大脑中活化的Th17细胞及其炎症细胞因子(如IL-17A、IL-21和IL-23)可能协同促进其神经病理学改变^[14]。与此观点相证,在AD的三重转基因小鼠模型大脑中发现了较高水平的IL-17A、TNF- α 、IL-2和GM-CSF^[15];另一项研究中,在注射了A β_{42} 肽的小鼠海马体、外周血和脑脊液中也发现IL-17A和IL-22显著增加^[16],可见IL-17A在AD进展中变化明显。Zenaro等^[17]的研究结果也表明A β 聚集物可介导嗜中性粒细胞的募集和趋化产生IL-17A,而IL-17A对神经元和BBB有直接毒性,并可能扩增CNS中的嗜中性粒细胞,从而导致病理恶化。现有数据充分提示Th17极化与AD的神经变性有关。因此,研究者提出,最佳的AD疫苗应抑制Th17对A β 的免疫应答^[18],以预防神经炎症和后续神经退行性变。

2.1.3 Th2 与Th1和Th17作用相反的是,Th2可分别抑制Th1和Th17对细胞因子IFN- γ 和IL-17产生的胶质诱导,可调节减弱A β 特异性Th1和Th17诱导的神经炎症激活,减低小胶质细胞反应性及A β 病理学^[19]。与此同时,Walsh等^[20]通过实验室研究表明Th2的细胞因子IL-4对受损的CNS神经具有保护和恢复作用;且在临床AD型MCI患者的外周血中发现较高浓度的IL-4,而随着疾病严重程度逐渐增加IL-4水平出现降低^[21]。Th2的作用机制研究为AD治疗提供了研究靶点,目前许多针对AD的预防性疫苗正在研发,为了延缓AD的发作,疫苗中含有的佐剂需能诱导有效抗炎作用的Th2免疫反应,这种免疫反应可能介导产生针对神经毒性A β 和抗炎细胞因子的中和抗体^[22],从而预防AD相关炎症。

2.2 CD8⁺ T细胞

在AD等认知相关疾病中,CD8⁺T细胞已被发现是浸润大脑结构的主要T细胞类型^[23],Unger等^[24]在小鼠模型脑实质中发现CD8⁺T细胞与小胶质细胞以及神经元结构密切相关,实验证明CD8⁺T细胞以年龄和病理依赖性的方式浸润脑实质,认为CD8⁺T细胞在功能上参与调节突触可塑性,可能塑造神经元。同时一项Tau转基因小鼠研究结果显示CD8⁺T细胞可穿过BBB,间接、直接地影响小胶质细胞的功能特性,促进神经炎症

和认知能力下降^[25],因而促进AD进展。在外周环境中,一项包括36项研究涉及2339例AD患者的荟萃分析显示,与健康对照组相比,AD患者外周的CD4/CD8比率增加以及CD8⁺T细胞百分比降低^[26]。

为进一步证实CD8⁺在疾病发病机制中的活性作用,在被诊断为AD和AD型MCI患者的外周血中,发现CD8⁺效应记忆CD45RA⁺细胞(TEMRA)的数量增加,这种T细胞群具有分泌促炎细胞因子和细胞毒性分子的强大效能,并与神经认知障碍的发展程度呈负相关,或许CD8⁺TEMRA细胞数量增多可作为AD的一个免疫特征^[27]。另有AD患者和动物模型的海马和皮质下白质中检测到具有组织驻留记忆T(Trm)细胞特征的CD8⁺T细胞^[28,29],且有最新研究发现,APP-PS1小鼠海马中的CD8⁺表达与Trm T细胞组织停留相关的蛋白,即CXCR6、LITAF和ISG20,且与慢性感染模型小鼠的脑Trm CD8⁺T细胞具有高相似性^[28]。然而,它们的具体作用还有待进一步探究。

2.3 调节性T细胞(Treg)

Treg是CD4⁺的一个抗炎亚群,可抑制其他Th亚群的促炎免疫反应,维持免疫稳态。在啮齿动物和人类中,它们的细胞表型由IL-2受体 α (CD25)及转录因子Foxp3的高表达和IL-7受体(CD127)的低表达所定义,稳定表达Foxp3的Treg细胞是维持外周免疫耐受的关键^[30]。近年多项探讨AD外周生物标志物的临床研究结果显示,AD痴呆患者的外周血中Treg细胞的比例明显降低且抑制功能受损,对于Treg在疾病过程中的明显活性抑制也成为一个新的治疗靶点,Treg扩增目前正在被转化为神经退行性疾病的细胞疗法^[31,32]。

早期研究发现Treg的早期损耗可加速小鼠认知障碍的发生,通过外周低剂量IL-2治疗扩增Treg有助于认知能力改善^[33],认为Treg可通过调节小胶质细胞对A β 沉积的反应减慢疾病进展。此外,Back等^[34]将Treg细胞移植到3xTg-AD小鼠体内,结果不仅改善了小鼠的空间学习和记忆,还利于减少大脑中A β 斑块的沉积和炎症细胞因子的产生,均提示Treg细胞诱导的免疫抑制对AD病理发展的重要。然而,Baruch等^[35]通过靶向Foxp3⁺Tregs破坏5XFAD小鼠的免疫耐受发现,Treg可增强IFN- γ 依赖的大脑的脉络丛通道活性,导致免疫细胞在病理部位积累,认为Treg并没有在AD病理学中起积极作用。近年,有研究通过早期接种灭活流感疫苗使小鼠的认知缺陷改善和A β 负担减轻,但灭活流感疫苗诱导的免疫反应激活小胶质细胞也降低了外周Treg活性,通过全反式维甲酸恢复外周Treg水平反而削弱了灭活流感疫苗对A β 负荷和认知功能的保护作用^[36]。由此Treg在AD中的功能作用仍存在矛盾和争议,其因果关系仍在继续研究中。

3 AD治疗药物

目前临床应用最为广泛的是作用于胆碱能系统的药物,如多奈哌齐、卡巴拉汀和加兰他敏,通过抑制乙酰胆碱酯酶(acetylcholinesterase, AChE)的作用,从而维持AD患者脑中乙酰胆碱含量^[37],另外N-甲基-D-天冬氨酸(N-methyl-D-aspartic

acid, NMDA)拮抗剂中美金刚是该类别中唯一批准用于治疗中度至重度AD的药物^[38]。近年多项研究显示不同治疗药物对于AD患者外周免疫也有影响。结果显示,多奈哌齐可抑制Th1数量,但不抑制Th2;给予卡巴拉汀可减少AD患者血液中的T细胞增殖,抑制Th1和Th17但不抑制Th2;美金刚可以选择性地抑制Th1,但无法抑制Th2或Treg^[39]。通过调节脑-肠轴改善认知功能的新型药物甘露特纳(GV-971)被发现可有效修复肠道微生物群的同时,也减少了大脑中Th1相关的神经炎症^[40],在临床亦取得良好的疗效。目前AD药物研发中淀粉样蛋白靶向疗法仍然是主要开发途径,炎症也成为了临床前和临床开发第2大类别^[41],今后将有更多药物进入临床以改善AD疾病的进程及预后。

4 总结

综上所述,大量研究已证明AD患者存在外周免疫功能紊乱,外周T淋巴细胞及其亚群直接或间接影响AD病程中神经炎症的发展,与病理学改变及认知损伤程度息息相关。但AD的发病机制复杂涉及因素众多,具体机制目前仍在研究探索中。同时,靶向神经炎症遗传通路的药物正在开发,通过改善免疫功能来减缓疾病进展也是AD治疗研究方向。

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