· 综述 ·

炎性免疫参与阿尔茨海默病发病机制的研究进展

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【摘要】 阿尔茨海默病(AD)是一类好发于老年人的退行性疾病，常表现为记忆障碍和行为失常，严重危害老年人的身心健康与生活质量。攻克AD已经成为世界性的热点问题。目前的研究表明，神经性炎性免疫反应在AD发病机制中发挥着重要的作用。本文就神经炎症与免疫因素对AD发病机制的作用研究进行综述，以期为预防和治疗AD提供新线索。

【关键词】 阿尔茨海默病；　神经炎症；　小胶质细胞；　星形胶质细胞；　综述

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【Abstract】 Alzheimer disease (AD) is a age-related progressive neurodegenerative disease, which is clinically manifested as memory impairment and behavioral disorders. It seriously endanger the physical and mental health and life quality of the elderly worldwide and represent a challenge for the public health. Current studies have shown that neuroinflammatory immune response plays an important role in the pathogenesis of AD. This paper reviews the role of neuroinflammation and immune factors in the pathogenesis of AD, in order to provide new clues for the prevention and treatment of AD.

【Key words】 Alzheimer disease；　Neuroinflammation；　Microglia；　Astrocytes；　Review

AD的概念是1907年由德国巴伐利亚精神病学家和神经学家Alois Alzheimer首次提出[1]。其是一类发病较为隐匿的进行性中枢神经系统(central nervous system，CNS)退行性疾病，常好发于老年人。AD在临床中表现为记忆力减退、语言丢失、执行功能的障碍以及人格和行为改变等[2]。随着人们生活水平的提高和习惯的改变，人类寿命普遍延长，社会人口老龄化趋势加剧，AD患者的人数在不断上升。有研究显示，在所有痴呆症的病例中，AD占60%～80%，全球现已有五千多万AD患者[3]，严重危害了老年人的身心健康与生活质量。

迄今为止，对于AD的发病机制仍未明确，其起病原因众说纷纭，包括Aβ淀粉样假说、tau蛋白过度磷酸化假说、基因突变假说、神经炎症反应假说、胆碱能假说、突触障碍假说、氧化应激假说等[4]。因AD发病原因是多种因素的共同作用，机制复杂，临床中亦无特效药治疗。越来越多的研究表明，神经炎症在AD的发展中起着至关重要作用，因此研究炎性免疫对攻克AD具有一定的现实意义。

一、炎性免疫反应在AD中的作用与临床依据

CNS是机体免疫系统的一个重要组成部分，机体通过大脑中的先天性免疫系统维持自稳状态。因为机体存在血-脑积液屏障(blood-brain barrier，BBB)，在正常情况下免疫细胞和免疫分子不能进入CNS内，所以CNS常被视作为“免疫豁免”区。但是BBB的通透性可以被外来因素所影响，例如，在AD中，当CNS中存在伤害性刺激时，就会刺激神经胶质细胞活化以修复受损区域和清除大脑中的Aβ，保护神经元免受Aβ毒性伤害[5]。虽然CNS对炎性的免疫反应是对机体大脑的一种保护性反应，但神经胶质细胞过度激活释放的神经毒性物质会引起CNS的慢性炎症，导致适应性免疫的发生，最终使得神经元的变性损伤，进一步加强AD的病程发展[6]。因此，炎性免疫与AD的发展密不可分。

在AD发病机制中，小胶质细胞和星形胶质细胞过度活化增殖能产生多种细胞因子(cytokine，

CK)。研究资料表明,在AD患者血液中,与先天性免疫和适应性免疫相关的细胞因子如IL-1β、IL-6、TNF-α的升高[7]。同样地,一项Meta分析表明,AD患者血清中的IL-6、转化生长因子β1(transforming growth factor-β1, TGF-β1)和IL-1α水平均显著高于正常对照组[8]。此外,有Meta分析表明,IL-6、IL-8、IL-10的基因多态性可能影响AD的易感性[9]。上述结果提示这些细胞因子可能成为AD诊断的标志物之一。在一项随机对照实验中,长期使用非甾体抗炎药阿司匹林的AD患者的认知能力的下降较对照组缓慢[10]。黎敏等[11]通过检测76例AD确诊患者血清中IL-1β的表达,发现IL-1β的表达随AD疾病程度加深而上调,且测试出IL-1β的受试者工作特征(receiver operating characteristic, ROC)曲线下面积为0.851,表明IL-1β在AD诊断中存在良好的诊断价值。这些结果均为炎性免疫密切参与了AD的发展提供了有力的证据。

二、炎性免疫在AD发病过程中的调控机制

1.神经胶质细胞(Glial cell)在AD发展中的作用机制:(1)小胶质细胞(Microglia)。其是神经炎症的重要调节因子[12]。在正常大脑中,成熟的小胶质细胞以静息态存在,通过表面受体监测CNS中的病原体,并且与神经元相互作用控制神经元的发育,包括神经回路形成和维持神经元突触可塑性[13]。当大脑环境稳态受到病理性损害时,小胶质细胞率先激活,并改变其表型和形态,启动防御程序[14],进入活化状态。钙离子结合衔接分子1(ionized calcium binding adaptor molecule 1, Iba1)是小胶质细胞内特异性钙结合蛋白,可以用来标记激活的小胶质细胞[15]。在使用β-淀粉样蛋白寡聚体(β-amyloid oligomers, AβO)刺激小胶质细胞后,能明显观察到用Iba1标记的小胶质细胞体积变大、分支变少变短的活化状态[16]。活化的小胶质细胞功能复杂多样。在受到病理性刺激的早期,小胶质细胞处于抗炎状态,可以吞噬侵入大脑中的病原体和受损细胞并释放神经生长因子(nerve growth factor, NGF)[17]。受细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)/c-myc信号通路的调节,小胶质细胞也能呈递抗原和激活早期T细胞维持大脑的稳态[12, 18]。另外,小胶质细胞可清除AD大脑内聚集的Aβ,减缓AD的发展[19]。当大脑恢复稳态时,小胶质细胞将变回静止状态[20]。但如果受到Aβ和过度磷酸化的tau蛋白等抗原的持续刺激,小胶质细胞会过度激活并转变为促炎状态,合成和分泌大量炎症介质诱导神经炎症的发生,加速AD的病理进程[21]。例如,在大鼠脑内注射AβO后,能够在海马区检测到小胶质细胞的持续激活,并且在脑脊液和血清中检测到相关促炎因子TNF、IL-12b、一氧化氮合酶2(nitric oxide synthase 2, NOS2)、谷氨酸以及NOD样受体家族蛋白3(NOD-like receptor family protein 3, NLRP3)炎性小体的上调;且持续激活的小胶质细胞能够导致AD大鼠的记忆障碍[22],也能通过激活磷酸化蛋白质激酶导致tau蛋白的过度磷酸化[23]。此外,活化的小胶质细胞释放的活性氧(reactive oxygen species, ROS)能作为第二信使启动核转录因子-κB(nuclearfactor κB, NF-κB)依赖的信号通路,导致NLRP3炎性小体和IL-1β的表达上调,生成活化的半胱天冬酶-1(caspase-1)。caspase-1能进一步介导IL-1β的成熟与释放,降低小胶质细胞对Aβ的清除能力[24],也能导致线粒体损伤、ATP失调和神经元死亡[25-27]。这种损伤会导致小胶质细胞正常代谢和功能受损[28],进一步影响AD的病程发展;而在尚未发现神经变性和脑萎缩的AD早期患者中,发现BBB内皮细胞中黏附分子和紧密连接蛋白的表达减少,小胶质细胞过度激活[29],释放相关炎性介质加重神经炎症的发生,而这种过度激活的慢性免疫炎性反应能够导致CNS稳态进一步失调,增加神经退行性疾病的发生率。(2)星形胶质细胞(astrocytes, AST)。AST的激活受正常衰老影响,活化的AST常表现出形态结构的变化,被称为反应性胶质增生(reactive gliosis)[30],其可以分泌脑源神经营养因子(brain-derived neurotrophic factor, BDNF)和生长因子促进神经元存活和突触的生长[31]。在缺失了活化的AST的APP23小鼠中检测到Aβ增加和突触的丢失,并且表现出记忆的缺陷和恶化[32]。另有研究表明,AST能够清除AD病理过程中功能失调的突触碎片[33]。在AD患者的大脑中,Aβ蓄积和清除的平衡处于失调状态,这种失调会导致Aβ沉积,诱发神经炎性反应发生,使AST过度活化产生负面作用。胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)作为AST活化增殖的标志,在AD大脑中的表达持续增加[34],证明了在AD中AST处于过度活化的状态。Clarke等[35]则在老龄小鼠脑中检测到AST的促炎表型的表达,并且编码神经营养因子(neurotrophic factors, NTFs)基因表达下调,表明过度活化的AST能导致自身抗炎表型转化为促炎表型参与AD的发生。AD疾病发展过程中另外一个重要表现是兴奋性神经元死亡,这个过程

受谷氨酸和钾的转运蛋白的调控。正常情况下，大脑中的谷氨酸被AST摄取，而Aβ能抑制这种功能并且增加谷氨酸的释放[36]，导致细胞外谷氨酸浓度过高，影响细胞间的信号传递。此外，活化的AST中的NF-κB结合位点的突变已被证实能导致谷氨酸–天冬氨酸转运体(glutamate-aspartate transporter，GLAST)和谷氨酸转运体–1(glutamate transporter-1，GLT-1)的表达下降[37]。这些改变均能使得神经元突触间隙的谷氨酸异常累积，最终导致兴奋性毒性神经元细胞死亡，从而加重AD进程。综上所述，神经胶质细胞作为大脑里的免疫细胞，被病理损伤所激活，能清除外来病原体和死亡细胞，并且释放抗炎介质和生长因子发挥神经保护作用。正常情况下，Aβ的蓄积和清除存在动态平衡维持相对恒定。随着AD的发生、发展，这种动态平衡被打破。Aβ作为抗原持续刺激使胶质细胞过度活化，释放细胞毒性物质(ROS、NOS等)和促炎介质(IL-1β、TNF等)等加速大脑内的炎性反应，一方面使自身抗炎表型向促炎表型转变，影响神经元细胞外谷氨酸的浓度导致神经元死亡；另一方面导致本身清除和吞噬Aβ的功能受损，持续刺激Aβ合成和蓄积，这种恶性循环最终致使AD病程进一步加重。见图1。

2.炎症介质在AD发展中的作用：神经炎性反应中的炎症介质主要由炎性细胞因子和趋化因子组成[23]，其中促炎因子如IL等在AD病程中发挥着重要的作用[38]。在AD大脑中，Aβ和过度磷酸化的tau蛋白均可以持续刺激小胶质细胞过度活化分泌IL和TNF[23]，而这些炎性介质会促使神经炎症的级联反应发生[39]。白介素4(interleukin 4，IL-4)能降低小胶质细胞对Aβ的清除率，增强Aβ的沉积，从而导致老年斑的形成[23]。同样地，TNF-α可以刺激Aβ生成过程中限速酶β–分泌酶(β-secretase，BACE)的表达，从而增加Aβ前体样蛋白(Aβ precursor like protein，APP)的加工，使Aβ合成增加[40]。Aβ能进一步刺激包括TNF-α、IL-1β、IL-6在内的促炎因子的释放，这种恶性循环会导致脑中促炎因子表达过量，持续刺激Aβ合成和神经元丢失，同时抑制小胶质细胞的吞噬作用。IL-6在AD和AD动物模型的大脑中增加时，会刺激APP的合成，诱导tau蛋白磷酸化，损害空间学习和记忆能力[41–42]。Escrig等[43]的实验表明，阻断IL-6信号通路后，3xTg-AD小鼠脑中的$A\beta_{40}$和$A\beta_{42}$水平明显减少。此外，IL-1β与IL-6的释放能反向诱导和调节小胶质细胞的活化，诱使神经胶质细胞向促炎表型转变[44–46]。由小胶质细胞过度活化释放的TNF、IL-1β能进一步刺激AST过度活化[47]，与AD之间形成恶性循环，导致CNS内稳态进一步受损。

三、小结与展望

综上所述，炎性免疫在AD的发展过程中起着至关重要的作用。CNS的免疫反应对于AD而言更像一把“双刃剑”，对于机体有利有弊。对于神经炎性的进一步研究对揭开AD的病理生理机制有着重大的意义，当前对于神经炎性领域的研究，应将继续在探索免疫反应与神经退行性疾病之间的联系方面努力。未来可能有更多与神经炎症有关的假说被探索和鉴定，可以利用这些研究成果进行AD早期诊断和开发治疗性干预措施，为AD的治疗提供新的方向和未来。

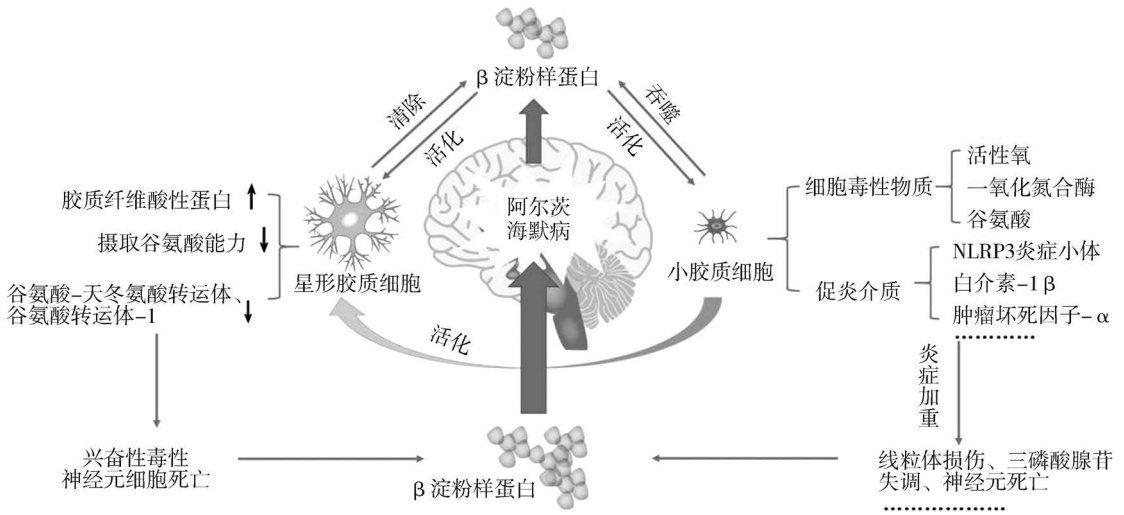

图1 神经胶质细胞在阿尔茨海默病中的调控机制

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