小胶质细胞及相关神经退行性疾病

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摘要 小胶质细胞(microglia, MG)是中枢神经系统(central nervous system, CNS)中重要的神经免疫细胞, 它在中枢神经系统中广泛分布, 对中枢神经系统起着重要的免疫监视作用。研究发现, 神经退行性疾病如阿尔茨海默病(Alzheimer's disease, AD)、帕金森病(Parkinson's disease, PD)、肌萎缩性侧索硬化症(Amyotrophic lateral sclerosis, ALS)等与小胶质细胞有着密切的关系。因此, 阐明小胶质细胞的致病机理对临床预防与治疗相关神经疾病有着重要的理论意义和实用价值。目前, 对于小胶质细胞的功能及调节机制虽研究较多, 但还不够系统, 该文就近年来人们对小胶质细胞的致病机理及其相关神经退行性疾病的研究进展作一综述。

关键词 小胶质细胞; 神经退行性疾病; 致病机理; 激活

Microglia and Related Neurodegenerative Diseases

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Abstract Microglia (MG) are resident immune cells of the central nervous system (CNS) and widely distribute in the central nervous system, which play an important role in immune surveillance. Researches have shown that microglia have a close relationship with neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and so forth. Hence, clarifying the pathogenesis of microglia has an important theoretical significance and practical value for clinical prevention and treatment of related neurological diseases. Nowadays, the microglial research contents have not been classified systematically, although the researches on its functions and regulation mechanisms are plentiful. Here, the recent research progress on microglial pathogenesis and some correlative neurodegenerative diseases are summarized.

Keywords microglia; neurodegenerative diseases; pathogenesis; activation

小神经胶质细胞是中枢神经系统中重要的神经免疫细胞, 分布于整个大脑和视网膜。成人脑细胞中约12%是小胶质细胞, 它对先天免疫反应起着重要作用[1]。正常情况下, 激活的小胶质细胞能释放神经营养因子、吞噬损伤的神经细胞、诱导组织修复, 从而发挥神经保护作用[2-4], 但当小胶质细胞过度激活后, 如在神经退行性疾病中, 小胶质细胞会诱发炎症反应并释放大量的神经炎症因子如NO、IL-6(interleukin-6)、IL-1β、TNF-α(tumor necrosis factor α)等, 炎症因子的堆积会导致中枢神经系统因氮氧失衡而使神经中毒[5-6]。研究发现, 小胶质细胞的过度激活与NF-κB信号通路[7]、MAPK(mitogen-activated protein kinase)信号通路、Toll样受体信号通路等有着密切的联系, 这些信号通路的阐明对研究小胶质

收稿日期: 2014-11-01 接受日期: 2015-01-09

国家自然科学基金(批准号: 81373429、81070973)和青年科学基金(批准号: 30901875)资助的课题

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Received: November 1, 2014 Accepted: January 9, 2015

This work was supported by the National Natural Science Foundation of China (Grant No.81373429, 81070973) and Youth Science Foundation (Grant No.30901875)

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网络出版时间: 2015-03-30 15:10 URL: http://www.cnki.net/kcms/detail/31.2035.Q.20150330.1510.002.html

细胞诱发的神经性疾病的发病机理有着重要的意义。

1 小胶质细胞的状态和功能

小胶质细胞的状态可分为两种: 静息状态和激活状态。处于静息状态的小胶质细胞不具有吞噬作用, 有不断伸缩的细胞突起[8]。当中枢神经系统受到病菌感染或损伤时, 小胶质细胞则发生形态、基因表达及功能上的一系列变化, 成为激活状态[9]。激活的小胶质细胞突起数目减少, 呈现阿米巴样形态。研究发现, 在中枢神经系统发育时期, 小胶质细胞具有重要作用[10], 在丘脑、小脑以及海马脑区中, 小胶质细胞参与了局部突触修剪过程[11]。激活后的小胶质细胞有M1和M2两种状态, 不同状态下的小胶质细胞发挥不同的作用。如图1所示, M2状态下的小胶质细胞能够释放抗炎因子(如IL-4、IL-13)、吞噬损伤的神经细胞碎片、促进组织修复和神经元的再生[12], 但当小胶质细胞被过度刺激激活(二次刺激激活, 也称为小胶质细胞的启动[13])后, 就会转向M1状态, 释放大量的神经炎症因子如IL-1β、IL-6、TNF-α、ROS(reactive oxygen species)、NO等, 这些炎症因子会对神经细胞产生毒性作用, 严重的会致使神经细胞凋亡。因此, 维持小胶质细胞正常的M2状态、减少神经炎症因子的释放对保护中枢神经有着深远的意义, 同时对寻找有效治疗相关神经退行性疾病的药物和方法有着重要的理论价值。

2 小胶质细胞激活状态的调控

就国内外对小胶质细胞的激活状态调控机制的研究可以归纳为: 药物调节、基因调节、蛋白和趋化因子调节三个方面。

2.1 药物调节小胶质细胞激活状态

药物调控激活的小胶质细胞主要是在NF-κB、ERK(extracellular signal-regulated kinase)、MAPK等信号通路中, 通过检测信号通路上下游物质及其相关基因和蛋白的表达情况来确定药物的作用机理。研究发现, 金属铜[14]、醋酸艾塞那肽[15]能够促进小胶质细胞向M2型转变, 而二甲胺四环素能有选择地抑制小胶质细胞向M1型的分化, 但对M2型的分化没有影响[16]。非瑟酮[17]、荭草素-2-O-半乳糖皮葸[18]、粉防己碱[19]能通过激活NF-κB和ERK信号通路抑制激活的小胶质细胞中的TNF-α、IL-1的生成和iNOS(inducible nitric oxide synthase)、COX-2(cyclooxygenase-2)的合成; 黄体素[20]能通过激活NF-κB、MAPK信号通路抑制激活的小胶质细胞中TNF-α的生成和iNOS、COX-2的表达, 从而减轻对神经系统造成的损伤。人参皂甙Rb1在神经系统中具有抗衰老、抗氧化、抗细胞凋亡和促进神经细胞再生的功能, 同时能够降低NO、TNF-α等炎症因子的

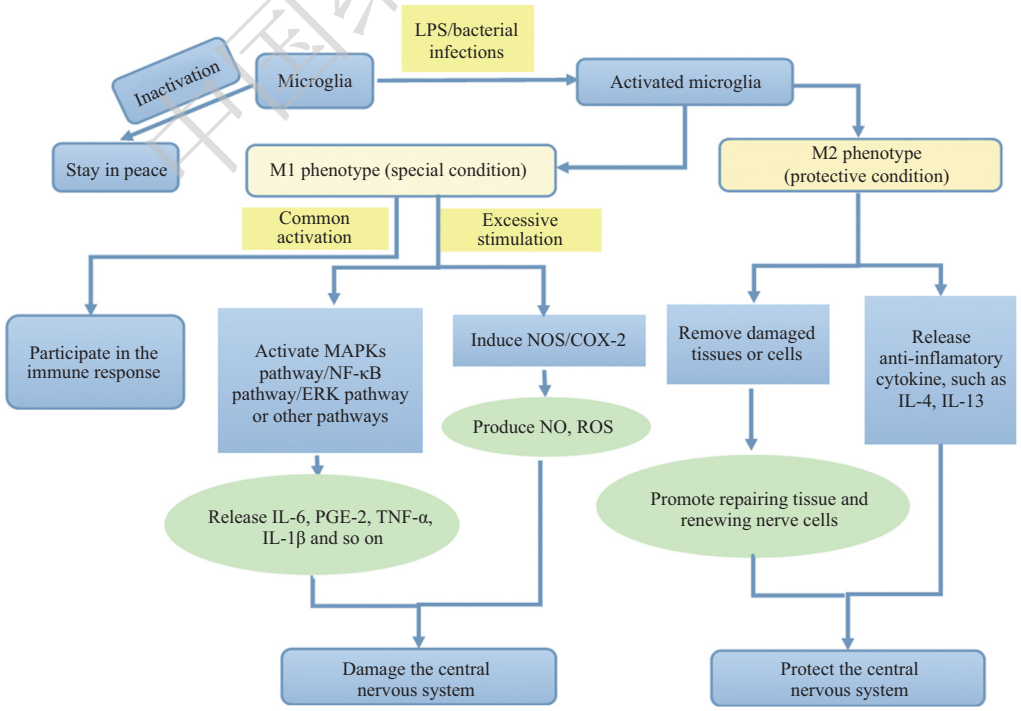

图1 激活的小胶质细胞在不同状态下的作用

Fig.1 The functions of activated microglia in different conditions

生成从而减轻M1型小胶质细胞造成的神经损伤[21], 这对研究抗神经炎症药物具有重要的理论价值。

2.2 基因调节小胶质细胞激活状态

Robert等[22]研究了mRNA和miRNA的表达对小胶质细胞激活状态的影响, 通过微阵列表达分析和生物信息学分析发现, miR-689、miR-124、miR-155和M1表型有着密切的联系, 且miR-155的调节作用最强, 在炎症反应中促进小胶质细胞向M1型转变; miR-124、miR-711、miR-145和M2表型相关, 且miR-145能够调节单核细胞/巨噬细胞分化并向M2型转变。Kim等[23]发现, 如果抑制小胶质细胞中miR-155的表达, 则会使神经抑制因子大量表达。Quintas等[24]研究发现, 当小胶质细胞被激活后, UTP会迅速转化成UTP, 然后激活胞质中的P2Y6受体诱导NO的释放, 同时促进星形胶质细胞的凋亡, 这对控制星形胶质细胞的生长与分化及小胶质细胞的毒性激活有重要的意义。

2.3 蛋白和趋化因子调节小胶质细胞激活状态

细胞内的一些蛋白和趋化因子也能调控小胶质细胞的激活状态。研究发现, 大脑中趋化因子CCL2的过量表达会使小胶质细胞持续激活并释放大量神经毒性的炎症因子[25], 并促使神经细胞凋亡[26]。干扰素调节因子3(interferon regulatory factor 3, IRF3)能够通过激活P13K/Akt信号通路来增强小胶质细胞中抗炎基因[如IL-1拮抗受体(IL-1 receptor antagonist)、*IL-10*、*IFN-β*]的表达, 同时抑制促炎症基因(如*IL-1α*、*IL-1β*、*TNF-α*、*IL-6*、*IL-8*、*CXCL1*)的表达[27]。脂质运载蛋白-2(lipocalin-2, LCN-2)能够促进小胶质细胞向M1型转化, 同时抑制其向M2型转化[28]。Lee等[29]发现, 金属蛋白酶组织抑制因子-2(tissue inhibitor of metalloproteinase-2, TIMP-2)能够抑制激活的小胶质细胞中促炎症因子NO、TNF-α、IL-1β、ROS的合成, 同时促进抗炎症因子IL-10的生成, 表明金属蛋白酶组织抑制因子-2具有神经保护作用。也有研究发现, 星形胶质细胞半乳糖凝集素-9(astrocyte galectin-9)能够促进激活的小胶质细胞中TNF和IL-6的生成, 同时小胶质细胞中的TNF也能够促进星形胶质细胞中的半乳糖凝集素-9上调[30], 可见神经胶质细胞之间也能够相互影响并发挥作用。

3 小胶质细胞与神经退行性疾病

3.1 小胶质细胞与阿尔茨海默病

阿尔茨海默病(Alzheimer's disease, AD)是一种以β-淀粉样蛋白(β-amyloid, Aβ)斑形成、神经纤维缠结、神经元丢失为主要病理特征的常见的老年神经变性疾病。在AD炎症反应中涉及的细胞有星形胶质细胞、小胶质细胞和少突胶质细胞等, 其中小胶质细胞是其主要的炎症细胞。研究发现, 小胶质细胞表面有Aβ受体[31], Aβ能够刺激小胶质细胞激活, 激活的小胶质细胞可以吞噬坏死、凋亡的细胞碎片, 清除Aβ沉积, 故Aβ与小胶质细胞相互影响[32]。但当小胶质细胞过度活化并持续释放大量炎症因子时, 一些炎症因子可以削弱由Aβ纤维激活的小胶质细胞的免疫防御功能, 并且大量炎症因子的堆积会使神经中毒, 加速患者病情的恶化。内分泌失调是AD患者的重要病理特征, 随着机体的衰老, 性激素的减少能够使机体转向促炎状态, 这也增加了AD患者病理转变的风险[33-34]。人载脂蛋白(apolipoprotein, APOE)的基因型能够影响Aβ在脑部的沉积[35], 临床数据表明, 免疫疗法可以有效清除AD患者脑中的Aβ沉积[36], 但这种免疫疗法存在一定风险, 可能会对中枢神经系统造成伤害[37]。

3.2 小胶质细胞与帕金森病

帕金森病(Parkinson's disease, PD)是以英国内科医生James Parkinson的名字来命名的退行性神经疾病[38], 其临床症状包括运动缓慢、肌肉僵直、静止性震颤等, 病理特点是中脑黑质多巴胺(dopamine, DA)神经元变性坏死和患者脑内出现lewy小体。在PD患者中90%都有精神并发症, 其中35%的患者有重度抑郁症[39], 这严重影响了患者的生活[40]。研究发现, PD患者大脑中有大量的氧自由基和激活的小胶质细胞[41]。在中枢神经系统中, 过度激活的小胶质细胞能够产生氧自由基, 氧自由基具有神经毒性, 能够促进神经元的凋亡。由于多巴胺能神经元是中枢神经系统重要的组成部分并且抗氧化能力低, 故在小胶质细胞过度激活后, 通过释放TNF-α、IL-1β、NO和O_2^-使多巴胺能神经元受伤或坏死[42-43]。目前, 还没有彻底治疗PD的方法, 常用的治疗方法是多巴胺能药物治疗[44](如Pimavanserin[45]), 对于细胞移植治疗PD[46]现在还处于理论和实验阶段。随着人们对小胶质细胞研究的深入, 从小胶质细胞入手对PD进行预防与治疗也将是一个重要的发展方向。

3.3 小胶质细胞与肌萎缩性侧索硬化症

肌萎缩性侧索硬化症(amyotrophic lateral sclerosis, ALS)是以选择性运动神经元变性、进行性瘫痪

为特点的慢性神经退行性疾病, 研究发现, ALS患者在发病前期会表现出严重的呼吸困难等症状[47], 且该病有很高的死亡率, 有报告称该病患者前期在一年内的死亡率能达到34.1%[48]。虽然ALS具体发病机制还不明确, 但研究结果给予我们很多新的启示和思考[49], 而且与之相关的基因[50]和蛋白[51]也逐渐被发现, 如超氧化物歧化酶1(superoxide dismutase 1, SOD1)、TAR DNA结合蛋白43(TAR DNA binding protein 43, TDP43)和9号染色体开放阅读框72(chromosome 9 open reading frame 72, C9ORF72)等。在ALS中, 运动性神经损伤的信号激起的早期免疫反应会修复损伤组织, 随着病情的增加, 由M2小胶质细胞和T细胞产生的有益的免疫反应会转向由M1小胶质细胞和Th1产生的毒性免疫反应[52-53]。通过正电子发射计算机断层扫描(positron emission computed tomography, PET)显影, 可以看到, 在ALS患者的脑中有激活的小胶质细胞[54]。研究发现, 突变SOD1能够通过CD14/TLR2/TLR4信号通路激活小胶质细胞, 激活的小胶质细胞会产生炎症因子, 如TNF-α、IFN-γ、MCP-1、IL-1α和IL-6等, 这些炎症因子会损害神经系统使相关神经疾病恶化[55]。目前, 对于ALS的治疗方法多是抑制神经传导及清除神经炎症因子的药物治疗法, 最近有研究指出, 干细胞移植治疗[56-57]也有很大的应用前景。

4 结语与展望

作为中枢神经系统中重要的神经免疫胶质细胞, 小胶质细胞具有双刃剑的作用, 其过度活化是神经退行性疾病发生和发展的重要因素。抑制小胶质细胞过度活化对预防和治疗神经退行性疾病的发生和发展具有重要的意义。目前, 对小胶质细胞的研究主要在于阐明激活状态的调控机制及相关信号转导途径, 对神经退行性疾病的研究主要集中于阐明发病机制和寻找有效的预防与治疗手段。随着对小胶质细胞在神经退行性疾病中作用研究的开展和相关机理的揭示, 以小胶质细胞为靶标预防和治疗神经退行性疾病也将成为一个重要的研究方向。

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