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·综 述·

小胶质细胞激活与抑郁症的研究进展

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[摘 要] 小胶质细胞过度活化介导的神经炎症和氧化应激是抑郁症的重要病理特征,重度抑郁症(MDD)患者表现出与大脑严重炎症相关的突触缺陷和小胶质细胞激活,从某种程度上讲,抑郁症就是小胶质细胞疾病。因此,本文从小胶质细胞激活的炎症表型、与抑郁症相关的小胶质细胞激活机制、小胶质细胞表型转换与抗抑郁治疗等方面进行综述,旨在进一步探索神经炎症导致抑郁、及小胶质细胞激活表型疗法治疗抑郁症的机制。

[关键词] 抑郁症;神经炎症;小胶质细胞激活;炎症表型;M1/M2极化

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Research progress in the microglia activation and depression

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Abstract: The neuroinflammation and oxidative stress mediated by overactivation of microglia cells are important pathological features of depression. Patients with major depressive disorder (MDD) show synaptic defects and microglial activation related with severe brain inflammation. To some extent, depression is a microglial disorder. Therefore, this article reviews the inflammation phenotype activated by microglia, microglia activation mechanism related to depression, microglia phenotypic conversion and antidepressant treatment, aiming at further exploring the mechanism of depression caused by neuroinflammation and microglia activation phenotypic therapy for depression.

Keywords: depression; neuroinflammation; microglia activation; inflammatory phenotype; M1/M2 polarization

小胶质细胞作为大脑的主要吞噬细胞,通过分泌细胞因子、趋化因子和生长因子,可以强烈地对应激源做出反应,在大脑稳态中发挥着重要作用[1]。重度抑郁症(major depressive disorder, MDD)前扣带皮层区域存在较高的谷氨酸和谷氨酰胺代谢异质性,并且在患抑郁症后自杀的患者腹侧前额叶的白质中出现更多活化的小胶质细胞[2]。社交失败等慢性压力因素也会增加脑细胞因子并诱导小胶质细胞激活,从而加剧免疫应激对抑郁的影响[3]。活化的小胶质细胞可以对压力引起的神经炎症快速做出反应,并通过分泌促炎细胞因子以及代谢产物,调控神经元与星形胶质细胞的功能以改善抑郁症状;此外,补体因子或应激诱导的神经元集落刺激因子Csf1激活小胶质细胞可直接影响与抑郁和痴呆相关的神经元完整性[4]。因此,小胶质细胞激活与抑郁症的发生发展密切相关,从某种程度上讲,抑郁症就是小胶质细胞疾病。

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1 小胶质细胞M1/M2极化对神经炎症的影响

小胶质细胞可根据刺激、环境和周期呈现不同的表型,称为小胶质细胞激活或极化,根据极化表型表现出神经毒性或神经保护功能[5]。M1型小胶质细胞呈变形虫形状,具有高流动性,可分泌导致组织损伤的促炎细胞因子;M2型小胶质细胞通过产生抗炎细胞因子,抑制神经损伤和促进组织修复,从而发挥神经保护作用[6],M1型和M2型小胶质细胞可以根据其激活途径相互转化。在1型辅助性T细胞(T helper type 1 cell,Th1)衍生的IFN-γ细胞因子的作用下,静息的小胶质细胞可能通过经典的激活途径转化为由IFN-γ诱导的M1型[7];或由脂多糖(lipopolysaccharide,LPS)及损伤相关分子模式(damage-associated molecular pattern,DAMP)刺激激活,从而产生多种促炎细胞因子,如白细胞介素(interleukin,IL)-23、IL-18、IL-12、IL-1β、IL-6、TNF-α、CCL2、CXCL10、TLR4、ROS、NO、蛋白水解酶基质金属蛋白酶(matrix metalloproteinase,MMP)-3和MMP-9[8]。相反,源自Th2的细胞因子IL-4和IL-13可以通过替代激活途径诱导小胶质细胞转化

为M2型[9],激活的M2型小胶质细胞由三种具有独特标记和生物学功能的亚型组成:M2a、M2b和M2c[10]。在IL-4、IL-13、M2a小胶质细胞的刺激下,精氨酸酶1(arginase-1,Arg-1)、Ym1、胰岛素样生长因子(insulin-like growth factor-1,IGF-1)、CD206和几丁质酶3(chitinase 3,CHI3)的表达在炎症组织中增加[11]。在免疫复合物和TLRs激动剂的诱导下,M2b表型出现IL-1β、CD86、细胞因子信号传导抑制因子3(suppressor of cytokine signaling 3,SOCS3)、IL-1β、IL-6、IL-10的表达增加,参与吞噬和组织碎片的清除过程[12]。当炎症反应减弱时,TGF-β、IL-10和糖皮质激素诱导小胶质细胞M2c表型,帮助组织再生[13]。

大量证据表明,小胶质细胞的M1/M2极化对中枢神经系统中神经炎症的产生有显著影响。在一些慢性神经系统疾病中,小胶质细胞被激活并逐渐改变形态和功能。小胶质细胞可以通过激活一些先天性免疫信号通路,如NOD、LRR和NLRP3炎症小体等,促使炎症介质的持续释放,导致多种神经退行性疾病的发生与发展[14];在具有抑郁症状的患者或小鼠大脑中同样发现了不同激活程度的小胶质细胞表型[15]。与抑郁症相关的小胶质细胞的激活机制值得深入探讨。

2 小胶质细胞激活诱发神经炎症在抑郁症中的作用

在临床抑郁症中,小胶质细胞激活如何发生是一个广受争议的话题,其包括以下几种可能的机制。

2.1 小胶质细胞通过血脑屏障与外周免疫相互作用

小胶质细胞激活与抑郁症密切相关,通过产生神经炎症促进抑郁的发生,外周免疫细胞和小胶质细胞之间的相互作用由脉络丛和血脑屏障调节,在病毒感染、中风和外伤等病理条件下,血脑屏障功能减弱,免疫细胞从外部渗入大脑。一些损伤信号通过与特定受体的结合直接刺激小胶质细胞的激活,使其分泌更多的炎症因子,从而加剧抑郁症状[16]。研究显示,在血浆和脑脊液中的促炎细胞因子水平升高会影响不同人群MDD的进展和严重程度[17]。保守的病原体和风险相关的分子模式分别负责感染性或非感染性炎症小胶质细胞反应,炎症因子通过体液和神经通路激活小胶质细胞。在经过治疗后,小鼠内源性海马小胶质细胞数量和海马小胶质细胞活化减少[18]。此外,小胶质细胞产生色氨酸2,3-二加氧酶(indoleamine 2,3-dioxygenase,IDO),将色氨酸转化为犬尿氨酸,而犬尿氨酸途径则是从压力应激的影响发展到抑郁症的重要转变因素[19]。小胶质细胞中IL-6和COX-1诱导的前列腺素合成对于炎症诱导的小鼠抑郁行为至关重要[20]。因此,中枢和外周免疫改变导致的促炎细胞因子水平增加与MDD的发展和复发密切相关。

2.2 肠脑轴参与小胶质细胞的激活

肠道微生物可能在应激相关的小胶质细胞激活中发挥重要作用。在人体和实验模型中,微生物种系与抑郁症密切相关。抑郁症患者的微生物种类组成发生了很大的改变。肠道微生物菌群在正常生理条件下受到调控可以影响免疫细胞的结构、功能和迁移。肠道微生物菌群失调会导致HPA轴功能障碍,抗抑郁药物可以调节HPA轴的功能失调[21]。抑郁症状与更高的皮质醇水平和更长时间的HPA轴激活及社会心理压力应激有关[22]。长期暴露于压力会诱导胃肠道中的微生物菌群易位以及循环骨髓细胞和大脑驻留神经胶质细胞中产生细胞因子的炎症小体的激活[23]。微生物菌群诱导的免疫炎症变化在抑郁症患者中增强,促炎细胞因子可以直接增加血脑屏障通透性,部分是通过上调内皮细胞黏附分子以促进淋巴细胞侵袭,还有一些肠道微生物菌群可在体外有效抑制LPS处理的小胶质细胞中NF-κB的活化;在经过粪便微生物菌移植后,受体小鼠和供体小鼠均出现小胶质细胞由M1型向M2型转换[24]。在一些情况下,压力会提高肠道的通透性,使肠道微生物菌群或其代谢物穿过肠黏膜,刺激免疫-大脑系统,最终导致免疫细胞激活,从而诱导小胶质细胞的激活并伴有抑郁样行为[25]。

2.3 NLRP3炎症小体激活小胶质细胞

NLRP3炎症小体是一种多蛋白复合物,由NLRP3、Pro-caspase-1和凋亡相关结构域CARD、ASC组成,其被过度激活后,释放IL-1β和IL-18驱动炎症反应,导致神经元呈病理性改变[26]。小胶质细胞是大脑中负责IL-1β和IL-18分泌的主要细胞类型,响应经典炎症小体的刺激[27]。小胶质细胞在维持脑稳态和调控NLRP3炎症小体介导的神经炎症中起重要作用[28],阻断NLRP3炎症小体可以降低可卡因诱导的小胶质细胞激活和神经炎症,抑制NLRP3表达可以防止LPS诱导小胶质细胞发生M1型极化[29]。因此,依赖小胶质细胞的NLRP3炎症小体激活在神经炎症状态中起着重要作用。

2.4 糖皮质激素诱导小胶质细胞活化

糖皮质激素受体是预防抑郁症的重要治疗靶点,其通过HPA轴维持神经元的分子、细胞和系统稳态,在应激系统中发挥关键作用。糖皮质激素一般具有抗炎作用,但其在某些情况下会加重炎症,特别是当大脑稳态被破坏时,糖皮质激素激活的小胶质细胞会对一系列免疫刺激做出反应,包括损伤、创伤或炎

症[30]。糖皮质激素可刺激小胶质细胞表达亮氨酸拉链与FK506,并与其蛋白基因结合;而亮氨酸拉链与FK506会加重应激反应和抑郁症状。皮质酮也被广泛用于诱导小鼠的类似抑郁行为。周围系统和中枢的免疫细胞作用于大脑,影响应激相关的神经内分泌反应,特别是小胶质细胞激活和HPA轴过度活跃。糖皮质激素水平的升高能够激活小胶质细胞,并在中枢神经系统内诱发炎症反应[31]。这些结果证实糖皮质激素可引起小胶质细胞的活化。

2.5 集落刺激因子1受体(colony-stimulating factor 1 receptor,Csf1r)对小胶质细胞的维持作用

Csf1r是一种关键的酪氨酸激酶跨膜受体,对大脑中小胶质细胞的发育和生存至关重要[32],可以被蛋白水解裂解成可溶性的外域和细胞内的蛋白片段,在两个配体Csf1和IL-34的激活下维持髓系干细胞的生存[33]。Csf1和IL-34以脑区域特异性方式调控小胶质细胞种群;在成年小鼠中,阻断Csf1和IL-34分别能显著减少脑白质区和灰质区小胶质细胞的数量[34]。Csf1r激酶抑制剂PLX3397对Csf1r信号传导的阻断可以消除大约99%的全脑小胶质细胞[35]。研究表明,中药复方交泰丸通过抑制Csf1r介导的小胶质细胞激活和炎症反应来改善皮质酮诱导的抑郁小鼠的神经元病理性改变,从而起到治疗抑郁症的作用[36]。

2.6 小胶质细胞通过神经炎症对压力做出反应

暴露在压力源下会导致大脑形成炎症环境,从而导致抑郁。应激源可以诱导特定的损伤分子模式,包括病原体相关的分子模式(pathogen-associated molecular pattern,PAMP),如来自细菌的LPS、来自病毒的RNA;和DAMP,如ATP、热休克蛋白、高迁移率族框1蛋白(high mobility group box-1,HMGB1)等介导信号传导激活小胶质细胞并放大神经炎症反应[37]。此外,慢性应激可诱导小胶质细胞上PAMP受体TLR的表达,从而增强PAMP诱导的促炎作用[38]。这些研究表明,应激暴露后刺激PAMP或DAMP信号通路会增强炎症反应,直接触发小胶质细胞的激活,并导致类似抑郁的行为。

2.7 神经元的活动增加引起小胶质细胞的活化

小胶质细胞在发育和成熟的中枢神经系统中都参与突触修剪。在某些条件下,小胶质细胞可刺激原代神经元表达,这涉及神经营养因子和抗炎细胞因子的表达,如BDNF、IGF-1和IL-4[39]。小胶质细胞生理功能及其作用对于维护大脑神经元的完整性、神经发生和网络功能很重要。压力通常会导致神经元活动增加。小胶质细胞在监测环境变化的同时,可能会被强烈的神经元信号所激活。小胶质细胞表面有多种受体,可以和许多与压力相关的神经递质相结合,包括去甲肾上腺素、谷氨酸盐和血清素。当面临压力、威胁、焦虑或疼痛时,许多小胶质细胞被激活并靠近大脑灰质区域的神经元[40]。因此,神经元活动与小胶质细胞激活存在相互作用。

2.8 趋化因子影响小胶质细胞的激活

在慢性不可预知性应激抑郁模型中,Fractalkine信号通路是重要的神经元-小胶质细胞调节通路。Fractalkine(也称为CXC3配体1或CX3CL1)是一种主要由神经元表达的趋化因子,其受体CX3CR1仅在大脑的小胶质细胞中表达[41]。CX3CL1主要在神经元和小胶质细胞中互补表达,并在这些细胞之间建立独特的通信系统,其中CX3CL1-CX3CR1信号传导负责控制小胶质细胞的激活[42]。CX3CL1可以通过与小胶质细胞上的CX3CR1结合,促使小胶质细胞向M2型极化来减弱辐射性脑损伤[43]。在反复的社交失败后,小鼠大脑中CX3CL1和CX3CR1表达降低;当小鼠面临不同的抑郁相关压力时,小鼠CX3CR1基因消融会导致混乱的后果:在注射LPS激活海马和前额皮质的小胶质细胞后,CX3CR1缺陷小鼠在尾悬试验中表现出绝望行为[44]。然而,有研究表明,CX3CR1信号丢失具有保护作用,CX3CR1缺乏减少了M1型小胶质细胞的激活,从而减少了炎症细胞因子的释放,缓解抑郁样症状[45];过表达CX3CL1-CX3CR1可以促进小鼠前扣带皮层谷氨酸神经元棘突周围小胶质细胞的激活和吞噬,从而导致抑郁[46]。虽然以上研究结论相互矛盾,其原因并不清楚;但这些研究有力地证明了CX3CL1-CX3CR1信号通路在小胶质细胞激活介导的抑郁症中发挥重要的作用。

3 小胶质细胞M1/M2表型转换与抗抑郁治疗有关

不同的内外部触发因素促使激活的小胶质细胞发挥神经毒性或神经保护作用。目前,尚不清楚哪些分子协同相互作用会引起小胶质细胞状态的改变,以及哪些是以基因特异性方式起作用以改变相反表型的后期发展。在体外,M2型小胶质细胞通过最初用LPS、IL-4或IL-10处理,随后改变刺激物的顺序来影响M1型的转换,一方面,在给予LPS之前应用IL-10预处理阻止了TNF-α、IL-6和COX2的表达[47];另一方面,在给予IL-10之前用LPS治疗会导致炎症的产生[48]。这些有助于小胶质细胞在不同激活剂下显示形态转换的证据。

PPARγ可以抑制小胶质细胞的激活,促进M1型

向M2型转换并减少相关炎症因子的表达。根据受到的刺激,小胶质细胞的激活特征从经典激活M1型细胞转换成替代激活的M2型细胞[49]。靶向抑制NLRP3炎症小体的过度激活促进了小胶质细胞由M1型转换为M2型;在慢性不可预测的应激小鼠中,药物诱导的小胶质细胞从促炎M1型向抗炎M2型的转换而表现出抗抑郁作用[50]。

综上所述,神经炎症参与了抑郁症的病理和生理过程。小胶质细胞作为中枢神经系统的组织特异性巨噬细胞,在神经炎症中发挥重要作用。在神经炎症过程中,常驻小胶质细胞向促炎M1型或抗炎M2型激活。小胶质细胞M1/M2表型转换与抗抑郁治疗有关。了解炎症、小胶质细胞活化和抑郁症之间的相关性可能对开发新一代抗抑郁药物具有重要价值。

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