· 精神分裂症专题 ·

细胞因子与精神分裂症机制关联研究进展

杨海东 杨曼 潘杨杨 栾凌淑 张晓斌
222000 南京医科大学康达学院附属连云港第四人民医院精神科(杨海东、杨曼、潘杨杨、栾凌淑); 215137 苏州大学附属广济医院精神科(张晓斌)
通信作者: 张晓斌, Email: zhangxiaobim@163.com
DOI: 10.3969/j.issn.1009-6574.2023.03.006

【摘要】 精神分裂症是一种严重的致残性精神障碍, 其病理生理机制仍不明确, 治疗方面存在个体差异及异质性, 造成较高的社会、经济负担。本文从多个角度对细胞因子在精神分裂症及其治疗中的变化最新进展进行综述, 以期从机制方面理解精神分裂症与细胞因子的关系, 为将来从更多维度对精神分裂症病因及个性化治疗提供新的思路。

【关键词】 精神分裂症; 细胞因子; 神经炎症; 治疗; 综述

基金项目: 江苏省社会发展项目(BE2020764); 江苏省卫生健康委员会医学科研项目(H2018041); 连云港市卫生健康委员会面上项目(202130); 苏州市心境障碍临床医学中心资助项目(Szlcyxzx202109); 苏州市重点诊疗项目(LCZX201919)

Progress on the study of the correlation between cytokines and pathological mechanism of schizophrenia

Yang Haidong, Yang Man, Pan Yangyang, Luan Lingshu, Zhang Xiaobin
Department of Psychiatry, the Fourth People's Hospital of Lianyungang, the Affiliated KangDa College of Nanjing Medical University, Lianyungang 222000, China (Yang HD, Yang M, Pan YY, Luan LS); Department of Psychiatry, the Affiliated Guangji Hospital of Soochow University, Suzhou 215137, China (Zhang XB)
Corresponding author: Zhang Xiaobin, Email: zhangxiaobim@163.com

【**Abstract**】 Schizophrenia is a serious disabling mental disorder. Its pathophysiological mechanism is still unclear, and there are individual differences and heterogeneity in treatment, resulting in high social and economic burden. In this paper, we review recent updates on the variations of cytokines in schizophrenia and their therapy from multiple perspective, with the aim of understanding the relationship between schizophrenia and cytokines from the mechanism, and providing new ideas for personalized treatment of schizophrenia patients from a more multidimensional perspective in the future.

【**Key words**】 Schizophrenia; Cytokines; Neuroinflammation; Treatment; Review

Fund programs: Jiangsu Province Social Development Project (BE2020764); Medical Scientific Research Project of Jiangsu Provincial Commission of Health and Family Planning (H2018041); General Program of Lianyungang Health Committee (202130); Suzhou Clinical Medical Center for Mood Disorders (Szlcyxzx202109); Key Diagnosis and Treatment Program of Suzhou (LCZX201919)

精神分裂症是一种严重的、致残率高的精神障碍, 全球终生患病率在1%左右, 对社会造成了巨大负担[1-2]。遗传易感性、环境因素、神经炎症机制、神经递质等生物学因素在精神分裂症发生过程中发挥着巨大作用[3-4]。1976年的研究发现炎症异常与精神分裂症的相关性[5], 但其确切的病理生理机制仍不明确。随着时间的推移, 免疫系统、炎症之间复杂的交互作用可以导致情绪、认知和行为的变化被发现[6], 与神经炎症机制密切相关的细胞因子影响多巴胺、5-HT、去甲肾上腺素间的神经传递, 导致精神症状或抑郁症状[7]。大量的研究聚焦于细胞因子与精神分裂症之间的关系, 以期寻找出精神分裂症的可能致病原因并给予有效治疗, 减少疾病带来的负担。因此, 本文着重对最近10年间细胞因子变化与精神分裂症的潜在病理生理及治疗机制最新进展进行简要综述。

一、细胞因子的分类

当机体受到病毒或细菌侵入、组织损伤或社会-心理应激状态时, 抗原递呈细胞与辅助T细胞(Th0)促进免疫作用分泌不同的细胞因子[8-9]。根据

免疫反应方式的不同，细胞因子分为获得性细胞因子[如IL-2、IL-3、IL-4、IL-5、IL-7、IL-9、IL-13、IL-15、IL-21、粒细胞巨噬细胞集落刺激因子(granulocyte macrophage colony stimulating factor, GM-CSF)]、炎症细胞因子[如IL-1、IL-6、IL-17、TNF-α、干扰素(interferon, IFN)]、抗炎细胞因子(如IL-10、IL-12家族)。根据细胞因子功能的不同，可以分为IL、TNF、IFN、GM-CSF、转移生长因子(transfer growth factor, TGF)等[10]。这样的分类并不足以概括众多的细胞因子，而作为炎症的关键调节因子，细胞因子通过复杂的相互作用网络在机体发挥重要的作用。

二、细胞因子进入大脑通路

细胞因子不易透过血-脑脊液屏障，而是经过体液通路、神经通路、细胞通路进入大脑[11-12]。在精神分裂症患者脑脊液研究中发现，血-脑脊液屏障缺陷与高水平炎症过程中的可溶性细胞间黏附分子相关[13]，表明精神分裂症患者的血-脑脊液屏障缺陷与炎症机制相关。此外，细胞因子还可以由微生物-肠-脑轴通路进入大脑。肠道环境的变化促进细胞因子如TNF-α、IFN-γ等的产生，进而增加肠道炎症和上皮细胞屏障的通透性。肠道内细菌产物脂多糖或短链脂肪酸进入循环系统，再通过神经通路或体液通路进入大脑[14-16]。外周免疫的激活使外周细胞因子进入大脑引起中枢细胞因子水平变化，可能影响中枢神经递质释放、神经内分泌功能、神经元可塑性以及神经环路架构，共同参与精神分裂症病理生理过程。

三、细胞因子在精神分裂症中作用机制

1.细胞因子在动物模型的研究：在精神分裂症动物模型研究中，同宗小鼠出现脱髓鞘、少突胶质细胞丢失、小胶质细胞聚集，当给予有效剂量的腺苷治疗后，抑制了小鼠前额叶和海马区炎症细胞因子IL-1β和TNF-α的异常升高，但在再髓鞘化过程中抗炎细胞因子IL-4或IL-10水平升高[17]。rTMS治疗的小鼠神经元突触和功能发生变化[18]，而IL-10可以使暴露于细菌脂多糖诱导的神经元恢复突触可塑性[19]。暴露于IL-1β、IL-6和TNF-α的大鼠，其树突发育和皮层神经元发育明显减少[20]，大鼠断奶之后长期的社会性隔离引起外周和中枢细胞因子IL-6、TNF-α、IL-10水平表达降低[21]。切断腹侧海马的初生大鼠成长中出现精神分裂症相关行为和突触改变，补充抗炎细胞因子TGF-1β可以为大鼠发育性腹侧海马损伤提供保护，减轻神经元树突损失[22]。猕猴母体免疫激活后，其子代产生的精神分裂症及孤独症谱系障碍样刻板行为与先天细胞因子如粒细胞集落刺激因子、趋化因子(CCL)-3、CCL-8、IL-1β、IL-6、IL-12p40、Th2细胞因子有关，自主行为则与IL-4、IL-10、IL-13有关[23]。细胞因子在精神分裂症动物模型的研究尽管没有发现特定种类的细胞因子解释精神分裂症症状的产生，但也从病因学更进一步阐释了细胞因子在精神分裂症中的关键作用。

2.细胞因子在基因及蛋白水平的研究：基因及蛋白水平研究表明，细胞因子异常蛋白表达与精神分裂症病理生理机制关系密切。IL-1α rs1800587、IL-6 rs1800796、TNF-α rs361525和IFN-γ rs2069718的炎症细胞因子基因多态性与精神分裂症相关[24]。在精神分裂症患者全基因组表达分析方面，CD40信号、趋化因子-3受体1、IL-17A信号通路与神经炎症机制有关[25]。首发精神分裂症患者血清中的IL-1β、IL-6、IL-8抗体IgG水平升高，IL-1α抗体IgG水平降低[26]，住院患者中的血管紧张素转换酶活性与IL-17a、TNF-α、IFN-γ水平呈正相关[27]。大脑尸检研究显示，精神分裂症患者前额叶皮质中的IL-2未被检测到，TNF-α、IL-6蛋白和mRNA水平明显升高，IL-10蛋白和mRNA水平降低明显，IL-8蛋白表达水平降低[28]，IFN-β mRNA表达增加[29]，前额叶皮质背外侧IL-6、IL-8、IL-1β mRNA表达增加[30]，颞上回IL-1α、IFN-γ诱导蛋白P表达降低，IFN-α蛋白表达增加[31]。Monji等[32]在尸检研究中发现，精神分裂症患者脑部小胶质细胞激活或密度增加，释放IL-6、TNF-α、IFN-γ等炎症细胞因子，导致神经元变性、神经发生减少、脑白质异常。精神分裂症患者的细胞因子基因及蛋白水平的变化表明神经炎症机制参与了这一疾病的产生。

3.细胞因子在血液水平及与临床症状关系的研究：既往研究结果表明，精神分裂症患者外周血细胞因子水平发生变化，且一些细胞因子与临床症状之间存在关联。如Aricioglu等[4]报道，母体接触细菌脂多糖、多核糖体和多核糖体酸(poly I：C)等感染因子后，其子代出现类似精神分裂症样的行为变化，同时，血液中炎症细胞因子水平增加。Wu等[33]的研究发现，慢性精神分裂症患者较健康人群的血清IL-2、IL-6、IL-8水平升高，降低的血清TNF-α水平与丙二醛交互作用和阴性症状相关，IL-8与丙二醛或者IL-8与过氧化物歧化酶交互作用和执行功能相关。在缺陷型精神分裂症患者中，血清IL-1β、IL-1RA、TNF-α、CCL-11、TNFR1可以部分预测其慢性疲劳综合征，且可能与激活的免疫途径有

关[34]。TNF-β、IL-6水平与精神分裂症阴性症状的高危人群、精神分裂症伴抑郁症状的严重程度显著相关[35]。患精神障碍超高风险人群中，血清IL-6水平升高，IL-17水平降低，并且血清IL-17水平与整体功能评估量表呈正相关[36]。精神分裂症患者升高的TGF-β1血浆水平与攻击行为和临床症状呈正相关，降低的补体C3与临床症状呈负相关，升高的IL-23水平与兴奋症状呈正相关[37]。在慢性精神分裂症患者中，血清中升高的IL-18水平与一般病理症状分和认知功能呈正相关[38]。外周血细胞因子失调支持神经炎症假说在精神分裂症中起着重要作用，值得将来进一步研究。

四、细胞因子与精神分裂症治疗

1.细胞因子与药物治疗：抗精神病药物可以改变细胞因子的水平，而抗精神病药物治疗效果可能与细胞因子的内表型有关，药物通过细胞因子或其受体基因表达调节单核细胞、T细胞和B细胞，继而影响免疫系统[9, 39]。在首发精神分裂症患者中，应用氟哌啶醇、利培酮、奥氮平等药物治疗后，血清TGF-β水平升高，IL-17水平降低，降低的血清IL-4、IL-6、IL-27水平与抗精神病药物治疗相关[39]。氯氮平、利培酮激活精神分裂症患者中枢神经系统小胶质细胞，降低IL-2、IL-6、TNF-α的表达水平，哌罗匹隆和喹硫平则对IFN-γ激活的小胶质细胞有抑制作用[32]。而且抗精神病药物治疗后可改变血清IL-6、IL-8水平，血清IL-6水平越高，IL-8水平越低，精神分裂症的阴性症状改善越好[40]。Zhang等[41]在一项大脑尸检研究中发现，IL-6 mRNA在精神分裂症患者脑内的表达与抗精神病药物摄入总量及每日摄入量显著相关，患者大脑皮质灰质体积缩小是神经炎症和抗精神病药物共同作用的结果。Stapel等[42]在体外细胞分离实验研究中发现，奥氮平和阿立哌唑影响免疫功能，体外治疗可降低IL-1β、IL-6、TNF-α mRNA在外周血单核细胞和单核THP-1细胞的表达和分泌，同时减少IL-2、IL-6、IFN-γ诱导蛋白IP-10和巨噬细胞炎症蛋白MIP-1β的分泌水平；两种药物治疗后的IL-9呈下降趋势，IL-1RA呈升高趋势，且均有减少IL-10、MIP-1α分泌的趋势。精神分裂症患者出现炎症反应时，氯氮平血药浓度升高，可能与作为细胞色素P-450酶抑制剂的炎症细胞因子的释放有关[43]。经过12周的药物治疗，药物治疗无效的首发精神分裂症患者的IL-6和IFN-γ水平升高[44]，而精神分裂症患者出现的轻度炎症与抗精神病药物治疗不良反应有关[45]。越来越多的研究表明，特定的抗炎药物和免疫调节剂对精神分裂症患者有益，抗精神病药物联合抗炎药物如阿司匹林、米诺环素、N-乙酰半胱氨酸、雌激素类药物能更好地改善精神分裂症患者的症状，有效降低精神分裂症患者的临床症状严重程度评分，而减少血清中IL-1水平、增加IL-10水平对精神分裂症的治疗有效[46-48]。抗精神病药物可以影响细胞因子水平，细胞因子反过来改善抗精神病药物的治疗效果。因此，从抗炎治疗的角度探索新型抗精神病药物可能是将来药物研发的新方向。

2.细胞因子与物理治疗：改良电休克治疗（modified electroconvulsive therapy，MECT）被认为是治疗精神分裂症的有效手段，其机制可能是MECT可以改善大脑内与神经递质相关区域的分子水平，改善犬尿氨酸代谢，影响神经递质的表达[49]。MECT后，细胞因子组织抑制剂基质金属蛋白酶-9和TNF-α血清浓度显著降低[50-51]，同时，显著降低炎症/免疫反应主要调控通路核转录因子κB（nuclear factor，NF-κB）的表达[52]。随着精神症状的好转，血浆IL-4、TGF-β水平显著增加，且增加的TGF-β与临床症状改善呈负相关[53]。另一种物理治疗方法rTMS可以激活炎症相关的神经元功能和细胞因子的表达[54]。物理治疗如MECT和rTMS可以调控细胞因子水平，间接表明细胞因子与精神分裂症的密切关系，这为将来推广精神分裂症的个性化治疗提供了新思路。

综上所述，细胞因子在动物模型、基因及蛋白水平、外周血、治疗中的变化均与精神分裂症密切相关，表明神经炎症机制参与精神分裂症的病理生理过程。但由于细胞因子种类众多、不同机制间的交互作用、研究方法不同、药物等的影响，探索其确切的病理生理机制面临着重大挑战。寻找潜在的、特异性的细胞因子作为精神分裂症的生物学标志物以指导临床仍需要进一步研究。

利益冲突 文章所有作者共同认可文章无相关利益冲突

作者贡献声明 构思与设计为张晓斌、杨海东，文献查阅、整理为杨曼、潘杨杨、栾凌淑，论文撰写为杨海东，论文修订为张晓斌

参 考 文 献

[1] McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-an overview[J]. JAMA Psychiatry, 2020, 77(2): 201-210. DOI: 10.1001/jamapsychiatry.2019.3360.

[2] Owen MJ, Sawa A, Mortensen PB. Schizophrenia[J]. Lancet, 2016, 388(10039): 86-97. DOI: 10.1016/S0140-6736(15)01121-6.

[3] Mohammadi A, Rashidi E, Amooeian VG. Brain, blood, cerebrospinal fluid, and serum biomarkers in schizophrenia[J]. Psychiatry Res, 2018, 265: 25-38. DOI: 10.1016/j.psychres.2018.04.036.

[4] Aricioglu F, Ozkartal CS, Unal G, et al. Neuroinflammation in schizophrenia: a critical review and the future[J]. Klinik Psikofarmakoloji Bülteni, 2017, 26(4): 429-437. DOI: 10.5455/bcp.20161123044657.

[5] Torrey EF, Peterson MR. The viral hypothesis of schizophrenia[J]. Schizophr Bull, 1976, 2(1): 136-146. DOI: 10.1093/schbul/2.1.136.

[6] Tavakoli P, Vollmer-Conna U, Hadzi-Pavlovic D, et al. A review of inflammatory bowel disease: a model of microbial, immune and neuropsychological integration[J]. Public Health Rev, 2021, 42: 1603990. DOI: 10.3389/phrs.2021.1603990.

[7] Engh JA, Ueland T, Agartz I, et al. Plasma levels of the cytokines B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) in schizophrenia, bipolar, and major depressive disorder: a cross sectional, multisite study[J]. Schizophr Bull, 2022, 48(1): 37-46. DOI: 10.1093/schbul/sbab106.

[8] Alam R, Abdolmaleky HM, Zhou JR. Microbiome, inflammation, epigenetic alterations, and mental diseases[J]. Am J Med Genet B Neuropsychiatr Genet, 2017, 174(6): 651-660. DOI: 10.1002/ajmg.b.32567.

[9] Reale M, Costantini E, Greig NH. Cytokine imbalance in schizophrenia. from research to clinic: potential implications for treatment[J]. Front Psychiatry, 2021, 12: 536257. DOI: 10.3389/fpsyt.2021.536257.

[10] Turner MD, Nedjai B, Hurst T, et al. Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease[J]. Biochim Biophys Acta, 2014, 1843(11): 2563-2582. DOI: 10.1016/j.bbamcr.2014.05.014.

[11] Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications[J]. Pharmacol Ther, 2011, 130(2): 226-238. DOI: 10.1016/j.pharmthera.2011.01.014.

[12] Dalli J, Serhan CN. Immunoresolvents signaling molecules at intersection between the brain and immune system[J]. Curr Opin Immunol, 2018, 50: 48-54. DOI: 10.1016/j.coi.2017.10.007.

[13] Schwarz MJ, Ackenheil M, Riedel M, et al. Blood-cerebrospinal fluid barrier impairment as indicator for an immune process in schizophrenia[J]. Neurosci Lett, 1998, 253(3): 201-203. DOI: 10.1016/s0304-3940(98)00655-7.

[14] D'Mello C, Swain MG. Immune-to-brain communication pathways in inflammation-associated sickness and depression[J]. Curr Top Behav Neurosci, 2017, 31: 73-94. DOI: 10.1007/7854_2016_37.

[15] Gitter AH, Bendfeldt K, Schulzke JD, et al. Leaks in the epithelial barrier caused by spontaneous and TNF-alpha-induced single-cell apoptosis[J]. FASEB J, 2000, 14(12): 1749-1753. DOI: 10.1096/fj.99-0898com.

[16] Kesika P, Suganthy N, Sivamaruthi BS, et al. Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease[J]. Life Sci, 2021, 264: 118627. DOI: 10.1016/j.lfs.2020.118627.

[17] Zhang J, Yang L, Fang Z, et al. Adenosine promotes the recovery of mice from the cuprizone-induced behavioral and morphological changes while effecting on microglia and inflammatory cytokines in the brain[J]. J Neuroimmune Pharmacol, 2018, 13(3): 412-425. DOI: 10.1007/s11481-018-9799-0.

[18] Lenz M, Platschek S, Priesemann V, et al. Repetitive magnetic stimulation induces plasticity of excitatory postsynapses on proximal dendrites of cultured mouse CA1 pyramidal neurons[J]. Brain Struct Funct, 2015, 220(6): 3323-3337. DOI: 10.1007/s00429-014-0859-9.

[19] Lenz M, Eichler A, Kruse P, et al. Interleukin 10 restores lipopolysaccharide-induced alterations in synaptic plasticity probed by repetitive magnetic stimulation[J]. Front Immunol, 2020, 11: 614509. DOI: 10.3389/fimmu.2020.614509.

[20] Gilmore JH, Fredrik Jarskog L, Vadlamudi S, et al. Prenatal infection and risk for schizophrenia: IL-1beta, IL-6, and TNF alpha inhibit cortical neuron dendrite development[J]. Neuropsychopharmacology, 2004, 29(7): 1221-1229. DOI: 10.1038/sj.npp.1300446.

[21] Corsi-Zuelli F, Fachim HA, Loureiro CM, et al. Prolonged periods of social isolation from weaning reduce the anti-inflammatory cytokine IL-10 in blood and brain[J]. Front Neurosci, 2018, 12: 1011. DOI: 10.3389/fnins.2018.01011.

[22] Joseph AT, Bhardwaj SK, Srivastava LK. Role of prefrontal cortex anti- and pro-inflammatory cytokines in the development of abnormal behaviors induced by disconnection of the ventral hippocampus in neonate rats[J]. Front Behav Neurosci, 2018, 12: 244. DOI: 10.3389/fnbeh.2018.00244.

[23] Rose DR, Careaga M, Van de Water J, et al. Long-term altered immune responses following fetal priming in a non-human primate model of maternal immune activation[J]. Brain Behav Immun, 2017, 63: 60-70. DOI: 10.1016/j.bbi.2016.11.020.

[24] Srinivas L, Vellichirammal NN, Alex AM, et al. Pro-inflammatory cytokines and their epistatic interactions in genetic susceptibility to schizophrenia[J]. J Neuroinflammation, 2016, 13(1): 105. DOI: 10.1186/s12974-016-0569-8.

[25] Fries GR, Dimitrov DH, Lee S, et al. Genome-wide expression in veterans with schizophrenia further validates the immune hypothesis for schizophrenia[J]. Schizophr Res, 2018, 192: 255-261. DOI: 10.1016/j.schres.2017.06.016.

[26] Liu S, Zhang X, Wang J, et al. Analysis of plasma autoantibodies for inflammatory cytokines in patients with first-episode schizophrenia among a Chinese population[J]. J Neuroimmunol, 2020, 341: 577165. DOI: 10.1016/j.jneuroim.2020.577165.

[27] Gadelha A, Yonamine CM, Nering M, et al. Angiotensin converting enzyme activity is positively associated with IL-17a levels in patients with schizophrenia[J]. Psychiatry Res, 2015, 229(3): 702-707. DOI: 10.1016/j.psychres.2015.08.018.

[28] Pandey GN, Rizavi HS, Zhang H, et al. Abnormal gene and protein expression of inflammatory cytokines in the postmortem brain of schizophrenia patients[J]. Schizophr Res, 2018, 192: 247-254. DOI: 10.1016/j.schres.2017.04.043.

[29] Volk DW, Chitrapu A, Edelson JR, et al. Molecular mechanisms and timing of cortical immune activation in schizophrenia[J]. Am J Psychiatry, 2015, 172(11): 1112-1121. DOI: 10.1176/appi.ajp.2015.15010019.

[30] Fillman SG, Cloonan N, Catts VS, et al. Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia[J]. Mol Psychiatry, 2013, 18(2): 206-214. DOI: 10.1038/mp.2012.110.

[31] Izumi R, Hino M, Wada A, et al. Detailed postmortem profiling of inflammatory mediators expression revealed post-inflammatory alternation in the superior temporal gyrus of schizophrenia[J]. Front Psychiatry, 2021, 12: 653821. DOI: 10.3389/fpsyt.2021.653821.

[32] Monji A, Kato T, Kanba S. Cytokines and schizophrenia: microglia hypothesis of schizophrenia[J]. Psychiatry Clin Neurosci, 2009, 63(3): 257-265. DOI: 10.1111/j.1440-1819.2009.01945.x.

[33] Wu ZW, Yu HH, Wang X, et al. Interrelationships between oxidative stress, cytokines, and psychotic symptoms and executive functions in patients with chronic schizophrenia[J]. Psychosom Med, 2021, 83(5): 485-491. DOI: 10.1097/PSY.0000000000000931.

[34] Almulla AF, Al-Hakeim HK, Abed MS, et al. Chronic fatigue and fibromyalgia symptoms are key components of deficit schizophrenia and are strongly associated with activated immune-inflammatory pathways[J]. Schizophr Res, 2020, 222: 342-353. DOI: 10.1016/j.schres.2020.05.003.

[35] Goldsmith DR, Haroon E, Miller AH, et al. Association of baseline inflammatory markers and the development of negative symptoms in individuals at clinical high risk for psychosis[J]. Brain Behav Immun, 2019, 76: 268-274. DOI: 10.1016/j.bbi.2018.11.315.

[36] Zeni-Graiff M, Rizzo LB, Mansur RB, et al. Peripheral immuno-inflammatory abnormalities in ultra-high risk of developing psychosis[J]. Schizophr Res, 2016, 176(2/3): 191-195. DOI: 10.1016/j.schres.2016.06.031.

[37] Li H, Zhang Q, Li N, et al. Plasma levels of Th17-related cytokines and complement C3 correlated with aggressive behavior in patients with schizophrenia[J]. Psychiatry Res, 2016, 246: 700-706. DOI: 10.1016/j.psychres.2016.10.061.

[38] Syed A, He L, Shi Y, et al. Elevated levels of IL-18 associated with schizophrenia and first episode psychosis: a systematic review and Meta-analysis[J]. Early Interv Psychiatry, 2021, 15(4): 896-905. DOI: 10.1111/eip.13031.

[39] Marcinowicz P, Więdłocha M, Zborowska N, et al. A Meta-analysis of the influence of antipsychotics on cytokines levels in first episode psychosis[J]. J Clin Med, 2021, 10(11): 2488. DOI: 10.3390/jcm10112488.

[40] He X, Ma Q, Fan Y, et al. The role of cytokines in predicting the efficacy of acute stage treatment in patients with schizophrenia[J]. Neuropsychiatr Dis Treat, 2020, 16: 191-199. DOI: 10.2147/NDT.S218483.

[41] Zhang Y, Catts VS, Sheedy D, et al. Cortical grey matter volume reduction in people with schizophrenia is associated with neuro-inflammation[J]. Transl Psychiatry, 2016, 6(12): e982. DOI: 10.1038/tp.2016.238.

[42] Stapel B, Sieve I, Falk CS, et al. Second generation atypical antipsychotics olanzapine and aripiprazole reduce expression and secretion of inflammatory cytokines in human immune cells[J]. J Psychiatr Res, 2018, 105: 95-102. DOI: 10.1016/j.jpsychires.2018.08.017.

[43] Clark SR, Warren NS, Kim G, et al. Elevated clozapine levels associated with infection: a systematic review[J]. Schizophr Res, 2018, 192: 50-56. DOI: 10.1016/j.schres.2017.03.045.

[44] Mongan D, Ramesar M, Föcking M, et al. Role of inflammation in the pathogenesis of schizophrenia: a review of the evidence, proposed mechanisms and implications for treatment[J]. Early Interv Psychiatry, 2020, 14(4): 385-397. DOI: 10.1111/eip.12859.

[45] Upthegrove R, Khandaker GM. Cytokines, oxidative stress and cellular markers of inflammation in schizophrenia[J]. Curr Top Behav Neurosci, 2020, 44: 49-66. DOI: 10.1007/7854_2018_88.

[46] Zhang L, Zheng H, Wu R, et al. The effect of minocycline on amelioration of cognitive deficits and pro-inflammatory cytokines levels in patients with schizophrenia[J]. Schizophr Res, 2019, 212: 92-98. DOI: 10.1016/j.schres.2019.08.005.

[47] Fond G, Lançon C, Korchia T, et al. The role of inflammation in the treatment of schizophrenia[J]. Front Psychiatry, 2020, 11: 160. DOI: 10.3389/fpsyt.2020.00160.

[48] Robertson OD, Coronado NG, Sethi R, et al. Putative neuroprotective pharmacotherapies to target the staged progression of mental illness[J]. Early Interv Psychiatry, 2019, 13(5): 1032-1049. DOI: 10.1111/eip.12775.

[49] Savitz J. The kynurenine pathway: a finger in every pie[J]. Mol Psychiatry, 2020, 25(1): 131-147. DOI: 10.1038/s41380-019-0414-4.

[50] Shibasaki C, Takebayashi M, Itagaki K, et al. Altered serum levels of matrix metalloproteinase-2, -9 in response to electroconvulsive therapy for mood disorders[J]. Int J Neuropsychopharmacol, 2016, 19(9): pyw019. DOI: 10.1093/ijnp/pyw019.

[51] Valiuliene G, Valiulis V, Dapsys K, et al. Brain stimulation effects on serum BDNF, VEGF, and TNF α in treatment-resistant psychiatric disorders[J]. Eur J Neurosci, 2021, 53(11): 3791-3802. DOI: 10.1111/ejn.15232.

[52] Bioque M, Mac-Dowell KS, Meseguer A, et al. Effects of electroconvulsive therapy in the systemic inflammatory balance of patients with severe mental disorder[J]. Psychiatry Clin Neurosci, 2019, 73(10): 628-635. DOI: 10.1111/pcn.12906.

[53] Kartalci S, Karabulut AB, Erbay LG, et al. Effects of electroconvulsive therapy on some inflammatory factors in patients with treatment-resistant schizophrenia[J]. J ECT, 2016, 32(3): 174-179. DOI: 10.1097/YCT.0000000000000303.

[54] Lenz M, Eichler A, Vlachos A. Monitoring and modulating inflammation-associated alterations in synaptic plasticity: role of brain stimulation and the blood-brain interface[J]. Biomolecules, 2021, 11(3): 359. DOI: 10.3390/biom11030359.

(收稿日期: 2022-06-06)

(本文编辑: 赵金鑫)