•综述•

中性粒−脑细胞互作介导“血−脑 crosstalk”影响神经炎症疾病及药物干预作用

王思梦[1,2], 江廷参[1,2], 李 星[3], 朱 彦[1,2], 董鹏志[1,2*], 吕 明[1,2*]

(1. 天津中医药大学, 现代中药创制全国重点实验室, 天津 301617; 2. 天津中医药大学, 组分中药国家重点实验室, 天津 301617; 3. 贵州百灵企业集团制药股份有限公司, 贵州 贵阳 550000)

摘要: “血−脑 crosstalk”是指系统中的免疫细胞浸润到脑实质与脑细胞互作从而影响中枢神经系统疾病的途径。中性粒细胞是首个通过血脑屏障从循环血液中进入病变部位的免疫细胞, 也是在神经炎症中发挥主要功能的免疫细胞之一。中性粒细胞与脑细胞 (如神经元、小胶质细胞、星形胶质细胞和脑微血管内皮细胞) 之间存在复杂的相互作用, 共同参与神经炎症疾病的进展。中性粒−脑细胞互作能够影响神经炎症导致的脑损伤。且一些中药与西药成分能够有效作用于中性粒−脑细胞互作, 因此, 本文综述了中性粒−脑细胞互作在神经炎症中的作用机制以及调节中性粒−脑细胞互作药物的研究进展, 以期为未来通过介导“血−脑 crosstalk”治疗神经炎症疾病提供依据和参考。

关键词: 血−脑 crosstalk; 神经炎症; 中性粒细胞; 脑细胞; 细胞互作

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2025)06-1573-09

Neutrophil-brain cell interactions mediate "blood-brain crosstalk" in neuroinflammatory diseases and the role of pharmacological intervention

WANG Si-meng[1,2], JIANG Ting-can[1,2], LI Xing[3], ZHU Yan[1,2], DONG Peng-zhi[1,2*], LÜ Ming[1,2*]

(*1. National Key Laboratory of Chinese Medicine Modernization, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; 2. State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; 3. Guizhou Bailing Enterprise Group Pharmaceutical Co., Ltd., Guiyang 550000, China*)

Abstract: The term "blood-brain crosstalk" refers to the approach by which systemic immune cells infiltrate into the brain parenchyma and interact with brain cells to affect central nervous system disease. Neutrophils are the first immune cells to cross the blood-brain barrier from the circulating blood to the site of disease and are one of the immune cells that play a major function in neuroinflammation. There are complex interactions between neutrophils and brain cells (such as neurons, microglia, astrocytes, and cerebral microvascular endothelial cells), which together are involved in the progression of neuroinflammatory diseases. Neutrophil-brain cell interactions can influence brain injury due to neuroinflammation. Therefore, this article summarizes the mechanism of neutrophil-brain cell interactions in neuroinflammatory diseases and the research progress of pharmacological

收稿日期: 2024-11-27; 修回日期: 2025-01-11.

基金项目: 天津市科技创新基地建设 (24ZYJDSS00320); 国家自然科学基金重点项目 (82430121); 国家自然科学基金青年项目 (82104431); 现代中药新质生产力科技创新工程专项 (24ZXZKSY00030); 京津冀基础研究合作专项 (23JCZXJC00380); 贵州省科技计划项目 (黔科合支撑[2023]一般100); 天津市教委科研计划项目 (2022KJ148); 组分中药国家重点实验室青苗基金项目 (CBCM2023205).

*通讯作者 Tel: 86-22-59596333, E-mail: minglyu@tjutcm.edu.cn; dongpengzhi@tjutcm.edu.cn

DOI: 10.16438/j.0513-4870.2024-1178

intervention, with a view to providing a basis and reference for the future mediation through "blood-brain crosstalk" in the treatment of neuroinflammatory diseases.

Key words: blood-brain crosstalk; neuroinflammation; neutrophil; brain cell; cell interaction

中枢神经系统 (central nervous system, CNS) 疾病是复杂的, 涉及的CNS疾病包括缺血性脑卒中 (ischemic stroke, IS)[1]、阿尔茨海默病 (Alzheimer's disease, AD)[2]、创伤性脑病 (traumatic brain injury, TBI)[3]、脑出血 (intracerebral hemorrhage, ICH)[4]、多发性硬化 (multiple sclerosis, MS)[5]等。它涉及循环系统和大脑之间的串扰[6]。2023年Chou等[7]提出基于“血−脑crosstalk”治疗CNS疾病的新策略。“血−脑crosstalk”是指循环系统中的免疫细胞浸润到脑实质, 随后与脑细胞互作从而治疗CNS疾病的一种途径。神经和免疫系统调节全身稳态, 并以协调的方式对各种类型的组织损伤做出反应。炎性免疫细胞浸润到脑实质中能够加重CNS细胞的损伤[8], 越来越多的研究结果证明, 在外周循环中发现的信号分子可以影响生理和病理条件下的认知功能[6]。如脑损伤以及随后的神经元死亡会激活常驻或浸润的免疫细胞, 从而触发神经炎症[8], 进而导致组织损伤和修复[9]。脑屏障包括血脑屏障 (blood-brain barrier, BBB)、血−脑脊液屏障 (blood-cerebrospinal fluid barrier, BCSFB) 和血−软脑膜屏障 (blood-leptomeningeal barrier, BLMB), 在损伤期间调节免疫细胞和神经毒性分子向CNS迁移是必不可少的。这些屏障对CNS的免疫监控、免疫保护和免疫病理至关重要[10]。当脑屏障发生改变时, 血液循环中的免疫细胞与大脑中的常驻免疫细胞相互作用, 从而影响大脑的稳态, 导致神经炎症、神经元死亡和神经退行性疾病[7]。

中性粒细胞是首个通过BBB从循环血液中进入病变部位的免疫细胞, 这一过程是由脑损伤诱导的内皮细胞快速激活所驱动的[11]。来自小脑膜血管的中性粒细胞浸润发生在脑损伤发作后6 h内, 是最快速的炎症事件特征[12,13]。随后, 中性粒细胞积累在脑损伤后几天内达到峰值[14-18]。在BBB修复期间, 持续浸润的少数中性粒细胞仍对BBB功能有害[19]。神经炎症是CNS相关疾病发病机制的关键过程[20-24], 调节中性粒细胞与脑细胞相互作用成为抑制神经炎症并改善神经功能的有效策略[25]。

本文介绍了中性粒−脑细胞 (神经元、小胶质细胞、星形胶质细胞和内皮细胞) 互作介导的神经炎症及其对神经炎症疾病的影响, 并总结了近年来中药与西药有效成分通过介导中性粒−脑细胞互作改善神经炎症疾病的作用和机制, 旨在为未来通过介导“血−脑crosstalk”治疗神经炎症疾病提供依据和参考。

1 中性粒−脑细胞互作介导的神经炎症

1.1 中性粒−神经细胞互作 神经细胞又称神经元, 是神经系统最基本的结构和功能单位[26]。一种具有未成熟中性粒细胞特征的细胞群能够通过分泌生长因子混合物来发挥神经保护作用, 这种细胞群在体内驱动CNS轴突再生, 促进神经和脊髓的修复, 证明其在CNS隔室和神经元群中的相关性[27]。NOD样受体蛋白3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3) 是一种精细调控的大分子蛋白复合物, 通过激活半胱氨酸天冬氨酸特异性蛋白酶1 (cysteine aspartic acid specific protease-1, CASP1) 来感知损伤并触发炎症[28]。在TBI中, 激活活性氧/核因子-kappa B (reactive oxygen species/nuclear factor-kappa B/NLRP3, ROS/NF-κB/NLRP3) 通路, 能够减少中性粒细胞的募集、抑制神经元变性, 降低TBI后的炎症因子释放[29]。在AD中, 中性粒细胞活化募集到大脑中并促进神经元凋亡, 释放包括线粒体和线粒体DNA (mitochondria DNA, mtDNA) 在内的细胞内容物。中性粒细胞募集到大脑的过程能上调干扰素基因刺激蛋白 (stimulator of interferon genes, STING)、NLRP3、和白细胞介素-1β (interleukin-1β, IL-1β) 的表达。这一过程分泌的炎性细胞因子与mtDNA一起构成mtDNA-STING-NLRP3-IL-1β轴, 是中性粒细胞浸润的先决条件。当该途径中的任何因子耗尽时, 中性粒细胞向脑组织的迁移就会停止, 神经元和认知功能就会受到保护[30]。在IS中, 脑内皮白细胞介素-1受体1型 (interleukin 1 receptor 1, IL-1R1) 特异性缺失能够改善脑血流, 并使脑损伤24 h后中性粒细胞浸润减少, 同时降低血管活化。使用他莫昔芬诱导的巢蛋白-Cre小鼠在神经元中条件性IL-1R1缺失能够导致神经元损伤减少25%, 并改变小胶质细胞−神经元相互作用[31]。中性粒−神经元主要相互作用机制如图1所示。

1.2 中性粒−小胶质细胞互作 小胶质细胞占CNS细胞的5%～10%, 是大脑中重要的髓系先天免疫细胞[32]。小胶质细胞可以被激活成为促炎M1表型或抗炎M2表型。促炎M1表型能够释放促炎细胞因子, 如肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)、IL-6、IL-1β和ROS等; 抗炎M2表型能分泌抑炎因子, 如IL-10、IL-4、IL-13和转化生长因子-β (transforming growth factor beta, TGF-β) 等[33]。研究表明, 中性粒细胞胞外

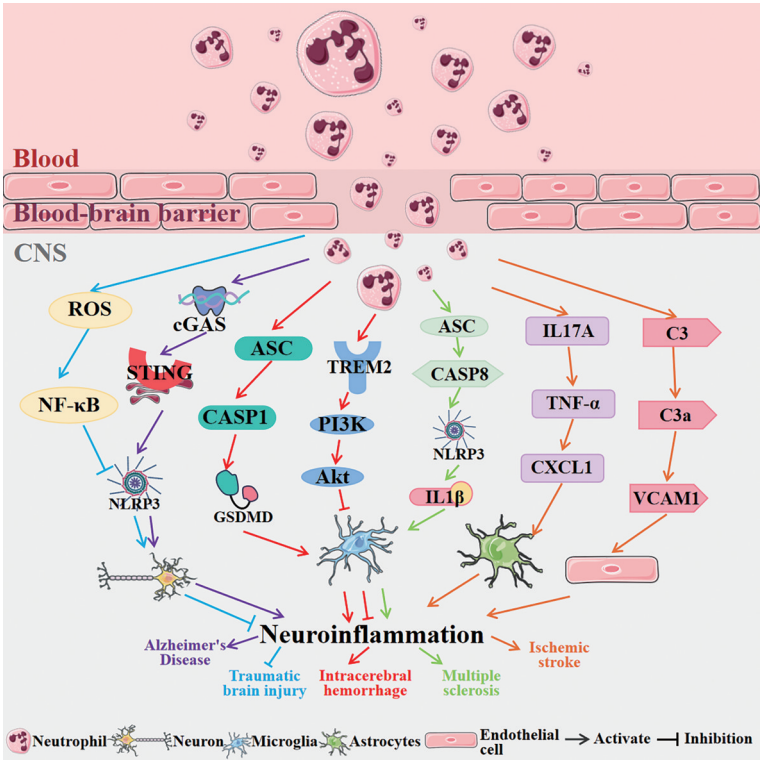


Figure 1 The action of mechanisms of neutrophil-brain cell interactions mediate "blood-brain crosstalk" in neuroinflammatory diseases. ROS: Reactive oxygen species; NF-κB: Nuclear factor-kappa B; NLRP3: NOD-like receptor thermal protein domain associated protein 3; cGAS: Cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; IL-1R1: Interleukin 1 receptor 1; ASC: Apoptosis-associated speck-like protein containing a CARD; CASP: Cysteine aspartic acid specific protease-1; GSDMD: Gasdermin D; TREM2: Triggering receptor expressed on myeloid cells 2; PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; IL-17A: Interleukin-17A; TNF-α: Tumor necrosis factor-α; CXCL1: C-X-C motif chemokine ligand 1; C3: Complement protein 3; C3a: Complement protein 3a; VCAM1: Vascular cell adhesion molecule-1

诱捕网 (neutrophil extracellular traps, NETs) 抑制剂 Cl-amidine 能够改善 TBI 后的短期神经功能, 减少脑缺血面积、脑水肿体积, 并恢复脑血流量。Cl-amidine 治疗抑制小胶质细胞向促炎 M1 表型极化, 并在 TBI 后 3 天促进其向抗炎 M2 表型极化[34]。N6-甲基腺苷 (m^6A) 甲基化是 RNA 中最丰富的表观遗传修饰之一, 影响 RNA 的转录、剪接、稳定性和转录后翻译。甲基转移酶样 3 (methyltransferase-like 3, METTL3) 是 m^6A 甲基转移酶复合体的关键组分, 通过修饰 m^6A 动态调控靶基因的表达[35]。动物实验研究结果表明, 髓样细胞触发受体 2 (triggering receptor expressed on myeloid cells 2, TREM2) 激活能够改善神经功能, 通过介导磷脂酰肌醇 3-激酶/蛋白激酶 B/METTL3 (phosphatidylinositol 3-kinase/protein kinase B/METTL3, PI3K/Akt/METTL3) 信号通路减轻 ICH 后的小胶质细胞极化和中性粒细胞募集[36]。在 TBI 中, METTL3 的蛋白表达在炎性小胶质细胞中上调。METTL3 能够促进碱性亮氨酸拉链 ATF 样转录因子 (the basic leucine zipper ATF-like transcription factor, BATF) 的表达, 增强 BATF 在小胶质细胞中的活性, 引起 TNF-α 依赖性神经毒性, 并且还可以通过释放 CXC 趋化因子配体 2 (CXC chemokine ligand 2, CXCL2) 促进中性粒细胞募集[37]。在 ICH 和炎症期间, IL-27 对中性粒细胞的极化抑制促炎分子的产生, 同时增加了包括乳铁蛋白在内的有益铁清除分子的产生[38]。在 MS 的动物模型发病过程中, 小胶质细胞特异性缺乏 ASC 会减弱中性粒细胞募集和 T 细胞扩增, 形成白细胞介素受体-1 相关激酶-M/半胱氨酸天冬氨酸蛋白酶 8/IL-1β (interleukin-1 receptor-related kinase M/cysteine aspartic acid specific protease-8/IL-1β, IRAKM/CASP8/IL-1β) 复合体, 并通过该复合体发挥其致病作用[39]。中性粒–小胶质细胞主要相互作用机制如图 1 所示。

1.3 中性粒–星形胶质细胞互作 星形胶质细胞是 CNS 中丰富的神经胶质细胞, 占 CNS 细胞总数的 20%～50%[40,41]。星形胶质细胞在维持大脑稳态和支持神经元功能方面起着至关重要的作用, 包括维持谷氨酸和离子稳态、消除氧化应激、储存糖原能量、组织修复, 以及通过释放神经递质调节突触活动和参

与突触形成等功能[42-44]。在炎症疼痛急性期, 中性粒细胞形成NETs, 禁食可以通过抑制星形胶质细胞中的单胺氧化酶B/5-羟基吲哚乙酸/G蛋白偶联受体(monoamine oxidase B/5-hydroxyindole acetic acid/G protein-coupled receptor 35, MAO-B/5-HIAA/GPR35)和MAO-B/ROS通路, 从而抑制NETs形成以及NETs诱导的神经炎症[45]。研究表明, 经dBET1 [一种新型有效的溴结构域蛋白4 (bromodomain-containing protein 4, BRD4) 降解剂] 治疗显著减弱IS诱导的BBB破坏、基质金属蛋白酶-9 (matrix metalloproteinase-9, MMP9)水平升高、中性粒细胞浸润和细胞黏附分子1 (intercellular cell adhesion molecule-1, ICAM-1) 升高。IS后给予dBET1可减轻缺血诱导的小胶质细胞和星形胶质细胞反应性胶质增生[46]。在IS中, 星形胶质细胞是中性粒细胞募集的靶细胞, 星形胶质细胞中TNF与白细胞介素-17A (interleukin-17A, IL-17A) 结合能够增强中性粒细胞趋化因子CXCL1的表达, 增强IS后炎症反应[47]。CNS减压病小鼠模型表明, 减压后炎症细胞外囊泡加剧中性粒细胞活化, 激活的中性粒细胞导致星形胶质细胞和小胶质细胞的扰动以及BBB完整性的破坏[48]。在胆管结扎术肝纤维化导致的肝性脑病中, 粒细胞集落刺激因子 (granulocyte colony-stimulating factor, G-CSF) 处理的小鼠肝脏中浸润的中性粒细胞表现出激活表型, 诱导小胶质细胞增殖和反应性星形胶质细胞的产生[49]。以2日龄脊髓粉碎小鼠作为模拟新生儿脊髓损伤 (neonatal spinal cord injury, SCI) 的模型, 流式细胞术结果显示, 与成年小鼠相比, 新生小鼠星形胶质细胞在SCI后分泌低水平的趋化因子, 如CXC趋化因子配体1 (CXC chemokine ligand 1, CXCL1) 和CXCL2, 来招募循环中性粒细胞[50]。中性粒−星形胶质细胞主要相互作用机制如图1所示。

1.4 中性粒−脑微血管内皮细胞互作 脑微血管内皮细胞是BBB的主要组成部分[51]。脓毒症患者皮层中性粒细胞浸润明显升高, 并伴有小胶质细胞和星形胶质细胞的增生, 同时影响内皮细胞屏障完整性[52]。内皮黏附分子促进白细胞黏附到内皮细胞上皮, 它的上调是内皮细胞介导的神经炎症的重要过程[53]。在IL-1β诱导的内皮细胞损伤的体外模型中, 神经调节蛋白-1 (beuregulin-1, NRG-1) 降低血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)、E-选择素和中性粒细胞对脑微血管内皮细胞的黏附水平[54]。血小板内皮细胞黏附分子1 (platelet endothelial cell adhesion molecule-1, PECAM-1) 控制IS小鼠模型中性粒细胞的跨内皮迁移, PECAM-1抗体可有效抑制IS后神经炎症、减少缺血性脑损伤并增强IS后脑重塑[55]。人脑型疟疾 (cerebral malaria, CM) 是由疟原虫感染引起的一种严重的神经系统并发症, 其病理表现与中性粒细胞积累相关[56]。在疟原虫感染的小鼠模型和伴有神经认知缺陷的小儿CM患者中, 神经网络形成失调与慢性炎症相关[57]。CM患者脑内寄生红细胞引发的细胞因子风暴导致BBB内皮损伤[57]。中性粒−内皮细胞主要相互作用机制如图1所示。

2 中性粒−脑细胞互作影响神经炎症疾病

2.1 脑卒中 IS是一种严重的急性神经系统疾病, 可导致残疾和死亡[58]。IS的发生常伴随着神经元的凋亡、神经炎症、氧化应激、脑血管损伤即BBB破坏等过程[59]。在严重缺血时, 小胶质细胞被激活, 产生炎症神经毒性分子, 有时会吞噬死亡或存活的神经元[60]。中性粒细胞和巨噬细胞渗入缺血脑组织。这些髓细胞被损伤的脑细胞或组织碎片释放的分子激活, 产生各种炎症细胞因子或趋化因子, 加剧缺血后无菌炎症和脑组织肿胀, 导致神经元损伤和不良的预后[8]。中性粒细胞和内皮细胞的黏附是缺血再灌注中炎症启动的基础。研究发现, 使用中性粒细胞来源负载Resolvin D2的纳米囊泡可以降低缺血导致的炎症, 并改善小鼠神经功能[61]。经过GEO数据库整理发现, 早期IS通过氧化应激与中性粒细胞串扰发挥作用, 研究者确定转录激活因子3 (signal transducer and activator of transcription 3, STAT3)、甲酰基肽受体1 (formyl peptide receptor 1, FPR1)、水通道蛋白9 (aquaporin-9, AQP9)、选择素L (L-selectin, SELL)、MMP9和白介素1受体相关激酶3 (interleukin-1 receptor associated kinase 3, IRAK3) 这6个与中性粒细胞反应和氧化应激相关的关键基因[62]。BBB损伤引起的出血转化 (hemorrhagic transformation, HT) 与IS的不良预后密切相关。IS后HT中性粒细胞异常募集, 其标志物淋巴细胞抗原6复合体位点G6D (lymphocyte antigen 6 complex locus G6D, Ly6G) 与微血管内皮细胞标志物血小板−内皮细胞黏附分子 (platelet endothelial adhesion molecule-1, CD31) 共定位, 并发现活化的中性粒细胞衍生的外泌体促进BBB损伤[63]。在大脑中动脉闭塞/再灌注 (middle cerebral artery occlusion/reperfusion, MCAO/R) 模型中, 过氧化氢酶经过被中性粒细胞有高度亲和力的配体内源性三肽修饰后, 能够增强过氧化氢酶在缺血亚区和脑神经元中的递送, 明显减少MCAO/R小鼠的梗死体积[64]。

2.2 阿尔茨海默病 AD是最常见的痴呆症。它是65岁及以上美国人的第五大死因[65]。AD的发病机制包括淀粉样β (amyloid-β, Aβ) 斑块和神经原纤维缠结[66,67]。越来越多的证据证明, 神经炎症是AD的关键诱因。AD特征性分子可溶性Aβ活化的人小胶质细胞

能够产生中性粒细胞的化学引诱剂, 包括IL-6、IL-8、CC趋化因子配体 (CC chemokine ligand, CCL) 2、CCL3/4、CCL5, 从而诱导中性粒细胞募集。而后小胶质细胞和中性粒细胞相互作用产生可上调AD神经炎症的介质, 包括移动抑制因子 (migration inhibition factor, MIF) 和IL-2[68]。AD和其他神经损伤疾病都会随着时间的推移对宿主微环境表现出巨大的变化。中性粒细胞的特异性免疫耗竭能够阻断病变中心附近星形胶质细胞的分化[69]。

2.3 多发性硬化 MS是一种神经退行性炎性自身免疫疾病[70]。这种疾病的主要机制特征是免疫细胞浸润到CNS。免疫细胞促进炎症过程, 导致少突胶质细胞死亡, 进而引起脱髓鞘和神经退化。研究表明, 转录因子过氧化物酶体增殖物激活型受体δ (peroxisome proliferator activated receptor δ, PPARδ)-芥酸相互作用抑制炎性酶、中性粒细胞弹性酶的产生, 阻断神经元死亡, 减轻神经炎症并诱导髓鞘形成, 从而在MS中发挥其潜在治疗作用[71]。一项网络数据分析研究表明, CXC型趋化因子受体4 (C-X-C motif chemokine receptor 4, CXCR4)、整合素αM (integrin alpha M, ITGAM)、β-肌动蛋白 (β-actin, ACTB) 等基因是MS潜在的生物标志物, 促进中性粒细胞跨内皮细胞迁移[72]。一项基于妊娠期间发生MS的转录组富集分析表明, 中性粒细胞脱颗粒可能作为MS治疗的可行性靶点[73]。金黄色葡萄球菌的细胞外黏附蛋白通过与ICAM-1相互作用以及阻断β2-整合素依赖中性粒细胞募集来发挥抗炎活性并减少炎症细胞浸润到CNS[74]。

3 药物靶向中性粒–脑细胞互作治疗神经炎症疾病

中药成分山柰酚、山柰酚苷、白藜芦醇通过介导中性粒–神经元相互作用来缓解IS导致的神经炎症[75-77]。虫草素和环黄芪醇通过介导中性粒–小胶质细胞的相互作用来改善CNS相关疾病导致的神经炎症损伤[78,79]。中药MLC901与藁本内酯能够减少CNS疾病中性粒细胞浸润以及小胶质细胞活化, 并且抑制反应性星形胶质细胞的激活, 以治疗CNS疾病导致的神经炎症[80,81]。红景天甙能够通过阻止C3及其活性片段C3a的增加, 从而降低MCAO/R后大鼠脑内皮细胞活化, 减少中性粒细胞浸润的标志物的表达, 以减轻MCAO/R后的炎症和神经元损伤[82]。在ICH疾病中, 鸢尾素治疗减少ICH后的脑水肿, 介导整合素αVβ5/腺苷酸活化蛋白激酶 (integrin-alpha V-beta 5/AMP-activated protein kinase, αVβ5/AMPK) 通路抑制小胶质细胞极化, 降低中性粒细胞浸润以及血肿周围区域的神经元凋亡, 从而发挥神经保护作用[83]。西药成分也能够通过介导中性粒–脑细胞互作在神经炎症疾病中发挥调控作用。氟西汀可减轻SAH后BBB破坏, 降低脑水肿, 改善神经功能。同时, 氟西汀通过下调TLR4和髓样分化因子88 (myeloid differentiation factor 88, MyD88) 的表达从而减少Iba1阳性小胶质细胞的数量、降低中性粒细胞浸润和细胞死亡[84]。本研究对目前药物改善中性粒–脑细胞相互作用抑制神经炎症进行总结, 如表1[29,75-93]。

Table 1 Traditional Chinese medicine and western medicine components regulate neutrophil-brain cell interaction to inhibit neuroinflammation. IS: Ischemic stroke; TBI: Traumatic brain injury; ICH: Intracerebral hemorrhage; SAH: Subarachnoid hemorrhage; CCH: Chronic cerebral hypoperfusion; NMOSD: Neuromyelitis optica spectrum disorders

Category	Agent	Dose	Brain cells interact with neutrophils	Subject	Mechanism of action	Disease	Ref.
Traditional Chinese medicine	Kaempferol glycosides	7.5 mg·kg^{-1}	Neuron	SD rat	NF-κB/STAT3	IS	[75]
	Kaempferol	25 mg·kg^{-1}	Neuron	SD rat	BDNF/TrkB/PI3K/AKT	IS	[76]
	Resveratrol	3 mg·kg^{-1}	Neuron	SD rat	STING/TBK1/IRF3	CCH	[77]
	Cordycepin	10 mg·kg^{-1}	Microglia	C57BL/6J mice	MMP9, MMP2	TBI	[78]
	Cycloastragenol	50 mg·kg^{-1}	Microglia	SD rat	SIRT1/FOXO1/p35	SAH	[79]
	MLC901	40 μg·kg^{-1}	Microglia, astrocyte	C57BL/6J mice	PRX6/NF-κB/TLR4	IS	[80]
	Ligustilide	20, 40 mg·kg^{-1}	Microglia, astrocyte	SD rat	Prx6/TLR4	IS	[81]
	Maraviroc	20 mg·kg^{-1}	Microglia, astrocyte, neuron	C57BL/6J mice	CCR5/HMGB1	TBI	[85]
	Salidroside	50 mg·kg^{-1}	Endothelial cell	SD rat	C3/C3a	IS	[82]
Western medicine	Irisin	80−750 μg·kg^{-1}	Neuron	C57BL/6J mice	αVβ5/AMPK	ICH	[83]
	Didymin	0.5−4.5 mg·kg^{-1}	Microglia	C57BL/6J mice	ASC/caspase-1/GSDMD	ICH	[86]
	RO27-3225	60−540 μg·kg^{-1}	Microglia	CD1 mice	AMPK/JNK/p38 MAPK	ICH	[87]
	TO901317	30 mg·kg^{-1}	Microglia	C57BL/6J mice	P38/JNK/MAPK/NF-κB	ICH	[88]
	Fluoxetine	10 mg·kg^{-1}	Microglia	SD rat	TLR4/MyD88/NF-κB	SAH	[84]
	Methylene blue	1 mg·kg^{-1}	Microglia	SD rat	Akt/GSK-3β/MEF2D	SAH	[89]
	INT-777	10−90 μg·kg^{-1}	Microglia	SD rat	TGR5/cAMP/PKA	SAH	[90]
	Memantine	60 mg·kg^{-1}	Microglia	C57BL/6J mice	AQP4/IgG	NMOSD	[91]
	Adjudin	50 mg·kg^{-1}	Microglia, astrocyte	C57BL/6 mice	AQP4, TNF-α, IL-1β	ICH	[92]
	COG1410	200 μg·mL^{-1}	Microglia	C57BL/6 mice	Akt/CREB/BDNF	TBI	[93]
	Deferoxamine	100 mg·kg^{-1}	Microglia, astrocyte	C57BL/6J mice	ROS/NF-κB/NLRP3	TBI	[29]

4 总结和展望

综上, 中性粒细胞在神经炎症的发生、发展和恢复过程中发挥着重要的作用。循环血液中的中性粒细胞调节脑细胞的炎症反应, 已经成为神经炎症疾病治疗的重要途径之一。中性粒细胞可以募集到病变部位并释放趋化因子、炎症因子以及损伤相关分子来启动神经炎症疾病的炎性反应。中性粒细胞参与各种CNS疾病中的复杂病理过程, 包括在CNS感染期间的急性神经炎症疾病, 如在IS、TBI及神经退行性疾病中尤为明显。中性粒细胞的活化, 脑微血管中NETs的形成, 都可能导致有毒分子的释放, 破坏BBB的完整性。也会导致中性粒细胞及其产物渗入脑实质, 从而引发胶质细胞的持续炎症反应, 进一步导致神经元损伤和认知障碍。

目前, 已有许多研究报道了中药来源的小分子化合物以及西药小分子化合物具有靶向中性粒细胞–脑细胞互作来治疗CNS疾病潜力。药物促进中性粒–脑细胞互作的方式还需要更深入的研究。“血–脑crosstalk”是外周血中活化的中性粒细胞浸润到脑实质与脑细胞发生互作导致神经炎症的途径, 包括中性粒–小胶质细胞、中性粒–星形胶质细胞、中性粒–神经元、中性粒–内皮细胞等中性粒–脑细胞的相互影响, 在越来越多的相关研究中被发现。值得注意的是中性粒–脑细胞互作的机制还不够清晰, 因此, 在设计干预措施之前有必要确定中性粒–脑细胞互作对CNS神经炎症的贡献。由于中性粒–脑细胞的互作机制复杂, 借用如单细胞测序、空间组学、3D类器官等研究细胞互作的前沿技术, 更加深入地阐明细胞互作机制, 从而促进神经炎症疾病的预防和治疗的研究。

作者贡献: 王思梦负责综述撰写图表绘制工作; 江廷参、李星、朱彦协助参与文章修改; 吕明、董鹏志完成文章修改、校对和审核。

利益冲突: 作者声明本文不存在任何利益冲突。

References

[1] Jayaraj RL, Azimullah S, Beiram R, et al. Neuroinflammation: friend and foe for ischemic stroke [J]. J Neuroinflammation, 2019, 16: 142.

[2] Thakur S, Dhapola R, Sarma P, et al. Neuroinflammation in Alzheimer's disease: current progress in molecular signaling and therapeutics [J]. Inflammation, 2023, 46: 1-17.

[3] Simon DW, McGeachy MJ, Bayır H, et al. The far-reaching scope of neuroinflammation after traumatic brain injury[J]. Nat Rev Neurol, 2017, 13: 171-191.

[4] Tschoe C, Bushnell CD, Duncan PW, et al. Neuroinflammation after intracerebral hemorrhage and potential therapeutic targets [J]. J Stroke, 2020, 22: 29-46.

[5] das Neves SP, Sousa JC, Sousa N, et al. Altered astrocytic function in experimental neuroinflammation and multiple sclerosis [J]. Glia, 2021, 69: 1341-1368.

[6] Gonçalves RA, De Felice FG. The crosstalk between brain and periphery: implications for brain health and disease [J]. Neuropharmacology, 2021, 197: 108728.

[7] Chou ML, Babamale AO, Walker TL, et al. Blood-brain crosstalk: the roles of neutrophils, platelets, and neutrophil extracellular traps in neuropathologies [J]. Trends Neurosci, 2023, 46: 764-779.

[8] Shichita T, Ooboshi H, Yoshimura A. Neuroimmune mechanisms and therapies mediating post-ischaemic brain injury and repair [J]. Nat Rev Neurosci, 2023, 24: 299-312.

[9] Garcia-Bonilla L, Shahanoor Z, Sciortino R, et al. Analysis of brain and blood single-cell transcriptomics in acute and subacute phases after experimental stroke [J]. Nat Immunol, 2024, 25: 357-370.

[10] Ayub M, Jin HK, Bae JS. The blood cerebrospinal fluid barrier orchestrates immunosurveillance, immunoprotection, and immunopathology in the central nervous system [J]. BMB Rep, 2021, 54: 196-202.

[11] Neumann J, Riek-Burchardt M, Herz J, et al. Very-late-antigen-4 (VLA-4)-mediated brain invasion by neutrophils leads to interactions with microglia, increased ischemic injury and impaired behavior in experimental stroke [J]. Acta Neuropathol, 2015, 129: 259-277.

[12] Chu HX, Kim HA, Lee S, et al. Immune cell infiltration in malignant middle cerebral artery infarction: comparison with transient cerebral ischemia [J]. J Cereb Blood Flow Metab, 2014, 34: 450-459.

[13] Perez-de-Puig I, Miró-Mur F, Ferrer-Ferrer M, et al. Neutrophil recruitment to the brain in mouse and human ischemic stroke [J]. Acta Neuropathol, 2015, 129: 239-257.

[14] Liesz A, Hagmann S, Zschoche C, et al. The spectrum of systemic immune alterations after murine focal ischemia: immunodepression *versus* immunomodulation [J]. Stroke, 2009, 40: 2849-2858.

[15] Grønberg NV, Johansen FF, Kristiansen U, et al. Leukocyte infiltration in experimental stroke [J]. J Neuroinflammation, 2013, 10: 115.

[16] Gelderblom M, Leypoldt F, Steinbach K, et al. Temporal and spatial dynamics of cerebral immune cell accumulation in stroke [J]. Stroke, 2009, 40: 1849-1857.

[17] Wang R, Zhu Y, Liu Z, et al. Neutrophil extracellular traps promote tPA-induced brain hemorrhage *via* cGAS in mice with stroke [J]. Blood, 2021, 138: 91-103.

[18] Puy L, Corseaux D, Perbet R, et al. Neutrophil extracellular traps (NETs) infiltrate haematoma and surrounding brain tissue after

intracerebral haemorrhage: a post-mortem study [J]. Neuropathol Appl Neurobiol, 2021, 47: 867-877.

[19] Kang L, Yu H, Yang X, et al. Neutrophil extracellular traps released by neutrophils impair revascularization and vascular remodeling after stroke [J]. Nat Commun, 2020, 11: 2488.

[20] Wu X, Zeng H, Xu C, et al. TREM1 regulates neuroinflammatory injury by modulate proinflammatory subtype transition of microglia and formation of neutrophil extracellular traps *via* interaction with SYK in experimental subarachnoid hemorrhage [J]. Front Immunol, 2021, 12: 766178.

[21] Guan X, Zhu S, Song J, et al. Microglial CMPK2 promotes neuroinflammation and brain injury after ischemic stroke [J]. Cell Rep Med, 2024, 5: 101522.

[22] Jiang R, Lu Z, Wang C, et al. Beta2 adrenergic receptor-mediated abnormal myelopoiesis drives neuroinflammation in aged patients with traumatic brain injury [J]. Sci Adv, 2024, 10: eadp5239.

[23] Keeler GD, Kumar S, Palaschak B, et al. Gene therapy-induced antigen-specific Tregs inhibit neuro-inflammation and reverse disease in a mouse model of multiple sclerosis [J]. Mol Ther, 2018, 26: 173-183.

[24] Cheng J, Dong Y, Ma J, et al. Microglial Calhm2 regulates neuroinflammation and contributes to Alzheimer's disease pathology [J]. Sci Adv, 2021, 7: eabe3600.

[25] Mu Q, Yao K, Syeda MZ, et al. Neutrophil targeting platform reduces neutrophil extracellular traps for improved traumatic brain injury and stroke theranostics [J]. Adv Sci, 2024, 11: e2308719.

[26] De Luca C, Colangelo AM, Alberghina L, et al. Neuro-immune hemostasis: homeostasis and diseases in the central nervous system [J]. Front Cell Neurosci, 2018, 12: 459.

[27] Sas AR, Carbajal KS, Jerome AD, et al. A new neutrophil subset promotes CNS neuron survival and axon regeneration [J]. Nat Immunol, 2020, 21: 1496-1505.

[28] Toldo S, Abbate A. The role of the NLRP3 inflammasome and pyroptosis in cardiovascular diseases [J]. Nat Rev Cardiol, 2024, 21: 219-237.

[29] Jia H, Liu X, Cao Y, et al. Deferoxamine ameliorates neurological dysfunction by inhibiting ferroptosis and neuroinflammation after traumatic brain injury [J]. Brain Res, 2023, 1812: 148383.

[30] Xia X, He X, Zhao T, et al. Inhibiting mtDNA-STING-NLRP3/IL-1β axis-mediated neutrophil infiltration protects neurons in Alzheimer's disease [J]. Cell Prolif, 2024, 57: e13529.

[31] Wong R, Lénárt N, Hill L, et al. Interleukin-1 mediates ischaemic brain injury *via* distinct actions on endothelial cells and cholinergic neurons [J]. Brain Behav Immun, 2019, 76: 126-138.

[32] Liddelow SA, Marsh SE, Stevens B. Microglia and astrocytes in disease: dynamic duo or partners in crime?[J]. Trends Immunol, 2020, 41: 820-835.

[33] Yu H, Chang Q, Sun T, et al. Metabolic reprogramming and polarization of microglia in Parkinson's disease: role of inflammasome and iron [J]. Ageing Res Rev, 2023, 90: 102032.

[34] Shi G, Liu L, Cao Y, et al. Inhibition of neutrophil extracellular trap formation ameliorates neuroinflammation and neuronal apoptosis *via* STING-dependent IRE1α/ASK1/JNK signaling pathway in mice with traumatic brain injury [J]. J Neuroinflammation, 2023, 20: 222.

[35] Jin Q, Qu H, Quan C. New insights into the regulation of METTL3 and its role in tumors [J]. Cell Commun Signal, 2023, 21: 334.

[36] Chen S, Peng J, Sherchan P, et al. TREM2 activation attenuates neuroinflammation and neuronal apoptosis *via* PI3K/Akt pathway after intracerebral hemorrhage in mice [J]. J Neuroinflammation, 2020, 17: 168.

[37] Wu X, Liu H, Wang J, et al. The m^6A methyltransferase METTL3 drives neuroinflammation and neurotoxicity through stabilizing BATF mRNA in microglia [J]. Cell Death Differ, 2025, 32: 100-117.

[38] Zhao X, Ting SM, Liu CH, et al. Neutrophil polarization by IL-27 as a therapeutic target for intracerebral hemorrhage [J]. Nat Commun, 2017, 8: 602.

[39] Zhang CJ, Jiang M, Zhou H, et al. TLR-stimulated IRAKM activates caspase-8 inflammasome in microglia and promotes neuroinflammation [J]. J Clin Invest, 2018, 128: 5399-5412.

[40] Lee HG, Lee JH, Flausino LE, et al. Neuroinflammation: an astrocyte perspective [J]. Sci Transl Med, 2023, 15: eadi7828.

[41] Hasel P, Liddelow SA. Astrocytes [J]. Curr Biol, 2021, 31: R326-R327.

[42] He L, Zhang R, Yang M, et al. The role of astrocyte in neuroinflammation in traumatic brain injury [J]. Biochim Biophys Acta Mol Basis Dis, 2024, 1870: 166992.

[43] Lee HG, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases [J]. Nat Rev Drug Discov, 2022, 21: 339-358.

[44] Chen Z, Yuan Z, Yang S, et al. Brain energy metabolism: astrocytes in neurodegenerative diseases [J]. CNS Neurosci Ther, 2023, 29: 24-36.

[45] Li T, Yue Y, Ma Y, et al. Fasting-mimicking diet alleviates inflammatory pain by inhibiting neutrophil extracellular traps formation and neuroinflammation in the spinal cord [J]. Cell Commun Signal, 2023, 21: 250.

[46] Liu L, Yang C, Lavayen BP, et al. Targeted BRD4 protein degradation by dBET1 ameliorates acute ischemic brain injury and improves functional outcomes associated with reduced neuroinflammation and oxidative stress and preservation of blood-brain barrier integrity [J]. J Neuroinflammation, 2022, 19: 168.

[47] Schädlich IS, Vienhues JH, Jander A, et al. Interleukin-1 mediates ischemic brain injury *via* induction of IL-17A in $\gamma\delta$ T cells and CXCL1 in astrocytes [J]. Neuromol Med, 2022, 24:

437-451.

[48] Thom SR, Bhopale VM, Bhat AR, et al. Neuroinflammation with increased glymphatic flow in a murine model of decompression sickness [J]. J Neurophysiol, 2023, 129: 662-671.

[49] Ortega-Ribera M, Zhuang Y, Brezani V, et al. G-CSF increases calprotectin expression, liver damage and neuroinflammation in a murine model of alcohol-induced ACLF [J]. Front Cell Dev Biol, 2024, 12: 1347395.

[50] Kitade K, Kobayakawa K, Saiwai H, et al. Reduced neuroinflammation *via* astrocytes and neutrophils promotes regeneration after spinal cord injury in neonatal mice [J]. J Neurotrauma, 2023, 40: 2566-2579.

[51] Long J, Sun Y, Liu S, et al. Targeting pyroptosis as a preventive and therapeutic approach for stroke [J]. Cell Death Discov, 2023, 9: 155.

[52] Nwafor DC, Chakraborty S, Brichacek AL, et al. Loss of tissue-nonspecific alkaline phosphatase (TNAP) enzyme activity in cerebral microvessels is coupled to persistent neuroinflammation and behavioral deficits in late sepsis [J]. Brain Behav Immun, 2020, 84: 115-131.

[53] Yan M, Leng T, Tang L, et al. Neuroprotectant androst-3β, 5α, 6β -triol suppresses TNF- α -induced endothelial adhesion molecules expression and neutrophil adhesion to endothelial cells by attenuation of CYLD-NF- κB pathway [J]. Biochem Biophys Res Commun, 2017, 483: 892-896.

[54] Wu L, Walas S, Leung W, et al. Neuregulin1-β decreases IL-1β-induced neutrophil adhesion to human brain microvascular endothelial cells [J]. Transl Stroke Res, 2015, 6: 116-124.

[55] Winneberger J, Schöls S, Lessmann K, et al. Platelet endothelial cell adhesion molecule-1 is a gatekeeper of neutrophil transendothelial migration in ischemic stroke [J]. Brain Behav Immun, 2021, 93: 277-287.

[56] Knackstedt SL, Georgiadou A, Apel F, et al. Neutrophil extracellular traps drive inflammatory pathogenesis in malaria [J]. Sci Immunol, 2019, 4: eaaw0336.

[57] Biswas I, Panicker SR, Giri H, et al. Antithrombin protects against *Plasmodium falciparum* histidine-rich protein II-mediated inflammation and coagulation [J]. Blood Adv, 2022, 6: 931-945.

[58] Jia J, Jiao W, Wang G, et al. Drugs/agents for the treatment of ischemic stroke: advances and perspectives [J]. Med Res Rev, 2024, 44: 975-1012.

[59] Long JP, Sun Y, Liu SS, et al. Progress on the neuroprotective effects of ginsenoside Rg1 [J]. Acta Pharm Sin (药学学报), 2023, 58: 21-26.

[60] Brown GC, Neher JJ. Microglial phagocytosis of live neurons [J]. Nat Rev Neurosci, 2014, 15: 209-216.

[61] Dong X, Gao J, Zhang CY, et al. Neutrophil membrane-derived nanovesicles alleviate inflammation to protect mouse brain injury from ischemic stroke [J]. ACS Nano, 2019, 13: 1272-1283.

[62] Mu C, Wang Y, Han C, et al. Crosstalk between oxidative stress and neutrophil response in early ischemic stroke: a comprehensive transcriptome analysis [J]. Front Immunol, 2023, 14: 1134956.

[63] Tang N, Gong XR, Huang H, et al. Activated neutrophil-derived exosomes contribute to blood-brain barrier damage and hemorrhagic transformation after cerebral ischemia/reperfusion [J]. Brain Res, 2023, 1810: 148374.

[64] Zhang C, Ling CL, Pang L, et al. Direct macromolecular drug delivery to cerebral ischemia area using neutrophil-mediated nanoparticles [J]. Theranostics, 2017, 7: 3260-3275.

[65] 2024 Alzheimer's disease facts and figures [J]. Alzheimer Dement, 2024, 20: 3708-3821.

[66] Zheng Q, Wang X. Alzheimer's disease: insights into pathology, molecular mechanisms, and therapy [J]. Protein Cell, 2024, 16: 83-120.

[67] Deng Z, Dong Y, Zhou X, et al. Pharmacological modulation of autophagy for Alzheimer's disease therapy: opportunities and obstacles [J]. Acta Pharm Sin B, 2022, 12: 1688-1706.

[68] Park J, Baik SH, Mook-Jung I, et al. Mimicry of central-peripheral immunity in Alzheimer's disease and discovery of neurodegenerative roles in neutrophil [J]. Front Immunol, 2019, 10: 2231.

[69] Nguyen HX, Hooshmand MJ, Saiwai H, et al. Systemic neutrophil depletion modulates the migration and fate of transplanted human neural stem cells to rescue functional repair [J]. J Neurosci, 2017, 37: 9269-9287.

[70] Blackmore S, Hernandez J, Juda M, et al. Influenza infection triggers disease in a genetic model of experimental autoimmune encephalomyelitis [J]. Proc Nat Acad Sci U S A, 2017, 114: E6107-E6116.

[71] Altinoz MA, Ozpinar A. PPAR-δ and erucic acid in multiple sclerosis and Alzheimer's disease. Likely benefits in terms of immunity and metabolism [J]. Int Immunopharmacol, 2019, 69: 245-256.

[72] Chen X, Hou H, Qiao H, et al. Identification of blood-derived candidate gene markers and a new 7-gene diagnostic model for multiple sclerosis [J]. Biol Res, 2021, 54: 12.

[73] Hernández-Preciado MR, Torres-Mendoza BM, Mireles-Ramírez MA, et al. Gene expression in multiple sclerosis during pregnancy based on integrated bioinformatics analysis [J]. Mult Scler Relat Disord, 2024, 82: 105373.

[74] Xie C, Alcaide P, Geisbrecht BV, et al. Suppression of experimental autoimmune encephalomyelitis by extracellular adherence protein of *Staphylococcus aureus* [J]. J Exp Med, 2006, 203: 985-994.

[75] Yu L, Chen C, Wang LF, et al. Neuroprotective effect of kaempferol glycosides against brain injury and neuroinflammation by inhibiting the activation of NF-κB and STAT3 in transient focal stroke [J]. PLoS One, 2013, 8: e55839.

[76] Zhang SS, Liu M, Liu DN, et al. Network pharmacology analysis

and experimental validation of kaempferol in the treatment of ischemic stroke by inhibiting apoptosis and regulating neuroinflammation involving neutrophils [J]. Int J Mol Sci, 2022, 23: 12694.

[77] Kang N, Shi Y, Song J, et al. Resveratrol reduces inflammatory response and detrimental effects in chronic cerebral hypoperfusion by down-regulating stimulator of interferon genes/TANK-binding kinase 1/interferon regulatory factor 3 signaling [J]. Front Aging Neurosci, 2022, 14: 868484.

[78] Wei P, Wang K, Luo C, et al. Cordycepin confers long-term neuroprotection *via* inhibiting neutrophil infiltration and neuroinflammation after traumatic brain injury [J]. J Neuroinflammation, 2021, 18: 137.

[79] Lin W, Yao H, Lai J, et al. Cycloastragenol confers cerebral protection after subarachnoid hemorrhage by suppressing oxidative insults and neuroinflammation *via* the SIRT1 signaling pathway [J]. Oxid Med Cell Longev, 2022, 2022: 3099409.

[80] Widmann C, Gandin C, Petit-Paitel A, et al. The traditional Chinese medicine MLC901 inhibits inflammation processes after focal cerebral ischemia [J]. Sci Rep, 2018, 8: 18062.

[81] Kuang X, Wang LF, Yu L, et al. Ligustilide ameliorates neuroinflammation and brain injury in focal cerebral ischemia/reperfusion rats: involvement of inhibition of TLR4/peroxiredoxin 6 signaling [J]. Free Radic Biol Med, 2014, 71: 165-175.

[82] Wang Y, Su Y, Lai W, et al. Salidroside restores an anti-inflammatory endothelial phenotype by selectively inhibiting endothelial complement after oxidative stress [J]. Inflammation, 2020, 43: 310-325.

[83] Wang Y, Tian M, Tan J, et al. Irisin ameliorates neuroinflammation and neuronal apoptosis through integrin *α*V*β*5/AMPK signaling pathway after intracerebral hemorrhage in mice [J]. J Neuroinflammation, 2022, 19: 82.

[84] Liu FY, Cai J, Wang C, et al. Fluoxetine attenuates neuroinflammation in early brain injury after subarachnoid hemorrhage: a possible role for the regulation of TLR4/MyD88/NF- *κ*B signaling pathway [J]. J Neuroinflammation, 2018, 15: 347.

[85] Liu XL, Sun DD, Zheng MT, et al. Maraviroc promotes recovery from traumatic brain injury in mice by suppression of neuroinflammation and activation of neurotoxic reactive astrocytes [J]. Neural Regen Res, 2023, 18: 141-149.

[86] Gu L, Sun M, Li R, et al. Didymin suppresses microglia pyroptosis and neuroinflammation through the ASC/caspase-1/GSDMD pathway following experimental intracerebral hemorrhage [J]. Front Immunol, 2022, 13: 810582.

[87] Chen S, Zhao L, Sherchan P, et al. Activation of melanocortin receptor 4 with RO27-3225 attenuates neuroinflammation through AMPK/JNK/p38 MAPK pathway after intracerebral hemorrhage in mice [J]. J Neuroinflammation, 2018, 15: 106.

[88] Wu CH, Chen CC, Lai CY, et al. Treatment with TO901317, a synthetic liver X receptor agonist, reduces brain damage and attenuates neuroinflammation in experimental intracerebral hemorrhage [J]. J Neuroinflammation, 2016, 13: 62.

[89] Xu H, Li J, Wang Z, et al. Methylene blue attenuates neuroinflammation after subarachnoid hemorrhage in rats through the Akt/GSK-3*β*/MEF2D signaling pathway [J]. Brain Behav Immun, 2017, 65: 125-139.

[90] Hu X, Yan J, Huang L, et al. INT-777 attenuates NLRP3-ASC inflammasome-mediated neuroinflammation *via* TGR5/cAMP/PKA signaling pathway after subarachnoid hemorrhage in rats [J]. Brain Behav Immun, 2021, 91: 587-600.

[91] Yick LW, Tang CH, Ma OKF, et al. Memantine ameliorates motor impairments and pathologies in a mouse model of neuromyelitis optica spectrum disorders [J]. J Neuroinflammation, 2020, 17: 236.

[92] Su Q, Su C, Zhang Y, et al. Adjudin protects blood-brain barrier integrity and attenuates neuroinflammation following intracerebral hemorrhage in mice [J]. Int Immunopharmacol, 2024, 132: 111962.

[93] Yan J, Zhang Y, Wang L, et al. TREM2 activation alleviates neural damage *via* Akt/CREB/BDNF signalling after traumatic brain injury in mice [J]. J Neuroinflammation, 2022, 19: 289.