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神经炎症及其体外模型*

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摘要 神经炎症是一种累及神经系统的炎症性疾病，通常表现为神经组织的异常反应或损伤，伴随着免疫系统的参与。小胶质细胞和星形胶质细胞作为中枢神经系统重要免疫细胞和支撑细胞，具有识别危险信号、产生炎症介质、清除病原微生物等功能，在维持稳态和调控神经炎症发生发展中发挥关键作用。神经炎症可以影响中枢神经系统或周围神经系统，参与多种神经系统疾病的发生发展。本文简述了神经炎症的相关通路研究现状，并介绍了目前常用的神经炎症细胞研究模型，对于深入了解神经炎症发生的分子机制和预防治疗药物的筛选提供参考。

关键词 神经炎症，细胞模型，信号通路
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1 神经炎症概述

当神经系统受到损伤、感染、氧化应激或其他激活因子的刺激时，血脑屏障的通透性增加，外周免疫细胞如中性粒细胞和巨噬细胞渗入中枢神经系统。随后中枢免疫系统（central nervous system，CNS）中的神经细胞如小胶质细胞和星形胶质细胞被激活，释放大量炎症介质（如细胞因子和趋化因子）诱发神经炎症[1]。脑内初期的急性神经炎症往往发挥着神经保护功能，有利于神经元的修复并维持内环境稳定[2]；而长期或过度激活的神经炎症会导致炎症介质过度释放，造成神经元的损伤和退化，影响神经功能导致神经系统疾病[3]。近年来，大量体内动物实验及临床研究的结果表明，脑内神经炎症与多种急、慢性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）、多发性硬化（multiple sclerosis，MS）和亨廷顿氏病（Huntington’s disease，HD）等的发生和发展密切相关[4-6]。建立神经炎症细胞模型有助于更深入地探究神经系统疾病的发生和发展机制，同时可用于神经炎症干预药物筛选。

小胶质细胞和星形胶质细胞作为CNS重要的免疫细胞和支撑细胞，具有识别危险信号、产生炎症介质、清除微生物等功能，在维持CNS稳态和调控神经炎症发生发展中发挥关键作用[7-10]。

1.1 小胶质细胞

小胶质细胞起源于胚胎卵黄囊祖细胞，占脑细胞总数的5%~15%，是CNS的常驻细胞[11]。在正常生理状态下，处于静息状态的小胶质细胞也能持续感知脑内微环境动态，具有敏感的免疫监视功能[12]。因此，小胶质细胞通常参与脑内第一道也是最主要的免疫防线，最先感知脑内异常信号如损伤、炎症等而被激活[13]。目前研究表明，小胶质细胞具有的吞噬清除死亡细胞碎片、凝集沉淀不溶性蛋白质和入侵病原体等功能，对维持CNS稳态起重要作用[14-15]。

激活态小胶质细胞根据其功能特性和不同标志物主要分为M1型和M2型[16]。M1表型的细胞表面标记主要有CD14、CD16、CD32、CD40、CD68和CD86，产生白介素（interleukin，IL）如IL-1β、IL-6、IL-8、肿瘤坏死因子α（tumor

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necrosis factor alpha，TNF-α）和趋化因子等细胞因子发挥杀灭清除微生物和促炎作用，而过度激活将产生神经毒性[17-18]；M2表型的细胞表面标记主要有CD206和CD163，其产生的细胞因子IL-10、IL-4、IL-13和转化生长因子β（transforming growth factor beta，TGF-β）等能抑制炎症反应并修复组织，进而保护神经[19]。活化小胶质细胞能感知微环境在两种表型之间动态转换，但多由M2转为M1产生神经炎症和神经毒性反应，加快神经系统疾病的进展。

1.2 星形胶质细胞

星形胶质细胞是CNS中含量最丰富的神经胶质细胞，脑组织、神经元和血管外的空间大部分由星形胶质细胞填充[20]。星形胶质细胞除了对神经元起营养和机械支撑作用外，在促进突触形成并吞噬修剪突触、形成及维持血脑屏障等方面也发挥重要作用，是维持脑稳定的关键细胞[21-22]。当CNS出现疾病或损伤时，星形胶质细胞也会发生结构和功能的改变，包括细胞增殖、炎症介质和神经营养因子分泌等，形成反应性星形胶质细胞[23]。

根据反应性星形胶质细胞的基因表达差异可将其分为A1和A2两种表型。研究发现，系统性注射脂多糖（lipopolysaccharide，LPS）产生的神经炎症可诱导A1型反应性星形胶质细胞，而大脑中动脉阻塞后的脑缺血诱导A2型反应性星形胶质细胞[24]。A1型反应性星形胶质细胞中H-2、D区位点1、补体C3等免疫通路相关基因表达上调，能抑制突触的形成、分泌神经毒素诱导神经元和少突胶质细胞凋亡，表现为神经毒性作用。A2型反应性星形胶质细胞上调许多神经营养因子和抗炎细胞因的基因表达，如心肌营养素样细胞因子1（cardiotrophin-like cytokine factor 1，Clcf1）、S100钙结合蛋白A10（S100 calcium binding protein A10，S100a10）、TGF-β等，促进神经元的存活，增强突触重塑能力，具有神经保护性[25]。

2 调控神经炎症的信号通路

2.1 TLR4/NF-κB信号通路

Toll样受体（Toll-like receptors，TLRs）是参与先天免疫和炎症反应的一种重要的信号转导膜蛋白，TLR4是CNS感染和损伤过程中调节免疫反应的关键宿主分子，在脑内主要在小胶质细胞中表达，能被LPS特异性识别[26]。

TLR4主要有两条激活途径：髓样分化因子88（myeloid differentiation factor 88，MyD88）途径和MyD88非依赖途径。在MyD88途径中，胞外信号传递至胞内后与MyD88的羟基端结合，同时MyD88与IL-1受体相关激酶4（interleukin-1 receptor-associated kinase 4，IRAK4）结合，激活IRAKs。磷酸化的IRAKs与肿瘤坏死因子受体相关因子6（TNF receptor–associated factor 6，TRAF6）相互作用，激活转录因子核因子κB（nuclear factor kappa-B，NF-κB）[27]。另一方面，MyD88非依赖途径由易位关联膜蛋白（translocation associated membrane protein，TRAM）启动后，TIR结构域衔接蛋白（TIR-domain-containing adaptor inducing interferon，TRIF）被招募并与受体相互作用蛋白1（receptor-interacting protein 1，RIP1）相互作用进而激活MyD88非依赖的NF-κB途径[28]。

2.2 MAPK级联信号通路

丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）是真核细胞中高度保守的信号转导通路，也是CNS细胞内经典炎症信号通路之一。MAPK级联信号通路能够响应如细胞因子、TNF-α、活性氧类（reactive oxygen species，ROS）、血管内皮生长因子（vascular endothelial growth factor，VEGF）等，主要参与调节免疫反应、氧化应激和细胞凋亡[29]。

研究证明，应激活化蛋白激酶（stress-activated protein kinase，SAPK）/c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）、p38和细胞外调节蛋白激酶（extracellular regulated protein kinases，ERK）在内的MAPK在神经退行性病变患者中均存在上调，促进淀粉样蛋白前体蛋白（amyloid precursor protein，APP）的磷酸化进而产生β淀粉样蛋白（amyloid β-protein，Aβ）[30]。同时在注射Aβ1-42的小鼠模型中，p38和ERK的磷酸化与Aβ诱导的小鼠神经炎症反应和认知功能障碍密切相关[31]。MAPK信号通路的活性增强以及其在转录和翻译水平上对促炎介质合成的调控，使其成为新的抗炎疗法的潜在靶点。

2.3 PI3K/AKT信号通路

小胶质细胞活化会诱导激活磷酸肌醇3-激酶（phosphatidylinositol-3-kinase，PI3K）/蛋白激酶B（protein kinase B，AKT）通路[32]。PI3K/AKT途径参与协调炎症反应、细胞活化和凋亡。PI3K是由三个家族成员组成的脂质激酶家族，AKT的激

活启动下游一系列的信号转导。活化的PI3K产生第二信使PIP3募集AKT后，AKT激活允许蛋白激酶向细胞质和细胞核移动，在细胞核中调节大量下游蛋白质。同时AKT激活哺乳动物雷帕霉素靶点（mammalian target of rapamycin， mTOR），提高NF-κB的活性并促进炎症介质诱导型一氧化氮合酶（inducible nitric oxide sythase， iNOS）和环氧化酶（cyclooxygenase 2， COX-2）的炎症介质的表达[33]。

2.4　NLRP3信号通路

核苷酸结合寡聚化结构域样受体蛋白3（nucleotide-binding oligomerization domain-like receptor protein 3， NLRP3）炎症小体是一种在中枢神经胶质细胞中大量表达的亚细胞多蛋白质复合物，是神经系统疾病的重要靶点之一[34]。

目前已明确NLRP3炎症小体的激活需要初始化启动和蛋白质复合物组装两个关键信号介导[35]，模式识别受体（pattern recognition receptor， PRR）如TLR等激活启动阶段后，诱导NF-κB信号通路的激活，上调NLRP3、proIL-1β和pro-IL-18等前体蛋白的转录和表达[36]。蛋白质复合物组装阶段，NLRP3、凋亡相关斑点样蛋白（apoptosis-associated speck-like protein containing a CARD，ASC）和半胱天冬酶原1（Pro-cysteinyl aspartate specific proteinase-1， Pro-caspase-1）结合并完成炎症小体的组装。同时Pro-caspase-1被催化切割成为具有酶活性的caspase-1，caspase-1将pro-IL-1β和pro-IL-18裂解为成熟且有生物活性的IL-1β和IL-18，从而促进炎症反应。而caspase-1还会切割消皮素D（gasdermin D， GSDMD），从而在细胞膜上形成孔洞，引起细胞焦亡[37]。

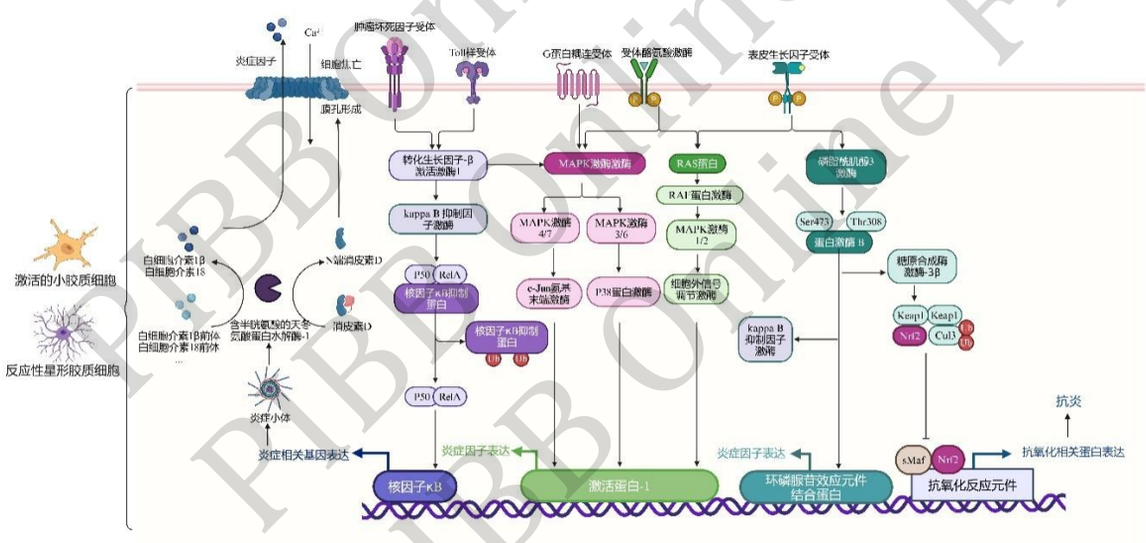

Fig. 1　Neuroinflammation related signaling pathway

图1　神经炎症相关信号通路

P50：核因子κB亚基1（nuclear factor kappa-B subunit 1）；RelA：V-rel网状内皮增生病毒癌基因同源物A（V-rel reticuloendotheliosis viral oncogene homolog A）；sMaf：Small maf转录因子（small Maf transcription factor）；ser473：磷酸化丝氨酸/苏氨酸激酶473位点（Serin 473）；Thr308：磷酸化丝氨酸/苏氨酸激酶308位点，（Threonine 308）；Nrf2：核因子红系2相关因子2（nuclear factor erythroid 2-related factor 2）；Cul3：卡林3蛋白（Cullin 3）.

相关研究表明，在AD、PD等神经退行性疾病中，Aβ、α突触核蛋白（alpha synuclein， α-syn）可通过激活NF-κB信号通路进一步激活NLRP3炎症小体活化的启动阶段，还可以通过破坏线粒体、释放活性氧促进炎症小体的组装和激活。NLRP3炎症小体激活后诱发神经炎症反应又加重脑内Aβ、α-syn的错误折叠和堆积，形成了错误折叠蛋白堆积和NLRP3炎症小体活化之间的恶性循环[38]。

2.5　Nrf2/HO−1信号通路

核转录因子红系2相关因子2（nuclear factor-erythroid 2-related factor 2， Nrf2）是细胞中调节氧化应激反应和炎症反应的关键因子[39]。在正常生理条件下，Nrf2通过与Kelch样环氧氯丙烷相关蛋白1（Kelch-like ECH-associated protein 1， Keap1）结合形成复合物被肌动蛋白锚定在细胞质中持续泛素化和降解而处于低活性状态。在应激条件下，Keap1在活性半胱氨酸残基处被氧化而失活，Nrf2从复合物中解离并易位到细胞核中[40]。Nrf2通过Nrf2/ARE信号通路激活先天抗氧化细胞机制，上调下游抗氧化酶和II期解毒酶，如血红素加氧酶-1（heme oxygenase 1， HO-1）、超氧化物歧化酶（superoxide dismutase， SOD）等，在维持细胞的氧化还原稳态中起关键作用[41]。HO-1及其代谢产物可以抑制iNOS、COX-2以及一系列炎症因子的产生从而发挥抗氧化应激和抗炎作用[42]。

研究表明，Nrf2/HO-1与NF-κB通路之间存在串扰。HO-1作为Nrf2的靶基因之一，可通过清除ROS和抑制NF-κB活性有效降低小胶质细胞M1和增强M2极化[43]。另有研究指出，Nrf2通过与NF-κB竞争性结合共有调节因子，抑制了NF-κB诱导的炎症反应，形成一种相互制约的关系[44]。反之，NF-κB通过这种竞争性结合也能抑制Nrf2的转录水平，从而在Nrf2与NF-κB通路之间构建了双向的调控网络[45]。

在炎症状态下，激活的神经胶质细胞内部涉及多个信号通路的同时激活，通常最终汇集到MAPK/NF-κB这两个关键因子上，引导炎症级联反应，并释放大量炎症因子和ROS。这些炎症因子和ROS一方面直接攻击邻近的神经元，促使异常蛋白质累积和神经元凋亡；另一方面，与细胞膜上的炎症因子受体结合形成正反馈回路，放大炎症反应。可见，神经炎症反应波及CNS中各种类型的细胞，形成一个相互交联、复杂而恶性的循环系统，最终导致不可逆的脑损伤。

3　神经炎症细胞模型

3.1　LPS模型

LPS又称内毒素，是革兰氏阴性菌外膜上具有强免疫原性的一段糖脂结构。LPS刺激小鼠小胶质细胞系BV2和小鼠原代小胶质细胞模型常被用于神经炎症的研究[46]。LPS作用于细胞后首先会被TLR4的适配体脂多糖结合蛋白（lipopolysaccharide binding protein， LBP）捕获，随后激活TLR4启动胞内信号转导，激活NF-κB和MAPK信号通路启动炎症级联反应[47-49]。小胶质细胞激活后，释放炎症介质iNOS、COX-2、TNF-α、IL-1β等破坏血脑屏障，同时作用于星形胶质细胞，诱导继发性炎症反应，最终引发一系列脑部疾病。

研究药物的抗炎潜能的第一步往往是在有LPS诱导的细胞炎症模型中进行试验。根据本课题组前期研究发现，BV2细胞经LPS处理30 min后可检测到多种炎症介质通路蛋白的磷酸化水平升高，包括P65、P38、JNK和AKT。经LPS处理后8 h，BV2细胞中炎症介质IL-1β、TNF-α和IL-18的mRNA水平上调，而经LPS处理24 h后检测BV2细胞中炎症因子水平，可观察到INOS和COX-2表达水平提高[50]。此外，人源小胶质细胞（human microglia clone 3， HMC3）也被应用于构建神经炎症模型。这些结果提示，LPS可以通过激活多种信号通路和促炎介质的表达，诱导小胶质细胞产生炎症反应，从而模拟神经炎症的发生过程[51]。

3.2　Aβ模型

Aβ是APP分解产生的一种跨膜糖蛋白[52]。Aβ片段的长度可以有所不同，其中Aβ40和Aβ42是大脑中Aβ的主要形式。Aβ42的聚集倾向更强，被认为与神经退行性疾病，尤其是AD的病理过程紧密相关[53]。

Aβ能够与小胶质细胞表面受体特异性结合，包括清道夫受体（scavenger receptor， SRs）、G蛋白偶联受体（G protein-coupled receptor， GPCR）和TLRs等，使小胶质细胞从静息状态转为活化的M1型，随后激活小胶质细胞内包括p38和ERK、Ca^{2+}依赖的富含脯氨酸的酪氨酸激酶2（Proline-rich tyrosine kinase 2， Pyk2）或蛋白激酶C（protein kinase C， PKC）信号活化途径等，驱动了炎症的系列反应[54]。Aβ激活的小胶质细胞能产生多种促炎因子，如IL-1β、TNF-α、TGF、单核

细胞趋化蛋白1（monocyte chemotactic protein-1，MCP-1）、补体等，介导神经炎症和神经毒性。

3.3　氧糖剥夺模型

氧糖剥夺（oxygen-glucose deprivation，OGD）通过对细胞培养条件的改变，在体外细胞水平上模拟缺血和缺氧情况的刺激模型而被广泛用于研究脑缺血损伤[55]。

脑缺血后的神经炎症反应特征包括小胶质细胞的激活、星形胶质细胞活化和炎性小体的增加等。脑血流中断后氧和葡萄糖的供应不足导致脑内细胞微环境稳态失衡，发生一系列细胞应激反应如细胞内K^+外排、线粒体损伤、ROS和细胞内Ca^{2+}升高等[56]。在刺激因子的作用下小胶质细胞被激活进而极化，分泌大量促炎因子如IL-1β、iNOS和COX-2等，活化NF-κB信号通路并激活NLRP3炎性小体。同时脑缺血早期，在相关刺激条件下星形胶质细胞也被激活[57-58]，星形胶质细胞由早期抗炎A2型将转化为促炎A1型，产生IL-6、TNF-α、IL-1α、IL-1β和γ干扰素（interferon-γ，IFN-γ），加重脑损伤[59]。

3.4　溶血物模型

自发性蛛网膜下腔出血（subarachnoid hemorrhage，SAH）是一种颅内出血，主要由动脉瘤破裂引起。SAH后小胶质细胞被激活并极化为M1或M2表型。研究表明溶血物、氧合血红蛋白等可以诱导BV-2细胞中5-脂氧合酶（5-lipoxygenase，5-LOX）的过表达，M1极化倾向增加，产生大量促炎因子[60]。暴露于溶血物24 h后，$OX42^+$小胶质细胞的数量显著增加，$GFAP^+$星形胶质细胞细胞体积变大，共培养物中促炎细胞因子IL-6和IL-1β mRNA表达升高[61]。

3.5　MPP+模型

1-甲基-4-苯基吡啶阳离子（1-methyl-4-phenylpyridinium，MPP^+）是1-甲基-4-苯基-1，2，3，6-四氢吡啶（1-methyl-4-phenyl-1，2，3，6-tetrahydropyridin，MPTP）的活性代谢产物，具有高度脂溶性的MPTP易透过血脑屏障，进入脑后可在神经胶质细胞B型单胺氧化酶（monoamine oxidase type B，MAO-B）的作用下转化为其有效成分MPP^+[62]。由于MPP^+结构与多巴胺类似，极易被多巴胺能神经元通过多巴胺转运体吸收，引起纹状体和黑质中三磷酸腺苷浓度迅速下降，从而导致黑质中多巴胺能神经元的进行性死亡以及纹状体内多巴胺水平的降低[63]，故常被用于构建PD模型。

尽管PD中多巴胺能神经元死亡的分子机制细节尚不清楚，但神经炎症也被认为在PD的发展过程中起关键作用。在原代小胶质细胞培养中，MPP^+可以直接诱导小胶质细胞活化，表现为CD11b和iNOS表达上调，促炎介质TNF-α、IL-1β等表达和分泌增加，胰岛素样生长因子1（insulin-like growth factor 1，IGF-1）表达和分泌减少等[64]。此外，MPTP/MPP^+可诱导NF-κB的核易位和p38 MAPK的磷酸化，还能增加了黑质中ROS的水平，进一步激活胶质细胞和NLRP3炎症小体[65-66]。另有研究表明，MPP^+处理小胶质细胞可以抑制PI3K/Akt蛋白的磷酸化以及核Nrf2的表达[67]，增强小胶质细胞M2极化。

3.6　鱼藤酮模型

鱼藤酮（Rotenone，ROT）是从鱼藤草的种子、茎部和根部提取的酮类化合物，鱼藤酮是一种环境毒素，通过小胶质细胞介导的神经元死亡引发帕金森病样病理。鱼藤酮引起线粒体功能障碍和氧化应激来增加ROS，激活小胶质细胞通过产生大量炎性物质损害多巴胺能神经元[68]。研究表明，鱼藤酮诱导的NF-κB激活依赖于p38 MAPK，分泌大量促炎因子TNF-α、IL-1β、iNOS和COX-2等诱导神经炎症[69]。此外，鱼藤酮可诱导的GSDMD的切割和激活以及NLRP3/Caspase-1的活性，从而诱导细胞焦亡，加剧神经炎性反应[70-71]。

3.7　IFN−γ模型

将一些细胞因子直接作用于细胞或机体也能直接诱导某些炎症现象。实验研究中显示，外源性IFN-γ或能产生IFN-γ的细胞（如T淋巴细胞和自然杀伤细胞）渗入中枢神经系统时，可诱导小胶质细胞的活化，引发一系列神经免疫调节事件[72]。具体而言，IFN-γ的诱导作用包括下游Janus激酶（Janus kinase，JAK）介导的信号转导及转录激活蛋白（signal transducer and activator of transcription，STAT）的磷酸化，通过增加Akt、ERK1/2等磷酸化状态，诱导促炎基因表达程序，进而影响MAPK、NF-κB等信号通路，诱导神经炎症[73-74]。在很多关于小胶质细胞激活的研究中，IFN-γ通常被用作引发因子。当小胶质细胞受到微生物、内源性配体（如LPS或Aβ）或高糖环境的刺激时，IFN-γ会引发强烈的小胶质细胞炎症反应[75-77]。

3.8 CPG−DNA模型

细菌脱氧核苷酸（deoxyribonucleic acid，DNA）中未甲基化的胞嘧啶-鸟嘌呤二核苷酸片段（DNA containing CpG dinucleotide motifs， CpG-DNA）是一种在中枢神经系统中具有强大促炎作用的刺激分子。研究表明，CpG-DNA在体内和体外均能直接调节小胶质细胞的功能。在体外实验中，CpG-DNA激活小胶质细胞，诱导产生TNF-α、IL-12 p40和IL-12 p70等促炎因子，并增强抗原呈递功能[78]。将CpG-DNA注射到小鼠脑脊液中刺激小胶质细胞产生炎症反应导致脑膜炎的产生[79]。同时，在大鼠侧脑室注射CpG-DNA可观察到海马周围大量胶质细胞的活化和炎症反应[80]。

在小胶质细胞中，TLR9被确认为未甲基化CpG-DNA特异性识别受体。在MyD88的介导下激活下游信号包括IRAK-1、TRAF6和转化生长因子-β激活激酶（transforming growth factor-β activated kinase 1，TAK1），从而激活NF-κB和MAPK信号通路。这一过程导致大量TNF-α、IL-12和NO等促炎因子的表达，最终诱导神经炎症的发生[81-82]。

3.9 病毒相关模型

自2019年新型冠状病毒感染（Corona virus disease 2019， COVID-19）暴发以来，越来越多的证据表明，COVID-19与中枢神经系统疾病之间存在密切关系，大约1/3患者出现包括焦虑、抑郁、创伤后应激障碍、认知缺陷等症状[83]。研究发现，将冠状病毒的S1蛋白直接注射到大鼠脑膜中可导致参与抗原呈递的分子增加，同时引发炎症小体信号的持续表达[84]。另有研究显示，S1在人血脑屏障3D模型中可促进屏障完整性丧失，并引发促炎反应[85]。S1激活小胶质细胞释放大量促炎细胞因子，如TNF-α、IL-6和IL-1β[86]，由NF-κB、p38、TLR4[84，87-89]等信号通路介导。此外S1蛋白还可以通过激活NLRP3炎症小体增加促炎效应[90-91]。

除冠状病毒S1蛋白能诱发神经炎症外，目前研究表明，其他病毒如人类免疫缺陷病毒1型（human immunodeficiency virus-1， HIV-1）感染时也会导致中枢神经系统中的小胶质细胞激活并释放大量促炎因子。这些促炎因子与病毒产物，如外膜糖蛋白（glycoprotrin 120， gp120）、转录反式激活因子（trans-activator of transcription， Tat）等神经毒性蛋白共同作用将引起HIV相关神经认知障碍（HIV-associated neurocognitive disorder， HAND）中的神经炎症[92]。脑源性神经营养因子（brain-derived neurotrophic factor， BDNF）作为胶质细胞与神经元之间的关键信号分子，不仅能促进神经发育，也能通过多种途径导致神经炎症，参与脑内神经系统疾病的发生发展[93]。HIV-1 gp120和Tat作为神经毒性蛋白本身可介导神经元损伤之外，gp120可通过Wnt/β-catenin信号通路刺激在BDNF在BV2细胞中大量表达[94]，而Tat可通过NF-κB通路上调脂肪酸结合蛋白（fatty acid-binding protein 4， Fabp4）表达。随后，Fabp4促进Tat激活的NF-κB信号通路，与NF-κB信号通路形成一个正反馈回路而加剧炎症反应[95]。

同时，一些抗HIV病毒药物也能产生中枢神经系统的副作用。一线抗艾滋病药物多替拉韦和恩曲他滨联合，以及替诺福韦可增加BV2细胞的最大线粒体呼吸。即这些抗逆转录药物参与对小胶质细胞代谢的重编程进而影响由小胶质细胞衍生的炎症[96]。本课题组前期研究发现，接受非核苷类逆转录酶抑制剂依法韦仑治疗5个月的C57BL/6小鼠体内NF-κB通路激活、过度表达和释放大量促炎细胞因子会导致小鼠神经突触功能障碍进而出现认知缺陷[97]。

3.10 BPA模型

双酚A（bisphenol A， BPA）学名2，2-二（4-羟基苯基）丙烷，是一种具有类甾体激素活性的环境内分泌干扰物，广泛出现在人们的日常生活中[98]。BPA的亲脂性使其可以通过血脑屏障进入大脑产生神经毒性，因此BPA也常被用于构建神经炎症细胞模型[99]。

大量研究表明，BPA能直接与小胶质细胞表面的受体如TLRs和GPCRs结合，引发NF-κB、MAPK等信号通路的激活[100]。BPA还扰乱细胞内钙离子平衡，导致钙离子异常增加，进一步激活了NF-κB和其他信号通路，加剧炎症反应[101]。同时，BPA可以诱导氧化应激，增加细胞内氧自由基生成，进一步引发炎症反应[102-103]。此外，BPA暴露削弱了细胞的吞噬功能和免疫调节作用，降低了其对细胞外废弃物和病原体的清除能力导致废弃物积累和病原体滞留。这些作用机制共同促使BPA诱导小胶质细胞炎症，加重了神经炎症的程度。

3.11 PM2.5模型

PM2.5是指空气动力学直径≤2.5 μm的细颗粒物，是重要的空气污染组分。PM2.5经呼吸进入支气管和肺泡后，透过肺部血气屏障进入外周血液循环[104]。目前研究表明，PM2.5具有潜在的神经毒

性，可通过血气屏障后进一步突破血脑屏障进入大脑，可能导致各种神经系统疾病的发展和加速，包括AD、PD等[105]。

体内外研究均表明，PM2.5暴露可通过激活小胶质细胞诱导神经炎症。过度激活的小胶质细胞转化为M1型小胶质细胞后，持续分泌大量促炎因子如IL-1β、IL-6和TNF-α等诱发炎症反应[106-107]。与此同时，PM2.5能够降低抗炎标志物IL-10和精氨酸酶1的mRNA表达，扰乱免疫平衡，加剧神经炎症进程[107]。此外，PM2.5暴露引起氧化应激产生高水平ROS能激活NF-κB、TRL4、NRLP3等信号传递通路，上调TNF-α、IL-1β和COX-2的表达水平，进一步加重神经炎症反应[108-109]。同时研究表明，星形胶质细胞也参与PM2.5暴露后相关损伤反应。PM2.5暴露导致星形胶质细胞活化的标志蛋白GFAP增加，并通过激活NF-κB信号通路上调下丘脑炎症基因表达诱导神经炎症[110]。

3.12　纳米颗粒模型

近年来，纳米技术迅速发展并广泛应用于材料科学、生物医学及日常生活中，纳米颗粒（nanoparticles，NPs）通常是指粒径在1~100 nm之间的粒子[111-112]。由于纳米颗粒特殊的结构和性质，经皮肤、呼吸道、胃肠道和药物注射等多种方式进入人体后，可通过直接透过血脑屏障或者破坏血脑屏障，以及通过感觉-神经-脑通路绕过血脑屏障等方式进入CNS，诱发氧化应激、炎症反应、DNA损伤产生神经毒性[113]。因此，纳米颗粒也经常被用于构建多种体内外疾病模型。

银纳米粒子（silver nanoparticles，AgNPs）作为一种优良的抗菌纳米材料广泛使用，在AgNPs暴露处理的BV2细胞中，AgNPS可促进M1型细胞的极化，同时增加IL-1β、NF-κB的表达，还能诱导自噬和溶酶体相关蛋白质失调，导致自噬不足，引神经炎症[114-115]。另有研究表明，AgNPs暴露后，可诱导APP基因表达，降低神经细胞内脑啡肽酶（neprilysin，NEP）和低密度脂蛋白受体（low density lipoprotein receptor，LDLR）的表达，表明AgNPs可能改变Aβ沉积的基因和蛋白质表达而潜在地诱导AD在神经细胞中的进展[116]。

二氧化硅纳米颗粒（silica nanoparticles，SiNPs）也可以穿过血脑屏障，对神经系统造成不可逆的损害[117]。研究表明，小胶质细胞能够迅速地吸收所有浓度的SiNPs，在低至4 NPs/μl（7.28×10^{-4} mg/L）的浓度下即可检测到ROS的显著增加，随着SiNPs暴露浓度的升高，COX2的表达含量也增加[118]。SiNPs对小胶质细胞有明显的毒性作用，SiNPs暴露于BV2细胞后，BV2细胞形态和超微结构改变，存活率降低。同时SiNPs可以增加BV2细胞中NLRP3、ASC和caspase-1蛋白的表达，随着SiNPs浓度的增加，炎症因子TNF-α、IL-1β和IL-18的水平也显著升高，表明SiNPs可能通过激活NLRP3炎性小体诱导小胶质细胞炎症反应[119]。

3.13　金属元素模型

随着各类金属在工业、农业以及日常生活等方面的广泛应用，对人类的暴露量也逐渐增加。然而，必需金属体内平衡失调和非必需金属的过度暴露对神经系统可能会导致氧化应激、神经炎症、自噬等一系列反应诱发脑损伤[120-121]。

铜（Cu）作为人体必需元素之一，也是一种高度重视的环境污染物，过量的铜积累可能会导致神经炎性损伤[122]。在CNS中，细胞外铜蓄积触发依赖于NF-κB的小胶质细胞激活和随后的神经毒性，铜刺激将导致IκBα降解、NF-κB p65磷酸化和核转位，激活NLRP3、IL-1β和IL-18的表达[123]。研究发现，铜可以激活M1型小胶质细胞分泌NO、TNF-α、IL-6等炎性产物，导致多巴胺能神经元死亡。同时小胶质细胞的激活可能与铜引起的氧化应激和NF-κB通路进一步激活有关。随着铜在细胞内的积累，将导致小胶质细胞线粒体自噬紊乱，NLRP3/Caspase-1/GSDMD轴蛋白过度表达，引起炎症的持续释放[124]。

锰（Mn）也是维持生理功能的一种必需微量元素，而长期或过度暴露于环境中的锰会导致锰中毒。现有研究显示，神经胶质激活在暴露于锰的人类大脑中很突出，在非人类灵长类动物和啮齿类动物的锰神经毒性模型中也是如此[125]。相关研究表明，锰可以显著增强LPS激活的小胶质细胞中TNF-α、IL-1β、IL-6和NO的表达量，激活NF-κB信号通路诱导神经元细胞损伤[126]。此外，单独锰处理BV2细胞也能激活NF-κB、NLRP3-Caspase-1信号通路，促进IL-1β，TNF-α等促炎因子释放。同时锰还能通过触发自噬溶酶体功能障碍激活NLRP3-Caspase-1炎性体通路增强炎症反应[127]。

3.14　成瘾类物质模型

大量体内外实验发现，短期或长期摄入酒精、吗啡、甲基苯丙胺等成瘾性物质能诱导神经炎症[128-130]。

研究表明，酒精能直接通过血脑屏障进入脑

内，作为配体与小胶质细胞细胞中TLR4结合、激活NLRP炎症小体等结合来激活炎症相关信号通路[131]。且酒精暴露能诱导脑内大麻素系统稳态失衡，而内源性大麻素系统可以通过调节炎症因子的表达来激活大麻素受体，进而通过调控小胶质细胞的增殖、活化、极化等生理功能来调控神经炎症[132]。同时研究证明，吗啡能够结合TLR4的髓样分化蛋白-2（myeloid differentiation protein-2，MD-2）来诱导TLR4寡聚化，以与经典TLR4配体相似的方式激活TLR4信号启动炎症反应[133]。吗啡诱导的小胶质细胞激活和神经炎症被认为是吗啡耐受的因素。而甲基苯丙胺可分别通过TLR4和Sigma-1受体间接或直接激活小胶质细胞和星形胶质细胞，触发下游信号通路包括NF-κB、PI3K/Akt和MAPK通路等，促进各种炎症因子表达[134]。此外，研究人员在尼古丁滥用模型中发现，长期服用尼古丁会导致大脑氧化应激，激活NF-κB引号通路导致神经炎症[135]。

上述模型中，如LPS、Aβ、CpG-DNA、病毒相关模型等病原相关模型能够有效模拟特定病原引发的神经炎症过程，具有较高的临床相关性。同样，细胞因子IFN-γ、TNF-α模型等能够深入研究特定细胞因子在炎症反应中的作用，具有良好的可控性和广泛的应用性。但局限于研究单一细胞因子的影响，难以全面反映多因素作用。环境毒素模型如BPA、PM2.5、金属元素、纳米颗粒模型等，在模拟环境污染对神经系统的影响过程中体现了实际应用价值。而由于环境毒素的复杂性，导致实验结果的标准化和具体机制的确定仍然具有挑战性。此外，代谢应激模型如OGD、MPP^+、鱼藤酮、氧合血红蛋白等，能够清晰地研究代谢紊乱和氧化应激引发的神经炎症，具有良好的稳定性和可重复性。然而，这些模型仅限于单一病原因素而未体现出神经炎症过程的复杂性和多因素作用，在全面理解炎症发病机制时存在一定局限性。总体而言，不同类型的模型各有其独特的优势和局限性。在疾病相关分子靶点、分子机制探索和药物筛选时可同时选用两种以上模型综合评判。

Table 1 Common neuroinflammatory cell models

表1 常见神经炎症细胞模型

刺激物	细胞	处理剂量和时间	检测指标	参考文献
LPS	BV2	1 mg/L；0.5~24 h	P65、P38、JNK、AKT、IL-1β、TNF-α、IL-18、INOS、COX-2	[50]
LPS	HMC3	1 mg/L；24 h	p-IKK、IKK、IκBα、p-P65、P65、NO、TNF-α、IL-1β	[51]
Aβ1－42	BV2，小鼠原代星胶	5 μmol/L；24 h	TLR4、MyD88、TRAF6、TNF-α、IL-1β、IL-6	[136]
Aβ1－40	BV2	5 μmol/L；24 h	TNF-α、IL-6、IL-1β	[137]
Aβ25－35	小鼠原代小胶	20 μmol/L；24 h	TNFα、iNOS、IL-1β、Arg1	[138]
低糖、低氧	BV2、HT-22	5% CO_2、95% N_2、37°C；6 h	TLR4、p65、IL1-β、caspase-1	[57]
溶血剂	BV2	1 mg/L；0.5 h	LTB-4、IL1-β、TNF-α、IL-10、TGF-β	[139]
MPP+	BV2	1 mg/L；12 h	TNF-α、IL-1β、IL-6、iNOS、COX-2	[140]
ROT	BV2	1 μmol/L；24 h	IL1-β、TNF-α、IκB、iNOS、COX-2、p65、p38	[69]
IFN-γ	BV2	50 units/ml；2~48 h	iNOS、TNF-α、ERK、 p38、JNK	[141]
CpG-DNA	BV2、小鼠原代小胶	1 μmol/L、3 μmol/L；5 h	TNF-α、IL12-p35、IL12-p40	[78]
刺突蛋白S1	BV2	10 μg/L，、50 μg/L、100 μg/L；24 h	IL-1β、TNF-α、iNOS、Iba-1、p65 、 IκBα	[86]
HIV-1	THP-1/PMA、HMC3、MT-4	100 μg/L p24；48 h	IL-6、HLA-B、CFB、OLR1	[92]
HIV-1 gp120	BV2	10 μg/L； 1~6 h	proBDNF、mBDNF、CD11b、Wnt5a、Wnt3a	[94]
LV-flag-Tat	BV2，HT-22	24 h	IL-1β、TNF-α、CCL2、Fabp4、P-NF-κB p65、NF-κB p65	[95]
BPA	BV2，HT-22	2.5、5、10 μmol/L；24 h	TNF-α、IL-1β、IL-6、iNOS 、COX-2	[142]
PM2.5	小鼠原代小胶	50 mg/L；4 h	IL-1β、ROS、caspase-1	[109]

续表

刺激物	细胞	处理剂量和时间	检测指标	参考文献
AgNPs	BV2	5 mg/L AgNPs；24 h	Iba-1、TNF-α、iNOS、IL-1β、NF-κB、MCP-1	[115]
SiNPs	BV2	50 mg/L；6 h	IL-18、 IL-1β、TNF-α、COX2、HO-1	[119]
Cu	BV2、MN9D	15、30、60 μmol/L；48 h	COX2、NF‐κB、p-p65、IκB-α、Caspase1、NLRP3、ASC、IL-1β、IL-18	[124]
Mn	BV2	100 μmol/L；24 h	IL1-β、TNF-α、iNOS、IL-6、	[126]
酒精	小鼠原代小胶	10 、50 mmol/L；24 h	IL-18、IL-33、IFN-c、IL-1b	[143]
吗啡	BV2	200 μmol/L；6 h	TNF-α、IL-6、IL-1β、iNOS、COX-2	[144]
METH	胚胎干细胞衍生小胶（ESdM）	100 μmol/L；4~72 h	IL-1β、TNF-α、IL-10、Iba-1	[145]

LPS：脂多糖（lipopolysaccharide）；Aβ：β淀粉样蛋白（amyloid β-protein）；MPP+：1-甲基-4-苯基吡啶阳离子（1-methyl-4-phenylpyridinium）；ROT：鱼藤酮（Rotenone）；IFN-γ：γ-干扰素（interferon-γ）；CpG-DNA：含未甲基化的胞嘧啶-鸟嘌呤二核苷酸的DNA（DNA containing CpG dinucleotide motifs）；HIV-1：人类免疫缺陷病毒1型（human immunodeficiency virus-1）；gp120：外膜糖蛋白（Glycoprotrin 120）；LV-flag-Tat：含flag-Tat慢病毒载体（lentiviruses with flag-Tat）；BPA：双酚A（Bisphenol A）；AgNPs：银纳米粒子（silver nanoparticles）；SiNPs：二氧化硅纳米颗粒（silica nanoparticles）；METH：甲基苯丙胺（methamphetamine）.

4　小结与展望

神经炎症是多种神经系统疾病的关键特征，随着对神经炎症的研究不断深入，神经学领域对其预防和治疗的关注也逐渐增加。神经炎症细胞模型的选择是根据研究问题的具体性，以及疾病的多样性来进行权衡。简单的体外模型无法完全还原人体内的复杂情境，以及模型间的差异性可能导致结果的不同解释。但这些模型可以提供直观的实验数据，并且在不同的条件下模拟神经炎症的不同侧面。通过这些模型，能更好地理解神经炎症在疾病发展中的作用，为未来的治疗策略提供参考。

在神经炎症信号通路的研究中，不仅关注炎症因子的释放，还涉及到多种分子和细胞参与的复杂网络。当前的研究已经揭示了一些关键的信号通路，如NF-κB、MAPK、PI3K/AKT、Nrf2/HO-1、NLRP3等[146-148]，这些通路在神经炎症的调控中发挥着关键作用。通过整合多层次的研究方法，包括基因组学、蛋白质组学和细胞学等，将有助于更全面地理解神经炎症的复杂性。此外，针对特定的信号通路和分子靶点开发创新性的治疗策略，有望为神经炎症相关疾病的治疗提供新的思路。

综合而言，神经炎症细胞模型及信号通路研究为神经炎症的深入理解和治疗手段的开发提供参考，同时也为未来的研究和临床实践提供了广阔的前景。

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Neuroinflammation and Its *In Vitro* Models*

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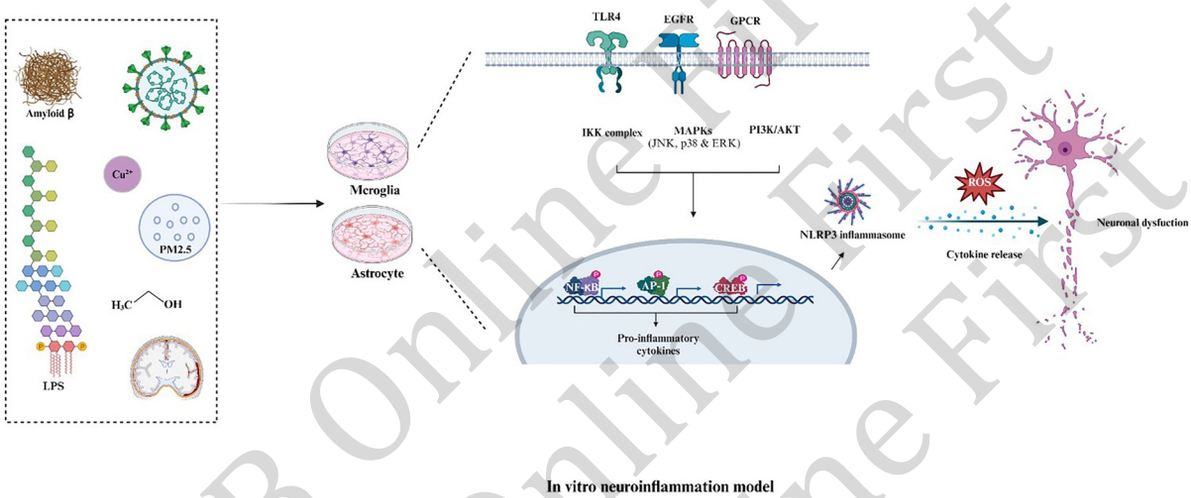
Graphical abstract



Abstract　Neuroinflammation is a complex process triggered by various factors such as injury, infection, oxidative stress, and other activators. In central immune system, microglia and astrocytes release a wide range of inflammatory mediators like cytokines and chemokines in response. Initially, acute neuroinflammation can have protective effects by promoting neuronal repair and maintaining homeostasis. However, chronic activation of neuroinflammation leads to excessive production of inflammatory mediators, resulting in neuronal dysfunction and degeneration. This can contribute to various neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and Huntington's disease (HD). *In vitro* cellular models are crucial for elucidating the underlying mechanisms of neuroinflammation. Investigating neuroinflammatory signaling pathways is essential for understanding the intricate network of molecules and cells involved. Key signaling pathways such as NF-κB, MAPK, PI3K/AKT, Nrf2/HO-1, and NLRP3 play critical roles in regulating neuroinflammation. During inflammation, activation of glial cells involves multiple signaling pathways simultaneously, primarily orchestrated by two key factors: MAPK and NF- κB. These pathways guide the inflammatory cascade, leading to the release of numerous inflammatory factors and reactive oxygen species (ROS). These inflammatory factors and ROS have dual effects. Firstly, they can directly harm neighboring neurons, promoting the accumulation of abnormal proteins and triggering neuronal apoptosis. Secondly, inflammatory factor receptors on cell membranes can initiate positive feedback loops that exacerbate the inflammatory response. Neuroinflammation encompasses various cell types within the central nervous system, forming a complex and interconnected malignant cycle. This ultimately culminates in irreversible brain damage. Moreover, innovative therapeutic approaches targeting specific signaling pathways and molecular targets show promise in treating diseases related to neuroinflammation. Various cellular models are commonly employed to

investigate neuroinflammation, each focusing on different aspects: pathogen-related models involve substances like LPS (lipopolysaccharide), Aβ (amyloid beta), CpG-DNA, and viruses; cytokine models utilize IFN-γ (interferon-gamma); metabolic stress models include OGD (oxygen-glucose deprivation), MPP+ (1-methyl-4-phenylpyridinium), rotenone, and oxyhemoglobin; environmental toxin models encompass substances such as BPA (bisphenol A), PM2.5 (particulate matter), various metals, and nanoparticles; additive substance models involve alcohol, morphine, and METH (methamphetamine). Each model offers distinct advantages and drawbacks for studying neuroinflammation. In conclusion, research on these cellular models and their associated signaling pathways provides crucial insights into the mechanisms underlying neuroinflammation-related diseases. These insights are essential for developing effective therapeutic strategies and advancing clinical practice to address the complexities of neuroinflammatory diseases.

Key words　neuroinflammation, cell model, signaling pathway
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