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Reviews 综 述

炎症小体在机体血脑屏障损伤中的作用机制研究进展

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摘　要：血脑屏障(blood-brain barrier，BBB)是一种天然的结构和功能屏障，可抑制病原体的进入并严格控制分子进入脑实质，完整的血脑屏障对于维持中枢神经系统内稳态至关重要。这一屏障功能是由特殊的多细胞结构决定的，每一种组成的细胞类型对血脑屏障的完整性都有不可或缺的贡献。炎症小体(inflammasome)是先天免疫系统最重要的组成部分之一，是一种多蛋白复合体。当病原侵入或机体产生过度免疫反应时，能够激活炎症小体并介导大量细胞因子以及趋化因子分泌。细胞因子及趋化因子表达上调会引起血脑屏障破坏，导致病原突破血脑屏障进入中枢神经系统，引发机体各种脑内疾病。本文就感染性疾病与非感染性疾病这两种情况下，对炎症小体介导机体血脑屏障的损伤进行综述，并列举了当前针对血脑屏障损伤的不同修复方式。

关键词：血脑屏障；炎症小体；天然免疫

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Role of inflammasome in blood-brain barrier injury: a review

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Abstract: Blood-brain barrier (BBB) is a natural structural and functional barrier, which can inhibit the entry of pathogens and control the entry of molecules into the brain parenchyma. An intact BBB is essential to maintain the homeostasis of the central nervous system. The function of this barrier is determined by its special multicellular structure. Each cell type has an indispensable contribution to the BBB integrity. Inflammasome known as a complex protein is a key component of the innate immune system and mediates the secretion of pro-inflammatory cytokines including IL-1β, IL-18, and IL-1α, which plays a critical role in the excessive inflammatory response. The up-regulated expression of proinflammatory cytokines results in the destruction of BBB. As a result, the pathogen breaks through BBB and enters the central nervous system, which finally causes brain diseases. In this paper, we reviewed infectious diseases and non-infectious diseases associated with the inflammasome-mediated injury of BBB.

Keywords: blood-brain barrier; inflammasome; innate immunity

血脑屏障(blood-brain barrier，BBB)是由脑微血管内皮细胞、星形胶质细胞及周细胞组成的动物体血液循环系统和神经系统之间的特殊结构和功能屏障。血脑屏障的选择渗透性使其严格调控离子、分子和细胞在血液和实质之间的运动，从而保护神经元[1−2]。脑毛细血管及脑微血管内皮细胞通过紧密连接(tight junctions，TJs)维持生物学功能，其中紧密连接蛋白主要包括咬合蛋白(occludin)、闭合蛋白(claudins)、连接黏附分子(junctional adhesion molecules，JAMs)和闭合小环蛋白(zonula occludens，ZOs)[3−4]。ZOs家族蛋白是一类与细胞骨架蛋白直接相连的蛋白，包括ZO-1、ZO-2和ZO-3[5]，其对血脑屏障的稳定性、组织和信号传导至关重要[6]。

天然免疫应答是机体抵抗病原体感染的第一道防线，它通过模式识别受体(pattern recognition receptors，PRRs)识别病原相关分子模式(pathogen-associated molecular patterns，PAMPs)或者损伤相关分子模式(damage-associated molecular patterns，DAMPs)。炎症小体是胞浆内的多蛋白复合体，在机体天然免疫应答中起重要作用。当炎症小体被激活时，会介导多种细胞因子的分泌[7−8]，从而导致BBB受损，引发神经性疾病，如NLRP3 (NLR family pyrin domain containing 3)炎症小体激活时可促进IL-1β和IL-18的分泌，NLRP6 (NLR family pyrin domain containing 6)炎症小体不仅通过产生IL-1β和IL-18参与炎症，还可以抑制核因子κB (nuclear factor kappa-B，NF-κB)和丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)信号通路从而抑制炎症和预防病理损伤。因此，本文旨在综述炎性小体在感染性疾病与非感染性疾病中血脑屏障损伤的机制，以

及与炎性小体相关的修复血脑屏障损伤的靶点，以期给血脑屏障损伤的治疗提供新的思路。

1 炎症小体简介

1.1 炎症小体的组成和类别

经典的炎症小体由模式识别受体、凋亡相关斑点样蛋白和半胱天冬酶 1 前体(pro-caspase-1)组成。参与组装炎症小体的 PRRs 主要是 NLRs 家族(NOD-like receptors，NLR)或 AIM2 样受体(AIM2-like receptors，ALRs)家族。根据识别病原体 PRRs 的不同可组装为不同的炎症小体，目前研究报道最多的是 NLRP3、NLRC4、NLRP1 和 AIM2 炎症小体，NLRP2、NLRP6、NLRP7、NLRP12 及 IFI16 等炎症小体也有报道[9]。

NOD 样受体家族[nucleotide-binding，oligomerization domain (NOD)-like receptors，NLR]主要由 C 端的 LRR 结构域(leucine-rich repeat)，中间的 NOD 结构域，以及 N 端的效应结构域 3 个部分组成。其中效应结构域主要由半胱天冬氨酸酶激活与募集结构域(caspase activation and recruitment domain，CARD)、热蛋白结合域(pyrin domain，PYD)组成，负责下游信号的传递。LRR 识别 PAMP 将引起自身构象变化，解除 LRR 对 NOD 结构域寡聚化的抑制，NOD 寡聚化引起效应结构域暴露[10]，继而募集凋亡相关微粒蛋白(apoptosis-associated speck like protein containing CARD，ASC)，招募 pro-caspase-1 形成炎症小体。类似地，AIM2、NLRPs、Pyrin、NAIPs 结构域等传感器与衔接分子 ASC 结合，pro-caspase-1 自身蛋白水解切割以产生活性 caspase-1[11]。

1.2 炎症小体的作用

病原体感染和各种内外源性刺激可引起炎症小体的组装和激活，NLRP3 炎症小体激活的典型例子为脂多糖(lipopolysaccharide，LPS)结合于 Toll 样受体 4 (Toll-like receptors 4，TLR4)，诱导 NLRP3 去泛素化，导致小鼠 NLRP3 炎性小体的激活[12]。ASC 分子聚集成的 ASC 斑点是 pro-caspase-1 活化为 caspase-1 的平台。活化的 caspase-1 可诱导细胞焦亡，并对 IL-1β 和 IL-18 的成熟分泌起关键作用[13]。在中枢神经系统(central nervous system，CNS)中，炎症小体被激活，产生大量细胞因子，如 IL-1β、IL-6、IL-18 等，可通过多条已知的信号通路降低紧密连接蛋白的表达，损伤脑微血管内皮细胞，从而破坏血脑屏障的完整性，导致机体外周血液中的细胞因子、炎性细胞等神经毒性物质进入中枢神经系统，破坏大脑的正常功能。此外，多种神经系统疾病，如阿尔茨海默病(Alzheimer's disease，AD)、帕金森病(Parkinson's disease，PD)，同样伴随着机体特异性炎症的发生。

2 感染性疾病中炎症小体参与破坏 BBB

细菌性脑膜炎、脓毒症和脑脓肿等神经系统疾病大多与病原体入侵有关。当病原体入侵机体时，炎症小体被激活，释放大量细胞因子，严重时会引起机体的"细胞因子风暴"。外周的炎症会导致脑内皮屏障完整性受到破坏，紧密连接蛋白变形，血脑屏障破坏，使得病原突破 BBB 进入 CNS，引起脑内神经炎症反应，并伴随出血性损伤和神经元损伤[14]。目前报道的感染性疾病破坏 BBB 大多与 NLRP3 炎症小体激活有关，其他炎症小体是否参与破坏 BBB 还有待研究。

2.1 病毒突破血脑屏障

现有研究表明 COVID-19 并发症与 SARS-CoV-2 感染后免疫炎症反应加重有关[15]。嘌呤能离子通道型 7 (P2X7)受体是中枢神经系统中广泛表达的 ATP 门控离子通道，其过度活化会诱导 NLRP3 炎症小体激活，介导 IL-1β 和 IL-18

的分泌[16]。有研究表明，SARS-CoV-2 感染后可与 P2X7 受体结合，促进血脑屏障内皮细胞和星形胶质细胞的死亡，最终导致 BBB 的通透性增加[17]。此外，SARS-CoV-2 可以通过与 CD147 受体结合感染单核细胞，被感染的单核细胞可携带 SARS-CoV-2 通过 BBB[18]。在 CNS 内，SARS-CoV-2 可以通过与血管紧张素转换酶 2 (angiotensin converting enzyme-2，ACE2)结合，感染神经元和其他神经细胞，血液中的细胞因子通过受损的 BBB 进入 CNS，促进各类神经疾病的发展[19]，见图 1。

1 型人类免疫缺陷病毒(HIV-1)在感染初期通过迁移的髓细胞和淋巴细胞突破血脑屏障，浸润中枢神经系统，感染血管周围的巨噬细胞和小胶质细胞，随后激活 NLRP3 炎症小体，在小胶质细胞中可检测到大量细胞因子的产生[20–21]。同时，HIV-1 蛋白 gp120 被证明会下调紧密连接蛋白，例如 ZO-1、ZO-2 和 Occludin，并诱导氧化损伤和活性氧(reactive oxygen species，ROS)的产生，导致 BBB 的通透性增加[22]。与之相似，本课题组发现伪狂犬病毒(pseudorabies virus，PRV)感染后可激活 NLRP3 炎症小体并以 ATP 依赖的方式促进大量 IL-1β 的分泌[23]，因此我们推测 PRV 感染所引起的神经症状与 NLRP3 炎症小体的激活有关。

寨卡病毒(Zika virus，ZIKV)是黄病毒科的虫媒病毒，已知会引起人类严重的神经系统综合征。Pinheiro 等发现人脑微血管内皮细胞(human

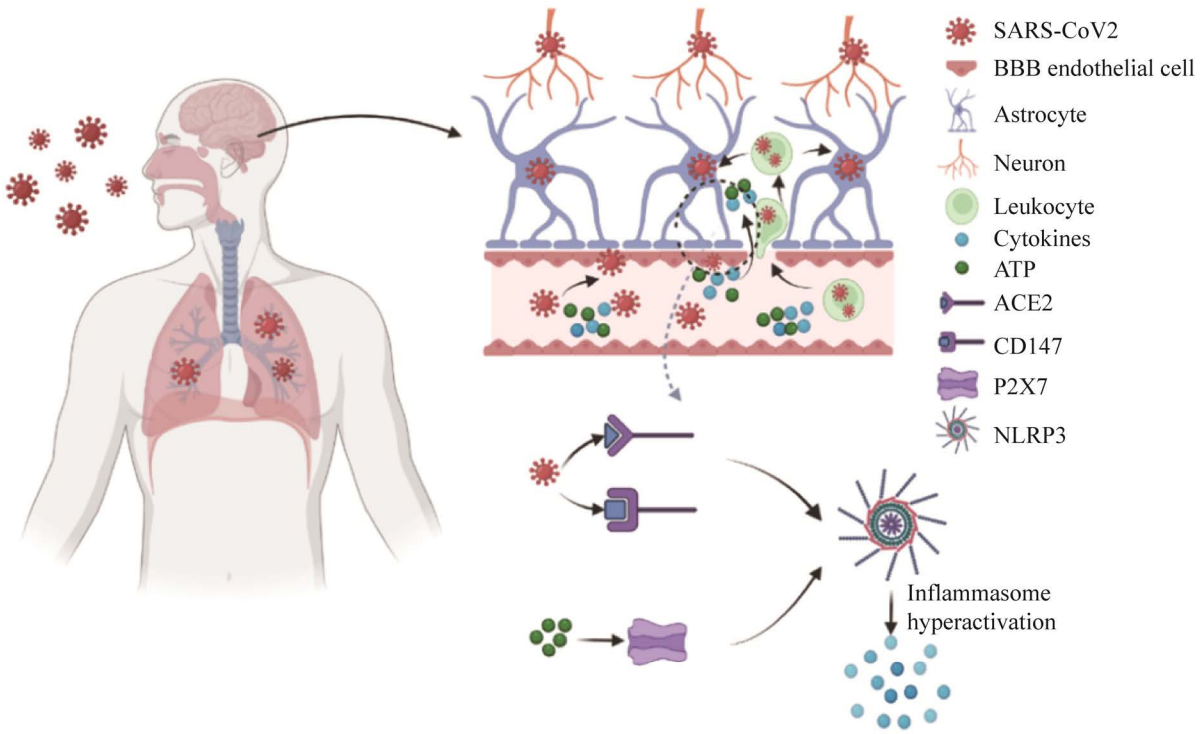

图 1 SARS-CoV-2 突破 BBB 的机制[15]

Figure 1 SARS-CoV-2 breaks through the BBB mechanism[15]. SARS-CoV-2 reaches blood-brain barrier endothelial cells and perivascular astrocytes by binding ACE2 and CD147. Hyperactivation of SARS-CoV-2 and P2X7 receptors activates the NLRP3 inflammasome, which mediates the secretion of cytokines, thereby increasing the permeability of the blood-brain barrier.

brain microvascular endothelial cells，HBMECs)感染ZIKV后，NLRP3炎症小体、ASC和caspase-1的表达量明显上调，并且IL-1β的分泌量显著上调。因此ZIKV感染所引起的神经症状与NLRP3炎症小体的激活和分泌IL-1β有关[24]。

2.2 细菌突破血脑屏障

脑膜炎是大脑及周围保护膜的一种炎症，BBB的损伤是引起脑内神经炎症的关键机制。细菌的黏附和侵入会破坏BBB的完整性，增加渗透性，最终导致脑膜炎。Wang等发现大肠杆菌(*Escherichia coli*) NMGCF-19的组分LPS能够与小胶质膜上TLR4受体结合，激活下游通路髓样分化因子88(myeloid differential factor 88，MyD88)，并且激活NLRP3炎症小体，诱导TNF-α、IL-6和IL-1β等炎症细胞因子的释放[25]。高迁移率族蛋白B1 (high mobility group B1，HMGB1)是一种高度保守的核蛋白[26]，TLR4是HMGB1诱导的炎症的关键受体[27]，NMGCF-19感染小鼠同样会引起HMGB1的表达水平升高。此外，NMGCF-19也可以介导脑组织Toll样受体2 (Toll-like receptors 2，TLR2)的激活。因此NMGCF-19可能通过激活HMGB1/TLR2/TLR4/MyD88通路来干扰BBB，从而促进其逃入脑组织。

研究表明，布鲁氏菌感染人脑微血管内皮细胞时可诱导IL-6、IL-8、MCP-1以及ICAM-1表达的上调，使HBMECs处于激活状态，经布鲁氏菌感染的胶质细胞(星形胶质细胞和小胶质细胞)的培养上清也能诱导HBMECs的活化。然而，布鲁氏菌感染caspase-1和ASC敲除的星形胶质细胞和小胶质细胞并不能诱导HBMECs的活化，表明布鲁氏菌感染中枢神经系统，破坏血脑屏障依赖于IL-1β[28]，而炎症小体是否参与布鲁氏菌破坏血脑屏障还需进一步研究。

本课题组研究表明在肺炎链球菌(*Streptococcus pneumoniae*)感染巨噬细胞时，NLRP6炎症小体调节细胞因子(IL-1β、IL-1α、IL-6等)的成熟和分泌，但不影响IL-1β转录的诱导。NLRP6还介导了caspase-1、caspase-11和gasdermin D (GSDMD)的激活以及ASC的寡聚[29]。同时也有相关研究表明*S. pneumoniae*感染会引起TNF-α、IL-1β、IL-6、IL-10等细胞因子的上调，从而导致血脑屏障被破坏[30]。同样，在金黄色葡萄球菌感染HBMECs时，细胞因子/趋化因子(IL-6、TNF-α、MCP-1)表达上升，紧密连接蛋白(VE-Cadherin、Claudin-5、ZO-1)表达下降[31]。

2.3 寄生虫突破血脑屏障

脑疟疾(cerebral malaria，CM)是由恶性疟原虫引起的血管内皮疾病，脑肿胀和血管周围水肿是CM常引发的症状，这些症状往往是由BBB的损伤引起的[32]。恶性疟原虫感染的一个显著特征是分泌富含组氨酸的蛋白(histidine-rich protein 2，HRPII)。Pal等证明恶性疟原虫感染的红细胞对人脑微血管内皮屏障的破坏取决于HRPII的表达，HRPII与脑内皮细胞的结合导致紧密连接蛋白的重排和BBB受损[33]。HRPII在血液中积累并通过与血管内皮上的受体结合，激活caspase-1，介导IL-1β的分泌及成熟。IL-1β可以与细胞表面受体IL-1R结合，IL-1R激活转录因子NF-κB的MyD88依赖性信号。NF-κB易位到细胞核并诱导许多基因的转录，包括细胞骨架成分，这些基因可以重新分布紧密连接蛋白并可以改变粘附受体如细胞间黏附分子-1 (intercellular adhesion molecule-1，ICAM-1)和血清血管细胞黏附分子-1 (vascular cell adhesion molecule-1，VCAM-1)的表达，导致TJs的完整性降低和BBB通透性增加[33]。

3 非感染性疾病中炎症小体参与破坏BBB

研究表明，多种神经系统疾病中均可见血脑屏障通透性的改变，如缺血性脑卒中、阿尔茨海默病。过度活化的炎症小体会释放促炎细胞因子、趋化因子、氧化代谢物和其他具有细胞毒性作用的化学物质，进而诱发神经元凋亡，导致BBB功能障碍，并且血脑屏障的完整性与神经系统疾病的发生、发展以及转归密切相关。

3.1 NLRP3过度激活导致BBB受损引发神经疾病

研究表明，许多因素都会导致缺血性脑中风后血脑屏障的功能障碍，尤其是紧密连接蛋白，如ZO-1和Claudin-5[34]。中枢神经系统中的小胶质细胞可以激活还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate，NADPH)，从而增加ROS的产生，损伤BBB，介导细胞因子的分泌，如IL-1β和TNF-α[35]。硫氧还蛋白互作蛋白(thioredoxin-interacting protein，TXNIP)的激活是与炎症相关的一个关键事件，最新的研究表明，发生中风后TXNIP会快速结合到NLRP3炎症小体上，引发一系列的炎症反应，从而损伤血脑屏障[36]。此外，MAPK在中风病理过程中对BBB的损伤和炎症激活同样起着重要的调节作用[37]。

除缺血性中风外，脑出血(intracerebral hemorrhage，ICH)也会导致BBB的损伤(图2)。

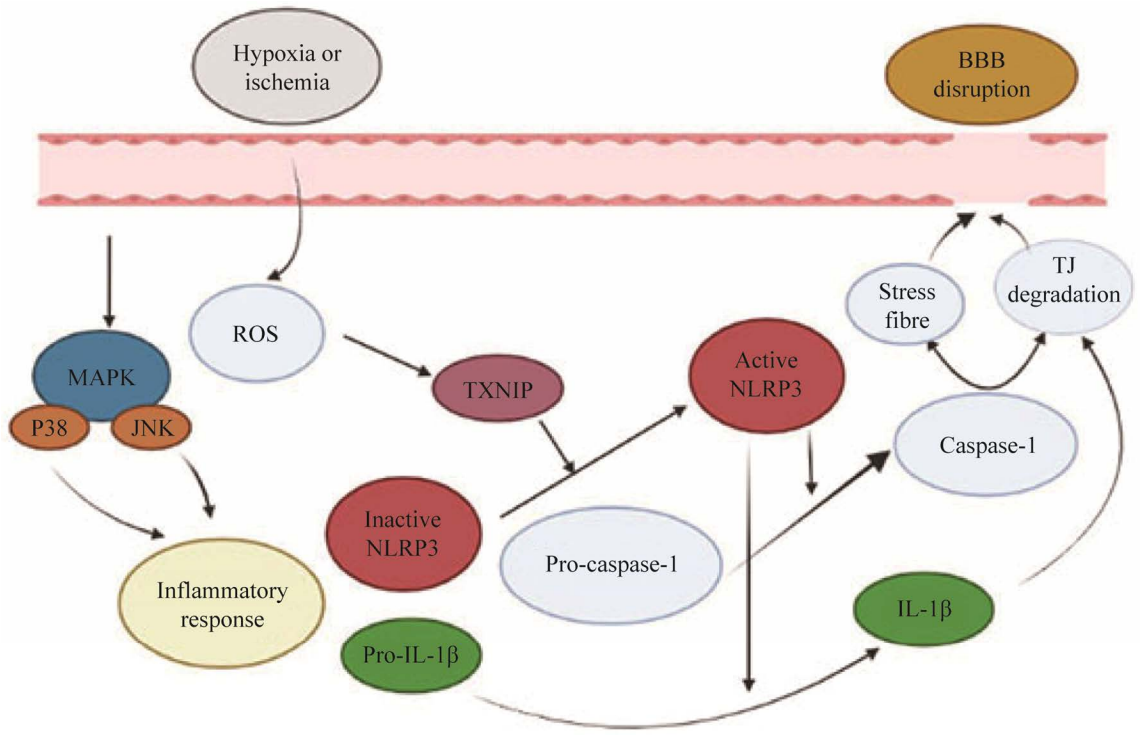

图2 缺血或缺氧导致BBB受损[38]

Figure 2 BBB damage caused by ischemia or hypoxia[38]. During ischemic stroke, ROS is generated and the MAPK pathway is activated; at the same time, TXNIP activates the NLRP3 inflammasome, triggers the expression of IL-1β and caspase-1, reduces the expression of tight junction proteins, and increases the permeability of the BBB.

ICH 会引发过度炎症反应，激活免疫细胞，随后释放促炎细胞因子，最终导致 BBB 完整性破坏和神经元死亡。并且 ICH 诱导的 BBB 障碍进一步加剧 NLRP3 炎症反应并干扰 BBB 的功能[39]。最近的证据表明 NLRP3 的上调在 ICH 后会显著放大神经炎症和增加脑水肿[40]，这对于 ICH 损伤和后期重塑起着至关重要的作用。

阿尔茨海默病是最常见的神经退行性疾病，BBB 功能障碍是导致阿尔茨海默病的关键病理机制之一。可靠的尸检证据表明，几乎 80%的 AD 患者患有脑淀粉样血管病(cerebral amyloid angiopathy，CAA)，其定义为血管淀粉样蛋白-β(Aβ)沉积在脑膜和实质动脉、小动脉、毛细血管和静脉壁中[41]。血管 Aβ 可以通过与晚期糖基化终产物(receptors for advanced glycation end products，RAGE)受体相互作用来激活内皮细胞和小胶质细胞，导致毛细血管 CAA 中促炎细胞因子的释放[42]，释放的促炎细胞因子抑制 TJs 的表达并诱导神经元退化[43]。有研究表明，NLRP3 炎症小体缺失小鼠的小胶质细胞会被改变为 M2 型，降低了血管淀粉样蛋白-β 在脑膜中沉积，并增强了患阿尔茨海默病小鼠的恢复能力[44]。

3.2 AIM2 过度激活导致 BBB 受损引发神经疾病

除 NLRP3 过度激活引发缺血性中风外，也有研究表明在小鼠脑缺血性中风后 AIM2 明显上调。Xu 等发现 AIM2 缺失型小鼠的脑梗死体积减少，神经及运动功能得到改善，并且 BBB 的完整性得到保护[45]。在缺血性中风体外模型中 AIM2 和 ICAM-1 的蛋白水平也显著上升，并且 Tj 蛋白被破坏，导致 BBB 受损。而 AIM2 敲低通过促进 TJ 蛋白的表达和降低 ICAM-1 表达和中性粒细胞粘附来有效保护 BBB 完整性。

4 抑制炎症小体相关通路保护 BBB

以往的研究表明，炎症反应在血脑屏障损伤中发挥着关键的作用。当病原体入侵机体时，炎性小体的组装和激活、细胞因子及趋化因子的释放都会导致 BBB 损伤，从而引起机体严重的神经性疾病，对健康乃至生命都造成了极大的威胁。因此，对炎症小体的调控可能作为修复受损的血脑屏障的潜在治疗机制。

4.1 炎症小体抑制剂

大部分 BBB 受损的原因都是因为 NLRP3 炎症小体被过度激活，介导 IL-1β 和 IL-18 等细胞因子被大量释放。因此如果可以阻断 NLRP3 炎症小体的活化，就可以减少细胞因子的产生，改善 BBB 的完整性。MCC950 是一种选择性小分子 NLRP3 抑制剂，它能抑制 NLRP3 诱导的 ASC 寡聚化，从而阻止 IL-1β 裂解成活性形式。MCC950 只作用于 NLRP3，而不作用于除 NLPR3 外的炎症小体，如 NLRP6、AIM2 或 NLRC4[46]。Ren 等通过小鼠自体血致脑出血模型证明，MCC950 通过减少脑白细胞浸润和 IL-6 等细胞因子的产生，改善了 BBB 的完整性，减少了细胞死亡[47]。

格列本脲(glibenclamide)是一种广泛使用的磺脲类药物，被认为可以通过抑制 NLRP3 炎症小体组装，从而有效地抑制炎症细胞的迁移，阻止炎症细胞的浸润[48]。研究表明格列本脲可以保护 BBB，减少血管外渗引起的炎症介质的产生，改善实验后的神经炎症[49]。

Ma 等对脑缺血小鼠腹腔注射清开灵溶液，发现可减轻神经功能缺陷、脑梗死、BBB 通透性、脑水肿和脑细胞凋亡[50]。清开灵能降低促炎细胞因子 TNF-α，IL-6 和 IL-1β 的分泌，增加抗炎细胞因子 IL-4 和 IL-10 的表达。并且清开灵能够激活腺苷酸活化蛋白激酶(AMP-activated

protein kinase，AMPK)，降低氧化应激，降低 NLRP3 炎症小体的激活。

此外，有大量研究表明，右美托咪啶(DEX)可以通过抑制 TLR4/NF-κB 途径和 NLRP3 炎症小体的组装，减少中性粒细胞浸润、小胶质细胞活化和促炎因子释放，缓解细胞凋亡，可用于血脑屏障受损的治疗[51−52]。表 1 总结了目前已研究报道保护 BBB 的机制及部分药物名称。

4.2 自噬诱导剂

自噬是一种自我消化过程，该过程可以降解受损的细胞器和异常聚集的蛋白质，在维持细胞稳态和存活方面起着重要作用[79]。大量研究表明自噬可以负调节 NLRP3 炎症小体的激活，抑制 IL-1β 和 IL-18 的释放[46]。因此，通过自噬诱导剂增强内皮细胞的自噬活性，抑制 NLRP3 炎症小体，可以维持 BBB 的完整性。荔枝籽(lychee seed polyphenol，LSP)是一种来自荔枝果实的传统中药。研究发现，LSP 通过 AMPK/mTOR/ULK1 途径激活自噬，显著抑制 NLRP3 炎症小体的活化，并上调体内外 TJs 的表达，对 BBB 的保护有积极作用[80]。

Al Rihani 等的研究结果表明，富含油黄醛(oleocanthal，OC)的特级初榨橄榄油(extra-virgin olive oil，EVOO)通过抑制 NLRP3 炎症小体来减少神经炎症，并通过激活 AMP 活化蛋白激酶诱导自噬，从而恢复 BBB 功能，降低 AD 相关症状[53]。

5 小结

炎症小体是先天免疫系统最重要的组成部分之一，它在 BBB 的受损机制中发挥重要的作用。近年来，炎症小体在 BBB 损伤机制方面的研究，为保护 BBB 奠定了坚实的理论基础。当机体患感染性疾病后，会引发机体产生免疫炎症反应，激活炎症小体，生成的细胞因子诱导血脑屏障的破坏，使病原突破 BBB 进入中枢神经系统，导致脑内疾病的产生。当机体自身引发过度免疫反应时，某些信号通路(如 NF-κB、TLR4)或受体蛋白被激活(如 TXNIP)，导致炎症小体组装并分泌细胞因子，引起 BBB 受损。目前，通过调控炎症小体改善受损 BBB 的治疗方案，为相关脑类疾病的治疗带来了新的角度。因此，对炎症小体在机体血脑屏障损伤中的作用机制的进一步深入研究，有利于为多种神经和脑内疾病提供更佳的治疗思路。

表 1 不同机制保护 BBB 的各种药物

Table 1 Various drugs that protect the BBB by different mechanisms

Ways to improve BBB integrity	Drug name
Inhibits NLRP3 inflammasome activation	MCC950[47]; Oridonin (Ori)[53]; XingNaoJing(XNJ)[54]; Glibenclamide[55]; Adiponectin (APN)[56]; Memantine[57]; Calcitriol[58]; Resolvin D1 (RVD1)[59]; Telmisartan[60]; Melatonin(MT)[61]; HIOC[62]; Minocycline[63]; Hydrogen (H2)[64]; 2-(2-benzofuranyl)-2-imidazoline (2-BFI)[65]; Nrf2/OPTN[66]; Verapamil[67]; Iptakalim (Ipt)[68]; ATN-161[69]
Inhibits AIM2 inflammasome activation	AG490[45]
Inhibits MAPK pathway	Ruscogenin[70]
Inhibits NF-κB pathway	Isoliquiritigenin (ILG)[71]; Maf1[72]; VX765[73]; Dexmedetomidine (DEX)[52]; Icariin (ICA)[38]; 20C[74]; Atorvastatin[75]; Antioxidant α-lipoic acid(LA)[76]
Inhibits AMPK/TXNIP/NLRP3 signaling pathway	Apelin-13/APJ system[77]; Umbelliferone (UMB)[78]; Qingkailing (QKL)[50]

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