综 述

动脉瘤性蛛网膜下隙出血的炎症机制与治疗研究进展

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[摘要] 动脉瘤性蛛网膜下隙出血(aSAH)主要由颅内动脉瘤破裂引起，出血发生在蛛网膜下隙，是一种致残率和病死率均较高的急性神经系统疾病。aSAH相关的脑损伤是多种损伤机制共同导致的，发病后72 h内发生的早期脑损伤(EBI)为随后脑内的病理生理变化和不良预后奠定了基础。其中，脑免疫炎症反应涉及多种免疫细胞和活性物质相互作用，在aSAH后EBI中起重要作用，也与延迟性脑损伤及远期预后有关。aSAH后的全身性炎症反应将影响患者的预后及转归。本文综述了局部和全身免疫炎症反应在aSAH发生和发展中的作用，以及相关的炎性生物标志物和治疗方法的研究进展，旨在为相关治疗方案的探索提供参考。

[关键词] 蛛网膜下隙出血；炎症机制；治疗；转归

Research progress on inflammatory mechanism and treatment in aneurysmal subarachnoid hemorrhage

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[**Abstract**] Aneurysmal subarachnoid hemorrhage (aSAH), primarily caused by the rupture of intracranial aneurysms with bleeding into the subarachnoid space, is an acute neurological disease associated with high disability and mortality. Brain injury after aSAH results from a combination of injury mechanisms, with early brain injury (EBI) occurring within 72 hours post-onset, laying the foundation for subsequent pathophysiological changes in the brain and poor prognosis of patients. Among them, the brain immunoinflammatory response, involving the interaction of various immune cells and active substances, plays a significant role in post-aSAH EBI, and is related to delayed brain injury and long-term prognosis. Systemic inflammatory response following aSAH can also affect the prognosis and outcome of patients. This review summarizes the role of local and systemic immune inflammatory responses in the occurrence and progression of aSAH, as well as the research progress on related inflammatory biomarkers and therapeutic prospects, aiming to provide a theoretical reference for new treatment for aSAH.

[**Key words**] subarachnoid hemorrhage; inflammatory pathogenesis; therapy; outcome

蛛网膜下隙出血(subarachnoid hemorrhage，SAH)是指因血管破裂致血液流入蛛网膜下隙引起的一种临床综合征[1]，可分为创伤性与非创伤性两大类。约85%的非创伤性SAH病例由颅内动脉瘤破裂引起，为动脉瘤性SAH(aneurysmal SAH，aSAH)[2]。尽管可通过开颅或介入手术控制出血[3]，但仍有1/3的aSAH患者在动脉瘤破裂3~14 d出现迟发性脑缺血(delayed cerebral ischemia，DCI)且预后较差(致残率约50%，病死率20%~30%)[4-5]。DCI通常被认为是脑血管痉挛(cerebrovascular spasm，CVS)导致[2]。尽管钙离子通道阻滞剂尼莫地平可降低aSAH患者发生DCI的风险[6]，但预防或延迟CVS和DCI进而改善aSAH

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患者预后的措施十分有限[7]。因此，迫切需要寻找新的aSAH治疗方案。

aSAH导致脑损伤的病理机制在动脉瘤破裂的瞬间被激活，早期脑损伤(early brain injury，EBI)发生在初始出血后的72 h内，并与aSAH后DCI的发生发展和长期预后及病死率相关[8-10]。中枢神经系统的免疫炎症是aSAH后EBI的重要因素，同时在DCI的发展中起关键作用[11]。同时，外周全身免疫炎症在aSAH发生后也会经历一系列动态演变，加重aSAH的预后不良[12]。因此，抑制aSAH后的免疫炎症有望成为新的治疗策略。本文综述免疫炎症反应在aSAH发生和发展中的作用及与其转归相关的几种炎症生物标志物和信号通路，讨论针对aSAH患者免疫炎症反应的潜在治疗方法的研究进展，旨在为相关治疗方案的探索提供参考。

1 aSAH后的颅内炎症机制

aSAH后的颅内炎症发生机制包括氧化应激和细胞因子介导，它们的共同作用导致aSAH后颅内炎症的发生发展[13]。

1.1 激活氧化应激 aSAH急性期损伤主要源于局部炎症的激活。aSAH后红细胞进入蛛网膜下隙内进而被降解，导致血红蛋白释放，血红蛋白裂解生成游离血红素。血红蛋白的部分裂解产物进入蛛网膜下隙，促进氧化应激进而激活炎症级联反应导致脑损伤，被称为损伤相关分子模式(damage-associated molecular patterns，DAMPs)[14]。DAMPs可被模式识别受体(pattern recognition receptor，PRR)[如Toll样受体(TLR)、细胞质NOD样受体(NLR)]识别[15]。TLR是一类典型的PRR，在中枢神经系统小胶质细胞和星形胶质细胞的膜中广泛表达[16]。TLR4在aSAH后的炎症反应中起主要作用[17]；游离血红素和高铁血红蛋白(metHb)均为TLR4的内源性配体[18-19]。aSAH发生后，metHb和TLR4可通过TLR4通路激活小胶质细胞中核因子-κB(NF-κB)介导的促炎级联反应，引起DNA转录、肿瘤坏死因子(TNF)-α和白细胞介素(IL)-1的释放[20]。Liu等[21]发现，CXC趋化因子受体4(CXCR4)可通过NLRP3炎性小体和NF-κB通路介导SAH EBI中细胞焦亡和脂质过氧化。

1.2 激活小胶质细胞 小胶质细胞是aSAH后的常驻免疫炎性细胞，存在两种极化状态(M1和M2表型)，可导致神经炎症的不同结局[12,22]。M1表型的小胶质细胞通常与促炎作用相关，而M2表型与抗炎和组织修复有关[23]。大量研究显示，小胶质细胞在aSAH后EBI中发挥着重要作用。aSAH后24 h内，小胶质细胞被激活出现形态学改变；aSAH后4~6 d，小胶质细胞活化较前减少，但仍高于aSAH前，并在第14天前后再次达到峰值[24-26]。研究显示，游离血红素可激活过氧化物还原蛋白-2(peroxiredoxin 2)，后者与TLR4结合后激活小胶质细胞，可促进促炎因子的表达和释放，导致神经元凋亡[27-28]。此外，小胶质细胞可激活星形胶质细胞发挥促炎作用[11]。

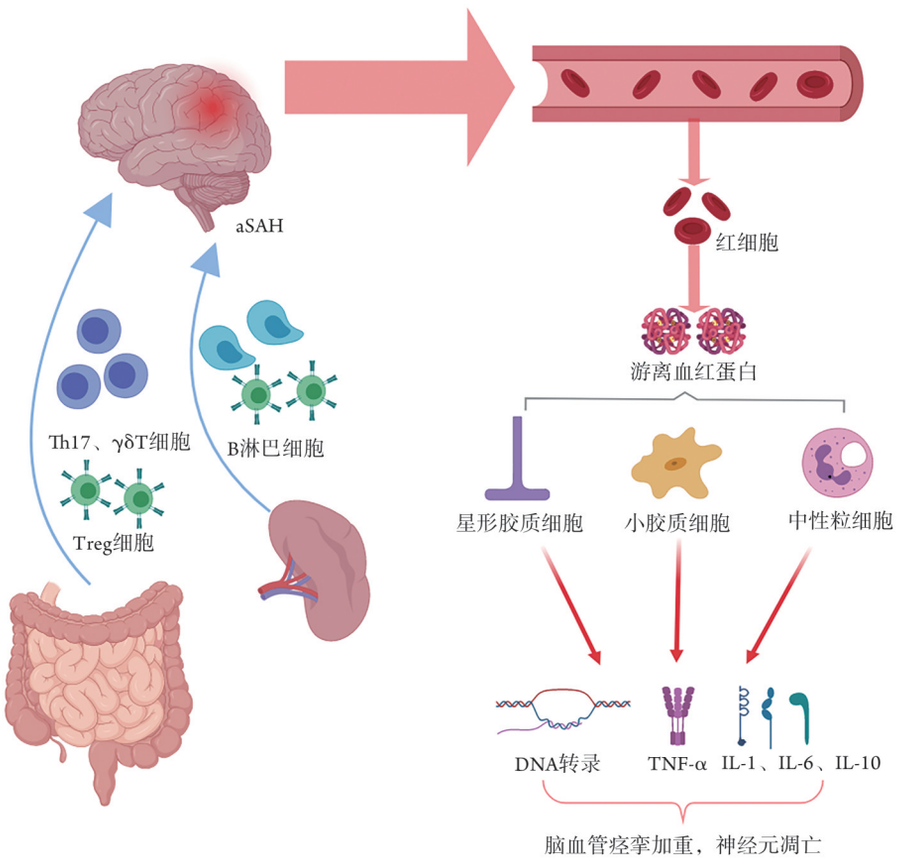
1.3 星形胶质细胞Ca^{2+}水平升高 星形胶质细胞是中枢神经系统中的支持细胞，是主要的神经胶质细胞类型，在维持血脑屏障的完整性方面发挥重要作用[29]。胶质纤维酸性蛋白(GFAP)是星形胶质细胞的一种特异性生物标志，在SAH模型大鼠中显著增加[25]。动物实验显示，aSAH后星形胶质细胞内Ca^{2+}水平升高，导致神经血管偶联反应的极性改变，进而使得周围血管由舒张变为收缩[30]；这可能是aSAH后脑血流量减少的重要因素。

1.4 外周免疫细胞聚集 外周免疫炎症细胞也参与aSAH后的脑免疫炎症反应，可在脑损伤和组织修复过程中发挥重要作用。aSAH后10 min内，中性粒细胞开始在中枢神经系统聚集[12,31]，是aSAH后首先渗入中枢神经系统的外周免疫炎性细胞，可能是导致aSAH后早期大脑皮质灌注不足和氧化应激的重要介质[32]；随后导致免疫细胞亚群如自然杀伤(NK)细胞、调节性T细胞(Treg)减少，进一步激活炎症级联反应，激活炎症通路产生下游炎症介质[33]。

1.5 炎症介质表达变化 除炎性细胞外，脑脊液和血液中的炎症介质在aSAH后也发生一系列动态变化，这些炎症介质通过免疫细胞激活的特定信号通路参与炎症反应。近期研究显示，P选择素、黏附分子和促炎细胞因子(包括IL-6、IL-1β和TNF-α)在aSAH发病后数小时内显著增加[11]。一些炎症介质如IL-10、IL-6和巨噬细胞炎症蛋白1β(MIP1β)的变化与aSAH患者EBI的临床表现和严重程度明显相关，可能是EBI的重要标志[34]。此外，TNF-α可通过诱导神经元凋亡导致aSAH后EBI[35]，抑制TNF-α功能，可明显减缓实验性SAH后大鼠海马中的神经元凋亡[36]。一项大鼠模型实验也显示，抗TNF-α抗体可减少下丘脑中的凋亡[37]。研究显示，促炎介质[如IL-1、IL-6和基质金属蛋白酶9(MMP-9)]的表达增多是由于脑血管中MEK-ERK1/2途径激活[38]。在T淋巴细胞表面，TLR4、TLR相关干扰素激活剂(TRIF)和髓样分化初级反应基因(*MyD88*)[通过NF-κB和IL-1受体相关激酶4(IRAK4)途径]被描述为神经元凋亡和CVS的重要因素[39]。上述炎症介质共同作为脑血管炎症发生发展的关键因素，提示aSAH后颅内炎症为多因素成因，其治疗面临巨大挑战。

总之，在aSAH后的炎症发展过程中，免疫细胞和炎症介质均可发挥重要作用。动脉瘤破裂后，脑内小胶质细胞首先被激活，随后中性粒细胞和单核

细胞从神经系统周围渗入到出血部位。虽然小胶质细胞的激活和中性粒细胞的鞘内浸润有助于清除进入蛛网膜下腔的血液，但它们也可通过加重炎症反应引起神经元凋亡。脑脊液和血液中的炎症介质也通过介导免疫炎症来促进aSAH后炎症反应；aSAH后的炎症反应也可能有助于组织修复(图1)。



aSAH. 动脉瘤性蛛网膜下隙出血；Th17. 辅助性T细胞17；Treg. 调节性T细胞；TNF-α. 肿瘤坏死因子-α；IL. 白细胞介素

图1 aSAH后炎症进展示意图

Fig.1 Inflammatory progression diagram after aSAH

2 aSAH后的全身炎症

aSAH曾长期被认为是一种单器官疾病，其最重要的病理生理过程发生在中枢神经系统，且这些病理生理过程决定aSAH的预后和转归；但近年来众多研究显示，aSAH实际上是一种全身性疾病，具有许多中枢神经系统外的表现，包括心功能障碍、肺损伤和全身性免疫失调等[40-42]。

2.1 脾的免疫调节 脾是外周免疫细胞的主要储存库。脾活化与炎症反应改变、免疫系统失调、神经炎症、感染风险增加和神经恢复受损有关[43-44]。

目前涉及SAH、脾和外周免疫系统的相关研究较少，对aSAH后脾的变化也知之甚少。Illanes等[45]观察了脑出血小鼠模型不同出血量(10、30、50 ml)时的血液免疫细胞组成、细胞因子谱和感染并发症的变化，结果显示，大量脑出血导致血液和脾中白细胞和淋巴细胞显著减少，单核细胞数量增加；同时，无论脑出血量多少，循环脾源性T和B淋巴细胞、辅助性和细胞毒性T淋巴细胞均明显减少；这项研究未报道脾大小的变化，但指出大量脑出血的小鼠脾细胞计数明显降低。Zhang等[46]在胶原酶注射和自体血液注射小鼠脑出血模型中发现，脑出血小鼠脾较对照组收缩，脑出血体积越大，脾收缩越多。还有实验证据显示，脾可能介导脑出血的神经保护治疗。Lee等[47]观察到大鼠脑出血诱导后，静脉输注人神经干细胞可明显抑制大鼠脑和脾中TNF-α、IL-6和NF-κB的上调，但是在脑出血诱导前脾切除的大鼠却未见类似的抑制作用。对缺血和出血性脑卒中人群的联合队列研究显示，脾体积在脑卒中发作后48 h降至最低点，而在发病后7~10 d再次扩张并恢复到正常体积[48-49]。脑卒中后脾收缩与外周免疫激活有关，其特征是外周血中性粒细胞计数增多[48,50]，淋巴细胞和NK细胞计数减少[46,48-49]。虽然目前对于aSAH的脾免疫系统仍未有系统阐述，但对脑卒中的相关研究可为未来此方面的研究提供参考。

2.2 肠道的免疫调节 近年来，肠道菌群在人体健

康中的作用受到关注，特别是微生物-肠道-大脑轴的相关研究；而肠道微生物群的改变影响大脑免疫系统这一猜想也逐渐得到验证。

目前aSAH后肠道免疫改变的研究较少，更多的关注点在缺血性脑卒中后的免疫炎症调节。脑卒中后，局部神经炎症反应和外周免疫可同时激活[51]，免疫稳态可能受到肠道菌群及其代谢产物的调节[52-53]，提示脑卒中与肠道微生物失调之间存在相互因果关系。在适应性免疫反应中，Tregs和B细胞具有抗炎作用，而Th17和γδT细胞具有促炎作用。肠道菌群对免疫细胞的分化和功能起着重要作用。肠道共生微生物已成为淋巴细胞包括Tregs和γδ T细胞的有效调节剂，这两种细胞均参与脑缺血损伤[52]。研究显示，脑卒中发生后IL-17阳性γδT细胞从肠道由下而上运输，进而在脑膜中积聚[52]。有研究显示，上述变化是由于肠道菌群的改变而造成的。使用克拉维酸清除肠道菌群的小鼠中，Treg细胞减少，IL-17阳性γδT细胞增多；而老年脑卒中小鼠行粪便移植时，会降低小鼠IL-6、TNF-α、eotaxin和趋化因子CCL5等细胞因子水平，并促进脑卒中预后改善[54]。Matsuura等[55]报道，脑卒中后肠道菌群发生的改变与TGF-β和IL-10的产生有关。

3 aSAH的治疗

aSAH的治疗包括破裂动脉瘤的修复以及神经与全身并发症的预防和治疗。在通过手术夹闭或血管内弹簧圈修复动脉瘤后，治疗应侧重于并发症，以改善预后。aSAH后的炎症进展是导致患者发病和死亡的主要原因[7]。然而，多种炎症机制的共同作用导致目前仍然缺乏有效的治疗方法[56]。根据动物实验和临床前研究揭示的免疫炎症在aSAH发展中的作用(包括EBI和DCI)，以下讨论可能改善aSAH患者预后的抗炎或免疫治疗。

3.1 传统的抗炎方案　人们一直在努力探索用不同方法治疗aSAH后的全身性炎症反应。非甾体抗炎药(NSAIDs)是常见的抗炎药物，可阻断环氧化酶(COX)的作用，减轻疼痛、炎症和发热。塞来昔布是COX-2抑制剂，在动物实验中可有效减少血管痉挛和神经功能障碍。在塞来昔布治疗的aSAH小鼠中，观察到整体活动性改善和血脑屏障破坏减少[57]。另一类常用的抗炎药—皮质类固醇，可能有助于减少血管痉挛和IL-6的产生[58]。而Edvinsson等[59]认为，通过早期抑制血管丝裂原活化蛋白激酶(MAPK)途径能够减轻血管收缩和减少炎性介质表达，维持血流预防DCI。

3.2 血红蛋白清除治疗　血红蛋白裂解会导致氧化应激反应，引起直接和间接的神经炎症。因此，针对血红蛋白的早期清除可能避免后续炎症反应的启动。研究显示，血红蛋白可通过3种方式被细胞吞噬：红细胞吞噬作用、结合珠蛋白介导的红细胞内吞作用和血红素结合蛋白介导的血红素内吞作用。

红细胞吞噬作用是指巨噬细胞吞噬异常的红细胞，其细胞膜上表达有Ⅱ型清道夫受体(CD36)。aSAH后，巨噬细胞通过CD36识别并介导吞噬红细胞。转录因子Nrf2能够调节小胶质细胞上CD36的表达，从而提高红细胞清除率[60]。结合珠蛋白主要由肝产生，红细胞破裂后产生的血红蛋白二聚体可立即且不可逆地与结合珠蛋白结合[61]。结合珠蛋白-血红蛋白复合物形成后，巨噬细胞和小胶质细胞上的CD163(清道夫膜受体)可导致吞噬溶酶体中的血红蛋白分解[62]。血红素结合蛋白可以高亲和力结合游离血红素形成复合物，随后与低密度脂蛋白受体相关蛋白-1(CD91)结合。CD91是一种跨膜蛋白，在各种细胞的膜上表达并介导复合物的内吞作用，加速游离血红素的清除[63]。这些内源性血红蛋白清除机制为针对血红蛋白的治疗方案提供了一个较好的切入点。

3.3 颅内免疫细胞介导的炎症治疗　小胶质细胞与星型胶质细胞在aSAH脑损伤中起着双重作用，如何提高其有益作用并减少其损害是目前研究的重点[64]。研究显示，姜黄素可通过抑制TLR4信号通路，促进小胶质细胞M1表型向M2表型转化，从而抑制神经炎症反应[65]。半乳糖凝集素-3(galectin-3)能够抑制aSAH后EBI中的小胶质细胞M1极化，减轻神经炎症损伤[66]。载脂蛋白E能够抑制JAK2/STAT3信号通路，减少小胶质细胞M1表型的激活，从而在大脑中发挥神经保护作用[67]。TNF-α刺激基因-6(TSG-6)蛋白由骨髓间充质干细胞(BMSCs)分泌，可下调星形胶质细胞中诱导型一氧化氮合酶(iNOS)的表达和抑制NF-κB/MAPK信号通路，保护血脑屏障。在BMSCs中沉默*TSG-6*基因会加重星形胶质细胞和血脑屏障的损伤[68]。Yang等[69]认为，牙髓干细胞来源的条件培养基可以促进M2小胶质细胞极化和减少星形胶质细胞肿胀来缓解SAH引起的微循环障碍。同样，抑制促炎免疫细胞激活、减少炎症介质产生也同样具有广阔的研究前景。Xie等[70]发现，静脉注射白蛋白可减少脑实质小胶质细胞的活化和中性粒细胞的浸润。

3.4 脾靶向治疗　越来越多的研究显示，脑-脾-外周免疫系统的相互作用对缺血性脑卒中的预后有明显影响，并可能对出血性脑卒中的预后有潜在影响。研究显示，在缺血性脑卒中的动物模型中，干细胞移植可逆转脑损伤后的脾收缩，增加脾Treg细胞群和抗炎细胞因子(如IL-10)，并防止缺血性脑损

伤[71-74]。这些变化与损伤后颅内抗炎免疫反应相关联，包括下调脑中TNF-α、IL-1β、IL-6和γ干扰素(IFN-γ)[75]。在自体血液注射建立的脑出血模型中，静脉输注骨髓来源的单核细胞可减少血肿周围的神经炎症和脑水肿，而这些单核细胞似乎更倾向于在脾内积聚[76]。在实验性脑出血后2 h予以神经干细胞移植，单核细胞也在脾内积聚，并可通过减少大脑和脾内的TNF-α和IL-6来促进神经功能恢复[47]。因此针对脾介导的外周免疫反应可能是一种新的aSAH治疗方法，需要进一步探究其内在机制。

3.5 微生物-肠-脑轴治疗 目前肠道微生物群与中枢神经系统之间的相关性研究逐渐成为关注点。已有研究显示，肠道微生物群可用于治疗神经系统疾病，包括自闭症谱系障碍[77]、帕金森病[78]、阿尔茨海默病[79]及缺血性脑卒中[80]。

粪便微生物群移植(fecal microbio-tatransplantation，FMT)又称粪便移植，是指将健康者的粪便转移到患者肠道中[81]。研究显示，脑卒中后小鼠的肠道菌群中促炎细胞因子明显增加，短链脂肪酸(short chain fatty acids，SCFAs)[54]水平降低。FMT可通过激活多种免疫介导途径缓解结肠炎症，恢复肠道内稳态[82]。抗微生物治疗不仅可减少记忆/效应T细胞、树突细胞和Treg细胞，还可减少炎性因子的产生，包括$CD4^+$ T细胞的IL-10、IL-17、IL-22和IFN-γ。He等[83]发现，肠道细菌中的葡萄糖生物合成I途径可能是对抗aSAH后外周炎症的保护因子。而也有临床研究报道aSAH后存在肠道菌群改变[84]。虽然aSAH后脑与肠道微生物之间的相互作用仍未阐明，但这将会是一个有价值的研究方向。

4 总结与展望

aSAH一旦发生，则有较高的致残率和病死率，目前其治疗措施仍然有限。EBI和DCI是当前aSAH研究的焦点。实验数据显示，涉及多种免疫细胞和免疫活性物质的免疫炎症可能诱导了aSAH后的部分病理过程，包括EBI和DCI等多种不良预后。针对免疫炎症的疗法在部分动物实验和临床研究中展现出良好的前景，但其有效性和安全性仍待进一步验证。对于颅内炎症，未来研究可聚焦于炎性细胞和炎症介质的促炎通路机制和各种不同炎症反应之间的相互作用。而关于aSAH如何引起外周免疫系统的变化，目前仍然缺乏更多的数据支持。因此，未来需要探究脑与其他器官之间的多器官相互作用以及与外周免疫细胞之间的可能联系。

【参考文献】

[1] 张峰涛, 王冠军, 赵中甫. 蛛网膜下腔出血患者脑血管痉挛危险因素分析[J]. 新乡医学院学报, 2022, 39(5): 450-453.

[2] Claassen J, Park S. Spontaneous subarachnoid haemorrhage[J]. Lancet, 2022, 400(10355): 846-862.

[3] Zhang Z, Zhang A, Liu Y, *et al*. New mechanisms and targets of subarachnoid hemorrhage: a focus on mitochondria[J]. Curr Neuropharmacol, 2022, 20(7): 1278-1296.

[4] 王小龙, 任光旭, 李春浩, 等. 动脉瘤性蛛网膜下腔出血后脑血管痉挛的研究进展[J]. 延边大学医学学报, 2023, 46(1): 70-74.

[5] Chen Y, Wright N, Guo Y, *et al*. Mortality and recurrent vascular events after first incident stroke: a 9-year community-based study of 0.5 million Chinese adults[J]. Lancet Glob Health, 2020, 8(4): e580-e590.

[6] Macdonald RL, Higashida RT, Keller E, *et al*. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2)[J]. Lancet Neurol, 2011, 10(7): 618-625.

[7] Geraghty JR, Testai FD. Delayed cerebral ischemia after subarachnoid hemorrhage: beyond vasospasm and towards a multifactorial pathophysiology[J]. Curr Atheroscler Rep, 2017, 19(12): 50.

[8] Fujii M, Yan J, Rolland WB, *et al*. Early brain injury, an evolving frontier in subarachnoid hemorrhage research[J]. Transl Stroke Res, 2013, 4(4): 432-446.

[9] Rass V, Helbok R. Early brain injury after poor-grade subarachnoid hemorrhage[J]. Curr Neurol Neurosci Rep, 2019, 19(10): 78.

[10] Wang X, Li S, Ma J, *et al*. Effect of gastrodin on early brain injury and neurological outcome after subarachnoid hemorrhage in rats[J]. Neurosci Bull, 2019, 35(3): 461-470.

[11] Zheng VZ, Wong GKC. Neuroinflammation responses after subarachnoid hemorrhage: A review[J]. J Clin Neurosci, 2017, 42: 7-11.

[12] Coulibaly AP, Provencio JJ. Aneurysmal subarachnoid hemorrhage: an overview of inflammation-induced cellular changes[J]. Neurotherapeutics, 2020, 17(2): 436-445.

[13] 褚冬, 张光敏, 李清泉, 等. 颅内动脉瘤发生发展中的炎症反应及信号通路研究进展[J]. 解放军医学杂志, 2022, 47(1): 89-96

[14] Chaudhry SR, Hafez A, Rezai Jahromi B, *et al*. Role of damage associated molecular pattern molecules (DAMPs) in aneurysmal subarachnoid hemorrhage (aSAH)[J]. Int J Mol Sci, 2018, 19(7): 2035.

[15] Zindel J, Kubes P. DAMPs, PAMPs, and LAMPs in immunity and sterile inflammation[J]. Annu Rev Pathol, 2020, 15: 493-518.

[16] Pascual M, Calvo-Rodriguez M, Núñez L, *et al*. Toll-like receptors in neuroinflammation, neurodegeneration, and alcohol-induced brain damage[J]. IUBMB Life, 2021, 73(7): 900-915.

[17] Okada T, Suzuki H. Toll-like receptor 4 as a possible therapeutic target for delayed brain injuries after aneurysmal subarachnoid hemorrhage[J]. Neural Regen Res, 2017, 12(2): 193-196.

[18] Figueiredo RT, Fernandez PL, Mourao-Sa DS, *et al*. Characterization of heme as activator of Toll-like receptor 4[J]. J Biol Chem, 2007, 282(28): 20221-20229.

[19] Kwon MS, Woo SK, Kurland DB, *et al*. Methemoglobin is an endogenous toll-like receptor 4 ligand-relevance to subarachnoid hemorrhage[J]. Int J Mol Sci, 2015, 16(3): 5028-5046.

[20] Blackburn SL, Kumar PT, Mcbride D, *et al*. Unique contribution of haptoglobin and haptoglobin genotype in aneurysmal subarachnoid hemorrhage[J]. Front Physiol, 2018, 9: 592.

[21] Liu C, Yao K, Tian Q, *et al*. CXCR4-BTK axis mediate pyroptosis and lipid peroxidation in early brain injury after subarachnoid hemorrhage *via* NLRP3 inflammasome and NF-κB pathway[J]. Redox Biol, 2023, 68: 102960.

[22] Qin C, Zhou L-Q, Ma X-T, *et al*. Dual functions of microglia in ischemic stroke[J]. Neurosci Bull, 2019, 35(5): 921-933.

[23] Orihuela R, Mcpherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states[J]. Br J Pharmacol, 2016, 173(4): 649-665.

[24] Heinz R, Brandenburg S, Nieminen-Kelhä M, *et al*. Microglia as target for anti-inflammatory approaches to prevent secondary brain injury after subarachnoid hemorrhage (SAH) [J]. J Neuroinflammation, 2021, 18(1): 36.

[25] Kooijman E, Nijboer CH, van Velthoven CTJ, *et al*. Long-term functional consequences and ongoing cerebral inflammation after subarachnoid hemorrhage in the rat[J]. PLoS One, 2014, 9(6): e90584.

[26] Provencio JJ, Altay T, Smithason S, *et al*. Depletion of Ly6G/C(+) cells ameliorates delayed cerebral vasospasm in subarachnoid hemorrhage[J]. J Neuroimmunol, 2011, 232(1-2): 94-100.

[27] Lu Y, Zhang XS, Zhang ZH, *et al*. Peroxiredoxin 2 activates microglia by interacting with Toll-like receptor 4 after subarachnoid hemorrhage[J]. J Neuroinflammation, 2018, 15(1): 87.

[28] Peng J, Xie Y, Pang J, *et al*. Toll-like receptor 4-mediated microglial inflammation exacerbates early white matter injury following experimental subarachnoid hemorrhage[J]. J Neurochem, 2023, 166 (2): 280-293.

[29] Jiang X, Andjelkovic AV, Zhu L, *et al*. Blood-brain barrier dysfunction and recovery after ischemic stroke[J]. Prog Neurobiol, 2018, 163-164: 144-171.

[30] Pappas AC, Koide M, Wellman GC. Astrocyte Ca^{2+} signaling drives inversion of neurovascular coupling after subarachnoid hemorrhage [J]. J Neurosci, 2015, 35(39): 13375-13384.

[31] Friedrich V, Flores R, Muller A, *et al*. Reduction of neutrophil activity decreases early microvascular injury after subarachnoid haemorrhage[J]. J Neuroinflammation, 2011, 8: 103.

[32] Neulen A, Pantel T, Kosterhon M, *et al*. Neutrophils mediate early cerebral cortical hypoperfusion in a murine model of subarachnoid haemorrhage[J]. Sci Rep, 2019, 9(1): 8460.

[33] Brait VH, Arumugam TV, Drummond GR, *et al*. Importance of T lymphocytes in brain injury, immunodeficiency, and recovery after cerebral ischemia[J]. J Cereb Blood Flow Metab, 2012, 32(4): 598-611.

[34] Savarraj J, Parsha K, Hergenroeder G, *et al*. Early brain injury associated with systemic inflammation after subarachnoid hemorrhage[J]. Neurocrit Care, 2018, 28(2): 203-211.

[35] O'connor JJ. Targeting tumour necrosis factor- α in hypoxia and synaptic signalling[J]. Ir J Med Sci, 2013, 182(2): 157-162.

[36] Jiang Y, Liu DW, Han XY, *et al*. Neuroprotective effects of anti-tumor necrosis factor-alpha antibody on apoptosis following subarachnoid hemorrhage in a rat model[J]. J Clin Neurosci, 2012, 19(6): 866-872.

[37] Ma L, Jiang Y, Dong Y, *et al*. Anti-TNF-alpha antibody attenuates subarachnoid hemorrhage-induced apoptosis in the hypothalamus by inhibiting the activation of Erk[J]. Neuropsychiatr Dis Treat, 2018, 14: 525-536.

[38] Maddahi A, Povlsen GK, Edvinsson L. Regulation of enhanced cerebrovascular expression of proinflammatory mediators in experimental subarachnoid hemorrhage *via* the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway [J]. J Neuroinflammation, 2012, 9: 274.

[39] Hanafy KA. The role of microglia and the TLR4 pathway in neuronal apoptosis and vasospasm after subarachnoid hemorrhage [J]. J Neuroinflammation, 2013, 10: 83.

[40] Chen Z, Venkat P, Seyfried D, *et al*. Brain-heart interaction: cardiac complications after stroke[J]. Circ Res, 2017, 121(4): 451-468.

[41] Hoffmann S, Harms H, Ulm L, *et al*. Stroke-induced immunodepression and dysphagia independently predict stroke-associated pneumonia - The PREDICT study[J]. J Cereb Blood Flow Metab, 2017, 37(12): 3671-3682.

[42] Santos Samary C, Pelosi P, Leme Silva P, *et al*. Immunomodulation after ischemic stroke: potential mechanisms and implications for therapy[J]. Crit Care, 2016, 20(1): 391.

[43] Mebius RE, Kraal G. Structure and function of the spleen[J]. Nat Rev Immunol, 2005, 5(8): 606-616.

[44] Rasouli J, Lekhraj R, Ozbalik M, *et al*. Brain-spleen inflammatory coupling: a literature review[J]. Einstein J Biol Med, 2011, 27(2): 74-77.

[45] Illanes S, Liesz A, Sun L, *et al*. Hematoma size as major modulator of the cellular immune system after experimental intracerebral hemorrhage[J]. Neurosci Lett, 2011, 490(3): 170-174.

[46] Zhang J, Shi K, Li Z, *et al*. Organ- and cell-specific immune responses are associated with the outcomes of intracerebral hemorrhage[J]. FASEB J, 2018, 32(1): 220-229.

[47] Lee ST, Chu K, Jung KH, *et al*. Anti-inflammatory mechanism of intravascular neural stem cell transplantation in haemorrhagic stroke [J]. Brain, 2008, 131(Pt 3): 616-629.

[48] Chiu NL, Kaiser B, Nguyen YV, *et al*. The volume of the spleen and its correlates after acute stroke[J]. J Stroke Cerebrovasc Dis, 2016, 25(12): 2958-2961.

[49] Liu Q, Jin WN, Liu Y, *et al*. Brain ischemia suppresses immunity in the periphery and brain *via* different neurogenic innervations[J]. Immunity, 2017, 46(3): 474-487.

[50] Sahota P, Vahidy F, Nguyen C, *et al*. Changes in spleen size in patients with acute ischemic stroke: a pilot observational study[J]. Int J Stroke, 2013, 8(2): 60-67.

[51] Chamorro Á, Meisel A, Planas AM, *et al*. The immunology of acute stroke[J]. Nat Rev Neurol, 2012, 8(7): 401-410.

[52] Benakis C, Brea D, Caballero S, *et al*. Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells[J]. Nat Med, 2016, 22(5): 516-523.

[53] Lee J, D'aigle J, Atadja L, *et al*. Gut microbiota-derived short-chain fatty acids promote poststroke recovery in aged mice[J]. Circ Res, 2020, 127(4): 453-465.

[54] Spychala MS, Venna VR, Jandzinski M, *et al*. Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome[J]. Ann Neurol, 2018, 84(1): 23-36.

[55] Matsuura J, Inoue R, Takagi T, *et al*. Analysis of gut microbiota in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[J]. J Clin Biochem Nutr, 2019, 65(3): 240-244.

[56] 韩雨薇, 陈立刚, 李晓明, 等. 冬凌草素对蛛网膜下腔出血后早期脑损伤作用机制研究[J]. 临床军医杂志, 2022, 50(1): 5-8, 13.
[57] Tso MK, Turgeon P, Bosche B, *et al*. Gene expression profiling of brain endothelial cells after experimental subarachnoid haemorrhage [J]. Sci Rep, 2021, 11(1): 7818.
[58] Osuka K, Suzuki Y, Tanazawa T, *et al*. Interleukin-6 and development of vasospasm after subarachnoid haemorrhage[J]. Acta Neurochir (Wien), 1998, 140(9): 943-951.
[59] Edvinsson L, Krause DN. Switching off vascular MAPK signaling: a novel strategy to prevent delayed cerebral ischemia following subarachnoid hemorrhage[J]. Transl Stroke Res, 2024, doi: 10.1007/s12975-024-01234-z.
[60] Zhao X, Sun G, Ting SM, *et al*. Cleaning up after ICH: the role of Nrf2 in modulating microglia function and hematoma clearance[J]. J Neurochem, 2015, 133(1): 144-152.
[61] Andersen CBF, Stødkilde K, Sæderup KL, *et al*. Haptoglobin[J]. Antioxid Redox Signal, 2017, 26(14): 814-831.
[62] Jing C, Zhang H, Shishido H, *et al*. Association of brain CD163 expression and brain injury/hydrocephalus development in a rat model of subarachnoid hemorrhage[J]. Front Neurosci, 2018, 12: 313.
[63] Garland P, Durnford AJ, Okemefuna AI, *et al*. Heme-hemopexin scavenging is active in the brain and associates with outcome after subarachnoid hemorrhage[J]. Stroke, 2016, 47(3): 872-876.
[64] 申学明, 韩秀鹏, 何超, 等. 急性脑出血患者脑组织中小胶质细胞/巨噬细胞极化状态与血肿周围水肿的关系[J]. 新乡医学院学报, 2023, 40(12): 1161-1166.
[65] Gao Y, Zhuang Z, Lu Y, *et al*. Curcumin mitigates neuro-inflammation by modulating microglia polarization through inhibiting TLR4 axis signaling pathway following experimental subarachnoid hemorrhage[J]. Front Neurosci, 2019, 13: 1223.
[66] Shen Y, Zhang W, Chang H, *et al*. Galectin-3 modulates microglial activation and neuroinflammation in early brain injury after subarachnoid hemorrhage[J]. Exp Neurol, 2024, 377: 114777.
[67] Pang J, Peng J, Matei N, *et al*. Apolipoprotein E exerts a whole-brain protective property by promoting M1? Microglia quiescence after experimental subarachnoid hemorrhage in mice[J]. Transl Stroke Res, 2018, 9(6): 654-668.
[68] Wan Y, Song M, Xie X, *et al*. BMSCs regulate astrocytes through TSG-6 to protect the blood-brain barrier after subarachnoid hemorrhage[J]. Mediators Inflamm, 2021, 2021: 5522291.
[69] Yang L, Chen Y, Lee J, *et al*. Dental pulp stem cell-derived conditioned medium alleviates subarachnoid hemorrhage-induced microcirculation impairment by promoting M2 Microglia polarization and reducing astrocyte swelling[J]. Transl Stroke Res, 2023, 14(5): 688-703.
[70] Xie Y, Guo H, Wang L, *et al*. Human albumin attenuates excessive innate immunity *via* inhibition of microglial Mincle/Syk signaling in subarachnoid hemorrhage[J]. Brain Behav Immun, 2017, 60: 346-360.
[71] Acosta SA, Tajiri N, Hoover J, *et al*. Intravenous bone marrow stem cell grafts preferentially migrate to spleen and abrogate chronic inflammation in stroke[J]. Stroke, 2015, 46(9): 2616-2627.
[72] Schwarting S, Litwak S, Hao W, *et al*. Hematopoietic stem cells reduce postischemic inflammation and ameliorate ischemic brain injury[J]. Stroke, 2008, 39(10): 2867-2875.
[73] Vendrame M, Gemma C, Pennypacker KR, *et al*. Cord blood rescues stroke-induced changes in splenocyte phenotype and function[J]. Exp Neurol, 2006, 199(1): 191-200.
[74] Yang B, Hamilton JA, Valenzuela KS, *et al*. Multipotent adult progenitor cells enhance recovery after stroke by modulating the immune response from the spleen[J]. Stem Cells, 2017, 35(5): 1290-1302.
[75] Srinivasan A, Aggarwal A, Gaudihalli S, *et al*. Impact of early leukocytosis and elevated high-sensitivity C-reactive protein on delayed cerebral ischemia and neurologic outcome after subarachnoid hemorrhage[J]. World Neurosurg, 2016, 90: 91-95.
[76] Suda S, Yang B, Schaar K, *et al*. Autologous bone marrow mononuclear cells exert broad effects on short- and long-term biological and functional outcomes in rodents with intracerebral hemorrhage[J]. Stem Cells Dev, 2015, 24(23): 2756-2766.
[77] Kang DW, Adams JB, Coleman DM, *et al*. Long-term benefit of microbiota transfer therapy on autism symptoms and gut microbiota [J]. Sci Rep, 2019, 9(1): 5821.
[78] Forsyth CB, Shannon KM, Kordower JH, *et al*. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease[J]. PLoS One, 2011, 6(12): e28032.
[79] Cattaneo A, Cattane N, Galluzzi S, *et al*. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly[J]. Neurobiol Aging, 2017, 49: 60-68.
[80] Yin J, Liao SX, He Y, *et al*. Dysbiosis of gut microbiota with reduced trimethylamine-n-oxide level in patients with large-artery atherosclerotic stroke or transient ischemic attack[J]. J Am Heart Assoc, 2015, 4(11): e002699.
[81] Gupta A, Khanna S. Fecal microbiota transplantation[J]. JAMA, 2017, 318(1): 102.
[82] Burrello C, Garavaglia F, Cribiù FM, *et al*. Therapeutic faecal microbiota transplantation controls intestinal inflammation through IL10 secretion by immune cells[J]. Nat Commun, 2018, 9(1): 5184.
[83] He M, Wang W, He Q, *et al*. Genetic causal association between the gut microbiome and intracranial aneurysm and subarachnoid hemorrhage: a two-sample mendelian randomization study[J]. Neurol Ther, 2023, 12(5): 1695-1707.
[84] Kawabata S, Takagaki M, Nakamura H, *et al*. Dysbiosis of gut microbiome is associated with rupture of cerebral aneurysms[J]. Stroke, 2022, 53(3): 895-903.

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