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小胶质细胞调控自主神经功能参与神经源性高血压的研究进展——中枢免疫细胞的非免疫功能

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摘要 高血压是心血管疾病最主要的危险因素, 影响全球近三分之一的成年人. 研究表明, 免疫激活在高血压进展中高度参与, 且与终末器官损害密切相关. 除了免疫系统, 自主神经系统, 尤其是交感神经系统, 是维持机体内稳态的最保守的系统之一. 高血压患者的免疫和交感神经活动同时增加, 提示这两个系统在疾病的发展过程中具有协同作用. 小胶质细胞是中枢神经系统中的主要免疫细胞, 参与交感神经张力的调节. 既往的研究指出小鼠模型中小胶质细胞的缺失改变了神经炎症以及高血压的进程. 本文综述了近年小胶质细胞在稳态和疾病状态下发生发展以及功能的研究进展. 在此基础上, 综述了高血压状态下自主神经系统与外周免疫的相互作用. 小胶质细胞通过调节交感神经活动在高血压病中桥接中枢和外周炎症, 对未来探索高血压及相关心血管疾病提供新的治疗角度.

关键词 高血压, 小胶质细胞, 交感神经系统, 免疫

高血压在我国乃至世界范围内成年人群的发病率高达30%, 是致死性心血管疾病(如心梗、心衰、中风)以及神经退行性疾病(如阿尔茨海默病)的首要独立危险因素, 占医疗系统费用支出47%以上(RMB: 191亿)[1~3]. 因此干预和控制高血压是提高公众健康水平, 解除医疗经济负担的当务之急. 最新获美国食品和药物管理局(Food and Drug Administration, FDA)批准的降压药是2007年诺华公司研发的Aliskiren(肾素抑制剂), 距今十多年该领域并未有新药问世. 这与高血压的复杂性(多系统多组织脏器)导致缺乏明确的药物靶点有关. 目前临床实践中迫切需要研发靶点明确、低耐药性的抗高血压药物. 过度激活的交感神经活性是高血压的标志之一[4,5]; 肾交感消融术作为临床治疗顽固性高血压的有效手段佐证了这一观点[6]. 交感神经通过改变外周调节血管小动脉的收缩舒张, 对血压进行实时调控; 同时交感神经还对脾脏、骨髓等免疫器官进行支配, 改善系统免疫状态[7,8]. 在高血压动物模型中去除肾交感神经降低血压, 同时抑制树突状细胞

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在肾脏的激活, 以及后续T细胞浸润[9]. 进一步提示了中枢交感神经活性的升高在高血压发病机制中的重要作用. 值得注意的是, 在高血压中, 中枢和外周免疫系统均被激活[10~13]; 这种神经免疫叠加放大了高血压研究的复杂性. 了解神经系统和免疫系统之间的相互作用将有助于解析高血压的发生发展机制, 并可能为治疗提供新的靶点. 本综述总结了近年来高血压中小胶质细胞相关中枢炎症和自主神经系统之间相互作用的研究进展, 并分析了神经通路调节外周免疫并反馈到血压的调节的机制.

1 小胶质细胞个体发育和功能研究进展

作为中枢神经系统实质中的常驻免疫细胞, 小胶质细胞占小鼠(*Mus musculus*)脑内细胞总数的5%~12%, 具体取决于脑区特异性[14]. 已有大量综述研究阐明了小胶质细胞的生理学特征[15~18]. 长期以来, 小胶质细胞的起源一直是个谜团, 直到谱系追踪技术解开了这个谜题: 小胶质细胞来源于胚胎(E)9.5天左右卵黄囊中的原始c-Kit$^+$红细胞髓系祖细胞, 明确了小胶质细胞与小鼠造血细胞(出现于E16.5后)之间的独立性[19]. 然而, 在稳态和疾病条件下, 小胶质细胞群体的维持模式(自我更新或来自血源性骨髓细胞的迁移)始终模糊不清[20,21]. 除此以外, 研究表明集落刺激因子1受体(colony-stimulating factor 1 receptor, CSF1R)和转化生长因子(transforming growth factor, TGF)β受体是小胶质细胞群体发育、维持和特性所必需的[22~24]. 通过深度RNA测序可确定小胶质细胞的标志性基因: 稳态基因包括*Tmem119*, *P2ry12*, *Tgfbr1*, *siglech*和*Sall1*, 疾病相关基因例如*Spp1*, *Gpnmb*, *Igf1*, *Clec7a*, *Lpl*, *Cd9*, *Cd63*, *Lgals3*, *Fabp5*, *Apoe*和*Tyrobp*[25,26]. 这些特征性分子由RNA测序识别, 但这些基因(如*Apoe*)如何调节小胶质细胞的功能和介导小胶质细胞与神经元之间对话的机制尚不清楚. 此外, 用于鉴别T细胞亚型的标记物已经得到充分证实, 但用于区分小胶质细胞活化状态的明确标记物尚未确定.

尽管小胶质细胞的个体发生的谜团已经解开, 另有研究发现来自造血髓细胞的再生小胶质细胞样细胞具有小胶质细胞的转录谱, 提示大脑在免疫细胞上留下了印记[21]. 作为中枢神经系统专职的吞噬细胞, 小胶质细胞通过不断巡逻和吞噬碎片或病原体来维持脑内稳态. 此外, 小胶质细胞在早期发育过程和成年期通过吞噬作用维持神经发生. 在发育早期, 阿米巴样小胶质细胞触发细胞程序性死亡[27,28]和吞噬凋亡神经元[29,30]调节神经元数量并重构网络连接[31]. 成年大脑的小胶质细胞通过突触修剪监察和塑造神经元回路, 从而消除冗余的突触和/或加强功能性突触[32,33].

与外周组织脏器中的巨噬细胞一样, 小胶质细胞也非均一群体. 小胶质细胞异质性可以通过生物活性分子和转录谱来表征[34,35]. 这可能是由于特定区域环境所造成的印记[25,36~39]. 例如, 脑室下区小胶质细胞通过特异性释放因子(如TGFβ)、肿瘤坏死因子(tumor necrosis factor, TNF)α、胰岛素样生长因子(insulin like growth factor, IGF)1和toll样受体(toll-like receptors, TLR)9调节神经发生[40,41]. 利用单细胞RNA测序, 小胶质细胞可以分成7个簇[25]. 一簇小胶质细胞仅分布于出生后早期的高增殖区域(胼胝体和小脑白质), 提示它们可能有助于神经胶质细胞的发生. 更有趣的是, 这些小胶质细胞高度表达*Clec7a*(也称为Dectin 1), 一种阿尔茨海默病(Alzheimer's disease, AD)中的损伤相关分子(damage associated molecules, DAM)[26,42,43]. 小胶质细胞表型的区域差异可能导致神经元暴露于各种小胶质细胞衍生因子, 如炎症介质和营养信号, 进而影响树突棘的形成/消除和突触增强[44].

除了免疫相关分子外, 小胶质细胞还表达多种神经递质受体, 包括谷氨酸-、γ-氨基丁酸-以及肾上腺素能受体[45]. 然而小胶质细胞并不能形成神经突触, 目前这些递质受体对小胶质细胞的作用被逐步解析. 早期研究显示, 谷氨酸盐可以诱导培养的小胶质细胞释放TNFα; 而α-氨基-3-羟基-5-甲基-4-异恶唑烯丙酸(AMPA)受体可阻断该反应[46]; 提示小胶质细胞受神经递质调控从免疫抑制状态向炎症状态的转变. 儿茶酚胺能受体有α和β两大类受体, 而相较于脑内其他类型的细胞, β2受体在小胶质细胞上特异性高表达[47]. 有研究发现, 激活β2受体显著抑制小胶质细胞的运动能力, 同时促进小胶质细胞突起的回缩; 相反阻断β2则促进了小胶质细胞的运动和分支化进程, 以及对ATP介导的损伤响应[48]. 2019年, 来自两个不同课题组背靠背发表在*Nature Neuroscience*上的文章指出, β2受体调控了小胶质细胞的运动能力, 并对神经元的可塑性产生影响[49,50]. 作为脑内的免疫细胞, 小胶质细胞直接参与调节神经元的兴奋性. 比如, 小胶质细胞可

以通过$GABA_B$受体感受神经元间的交流, 特异性地调控GABA能神经元突触连接, 进而影响小鼠的行为[51]. 近来有研究报告, $P2Y_{12}$受体介导了小胶质细胞的迁移[52], 扰乱$P2Y_{12}$信号通路, 在损害了小胶质细胞运动能力的同时解除了其对神经元的抑制[53]. 另外, 小胶质细胞也可以通过水解细胞外ATP/ADP为腺苷(adenosine)间接地参与神经元兴奋性的调控[54]. 再次提示小胶质细胞作为免疫细胞可以通过非免疫的功能调控神经元活性.

除了小胶质细胞外, 中枢神经系统中骨髓来源的巨噬细胞也有助于中枢神经系统的免疫稳定性[55]. 血管周围巨噬细胞(perivascular macrophages, PVM)因靠近脑血管而得名. 尽管PVM与实质小胶质细胞有很多相似之处, 但其个体发生发育方式不同, 具有不同的标记物, 包括MHC-II, H2-Ab1和CD74[25]. PVM和循环造血髓细胞也有助于中枢神经系统感染期间的免疫应答. 更重要的是, 它们可能在小胶质细胞耗竭后和病理条件下作为小胶质细胞的储存库, 尽管这个结论具有争议性[20,21,56~59]. Harris团队[60]最近的研究表明, 消除成年小鼠大脑中小胶质细胞后, 约95%的再生群体来源于骨髓源性髓细胞. 有趣的是, 这些单核细胞来源的细胞在脑实质中驻留后, 在转录、表观遗传和功能方面获得了小胶质细胞特征[21]. 总之, 骨髓源性髓细胞可能是维持小胶质细胞稳态的第二储蓄池. 近来的研究指出, PVM是产生超氧化物的主要免疫细胞, 导致淀粉样蛋白β(amyloid-β, Aβ)在血管旁间隙的蓄积、神经血管损伤以及降低认知能力[61]. 高血压模型小鼠中去除PVM增强了血脑屏障的完整性[62], 再次提示激活的PVM介导了中枢的损伤.

2　小胶质细胞介导的神经炎症参与调控交感神经活性

高血压的发生发展有两个显著特征: 交感神经元兴奋性和神经炎症的升高[5,12,63]. 大约50%的原发性高血压患者观察到交感神经活性(sympathetic nerve activity, SNA)增强[64,65]. 此外, 在各种实验性高血压动物模型, 如血管紧张素(Angiotensin, Ang) II或醋酸脱氧皮质酮(deoxycorticosterone acetate, DOCA)盐诱导的高血压模型、自发性高血压模型(spontaneously hypertensive rats, SHR)和Goldbaltt两肾一夹(一侧肾动脉狭窄; 2 kidneys 1 clip, 2K1C)高血压模型中, 都发现了SNA显著性增加[24,66~70]. 大量证据表明, 与高血压密切相关的神经炎症可以导致交感张力增强[71,72]. 直接输注白介素(interleukin, IL)1β到前脑第三脑室上的穹窿下器(subfornical organ, SFO)区域可显著提高SNA和血压[73]. 同时在高血压动物模型中, 中枢给予抗炎药物(如IL-10或米诺环素)可抑制SNA和血压升高[72]. 因此, 神经炎症是导致SNA和高血压恶化的关键因素. 有趣的是, 有报道称巨噬细胞迁移抑制因子(macrophage migration inhibitory factor, MIF)是一种免疫调节介质, 在高血压中充当Ang II信号的负调节因子[45,74,75]. MIF通过自身巯基蛋白氧化还原酶活性对AT1受体产生拮抗作用, 清除活性氧(reactive oxygen species, ROS)[45]. 这项工作表明, 免疫介质对神经元活动有直接影响.

最近的研究表明, 小胶质细胞在神经炎症和血压调节中起着重要作用[73,76~80]. 在高血压期间, 小胶质细胞被高血压刺激物(如Ang II)激活[77], 并释放多种促炎因子(如 TNFα, IL-1β和IL-6)和抗炎因子(如IL-10)[79,81]. 另外, 抑制中枢Ang II信号可以减轻神经炎症[82,83], 恢复血压[84]. 活化的小胶质细胞在形态和表型上都发生变化[72,76]. 去除激活态小胶质细胞[79]或药理学抑制小胶质细胞激活[76]都能够缓解神经炎症和高血压进程. 这些观察结果有力地支持了小胶质细胞参与神经炎症和血压调节的观点. 另一个发现是, 小胶质细胞的激活导致神经元上谷氨酸受体的表达增加, 这表明激活的小胶质细胞可以调节神经元的可塑性[79]. 这些研究表明, 小胶质细胞激活状态的改变可能直接影响神经元的激活[85,86]. 研究发现, 静息态下小胶质细胞通过血小板衍生生长因子B(Platelet derived growth factor B, PDGFB)的旁分泌作用直接调控室旁核前交感神经元K^+通道蛋白Kv4.3的表达, 从而抑制前交感神经元过度兴奋[87]. 因此, 从静息态到激活态的转变是高血压进程中交感高张的关键.

如上所述, 在高血压形成后, 激活的小胶质细胞会促进神经炎症并加剧高血压[76,79]. 然而, 在稳定状态下, 小胶质细胞则处于类似于免疫抑制的状态[88]. 研究发现, TGFβ在中枢神经系统中呈组成性表达, 是小胶质细胞表型命运和中枢血压调节的决定因素[80]. 中枢TGFβ的缺乏会导致神经炎症加剧和高血压恶化. 通过侧脑室灌流外源性重组蛋白TGFβ可减少小胶质细

胞的激活, 并预防Ang II诱导的高血压. 此外, 利用小胶质细胞去除和过继转移策略发现, TGFβ通过抑制小胶质细胞激活来调节血压. 与本研究组的研究结果一致, 侧脑室注射TGFβ通过抑制小胶质细胞激活可以改善出血性卒中的恢复[89]; 靶向消除小胶质细胞上的TGFβ受体促进了静止小胶质细胞向炎症状态的快速分化[90]. 总之, 认为小胶质细胞诱导的神经炎症有助于高血压的发展, 而TGFβ作为一种关键的体内稳态因子, 通过调节小胶质细胞的激活来抑制高血压. 小胶质细胞上TGFβ受体的靶向缺失促进了静止小胶质细胞向炎症状态的快速分化. 目前尚不清楚, 在高血压状态下, 小胶质细胞如何参与调节前交感神经元, 如下丘脑室旁核(paraventricular nucleus, PVN)中的神经元. 小胶质细胞能否通过如其他神经元中所报道的直接作用(如突触修剪)或间接作用(如释放ROS或细胞因子)参与自主神经活动的调节, 还需要进一步探究[91,92].

除小胶质细胞外, 脑内PVMs也可能参与神经炎症和高血压的发展. 在心肌梗死动物模型中, 通过侧脑室给予氯膦酸盐脂质体(liposome clodronate)去除脑内PVM可减少TNFα引起的神经炎症, 并减轻肾SNA和血压升高[93]. 最近, Faraco等人[94]的研究报道, 由血源性Ang II激活的PVM通过上调Nox2增加ROS, 进而破坏血脑屏障(blood-brain barrier, BBB)的完整性, 导致认知功能障碍. 与之相呼应的另一项研究表明, 高血压导致BBB渗漏, 从而允许循环中的Ang II进入脑实质[95]. 因此, PVMs可以通过维持高血压患者血脑屏障的完整性参与神经元功能的调节, 这可能为高血压患者血脑屏障异常提供了一定的分子机制.

3 脾交感神经活性与免疫激活

去甲肾上腺素能交感神经纤维高度分布于免疫器官, 包括胸腺、脾脏、淋巴结和骨髓[96]. 脾脏是最大的淋巴器官, 参与调节免疫反应. 脾神经是传出交感神经, 起源于腹腔肠系膜丛; 后者来自交感神经节链[96]. 一直以来, α和β等肾上腺素能受体在多种免疫细胞(巨噬细胞、单核细胞、中性粒细胞和T细胞)上高表达. 长期以来的观点是, 自主神经(交感神经和迷走神经)激活会产生免疫抑制[97~100]. 例如, 肾上腺素能β2受体的激活抑制趋化因子受体介导的T淋巴细胞的迁移[100]. 交感神经激活诱导的免疫抑制在致死性炎症状态(如中风和败血症)具有保护作用[101,102]. 然而, 目前研究表明, 高血压患者的自主神经升高会加剧免疫激活. 例如, 侧脑室灌流Ang II诱导脾神经活动增加, 在mRNA水平上调了脾细胞的一系列促炎细胞因子[103]; 另一项研究表明, 交感神经激活引起的脾脏胎盘生长因子(placental growth factor, PlGF)增加导致T细胞激活并向主动脉和肾脏转移, 从而导致高血压的发生[104]. 值得注意的是, 来自同一课题组的其他研究表明, 副交感迷走神经促进了高血压患者交感驱动的免疫反应[105]. 另有研究通过针灸方式调控外周交感神经活性以调控对外周免疫状态, 并发现交感神经在正常以及LPS诱导的败血症中的作用是截然相反的[106,107]; 该结果在一定程度上解释了为何不同状态下机体对自主神经功能的响应不同. 此外有研究指出脑内的中央杏仁核以及下丘脑室旁核参与调控脾神经的输出, 调控脾内B细胞活性进而影响系统免疫[108], 解析了中枢调控外周免疫的环路机制.

这些关于自主神经活动对外周免疫反应影响的相互矛盾的观察结果可能反映了一个事实, 即与中风和败血症不同, 高血压是一种慢性低度炎症状态. Tracey的研究小组发现, 在中风时, 用内毒素或促炎细胞因子刺激迷走神经传入纤维, 可激活下丘脑-垂体-肾上腺抗炎反应[109]. 电刺激迷走神经抑制促炎细胞因子(如TNFα)的释放. 因此, 他们将神经免疫相互作用描述为以副交感神经活动的激活为中心的“炎症反射”[97]. 在高血压中, 由于血流动力学紊乱, 免疫系统轻度但持续暴露于应激组织(如内皮细胞)导致激活[5]. 据报道, 剪切应力增加会刺激红细胞和血管内皮细胞, 进而释放ATP[110]. 作为损伤相关分子模式(damage associated molecular patterns, DAMP)的一种分子, 增加的细胞外ATP通过嘌呤类受体激活抗原递呈细胞, 如单核细胞和树突状细胞[111~113], 从而激活高血压相关炎症事件, 并进一步推动高血压的发展. 在这种情况下, 自主神经系统通过何种神经回路或者血源性通路作出反应仍需进一步探索.

4 肾交感神经活动与免疫激活

作为交感神经支配的主要脏器之一, 肾脏也是高血压病损伤最主要的器官. 肾脏受损导致水盐潴留进一步加重高血压的进展. 肾交感神经直接靶向肾入球/

出球小动脉, 减少肾脏对水盐的清除率(降低肾小球滤过率和增加肾小管对原尿中水盐的重吸收), 达到水盐潴留的效果. 最近的研究表明, 肾交感的激活还有助于肾脏免疫活性[9]. 据报道, 肾交感神经消融术可阻断肾脏树突状细胞活化以及随后的T细胞浸润到肾脏和主动脉. 因此, 肾交感消融术可预防终末器官损伤和Ang II引起的高血压[9]. 研究发现, 高血压状态下血管细胞黏附分子(vascular cell adhesion molecule, VCAM)1作为抗原激活和招募免疫细胞[9], 而肾交感消融术后肾脏VCAM1的表达明显降低. 此外, 交感神经还能增强肾脏素-血管紧张素系统的活性. Giani团队[114]最近的研究表明, 肾脏中的血管紧张素转换酶(angiotensin converting enzyme, ACE)会加剧肾纤维化和炎症, 糖尿病肾病中ACE的催化N-结构域介导了肾纤维化和炎症[115]. 肾交感神经活动是否介导ACE的激活还有待进一步研究. 按时间顺序, 交感神经过度兴奋已被证明发生在高血压发病之前, 表明肾交感过度激活在整个高血压发展过程中持续存在[5].

5　交感神经活动和骨髓

大量证据表明, 包括单核细胞和树突状细胞在内的免疫细胞构成了高血压的免疫病因[10,116,117]. 值得注意的是, 这两种免疫细胞都来源于骨髓, 这促使骨髓成为高血压研究的热点之一. 骨髓主要受交感神经支配, 主要为肾上腺素能神经纤维[7]. 将血压正常的Wistar-Kyoto大鼠骨髓移植至SHR中可降低动脉血压、SNA和神经炎症[118]. 这一结果可能是通过正常化的外周免疫状态降低了中枢对小胶质细胞的激活和对SNA的兴奋作用, 表明中枢和外周免疫之间存在对话机制. 骨髓细胞高度表达肾上腺素能受体. 接受β1和β2缺失骨髓的嵌合小鼠基线血压较低, 体内和循环免疫细胞数量也有所减少[119], 这指示了交感神经系统和免疫系统之间的另一种直接相互作用. 同样, Zubcevic等人[120]发现, SHR骨髓中去甲肾上腺素水平升高, 表明骨髓交感神经输入的增加. SNA升高使骨髓和循环中的炎症细胞增多, 同时循环内皮祖细胞(endothelial progenitor cells, EPC)减少[120]. EPCs是血管内皮细胞的前体细胞, 在高血压中可替代受损的内皮细胞[110]. 该项研究表明, 交感神经传出过度会加剧炎症并损害血管修复. 相反, 通过药物阻断或基因敲除骨髓细胞中的肾上腺素能受体可抑制造血细胞的向外迁移[7,121]. 肾素-血管紧张素系统的过度激活可能是高血压的另一种机制. Kim等人[122]研究发现, Ang II对促进造血骨髓细胞的增殖、分化和排除有直接作用; 反之, 这些造血细胞则会加剧外周炎症和高血压进程. 未来需要进一步探究Ang II对免疫细胞的激活是直接作用还是通过交感神经介导的继发性作用. 另外, 交感神经输入对不同亚型骨髓细胞的作用是否存在差异也需要进一步的研究.

6　高血压中免疫和交感神经的相互作用

高血压本质上是一种血流动力学紊乱, 是心脏输出量增加和/或全身血管阻力增加的产物. 慢性血压升高引起的主要损害是血管纤维化和硬化[111]. 炎症细胞在这一过程起到了重要的作用. 炎症细胞在血管发病机制中的作用已通过观察得到进一步证明, 即在高血压诱导后, 缺乏T细胞或巨噬细胞的小鼠发生了更轻的主动脉纤维化[10,116]. 脑血管系统也是如此, 但并发症更多. 除了动脉硬化, 高血压还会导致BBB渗漏[94]. 有趣的是, 渗漏的BBB使血源性物质, 如纤维蛋白原和低密度脂蛋白, 进入脑实质并激活小胶质细胞[91,92]. 血管神经单元(neurovascular unit, NVU)是维持神经元正常生理功能的基本结构, 由血管内皮细胞、周细胞、星型角质细胞、小胶质细胞以及神经元组成[123]. 成年小鼠脑内30%的小胶质细胞贴服于毛细血管外壁[124]. 近期研究指出, 去除脑内的小胶质细胞或者阻断小胶质细胞上的$P2Y_{12}$受体极大地改变了脑血流[125,126], 说明小胶质细胞在调节NVU结构与功能方面发挥了重要的作用. 在高血压和衰老进程中, BBB渗漏、小胶质细胞激活和中枢血管系统损伤有很多相似之处, 这表明高血压和认知疾病中小胶质细胞/血管介导的功能障碍具有共同的途径. 高血压期间, 内皮细胞功能受损, 一氧化氮生成和再生能力降低[127]. 同时, 高血压增加了内皮细胞中黏附分子(如VCAM1的表达), 趋化外周免疫细胞进入脑实质[128]. 在老龄小鼠大脑中, 内皮细胞被激活的特征是在转录水平上上调与细胞黏附、炎症、应激反应和血管重构相关的基因, 这与高血压状态一致[129]. 老龄小鼠内皮细胞VCAM1升高诱导小胶质细胞活化, 阻断VCAM1可恢复小胶质细胞状态[129], 这暗示着大脑和外周免疫之间在脑血管单元存在潜在界面[129]. 如前所述, 高血压引起BBB渗漏[94],

从而导致血源性因子进入实质诱导小胶质细胞活化[130]. 活化的小胶质细胞通过释放ROS促进海马神经元树突和棘突的消除[92]. 在DOCA盐高血压模型中, 小胶质细胞在高血压发生前被募集到脑血管内皮周围[69]. 随后, 这些血管周围的小胶质细胞可能会破坏血管的完整性[131,132], 进一步加剧了小胶质细胞的激活.

在高血压早期抑制中枢免疫激活可获得显著的降压反应, 这是通过抑制交感张力实现的[133,134]. 后者会加重外周炎症, 加速高血压的发展. 在高血压状态下, 血源性信号或脑源性局部线索可能诱发小胶质细胞的激活. 激活的小胶质细胞调节下丘脑和脑干核团(如下丘脑室旁核、头端腹侧延髓、孤束核)的自主神经活动. 交感神经和/或副交感神经的改变支配免疫器官/组织、血管系统和肾脏从而导致高血压症状, 如炎症、血管收缩和肾功能不全. 高血压引起的全身形性炎症可进一步刺激中枢神经系统的小胶质细胞, 增强交感输出, 从而加重高血压. 因此, 抑制肾交感(如肾交感消融术)而非抗炎在顽固性高血压的治疗中取得了多次成功[9]. 为了打破这种恶性循环, 靶向小胶质细胞等交感神经调节因子将是一个潜在的治疗窗口[135]. 通过检测小胶质细胞状态, 可以维持血脑屏障的完整性, 恢复自主神经活动, 从而降低交感神经传出活动和血压.

7 结论

本综述重点介绍了神经-免疫交互途径. 在该途径中, 高血压诱导的神经炎症增加交感神经活动, 从而驱动脾、肾或骨髓神经激活, 并调节周围免疫反应, 从而加剧高血压. 中枢和外周免疫系统都参与了炎症状态, 而自主神经系统尤其是交感神经系统共同协调了高血压发生发展中的所有器官. 为了打破高血压-炎症这一恶性循环, 未来的研究可能会探索自主神经活动在高血压中的调节机制.

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参考文献

1 Lewington S, Lacey B, Clarke R, et al. The burden of hypertension and associated risk for cardiovascular mortality in China. JAMA Intern Med, 2016, 176: 524–532
2 Lu J, Lu Y, Wang X, et al. Prevalence, awareness, treatment, and control of hypertension in China: data from 1.7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet, 2017, 390: 2549–2558
3 Xie X, He T, Kang J, et al. Cost-effectiveness analysis of intensive hypertension control in China. Prev Med, 2018, 111: 110–114
4 Fisher J P, Paton J F R. The sympathetic nervous system and blood pressure in humans: implications for hypertension. J Hum Hypertens, 2012, 26: 463–475
5 Oliveira-Sales E B, Colombari E, Abdala A P, et al. Sympathetic overactivity occurs before hypertension in the two-kidney, one-clip model. Exp Physiol, 2016, 101: 67–80
6 Azizi M, Schmieder R E, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet, 2018, 391: 2335–2345
7 Katayama Y, Battista M, Kao W M, et al. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. Cell, 2006, 124: 407–421
8 Nance D M, Sanders V M. Autonomic innervation and regulation of the immune system (1987–2007). Brain Behav Immun, 2007, 21: 736–745
9 Xiao L, Kirabo A, Wu J, et al. Renal denervation prevents immune cell activation and renal inflammation in angiotensin II-induced hypertension. Circ Res, 2015, 117: 547–557
10 Guzik T J, Hoch N E, Brown K A, et al. Role of the T cell in the genesis of angiotensin II-induced hypertension and vascular dysfunction. J Exp Med, 2007, 204: 2449–2460
11 Shah K H, Shi P, Giani J F, et al. Myeloid suppressor cells accumulate and regulate blood pressure in hypertension. Circ Res, 2015, 117: 858–

869
12 Shi P, Raizada M K, Sumners C. Brain cytokines as neuromodulators in cardiovascular control. Clin Exp Pharmacol Physiol, 2010, 37: e52–e57
13 Kang Y M, Wang Y, Yang L M, et al. TNF-α in hypothalamic paraventricular nucleus contributes to sympathoexcitation in heart failure by modulating AT1 receptor and neurotransmitters. Tohoku J Exp Med, 2010, 222: 251–263
14 Aguzzi A, Barres B A, Bennett M L. Microglia: scapegoat, saboteur, or something else? Science, 2013, 339: 156–161
15 Salter M W, Stevens B. Microglia emerge as central players in brain disease. Nat Med, 2017, 23: 1018–1027
16 Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. Annu Rev Immunol, 2017, 35: 441–468
17 Norris G T, Kipnis J. Immune cells and CNS physiology: microglia and beyond. J Exp Med, 2019, 216: 60–70
18 Wolf S A, Boddeke H W G M, Kettenmann H. Microglia in physiology and disease. Annu Rev Physiol, 2017, 79: 619–643
19 Ginhoux F, Greter M, Leboeuf M, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science, 2010, 330: 841–845
20 Huang Y, Xu Z, Xiong S, et al. Repopulated microglia are solely derived from the proliferation of residual microglia after acute depletion. Nat Neurosci, 2018, 21: 530–540
21 Lund H, Pieber M, Parsa R, et al. Competitive repopulation of an empty microglial niche yields functionally distinct subsets of microglia-like cells. Nat Commun, 2018, 9: 4845
22 Wang Y, Szretter K J, Vermi W, et al. IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia. Nat Immunol, 2012, 13: 753–760
23 Elmore M R P, Najafi A R, Koike M A, et al. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. Neuron, 2014, 82: 380–397
24 Barbosa R M, Speretta G F, Dias D P M, et al. Increased expression of macrophage migration inhibitory factor in the nucleus of the solitary tract attenuates renovascular hypertension in rats. Am J Hypertension, 2017, 30: 435–443
25 Li Q, Cheng Z, Zhou L, et al. Developmental heterogeneity of microglia and brain myeloid cells revealed by deep single-cell RNA sequencing. Neuron, 2019, 101: 207–223.e10
26 Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. Cell, 2017, 169: 1276–1290.e17
27 Bessis A, Béchade C, Bernard D, et al. Microglial control of neuronal death and synaptic properties. Glia, 2007, 55: 233–238
28 Marın-Teva J L, Dusart I, Colin C, et al. Microglia promote the death of developing Purkinje cells. Neuron, 2004, 41: 535–547
29 Ashwell K. Microglia and cell death in the developing mouse cerebellum. Dev Brain Res, 1990, 55: 219–230
30 Marın-Teva J L, Cuadros M A, Calvente R, et al. Naturally occurring cell death and migration of microglial precursors in the quail retina during normal development. J Comp Neurol, 1999, 412: 255–275
31 Squarzoni P, Oller G, Hoeffel G, et al. Microglia modulate wiring of the embryonic forebrain. Cell Rep, 2014, 8: 1271–1279
32 Askew K, Li K, Olmos-Alonso A, et al. Coupled proliferation and apoptosis maintain the rapid turnover of microglia in the adult brain. Cell Rep, 2017, 18: 391–405
33 Hua J Y, Smith S J. Neural activity and the dynamics of central nervous system development. Nat Neurosci, 2004, 7: 327–332
34 Lawson L J, Perry V H, Dri P, et al. Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. Neuroscience, 1990, 39: 151–170
35 Olah M, Biber K, Vinet J, et al. Microglia phenotype diversity. CNS Neurol Disord Drug Targets, 2011, 10: 108–118
36 De Biase L M, Schuebel K E, Fusfeld Z H, et al. Local cues establish and maintain region-specific phenotypes of basal ganglia microglia. Neuron, 2017, 95: 341–356.e6
37 Grabert K, Michoel T, Karavolos M H, et al. Microglial brain region-dependent diversity and selective regional sensitivities to aging. Nat Neurosci, 2016, 19: 504–516
38 Yang T T, Lin C, Hsu C T, et al. Differential distribution and activation of microglia in the brain of male C57BL/6J mice. Brain Struct Funct, 2013, 218: 1051–1060
39 de Haas A H, Boddeke H W G M, Biber K. Region-specific expression of immunoregulatory proteins on microglia in the healthy CNS. Glia, 2008, 56: 888–894

40 Fietz S A, Kelava I, Vogt J, et al. OSVZ progenitors of human and ferret neocortex are epithelial-like and expand by integrin signaling. Nat Neurosci, 2010, 13: 690–699

41 Martínez-Cerdeño V, Cunningham C L, Camacho J, et al. Comparative analysis of the subventricular zone in rat, ferret and macaque: evidence for an outer subventricular zone in rodents. PLoS ONE, 2012, 7: e30178

42 Krasemann S, Madore C, Cialic R, et al. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity, 2017, 47: 566–581.e9

43 Kang S S, Ebbert M T W, Baker K E, et al. Microglial translational profiling reveals a convergent APOE pathway from aging, amyloid, and tau. J Exp Med, 2018, 215: 2235–2245

44 Pribiag H, Stellwagen D. Neuroimmune regulation of homeostatic synaptic plasticity. Neuropharmacology, 2014, 78: 13–22

45 Freiria-Oliveira A H, Blanch G T, Li H, et al. Macrophage migration inhibitory factor in the nucleus of solitary tract decreases blood pressure in SHRs. Cardiovasc Res, 2013, 97: 153–160

46 Hu L, Zhang S, Wen H, et al. Melatonin decreases M1 polarization via attenuating mitochondrial oxidative damage depending on UCP2 pathway in prorenin-treated microglia. PLoS ONE, 2019, 14: e0212138

47 Zhang Y, Chen K, Sloan S A, et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci, 2014, 34: 11929–11947

48 Gyoneva S, Traynelis S F. Norepinephrine modulates the motility of resting and activated microglia via different adrenergic receptors. J Biol Chem, 2013, 288: 15291–15302

49 Stowell R D, Sipe G O, Dawes R P, et al. Noradrenergic signaling in the wakeful state inhibits microglial surveillance and synaptic plasticity in the mouse visual cortex. Nat Neurosci, 2019, 22: 1782–1792

50 Liu Y U, Ying Y, Li Y, et al. Neuronal network activity controls microglial process surveillance in awake mice via norepinephrine signaling. Nat Neurosci, 2019, 22: 1771–1781

51 Favuzzi E, Huang S, Saldi G A, et al. GABA-receptive microglia selectively sculpt developing inhibitory circuits. Cell, 2021, 184: 4048–4063. e32

52 Haynes S E, Hollopeter G, Yang G, et al. The P2Y12 receptor regulates microglial activation by extracellular nucleotides. Nat Neurosci, 2006, 9: 1512–1519

53 Merlini M, Rafalski V A, Ma K, et al. Microglial Gi-dependent dynamics regulate brain network hyperexcitability. Nat Neurosci, 2021, 24: 19–23

54 Badimon A, Strasburger H J, Ayata P, et al. Negative feedback control of neuronal activity by microglia. Nature, 2020, 586: 417–423

55 Lapenna A, De Palma M, Lewis C E. Perivascular macrophages in health and disease. Nat Rev Immunol, 2018, 18: 689–702

56 Prokop S, Miller K R, Drost N, et al. Impact of peripheral myeloid cells on amyloid-β pathology in Alzheimer's disease-like mice. J Exp Med, 2015, 212: 1811–1818

57 Bruttger J, Karram K, Wörtge S, et al. Genetic cell ablation reveals clusters of local self-renewing microglia in the mammalian central nervous system. Immunity, 2015, 43: 92–106

58 Varvel N H, Grathwohl S A, Baumann F, et al. Microglial repopulation model reveals a robust homeostatic process for replacing CNS myeloid cells. Proc Natl Acad Sci USA, 2012, 109: 18150–18155

59 Cronk J C, Filiano A J, Louveau A, et al. Peripherally derived macrophages can engraft the brain independent of irradiation and maintain an identity distinct from microglia. J Exp Med, 2018, 215: 1627–1647

60 Lund H, Pieber M, Parsa R, et al. Fatal demyelinating disease is induced by monocyte-derived macrophages in the absence of TGF-β signaling. Nat Immunol, 2018, 19: 1–7

61 Park L, Uekawa K, Garcia-Bonilla L, et al. Brain perivascular macrophages initiate the neurovascular dysfunction of Alzheimer Aβ peptides. Circ Res, 2017, 121: 258–269

62 Santisteban M M, Ahn S J, Lane D, et al. Endothelium-macrophage crosstalk mediates blood-brain barrier dysfunction in hypertension. Hypertension, 2020, 76: 795–807

63 Kopp U C. Neural Control of Renal Function. San Rafael (CA): Morgan & Claypool Life Sciences, 2011

64 Esler M. The sympathetic nervous system through the ages: from Thomas Willis to resistant hypertension. Exp Physiol, 2011, 96: 611–622

65 Esler M, Kaye D. Sympathetic nervous system activation in essential hypertension, cardiac failure and psychosomatic heart disease. J

Cardiovasc Pharmacol, 2000, 35: S1–S7
66 Judy W V, Watanabe A M, Henry D P, et al. Sympathetic nerve activity: role in regulation of blood pressure in the spontaenously hypertensive rat.. Circ Res, 1976, 38: 21–29
67 Mong J A, Devidze N, Frail D E, et al. Estradiol differentially regulates lipocalin-type prostaglandin D synthase transcript levels in the rodent brain: evidence from high-density oligonucleotide arrays and *in situ* hybridization. Proc Natl Acad Sci USA, 2003, 100: 318–323
68 Kandlikar S S, Fink G D. Splanchnic sympathetic nerves in the development of mild DOCA-salt hypertension. Am J Physiol-Heart Circ Physiol, 2011, 301: H1965–H1973
69 Koizumi T, Taguchi K, Mizuta I, et al. Transiently proliferating perivascular microglia harbor M1 type and precede cerebrovascular changes in a chronic hypertension model. J Neuroinflammation, 2019, 16: 79
70 Melo M R, Gasparini S, Speretta G F, et al. Importance of the commissural nucleus of the solitary tract in renovascular hypertension. Hypertens Res, 2019, 42: 587–597
71 Masson G S, Nair A R, Silva Soares P P, et al. Aerobic training normalizes autonomic dysfunction, HMGB1 content, microglia activation and inflammation in hypothalamic paraventricular nucleus of SHR. Am J Physiol-Heart Circ Physiol, 2015, 309: H1115–H1122
72 Shi P, Diez-Freire C, Jun J Y, et al. Brain microglial cytokines in neurogenic hypertension. Hypertension, 2010, 56: 297–303
73 Wei S G, Yu Y, Zhang Z H, et al. Proinflammatory cytokines upregulate sympathoexcitatory mechanisms in the subfornical organ of the rat. Hypertension, 2015, 65: 1126–1133
74 Sun C, Li H, Gao Y, et al. Lack of macrophage migration inhibitory factor regulation is linked to the increased chronotropic action of angiotensin II in SHR neurons. Hypertension, 2007, 49: 528–534
75 Li H, Gao Y, Qi Y, et al. Macrophage migration inhibitory factor in hypothalamic paraventricular nucleus neurons decreases blood pressure in spontaneously hypertensive rats. FASEB J, 2008, 22: 3175–3185
76 Sharma R K, Yang T, Oliveira A C, et al. Microglial cells impact gut microbiota and gut pathology in Angiotensin II-induced hypertension. Circ Res, 2019, 124: 727–736
77 Biancardi V C, Stranahan A M, Krause E G, et al. Cross talk between AT1 receptors and Toll-like receptor 4 in microglia contributes to angiotensin II-derived ROS production in the hypothalamic paraventricular nucleus. Am J Physiol-Heart Circ Physiol, 2016, 310: H404–H415
78 Yu Y, Xue B J, Wei S G, et al. Activation of central PPAR-γ attenuates Angiotensin II-induced hypertension. Hypertension, 2015, 66: 403–411
79 Shen X Z, Li Y, Li L, et al. Microglia participate in neurogenic regulation of hypertension. Hypertension, 2015, 66: 309–316
80 Li Y, Shen X Z, Li L, et al. Brain transforming growth factor-β resists hypertension via regulating microglial activation. Stroke, 2017, 48: 2557–2564
81 Krishnan S M, Sobey C G, Latz E, et al. IL-1β and IL-18: inflammatory markers or mediators of hypertension? Br J Pharmacol, 2014, 171: 5589–5602
82 Liu M, Shi P, Sumners C. Direct anti-inflammatory effects of angiotensin-(1-7) on microglia. J Neurochem, 2016, 136: 163–171
83 Yu Y, Wei S G, Weiss R M, et al. Angiotensin II Type 1a receptors in the subfornical organ modulate neuroinflammation in the hypothalamic paraventricular nucleus in heart failure rats. Neuroscience, 2018, 381: 46–58
84 Kang Y M, Ma Y, Zheng J P, et al. Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. Cardiovasc Res, 2009, 82: 503–512
85 Kettenmann H, Kirchhoff F, Verkhratsky A. Microglia: new roles for the synaptic stripper. Neuron, 2013, 77: 10–18
86 Schafer D P, Lehrman E K, Kautzman A G, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron, 2012, 74: 691–705
87 Bi Q, Wang C, Cheng G, et al. Microglia-derived PDGFB promotes neuronal potassium currents to suppress basal sympathetic tonicity and limit hypertension. Immunity, 2022, 55: 1466–1482.e9
88 Hanisch U K, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci, 2007, 10: 1387–1394
89 Taylor R A, Chang C F, Goods B A, et al. TGF-β1 modulates microglial phenotype and promotes recovery after intracerebral hemorrhage. J Clin Invest, 2017, 127: 280–292
90 Buttgereit A, Lelios I, Yu X, et al. Sall1 is a transcriptional regulator defining microglia identity and function. Nat Immunol, 2016, 17: 1397–1406

91 Paolicelli R C, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. Science, 2011, 333: 1456–1458

92 Merlini M, Rafalski V A, Rios Coronado P E, et al. Fibrinogen induces microglia-mediated spine elimination and cognitive impairment in an Alzheimer's disease model. Neuron, 2019, 101: 1099–1108.e6

93 Yu Y, Zhang Z H, Wei S G, et al. Brain perivascular macrophages and the sympathetic response to inflammation in rats after myocardial infarction. Hypertension, 2010, 55: 652–659

94 Faraco G, Sugiyama Y, Lane D, et al. Perivascular macrophages mediate the neurovascular and cognitive dysfunction associated with hypertension. J Clin Invest, 2016, 126: 4674–4689

95 Biancardi V C, Son S J, Ahmadi S, et al. Circulating angiotensin II gains access to the hypothalamus and brain stem during hypertension via breakdown of the blood-brain barrier. Hypertension, 2014, 63: 572–579

96 Romano T A, Felten S Y, Olschowka J A, et al. Noradrenergic and peptidergic innervation of lymphoid organs in the beluga, *Delphinapterus leucas*: an anatomical link between the nervous and immune systems. J Morphol, 1994, 221: 243–259

97 Pavlov V A, Tracey K J. Neural regulation of immunity: molecular mechanisms and clinical translation. Nat Neurosci, 2017, 20: 156–166

98 Sternberg E M. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol, 2006, 6: 318–328

99 Marino F, Cosentino M. Adrenergic modulation of immune cells: an update. Amino Acids, 2013, 45: 55–71

100 Nakai A, Hayano Y, Furuta F, et al. Control of lymphocyte egress from lymph nodes through β2-adrenergic receptors. J Exp Med, 2014, 211: 2583–2598

101 Winklewski P J, Radkowski M, Demkow U. Cross-talk between the inflammatory response, sympathetic activation and pulmonary infection in the ischemic stroke. J Neuroinflammation, 2014, 11: 213

102 Sanfilippo F, Santonocito C, Morelli A, et al. Beta-blocker use in severe sepsis and septic shock: a systematic review. Curr Med Res Opin, 2015, 31: 1817–1825

103 Ganta C K, Lu N, Helwig B G, et al. Central angiotensin II-enhanced splenic cytokine gene expression is mediated by the sympathetic nervous system. Am J Physiol-Heart Circ Physiol, 2005, 289: H1683–H1691

104 Carnevale D, Pallante F, Fardella V, et al. The angiogenic factor PlGF mediates a neuroimmune interaction in the spleen to allow the onset of hypertension. Immunity, 2014, 41: 737–752

105 Carnevale D, Perrotta M, Pallante F, et al. A cholinergic-sympathetic pathway primes immunity in hypertension and mediates brain-to-spleen communication. Nat Commun, 2016, 7: 13035

106 Liu S, Wang Z F, Su Y S, et al. Somatotopic organization and intensity dependence in driving distinct NPY-expressing sympathetic pathways by electroacupuncture. Neuron, 2020, 108: 436–450.e7

107 Liu S, Wang Z, Su Y, et al. A neuroanatomical basis for electroacupuncture to drive the vagal-adrenal axis. Nature, 2021, 598: 641–645

108 Zhang X, Lei B, Yuan Y, et al. Brain control of humoral immune responses amenable to behavioural modulation. Nature, 2020, 581: 204–208

109 Hosoi T, Okuma Y, Matsuda T, et al. Novel pathway for LPS-induced afferent vagus nerve activation: possible role of nodose ganglion. Autonomic Neurosci, 2005, 120: 104–107

110 Luo S, Xia W, Chen C, et al. Endothelial progenitor cells and hypertension: current concepts and future implications. Clin Sci, 2016, 130: 2029–2042

111 Cipolla M J, Liebeskind D S, Chan S L. The importance of comorbidities in ischemic stroke: impact of hypertension on the cerebral circulation. J Cereb Blood Flow Metab, 2018, 38: 2129–2149

112 Muller M, van der Graaf Y, Visseren F L, et al. Hypertension and longitudinal changes in cerebral blood flow: the SMART-MR study. Ann Neurol, 2012, 71: 825–833

113 Zhao T V, Li Y, Liu X, et al. ATP release drives heightened immune responses associated with hypertension. Sci Immunol, 2019, 4: eaau6426

114 Eriguchi M, Lin M, Yamashita M, et al. Renal tubular ACE-mediated tubular injury is the major contributor to microalbuminuria in early diabetic nephropathy. Am J Physiol-Renal Physiol, 2018, 314: F531–F542

115 Eriguchi M, Bernstein E A, Veiras L C, et al. The absence of the ACE N-domain decreases renal inflammation and facilitates sodium excretion during diabetic kidney disease. J Am Soc Nephrol, 2018, 29: 2546–2561

116 Wenzel P, Knorr M, Kossmann S, et al. Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular

dysfunction. Circulation, 2011, 124: 1370–1381
117 Kirabo A, Fontana V, de Faria A P C, et al. DC isoketal-modified proteins activate T cells and promote hypertension. J Clin Invest, 2014, 124: 4642–4656
118 Santisteban M M, Ahmari N, Carvajal J M, et al. Involvement of bone marrow cells and neuroinflammation in hypertension. Circ Res, 2015, 117: 178–191
119 Ahmari N, Schmidt J T, Krane G A, et al. Loss of bone marrow adrenergic β 1 and 2 receptors modifies transcriptional networks, reduces circulating inflammatory factors, and regulates blood pressure. Physiol Genomics, 2016, 48: 526–536
120 Zubcevic J, Jun J Y, Kim S, et al. Altered inflammatory response is associated with an impaired autonomic input to the bone marrow in the spontaneously hypertensive rat. Hypertension, 2014, 63: 542–550
121 Moll N M, Ransohoff R M. CXCL12 and CXCR4 in bone marrow physiology. Expert Rev Hematol, 2010, 3: 315–322
122 Kim S, Zingler M, Harrison J K, et al. Angiotensin II regulation of proliferation, differentiation, and engraftment of hematopoietic stem cells. Hypertension, 2016, 67: 574–584
123 McConnell H L, Kersch C N, Woltjer R L, et al. The translational significance of the neurovascular unit. J Biol Chem, 2017, 292: 762–770
124 Mondo E, Becker S C, Kautzman A G, et al. A developmental analysis of juxtavascular microglia dynamics and interactions with the vasculature. J Neurosci, 2020, 40: 6503–6521
125 Császár E, Lénárt N, Cserép C, et al. Microglia modulate blood flow, neurovascular coupling, and hypoperfusion via purinergic actions. J Exp Med, 2022, 219: e20211071
126 Bisht K, Okojie K A, Sharma K, et al. Capillary-associated microglia regulate vascular structure and function through PANX1-P2RY12 coupling in mice. Nat Commun, 2021, 12: 5289
127 Perenin M T, Jeannerod M. Residual vision in cortically blind hemiphields. Neuropsychologia, 1975, 13: 1–7
128 Tummala P E, Chen X L, Sundell C L, et al. Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature. Circulation, 1999, 100: 1223–1229
129 Yousef H, Czupalla C J, Lee D, et al. Aged blood impairs hippocampal neural precursor activity and activates microglia via brain endothelial cell VCAM1. Nat Med, 2019, 25: 988–1000
130 Stewart C R, Stuart L M, Wilkinson K, et al. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. Nat Immunol, 2010, 11: 155–161
131 Jolivel V, Bicker F, Binamé F, et al. Perivascular microglia promote blood vessel disintegration in the ischemic penumbra. Acta Neuropathol, 2015, 129: 279–295
132 Chen A Q, Fang Z, Chen X L, et al. Microglia-derived TNF-α mediates endothelial necroptosis aggravating blood brain-barrier disruption after ischemic stroke. Cell Death Dis, 2019, 10: 487
133 Zubcevic J, Richards E M, Yang T, et al. Impaired autonomic nervous system-microbiome circuit in hypertension. Circ Res, 2019, 125: 104–116
134 Wenzel U, Turner J E, Krebs C, et al. Immune mechanisms in arterial hypertension. J Am Soc Nephrol, 2016, 27: 677–686
135 Yang T, Richards E M, Pepine C J, et al. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol, 2018, 14: 442–456

Microglia contribute to the autonomic function and participate in neurogenic hypertension: non-immune function of central immune cells

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Hypertension is also called silent killer, which attacks over 30% of adult population in the world. Studies have shown that immune activation is highly involved in the whole process of hypertension and is closely associated with end-organ damage. In addition to the immune system, the autonomic nervous system, especially the sympathetic nervous system, is one of the most conservative systems that maintain homeostasis in the body. The simulation in both immune and sympathetic nervous activity in the hypertensive suggests a synergistic role of these two systems in the progression of this disease. Microglia are the main immune cells in the central nervous system and are involved in the regulation of sympathetic tension. Previous studies have shown that the loss of microglia in mouse models alters the course of neuroinflammation and hypertension. This review summarizes the progress in the development and function of microglia in both homeostasis and disease. On this basis, the interaction between autonomic nervous system and peripheral immunity in hypertension was reviewed. Microglia bridge central and peripheral inflammation in hypertension by regulating sympathetic nerve activity, providing a new therapeutic perspective for hypertension and related cardiovascular diseases in the future.

hypertension, microglia, sympathetic nervous system, immunity

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