doi: 10.3978/j.issn.2095-6959.2020.05.034
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2020.05.034

·综述·

小胶质细胞活化抑制与中枢炎症反应关系的研究进展

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[摘 要] 近年来，小胶质细胞活化成为中枢神经系统疾病的研究热点，其活化导致的中枢神经系统炎症反应对帕金森病、阿尔茨海默病、脊髓损伤及脑损伤等许多神经系统疾病的发生、发展都有重要的影响。随着局部微环境的改变，小胶质细胞的表型及功能会发生不同的变化，从而产生促进或抑制炎症的效果，对疾病产生相应的影响。抑制小胶质细胞的活化从而改善中枢神经系统炎症反应是治疗上述多种疾病的重要研究方向。

[关键词] 小胶质细胞；活化；抑制；神经系统炎症

Research progress in the relations between inhibition mechanisms of microglia activiation and neuroinflammation

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Abstract In recent years, it has been found that the inflammation of central nervous system caused by microglia activation has an important impact on the occurrence and development of many nervous system diseases, such as Parkinson's disease, Alzheimer's disease, spinal cord injury and brain injury. With the change of local microenvironment, the phenotype and function of microglia will change differently, which can promote or inhibit inflammation and have corresponding effects on diseases. Inhibiting the activation of microglia and improving the inflammatory response of central nervous system is an important research direction in the treatment of these diseases.

Keywords microglia; activation; inhibition; central nervous system; inflammatory response

小胶质细胞(microglia，MG)是中枢神经系统(central nervous system，CNS)内固有的免疫细胞，在CNS的生理、病理过程中发挥极其重要的作用。任何原因引起的神经系统内环境紊乱都可激活MG及炎症反应。MG的过度激活及其活化后导致的神经炎症反应是许多神经系统疾病发生的关键。

1 小胶质细胞

CNS主要由2种细胞组成：神经元细胞和胶质细胞，胶质细胞又分为少突胶质细胞、星形胶质细胞和MG。MG是免疫活性细胞，充当着神经病理传感器和CNS损伤的第一道防线。

收稿日期 (Date of reception)：2019–05–27
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1.1 MG 的活化

MG激活的定义最初主要是基于其形态学的变化。正常脑组织中，MG呈高度分枝状，具有三级和四级分枝结构，且细胞间的分枝很少发生重叠，此时的MG为静息状态。当脑组织因或内或外的因素受到损伤、产生炎症或感染时，MG迅速被激活，激活的MG胞体增大、突起变短、细胞形态呈圆形或杆状，最终细胞突起消失、细胞形态呈阿米巴状，即活化状态。

1.2 活化后 MG 的分型及功能

活化后的MG主要分为M1型和M2型。M1型MG高表达主要组织相容性复合体II(major histocompatibility complex，MHCII)，CD86，CD80，CD11b，CD16和CD32等；M2型MG则高表达Arg1，CD206，血红素氧合酶(heme oxygenase-1，HO-1)和胰岛素样生长因子1(insulin like growth factor 1，IGF-1)等。M1型MG通过分泌肿瘤坏死因子(tumor necrosis factor α，TNF-α)，白细胞介素-12(interluekin-12，IL-12)和白细胞介素-23(interluekin-23，IL-23)以及各种趋化因子和炎症因子，来清除病原体、肿瘤细胞和损伤来发挥免疫效应，但过多的释放炎症介质如一氧化氮(NO)、氧自由基等也会引起神经毒性，损伤正常神经细胞，加重神经损伤[1]。M2型MG可分泌大量转化生长因子β(transforming growth factor β，TGF-β)、白细胞介素-10(interluekin-10，IL-10)等细胞因子，及一些神经营养因子如神经生长因子(nerve growth factor，NGF)及胶质细胞源性神经营养因子(glial cell derived neurotrophic factor，GDNF)等促进损伤神经的修复与再生[2]，从而减轻或抑制炎症反应。

2 神经炎症反应

中枢神经炎症是由于MG的活化和细胞因子及炎症介质的释放所产生的[3]。正常生理状态下，MG因神经元细胞分泌抑制因子而处于静息状态；在损伤或疾病期间，如颅脑损伤、脊髓损伤、病原体感染、蛋白质沉积等，出现促炎性刺激时，MG被激活并产生细胞因子和趋化因子，并将血液源性免疫细胞招募到CNS，从而导致CNS炎症反应的放大。然而，由于促炎细胞因子和神经毒素的过度释放，M1型MG过度激活，产生过量的细胞因子及趋化因子，可诱导神经毒性[4-6]，损坏神经元细胞，甚至导致其死亡，从而加重CNS炎症。

2.1 MG 活化与神经炎症反应密切相关

如帕金森病(Parkinson's disease，PD)，其临床特点是黑质致密部的中脑多巴胺能(dopaminergic，DA)神经元的进行性变性[7]。受损或死亡的中脑DA神经元可直接诱导MG的活化，增加活性氧(reactive oxygen，ROS)和促炎细胞因子的产生[8]，而这些促炎因子又会进一步导致中脑DA神经元凋亡或死亡，加重神经损伤。脊髓损伤(traumatic spinal cord injury，SCI)除因车祸、高空坠落等原因造成的脊髓神经结构的原发性损伤外，还有脊髓损伤后被大量激活的MG[9]产生的炎症介质所导致的继发性神经损伤。同时SCI产生的分泌因子(如细胞因子)，能结合细胞表面受体进一步激活MG并使其参与细胞信号通路，从而放大炎症并加重继发性损伤[10]。阿尔茨海默病(Alzheimer disease，AD)以β-淀粉样蛋白(Aβ)斑块和神经纤维原缠结为主要病理表现。Aβ沉积能激活MG，释放炎症介质并清除Aβ斑块。但是免疫反应的长期激活会降低MG结合和吞噬Aβ的效率，并导致MG介导的Aβ降解酶活性降低，进而导致MG分解Aβ斑块的能力降低[11-12]。然而，MG产生促炎细胞因子的能力并不受影响[13]。以上说明MG作为CNS的固有免疫细胞，在调节神经炎症的过程中起着重要作用[14-15]。

2.2 MG 活化与神经元损伤

急性损伤后，MG激活，产生促炎及抗炎因子，清除、修复损伤。持续的刺激导致M1过度激活，促炎因子、趋化因子过度释放，引起神经元功能紊乱、损伤，甚至神经元丢失[16]。研究[17]发现：AD，PD及青光眼中均有神经元细胞的损伤及丢失。SCI模型中[18-19]，损伤激活MG释放炎症因子，加重神经炎症反应，炎症反应包围损伤区域导致神经元死亡。Gushchina等[20]也发现：集落刺激因子-1(colony-stimulating factor-1，CSF1)高表达于急、慢性实验自身免疫性脑炎(experimental autoimmune encephalomyelitis，EAE)模型中，激活MG，促进其增殖，激活后的MG释放促炎因子、趋化因子，最终导致运动神经元损伤、丢失。

近年来研究发现除MG外，单核细胞激活及浸润[21]、基质金属蛋白表达[22]、表观遗传因素[23]、MicrRNAs[24]亦与神经炎症反应有关。

3 MG 活化与中枢炎症反应的调控

3.1 MG 活化抑制与中枢炎症反应

中枢炎症反应是由于MG活化及炎症因子释

放所致，那么抑制MG过度活化及减轻细胞因子、炎症介质的释放就能够减轻中枢系统的炎症反应，从而保护神经元。研究[25]发现在线粒体通透性转化孔诱导的小鼠PD模型中，CD200抑制了MG的活化，同时还抑制了三磷酸腺苷(adenosine triphosphate，ATP)和促炎因子释放，减轻了神经炎症，从而保护DA神经元。Wang等[26]报道丹酚酸B能够抑制MG的激活，降低NO，TNF-α，IL-1β和ROS等的释放，在改善CNS疾病的症状和病理的同时，伴有明显的促神经发生的作用，从而改善抑郁症状。Yu等[27]在使用异丙酚治疗大鼠暂时性大脑中动脉闭塞/再灌注模型的研究中证实，异丙酚能通过A2B受体抑制MG的异常增殖，降低白细胞介素-6(interluekin-6，IL-6)，IL-1β，TNF-α和NO的表达水平，从而减轻脑梗死后的炎性损伤。上述研究结果均能证明通过各种方法抑制MG的活化，确实能够改善神经炎症反应，从而达到缓解或治疗多种神经系统疾病的效果。

3.2 MG 活化及炎症介质释放相关信号通路

近年来随着对MG越来越深入的研究，科学家们发现了许多与MG活化相关的信号通路。研究[28]报道：脂多糖(lipopolysaccharide，LPS)诱导活化的MG大量表达Notch1，Notch2，配体Jagged1和下游靶基因Hes-1。核因子κB(nuclear factor kappa-B，NF-κB)和两面神激酶/信号转导及转录激活因子(Janus kinase/signal transducers and activators of transcription，JAK/STAT)信号通路也是MG激活常见通路。Xiong等[29]发现Aβ诱导的MG活化能够增强JAK2和STAT3的磷酸化，黄芩苷预处理BV-2MG后，JAK2和STAT3的磷酸化显著降低，CD11b的表达及IL-6, TNF-α和NO的生成也减少了。Weng等[30]在使用蛇葡萄素预处理LPS诱导的MG后发现，蛇葡萄素通过抑制NF-κB和JAK2/STAT3信号通路的激活，从而减轻LPS有道德MG的炎症反应。Alhadidi等[31]在敲除丝切蛋白基因后发现：NF-κB和JAK/STAT信号通路被抑制，从而抑制了LPS诱导的MG活化。Lee等[32]发现大蒜素抑制CXCL12/CXCR4轴的激活与Toll样受体4(Toll-like receptor 4，TLR4)相关拮抗反应有关，并能阻断NF-κB信号通路，从而抑制LPS诱导的MG的炎症反应。

除Nocth，NF-κB和JAK/STAT信号通路外，磷脂酰肌醇3激酶/蛋白激酶B(PI3K/AKt)、丝裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)信号通路也被发现与MG激活有关。Dang等[33]发现：粉防己碱预处理过的MG，在LPS诱导激活后，可以通过调节NF-kB和细胞外调节蛋白激酶(extracellular regulated protein kinases，ERK)信号通路抑制MG的激活，有效地抑制IL-1β和TNF-α的表达。Kinsella等[34]发现胶质细胞和巨噬细胞中若缺乏BH3相关域死亡激动剂(BH3-interacting domain death agonist，BID)，能够抑制TLR3和TLR4激活时传向NF-κB，MAPK的信号，从而减少炎症介质释放发挥抗炎作用。Zhao等[35]发现岩藻黄素通过阻断AKt/NF-κB和MAPK信号通路，减少IL-6，TNF-α，NO，ROS，前列腺素E2(dinoprostone E2，PGE_2)的生成，从而抑制LPS诱导的MG炎症反应。以上研究结果说明Notch，NF-κB，MAPK，JAK/STAT，PI3K/AKt等信号通路均可作为抑制MG过度活化及炎症介质释放的靶点。

4 结语

MG在神经炎症反应中发挥重要作用。在AD，PD，青光眼及SCI等疾病中过度激活的MG产生过量的促炎因子等造成神经元细胞不可逆的损伤。如何抑制M1型MG激活，而不影响M2型的修复及神经保护作用，如何抑制过多的促炎因子、细胞毒性因子的释放，减少神经元的损伤是治疗CNS疾病的研究热点和方向。作者认为，抑制MG激活并不是完全抑制其活性，而是通过抑制M1型的过度激活，达到调节M1/M2平衡的作用，从而使MG的激活向改善神经炎症的方向发展，保护神经元不受损坏。但MG激活以及M1，M2型转化的相关机制仍有待进一步深入研究，以期为治疗CNS疾病提供更好的方法。

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本文引用：邓佳丽, 丁维俊. 小胶质细胞活化抑制与中枢炎症反应关系的研究进展[J]. 临床与病理杂志, 2020, 40(5): 1286-1290. doi: 10.3978/j.issn.2095-6959.2020.05.034

Cite this article as: DENG Jiali, DING Weijun. Research progress in the relations between inhibition mechanisms of microglia activiation and neuroinflammation[J]. Journal of Clinical and Pathological Research, 2020, 40(5): 1286-1290. doi: 10.3978/j.issn.2095-6959.2020.05.034