

· 综述 ·

## 巨噬细胞极化在神经系统疾病中的作用及药物研究进展

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**[摘要]** 神经系统疾病一直是医学领域的重大挑战, 近年来, 巨噬细胞极化在其中的作用备受关注。巨噬细胞具有不同的极化状态, 包括M1型和M2型, 它们在神经系统疾病的发生发展中发挥着关键作用。在神经炎症中, M1型巨噬细胞可能加剧损伤, 而M2型巨噬细胞则有助于组织修复和神经再生。研究发现, 巨噬细胞极化失衡与多种神经系统疾病如阿尔茨海默病、多发性硬化、创伤性脑损伤等密切相关。针对这一现象, 药物研究取得了一定进展, 新型药物旨在调节巨噬细胞的极化状态, 以减轻炎症反应、促进神经修复。一些药物通过抑制特定信号通路来实现对巨噬细胞极化的调控, 另一些则通过靶向细胞因子或受体发挥作用。然而, 目前的研究仍存在诸多挑战, 如药物的安全性和有效性、作用机制的复杂性等。文章总结了不同微环境信号刺激下巨噬细胞的不同极化表型及其主要功能, 并重点介绍了巨噬细胞极化在神经系统疾病中的作用以及以巨噬细胞极化为靶点的临床疾病治疗策略, 为神经系统疾病的治疗带来新的希望。

**[关键词]** 巨噬细胞; 极化; 阿尔茨海默病; 多发性硬化; 创伤性脑损伤

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## The role of macrophage polarization in nervous system diseases and drug research progress

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**[Abstract]** Neurological diseases have always been a major challenge in the field of medicine, and the role of macrophage polarization in them has attracted much attention in recent years. Macrophages have different polarization states, including M1 type and M2 type, which play a key role in the occurrence and development of neurological diseases. In neuroinflammation, M1-type macrophages may exacerbate damage, while M2-type macrophages contribute to tissue repair and nerve regeneration. Studies have found that the imbalance of macrophage polarization is closely correlated with a variety of neurological diseases, such as Alzheimer's disease, multiple sclerosis, and traumatic brain injury. In response to this phenomenon, some progress has been made in drug research, and new drugs are designed to regulate the polarization of macrophages to reduce inflammation and promote nerve repair. Some drugs regulate the polarization of macrophages by inhibiting specific signaling pathways, while others work by targeting cytokines or receptors. However, there are still many challenges in the current research, such as the safety and effectiveness of the drug, and the complexity of the mechanisms. This paper summarizes the different polarization phenotypes and main functions of macrophages stimulated by different microenvironmental signals, and focuses on the role of macrophage polarization in nervous system diseases as well as clinical disease treatment strategies targeting macrophage polarization, which will bring new hope for the treatment of nervous system diseases.

**[Key words]** macrophages; polarization; Alzheimer's disease; multiple sclerosis; traumatic brain injury

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巨噬细胞参与先天性和适应性免疫反应且在伤口修复和组织重建中发挥重要作用,其功能包括杀死入侵的病原体、处理和传递抗原、引发炎症、分泌细胞因子和其他炎症介质等<sup>[1]</sup>。研究表明,在各种细胞因子的刺激下,巨噬细胞可分化为两种类型,表现出不同的功能:M1型巨噬细胞通常与炎症和免疫应答相关,而M2型巨噬细胞则与组织修复、抗炎和免疫调节相关<sup>[2]</sup>。巨噬细胞极化在炎症、免疫应答、组织修复等过程中发挥着重要作用。神经损伤可能导致感觉、运动、认知和自主神经功能等方面的异常,严重影响患者的生活质量,多项研究报告,巨噬细胞极化与神经系统疾病密切相关<sup>[3]</sup>。因此,了解巨噬细胞极化在神经系统疾病中的作用,可为神经系统疾病的治疗提供新的视角。

## 1 巨噬细胞概述

巨噬细胞源自单核细胞,是机体免疫的重要组成部分,参与免疫防御的多个方面,包括特异性和非特异性免疫应答,也作为关键的辅助细胞在创伤愈合过程中发挥作用<sup>[4]</sup>。巨噬细胞具有较强的可塑性,表型受体内微环境的影响而改变,发挥不同功能,即巨噬细胞极化<sup>[5]</sup>。根据表型和分泌细胞因子的差异可将巨噬细胞分为经典活化的巨噬细胞(M1型)和替代活化的巨噬细胞(M2型),M1和M2之间可相互转化,发挥不同的生物学功能<sup>[6]</sup>。

### 1.1 M1型巨噬细胞的作用

M1型巨噬细胞受干扰素(interferon, IFN)- $\gamma$ 、细菌脂多糖(lipopolysaccharide, LPS)和粒细胞-巨噬细胞集落刺激因子(granulocyte macrophage colony-stimulating factor, GM-CSF)等诱导<sup>[7]</sup>,分泌促炎细胞因子,增强杀菌和抗肿瘤活性,调节并促进Th1反应。表征上,M1型巨噬细胞不仅高水平表达MHC II、CD68、CD80和CD86等标志物,还上调细胞因子信号转导抑制因子(suppressors of cytokine signaling 3, SOCS3)以及激活诱导型一氧化氮合成酶(inducible nitric oxide synthase, iNOS)产生NO这一促炎介质<sup>[8]</sup>。M1极化受多种因素调节。一个由转录因子和翻译后调控因子组成的网络参与了M1极化,典型的干扰素调节因子(interferon regulatory factor, IRF)/STAT信号通路被IFN和Toll样受体(Toll like receptor, TLR)信号激活,促使巨噬细胞通过STAT1向M1表型转变<sup>[9]</sup>。Ower等<sup>[10]</sup>发现,M1巨噬细胞上调IRF5,这对于诱导白介素(interleukin, IL)-12、IL-23和肿瘤坏死因子(tumor necrosis factor, TNF)以及Th1和Th17反

应至关重要,LPS/TLR4通路也通过激活STAT1- $\alpha/\beta$ ,在M1极化中发挥作用。其他参与M1表型状态诱导的分子包括G蛋白偶联受体,通过一氧化氮合成酶2(nitric oxide synthase 2, NOS2)诱导NO、SOCS3,激活NF- $\kappa$ B/PI3K途径产生NO和生长分化因子,促进M1标志物表达<sup>[11]</sup>。

### 1.2 M2型巨噬细胞的作用

M2型巨噬细胞通常被认为是抗炎型巨噬细胞,其分泌的细胞因子,如IL-10、转化生长因子(transforming growth factor, TGF)- $\beta$ 等,有助于维持免疫平衡和减轻过度炎症反应,同时分泌多种生长因子和细胞因子,如表皮生长因子(epidermal growth factor, EGF)、碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)和血管生成素(angiopoietin, Ang)等,有助于刺激细胞增殖、促进血管生成和组织修复<sup>[12]</sup>。M2巨噬细胞被分为不同的亚型,包括M2a、M2b、M2c和M2d<sup>[1]</sup>,其中M2a最为常见,由IL-4或IL-13诱导产生<sup>[1,13]</sup>。IL-4极大地刺激甘露糖受体的表达,其被认为是M2a的典型标志物。CD206和精氨酸酶表达增高,内吞能力增强,在寄生虫免疫反应、变态反应、伤口愈合和组织重构中发挥重要作用。M2b由LPS和抗卵白蛋白(ovalbumin, OVA) IgG/OVA免疫复合物(immune complex, IC)或抗绵羊红细胞IgG/红细胞IC诱导,IC由Fc $\gamma$ 受体家族(CD64、CD32、CD16a和CD16b)识别<sup>[14]</sup>。CD32似乎对巨噬细胞的M2型激活至关重要<sup>[15]</sup>。在LPS激活的巨噬细胞上连接Fc $\gamma$ 受体,除了上调抗原提呈和促进Th2应答外,还可减少IL-12并诱导IL-10分泌。Fc受体信号通路涉及酪氨酸激酶(Syk)和PI3K的激活<sup>[16]</sup>。M2c型巨噬细胞又称失活型巨噬细胞,由糖皮质激素、IL-10和TGF- $\beta$ 诱导。失活是指巨噬细胞在M1激活后,在体外触发M2的激活,从而使M1样基因的转录失活<sup>[17]</sup>。活性糖皮质激素具有亲脂性,通过膜扩散结合糖皮质激素受体- $\alpha$ ,引发复合物核内迁移,直接与DNA结合以调控基因转录,或者通过与转录因子(如NF- $\kappa$ B或AP1)相互作用来间接调节基因转录<sup>[2]</sup>。糖皮质激素诱导的失活巨噬细胞上调C1QA、TSC22结构域家族、MRC1、IL-1R2和CD163的表达<sup>[18]</sup>,使细胞黏附、扩散、吞噬和凋亡功能受到影响。腺苷与TLR4、TLR2、TLR7和TLR9激动剂协同作用,可以将巨噬细胞转换为M2d样表型<sup>[2]</sup>。TNF- $\alpha$ 、IL-12等炎症因子在腺苷信号下表达受到抑制,而血管内皮生长因子和IL-10的表达却升高。Wang等<sup>[19]</sup>发现Fos相关抗原-1通过结合

RAW264.7细胞中IL-6启动子,上调IL-6的表达,从而促进RAW264.7细胞与4T1细胞共培养的M2d分化。

## 2 巨噬细胞极化与神经系统疾病

巨噬细胞在机体免疫调节、组织修复和新陈代谢方面起着重要作用。对巨噬细胞极化机制的研究,有助于深入了解阿尔茨海默病(Alzheimer's disease, AD)、多发性硬化(multiple sclerosis, MS)、创伤性脑损伤(traumatic brain injury, TBI)等神经系统疾病的免疫调节过程,为新型免疫治疗策略的开发提供理论基础。疾病组织中巨噬细胞的极化方向可以通过药物来调节,研究巨噬细胞极化的调节机制也有助于此类药物的研发。

### 2.1 巨噬细胞极化在AD中的作用

AD是一种主要表现为进行性认知功能障碍的神经退行性疾病,是老年期痴呆的最常见原因之一。研究表明,AD患者体内总体巨噬细胞百分比增加<sup>[20]</sup>,而M2b巨噬细胞亚群减少,M1巨噬细胞亚群增加<sup>[21]</sup>。M2b巨噬细胞亚群减少与认知能力下降相关,这是导致AD神经炎症病变的原因<sup>[22]</sup>。AD患者M1巨噬细胞亚群的增加表明AD患者的促炎症反应增强,这与AD病理中的神经炎症反应一致。M2a增加吞噬作用,产生生长因子,清除细胞碎片,促进组织修复。M2b与AD脑小胶质细胞中CD32和CD64的表达增加有关。M2c可由抗炎细胞因子IL-10或糖皮质激素诱导,并增加TGF- $\beta$ 在大脑中的表达,M1降低淀粉样蛋白负荷,但加剧神经元纤维缠结病变<sup>[23]</sup>。相反,M2a增加淀粉样蛋白负荷,并在一定程度上改善AD早期和晚期的神经元纤维病变情况。在AD早期,标志物偏向于两种表型之一,即M1或M2a。然而,M1、M2a和M2c的标志物在AD晚期升高。M1和M2(M2b除外)共同作用,调节AD所有阶段的神经炎症反应。M2b亚群在散发性AD中很少出现,但在AD唐氏综合征患者中升高,并与认知能力相关<sup>[24-25]</sup>。M2b亚群受小胶质细胞IC和TLR刺激的刺激<sup>[26]</sup>,通过TLR2途径刺激小胶质细胞诱导IFN- $\beta$ 表达,这可能促进寡聚物A $\beta$ 的分泌。

### 2.2 巨噬细胞极化在MS中的作用

MS是一种自身免疫性疾病,其特征是慢性炎症,脱髓鞘,以及轴突和神经元损失<sup>[27]</sup>。巨噬细胞极化参与了MS的发生发展。MS初期阶段,巨噬细胞在IFN- $\gamma$ 、IL-12作用下极化为M1型,释放TNF- $\alpha$ 等炎性细胞因子,引发中枢神经系统损伤。M1型巨噬细胞中CD86、CD40以及MHC II呈高表达状态<sup>[28-29]</sup>,

并可激活T细胞分化迁移,这种现象可以通过iNOS抑制剂得以缓解,从而减少了T细胞的招募并促进了神经再生<sup>[30]</sup>。因此,使用iNOS抑制剂可能对缓解神经系统中的髓鞘损伤和脱髓鞘现象有潜在疗效,有利于神经修复。在恢复期,IL-4和IL-13诱导巨噬细胞极化为M2型,使炎症得到控制,且促进髓鞘修复<sup>[31]</sup>。M2型巨噬细胞分泌相关因子,如IL-10、TGF- $\beta$ 等因子协同Th2和Treg细胞抑制炎症的进展<sup>[32-33]</sup>。

### 2.3 巨噬细胞极化在TBI中的作用

不同极化的巨噬细胞群体在包括TBI在内的主要中枢神经系统疾病中已被证实具有双重作用<sup>[34]</sup>。研究证实,脑损伤后同时激活了M1型和M2型巨噬细胞,但其作用时长不一样,M1样效应在脑损伤后持续很长一段时间,而M2样反应的活性则逐渐下降<sup>[34]</sup>。调节M1、M2极化平衡已被证明对机体功能恢复有益。然而,TBI中巨噬细胞极化的分子机制尚不完全清楚。值得注意的是,TBI后的神经炎症反应非常复杂,不能仅通过M1/M2细胞极化去解释<sup>[35]</sup>。例如,研究者在控制性皮质冲击小鼠脑损伤模型中发现,损伤后多个时间点,邻近同侧病灶周围皮质组织的活化巨噬细胞同时表达“M1”和“M2”表型标志物<sup>[36]</sup>。在中枢神经系统损伤和疾病期间,这些细胞不是切换到极化的“M1”或“M2”表型,而是形成复杂和混合表型的反应。脑损伤后,这些细胞的极化反应表现出复杂多样和相互交织的特点,促炎、抗炎以及组织修复同时发生。

### 2.4 巨噬细胞极化在其他神经系统疾病中的作用

帕金森病(Parkinson's disease, PD)是第2常见的神经退行性疾病,且发病率不断上升。研究表明,在PD早期阶段,巨噬细胞M2极化后分泌抗炎细胞因子来减轻炎症反应,促进组织愈合和修复<sup>[37-38]</sup>。随着病情进展,长时间的刺激以及聚集的 $\alpha$ -Syn可以直接激发巨噬细胞向M1型转变,加重运动障碍并严重损害相邻神经元<sup>[39]</sup>。此外,癫痫是一种常见的慢性神经系统疾病,其特点是反复发生无端发作。强有力的证据表明,癫痫与神经炎症有关,促炎细胞因子可以调节与癫痫发生相关的神经元兴奋性和神经病理结果<sup>[39]</sup>。研究表明,M1型巨噬细胞在颞叶癫痫患者和动物模型的大脑中高表达,兴奋性神经传递促进神经元的兴奋性增加,影响配体门控和电压门控离子通道,导致兴奋性/抑制性神经信号传递的不平衡,有利于癫痫发作并促进癫痫发生<sup>[40]</sup>。

### 3 药物研究进展

巨噬细胞在不同环境中可以分化为M1型和M2型,对调控神经系统疾病具有重要作用。M1型具有促炎作用,可能会加剧疾病严重程度;而M2型则能够抑制炎症反应,促进神经系统的修复和恢复。因此,通过调控巨噬细胞的类型和数量,可为神经系统疾病的治疗提供重要靶点和途径。这一发现为疾病治疗提供了新的方向,也为未来的研究和临床实践提供参考。为此,文章总结了已证实可影响M1型或M2型巨噬细胞分化的不同类型药物(表1)。

### 4 总结与展望

综上所述,巨噬细胞作为免疫系统的重要组成部分,在神经系统疾病发生发展中扮演着重要角色。极化后的抗炎型巨噬细胞不仅能清除炎症介质和废弃物质,还可以促进组织修复和再生,进而有助于减轻机体炎症反应,使组织免受进一步损害,减缓炎症性疾病的进展。深入研究巨噬细胞极化调

控及其在疾病进展中的动态变化机制,有助于开发新型疾病治疗策略,提高治疗效果。未来,需要更深入地探究巨噬细胞极化的详细机制,以精准调控其极化状态,充分阐明如何通过巨噬细胞极化来改善神经系统疾病的预后;同时开发更具特异性和高效性的药物,降低不良反应;此外,还需开展大规模临床试验,验证药物的实际效果和安全性。随着研究的不断深入,巨噬细胞极化相关药物的研究有望取得更大突破,为神经系统疾病的诊疗提供新思路和方法。

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陈伟凯撰写论文初稿,使用软件,并修改论文;唐金荣设计研究思路,撰写、审阅和修改论文。

**Author's Contributions:**

CHEN Weikai wrote the initial draft of the manuscript, used software, and revised the manuscript; TANG Jinrong de-

表1 药物通过调控巨噬细胞极化治疗神经系统疾病的机制

Figure 1 The mechanism of drugs treating neurological diseases by regulating macrophage polarization

Therapeutic drugs	Target of action	Mechanism	Reference
Carnosol	IL-1, IL-6, iNOS, NF-κB, COX-2, IL-17, Rorc, Irf4, and Batf	Inhibiting NF-κB and STAT3 phosphorylation, blocking Th17 differentiation and NF-κB nuclear translocation, reducing the infiltration of inflammatory cells into the central nervous system, and alleviating demyelination	[41]
Antibiotic mixture (ampicillin, metronidazole, neomycin sulfate, and vancomycin)	CCR1/CCL7, CCR7, CCR8, CXCL12(SDF-1α), CD4 <sup>+</sup> FoxP3 <sup>+</sup> , CXCL13, Arg1, and TNFα	Regulating chemokines and their receptor expression associated with regulatory Th cells (CD4 <sup>+</sup> and FoxP3 <sup>+</sup> )	[42]
Lenalidomide	CD4 <sup>+</sup> , IL-10, STAT3, Tyr1, and Arg1	Promoting the expression and secretion of IL10, subsequently phosphorylating STAT3 Tyr1, and inducing the formation of M2 macrophages	[43]
Forskolin	Arg1, Mrc1, Fizz1, Ym1, CD86, NO, CD4 <sup>+</sup> , and Cyclic AMP	Synergistically activating the ERK pathway with IL-4 to promote M2 polarization	[44]
Ivermectin	CD4 <sup>+</sup> , CD8 <sup>+</sup> , iNOS, MRC1 <sup>+</sup> , and Ca <sup>2+</sup>	Enhancing P2X4R signaling through the allosteric regulator ivermectin, facilitating the transition of microglia cells to an anti-inflammatory phenotype, enhancing myelin phagocytosis	[45]
Myeloid epithelial reproductive tyrosine kinase	CD16, CD32, iNOS, IL-10, and STAT1	Activating the signal transducer and activator of transcription 1 (STAT1)/cytokine signal transducer repressor 1/3 (SOCS1/3) pathway, significantly reducing M2-like polarization of microglia/macrophages while increasing M1-like polarization by inhibiting Mer	[46]

signed the research, wrote, reviewed, and revised the manuscript.

[参考文献]

- [1] LIU L Y, STOKES J V, TAN W, et al. An optimized flow cytometry panel for classifying macrophage polarization[J]. *J Immunol Meth*, 2022, 511: 113378
- [2] HUANG X, LI Y, FU M G, et al. Polarizing macrophages *in vitro*[J]. *Methods Mol Biol*, 2018, 1784: 119-126
- [3] DONNINELLI G, SARAF-SINIK I, MAZZIOTTI V, et al. Interleukin-9 regulates macrophage activation in the progressive multiple sclerosis brain [J]. *J Neuroinflammation*, 2020, 17(1): 149
- [4] ROSS E A, DEVITT A, JOHNSON J R. Macrophages: the good, the bad, and the gluttony[J]. *Front Immunol*, 2021, 12: 708186
- [5] YUNNA C, MENGRU H, LEI W, et al. Macrophage M1/M2 polarization[J]. *Eur J Pharmacol*, 2020, 877: 173090
- [6] ANDERS C B, LAWTON T M W, AMMONS M C B. Metabolic immunomodulation of macrophage functional plasticity in nonhealing wounds [J]. *Curr Opin Infect Dis*, 2019, 32(3): 204-209
- [7] LIN Y H, WANG Y H, PENG Y J, et al. Interleukin 26 skews macrophage polarization towards M1 phenotype by activating c-Jun and the NF- $\kappa$ B pathway[J]. *Cells*, 2020, 9(4): 938
- [8] WANG F F, RAO D C, JIN S Y, et al. The effect of osthole on lipopolysaccharide-induced macrophages polarization and inflammatory reaction [J]. *Shanghai J Stomatol*, 2022, 31(3): 255-259
- [9] CARTY M, KEARNEY J, SHANAHAN K A, et al. Cell survival and cytokine release after inflammasome activation is regulated by the toll-IL-1R protein SARM[J]. *Immunity*, 2019, 50(6): 1412-1424
- [10] OWEN A M, LUAN L M, BURELBACH K R, et al. MyD88-dependent signaling drives toll-like receptor-induced trained immunity in macrophages [J]. *Front Immunol*, 2022, 13: 1044662
- [11] LYU Q K, VELDHUIZEN E J A, LUDWIG I S, et al. Characterization of polarization states of canine monocyte derived macrophages[J]. *PLoS One*, 2023, 18(11): e0292757
- [12] 王旭蒲. 重组 TRAIL 在肿瘤微环境中的免疫调节作用和机制研究[D]. 长春: 吉林大学, 2023  
WANG P X. Immunomodulatory effects and mechanisms of recombinant TRAIL in the tumor microenvironment[D]. Changchun: Jilin University, 2023
- [13] LEE J Y, WONG C Y, KOH R Y, et al. Natural bioactive compounds from macroalgae and microalgae for the treatment of Alzheimer's disease: a review[J]. 2024, 97(2): 205-224
- [14] WANG L X, ZHANG S X, WU H J, et al. M2b macrophage polarization and its roles in diseases[J]. *J Leukoc Biol*, 2019, 106(2): 345-358
- [15] HU S J, XU J M, WU M D, et al. Exploration of the mechanism of reinfusion of fresh autologous blood in type 2 diabetes mice to induce macrophage polarization and inhibit erythrocyte damage[J]. *J Diabetes Investig*, 2024, 15(1): 70-77
- [16] XIA T T, ZHANG M, LEI W, et al. Advances in the role of STAT3 in macrophage polarization[J]. *Front Immunol*, 2023, 14: 1160719
- [17] DING L, FU W J, DI H Y, et al. Expression of long non-coding RNAs in complete transection spinal cord injury: a transcriptomic analysis [J]. *Neural Regen Res*, 2020, 15(8): 1560-1567
- [18] NAKAMURA R, BING R J, GARTLING G J, et al. Glucocorticoid dose dependency on gene expression in vocal fold fibroblasts and macrophages [J]. *Laryngoscope*, 2023, 133(5): 1169-1175
- [19] WANG Q S, NI H, LAN L, et al. Fra-1 protooncogene regulates IL-6 expression in macrophages and promotes the generation of M2d macrophages [J]. *Cell Res*, 2010, 20(6): 701-712
- [20] 王玉银, 魏文悦, 郭敏芳, 等. 补肾益智抗衰方通过调节小胶质细胞和巨噬细胞的极化转变改善 APP/PS1 小鼠认知功能[J]. *中国组织工程研究*, 2022, 26(26): 4166-4172  
WANG Y Y, WEI W Y, GUO M F, et al. Bushen Yizhi Anti-aging prescription improves cognitive function of APP/PS1 mice by regulating microglia and macrophage polarization [J]. *Chin J Tissue Eng Res*, 2022, 26(26): 4166-4172
- [21] HSIEH S W, HUANG L C, CHANG Y P, et al. M2b macrophage subset decrement as an indicator of cognitive function in Alzheimer's disease[J]. *Psychiatry Clin Neurosci*, 2020, 74(7): 383-391
- [22] TWAROWSKI B, HERBET M. Inflammatory processes in Alzheimer's disease - pathomechanism, diagnosis and treatment: a review[J]. *Int J Mol Sci*, 2023, 24(7): 6518
- [23] DEVANNEY N A, STEWART A N, GENSEL J C. Microglia and macrophage metabolism in CNS injury and disease: the role of immunometabolism in neurodegeneration and neurotrauma[J]. *Exp Neurol*, 2020, 329: 113310
- [24] WILCOCK D M, HURBAN J, HELMAN A M, et al. Down syndrome individuals with Alzheimer's disease have a distinct neuroinflammatory phenotype compared to sporadic Alzheimer's disease[J]. *Neurobiol Aging*, 2015, 36(9): 2468-2474
- [25] BELLENGUEZ C, KÜÇÜKALI F, JANSEN I E, et al. New insights into the genetic etiology of Alzheimer's disease

- and related dementias[J]. *Nat Genet*, 2022, 54(4): 412–436
- [26] KANG N N, LIANG X, FAN B X, et al. Endothelial-specific molecule 1 inhibition lessens productive angiogenesis and tumor metastasis to overcome bevacizumab resistance[J]. *Cancers*, 2022, 14(22): 5681
- [27] TRAVERS B S, TSANG B K T, BARTON J L. Multiple sclerosis: diagnosis, disease-modifying therapy and prognosis[J]. *Aust J Gen Pract*, 2022, 51(4): 199–206
- [28] CHEN Y Q, WANG S N, SHI Y J, et al. CRID3, a blocker of apoptosis associated speck like protein containing a card, ameliorates murine spinal cord injury by improving local immune microenvironment [J]. *J Neuroinflammation*, 2020, 17(1): 255
- [29] MANTOVANI A, SICA A, SOZZANI S, et al. The chemokine system in diverse forms of macrophage activation and polarization [J]. *Trends Immunol*, 2004, 25(12): 677–686
- [30] SKOTLAND T, HESSVIK N P, SANDVIG K, et al. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology [J]. *J Lipid Res*, 2019, 60(1): 9–18
- [31] SHECHTER R, MILLER O, YOVEL G, et al. Recruitment of beneficial M2 macrophages to injured spinal cord is orchestrated by remote brain choroid plexus[J]. *Immunity*, 2013, 38(3): 555–569
- [32] LI T, PENG M Z, YANG Z Z, et al. 3D-printed IFN- $\gamma$ -loading calcium silicate- $\beta$ -tricalcium phosphate scaffold sequentially activates M1 and M2 polarization of macrophages to promote vascularization of tissue engineering bone[J]. *Acta Biomater*, 2018, 71: 96–107
- [33] YAO A H, LIU F F, CHEN K, et al. Programmed death 1 deficiency induces the polarization of macrophages/microglia to the M1 phenotype after spinal cord injury in mice[J]. *Neurotherapeutics*, 2014, 11(3): 636–650
- [34] KUMAR A, ALVAREZ-CRODA D M, STOICA B A, et al. Microglial/macrophage polarization dynamics following traumatic brain injury[J]. *J Neurotrauma*, 2016, 33(19): 1732–1750
- [35] GAN Z S, WANG Q Q, LI J H, et al. Iron reduces M1 macrophage polarization in RAW<sub>264.7</sub> macrophages associated with inhibition of STAT1 [J]. *Mediators Inflamm*, 2017, 2017: 8570818
- [36] PANTANO F, BERTI P, GUIDA F M, et al. The role of macrophages polarization in predicting prognosis of radically resected gastric cancer patients[J]. *J Cell Mol Med*, 2013, 17(11): 1415–1421
- [37] DU R H, SUN H B, HU Z L, et al. Kir6.1/K-ATP channel modulates microglia phenotypes: implication in Parkinson's disease[J]. *Cell Death Dis*, 2018, 9(3): 404
- [38] TANG Y, LE W D. Differential roles of M1 and M2 microglia in neurodegenerative diseases[J]. *Mol Neurobiol*, 2016, 53(2): 1181–1194
- [39] SONG G J, SUK K. Pharmacological modulation of functional phenotypes of microglia in neurodegenerative diseases[J]. *Front Aging Neurosci*, 2017, 9: 139
- [40] VEZZANI A, VIVIANI B. Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability[J]. *Neuropharmacology*, 2015, 96(Pt A): 70–82
- [41] LI X, ZHAO L, HAN J J, et al. Carnosol modulates Th17 cell differentiation and microglial switch in experimental autoimmune encephalomyelitis[J]. *Front Immunol*, 2018, 9: 1807
- [42] SEIFERT H A, BENEDEK G, NGUYEN H, et al. Antibiotics protect against EAE by increasing regulatory and anti-inflammatory cells [J]. *Metab Brain Dis*, 2018, 33(5): 1599–1607
- [43] WENG Q J, WANG J Y, WANG J J, et al. Lenalidomide regulates CNS autoimmunity by promoting M2 macrophages polarization[J]. *Cell Death Dis*, 2018, 9(2): 251
- [44] VEREMEYKO T, YUNG A W Y, DUKHINOVA M, et al. Cyclic AMP pathway suppress autoimmune neuroinflammation by inhibiting functions of encephalitogenic CD4 T cells and enhancing M2 macrophage polarization at the site of inflammation[J]. *Front Immunol*, 2018, 9: 50
- [45] ZABALA A, VAZQUEZ-VILLOLDO N, RISSIEK B, et al. P2X4 receptor controls microglia activation and favors remyelination in autoimmune encephalitis [J]. *EMBO Mol Med*, 2018, 10(8): e8743
- [46] WU H J, ZHENG J W, XU S B, et al. Mer regulates microglial/macrophage M1/M2 polarization and alleviates neuroinflammation following traumatic brain injury [J]. *J Neuroinflammation*, 2021, 18(1): 2

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