

小胶质细胞极化及重编程在脑缺血再灌注损伤中的研究进展

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[摘要] 小胶质细胞(MG)是脑组织中重要的、固有先天性免疫细胞,可发挥吞噬病原体、杀伤靶细胞、抗原提呈、免疫调节、抗炎修复、促进神经元存活等功能。脑缺血再灌注损伤(CIRI)是继发于缺血性脑卒中后血管血流再通引起的严重脑血管疾病。在CIRI早期,过度激活的M1型MG可导致炎症风暴和血脑屏障破坏等损伤,而后期M2型极化对于组织抗炎、功能修复则起着至关重要的作用。但MG及其重编程在CIRI中的相关干预治疗机制尚未明确。本文综述基于MG表型调控的CIRI潜在治疗策略,即MG通过吞噬功能及抗炎修复作用参与缓解CIRI;通过代谢重编程及极化为M2表型后,其抗炎、抗氧化应激及促再生能力显著增强;通过清除细胞碎片、抑制神经炎症及促进组织重塑改善预后,以期MG治疗CIRI的深入研究提供参考。

[关键词] 脑缺血再灌注损伤;巨噬细胞;小胶质细胞;小胶质细胞极化;代谢重编程

Research advances on microglia polarization and reprogramming in cerebral ischemia-reperfusion injury

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[Abstract] Microglia (MG) is an important and inherently innate immune cell in brain tissue. It can play the roles of phagocytosis of pathogens, killing of target cells, antigen presentation, immunomodulation, anti-inflammatory repair, and promotion of neuronal survival, etc. Cerebral ischemia-reperfusion injury (CIRI) is a severe cerebrovascular disease caused by vascular blood flow recanalization secondary to ischemic stroke. In the early stage of CIRI, over-activated M1-type MGs lead to injuries such as inflammatory storm and blood-brain barrier disruption, and in the later stage, M2-type polarization plays a crucial role in anti-inflammatory and functional repair of tissues. However, the interventional therapeutic mechanisms associated with MG and its reprogramming in CIRI have not been clarified. The aim of this paper is to review the potential therapeutic strategies of CIRI based on MG phenotypic regulation, i.e., MG is involved in alleviating CIRI through phagocytosis and anti-inflammatory and repairing effects, and its anti-inflammatory, anti-oxidative stress, and pro-regenerative abilities are significantly enhanced by metabolic reprogramming and polarization to M2 phenotype, which improves the prognosis by removing cellular debris, inhibiting neuroinflammation, and promoting tissue remodeling, and provides a reference for the in-depth research on MG therapy for CIRI.

[Key words] cerebral ischemia-reperfusion injury; macrophages; microglia; microglia polarization; metabolic reprogramming

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缺血性脑卒中是一种急性脑血管疾病,是由于脑部血液供应中断而引起脑组织损伤的疾病,具有高发病率、高致死率、高致残率、高复发率等特点。根据《中国脑卒中防治报告(2023)》,我国脑卒中每年新发约250万例,发病人群呈年轻化,40~50岁人群的发病率逐年上升;总死亡率约150/10万,而缺血性脑卒中占全部脑卒中的70%~80%;而根据2024年美国心脏协会(American Heart Association, AHA)的统计数据显示,美国每年约有79.5万例新发或复发脑卒中,其中87%为缺血性脑卒中(约69.2万例)^[1]。脑缺血再灌注损伤(cerebral ischemia-reperfusion injury, CIRI)是继发于缺血性脑卒中后血管血流再通引起的严重脑血管疾病,其发生和发展可直接导致脑组织及其功能的继续损害,引起严重的继发神经功能障碍^[2],对患者的身心健康和生活质量构成严重威胁。如何减轻再灌注损伤引起的损害及其对患者的影响仍是亟待解决的难题。小胶质细胞(MG)作为中枢神经系统(CNS)的常驻巨噬细胞,在CIRI中扮演着复杂且动态变化的角色。本文综述了MG表型调控对CIRI发生发展的影响,并总结靶向MG表型与代谢干预的关键信号通路及相关调节因子,以期对CIRI的临床治疗提供更多靶点。

1 CIRI的病理机制

CIRI的发生发展涉及诸多病理生理机制。缺血再灌注后,细胞内钙超载,氧化应激及自由基风暴,中性粒细胞胞外陷阱,免疫细胞的聚集和激活,以及线粒体动态失衡等均是CIRI的病理生理机制。此外,微循环无复流现象、出血转化和继发神经功能障碍也被发现在CIRI中发挥着重要作用。微循环无复流即血流再灌注后大血管再通,但由于血管内皮受损、血小板活性机制、周细胞死亡引起毛细血管腔狭窄、实质小动脉阻力血管强烈收缩等导致微血管无法有效灌注,引起微循环功能障碍,加重缺血区域损伤^[3-4]。最新研究表明,这可能与内皮细胞糖萼损伤、中性粒细胞胞外陷阱等有关^[4]。出血转化^[5]通常发生在缺血性脑卒中及再灌注之后,缺血区域的血管壁受损,进而形成出血或渗血现象,导致患者的临床预后欠佳,此情况可能与基质金属蛋白酶(MMPs)存在相关性。神经血管耦合失调、氧化应激、线粒体功能障碍可引发感觉、运动或语言等继发性神经功能障碍,进而通过兴奋性毒性、钙超载等导致神经元继发性死亡和功能丧失,致使脑损伤加重。已有研究证实,针对CIRI的相关治疗包括手术取栓、药物溶栓、抗氧化应激、清除氧自由基、抑制脑水肿形成、线粒体靶向治疗、靶向血管修复、神经血管保护及神经环路重塑等方式^[6-10]。

2 巨噬细胞与MG

巨噬细胞最早在1893年由Metchnikoff所描述,在缺乏适应性免疫反应的无脊椎动物中,组织巨噬细胞可促进损伤组织愈合。MG是一种在脑组织中常驻的巨噬细胞,发挥巨噬细胞的作用,通过表面受体[如Toll样受体(TLR)]感知危险信号发挥免疫监视的作用,通过吞噬作用清除损伤部位的细胞碎片以及阿尔兹海默病、帕金森病等疾病中的异常蛋白(β -淀粉样蛋白、 α -突触核蛋白)等,处理并呈递抗原启动适应性免疫反应,并释放促炎因子[如白细胞介素(IL)-1 β]和抗炎因子[如转化生长因子(TGF)- β]等调节炎症反应,在大脑中可分泌生长因子促进神经元存活,参与突触修剪、组织重塑、发育调控等作用^[11-12]。外周巨噬细胞和CNS中的MG均起源于胚胎期的卵黄囊祖细胞,他们在功能和微环境调控方面存在显著差异,然而,两种来源的MG并非完全隔离,而是通过多种机制相互作用,形成复杂的中枢-外周交互网络,具体如下:(1)细胞迁移和血脑屏障(BBB)的通透性。健康状态下, BBB严格限制外周免疫细胞进入CNS,此时, MG是CNS的主要免疫守卫,而在炎症、感染、损伤等病理情况下, BBB通透性增加,允许外周免疫细胞进入CNS,并参与免疫反应^[13]。(2)神经-免疫轴。迷走神经激活后可释放乙酰胆碱,乙酰胆碱结合外周巨噬细胞,抑制核苷酸结合寡聚化结构域样受体蛋白3(NLRP3)炎症小体活化,减少全身炎症因子[如肿瘤坏死因子(TNF)- α]向CNS扩散,从而间接影响CNS的炎症状态^[14],而MG感知神经元损伤信号(如ATP),激活嘌呤能离子通道受体,调控神经递质释放,间接影响外周免疫。(3)代谢和肠道-脑轴。肠道菌群代谢物(如短链脂肪酸)穿透BBB作用于MG,抑制核因子 κ B(NF- κ B)通路,减轻神经炎症,而MG释放的脑源性神经营养因子(BDNF)能调控肠神经节细胞,影响肠道通透性及菌群组成^[15],这种中枢-外周交互作用在神经退行性疾病、脑损伤和修复、全身感染和炎症中可能加剧或缓解疾病进程。

大量研究表明,在组织损伤后,巨噬细胞具有抗炎^[16]、抗纤维化、促进损伤组织愈合和血管再生的作用,并在急慢性炎症中起关键作用^[17-19]。在CIRI中, MG作为神经免疫网络的指挥中枢,通过动态极化双向调控病理进程:在CIRI早期,过度激活的M1型MG释放促炎因子,激活炎症小体加重损伤,后期M2型极化则通过清除损伤碎片,释放神经营养因子及促进血管修复等发挥保护作用。在大脑受到损伤后, MG能发挥吞噬功能和抗炎修复功能从而减轻脑损伤。(1)吞噬功能: MG可通过清除死

亡神经元促进脑部炎症消退,吞噬中性粒细胞,从而减轻对缺血组织的不良影响。据报道,炎症消退的完整过程涉及巨噬细胞通过胞吞作用清除凋亡细胞和炎症介质,同时可促进抗炎重编程并分泌促消退因子,促进炎症消退^[20-21]。此外,在大脑恢复过程中, MG可清除有毒细胞碎片,引导大脑修复和生理功能恢复^[22-23]。(2)抗炎修复功能: MG通过调控炎症、参与免疫调节和介导神经保护等多种机制,在 CIRI 中发挥重要作用^[24-25]。在脑损伤后, MG的激活和长期活化与神经炎症、功能恢复以及损伤后的神经修复愈合有关^[26]。在缺血性脑卒中中, MG可通过自分泌和旁分泌控制自身极化为 M2 表型,产生抗炎细胞因子发挥抗炎作用,保护神经^[27]。

3 MG 极化

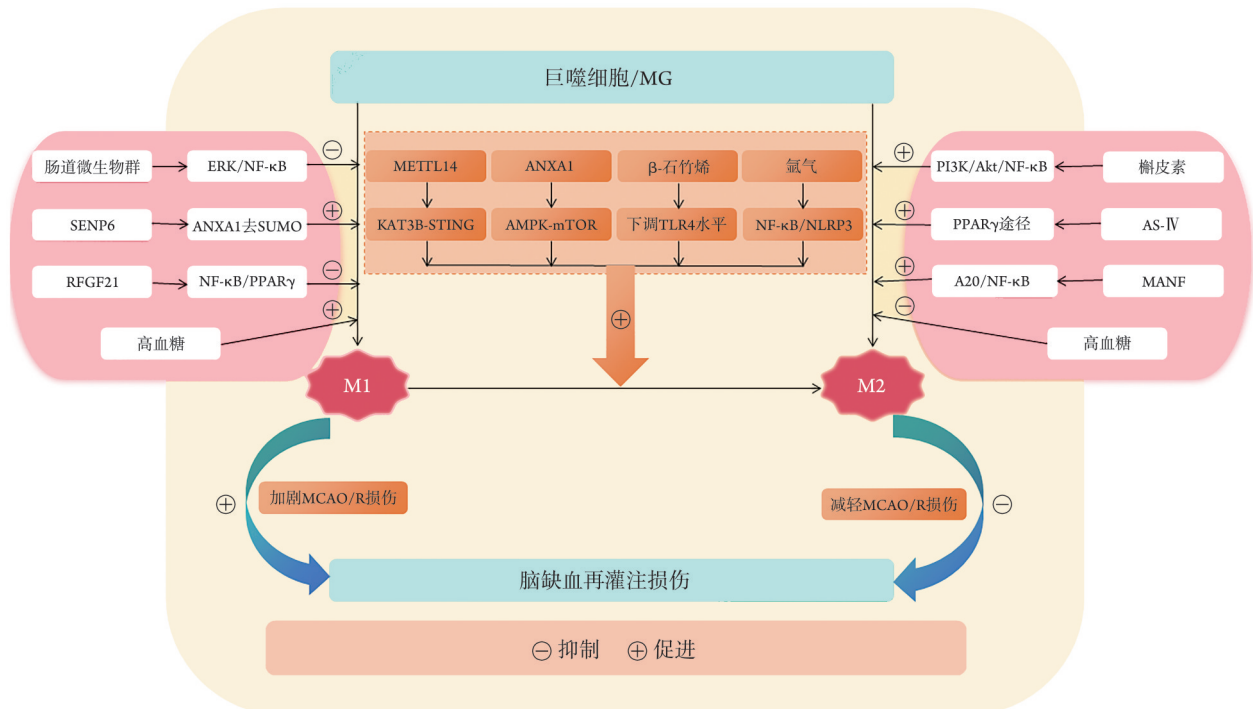
MG 极化是 MG 在不同空间和时间点被激活,表现出不同的功能和表型特征,其中涉及多种信号通路和分子调节机制。在组织微环境中的某些细胞因子水平发生变化时, MG 会转化为不同表型,通常分为 M1 型(促炎,经典活化途径)和 M2 型(抗炎,替代活化途径)^[28-29],发挥特定功能。有研究表明,巨噬细胞 M1/M2 表型转换可能有利于伤口的愈合^[18,30],在此基础上,局部顺序递送细胞因子将调节巨噬细胞极化为 M1/M2 表型,可改善骨愈合状态并为骨再生提供一种有效策略^[31]。目前,巨噬细胞极化表型已被发现在不同疾病的发生发展中起关键作用,如在各种肿瘤^[32-33]、糖尿病引起的创口愈合^[34-36]、缺损骨组织修复、骨关节炎恢复^[37]、肺纤维化、急性肺损伤^[38-39]、病毒性心肌炎^[40]、各种炎症性肠病等中起着积极促进作用,基于以上相关研究,对 MG 进行更深入的研究,有助于对这些疾病提供新的治疗策略和干预手段,以期更好地改善预后。

3.1 MG 极化调控机制 M1 型极化相关信号通路包括干扰素调节因子(IRF)/信号转导和转录激活因子 1(STAT1)/脂多糖(LPS)/TLR4、NF- κ B/磷脂酰肌醇 3-激酶(PI3K)通路等(图 1)。M1 型 MG 主要由 TNF、LPS、 γ 干扰素(IFN- γ)激活,分泌细胞因子和化学因子[如 TNF- α 、诱导型一氧化氮合酶(iNOS)、IL-6、C-X-C 基序趋化因子配体 9(CXCL9)]来促进炎症反应,过量的 M1 型细胞可能导致组织损伤^[41]。M2 型极化相关通路包括 STAT6、IRF4、过氧化物酶体增殖物激活受体 γ (PPAR γ)、精氨酸酶(Arg-1)等, M2 型 MG 主要由 IL-4、IL-13、巨噬细胞集落刺激因子(M-CSF)等激活,以 M2 型特征基因(如 Arg、CD206、IL-10、CCL1)的表达为特征,参与组织重塑和再生以及免疫调节等功能,并能通过消除/修复受损的细胞和基质来促进伤口愈合和抗炎^[30,42-45]。根据刺激源

及转录变化不同, M2 型 MG 又可细分为 4 种亚型(M2a、M2b、M2c、M2d), IL-4、IL-13 激活 M2a, TLR 配体、LPS、IL-1 β 激活 M2b, 糖皮质激素和 TGF- β 激活 M2c, LPS、腺苷、IL-6 激活 M2d^[46]。研究表明, 4 种亚型发挥相似而又不同的功能, M2a 型倾向于抗炎、组织修复, M2b 型则倾向于免疫调节、肿瘤进展、促进感染, M2c 型主要功能表现在血管生成、吞噬、组织重塑、抗炎等方面, M2d 型主要在肿瘤进展、免疫抑制、血管生成等方面起作用^[47]。

3.2 MG 极化在 CIRI 中的作用 MG 的极化状态在 CIRI 中起着重要作用。当组织细胞发生细菌感染时,促炎 M1 型 MG 首先被激活,释放大量促炎介质引起炎症反应。在组织损伤早期, M1 型 MG 迅速增多,针对组织局部缺血引发经典的炎症反应,进而造成组织继发性损伤;而在较长一段时间后,抗炎 M2 型 MG 才逐渐增加,其对组织修复程度起着决定性作用。研究表明, MG 的极化状态(促炎性 M1 型和抗炎性 M2 型)及其表型转换对 CNS 损伤修复具有不同的作用: M1 型活化干扰修复,而 M2 型活化则促进修复,因此调节 MG 的极化也可作为治疗 CIRI 的一种方法^[18,43,48-50]。具体而言, M1 型 MG 倾向于释放自由基和促炎因子,损害大脑修复/再生, M2 型 MG 则通过减轻脑部炎症、促进神经重塑、增强吞噬作用来改善脑修复/再生^[28,47]。在缺血性脑卒中后早期, M1 型 MG 显著增多,引发炎症反应并导致神经元损伤。随后, M2 型 MG 逐渐增多,其通过抑制炎症、增强吞噬作用、分泌保护性因子促进组织修复等,发挥关键的神经保护作用。因此,促进 MG 由 M1 型向 M2 型转换可作为再灌注损伤的简单治疗策略^[51-53]。

综合分析文献发现,多种信号通路和分子调节因子参与 M1 型和 M2 型 MG 极化表型的转换,在再灌注损伤的免疫炎症反应调控中起着重要作用(图 1)。研究发现,槲皮素在大鼠大脑中动脉闭塞/再灌注(MCAO/R)模型中可通过 PI3K/蛋白激酶 B(Akt)/NF- κ B 信号通路促进 MG 极化成 M2 表型从而减轻 CIRI^[29];同样,甲基转移酶样 14(METT14)在大鼠大脑中动脉阻塞和氧糖剥夺/再灌注(OGD/R)模型中通过赖氨酸乙酰转移酶 3B-干扰素基因刺激因子组蛋白乙酰转移酶 3B/干扰素基因刺激因子(KAT3B-STING)通路促进 MG 从 M1 型转化为 M2 型从而缓解大鼠大脑中动脉阻塞诱导的脑损伤^[54];此外,在小鼠短暂性大脑中动脉闭塞(TMCAO)发生的 CIRI 模型中,氩气通过抑制 NF- κ B/NLRP3 炎症小体信号转导并促进 NLRP3 介导的缺血半暗带的 MG 由 M1 型极化转向 M2 型极化,从而抑制炎症反应,最终减轻 I/R 损伤^[55];在 TMCAO/R、BV2 MG 和 HT22 神经元



ERK/NF- κ B. 细胞外调节蛋白激酶/核因子 κ B; METTL14. 甲基转移酶样14; ANXA1. 膜联蛋白A1; PI3K/Akt/NF- κ B. 磷脂酰肌醇3-激酶/蛋白激酶B/核因子 κ B; SENP6. 特异性蛋白酶6; SUMO. 小泛素样修饰蛋白; KAT3B-STING. 赖氨酸乙酰转移酶3B-干扰素基因刺激因子; AMPK-mTOR. 腺苷单磷酸激活蛋白激酶-哺乳动物雷帕霉素靶蛋白; TLR4. Toll样受体4; NLRP3. 核苷酸结合寡聚化结构域样受体蛋白3; PPAR γ . 过氧化物酶体增殖物激活受体 γ ; AS-IV. 黄芪苷四; RFGF21. 重组人成纤维细胞生长因子21; A20. 强效抗炎蛋白A20; MANF. 中脑星形胶质细胞源性神经营养因子; M1. 促炎型小胶质细胞; M2. 抗炎型小胶质细胞; MCAO/R. 大脑中动脉栓塞/再灌注

图1 M1和M2表型小胶质细胞(MG)在MCAO/R中的相关通路和调节因子

Fig.1 Pathways and regulators associated with M1 and M2 phenotypes microglia (MG) in MCAO/R

(OGD/R)模型中,膜联蛋白A1(ANXA1)通过甲酰胺受体2/脂氧素A4受体(FPR2/ALX)依赖的腺苷单磷酸激活蛋白激酶-哺乳动物雷帕霉素靶蛋白(AMPK-mTOR)通路调节MG从促炎M1表型向抗炎M2表型的转换来减轻CIRI^[56];黄芪苷四(AS-IV)在MCAO/R大鼠模型中通过PPAR γ 途径促进MG极化为M2表型,促进大鼠CIRI后神经功能恢复^[57];在脑缺血再灌注模型中,特异性蛋白酶6(SENP6)通过ANXA1的去小泛素样修饰蛋白(SUMO)化促进NF- κ B信号通路激活,诱导MG极化为促炎M1表型,并加重神经元损伤^[58];中脑星形胶质细胞源性神经营养因子(MANF)在小鼠MCAO/R模型和BV-2 OGD/R细胞模型中通过强效抗炎蛋白A20(A20)/NF- κ B通路促进MG的M2型极化,从而减轻小鼠CIRI^[59]。上述研究揭示了MG表型极化在CIRI中的调控作用。不同分子通过靶向关键通路,抑制炎症反应并促进MG向M2型极化,显著改善神经功能,减轻CIRI损伤。然而,多靶点协同作用、临床转化可行性(如氩气的给药方式)及长期安全性仍需进一步探索。

近年来的研究表明,在大鼠CIRI模型中,调节肠道微生物群可通过细胞外调节蛋白激酶[细胞外信号调节激酶(ERK)]和NF- κ B途径抑制MG M1型极

化,从而减轻大鼠CIRI^[60]。重组人成纤维细胞生长因子21(RFGF21)在脑卒中后可抑制微胶质细胞向M1表型的极化,并促进实验性脑卒中的功能恢复^[61]。高血糖可抑制CIRI后脑组织MG增殖从而加重CIRI^[62],同时在高血糖大鼠CIRI模型中,高血糖可能通过促进MG向M1型极化,并抑制M2型极化,进而加剧糖尿病高血糖中缺血再灌注引起的损伤^[63]。此外, β -石竹烯(BCP)部分通过抑制TLR4在小鼠I/R模型中介导MG激活并促进其极化为M2抗炎表型,从而保护缺血脑^[64]。相关MG极化信号通路如NF- κ B、TLR、mTOR、MAPK及JAK-STAT等也被发现在神经炎症中起着不同的调控作用^[53,65-69]。以上研究提示,临床可考虑代谢干预如肠道菌群和血糖水平等代谢微环境来靶向MG的极化,从而减轻CIRI,这为神经炎症相关疾病的免疫代谢调控提供了新视角,但需结合病理阶段动态优化治疗方法。

4 MG代谢重编程

代谢重编程是指将酶和代谢物重新利用,重新编程细胞内代谢途径以调节和改变生物体内活性物质或细胞内信号转导途径,最终改变生物体基因表达谱和代谢产物以改善其性能。MG代谢重编程是

指MG的代谢方式可根据神经系统微环境变化,调控代谢途径进行代谢重编程,从而改变MG转录表型及功能表型,最终影响疾病进展。MG在其激活、极化表型及发挥功能过程中均伴随着代谢重编程,因此在多种疾病进程中发挥重要作用,也是神经炎症、多种脑部疾病发病机制的核心因素^[70-72]。

4.1 MG代谢重编程的调控机制 目前研究较多的MG代谢重编程调控包括:(1)糖代谢。MG代谢在糖酵解与氧化磷酸化途径间转换与其不同表型相关,促炎型MG表现为糖酵解途径增强而氧化磷酸化途径减弱,而抗炎型MG更倾向于依赖氧化磷酸化提供能量来发挥组织修复功能。(2)脂质代谢。脂质代谢影响促炎和抗炎MG表型的转换和维持,促炎型MG发挥抗原呈递等功能需要大量脂质及大量脂肪酸合成,相反脂肪酸氧化不仅维持M2抗炎表型,而且在M2型MG发挥抗炎作用时起重要作用。(3)氨基酸代谢。氨基酸中的谷氨酰胺在MG表型转换中发挥双重作用,既有助于重建促炎型MG截断的线粒体三羧酸(TCA)循环,同时又有助于维持抗炎型MG的免疫应答功能^[70-71,73]。此外,更多MG代谢重编程的方法,如有促抗炎功能的受体和通道组胺、神经肽、钾通道、脂质信使脂肪酸、促再生表型的微小RNA、细胞疗法间充质干细胞等,以及驱动MG为神经支持表型的药物制剂如二氯乙酸(DCA)和二甲双胍等,均能重新编程使MG定向为有益保护功能,最终实现神经保护与修复^[74]。

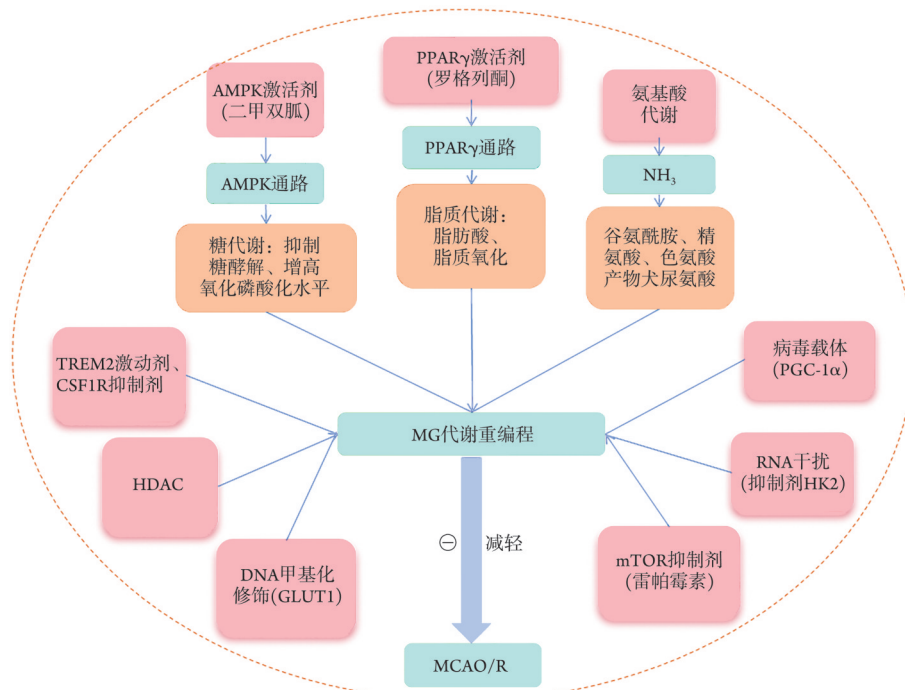
4.2 MG代谢重编程在CIRI中的作用 缺血缺氧条件下,MG从依赖氧化磷酸化的静息状态,转向糖酵解为主的代谢模式,为其快速激活提供能量。研究表明,通过操控MG代谢重编程可使MG发挥有益功能,用于减轻CIRI^[75]。正常情况下,MG通过吞噬作用清除因缺血缺氧而死亡的神经元和细胞碎片以防止继发性损伤(如“炎症瀑布”)^[76];在代谢重编程过程中,MG能通过代谢途径如代谢调节药物AMPK激活剂(二甲双胍)激活AMPK通路,以及增强氧化磷酸化或通过PPAR γ 激动剂激活PPAR γ 通路促进脂质代谢,从而提供吞噬作用所需的能量和物质,最终提高MG的吞噬效率^[77];还能通过抗炎和促吞噬药物如髓系细胞触发受体2(TREM2)激动剂激活TREM2受体,进而增强MG的吞噬功能,促进细胞碎片清除,最终减轻神经炎症^[78];此外,表观遗传调控可通过多种机制影响MG的功能:例如,组蛋白去乙酰化酶(HDAC)抑制剂能够通过调节特定基因的表达,促进MG向M2型转化来增强抗炎和吞噬功能;而DNA甲基化修饰则通过调控代谢相关基因(如GLUT1/GPT1)的表达,从而优化MG的代谢状态,进一步支持其修复功能。而基因编辑技术(如敲

除或敲入特定基因)及基因治疗技术(如相关病毒载体等)能实现精准调控促进MG的吞噬功能,从而增强其在CIRI中的作用。

调节细胞代谢可影响MG的表型变化,通过抑制MG的糖酵解代谢途径来抑制炎症反应,可能成为阿尔兹海默病的新治疗策略^[79]。LPS可促发MG代谢重编程将其代谢途径转为有氧糖酵解,通过抑制糖酵解途径可抑制神经炎症、调节免疫功能及神经元活性^[80-81]。在创伤性脑损伤模型中,MG代谢向细胞糖酵解升高的转变是控制MG炎症表型的关键致病机制,因此导致促炎型MG激活,并促进相关的神经退行性变^[82]。使用转录因子NeuroD1在小鼠模型中将MG利用细胞重编程直接转换为神经元,可为神经退行性疾病提供新的治疗方案^[83]。据报道,电压门控H通道(Hv1)抑制剂2-胍基苯并咪唑(2-GBI)可通过调节MG代谢重编程从而减轻神经炎症反应和认知功能障碍^[84]。纳米药物可通过调节CCAAT增强子结合蛋白 β (Cebpb)调节的NLRP3炎症小体的激活和CXCL2趋化因子的分泌将MG重编程为抗炎表型,从而减轻缺血性卒中后的炎症反应^[85]。在创伤性脑损伤和神经炎症中,戊糖磷酸途径、谷氨酰胺分解、继发性损伤和恢复过程中的脂质氧化,都可通过重新编程导致MG表型改变,最终发挥抗炎、减轻脑损伤等关键保护作用(图2)。

5 总结与展望

CIRI是导致脑卒中后神经损伤和功能障碍的重要机制,其中炎症反应是再灌注损伤的重要因素之一。首先,MG及其极化M1/M2表型的转换和代谢重编程在CIRI的免疫炎症反应中发挥关键调控作用。尽管有研究提出可通过促进MG极化M2表型或M1向M2表型转换来有效减轻再灌注损伤、促进神经再生、保护脑组织等,然而促进转换的具体时机、有效促进因子及分子调控机制尚不清楚;因此进一步研究并揭示MG代谢重编程在CIRI中的作用及功能有望达到最优治疗效果。其次,目前对于MG极化状态、代谢重编程及炎症效应在CIRI后的组织及神经修复和再生能力尚未明确,且MG代谢重编程在CIRI中相关作用的研究相对较少,这也是亟待解决的关键问题。此外,多数研究主要集中在动物实验和细胞模型上,对于MG及其相关研究在人类CIRI中的作用了解甚少。因此,未来的研究可通过临床样本进一步验证MG的免疫炎症反应和保护作用,并探索其在临床治疗中的应用潜力。最后,多种信号通路及分子参与CIRI的进展,未来可继续探究关键调控蛋白的相互作用网络,确定相关基因组,以期CIRI的治疗提供新的有效靶点或策略。



AMPK. 腺苷酸活化蛋白激酶; PPAR γ . 过氧化物酶体增殖物激活受体; NH₃. 氨气; TREM2. 髓系细胞触发受体2; CSF1R. 集落刺激因子1受体; PGC-1 α . 转录共激活因子-1 α ; HDAC. 组蛋白去乙酰化酶; HK2. 己糖激酶2; GLUT1. 葡萄糖转运蛋白1; mTOR. 哺乳动物雷帕霉素靶蛋白; MCAO/R. 大脑中动脉栓塞/再灌注

图2 小胶质细胞(MG)代谢重编程及其调控

Fig.2 Microglia (MG) metabolic reprogramming and its regulation

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