·论著·

骨髓间充质干细胞调节小胶质细胞极化减轻SNI大鼠神经病理性疼痛

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摘要 目的 探讨骨髓间充质干细胞(BMSCs)调节小胶质细胞极化对坐骨神经分支选择性损伤(SNI)大鼠神经病理性疼痛的作用及其机制。**方法** 将50只SD大鼠随机分为sham组(大鼠仅暴露坐骨神经而不结扎)、SNI组(SNI模型建立)、BMSCs组[大鼠SNI造模后连续3 d经鞘内注射BMSCs(1×10^6)]、BMSCs+sh-NC组[大鼠SNI造模后连续3 d经鞘内注射BMSCs(1×10^6),同时鞘内注射敲减对照腺病毒(2.5×10^7 IU)]和BMSCs+sh-YY1组[大鼠SNI造模后连续3 d经鞘内注射BMSCs(1×10^6),同时鞘内注射敲减YY1腺病毒(2.5×10^7 IU)],每组10只。采用机械刺激缩足反射阈值(PWT)和热缩足潜伏期(PWTL)评价大鼠神经病理性疼痛程度;免疫荧光染色检测大鼠脊髓组织中CD86、CD206、iNOS和Arg1蛋白阳性率;Western blotting检测大鼠脊髓组织中YY1和KLF4表达。**结果** 与sham组比较,SNI组大鼠PWTL和PWT值降低(均$P<0.05$);脊髓组织中iNOS和CD86蛋白阳性率增加,CD206和Arg1蛋白阳性率降低,YY1和KLF4表达降低(均$P<0.05$)。与SNI组比较,BMSCs组和BMSCs+sh-NC组大鼠PWTL和PWT值增加(均$P<0.05$);脊髓组织中CD86蛋白阳性率降低,CD206蛋白阳性率增加,YY1和KLF4表达增加(均$P<0.05$);BMSCs组大鼠脊髓组织中iNOS蛋白阳性率降低,Arg1蛋白阳性率增加。与BMSCs组和BMSCs+sh-NC组比较,BMSCs+sh-YY1组大鼠PWTL和PWT值降低(均$P<0.05$);脊髓组织中CD86蛋白阳性率增加,CD206蛋白阳性率降低,YY1和KLF4表达降低(均$P<0.05$)。**结论** SNI大鼠鞘内注射BMSCs可促进脊髓中小胶质细胞M2极化,缓解神经病理性疼痛,其机制可能与上调YY1介导的KLF4表达有关。

关键词 骨髓间充质干细胞; 神经病理性疼痛; 小胶质细胞极化; 转录因子阴阳1; Krüppel样因子4
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Bone marrow mesenchymal stem cells regulate microglial polarization to alleviate neuropathic pain in SNI rats

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Abstract Objective To explore the effects and mechanisms of bone marrow mesenchymal stem cells (BMSCs) in regulating microglial polarization on neuropathic pain in rats with sciatic nerve branch-selective injury (SNI). **Methods** Fifty SD rats were randomly divided into five groups with ten rats in each group; sham group (rats only exposed sciatic nerve without ligation), SNI group (SNI model was established), BMSCs group [rats were injected with BMSCs (1×10^6) through the sheath for 3 days after SNI modeling], BMSCs+sh-NC group [rats were intrathecally injected with BMSCs (1×10^6) and intrathecally injected with knock-down control (adenovirus 2.5×10^7 IU) for 3 days after SNI modeling], and BMSCs+sh-YY1 group [rats were intrathecally injected with BMSCs (1×10^6) and intrathecally injected with YY1 knockdown adenovirus (2.5×10^7 IU) for 3 days after SNI modeling]. Neuropathic pain was assessed using paw withdrawal threshold (PWT) and paw withdrawal thermal latency (PWTL) following mechanical stimulation. Immunofluorescence was used to detect the expression of CD86, CD206, iNOS, and Arg1 in the rat spinal cord tissues. Western blotting was used to measure the expression of YY1 and KLF4 in spinal cord tissue. **Results** Compared with sham group, the values of PWTL and PWT in the SNI group significantly reduced (both $P<0.05$). In spinal cord tissue, the positive rates of iNOS and CD86 protein increased, whereas the positive rates of CD206 and Arg1 protein and the expression of YY1 and KLF4 decreased (all $P<0.05$). Compared with the SNI group, the values of PWTL and

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PWT in the BMSCs and BMSCs+sh-NC groups increased (all $P < 0.05$), the positive rate of CD86 protein in the spinal cord decreased, whereas the positive rate of CD206 protein and the expression of YY1 and KLF4 increased (all $P < 0.05$). Also, the positive rate of iNOS protein in the spinal cord tissue decreased and the positive rate of Arg1 increased in the BMSCs group (all $P < 0.05$). Compared with the BMSCs and BMSCs+sh-NC groups, the PWTL and PWT values in the BMSCs+sh-YY1 group decreased (all $P < 0.05$). The positivity rate of CD86 protein increased, the positivity rate of CD206 protein decreased, and the expression of YY1 and KLF4 decreased in the spinal cord tissue (all $P < 0.05$). **Conclusion** Intrathecal injection of BMSCs promotes M2 polarization of microglia in the spinal cord and relieves neuropathic pain in rats with SNI, and its mechanism may be related to the upregulation of KLF4 expression mediated by YY1.

Keywords bone marrow mesenchymal stem cell; neuropathic pain; microglial polarization; Yin Yang 1; Krüppel-like factor 4

神经病理性疼痛由影响躯体感觉系统的病变或疾病引起，其病因复杂多样[1-3]。目前，神经病理性疼痛的治疗方法主要包括药物治疗、神经调控技术以及微创治疗等[3]，然而这些治疗方法都不能完全有效地缓解神经病理性疼痛。因此，开发新的有效治疗方法是目前急需解决的问题。骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMSCs）是免疫原性相对较低的多能干细胞，已成为治疗多种炎症疾病的候选药物[4]。BMSCs易于分离培养并具有多向分化能力，可迁移至受损部位分化取代受损细胞或通过分泌生物活性分子发挥免疫调节和免疫抑制特性[5]。最近研究[6]表明，BMSCs移植可缓解周围神经损伤动物模型的神经病理性疼痛[6]；然而，BMSCs发挥作用的具体机制尚不明确。

小胶质细胞是中枢神经系统中调节大脑和脊髓内环境稳定的主要免疫活性细胞，占中枢神经系统中神经胶质细胞的5%~10%[7]。脊髓背角中活化的小胶质细胞在神经病理性疼痛中起着关键作用；它通过释放促炎性细胞因子激活和敏化脊髓损害感受神经元，将其从静止的分支形状改变为活跃的变形形状，加剧了神经病理性疼痛[8-9]。活化的小胶质细胞极化为经典活化的促炎性M1型小胶质细胞或选择性活化的抗炎性M2型小胶质细胞[10]。在神经病理性疼痛过程中，小胶质细胞激活并极化为M1型小胶质细胞，导致神经炎症并最终诱发神经病理性疼痛，而M2型小胶质细胞抑制此过程[11]。最近的研究[12]发现BMSCs对小胶质细胞极化具有调节作用，可促进小胶质细胞M2极化并抑制神经炎症。因此，BMSCs可能通过靶向小胶质细胞极化来缓解神经病理性疼痛。

本研究建立大鼠坐骨神经分支选择性损伤（spared nerve branch-selective injury，SNI）模型，探究BMSCs介导小胶质细胞极化对SNI大鼠神经病理性疼痛的作用及其机制，旨在为BMSCs在神经病理性疼痛治疗中的应用提供新思路。

1　材料与方法

1.1　主要试剂和仪器

50只雄性、体重220~250 g、6~8周龄SD大鼠购自北京维通利华实验动物技术有限公司；BMSCs购自武汉普诺赛生命科技有限公司；敲减转录因子阴阳1（Yin Yang 1，YY1）及敲减对照腺病毒购自上海吉凯基因医学科技股份有限公司；Western blotting相关试剂均购自上海碧云天生物技术有限公司；YY1、Krüppel样因子（Krüppel-like factor，KLF）4和GAPDH抗体购自武汉三鹰生物技术有限公司；免疫荧光试剂盒购自北京索莱宝科技有限公司。酶标仪购自美国BioTek公司，凝胶扫描成像系统购自美国Bio-Rad公司。

1.2　方法

1.2.1　大鼠SNI模型建立：大鼠腹腔注射2%戊巴比妥钠麻醉后消毒并备皮，暴露坐骨神经分支腓总神经、腓肠神经和胫神经。于三叉处结扎并在远心端剪断腓总神经和胫神经，避免损伤腓肠神经。手术结束后消毒并逐层缝合伤口。

1.2.2　动物分组及处理：将50只SD大鼠随机分为sham组、SNI组、BMSCs组、BMSCs+sh-NC组和BMSCs+sh-YY1组，每组10只。Sham组大鼠仅暴露坐骨神经而不进行结扎，其他组大鼠按1.2.1方法建立SNI模型。BMSCs组、BMSCs+sh-NC组和BMSCs+sh-YY1组大鼠造模手术后连续3 d经鞘内注射BMSCs（1×10^6），BMSCs+sh-NC组和BMSCs+sh-YY1组大鼠分别在鞘内注射BMSCs的同时注射敲减对照或敲减YY1腺病毒（2.5×10^7 IU）。造模后第14天，各组随机选择

5只大鼠检测机械刺激缩足反射阈值(paw withdraw threshold,PWT),余下5只大鼠用于检测热缩足潜伏期(paw withdrawal thermal latency,PWTL)。PWT和PWTL检测结束后,脱颈椎法处死大鼠并取大鼠脊髓组织,一部分固定于4%多聚甲醛中,另一部分冻存于−80 ℃冰箱中。

1.2.3　大鼠PWT检测:将各组大鼠置于透明玻璃笼中并用不同作用力的von-Frey纤维丝刺激大鼠2只后爪足底直至出现缩足反应并记录。

1.2.4　大鼠PWTL检测:用热痛刺激仪照射大鼠后足掌正中,缩足反应的潜伏期即为热痛阈值。

1.2.5　免疫荧光染色:将固定于4%多聚甲醛中的大鼠脊髓组织常规方法制备石蜡切片(4 μm)。切片经二甲苯脱蜡和梯度乙醇水化后进行柠檬酸钠抗原修复,BSA封闭1 h后,CD86、CD206、诱导型一氧化氮合酶(inducible nitric oxide synthase,iNOS)和精氨酸酶1(arginase 1,Arg1)抗体4 ℃孵育过夜,PBS洗涤后用荧光二抗室温孵育1 h,PBS洗涤后用DAPI染色液室温孵育1 h,PBS洗涤后抗荧光淬灭封片剂封片,荧光显微镜下观察并拍照。

1.2.6　Western blotting:将冻存于−80 ℃冰箱中的大鼠脊髓组织提取总蛋白后BCA法定量,取20 μg蛋白进行电泳和转膜后,5 %脱脂牛奶室温封闭1 h,YY1、KLF4和GAPDH抗体4 ℃孵育过夜。PBST洗膜3次,二抗室温孵育1 h,PBST洗膜3次,ECL化学发光,使用ImageJ软件进行灰度分析。

1.3　统计学分析

采用SPSS 22.0软件进行统计学分析。符合正态分布的计量资料采用$\bar{x} \pm s$表示,多组间比较采用单因素方差分析,并采用Tukey事后检验进行组间两两比较。$P<0.05$为差异有统计学意义。

2　结果

2.1　BMSCs对SNI大鼠神经病理性疼痛的影响

与sham组比较,SNI组大鼠PWTL和PWT明显降低($P<0.05$);与SNI组比较,BMSCs组大鼠PWTL和PWT明显升高($P<0.05$)。见表1。

2.2　BMSCs对SNI大鼠脊髓组织小胶质细胞极化的影响

免疫荧光检测结果显示,与sham组比较,SNI组大鼠脊髓组织中CD86和iNOS蛋白阳性率明显升高,CD206和Arg1蛋白阳性率明显降低($P<0.05$);与SNI组比较,BMSCs组大鼠脊髓组织中CD86和iNOS蛋白阳性率明显降低,CD206和Arg1蛋白阳性率明显升高($P<0.05$)。见图1、表2。

表1　BMSCs对SNI大鼠神经病理性疼痛的影响

Tab.1　Effect of BMSCs on neuropathic pain in SNI rats

Group	n	PWTL(s)	PWT(g)
Sham	5	11.68 ± 1.10	23.80 ± 4.92
SNI	5	4.54 ± 0.56[1)]	1.80 ± 1.30[1)]
BMSCs	5	9.38 ± 0.65[2)]	10.20 ± 2.86[2)]

1) $P<0.05$ vs. sham group; 2) $P<0.05$ vs. SNI group.

2.3　BMSCs对SNI大鼠脊髓组织中YY1和KLF4蛋白表达的影响

Western blotting检测结果显示,与sham组比较,SNI组大鼠脊髓组织中YY1和KLF4蛋白表达水平明显降低($P<0.05$);与SNI组比较,BMSCs组大鼠脊髓组织中YY1和KLF4蛋白表达水平明显升高($P<0.05$)。见图2。

2.4　敲减YY1对BMSCs干预的SNI大鼠神经病理性疼痛的影响

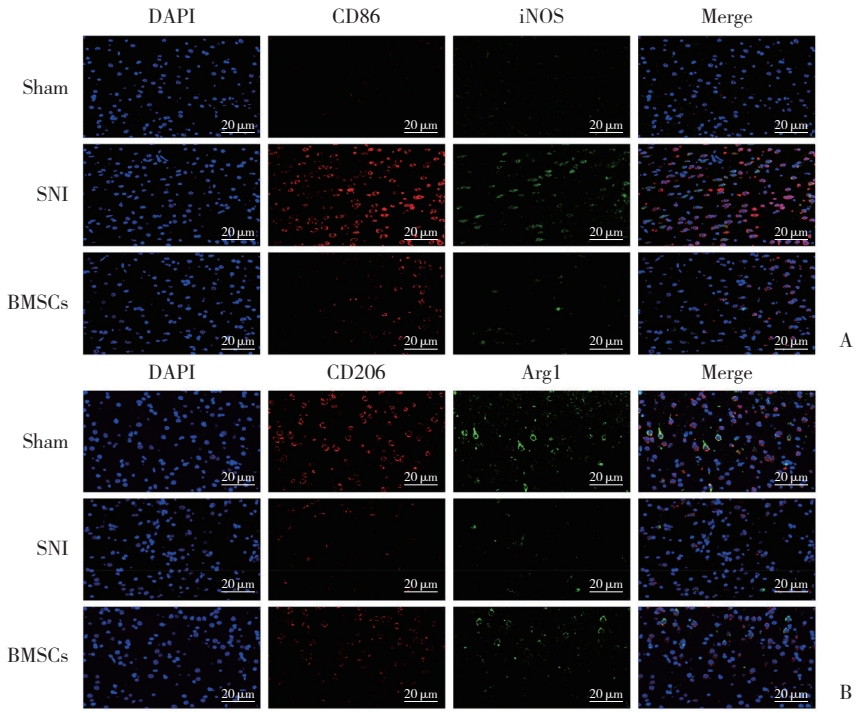
与SNI组比较,BMSCs组和BMSCs+sh-NC组大鼠PWTL和PWT明显升高($P<0.05$);与BMSCs组和BMSCs+sh-NC组比较,BMSCs+sh-YY1组大鼠PWTL和PWT明显降低($P<0.05$)。见表3。

2.5　敲减YY1对给予BMSCs的SNI大鼠脊髓组织中KLF4蛋白表达的影响

Western blotting检测结果显示,与SNI组比较,BMSCs组和BMSCs+sh-NC组大鼠脊髓组织中YY1和KLF4蛋白表达明显增加($P<0.05$);与BMSCs组和BMSCs+sh-NC组比较,BMSCs+sh-YY1组大鼠脊髓组织中YY1和KLF4蛋白表达明显减少($P<0.05$)。见图3。

2.6　敲减YY1对BMSCs干预的SNI大鼠脊髓组织小胶质细胞极化的影响

免疫荧光检测结果显示,与SNI组比较,BMSCs组和BMSCs+sh-NC组大鼠脊髓组织中CD86蛋白阳性率明显降低,CD206蛋白阳性率明显升高($P<0.05$);与BMSCs组和BMSCs+sh-NC组比较,BMSCs+sh-YY1组大鼠脊髓组织中CD86蛋白阳性率明显升高,CD206蛋白阳性率明显降低($P<0.05$)。见图4、表4。



A, CD86 and iNOS; B, CD206 and Arg1.

图1　BMSCs对SNI大鼠脊髓组织中CD86、CD206、iNOS和Arg1蛋白阳性率的影响×200

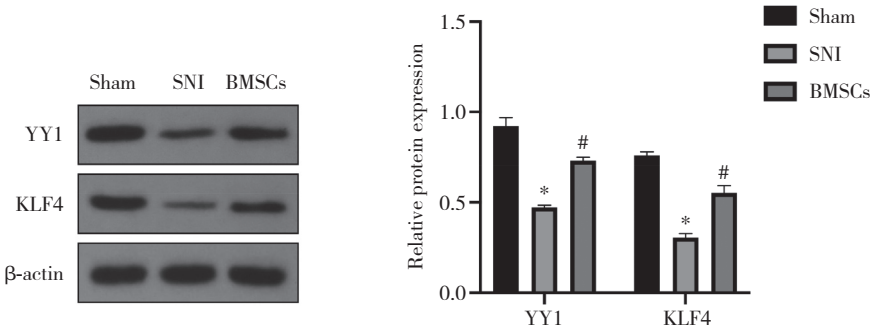
Fig.1　Effect of BMSCs on the positive rates of CD86, CD206, iNOS, and Arg1 proteins in spinal cord tissue of SNI rats×200

表2　各组大鼠脊髓组织中CD86、iNOS、CD206和Arg1蛋白阳性率比较 (%)

Tab.2　Comparison of the positive rates of CD86, iNOS, CD206, and Arg1 proteins in the spinal cord tissue of rats in each group (%)

Group	CD86	iNOS	CD206	Arg1
Sham	1.28 ± 0.46	1.27 ± 1.02	64.34 ± 3.64	47.62 ± 4.20
SNI	78.58 ± 4.21[1)]	53.65 ± 3.28[1)]	12.87 ± 4.53[1)]	7.01 ± 1.18[1)]
BMSCs	36.42 ± 2.74[2)]	13.59 ± 2.11[2)]	32.06 ± 2.16[2)]	21.59 ± 5.50[2)]

1) $P<0.05$ vs. sham group; 2) $P<0.05$ vs. SNI group.



* $P<0.05$ vs. sham group; # $P<0.05$ vs. SNI group.

图2　BMSCs对SNI大鼠脊髓组织中YY1和KLF4蛋白表达的影响

Fig.2　Effect of BMSCs on YY1 and KLF4 protein expression in spinal cord tissue of SNI rats

3　讨论

SNI模型造模过程较简单，具有很高的可重复性；与慢性缩窄性损伤模型比较，引起的疼痛更加强烈且持续时间更长，与临床情况更加类似[13]。因此，本研究采用大鼠SNI模型探究BMSCs改善神经病

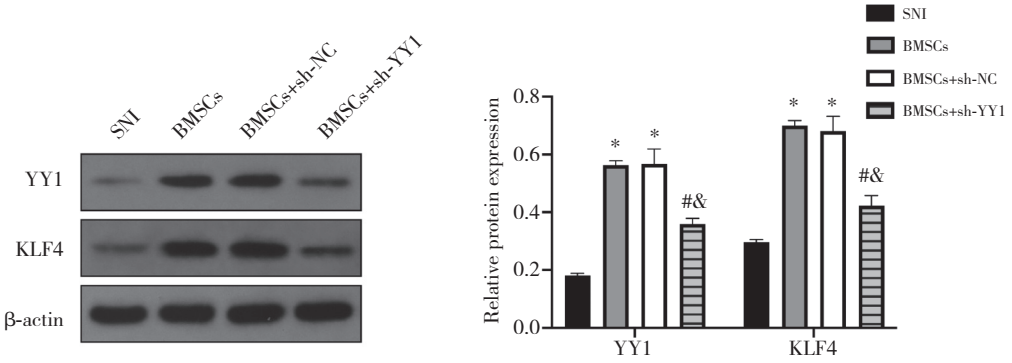
理性疼痛的机制。大鼠鞘内注射BMSCs具有良好的安全性，对生理性疼痛无不良影响，而且对机体的感觉功能和运动功能无明显损伤[14]。最近一项临床Ⅱ期随机对照试验[15]发现BMSCs和施万细胞鞘内联合注射在改善完全性脊髓损伤患者的神经性疼痛和生活质量方面疗效显著。然而，关于BMSCs改善神经病理性疼痛分子机制的相关报道较少。已有研究[16-17]表明，鞘内注射BMSCs对神经病理性疼痛的改善作用与分泌TSG-6抑制同侧脊髓背角Toll样受体2/髓样分化因子88/核因子κB通路的激活以及降低脊髓小胶质细胞中P2X嘌呤受体4表达有关。还有研究[18]发现BMSCs可通过增加脊髓背角中miR-547-5p表达抑制白细胞介素（interleukin，IL）-33/肿瘤发生抑制因子2信号通路改善神经病理性疼痛。本研究结果显示，鞘内注射BMSCs使SNI大鼠PWTL和PWT增加，表明BMSCs可缓解SNI大鼠神经病理性疼痛。

表3　敲减YY1对给予BMSCs的大鼠神经病理性疼痛的影响

Tab.3　Effect of YY1 knockdown on neuropathic pain in rats treated with BMSCs

Group	*n*	PWTL(s)	PWT(g)
SNI	5	3.70 ± 0.32	1.64 ± 0.33
BMSCs	5	8.76 ± 0.44[1)]	11.60 ± 3.21[1)]
BMSCs+sh-NC	5	8.46 ± 0.72[1)]	11.00 ± 2.34[1)]
BMSCs+sh-YY1	5	5.70 ± 0.42[2),3)]	7.20 ± 1.79[2),3)]

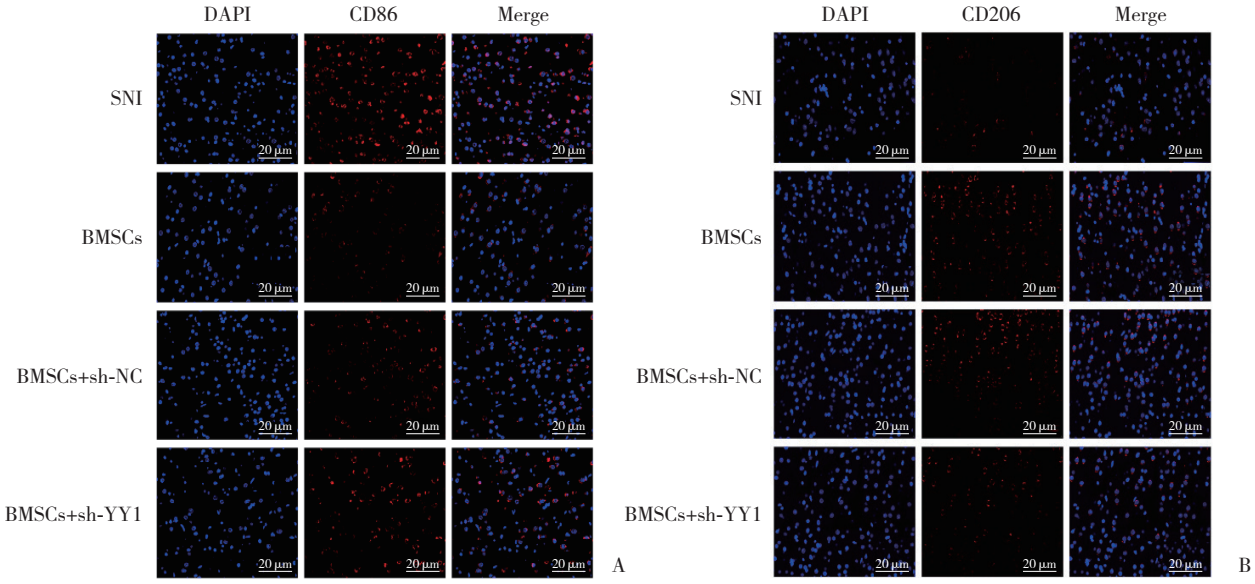
1) $P < 0.05$ vs. SNI group; 2) $P < 0.05$ vs. BMSCs group; 3) $P < 0.05$ vs. BMSCs+sh-NC group.



* $P < 0.05$ vs. SNI group; # $P < 0.05$ vs. BMSCs group; & $P < 0.05$ vs. BMSCs+sh-NC group.

图3　敲减YY1对BMSCs干预的SNI大鼠脊髓组织中KLF4蛋白表达的影响

Fig.3　Effect of YY1 knockdown on the expression of KLF4 protein in spinal cord tissue of SNI rats treated with BMSCs



A，CD86；B，CD206.

图4　敲减YY1对BMSCs干预的SNI大鼠脊髓组织小胶质细胞极化的影响

Fig.4　Effect of YY1 knockdown on the microglial polarization in spinal cord tissue of SNI rats treated with BMSCs

表4　各组大鼠脊髓组织中CD86、CD206蛋白阳性率比较 (%)

Tab.4　Comparison of the positive rates of CD86 and CD206 proteins in the spinal cord tissue of rats in each group (%)

Group	CD86	CD206
SNI	79.33 ± 2.81	8.41 ± 2.09
BMSCs	32.28 ± 2.32[1)]	27.13 ± 3.69[1)]
BMSCs+sh-NC	33.07 ± 6.02[1)]	27.52 ± 4.36[1)]
BMSCs+sh-YY1	54.33 ± 3.08[2),3)]	17.47 ± 2.05[2),3)]

1) $P < 0.05$ vs. SNI group; 2) $P < 0.05$ vs. BMSCs group; 3) $P < 0.05$ vs. BMSCs+sh-NC group.

越来越多的证据表明，小胶质细胞在神经病理性疼痛的发展和维持中发挥至关重要的作用。小胶质细胞激活并与神经元的相互作用介导神经炎症和中枢敏化，从而导致持续痛觉过敏[19-20]。外周神经受损刺激脊髓背角小胶质细胞增殖和M1极化，M1极化的小胶质细胞释放肿瘤坏死因子α、IL-1β和IL-6等炎性细胞因子，这些细胞因子作用于脊髓背角神经元并迅速增强兴奋性突触传递的强度，导致神经元向兴奋性转变[21]。相反，小胶质细胞M2极化分泌抗炎和神经营养因子来修复神经损伤[22]。因此，调节小胶质细胞极化可缓解神经病理性疼痛。本研究结果显示，鞘内注射BMSCs降低SNI大鼠脊髓组织中CD86和iNOS蛋白表达并增加CD206和Arg1蛋白表达，表明BMSCs促进SNI大鼠脊髓中小胶质细胞M2极化。

KLF4是KLF家族成员中研究最多的转录因子之一，其编码基因位于染色体9q31，其蛋白由513个氨基酸组成，包含转录激活和抑制结构域，特异性结合含有CCACC核心序列的反应元件[23]。KLF4不仅调节增殖、分化和凋亡等细胞生理过程，还参与炎症和肿瘤发生[23]。最近的研究[24]表明KLF4在小胶质细胞极化中发挥作用，即KLF4可通过直接结合*Agr1*启动子区促进其转录，从而诱导小胶质细胞M2极化。研究[25]表明，KLF4表达受YY1调控，可结合*KLF4*启动子并促进其转录。YY1是细胞中常见的锌指DNA结合转录因子，可与其他转录因子相互作用激活或抑制下游基因转录[26]。研究[27]表明YY1可缓解神经病理性疼痛。本研究结果显示，鞘内注射BMSCs增加SNI大鼠脊髓组织中YY1和KLF4表达。本研究结果显示，敲减YY1降低了BMSCs干预的SNI大鼠脊髓组织中KLF4表达，并逆转了BMSCs干预对SNI大鼠神经病理性疼痛的缓解作用以及小胶质细胞M2极化的促进作用。因此可以推测BMSCs可能是通过YY1/KLF4来缓解神经病理性疼痛。

综上所述，SNI大鼠鞘内注射BMSCs可促进脊髓中小胶质细胞M2极化，缓解神经病理性疼痛，其机制可能与上调YY1介导的KLF4表达有关。然而，本研究仅验证了BMSCs介导YY1改善SNI诱导的神经病理性疼痛，而KLF4是否参与该过程仍有待进一步验证。此外，BMSCs调节SNI大鼠脊髓组织中YY1表达的分子机制有待进一步论证。

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