

静脉注射骨髓间充质干细胞在脊髓损伤后的膀胱功能修复中的作用

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[摘要] 对骨髓间充质干细胞(MSCs)的生物学特性、脊髓损伤后下尿路功能改变及其机制、干细胞修复脊髓损伤后膀胱功能的研究及其作用机制进行综述。

[关键词] 脊髓损伤;膀胱;骨髓间充质干细胞(MSCs);综述

Intravenously Injected Bone Marrow Mesenchymal Stem Cells Can Promote Recovery of Bladder Function after Spinal Cord Injury (review) HU Yang, LIAO Li-ming. Capital Medical University School of Rehabilitation Medicine, Department of Urology, Beijing Charity Hospital, China Rehabilitation Research Centre, Beijing 100068, China

Abstract: The feasibility and mechanism study on intravenously injected bone marrow mesenchymal stem cells (MSCs) improving bladder function after spinal cord injury (SCI) were discussed by review the biological characteristics of MSCs, the changes and mechanism of the lower urinary tracts after SCI, and the study on the MSCs promoting recovery of bladder function.

Key words: spinal cord injury (SCI); bladder; mesenchymal stem cells (MSCs); review

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脊髓损伤患者常出现运动功能障碍、二便障碍以及性功能障碍。尽管医学不断发展,但是医学传统的治疗手段仍不能使脊髓损伤患者完全恢复功能,尤其是下尿路功能^[1-2],这严重影响患者的生活质量^[3-4]。干细胞移植在治疗神经系统损伤和病变方面显示出巨大潜力,如脊髓损伤^[5-6]、脑外伤^[7]、帕金森病^[8]和脑卒中^[9],其中可进行脊髓损伤后细胞移植的干细胞有骨髓间充质干细胞(BMSCs)^[10]、胚胎干细胞^[5]、嗅鞘细胞^[11]、施万细胞^[11]等。

1 骨髓间充质干细胞

骨髓间充质干细胞(mesenchymal stem cells, MSCs)是骨髓中除造血干细胞(hematopoietic stem cells, HSCs)外的另一类干细胞,由德国病理学家 Cohnheim 于 1867 年首次提出。早在十九世纪六七十年代, Friedenstein 和他在莫斯科的工作组就在大量的文献中将 MSCs 一度命名为“骨髓克隆和塑料粘附干细胞”^[12-14]。早期的研究表明,这些细胞在体外培养时呈成纤维细胞集落样生长,后又有人将其命名为成纤维细胞集落形成单位(F-CFU),而且在体外特定的条件下还可以转化为骨细胞、软骨细胞和脂肪细胞等。

1.1 生物学特性 MSCs 属于成体干细胞的一种,广泛存在于胎儿和成人的各种组织和脏器中,除了骨髓,还发现存在于循环系统^[15-16]、脐带血^[17-18]、胎盘^[19]、羊水^[20]、心脏^[21]、骨骼肌^[22]、脂肪组织^[23]、滑膜组织^[24]以及胰腺组织^[25]中。这说明存在于活体组织中的 MSCs 具有多样性,即基本上所有的器官包括结缔组织都存在 MSCs。但到目前为止,骨髓仍然是间充质干细胞储存最合适的场所,而且现在用于研究向各种细胞分化的间充质干细胞几乎都是来源于骨髓。和其他组织中能够

自我更新的间充质干细胞一样, MSCs 在骨髓中的含量很低,经统计,骨髓中大约 10^6 个细胞中含有 MSC 10 个^[26];由于现在还缺乏 MSC 特异性的鉴定标记,因此 MSCs 在骨髓中的确切含量有可能更少。

MSCs 的形态与成纤维细胞相似,电镜下观察可见静止期 MSCs 胞核较大,呈椭圆形,含 1 个核仁,核浆比较大,细胞器少。活跃期的 MSCs 细胞体积较大,细胞核形态不规则,含 2~3 个核仁,细胞器丰富,提示该细胞具有较强的蛋白质合成能力。另外, MSCs 具有在塑料组织培养皿中贴壁生长的特性,可聚集成均匀的集落。

MSCs 作为一种多潜能细胞,可分化为成纤维细胞、成骨细胞、软骨细胞、脂肪细胞^[27]和肺泡上皮细胞^[28]等。在正常生物体内,绝大多数 MSCs 处于 G0 期和 G1 期,即处于相对静止的状态。只有在某些信号的诱导下,其分化潜能才被激发出来,经过多个细胞分裂周期,最终分化成为某种成熟细胞。MSCs 的分裂方式有两种,一种是对称分裂,形成两个相同的 MSCs 细胞;另一种是非对称方式^[29],一个子细胞保持亲代的特征,仍作为干细胞保留下来,另一个子细胞不可逆地分化成为功能专一的分化细胞。在理论上, MSCs 可以无限地分裂和增殖,但实际上 MSCs 并不是永生不灭的。它的数量取决于患者的年龄、取材部位、全身状况^[30]和体外培养的环境等。Burder 指出,从人髌骨处取出的 MSCs 细胞经过体外培养(38±4)代后出现老化现象^[31]。

1.2 分离和鉴定 目前有关 MSCs 的表面抗原及表面标志物的研究发现, CD34 是 HSCs 所特有的表面标志物;但是从人骨髓中分离出的 MSCs,经过体外培养,其表面抗原 CD34 转阴,因此认为骨髓造血干细胞和骨髓间充质干细胞可能是来源于同一个前体细胞的两类不同细胞, CD34 在鉴别这两类细胞上有一定的意义^[31];另外, CD56 是 HSCs 特有的表面标志,骨髓来源的 MSCs 细胞此抗原呈阴性^[32],由此可鉴别两类细胞。除此之外, MSCs 还表达以下抗原: SH-2、SH-3、SH-4、CD105^[33]、

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CD₇₃^[34]、CD₉₀、CD₁₀₆、CD₂₉、CD₄₄、CD₁₂₀ 等。但是,这类抗原的生物化学特性尚不清楚。MSCs 表达的细胞因子包括:白细胞介素(IL)-1、IL-6、IL-7、IL-8、IL-11、IL-12、IL-14、IL-15 和粒细胞集落刺激因子(G-CSF)等^[35],及这些细胞因子的相应受体。此外, MSCs 还表达干扰素受体(IFNR)、肿瘤坏死因子受体(TNFR) I、TNFR II、转移生长因子-B 受体(TGF-βR) I 和 TGF-βR II 等受体^[36-37]。MSCs 表达的细胞外基质包括 I 型、II 型、IV 型、V 型和 VI 型胶原蛋白、粘连蛋白、透明质酸酶和层粘连蛋白^[35,37]。因为 MSCs 的抗原表型并不是单一的,兼有内皮、间充质和肌肉细胞特征,至今尚未发现 MSCs 的特异性表面标志,在 MSCs 的分离和鉴定上存在困难。目前 MSCs 的鉴定主要根据其形态和培养特性,一般认为, MSCs 经体外培养,其细胞体积小,呈梭形,核浆比例较大,能传代培养。但是最可靠的检测方法是其多能的分化特性。另外,某些标记分子如 CD₄₄、CD₉₀ 等也有助于进一步认定 MSCs 细胞。

1.3 分化 目前,干细胞移植治疗神经系统疾病已成为神经科学研究的热点,目的是替代、修复受损神经组织以恢复其生理功能,为多种疾病的临床治疗开创新纪元。其中 MSCs 因其取材方便,而且能满足自体移植条件,被广泛用于神经系统外伤和疾病后干细胞移植治疗的研究。例如, Pittenger 等在体外以视黄酸和脑源性神经生长因子(BDNF)诱导 7~14 d 后, MSCs 转化为卵圆形或梭形细胞,伴有短突触,并表达巢蛋白、神经特异核蛋白(NeuN)、神经胶质纤维酸性蛋白(GFAP)等神经元和星形胶质细胞的标志物^[36]。Azizi 等将人 MSCs 用荧光素标记后注入大鼠纹状体中,发现有 20% 的供体细胞成活,分化为星形胶质样细胞,且这种细胞与脑内神经干细胞有相似的迁移方式^[38]。MSCs 能穿越血脑屏障,促进胶质的形成,为静脉输注干细胞提供可能^[39]。另外,在脑内微环境中存在的一些营养因子,如神经生长因子(NGF)等有保护 MSCs 不被破坏,促进其增殖分化,发挥其相应功能的作用。总之,在不同条件的诱导分化下, MSCs 可分化为神经元和神经胶质细胞,并表达各自的特异性标志。因此, MSCs 被认为是进行神经系统疾病干细胞治疗的理想种子细胞之一。

2 脊髓损伤后下尿路功能改变及其机制

下尿路的储尿和排尿功能有赖于大脑、脊髓、周围神经组成神经传导通路的完整性^[40]。而脊髓损伤破坏了这种神经传导通路的完整性,因而脊髓损伤患者不可避免地出现下尿路功能障碍,甚至最终出现上尿路功能损毁。

2.1 功能改变 ①脊髓休克期:膀胱处于无反射、无收缩状态,括约肌张力仍然存在,因此主要表现为急性尿潴留,除非膀胱出现严重的过度充盈,一般不发生尿失禁;②骶上脊髓损伤:因失去上位中枢主要是脑桥、中脑的抑制作用,逼尿肌出现过度活动,内括约肌协同功能正常(胸腰髓交感神经中枢以下损伤)或协同失调(胸腰髓交感神经中枢以上损伤),逼尿肌外括约肌协同失调;患者表现为贮尿和排尿功能双重障碍,出现频繁的尿失禁,同时伴有大量残余尿,并且因长期的膀胱高压可导致膀胱-输尿管返流,发生肾积水,最终发展为肾功能不全而危及患者的生命;③骶髓损伤:因为失去骶副交感神经的支配,逼尿肌无反射,膀胱高顺应性,同时受完整的交感神经支配的尿道内括约肌失弛缓,可表现为排尿困难,大量残余尿。

2.2 脊髓损伤后下尿路功能改变的机制 近些年有关脊髓损

伤后下尿路功能改变的研究表明^[41],脊髓损伤后出现膀胱过度活动以及逼尿肌括约肌协同失调(DSD)可能与以下几种机制有关:①球-脊抑制通路的消失,节段兴奋性脊髓反射的出现^[42];②膀胱传入纤维成分发生改变,C-传入纤维活化;③残存的脊髓灰质神经元可塑性改变(突触联系增强和/或形成新的突触联系);④神经递质与神经营养因子的合成、释放和/或功能发生改变^[43-44]。

2.2.1 节段兴奋性脊髓反射

2.2.1.1 对膀胱功能的影响 腰髓水平以上的脊髓损伤后,节段兴奋性脊髓反射出现,下尿路功能不能自主控制^[45]。正常下尿路的排尿功能通过接受传递膀胱膨胀牵张刺激的传入神经冲动,协调膀胱-脊髓、尿道-脊髓之间反射来完成。而在猫、鼠和人类中,脊髓损伤数周后就会出现节段脊髓反射,并使膀胱逼尿肌不自主地收缩^[40]。即使膀胱内只有很少的尿液,这种脊髓损伤后易化的脊髓反射也会使膀胱逼尿肌收缩,即出现逼尿肌过度活动(DH)^[46-48]。尽管 DH 的神经机制还不完全清楚,但是节段脊髓反射在 DH 起重大作用。当膀胱内尿量很多时,节段脊髓反射可促使逼尿肌收缩产生高膀胱压,以试图克服尿道括约肌的阻力使尿液排出^[1-2];但是膀胱充盈刺激传入冲动的同时也兴奋阴部传出神经来收缩尿道外括约肌,阻止排尿,即出现 DSD^[49]。DSD 主要是因为脊髓损伤后失去大脑高级中枢对尿道-脊髓反射的抑制作用。

总之,脊髓损伤后 DH 导致膀胱不能顺利储尿且频繁发生尿失禁。同时 DSD 导致膀胱也不能有效排空尿液,产生大量的残余尿。因此脊髓损伤的患者大多需要导尿来排空尿液。但是大量残余尿和不清洁导尿可导致膀胱炎和上尿路感染的发生^[1-2],而长期膀胱高压可导致膀胱输尿管返流、肾积水、肾结石、肾功能不全的发生^[49-50]。

2.2.1.2 对尿道括约肌功能的影响 腰髓水平以上的脊髓损伤,尿道外括约肌失去上位中枢的控制,不能随意地关闭和打开,表现为膀胱逼尿肌收缩时其不能协调地松弛,即 DSD^[51-52],或者尿道外括约肌出现部分松弛,表现为逼尿肌括约肌协同^[53-54]。这两种情况的出现与脊髓损伤后节段兴奋性脊髓反射有关^[42]。尽管脊髓损伤后尿道内括约肌不能防止因 DH 所引起的漏尿,但是在大多数脊髓损伤后患者中,当膀胱压不高时,尿道内括约肌可产生一相对恒定的张力以便膀胱储尿^[54]。脊髓损伤后膀胱充盈牵张,刺激反射性逼尿肌收缩时,尿道内括约肌可打开^[55];但是在排尿时交感神经兴奋,收缩近端尿道内括约肌,以及异常的尿道外括约肌收缩都会导致 DSD,出现排尿困难。另外,因为尿道外括约肌属于横纹肌,具有易疲劳特性,不能长时间持续收缩,产生持久的尿道高阻力,因此膀胱充盈所产生的膀胱高压就有可能在短时间内超过尿道的阻力,表现为间断性漏尿,同时伴有大量的残余尿。故脊髓损伤的患者常常表现为膀胱容量增大同时伴有频繁尿失禁。

尽管脊髓损伤后患者常常表现为 DSD,但是许多动物实验^[56-58]也显示,脊髓损伤后膀胱逼尿肌的收缩或刺激盆神经的传入纤维仍可抑制或压制尿道外括约肌的收缩。同样,在人类脊髓损伤后也可观察到损伤初期,排尿时尿道外括约肌表现为与逼尿肌协同,之后随病程延长表现为不协同的收缩^[59]。这些研究说明,在腰骶髓确实存在膀胱对尿道外括约肌的抑制性脊髓反射,但是这种抑制性脊髓反射很容易被其他几种兴奋性脊

髓反射所掩盖。例如,脊髓损伤后排尿时,尿流对尿道的刺激可兴奋尿道外括约肌并使其收缩^[60];另外,尿道外括约肌传入神经可通过会阴-会阴兴奋性反射引起尿道外括约肌的收缩^[61-62]。一般而言,脊髓损伤后会阴-会阴反射(一种原始反射)亢进,包括会阴皮肤-尿道外括约肌反射^[54, 63-64]、肛门括约肌-尿道外括约肌反射^[61, 65]、阴茎-尿道外括约肌反射^[66-68]。脊髓损伤后,除了会阴-会阴反射亢进,屈曲反射也是亢进的,这导致患者下肢的痉挛^[69]。有研究显示,脊髓损伤后的人^[51, 68]和动物^[57, 70-71]膀胱逼尿肌收缩可引起屈曲反射;而尿道外括约肌也属于屈曲反射弧效应器的一部分,猫当下肢发生屈曲反射时,尿道外括约肌也会出现兴奋收缩^[72-73]。因此,膀胱收缩可能通过诱发屈曲反射亢进,间接兴奋尿道外括约肌收缩,干扰排尿。尽管 DSD 的机制仍不清楚,但是这些兴奋性脊反射亢进在脊髓损伤后出现 DSD 中起一定作用。

脊髓损伤后,尿道外括约肌兴奋性反射亢进并占主导,但是对尿道外括约肌的抑制性脊髓反射也存在。除了膀胱-尿道外括约肌之间的抑制性反射^[56-58, 74-75]、肛门括约肌的牵张(不是收缩)也可抑制尿道外括约肌的强直性收缩^[63-65, 70, 76-78],还有躯体-会阴抑制性收缩,下肢伸肌收缩可抑制尿道外括约肌的收缩并降低尿道阻力^[72-73]。因此,治疗 DSD 的关键是促进抑制性尿道外括约肌反射并抑制兴奋性尿道外括约肌反射。

2.2.2 C 传入纤维活化 正常排尿过程最主要的传入神经是有髓的 A δ 纤维和无髓的 C 纤维,走行于盆神经,传递从膀胱壁来的刺激。其中 A δ 纤维对被动牵张和主动收缩起作用,传递膀胱充盈的信息。它的激活阈值为 5 ~ 15 cm H₂O (1 cm H₂O = 98.0665 Pa),相当于膀胱充盈初感时的膀胱内压力^[40]。C 纤维具有很高的机械阈值,主要对膀胱粘膜的化学刺激或冰冷起反应^[79]。在正常情况下,C 纤维失活,因此被称为“静止的 C 纤维”。但是脊髓损伤后,C 纤维可能活化,并成为传导膀胱感觉的主导传入纤维^[41]。

脊髓损伤后失去了脑干对骶髓的支配,骶髓节段反射使膀胱逼尿肌反射性收缩,这种脊髓节段性反射就是通过辣椒素敏感性 C 传入纤维传导的^[80-81]。这种由 C 纤维传导的脊髓反射正是脊髓损伤的动物出现低容量的逼尿肌反射性收缩和 DH 的主要原因^[82]。大量临床资料也证实了这一点,脊髓损伤患者下尿路功能也出现相似的改变,所以人们已经在广泛研究如何通过减少脊髓损伤 C 传入纤维活化来治疗神经源性膀胱。C 纤维介导的脊髓反射活化可能与脊髓损伤后神经元间突触连接的改变和膀胱壁传入神经受体性质的改变有关,这些改变导致 C 传入纤维活化、阈值降低以及对化学刺激反应的暴露^[83]。

另外,对膀胱传入神经元的电生理研究显示,脊髓损伤后神经元的生理学特性发生改变,这从另一方面说明脊髓损伤后 C 传入纤维活化对下尿路功能的影响。通过逆行轴突运输荧光染料的示踪技术定位脊髓灰质中膀胱传入神经元,并迅速分离正常大鼠和慢性脊髓损伤大鼠的腰骶髓神经节,用完整细胞膜电钳技术记录细胞膜电位变化,结果显示,脊髓损伤后 K⁺ 和 Na⁺ 通道发生改变^[84-86],绝大部分(80%)的对照组(脊髓完整)动物的膀胱传入神经元表现为可被河豚毒素(TTX)阻断的高阈值的钠通道和可在 -60 ~ -50 mV 电压激活的低阈值的钾通道(A 型),但因为离子通道的结合,正常膀胱传入神经元相对

无反应;但是在慢性脊髓损伤并伴有膀胱增生的动物中,大多数(75%)的传入神经元表现为低阈值的 TTX 敏感的钠通道,A 型钾通道消失。这些离子通道的改变增加传入神经元的兴奋性,而且在膀胱壁上传入神经受体的电生理兴奋性也有相似的改变。这就说明脊髓损伤后动物 C 传入纤维对膀胱壁刺激的敏感性增加。这些改变可能与脊髓损伤后中枢突触再生和膀胱功能恢复有关。

2.2.3 神经元的可塑性改变 有关脊髓损伤后传入神经元的形态学研究表明^[80, 87],脊髓损伤后传入神经元的可塑改变与 DSD 和功能性出口梗阻有关。脊髓横断 4 ~ 6 周的慢性脊髓损伤大鼠虽然出现反射性排尿,但是由于尿道括约肌的强直收缩,尿液不能完全排空^[88-89],膀胱容量显著增大(体重增加 5 倍),在膀胱测压中显示为逼尿肌过反射,这种收缩可被抗辣椒辣素抗体消除^[89]。对这些慢性脊髓损伤的大鼠进行解剖示踪技术研究发现,慢性脊髓损伤动物与正常对照组相比,支配膀胱的传入神经元体积显著增大(大约增大 50%)^[90]。传入神经元的增大可能与膀胱壁上传入神经树突的萌芽有关,这样可接受更多的靶组织信息。膀胱传入纤维神经元的形态学改变与脊髓损伤后排尿反射的恢复有关。

有关脊髓损伤后传入神经元可塑性的机制,不少研究者通过其他实验途径来验证。一种途径是通过尿路改道来防止截瘫后膀胱膨胀和增生^[90-91],结果发现膀胱内释放的神经营养因子减少,传入神经元体积不再增大,说明膀胱增生过程中释放的神经因子可导致神经元的改变。但是值得注意的是,尿路改道并不能防止脊髓排尿反射的出现。另外一种途径是通过局部结扎尿道造成流出道梗阻的模型来诱导神经元的可塑性改变^[92-95]。尿道结扎后增加了流出道阻力并引起膀胱增生,但是不能消除正常脊上中枢的排尿控制^[93];4 ~ 6 周的流出道梗阻可导致膀胱传入神经元(45%)和传出神经元(100%)体积增大^[92-93],并伴有膀胱内神经生长因子(NGF)的增加^[95],以及脊髓中膀胱传入纤维突触增多,脊髓排尿反射的易化^[92-93]。对 NGF 免疫排斥的大鼠研究发现,体积增大的传出神经元减少,这提示膀胱内神经营养因子水平改变可显著影响支配膀胱的神经元^[95-96]。因此,脊髓损伤后膀胱功能改变可间接地影响脊髓反射机制。

2.2.4 神经递质与神经营养因子的合成、释放和/或功能发生改变 免疫细胞化学和示踪研究显示,许多递质参与下尿路储尿和排尿。其中包括乙酰胆碱(Ach)、氨基酸(兴奋性或抑制性)、速激肽、垂体腺苷酸环化酶激活肽(PACAP)^[97]、一氧化氮(NO)^[98]、ATP^[99]、类阿片活性肽、多巴胺、5-羟色胺(5-HT)^[100]、去甲肾上腺素、促肾上腺皮质激素释放素、血管活性肽(VIP)等^[43]。

近些年,有关脊髓损伤后神经递质的改变研究比较多是 VIP、NO、NGF。其中 VIP 在 DH 的研究证实脊髓损伤后传入神经纤维成分的改变。VIP 的免疫反应性被认为是 C 传入纤维的标志^[80, 101-102],同时也是猫骶髓部分膀胱传入神经末梢突触的标志^[80]。VIP 免疫组化染色显示分布于脊髓损伤后猫的骶髓后角外侧广泛区域^[103]。这与脊髓损伤后 C 传入纤维活化的观念相符。另外,在脊髓损伤后猫鞘内注射 VIP,发现其对膀胱的作用发生改变。在正常猫中,VIP 可抑制膀胱反射而在脊髓损伤的猫中,小剂量 VIP 可易化反射^[80]。这些发现提示一

种被假定的 C-传入纤维的神经递质(VIP)随着 C-传入纤维反射活化,其作用发生改变。

除了 VIP 对脊髓损伤后下尿路功能改变有影响外,其他神经递质改变也引起脊髓损伤后膀胱传入纤维的急性改变,如类花生酸类物质、缓激肽、组织胺和 $\text{NO}^{[44]}$ 。其中,传入神经元合成的 NO 对传入通路起兴奋作用^[104+105]。另外,NO 与轴突损伤诱发的传入神经元的紧张性放电有关^[104]。最近研究发现,辣椒素敏感的 C-传入神经纤维以及膀胱粘膜上皮也可释放 $\text{NO}^{[106+107]}$ 。这些发现可能与膀胱慢性炎症^[108]上调膀胱传入神经元中 NO 合酶的含量有关,并使 NO 在脊髓损伤后增加膀胱传入途径的敏感性起作用。同时推测,膀胱粘膜上皮可能释放 NO 和其他神经活性物质,使得膀胱粘膜上皮作为尿液中有毒物质或细菌感染的感受器并传递信息给排尿中枢来诱发膀胱排空。因此膀胱粘膜信号的异常可能与脊髓损伤后膀胱过度活动有关。据报道,脊髓损伤后 NO 释放可通过膀胱的化学刺激来诱导膀胱过度活动的产生^[106]。

在脊髓损伤后鼠实验中发现,膀胱传入神经元发生形态学和生理学上改变可能是通过脊髓或膀胱释放的神经营养因子介导,如 NGF^[43]。在鼠的膀胱内长期注射 NGF 可导致膀胱过反射和膀胱传入神经元的兴奋性增加^[109]。反之,鞘内注射 NGF 的阻断剂可抑制脊髓损伤后大鼠的神经原性膀胱过度活动^[110]和 DSD^[111]的发生。

3 干细胞修复脊髓损伤后膀胱功能的研究及可能的机制

有关干细胞修复脊髓损伤后膀胱功能的研究并不多,但结果都是可喜的。2003 年, Mirsui 等对 14 只雌性脊髓损伤 Wistar 大鼠注射 BrdU 标记的 EG6 永生性神经干细胞,细胞免疫学证实移植的 EG6 永生性神经干细胞于损伤的脊髓存活并分化,且与对照组相比,实验组大鼠排尿时膀胱压显著下降,残余尿量显著下降^[112]。2005 年, Mirsui 等用限制性神经前体/限制性神经胶质前体(NRP/GRP)进行研究发现,实验组和对照组在损伤初期都出现膀胱无反射,但实验组节段脊髓排尿反射恢复更快,排尿时膀胱压降低,逼尿肌过反射发生率更低,且实验组鞘内注射坦索洛新(α -1 A 受体抑制剂)后,排尿时膀胱压可降至正常水平^[113]。

干细胞移植修复脊髓损伤后膀胱功能的机制尚未清楚,但推测可能与以下几种机制有关:①移植的干细胞存活、选择性定植于损伤脊髓中,分化为成熟的神经元细胞和/或少突胶质细胞^[114+116],形成新的传导通路恢复膀胱功能;②移植的干细胞也可能通过提供促生长因子或诱导活化自身内在“静止”的干细胞,参与神经元再生,形成新的传导通路^[117];③移植的干细胞通过诱导机体自身分泌营养因子^[118]减少继发脊髓损伤,对残存的脊髓起到局部保护作用,这种局部保护作用促进脊髓下行传导通路的萌芽,并可减少背根膀胱传入神经轴突的萌芽^[113, 118],抑制导致膀胱功能障碍的神经突触形成^[113];④移植的干细胞可诱导改变机体自身的神经递质的合成、分泌和/或功能^[113, 118]。

[参考文献]

- [1] Burns AS, Rivas DA, Ditunno JF. The management of neurogenic bladder and sexual dysfunction after spinal cord injury[J]. Spine, 2001, 26(24 Suppl):129-136.
- [2] Jamil F. Towards a catheter free status in neurogenic bladder dysfunction: a review of bladder management options in spinal cord injury

- ry (SCI)[J]. Spinal Cord, 2001, 39(7):355-361.
- [3] Hallin P, Sullivan M, Kreuter M. Spinal cord injury and quality of life measures: a review of instrument psychometric quality[J]. Spinal Cord, 2000, 38(9):509-523.
- [4] North NT. The psychological effects of spinal cord injury: a review[J]. Spinal Cord, 1999, 37(10):671-679.
- [5] McDonald JW, Becker D. Spinal cord injury: promising interventions and realistic goals[J]. Am J Phys Med Rehabil, 2003, 82(10 Suppl):38-49.
- [6] Murray M, Fischer I. Transplantation and gene therapy: combined approaches for repair of spinal cord injury[J]. Neuroscientist, 2001, 7(1):28-41.
- [7] Riess P, Zhang C, Saatman KE, et al. Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury[J]. Neurosurgery, 2002, 51(4):1043-1054.
- [8] Bjorklund A, Dunnett SB, Brundin P, et al. Neural transplantation for the treatment of Parkinson's disease[J]. Lancet Neurol, 2003, 2(7):437-445.
- [9] Savitz SI, Rosenbaum DM, Dinsmore JH, et al. Cell transplantation for stroke[J]. Ann Neurol, 2002, 52(3):266-275.
- [10] Chopp M, Li Y. Treatment of neural injury with marrow stromal cells[J]. Lancet Neurol, 2002, 1(2):92-100.
- [11] Bunge MB. Bridging the transected or contused adult rat spinal cord with Schwann cell and olfactory ensheathing glia transplants[J]. Prog Brain Res, 2002, 137:275-282.
- [12] Friedenstein AJ, Petrakova KV, Kurolesova AI, et al. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues[J]. Transplantation, 1968, 6(2):230-247.
- [13] Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells[J]. Cell Tissue Kinet, 1970, 3(4):393-403.
- [14] Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs[J]. Exp Hematol, 1976, 4(5):267-274.
- [15] Luria EA, Panasyuk AF, Friedenstein AY. Fibroblast colony formation from monolayer cultures of blood cells[J]. Transfusion, 1971, 11(6):345-349.
- [16] Kuznetsov SA, Mankani MH, Gronthos S, et al. Circulating skeletal stem cells[J]. J Cell Biol, 2001, 153(5):1133-1140.
- [17] Bieback K, Kern S, Kluter H, et al. Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood[J]. Stem Cells, 2004, 22(4):625-634.
- [18] Romanov YA, Svintsitskaya VA, Smirnov VN. Searching for alternative sources of postnatal human mesenchymal stem cells: candidate MSC-like cells from umbilical cord[J]. Stem Cells, 2003, 21(1):105-110.
- [19] Igura K, Zhang X, Takahashi K, et al. Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta[J]. Cytotherapy, 2004, 6(6):543-553.
- [20] Tsai MS, Lee JL, Chang YJ, et al. Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol[J]. Hum Reprod, 2004, 19(6):1450-1456.
- [21] Warejcka DJ, Harvey R, Taylor BJ, et al. A population of cells isolated from rat heart capable of differentiating into several mesodermal phenotypes[J]. J Surg Res, 1996, 62(2):233-242.
- [22] Young HE, Mancini ML, Wright RP, et al. Mesenchymal stem cells reside within the connective tissues of many organs[J]. Dev Dyn, 1995, 202(2):137-144.
- [23] Katz AJ, Tholpady A, Tholpady SS, et al. Cell surface and transcriptional characterization of human adipose-derived adherent stromal (hADAS) cells[J]. Stem Cells, 2005, 23(3):412-423.
- [24] Fickert S, Fiedler J, Brenner RE. Identification, quantification and isolation of mesenchymal progenitor cells from osteoarthritic synovium by fluorescence automated cell sorting[J]. Osteoarthritis Cartilage, 2003, 11(11):790-800.
- [25] Hu Y, Liao L, Wang Q, et al. Isolation and identification of mesenchymal stem cells from human fetal pancreas[J]. J Lab Clin Med, 2003, 141(5):342-349.
- [26] Baksh D, Song L, Tuan RS. Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy[J]. J Cell Mol Med, 2004, 8(3):301-316.

- [27] Verfaillie CM, Gupta P, Prosper F, et al. The hematopoietic microenvironment: stromal extracellular matrix components as growth regulators for human hematopoietic progenitors[J]. *Hematology*, 1999, 4(4): 321 - 333.
- [28] Kotton DN, Ma BY, Cardoso WV, et al. Bone marrow-derived cells as progenitors of lung alveolar epithelium[J]. *Development*, 2001, 128(24): 5181 - 5188.
- [29] Lin H. The tao of stem cells in the germline[J]. *Annu Rev Genet*, 1997, 31: 455 - 491.
- [30] Majors AK, Boehm CA, Nitto H, et al. Characterization of human bone marrow stromal cells with respect to osteoblastic differentiation[J]. *J Orthop Res*, 1997, 15(4): 546 - 557.
- [31] Simonsen JL, Rosada C, Serakinci N, et al. Telomerase expression extends the proliferative life-span and maintains the osteogenic potential of human bone marrow stromal cells[J]. *Nat Biotechnol*, 2002, 20(6): 592 - 596.
- [32] Waller EK, Olweus J, Lund-Johansen F, et al. The "common stem cell" hypothesis reevaluated: human fetal bone marrow contains separate populations of hematopoietic and stromal progenitors[J]. *Blood*, 1995, 85(9): 2422 - 2435.
- [33] Barry FP, Boynton RE, Haynesworth S, et al. The monoclonal antibody SH-2, raised against human mesenchymal stem cells, recognizes an epitope on endoglin (CD105)[J]. *Biochem Biophys Res Commun*, 1999, 265(1): 134 - 139.
- [34] Barry F, Boynton R, Murphy M, et al. The SH-3 and SH-4 antibodies recognize distinct epitopes on CD73 from human mesenchymal stem cells[J]. *Biochem Biophys Res Commun*, 2001, 289(2): 519 - 524.
- [35] Minguell JJ, Erices A, Conget P. Mesenchymal stem cells[J]. *Exp Biol Med (Maywood)*, 2001, 226(6): 507 - 520.
- [36] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells[J]. *Science*, 1999, 284(5411): 143 - 147.
- [37] Conget PA, Minguell JJ. Phenotypical and functional properties of human bone marrow mesenchymal progenitor cells[J]. *J Cell Physiol*, 1999, 181(1): 67 - 73.
- [38] Azizi SA, Stokes D, Augelli BJ, et al. Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats - similarities to astrocyte grafts[J]. *Proc Natl Acad Sci USA*, 1998, 95(7): 3908 - 3913.
- [39] Takeuchi H, Natsume A, Wakabayashi T, et al. Intravenously transplanted human neural stem cells migrate to the injured spinal cord in adult mice in an SDF-1- and HGF-dependent manner[J]. *Neurosci Lett*, 2007, 426(2): 69 - 74.
- [40] De Groat W, Am Booth NY. Nervous Control of the Urogenital System[M]. London: Harwood Academic Publishers, 1993: 227 - 289.
- [41] De GW, Yoshimura N. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury[J]. *Prog Brain Res*, 2006, 152: 59 - 84.
- [42] Tai C, Roppolo JR, De GW. Spinal reflex control of micturition after spinal cord injury[J]. *Restor Neurol Neurosci*, 2006, 24(2): 69 - 78.
- [43] Fowler CJ, Griffiths D, De GW. The neural control of micturition[J]. *Nat Rev Neurosci*, 2008, 9(6): 453 - 466.
- [44] De GW. A neurologic basis for the overactive bladder[J]. *Urology*, 1997, 50(6A Suppl): 36 - 56.
- [45] Craggs M, McFarlane J. Neuromodulation of the lower urinary tract[J]. *Exp Physiol*, 1999, 84(1): 149 - 160.
- [46] Kirkham AP, Knight SL, Craggs MD, et al. Neuromodulation through sacral nerve roots 2 to 4 with a Finetech-Brindley sacral posterior and anterior root stimulator[J]. *Spinal Cord*, 2002, 40(6): 272 - 281.
- [47] Kirkham AP, Shah NC, Knight SL, et al. The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury[J]. *Spinal Cord*, 2001, 39(8): 420 - 428.
- [48] Chartier-Kastler EJ, Ruud BJ, Perrigot M, et al. Long-term results of sacral nerve stimulation (S3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia[J]. *J Urol*, 2000, 164(5): 1476 - 1480.
- [49] Chancellor MB, Gajewski J, Ackman CF, et al. Long-term follow-up of the North American multicenter UroLume trial for the treatment of external detrusor-sphincter dyssynergia[J]. *J Urol*, 1999, 161(5): 1545 - 1550.
- [50] Blaivas JG. The neurophysiology of micturition: a clinical study of 550 patients[J]. *J Urol*, 1982, 127(5): 958 - 963.
- [51] Siroky MB, Krane RJ. Neurologic aspects of detrusor-sphincter dyssynergia, with reference to the guarding reflex[J]. *J Urol*, 1982, 127(5): 953 - 957.
- [52] Blaivas JG, Sinha HP, Zayed AA, et al. Detrusor-external sphincter dyssynergia[J]. *J Urol*, 1981, 125(4): 542 - 544.
- [53] Iwatsubo E. Bladder recovery in patients with traumatic cervical cord injury evaluated by voiding synchronous cystospheneterometry with uroflowmetry[J]. *J Urol*, 1981, 126(4): 503 - 508.
- [54] Yalla SV, Rossier AB, Fam B. Dyssynergic vesicourethral responses during bladder rehabilitation in spinal cord injury patients: effects of suprapubic percussion, crede method and bethanechol chloride[J]. *J Urol*, 1976, 115(5): 575 - 579.
- [55] McGuire EJ, Brady S. Detrusor-sphincter dyssynergia[J]. *J Urol*, 1979, 121(6): 774 - 777.
- [56] Rampil G, Mignard P. Behaviour of the urethral striated sphincter and of the bladder in the chronic spinal cat. Implications at the Central Nervous System Level[J]. *Pflugers Arch*, 1975, 353(1): 33 - 42.
- [57] Walter JS, Wheeler JS, Wurster RD, et al. Preliminary observations of a synergistic bladder-sphincter relationship following spinal cord injury in a quadruped animal[J]. *J Spinal Cord Med*, 2003, 26(4): 372 - 379.
- [58] Shefchyk SJ, Buss RR. Urethral pudendal afferent-evoked bladder and sphincter reflexes in decerebrate and acute spinal cats[J]. *Neurosci Lett*, 1998, 244(3): 137 - 140.
- [59] Denny-Brown EGR. The state of the bladder and its sphincter in complete transverse lesions of the spinal cord and cauda equina[J]. *Brain*, 1933, 56: 397 - 469.
- [60] Park JM, Bloom DA, McGuire EJ. The guarding reflex revisited[J]. *Br J Urol*, 1997, 80(6): 940 - 945.
- [61] Mackel R. Segmental and descending control of the external urethral and anal sphincters in the cat[J]. *J Physiol*, 1979, 294: 105 - 122.
- [62] Reitz A, Schmid DM, Curt A, et al. Afferent fibers of the pudendal nerve modulate sympathetic neurons controlling the bladder neck[J]. *NeuroUrol Urodyn*, 2003, 22(6): 597 - 601.
- [63] Wu YC, Nanninga JB, Hamilton BB. Inhibition of the external urethral sphincter and sacral reflex by anal stretch in spinal cord injured patients[J]. *Arch Phys Med Rehabil*, 1986, 67(2): 135 - 136.
- [64] Wyndaele JJ. Urethral sphincter dyssynergia in spinal cord injury patients[J]. *Paraplegia*, 1987, 25(1): 10 - 15.
- [65] Rodriguez AA, Awad E. Detrusor muscle and sphincteric response to anorectal stimulation in spinal cord injury[J]. *Arch Phys Med Rehabil*, 1979, 60(6): 269 - 272.
- [66] Sethi RK, Bauer SB, Dyrro FM, et al. Modulation of the bulbocavernosus reflex during voiding: loss of inhibition in upper motor neuron lesions[J]. *Muscle Nerve*, 1989, 12(11): 892 - 897.
- [67] Walter JS, Wheeler JS, Dunn RB. Dynamic bulbocavernosus reflex: dyssynergia evaluation following SCI[J]. *J Am Paraplegia Soc*, 1994, 17(3): 140 - 145.
- [68] Krane RJ, Siroky MB. Studies on sacral-evoked potentials[J]. *J Urol*, 1980, 124(6): 872 - 876.
- [69] Hornby TG, Rymer WZ, Benz EN, et al. Windup of flexion reflexes in chronic human spinal cord injury: a marker for neuronal plateau potentials? [J]. *J Neurophysiol*, 2003, 89(1): 416 - 426.
- [70] Van GJ, Schmidt RA, Tanagho EA. Development of reflex activity of detrusor and striated sphincter muscles in experimental paraplegia[J]. *Urol Int*, 1978, 33(5): 293 - 303.
- [71] Thor KB, Roppolo JR, Degroat WC. Naloxone induced micturition in unanesthetized paraplegic cats[J]. *J Urol*, 1983, 129(1): 202 - 205.
- [72] Jolesz FA, Cheng Tao X, Ruenzel PW, et al. Flexor reflex control of the external sphincter of the urethra in paraplegia[J]. *Science*, 1982, 216(4551): 1243 - 1245.
- [73] Jolesz FA, Ruenzel PW, Henneman E. Reflex inhibition of urethral sphincters to permit voiding in paraplegia[J]. *Arch Neurol*, 1988, 45(1): 38 - 40.
- [74] Bradley WE, Teague CT. Synaptic events in pudendal motoneurons of the cat[J]. *Exp Neurol*, 1977, 56(1): 237 - 240.
- [75] Bradley WE, Teague CT. Electrophysiology of pelvic and pudendal

- nerves in the cat[J]. *Exp Neurol*, 1972, 35(2) : 378 - 393 .
- [76] Donovan WH, Clowers DE, Kiviat MD, et al. Anal sphincter stretch: a technique to overcome detrusor-sphincter dyssynergia[J]. *Arch Phys Med Rehabil*, 1977, 58(7) : 320 - 324 .
- [77] Kiviat MD, Zimmermann TA, Donovan WH. Sphincter stretch: a new technique resulting in continence and complete voiding in paraplegics[J]. *J Urol*, 1975, 114(6) : 895 - 897 .
- [78] Gans BM, Zimmerman T, Stolov WC. Urinary catheterization in severe sphincter spasticity: report of two cases[J]. *Arch Phys Med Rehabil*, 1975, 56(11) : 498 .
- [79] Ikoma M, Kohno T, Baba H. Differential presynaptic effects of opioid agonists on Aδ and C-afferent glutamatergic transmission to the spinal dorsal horn[J]. *Anesthesiology*, 2007, 107(5) : 807 - 812 .
- [80] De GW, Kawatani M, Hisamitsu T, et al. Mechanisms underlying the recovery of urinary bladder function following spinal cord injury[J]. *Auton Nervous Syst*, 1990, 30(suppl) : 71 - 77 .
- [81] De GW, Araki I, Vizzard MA, et al. Developmental and injury induced plasticity in the micturition reflex pathway[J]. *Behav Brain Res*, 1998, 92(2) : 127 - 140 .
- [82] Bakshi A, Hunter C, Swanger S, et al. Minimally invasive delivery of stem cells for spinal cord injury: advantages of the lumbar puncture technique[J]. *J Neurosurg Spine*, 2004, 1(3) : 330 - 337 .
- [83] De GW. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury[J]. *Paraplegia*, 1995, 33(9) : 493 - 505 .
- [84] Yoshimura N, Erdman SL, Snider MW, et al. Effects of spinal cord injury on neurofilament immunoreactivity and capsaicin sensitivity in rat dorsal root ganglion neurons innervating the urinary bladder[J]. *Neuroscience*, 1998, 83(2) : 633 - 643 .
- [85] de Yoshimura NGW. Changes in electrophysiological and pharmacological properties of rat bladder afferent neurons following spinal cord injury[J]. *Urol*, 1995, 149 : 340 A .
- [86] de Yoshimura N, Yoshida OGW. Regional differences in plasticity of membrane properties of rat bladder afferent neurons following spinal cord injury[J]. *Urol*, 1995, 153 : 262 A .
- [87] Haferkamp A, Dorsam J, Resnick NM, et al. Structural basis of neurogenic bladder dysfunction. III. Intrinsic detrusor innervation[J]. *J Urol*, 2003, 169(2) : 555 - 562 .
- [88] Kruse MN, Belton AL, De GW. Changes in bladder and external urethral sphincter function after spinal cord injury in the rat[J]. *Am J Physiol*, 1993, 264(6 Pt 2) : 1157 - 1163 .
- [89] Cheng CL, Ma CP, De GW. Effect of capsaicin on micturition and associated reflexes in chronic spinal rats[J]. *Brain Res*, 1995, 678(1 - 2) : 40 - 48 .
- [90] Kruse MN, Bray LA, De GW. Influence of spinal cord injury on the morphology of bladder afferent and efferent neurons[J]. *J Auton Nerv Syst*, 1995, 54(3) : 215 - 224 .
- [91] Kruse MN, Bennett B, De GW. Effect of urinary diversion on the recovery of micturition reflexes after spinal cord injury in the rat[J]. *J Urol*, 1994, 151(4) : 1088 - 1091 .
- [92] Steers WD, Ciambotti J, Etzel B, et al. Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction[J]. *J Comp Neurol*, 1991, 310(3) : 401 - 410 .
- [93] Steers WD, De GW. Effect of bladder outlet obstruction on micturition reflex pathways in the rat[J]. *J Urol*, 1988, 140(4) : 864 - 871 .
- [94] Steers WD, Ciambotti J, Erdman S, et al. Morphological plasticity in efferent pathways to the urinary bladder of the rat following urethral obstruction[J]. *J Neurosci*, 1990, 10(6) : 1943 - 1951 .
- [95] Steers WD, Kolbeck S, Creedon D, et al. Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function[J]. *J Clin Invest*, 1991, 88(5) : 1709 - 1715 .
- [96] Steers WD, Creedon DJ, Tuttle JB. Immunity to nerve growth factor prevents afferent plasticity following urinary bladder hypertrophy[J]. *J Urol*, 1996, 155(1) : 379 - 385 .
- [97] Zvarova K, Dunleavy JD, Vizzard MA. Changes in pituitary adenylate cyclase activating polypeptide expression in urinary bladder pathways after spinal cord injury[J]. *Exp Neurol*, 2005, 192(1) : 46 - 59 .
- [98] Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence[J]. *Pharmacol Rev*, 2004, 56(4) : 581 - 631 .
- [99] Sugaya K, Nishijima S, Miyazato M, et al. Central nervous control of micturition and urine storage[J]. *J Smooth Muscle Res*, 2005, 41(3) : 117 - 132 .
- [100] Dolber PC, Gu B, Zhang X, et al. Activation of the external urethral sphincter central pattern generator by a 5-HT(1A) receptor agonist in rats with chronic spinal cord injury[J]. *Am J Physiol Regul Integr Comp Physiol*, 2007, 292(4) : 1699 - 1706 .
- [101] Kawatani M, Erdman SL, De GW. Vasoactive intestinal polypeptide and substance P in primary afferent pathways to the sacral spinal cord of the cat[J]. *J Comp Neurol*, 1985, 241(3) : 327 - 347 .
- [102] Kawatani M, Nagel J, De GW. Identification of neuropeptides in pelvic and pudendal nerve afferent pathways to the sacral spinal cord of the cat[J]. *J Comp Neurol*, 1986, 249(1) : 117 - 132 .
- [103] Goldberger ME, Gorio AMM. Development and Plasticity of the Mammalian Spinal Cord[M]. Padova, Italy: Liviana Press, 1986 : 65 - 80 .
- [104] Wiesenfeldt Hallin Z, Hao JX, Xu XJ, et al. Nitric oxide mediates ongoing discharges in dorsal root ganglion cells after peripheral nerve injury[J]. *J Neurophysiol*, 1993, 70(6) : 2350 - 2353 .
- [105] Morris R, Southam E, Braid DJ, et al. Nitric oxide may act as a messenger between dorsal root ganglion neurones and their satellite cells[J]. *Neurosci Lett*, 1992, 137(1) : 29 - 32 .
- [106] Kakizaki H, De GW. Role of spinal nitric oxide in the facilitation of the micturition reflex by bladder irritation[J]. *J Urol*, 1996, 155(1) : 355 - 360 .
- [107] Birder LA, Apodaca G, De GW, et al. Adrenergic and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder[J]. *Am J Physiol*, 1998, 275(2 Pt 2) : 226 - 229 .
- [108] Vizzard MA, Erdman SL, De GW. Increased expression of neuronal nitric oxide synthase (NOS) in visceral neurons after nerve injury[J]. *J Neurosci*, 1995, 15(5 Pt 2) : 4033 - 4045 .
- [109] Vizzard MA. Neurochemical plasticity and the role of neurotrophic factors in bladder reflex pathways after spinal cord injury[J]. *Prog Brain Res*, 2006, 152 : 97 - 115 .
- [110] Seki S, Sasaki K, Fraser MO, et al. Immunoneutralization of nerve growth factor in lumbosacral spinal cord reduces bladder hyperreflexia in spinal cord injured rats[J]. *J Urol*, 2002, 168(5) : 2269 - 2274 .
- [111] Seki S, Sasaki K, Igawa Y, et al. Suppression of detrusor-sphincter dyssynergia by immunoneutralization of nerve growth factor in lumbosacral spinal cord in spinal cord injured rats[J]. *J Urol*, 2004, 171(1) : 478 - 482 .
- [112] Mitsui TA, Kakizaki HI, Tanaka HI, et al. Immortalized neural stem cells transplanted into the injured spinal cord promote recovery of voiding function in the rat[J]. *J Urol*, 2003, 170(4, Part 1) : 1421 - 1425 .
- [113] Mitsui T, Shumsky JS, Lepore AC, et al. Transplantation of neuronal and glial restricted precursors into contused spinal cord improves bladder and motor functions, decreases thermal hypersensitivity, and modifies intraspinal circuitry[J]. *J Neurosci*, 2005, 25(42) : 9624 - 9636 .
- [114] Han SS, Kang DY, Mujtaba T, et al. Grafted lineage-restricted precursors differentiate exclusively into neurons in the adult spinal cord[J]. *Exp Neurol*, 2002, 177(2) : 360 - 375 .
- [115] Han SS, Liu Y, Tyler-Polsz C, et al. Transplantation of glial-restricted precursor cells into the adult spinal cord: survival, glial-specific differentiation, and preferential migration in white matter[J]. *Glia*, 2004, 45(1) : 1 - 16 .
- [116] Lepore AC, Han SS, Tyler-Polsz CJ, et al. Differential fate of multipotent and lineage-restricted neural precursors following transplantation into the adult CNS[J]. *Neuron Glia Biol*, 2004, 1(2) : 113 - 126 .
- [117] Rao MS, Mayer-Proschel M. Precursor cells for transplantation[J]. *Prog Brain Res*, 2000, 128 : 273 - 292 .
- [118] Mitsui T, Fischer I, Shumsky JS, et al. Transplants of fibroblasts expressing BDNF and NT-3 promote recovery of bladder and hindlimb function following spinal contusion injury in rats[J]. *Exp Neurol*, 2005, 194(2) : 410 - 431 .