

• 综述 •

经血源性子宫内膜干细胞及其修复外周神经损伤的应用前景

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[摘要] 外周神经损伤带给患者长期病痛的同时严重影响了患者的生活质量,目前临床上除显微外科手术外,移植施万细胞(SC)也成为有效的治疗方法。然而SC移植的先天不足限制了其在临床上的大规模使用,因此,干细胞治疗神经损伤逐渐成为近年来的研究热点。而近来发现的经血源性子宫内膜干细胞(MenESCs)凭借其丰富的来源,无创伤的分离方式以及较高的增殖活性和分化潜能等方面的优势获得广泛关注,并在成骨、心肌、肝脏、子宫内膜及中风等疾病的治疗过程中显示了良好的效果。因此,我们在明确外周神经损伤发生机制的基础上,着重阐明MenESCs的生物学特性及其在治疗外周神经损伤的机制,以期为MenESCs在外周神经损伤的治疗提供借鉴。

[关键词] 干细胞; 经血源性子宫内膜干细胞; 外周神经损伤; 神经再生

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Therapeutic potential of menstrual blood derived endometrium stem cells on the repair of peripheral nerve injury

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[Abstract] Peripheral nerve injuries not only bring long-term pain to the patients, but also seriously affect their quality of life. Of current techniques for the treatment of peripheral nerve injuries, besides the accurate microscopic surgery, Schwann cell (SC) transplantation has become an effective treatment, which plays a key role in the response of the peripheral nervous system to axonal injury. However, several drawbacks of autologous SC transplants, such as the limited sources for harvest, donor site morbidity, and difficulty expanding cells to obtain enough for transplant, have limited their use. Therefore, stem cells based therapy for improving peripheral nerve regeneration has gradually become a research hotspot in recent years. Menstrual blood derived endometrium stem cells (MenESCs) was first reported in 2007, and gained wider attention with its accessibility, no secondary surgical risk, rich source and genetic stability. Its multipotency has been demonstrated by directly differentiating them into chondrogenic, adipogenic, osteogenic, neurogenic, and cardiogenic cell lineages using the specific differentiation culture medium. This paper focuses on evaluating the therapeutic potential of MenESCs on the repair of peripheral nerve injury, and provides references to promote the clinical application of MenESCs on the peripheral nerve regeneration.

[Key words] Stem cell; Menstrual blood derived endometrium stem cell; Peripheral nerve injury; Nerve regeneration

作为外科创伤性损伤的后遗症,外周神经损伤(peripheral nerve injury, PNI)发病率高达5%,其所

带给患者的病痛及经济负担已远超疾病自身,严重影响患者的生活质量^[1,2]。尽管相对于中枢神经系统,外周神经系统具有较强的神经再生能力,但这与患者的年龄、手术时间以及损伤类型有密切的关系,而临床实践也表明,这种自发修复远不能达到令人满意的效果^[3]。实际上,外周神经损伤中轴突的再生经常被延误并且极少能完全恢复功能,Witzel等^[4]及Irintchev^[5]的研究表明,外周神经损伤经过手术治疗后也仅有10%左右的轴突能够到达靶组织。

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目前临床上除通过精确的显微外科手术接续损伤的神经外,非手术方法的联合使用在促进外周神经损伤恢复过程中也取得了长足的发展,尤其是基于细胞移植的治疗方法已受到国内外广泛的关注^[6]。近年来,细胞疗法的兴起激发了对各种干细胞的研究热潮,而存在于骨髓、脐带、脐带血、脂肪、经血等多种成体或胚胎组织中的成体干细胞(adult stem cells, ASCs),不仅克服了胚胎干细胞(embryonic stem cells, ESCs)取材难、分化不确定及伦理问题等限制,同时保持高效增殖能力和多向分化潜能,并且在体外特定培养条件下可向神经样细胞分化,为外周神经再生的细胞治疗提供了良好的种子细胞^[7~9]。

1. 外周神经损伤的发病机制及施万细胞(Schwann cell, SC)移植

当外周神经受损时,受损神经元近端在损伤发生的数小时内,即可快速地由“信号传导”模式转变为“轴突再生”模式,从以合成信号传导介质为主转变为合成轴突生长所需蛋白为主,在受损轴突处发出相当数量的侧芽向远端前进;而受损神经元远端则会经历沃勒变性(Wallerian degeneration),促进围绕受损神经末梢的SC分泌神经营养因子促进轴突再生,进一步协同巨噬细胞迅速清理具有抑制轴突再生活性的残留物,形成Büngner带引导胞体近端新生的轴突芽成功穿过损伤区域^[10~12]。然而促进神经再生的微环境具有时效性。已有研究表明,啮齿类动物外周神经损伤发生8周后远端微环境促进轴突再生的能力显著减弱,6个月后完全消失,其主要原因是SC萎缩所导致基板和Büngner带变性消失,以及受损神经元所控制的靶组织随时间推移出现萎缩。因此,在有限的时间里重建近端再生的轴突与靶组织的神经联系,既是外周神经损伤修复的关键^[3,13]。

施万细胞在沃勒变性、髓鞘再生及促进轴突生长中均扮演重要角色。当损伤发生时SC被激活,从髓鞘生成表型转分化为更原始的修复表型,下调与髓鞘生成相关基因的表达的同时,上调内在神经生长因子及与再生相关的关键转录因子表达来促进轴突的生长^[3,14,15]。进一步,SC通过分泌细胞黏附因子,如白细胞介素1(IL-1)、神经钙黏蛋白(N-cadherin)及神经黏附因子(nerve adhesion molecule, N-CAM)等募集与修复相关的细胞,共建促进轴突再生的有利环境^[16]。因此,SC移植一度成为外周神经损伤修复的研究热点,并取得了积极的治疗效果^[12,16,17]。然而SC移植的先天不足限制了其在临床上的大规模使用,如种子细胞获取较难,对供体造成的二次伤害以及其在体外增殖乏力难以达到治疗

所需细胞浓度等^[18]。所以选择合适的替代细胞将成为外周神经再生的关键。

目前,常用的骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)和脂肪间充质干细胞(adipose tissue-derived stem cells, ADSCs)已在动物模型的外周神经再生中取得良好治疗效果,并且若干研究已进入临床实验阶段,这为ASCs修复外周神经损伤提供了有力支持^[17~20]。而经血源性子宫内膜干细胞(menstrual blood-derived endometrium stem cells, MenSCs)凭借其无创的分离方式、较强的增殖活性及多向分化潜能等优势亦获得了国内外广泛关注(表1)。

2. 经血源性子宫内膜干细胞生物学特性及临床前研究

2.1 来源:子宫作为人体中具有超强再生能力的器官,其子宫内膜在每个月经周期中会增长5~7mm,而以这种增长速率,子宫内膜会在妇女育龄期经过500次左右有规律的脱落和再生过程,这不仅表明, MenSCs的来源丰富,同时也暗示MenSCs具有较强的增殖活性^[21,22]。已有研究推测, MenSCs的最初来源有两种,一是源于残留的胚胎干细胞,二是源于骨髓来源的干细胞,而最新的证据显示源于前者的可能性较大。此外,存在于正常生理活动的废弃物中的MenSCs除取材方便,对供体无二次手术风险外,其存在于世界上50%的口中,能同时满足自体及异体移植的需求^[22~26]。

2.2 表面标志物及亚群:作为ASCs家族成员之一, MenSCs除表达CD29(>99%)、CD44(>99%)、CD73(>99%)、CD90(>95%)及CD105(>99%)等ASCs表面标志物外,同时表达多向分化潜能标志物Oct-4、SSEA-4、性别决定基因高迁移率组蛋白-2(sex determining region Y-box-2, Sox-2)及Nanog,提示MenSCs具有较高分化潜能^[24,25,27]。进一步,为稳定及优化MenSCs的临床治疗效果, Schwab等^[28]和Masuda等^[29]先后通过免疫磁珠及流式分选等方法纯化获得共表达CD146/CD140b以及单独表达W5C5表面受体的MenSCs,并在动物实验中证明该亚型细胞可促进子宫内膜组织的再生,表明该亚群细胞的MenSCs可作为细胞治疗首选。此外,通过Hoechst33342染色可从MenSCs中分离获得约2%的侧群(side population)细胞,该类细胞不仅具有良好的增殖、分化活性,同时表达多向分化潜能标志物Oct-4,且端粒酶活性介于ESCs和成熟细胞之间;然而该类侧群细胞阳性表达CD146和CD140b表面受体,但阴性表达W5C5,因此对于MenSCs中的细胞亚群还有待进一步的研究^[30,31]。另外,Du等^[32]未采用传统的密度梯度离心法分离

表 1 8 种干细胞的特点比较

Table 1 The biological characteristics of eight kinds of stem cells

	ESCs	iPCs	成体干细胞(adult stem cells)					
			NSCs	BMSCs	ADSCs	UcMSCs	DPSCs	MenESCs
来源 origin	胚胎 embryo	体细胞 somatic cells	大脑 brain	骨髓 bone marrow	脂肪 adipose	脐带 umbilical cord	牙髓 dental pulp	经血 menstrual blood
伦理问题 ethical problem	+	-	-	-	-	-	-	-
资源丰富 richness	-	+	-	-	+	-	-	+
获取方式 有无创伤 invasiveness in sample collection	+	+	+	+	+	-	+	-
免疫原型 immunogenicity	+	+	-	-	-	-	-	-
免疫调节 immunomodulation	-	-	+	+	+	+	+	+
自体移植 autologous transplantation	-	+	+	+	+	-	+	+

+, 优点; -, 不足。

ESCs, 胚胎干细胞; iPCs, 诱导性多能干细胞; NSCs, 神经干细胞; BMSCs, 骨髓间充质干细胞; ADSCs, 脂肪间充质干细胞; UcMSCs, 脐带间充质干细胞; DPSCs, 牙髓干细胞; MenESCs, 经血源性子宫内膜干细胞

+, Advantages; -, Disadvantages

ESCs, Embryonic stem cells; iPCs, Induced pluripotent stem cells; NSCs, Neural stem cells; BMSCs, Bone marrow mesenchymal stem cells; ADSCs, Adipose tissue-derived stem cells; UcMSCs, Umbilical cord mesenchymal stem cells; DPSCs, Dental pulp stem cells; MenESCs, Menstrual blood-derived endometrium stem cells

MenESCs, 而直接通过裂解经血样本中的红细胞后, 经过贴壁黏附亦成功分离获得了 MenESCs。

2.3 增殖及分化潜能: 相较于 BMSCs 和脐带血来源的 ASCs 等, MenESCs 不仅具有更佳的增殖活性 (根据不同的培养技术和条件, 其倍增时间为 18 ~ 36h); 同时亦具有较强的遗传稳定性, 传至 68 代时核型无畸变^[24, 27, 33]; 而该结果已在本课题组的前期研究中获得证实, 原代 MenESCs 在经过 2 ~ 3 周的潜伏期后, 进入快速增长阶段。对于 MenESCs 分化潜能的研究, 不同实验室通过标准诱导条件已将其诱导分化成脂肪、骨、软骨、心肌、神经、肝脏及胰腺等 9 种源于 3 个不同胚层的细胞类型^[27, 31, 34 ~ 40]。此外, MenESCs 更易被转化为诱导性多能干细胞 (induced pluripotent stem cells, iPSCs), 仅需同时转染 Oct-4 和 Sox-2 即可; 而已知的成纤维细胞则需要同时转染 Oct-4、Sox-2、c-MYC 及 KLF4 4 个转录因子。上述结果均表明 MenESCs 自身具有较强的多向分化潜能^[41]。

2.4 免疫原性及安全性: 研究表明, MenESCs 不表达 MHC II 类受体, 极微量表达 MHC I 类受体 (< 1%) , 提示 MenESCs 具有较低的免疫原性^[34]。且体外实验通过与外周血单核细胞 (peripheral blood mononuclear cells, PBMCs) 共培养的结果也证明, MenESCs 仅具有极微弱的免疫刺激反应; 进一步动

物模型 (小鼠、大鼠及猪等) 的体内实验结果也验证了上述观点^[39]。而在裸鼠皮下注射 2×10^6 MenESCs 后, 在注射位置未发现肿瘤形成, 并且各脏器 HE 染色结果表明, MenESCs 无致瘤性^[36]。同时 MenESCs 在临床上异体移植的安全性已于 2009 年进行过首次报道, 4 名患多发性硬化症的女性患者通过静脉或鞘内注射的方式输注 MenESCs 后 12 个月无副作用产生。随后, Medistem 公司启动了 MenESCs 治疗充血性心脏衰竭的 II 期临床试验, 17 位接受 MenESCs 治疗的患者未发现与干细胞输入相关的不良反应。而近来的另外 2 例输注 MenESCs 患者也均无副作用及免疫反应产生, 上述实验结果为 MenESCs 临床应用的安全性提供了保障^[23]。

2.5 临床前研究: 凭借 MenESCs 的上述优势, 其作为细胞治疗的种子细胞近年来得到了国内外的广泛关注, 通过啮齿类动物模型已发现其在心肌梗塞、Duchenne 型肌营养不良、1 型糖尿病、结肠炎及子宫内膜修复等疾病的治疗中均展示了良好的应用前景, 详见表 2。

3. 经血源性子宫内膜干细胞修复外周神经损伤的潜在机制

尽管目前对于 MenESCs 修复外周神经损伤的机制相对缺乏, 但近来食品及药物管理局 (Food and Drug Administration, FDA) 已启动 1 个 I / II 期临床

表2 MenESCs 在动物模型中对相关疾病治疗的研究进展

Table 2 Preclinical animal trials using MenESCs

动物疾病模型 animal disease model	方法 method	实验结果 result	参考文献 reference
小鼠杜氏肌营养不良模型 murine model of Duchenne muscular dystrophy	腿部肌肉注射 2×10^7 个细胞, 3 周后检测 2×10^7 cells were locally injected into thigh muscle of animal models	MenESCs 体内移植可通过与宿主细胞融合促进肌营养不良蛋白的产生 transplanted MenESCs could restore sarcolemmal expression of dystrophin, due to cell fusion between host myocytes and implanted cells	2007 [42]
大鼠心肌梗死模型(裸大鼠) nude rat model of myocardial infarction	心肌梗死区域局部注射 $(1 \sim 2) \times 10^6$ 个细胞, 2 周后检测 $(1 \sim 2) \times 10^6$ cells were injected into the myocardial infarction area	MenESCs 可融入心肌梗死区域的心肌中, 改善动物模型的心肌功能, 并阳性表达心肌细胞表面标志物 transplanted MenESCs restored impaired cardiac function, decreasing the myocardial infarction area, MenESCs-derived cardiomyocytes could be observed in the myocardial infarction area <i>in vivo</i> .	2008 [39]
大鼠颅内胶质瘤模型 rat model of glioma	大鼠颅内成瘤后, 颅内或静脉注射 $(1 \sim 3) \times 10^6$ 个细胞, 2 周后检测 $(1 \sim 3) \times 10^6$ cells were transplanted into animal models by i. v or intratumoral injection	MenESCs 能够显著抑制瘤内新血管生成, 减少肿瘤体积 transplanted MenESCs exert a therapeutic effect associated with inhibition of angiogenesis and reduction in tumor volume	2009 [43]
大鼠中风模型 rat model of experimental stroke	颅内纹状体或静脉注射 $(4 \sim 40) \times 10^6$ 个细胞, 2 周后检测 $(4 \sim 40) \times 10^6$ cells were transplanted into animal models by i. v or intracerebral injection	MenESCs 能够保护中风后的大鼠神经元, 并改善中风后的治疗效果 transplanted MenESCs could protect neurons, and improve the therapeutic effect of rats after stroke	2010 [37]
小鼠子宫内膜再生模型(NOG 小鼠) murine model of endometrial regeneration	$(1 \sim 10) \times 10^4$ 个细胞移植入模型动物肾脏中, 8~10 周后检测 $(1 \sim 10) \times 10^4$ cells were transplanted under the kidney capsule of severely immunodeficient mice	MenESCs 可再生有序的子官内膜组织, 并在模型动物肾脏中形成新血管 transplanted MenESCs generated endothelial cells that migrated into the mouse kidney parenchyma and formed mature blood vessels	2010 [31]
小鼠肝切除移植模型 murine model of liver injury	1.5×10^6 个细胞经脾脏注射入小鼠肝切除模型, 2 周后检测 1.5×10^6 cells were transplanted into animal models by intrasplenic injection	可在肝脏中检测到 MenESCs 来源的肝样细胞, 表达人白蛋白; 可恢复模型动物血清白蛋白水平并显著抑制转氨酶活性 the MenESC-derived hepatocyte-like cells were detected in recipient livers and expressed human ALB protein, and suppressed transaminase activity of liver injury animals.	2013 [44]
小鼠卵巢功能早衰模型 murine model of premature ovarian failure	模型制作成功后, 卵巢局部注射 1×10^4 个细胞, 3 周后检测 1×10^4 cells were locally injected into ovarian of animal models	MenESCs 可在注射部位至少存活 2 周, 并在子宫微环境下向子宫样细胞转化, 改善早衰性子官功能 transplanted MenESCs could survive within POF mouse ovaries for at least 14 days, could be stimulated to differentiate into ovarian tissue-like cells in an ovarian microenvironment in POF ovarian tissue	2014 [45]
小鼠 1 型糖尿病模型 murine model of type 1 diabetes	尾静脉注射 3×10^5 个细胞, 3、7、10、14、21 及 28d 后检测 3×10^5 cells were transplanted into animal models by i. v, and the tests were performed at day 3, 7, 10, 14, 21, and 28	MenESCs 可降低模型动物的血糖及体重损失, 延长动物寿命并增加胰岛素分泌 transplanted MenESCs could reverse hyperglycemia and weight loss, prolong lifespan, and increase insulin production in diabetic mice	2014 [46]
小鼠结肠炎模型 murine model of experimental colitis	静脉注射 10^6 个细胞, 模型制作后 2、5 及 8d 后注射 1 次, 2 周后检测 10^6 cells were transplanted into animal models by i. v at day 2, 5 and 8	MenESCs 处理组可显著减轻结肠炎的症状及体征, 如体重减轻、血便、腹泻和黏膜溃疡等 transplanted MenESCs attenuated colitis with significantly reduced disease activity index, decreased levels of intra-colon IL-2 and TNF- α , but increased expressions of IL-4 and IL-10	2014 [47]
小鼠败血症模型 murine model of sepsis	腹腔或静脉注射 7.5×10^5 个细胞, 12h 到 4d 内检测 7.5×10^5 were transplanted into animal models by i. v or i. p	MenESCs 联合抗生素使用可显著增大小鼠生存率, 并且改善多种器官功能 transplanted MenESCs in synergy with the antibiotic treatment markedly improved survival in CLP-induced sepsis by acting on multiples targets	2015 [48]
小鼠肾脏缺血再灌注模型 murine model of renal ischemia reperfusion injury	提前 2h 静脉注射 10^6 个细胞, 模型构建 48h 检测 10^6 cells were transplanted into animal models by i. v before animal model	MenESCs 处理组可显著减轻肾脏损伤, 并保存较好功能 transplanted MenESCs could significantly attenuate renal ischemia-reperfusion injury, and effectively prevented renal damage in animal model	2016 [49]

试验,研究不适合进行外科手术的严重肢体缺血损伤后 MenESCs 治疗效果。并且 MenESCs 在修复中枢神经系统疾病如,中风及帕金森病等疾病的过程中已获得了明显的效果。结果表明 MenESCs 可迁移到神经受损部位,通过免疫调节作用及旁分泌神经营养因子来修复神经损伤^[27,37,40]。进一步结合 BMSCs 和 ADSCs 等 ASCs 在修复外周神经损伤中的研究结果,推测 MenESCs 促进外周神经再生机制主要包括以下两个方面(图 1):(1) 转化为神经样细胞(SC 等),替代受损细胞行使相关功能;同时旁分泌神经营养因子促进外周神经再生,如脑源性神经营养因子(brain derived neurotrophic factor, BDNF)、神经生长因子(NGF)以及神经胶质细胞源性的神经营养因子(glial cell line derived neurotrophic factor, GDNF)等;(2) 通过免疫调节作用抑制炎症反应,为神经再生提供有利微环境。

3.1 成神经样细胞分化潜能: 自 2007 年 Meng^[24]和 Patel^[27]等对 MenESCs 的生物学特性展开深入研究以来,其跨胚层向神经样细胞分化的潜能便已得到证实。研究表明,未分化的 MenESCs 阳性表达神经干细胞标志物 Nestin,进一步通过不同诱导剂组合[β -巯基乙醇、全反式视黄醛、EGF、bFGF、血小板源性生长因子(platelet derived growth factor, PDGF)等]可定向诱导 MenESCs 表达神经元表面标志物神经元核抗原(neuronal nuclei, NeuN)、微管相关蛋白-2(microtubule associated protein-2, MAP-2)、 β -III 微管蛋白(β -III-tubulin),以及神经胶质细胞标志物 GFAP、S100、Olig-2 等^[24,27,50,51]。此外,与 BMSCs 相比, MenESCs 在分化过程中尽管胶质样细胞表面标志物的表达种类和模式有所差异,但两者向神经胶质样细胞分化的潜能无显著差异;而且在向神经样细胞诱导分化前后, MenESCs 均高表达 BDNF^[52]。

3.2 免疫调节作用: 炎症反应对于外周神经再生是不利的,尽管早期炎症可能加速修复反应,但引起的纤维化最终将阻碍外周神经再生。而 ASCs 除通过较强的自我更新能力及多向分化潜能来促进受损组

织再生外,其还可通过调节免疫细胞的增殖、分化和免疫因子分泌,如先天免疫反应中的巨噬细胞、NK 细胞和嗜中性粒细胞,以及获得性免疫中的 T、B 淋巴细胞和树突状细胞等,最终通过抑制免疫炎症反应为受损组织的再生提供良好微环境^[53,54]。已有研究表明,在脊髓损伤实验中, BMSCs 移植能显著减轻实验性脊髓损伤的慢性炎症,并且证实 BMSCs 对于感觉运动功能的增强作用至少有部分是依赖其免疫抑制(抗炎)作用来实现的;而在应用脐带血来源的 ASCs 移植治疗犬类脊髓损伤中亦发现,细胞移植后可显著降低与炎症相关的转录因子和分子的表达,如 pSTAT3、GALC 和环氧化酶 2(cyclooxygenase 2, COX2);同时利用三碘甲腺氨酸诱导的 NSCs 要较未诱导的 NSCs 更加明显地改善实验性变态反应性脑脊髓炎大鼠脑内的炎症浸润和脱髓鞘^[55~57]。另外,对于 MenESCs 的免疫调节作用在小鼠结肠炎和败血症等实验动物模型中均已获得验证^[47,48]。

3.3 细胞移植类型: 对于治疗外周神经损伤是使用未分化的 ASCs 还是通过定向诱导预分化所获得的神经样细胞目前仍存在争议。尽管有观点认为,将 ASCs 预先定向分化为神经胶质样细胞或其它神经样细胞在促神经再生的潜能上与直接使用未分化的 ASCs 没有明显改善^[58]。但 Tomita 等^[59]近期通过比较分析未分化和分化的人 ADSCs 在体内外促进神经再生能力的研究表明,相较于未分化的 ADSCs,分化成为施万样细胞的 ADSCs 能够分泌更多 BDNF、NGF 以及 GDNF,并且明显改善髓鞘形成速率及存活时间;并且杜杰等^[57]研究发现,预诱导的 NSCs 和未诱导的 NSCs 均能显著保护实验性变态反应性脑脊髓炎大鼠中枢神经系统功能,且诱导后的 NSCs 保护效果更佳。推测除分泌更多神经营养因子来促进外周神经再生以外,定向分化后的施万样或神经胶质样 ASCs 能够更容易地整合到新形成的髓鞘中,补充因损伤而丢失或死亡的施万细胞,持续发挥促进神经再生的潜能,同时避免因大量摄入未分化的 ASCs 后对人体健康造成的不确定性^[60]。然

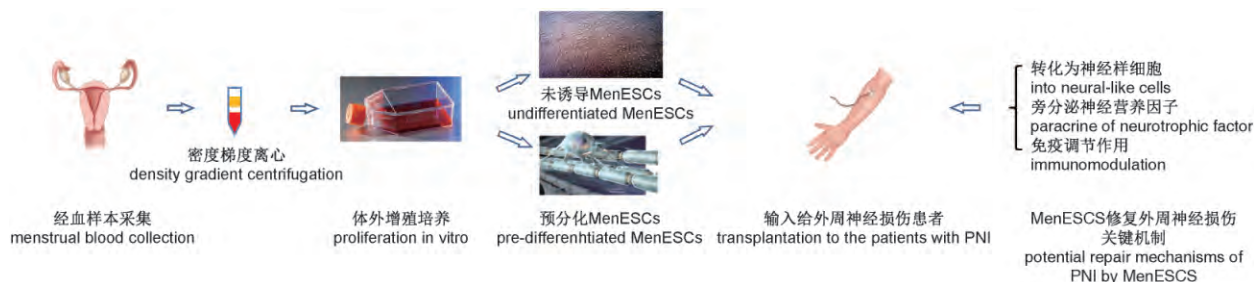


图 1 MenESCs 治疗外周神经损伤策略及潜在修复机制

Fig. 1 The potential treatment of peripheral nerve injury by MenESCs

而目前将 MenESCs 预先诱导分化为神经胶质样细胞的主流方法均为通过相关化学或神经生长因子诱导,不仅诱导周期长、成本高,而且所获得的预分化细胞活力差^[24,27,61,51]。因此若通过高通量测序技术分析 MenESCs 诱导成胶质样细胞前后相关基因的表达变化,寻找出潜在的促分化的关键基因后,通过基因工程转染关键基因,促进 MenESCs 向神经胶质样细胞或施万样细胞方向分化,为外周神经损伤的治疗提供更优良种子细胞。

4. 展望

作为 ASCs 家族的重要成员, MenESCs 凭借其来源丰富、无创伤的分离方式以及较高的增殖活性和分化潜能等方面的优势获得了国内外的广泛关注。在临床应用 MenESCs 的安全性获得保障的前提下,其已在成骨、心肌、肝脏、子宫内膜及中风等疾病的治疗过程中展示了令人满意的效果,为其作为外周神经损伤修复的优良种子细胞提供实验依据。因此,在明确 MenESCs 修复外周神经损伤机制的基础上,规范 MenESCs 的分离培养方法,同时探索合适的给药方式(静脉、动脉及局部注射等),细胞输注量以及细胞移植类型(未分化或预分化后的 MenESCs)等,将会加速其在临床上的应用。

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