

干细胞治疗女性压力性尿失禁研究进展

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摘 要

压力性尿失禁(stress urinary incontinence, SUI)是一个影响女性身心健康的难题,近年来,随着我国人口政策的调整、社会老龄化的发展,其发病率也逐年上升。压力性尿失禁不仅严重降低了患者的生活质量,还增加了患者焦虑、抑郁等精神心理负担。现有疗法只能缓解患者症状,无法彻底治愈。干细胞是一类具有多向分化、自我更新能力的细胞,随着细胞生物学和组织工程技术的发展,其潜在的临床治疗作用引起了人们的关注。本文总结了近年来干细胞在治疗压力性尿失禁中的研究进展,并对其局限性和未来应用进行了讨论和展望。

关键词

干细胞, 压力性尿失禁, 综述

Research Progress on Stem Cell Therapy for Female Stress Urinary Incontinence

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Abstract

Stress urinary incontinence is a challenging issue affecting women's physical and mental health. In recent years, with adjustments in population policies and the development of social aging in China, its incidence has been increasing annually. Stress urinary incontinence not only severely reduces patients' quality of life but also increases their psychological burdens such as anxiety and

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depression. Current therapies can only alleviate symptoms without providing a complete cure. Stem cells are a type of cell with multi-directional differentiation and self-renewal capabilities. With advancements in cell biology and tissue engineering technology, their potential clinical therapeutic effects have garnered attention. This paper summarizes recent research progress on the use of stem cells in treating stress urinary incontinence, discusses their limitations, and explores future applications.

Keywords

Stem Cells, Stress Urinary Incontinence, Review

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1. 引言

压力性尿失禁(stress urinary incontinence, SUI)是指喷嚏、咳嗽、大笑或运动等活动使腹压增加时,尿液不自主地自尿道流出[1],其发病机制主要与骨盆底支持结构的丧失和内在的尿道括约肌缺陷有关[2]。阴道分娩次数、肥胖、吸烟、年龄等都是与其发病相关的高危因素[3]。有研究表明,全球范围内女性尿失禁的发病率为10%~40%[4],而SUI占有尿失禁类型的50%[5]。在我国成年女性中SUI的发病率为18.9%,发病率最高的年龄段是50~59岁,高达28%[6]。SUI不仅严重影响患者日常生活、工作、社交等方面,还容易引起患者产生焦虑、抑郁等不良情绪,损害患者的身心健康[7]。

干细胞是一类具有多向分化和自我更新能力的细胞,在适当条件下可以定向分化为特定功能的组织细胞,替代已损伤、老化、凋亡的细胞,进而恢复和维持组织的正常功能。现有研究表明,干细胞具有抗炎、抗凋亡、抗氧化应激、促血管生成等作用[8][9],此外,干细胞还可分泌细胞因子、趋化因子、生长因子等可溶性因子,为组织修复提供支持[10]。故可利用干细胞上述功能和特性来解决因组织损伤所致的尿路功能障碍。本文基于此,对干细胞在治疗女性SUI的研究进展进行综述,探讨其局限,展望其未来发展和应用。

2. 有关 SUI 治疗的干细胞类型及研究

2.1. 肌源性干细胞(Muscle-Derived Stem Cells, MDSCs)

通过局部麻醉后,可从肌肉组织中分离成肌细胞和MDSCs。成肌细胞是单能干细胞,在肌细胞出现损伤时可自我更新并分化为肌细胞,用于机体组织修复和生理运转[11]。MDSCs不仅可以分化为骨骼肌、心肌和平滑肌细胞[9],在体外还可以分化为神经元、内皮细胞等不同细胞系[12],且其移植后存活率也高于成肌细胞[13],故MDSCs是SUI治疗研究较理想的细胞。

动物研究表明,在大鼠体内注射MDSCs,可促进肌管和肌纤维的形成,恢复受损尿道括约肌功能,达到初始闭合值的80%[14]。有研究对比MDSCs与其他类型干细胞移植治疗SUI的效果发现:MDSCs组的治疗效果较其他类型的干细胞更加明显[15]。另外,有研究发现,纤维蛋白胶可增加移植后MDSCs的存活率,进而改善、恢复SUI大鼠尿道括约肌组织学和功能的作用[16]。上述研究在动物实验层面证明了MDSC移植治疗SUI的可行性和有效性。现有的部分临床研究显示,自体MDSCs移植治疗SUI的有效率为41%~77%[17][18],且其并发症较少,短期随访结果表明,是治疗SUI一种安全、有效的方法。

近期一项对比干细胞注射与传统手术疗效差异的研究表明,两种治疗方式都显著改善了患者生活质量、临床症状,干细胞注射治疗较手术治疗并发症少,但其治疗有效率还是明显低于手术组[19]。虽然较传统手术 MDSC 移植治疗 SUI 有其优势,但其自身增殖活性较其他干细胞弱,可能需要多次注射来保证疗效,这增加了治疗相关的风险,且现有的相关临床研究较少,部分研究结果间存在矛盾,故其治疗结果的有效性、安全性仍待进一步研究。

2.2. 脂肪干细胞(Adipose-Derived Stem Cells, ADSCs)

ADSCs 可从脂肪组织中提取,它的提取方法简便,创伤较小,一次可收获数量满意的干细胞,且其增殖活性强,在体外也可被诱导分化为脂肪细胞、软骨细胞、神经细胞、骨骼肌和平滑肌细胞等不同细胞[20],也是用于研究 SUI 治疗的理想干细胞来源。

有学者将 ADSCs 形成的微组织注射到尿失禁模型雌鼠尿道后,干预组大鼠排尿功能和组织病理学结构恢复均优于对照组[21];Li 等人对比不同移植方式对于 SUI 大鼠治疗效果的发现,尿道周围和静脉注射 ADSCs 均可促进 SUI 组织修复、排尿功能改善,两组间相关测量指标无统计学差异[22]。Wang 等人利用超顺磁性氧化铁纳米颗粒的磁性靶向标记辅助 ADSC 移植定位,提高了其在受损部位的保存率,促进了 SUI 大鼠括约肌结构和功能的恢复[23]。临床研究方面,Kuismanen 等人对 5 名 SUI 女性患者经膀胱镜经尿道注射 ADSCs 和胶原蛋白的混合物的研究显示,随访 6 个月和 1 年时,分别有 1 名、3 名患者咳嗽试验阴性,所有患者症状均有主观改善[24]。一项针对 10 名 SUI 妇女进行尿道自体 ADSCs 移植治疗并进行随访的临床试验表明,患者尿失禁症状在注射治疗后的前 2 周、第 6 周和第 24 周显著减少,尿垫试验(pad-test)结果和尿失禁问卷简表评分较治疗前均有显著性差异,证明了其治疗的短期有效性[25]。近来,Garcia 等人开展的两项 I 期和 II 期临床研究也均表明 ADSC 移植治疗 SUI 可显著改善患者临床症状和 pad-test 结果[26]。以上研究均表明了 ADSC 移植治疗 SUI 的巨大潜力和应用前景。

2.3. 骨髓间充质干细胞(Bone Marrow-Derived Mesenchymal Stem Cells, BMSCs)

BMSCs 是最早被人们发现证实的干细胞[27],它是存在于骨髓内的一种非造血多功能干细胞,一般麻醉后通过骨髓活检取得,具有多向分化潜能,可向成骨系细胞、脂肪细胞、成纤维系细胞等分化[28],是目前细胞治疗和组织工程中最常用的干细胞。

Kim 和 Corcos 等人的研究均表明,向 SUI 大鼠尿道移植 BMSC,可显著提高其漏尿点压力值(leak point pressure, LPP)且移植的 BMSC 表达肌细胞特异性标志物,提示 BMSC 可能通过肌源性分化,修复受损组织,改善 SUI 症状[29][30]。有学者通过在尿道注射过表达趋化因子受体(chemokine receptor, CCR)的 BMSC 和趋化因子 7 配体(chemokine (c-c motif) ligand 7, CCL7),发现组织损伤处干预组 BMSC 数量远高于其他组,且干预组大鼠尿动力学参数改善明显[31],为治疗 SUI 提供了新的可能。Janssen 等通过向 SUI 模型大鼠接种不同剂量的 BMSC,发现多剂治疗的 SUI 大鼠促进了尿道结缔组织的修复和神经肌肉连接,显著改善了 LPP,而单剂治疗的 SUI 大鼠则效果不明显[32],为今后 SUI 治疗方式和剂量的选择做出了初步探索。近期,Jiang 等的研究表明,BMSC 外泌体可以通过激活阴道前壁的成纤维细胞,促进其增生和分泌胶原蛋白,进而帮助模拟产伤所致的 SUI 大鼠的功能及解剖恢复[33]。但由于 BMSC 提取过程较其他类型干细胞复杂,并发症风险高,故现有研究均集中于动物实验,后续临床研究和应用受到较大限制,仍有诸多难题需要解决。

2.4. 人脐带间充质干细胞(Human Umbilical Cord Mesenchymal Stem Cells, hUCMSCs)

hUCMSCs 可从人脐带血中获得,其制备方法简单、无创,具有较低的免疫原性和病毒污染风险,还

可以从捐赠者库中获取[34],且较成体干细胞分化能力更好[35],也具有自我更新和多向分化能力[36]。

Lim 等的研究表明,在内在括约肌缺陷(intrinsic sphincter deficiency, ISD)的模型大鼠注射 hUCMSCs 4 周后,组织学检查发现,对照组的括约肌受到破坏,肌层萎缩和胶原沉积明显,而干预组促进了括约肌修复,在组织切片中发现了被标记的注射的 hUCMSCs 细胞;平均漏点压力测量结果表明实验组的括约肌功能较对照组有明显改善[37]。Luo 等对 SUI 模型大鼠在尿道周围注射 hUCMSCs 后,对比发现两组大鼠在喷嚏试验阳性率、漏尿点压力等数据均具有统计学差异,干预组大鼠尿道及周围组织中结缔组织含量增加,荧光标记细胞增多。表明尿道周围注射 hUCMSCs 可促进 SUI 大鼠尿道周围的支撑结构的修复和更新,改善其 SUI 症状[38]。目前关于 hUCMSCs 治疗 SUI 的临床研究较少, Lee 等在 2005 年 7 月至 2006 年 7 月期间,对 39 名 SUI 妇女进行的经尿道 hUCMSCs 注射治疗,分别于术后 1、3、12 个月进行评估。结果表明:所有患者术后均无并发症发生;大部分患者症状较前改善明显,且对于干细胞移植前最大尿道关闭压力(maximal urethral closing pressure, MUCP)结果小于 30 cmH₂O 的内在括约肌缺陷所致的 SUI 患者和混合性尿失禁的患者,移植 3 个月后经尿动力学研究评估, MUCP 值均超过 30 cmH₂O,证实了该疗法的安全性和有效性[34]。

2.5. 人羊水干细胞(Human Amniotic Fluid Stem Cells, hAFSCs)

hAFSCs 可从妊娠中期的羊膜腔穿刺术中获取,在体外培养时其细胞表型和基因型较稳定,虽有较强的增殖活性,但不形成肿瘤,在体外也可分化为内皮细胞、神经细胞、肌源性细胞、脂肪细胞和成骨细胞[39]。

Jae 等人对 hAFSCs 注射治疗 SUI 的有效性和安全性进行了研究,发现干预组 SUI 大鼠 LPP、闭合压力(closing pressure, CP)得到了改善,且未引起大鼠明显的炎症反应和组织损伤,也无致癌性[40]。Kim 等将小鼠双侧阴部神经横断以产生 SUI 模型,并在尿道周围注射 hAFSCs,分别于两周后和四周后行组织学和尿动力学检测,证实了体内注射 hAFSCs 部位的神经再生和神经肌肉接点的形成;且 hAFSCs 注射组的平均 LPP 和 CP 较对照组显著升高,提示 hAFSCs 注射到 SUI 动物模型尿道周围,可恢复尿道括约肌正常的组织结构和功能[41]。上述研究表明, hAFSCs 可通过刺激神经再生、重建神经肌肉连接来治疗 SUI,为其今后临床研究和应用奠定了基础。

2.6. 尿源性干细胞(Urine-Derived Stem Cells, USCs)

USCs 取材方便、安全,通过简单无创的方法即可从尿液中分离获取,降低了患者的治疗风险和成本,且较其他类型干细胞对尿液毒性有较强的抵抗能力[42],同时还可较大程度地保持其干性[43],故其是研究 SUI 治疗中最有潜力的干细胞。

Liu 等人的研究表明,将 USCs 同藻酸盐微珠和 I 型胶原凝胶混合后,皮下注入到裸鼠体内,4 周后与对照组比较,干预组提高了细胞存活率,促进了血管和神经再生,促进了成肌谱系细胞的生长[44]。Wu 等将从健康个体尿液中提取的 USCs 通过含有小鼠 VEGF 基因的腺病毒载体转染后,同 I 型凝胶一起注入无胸腺小鼠体内,4 周后进行形态学和细胞免疫学评价,发现转染后促进了血管和神经细胞的再生,提高了 USCs 的存活率、增强了 USCs 的肌性分化[45]。上述研究均表明 USCs 有望通过自身肌性分化、加强受损部位的营养支持和神经支配来改善 SUI 症状,为 USCs 应用治疗 SUI 提供了可能。但目前尚缺乏 USCs 移植治疗 SUI 相关临床试验研究。

2.7. 牙髓干细胞(Human Dental Pulp Stem Cells, hDPSCs)

hDPSCs 是 SUI 治疗研究中出现的新型干细胞,目前其相关研究较少。Zordani 等人的研究表明,用 5-aza-2'-脱氧胞苷(5-Aza)预处理 24 小时后,体外诱导 hDPSCs 向肌源性细胞分化,再将预分化的 hDPSCs

经尿道注射到 SUI 大鼠体内。4 周后,通过组织学、功能和免疫组化分析发现:hDPSCs 移植到尿道外括约肌,在体内形成肌源性谱系,使其厚度几乎恢复,促进了血管生成和排尿功能的恢复。此外,在神经内检测到 hDPSCs,提示它们参与了横断神经的修复[46]。这一研究结果有力地证实了 hDPSCs 用于治疗 SUI 的可行性和有效性。

2.8. 人黏膜干细胞(Human Mucosa Stem Cell, hMSC)

hMSC 在治疗 SUI 相关方面的研究较少, Mahboubeh 等人开展的一项临床随机对照研究结果表明,在中期随访时间内,尿道周围注射 hMSC 的治疗效果与微型悬吊手术相当;且干细胞组的干预时间和住院时间短,并发症更少[47]。但目前该细胞相关动物和临床研究较少,治疗结果的有效性仍需更多研究进一步佐证。

2.9. 干细胞外泌体

外泌体(Exosome)是由活细胞分泌的纳米级囊泡,其内含有蛋白质、核酸、脂质等多种生物活性分子,参与了细胞分化、免疫调节、组织修复等生物学活动。近期有学者发现将 ADSC 来源的外泌体注射到 SUI 大鼠外周尿道,可能通过调节与骨骼肌和神经再生及增殖信号通路,改善 SUI 大鼠膀胱容量和 LPP,其尿道功能改善和组织学检验结果甚至略优于 ADSC 移植治疗[48]。还有学者研究表明 USCs 外泌体可促进肌肉卫星细胞的活化、增殖和分化,同时促进了肌肉组织恢复,显著改善了 SUI 模型鼠的尿动力学参数[49]。上述研究均肯定了外泌体局部注射对 SUI 的潜在治疗价值,但目前外泌体提取工序复杂,一次需耗费大量细胞样本,且鉴定也较为繁琐,对仪器设备要求较高,这限制了其进一步开展临床研究和应用。

3. 干细胞治疗压力性尿失禁的挑战

尽管目前的基础研究和部分临床研究肯定了干细胞治疗的有效性和广泛的应用前景,但我们仍不能忽略其存在的问题与不足:1、部分干细胞增殖活力旺盛,成瘤风险大[50],且某些干细胞研究涉及伦理问题,这极大地限制了其研究和应用;2、一些干细胞的提取过程较繁琐,容易引起患者疼痛等不适,且并发症较严重(皮下血肿、感染等),增加了患者治疗成本和风险;3、目前干细胞治疗 SUI 和其定向分化的机制尚未完全清晰明确,其在体内存活时间也较短,如何精确控制引导干细胞定向分化、提高其存活率是急趋解决的难题;4、对于干细胞治疗 SUI 的方案,目前国内外尚无统一标准:不同种类干细胞治疗 SUI 的效果不一,干细胞种类的选取、移植细胞数量的确定、注射方式的选择等仍无确切定论,相关治疗标准的制定仍需大量研究提供高质量的证据参考;5、干细胞治疗 SUI 的有效性存在争议,目前部分研究表明其治疗效果仍劣于传统手术治疗,且现有研究绝大多数仅聚焦于短期效果,尚缺乏长期随访数据,验证其长期疗效;6、干细胞外泌体提取和鉴定较繁琐,一次性难以提取较为满意的样本量。

4. 展望

SUI 是一种在中老年女性中发病率较高的疾病,严重危害患者的身心健康,影响患者生活质量,传统的手术治疗费用高、创伤较大,且并发症较多。随着人们健康意识的提升和医疗技术的发展,追求治疗的微创化、低成本、低并发症和低复发率已成趋势,干细胞疗法的出现为实现这一目标提供了可能,现阶段大量的基础研究和部分临床试验已经证明了其治疗的有效性和安全性,取得了不错的效果。但真正开展其临床治疗应用仍面临前文所提及的诸多挑战,未来其发展一方面应该将重点聚焦于其定向分化机制的研究,共同合作制定标准规范的诊疗方案,另一方面应该增加临床研究案例和长期随访资料,了解其治疗并发症及风险,证明其远期疗效,为其今后的临床应用和推广做好铺垫。

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