

间充质干细胞在整形美容领域的应用

李竹君^{1,2}, 王晨羽³, 龙笑^{1,2}

中国医学科学院北京协和医院¹ 整形美容外科² 疑难重症及罕见病国家重点实验室, 北京 100730

³ 上海交通大学医学院附属第九人民医院整复外科, 上海 200011

通信作者: 龙笑, E-mail: pumclongxiao@126.com

【摘要】 间充质干细胞是具有自我更新和多向分化潜能的成体干细胞, 存在于脂肪、骨髓和脐带等多种组织中, 能通过直接分化或旁分泌的方式发挥修复组织缺损、促进血管生成、免疫调节、抗纤维化等多种作用。间充质干细胞在抗衰老、毛发/组织再生、创面愈合、抗纤维化等多个方面已有较为深入的研究, 效果与安全性良好。未来仍需开展深入的基础研究以揭示其治疗机制, 并进行长期的临床试验随访以考察其远期安全性。

【关键词】 间充质干细胞; 整形手术; 美容; 组织再生

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Application of Mesenchymal Stem Cells in Plastic and Cosmetic Surgery

LI Zhujun^{1,2}, WANG Chenyu³, LONG Xiao^{1,2}

¹Department of Plastic Surgery, ²State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China

³Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

Corresponding author: LONG Xiao, E-mail: pumclongxiao@126.com

【Abstract】 Mesenchymal stem cells (MSCs) are adult stem cells that possess the ability of self-renewal and multi-lineage differentiation. They can be found in multiple tissue types, including adipose tissue, bone marrow and umbilical cord. MSCs can exert the effects of tissue repair, angiogenesis, immunoregulation, and anti-fibrosis through differentiation or paracrine function. Promising therapeutic effects of MSCs on skin aging, alopecia, tissue regeneration, wound healing, and anti-fibrosis have been observed. In general, MSCs exhibit favorable therapeutic effects and safety, but scrutinized research and clinical trials are still needed to reveal the mechanism of action as well as long-term efficacy and safety.

【Key words】 mesenchymal stem cells; plastic surgery; cosmetic; tissue regeneration

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干细胞是一类具有自我更新和多向分化潜能的细胞。存在于成体组织中的干细胞统称为成体干细胞,在维持稳态、组织修复和再生等过程中发挥关键作用。其中,间充质干细胞(mesenchymal stem cell, MSC)是一类能贴壁生长,具有特定表面标志物,并能够向骨、软骨和脂肪细胞分化的成体干细胞,最常见的来源是骨髓、脂肪、脐带等^[1]。以脂肪来源间充质干细胞(adipose-derived mesenchymal stem cell, ADSC)为例,一般通过吸脂手术获取脂肪组织,经洗涤、酶消化、离心后可获得含ADSC、内皮细胞、平滑肌细胞、巨噬细胞、淋巴细胞、周细胞、脂肪前体细胞等多种细胞成分的基质血管组分(stromal vascular fraction, SVF);SVF经体外培养、细胞传代即可获取ADSC^[2]。ADSC的来源最为广泛,获取最为容易,因此得到了广泛研究与应用。本文将阐述MSC的研究进展及其在整形美容领域的应用,并探讨细胞治疗的安全性问题。

1 MSC的作用机制

MSC能向脂肪、骨和软骨三向分化,但目前认为,MSC主要通过旁分泌的方式发挥作用^[3]。例如,ADSC分泌的血管内皮生长因子(vascular endothelial growth factor, VEGF)可促进血管生成,改善血运,促进缺血组织存活;MSC可分泌多种免疫调节因子,如转化生长因子(transforming growth factor, TGF)- β 、白细胞介素(interleukin, IL)-10、前列腺素E2等,诱导巨噬细胞极化,调节巨噬细胞从M1向M2转化,调节Th1、Th17、Treg细胞的比例与功能,降低肿瘤坏死因子(tumor necrosis factor, TNF)- α 、IL-1 β 水平^[4-5]。此外,MSC在多种纤维化疾病模型中,能够抑制TGF- β /Smad通路,提高基质金属蛋白酶(matrix metalloproteinases, MMP)活性,降解细胞外基质(extracellular matrix, ECM)中多余的胶原,发挥抗纤维化作用^[6]。

MSC注射至体内后,可随机体代谢而逐渐消失。将绿色荧光蛋白标记的ADSC注射至D-半乳糖诱导的小鼠衰老模型皮下后,通过活体成像,观察到14 d时荧光标记的ADSC信号基本消失,28 d时已经观察不到荧光信号^[7]。事实上,MSC的凋亡可能是其发挥功能的重要途径。在小鼠肺部炎症模型中静脉注射MSC,发现富集在肺部的MSC即刻开始凋亡,在24 h内即被清除,而阻止MSC的凋亡会阻断其免疫调节作用。凋亡的MSC被巨噬细胞和单核细胞吞噬后,

可诱导巨噬细胞和单核细胞分泌抗炎细胞因子,如TGF- β 、IL-10、前列腺素E2等,去除疾病模型中的巨噬细胞同样可抵消MSC的免疫调节作用^[5,8]。单核细胞中可观察到被标记的MSC碎片,证明单核细胞的吞噬了凋亡的MSC并向抗炎表型转变,且吞噬了MSC的单核细胞能够进入血液循环,将这种免疫调节作用输送至全身^[9]。这可能是MSC注射后虽然很快在体内消失,但免疫调节功能却可存续较长时间的原因。

基于上述研究,无细胞的MSC衍生物是MSC临床应用的另一种可能。无细胞脂肪组织提取物、条件培养基、MSC分泌的细胞外囊泡、小细胞外囊泡和外泌体具有多种生物学活性。不同衍生物的制备工艺存在差异,但发挥作用的因子具有相似之处。除细胞因子和生长因子外,已有多项研究证明非编码RNA也可能是MSC发挥功能的重要途径。例如,ADSC外泌体中的非编码长链RNA H19,可通过吸附微RNA(microRNA, miRNA)-19b抑制其功能,从而上调靶点SOX9的水平,激活Wnt/ β -catenin通路,促进皮肤成纤维细胞的增殖与迁移,促进皮肤创伤愈合^[10]。ADSC细胞外囊泡中的miRNA-375可通过FOXF1发挥抗纤维化作用^[11],外泌体可通过miRNA-192-5p/IL-17RA/Smad轴抑制增生性瘢痕^[12]。无细胞的MSC衍生物能够规避抗原性、安全性等方面的一些问题,但在治疗效果和机制方面仍需进一步对比研究加以证实。

2 MSC在整形美容领域的应用

2.1 抗衰老

随着组织干细胞的老化与流失,可能导致许多衰老相关疾病。补充外源性干细胞是抗衰老的有效方法。研究显示,ADSC条件培养基可缓解皮肤成纤维细胞接受紫外线照射后的光老化损伤,提高细胞增殖能力,缓解细胞衰老,降低MMP水平,促进胶原蛋白与弹性蛋白的合成,机制可能与分泌血小板源生长因子AA有关^[13]。ADSC外泌体在大鼠皮肤光老化模型中可发挥抗衰老、修复作用,促进胶原表达并降低MMP的水平,增加真皮厚度,降低表皮厚度和角质层的比例,恢复皮肤的正常结构^[14]。ADSC的抗衰老作用可能有多种机制,包括降低活性氧(reactive oxygen species, ROS)、MMP和IL-6的水平,抑制光老化相关的丝裂原活化蛋白激酶(MAP kinase, MAPK)/AP-1和核因子(nuclear factor, NF)- κ B

通路活性, 激活 TGF- β /Smad 通路, 缓解光老化导致的炎症、氧化应激和胶原降解, 促进胶原合成^[15]。有研究在面部光老化区域皮下注射 ADSC 后可观察到局部免疫细胞聚集明显下降, MMP 水平降低, 弹性纤维合成增加, 效果优于富血小板血浆, 且未发生不良事件^[16]。

目前, 整形美容领域常见的抗衰老疗法包括药物、光电治疗、填充治疗和面部提拉手术等。其中, 面部提拉手术创伤相对较大, 仅适用于重度皮肤松弛患者^[17]。外用药物包括维生素 A 衍生物、果酸剥脱等, 但效果不显著, 持续时间短, 主要适用于轻度皱纹^[18]。肉毒素注射对动态皱纹效果好, 但持续时间较短, 需反复注射才能维持^[19]。光电治疗除皱效果较好, 相对无创, 但个别案例中可能遗留瘢痕, 影响外貌^[20]。填充治疗主要分为玻尿酸与自体脂肪填充, 前者需重复注射才能维持效果, 后者需先进行吸脂手术, 且脂肪存活率随时间推移而降低^[21-22]。自体脂肪干细胞及其衍生物疗法相较于以上方法, 具有操作便捷、相对无创、不易遗留瘢痕、效果稳定等优势, 是未来抗衰老治疗的新方向。

2.2 促进毛发/组织再生

2.2.1 促进毛发再生

目前, 治疗脱发的方法包括外用非那雄胺、螺内酯, 外用或口服米诺地尔, 点阵激光, 毛发移植等^[23], 但效果不够显著, 移植的毛发不易成活。近年来, 脂肪移植诱导毛发再生取得了良好效果, 且相比毛发移植具有简便易行的优点^[24]。脂肪移植能够使毛发再生已有基础研究支持。CD24⁺ ADSC 中的 Pdgfa/Akt 通路激活能够促进真皮白色脂肪的生成^[25], 而真皮白色脂肪对于毛发生长必不可少^[24]。ADSC 分泌的 VEGF 等因子能显著促进毛囊周围血管生成, 从而促进毛发生长^[26]。在应用研究中, 例如自身免疫导致的斑秃, MSC 可拮抗干扰素 γ 诱导的炎症反应, 减轻脱发, 促进毛发再生^[27]。在两项临床案例报道中, 使用脐带或华通胶来源的 MSC 治疗斑秃均取得了良好疗效^[28-29]。雄激素性脱发亦可使用 MSC 治疗。ADSC 条件培养基可改善雄激素性脱发患者的毛发密度^[30]。在一项纳入 9 例患者的临床试验中, 注射自体 SVF 的一侧毛发密度显著高于未加干预的一侧^[31]。MSC 的治疗机制多样, 初步观察疗效良好, 得到了广泛关注, 但仍需深入的机制探索与大规模临床研究加以验证。

2.2.2 促进组织再生

MSC 已广泛应用于多种组织再生中。利用 ADSC

能够向软骨、成骨分化的特性, 将 ADSC 接种在 3D 打印的耳廓支架上, 能保持细胞粘附与增殖功能, 有望应用于耳廓再造^[32]。与之相似, 使用与骨组织相似的材料作为支架接种 MSC, 可以构造出性能良好的组织工程骨^[33]。例如, 以 3D 打印的多孔生物陶瓷作为支架表面接种 MSC, 可诱导 MSC 成骨分化, 最终形成可用于移植的骨组织^[34]。ADSC 除能够通过旁分泌多种生长因子促进血管和淋巴管的生成外, 还能直接分化为淋巴管内皮细胞标志物 LYVE-1 阳性的细胞, 移植后可缓解淋巴水肿模型小鼠的水肿程度^[35]。ADSC 治疗淋巴水肿已开展了相关临床研究, ADSC 注射能够显著改善肢体沉重感等主观症状和肢体水肿, 且无严重不良事件发生^[36]。

2.3 促进创面愈合

MSC 可用于慢性创面的治疗。研究显示, ADSC 细胞外囊泡可降低糖尿病小鼠模型创面中的 MMP-9 水平, 促进胶原合成与上皮化, 提高创面愈合速度^[37]。VEGF-C 和其他生长因子可能在此过程中发挥重要作用^[38]。皮下注射 ADSC 外泌体可被皮肤成纤维细胞和血管内皮细胞内吞, 通过 miRNA-126-3p 激活 PI3K 通路, 促进皮肤成纤维细胞增殖、迁移和内皮细胞血管生成, 使大鼠模型的胶原沉积与新生血管数目增加^[39]。ADSC 外泌体内的 miRNA-125a-3p/PTEN 相互作用也可达到类似效果^[40]。一项随机对照临床试验显示, 慢性溃疡患者皮下注射自体 SVF 可显著提高创面的愈合率, 缩短愈合时间且无明显不良反应, 组织切片可见胶原合成增多, 炎症细胞浸润减少^[41]。此外, 还可将 MSC 或 MSC 衍生物与 3D 打印、水凝胶材料结合, 制备成敷料用于创面治疗^[42]。由于 MSC 能够分泌 VEGF 等因子, 促进血管生成, 因此还可促进皮瓣或其他移植组织的存活^[43]。

2.4 治疗纤维化疾病

在纤维化疾病中, MSC 可发挥抑制胶原合成与过度沉积的抗纤维化作用。在增生性瘢痕中, 使用 ADSC 条件培养基冻干粉辅以多糖凝胶, 注射到兔耳增生性瘢痕模型中, 可降低平滑肌肌动蛋白 α 水平, 抑制瘢痕形成, 但高剂量可能导致伤口愈合延迟^[44]。在瘢痕疙瘩成纤维细胞和小鼠移植瘤瘢痕疙瘩模型中, 注射 MSC 条件培养基可抑制细胞增殖, 增加细胞凋亡, 缩小移植瘤体积^[45]。放射纤维化是肿瘤治疗可能导致的皮肤损伤, ADSC 可通过分泌肝细胞生长因子 (hepatocyte growth factor, HGF) 降低皮肤放射损伤模型中成纤维细胞分泌 TGF- β 、结缔组织生长因子、IL-1、NF- κ B、TNF- α 及胶原 1~6 的水平^[46]。

硬皮病导致的皮肤纤维化、皮下组织萎缩与肢体功能受限是临床治疗的难点。目前,系统性硬化症的治疗主要使用免疫抑制剂延缓疾病进展,却不能改善已经出现的萎缩、硬化与功能受限^[47]。自体 SVF 皮下注射可用于缓解系统性硬化症手部皮肤纤维化,患者的 Cochin 手功能量表评分、改良的 Rodnan 皮肤评分、雷诺现象、疼痛症状均有改善,仅个别患者出现疼痛、淤青等轻微不良反应且能够自行缓解^[48]。除单独应用外,SVF 或 ADSC 还可用于辅助脂肪移植,以增加脂肪存活率。系统性硬化症口周皮肤纤维化患者进行 ADSC 辅助脂肪移植后,张口度和外观得到了显著改善^[49],ADSC 或 SVF 辅助脂肪移植比单纯脂肪移植的存活率显著提高,且 ADSC 的效果优于 SVF^[50]。在创面愈合与纤维化疾病中,MSC 的相反作用提示疾病微环境可能对 MSC 的功能有重要影响,MSC 可能具有双向调节功能。

3 新技术助推 MSC 在整形美容领域的应用

传统的 2D 培养并不能很好地模拟体内环境,3D 培养的 MSC 分泌多种细胞因子的能力高于 2D 培养的 MSC^[51]。因此,近年来 3D 培养、3D 打印和类器官等技术受到了越来越多的关注。其中,类器官最为复杂,在组成和结构上也最能模拟生理状态。首先需要构建人造 ECM,以诱导细胞的极化生长,并形成类似体内组织的结构;种子细胞可以选用成体干细胞,诱导多能干细胞、上皮细胞等;还需添加必要的生长因子以促进细胞增殖与分化,并形成所需结构。类器官更能模拟组织内的微环境,可分泌更多的细胞外囊泡,在多种信号通路和免疫微环境方面与 2D 培养的细胞均有显著差异^[52]。目前,类器官更多地应用于肿瘤研究,相信不久的将来,成体干细胞构建的类器官将能够用于组织重建与再生。

4 MSC 疗法的安全性

MSC 疗法用于肿瘤患者的安全性一直是临床关注的重点。有研究在体外将 ADSC 与乳腺癌细胞共培养,观察到乳腺癌细胞凋亡增加,抗凋亡蛋白减少,为其安全性提供了基础研究证据^[53]。但也有观点认为,ADSC 会促进卵巢癌转移,其可能的机制包括巨噬细胞 M2 极化、TMSB4X 蛋白以及 ADSC 分泌的多种生长因子与 miRNA 等^[54]。一项针对肥胖患者的结肠癌转移研究中,肿瘤旁内脏脂肪 ADSC 分泌的

IL-6 和 HGF 可促进肿瘤转移,转移的肿瘤细胞则进一步招募 ADSC,而 ADSC 又通过激活 STAT3 通路将肿瘤转变为易发生转移的表型^[55]。提示有肿瘤史的患者慎重使用 MSC,其可能会增加肿瘤复发或转移风险。另一种观点则认为,可通过 MSC 富集于肿瘤这一特性携带靶向药物,用于肿瘤的治疗,且 MSC 本身可能具有抗肿瘤作用^[56]。目前,MSC 与肿瘤的相互作用尚无定论,因此临床应用应十分谨慎。

对于无肿瘤史的患者,已有多个 MSC 临床试验证明其安全性及有效性良好。一项自体 ADSC 脑内给药治疗脑卒中的 I 期临床试验结果显示,6 个月的随访期内无不良事件发生^[57]。同种异体 ADSC 治疗膝关节炎的 I/II 期临床试验在 96 周(约 2 年)的随访期内患者未出现治疗相关的严重不良事件,但大部分受试者治疗后出现了一定程度的不良反应,包括骨骼肌肉结缔组织系统失调、注射点不适、感染等^[58]。同种异体 ADSC 用于治疗克罗恩病肛周瘘管的 III 期临床试验在 104 周随访期内共观察到 7 例严重不良事件^[59];24 周随访期内,17% 的治疗组和 29% 的对照组患者发生了治疗相关不良事件,其中最常见的是肛周脓肿(共 15 例)^[60]。韩国一项 ADSC 治疗克罗恩病复杂肛周瘘管的 IV 期临床研究在 6 个月内未观察到治疗相关的不良反应^[61]。这些临床试验数据在一定程度上证明了 MSC 的安全性,但仍然需要长时间随访以证实 MSC 疗法的远期安全性。

5 小结与展望

MSC 及其衍生物的治疗效果和机制多样,各具优势与不足。3D 培养、3D 打印、类器官等新技术与 MSC 的结合将促进组织工程与再生医学的发展。对于不适宜进行吸脂术的患者,越来越多的研究者开始关注异体应用 MSC 的可能性。例如同种异体 ADSC 用于治疗骨关节炎和克罗恩病的临床试验^[58-61]。而在一些免疫疾病中,异体 MSC 的治疗效果甚至可能优于自体 MSC^[62]。MSC 低表达 MHC II 类分子,抗原性低,本身具有免疫调节作用,进入体内后不易诱发免疫反应^[63],因此具有异体应用的可能。

总体来说,MSC 的效果和安全性良好,但对于肿瘤患者,仍需开展深入的基础研究以揭示 MSC 的治疗机制,并应进行长期的临床试验随访以考察其远期安全性。

作者贡献:李竹君负责查阅文献、撰写论文;王晨

羽、龙笑负责论文构思及终稿审核、修订。

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