·综述·

脂肪干细胞及其衍生物在不同创面愈合中应用的研究进展

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【摘要】 创面愈合是一个由多种细胞相互作用及复杂信号转导网络共同调控的过程。当局部微环境发生紊乱时，创面愈合延缓甚至不愈合，难愈性创面仍是目前临床上面临的一大挑战。脂肪干细胞来源丰富、获取方便，且具备强大的旁分泌功能和多向分化潜能，在创面修复与再生中发挥着重要作用。通过对脂肪干细胞的生物学特性、衍生物的种类和特点以及在不同创面愈合中的应用进行综述，旨在为干细胞疗法在创面治疗领域的后续研究提供新思路。

【关键词】 伤口愈合；　脂肪干细胞；　衍生物；　慢性难愈合创面

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Research progress on the application of adipose-derived stem cells and their derivatives in different wound healing

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【Abstract】 Wound healing is regulated by the interactions of various cells and a complex network of signaling pathways. When the local microenvironment is dysregulated, wound healing can be delayed or even fail to occur, and refractory wounds remain a major clinical challenge. Adipose-derived stem cells (ADSCs), which are abundant and easily accessible, possess strong paracrine functions and multi-directional differentiation potential, playing a crucial role in wound repair and regeneration. This article reviews the biological characteristics of adipose-derived stem cells, the types and features of their derivatives, and their applications in different types of wound healing, aiming to provide new insights for future research on stem cell therapy in wound healing.

【Key words】 Wound healing;　Adipose-derived stem cells;　Derivatives;　Chronic refractory wounds

皮肤创面是由外在因素或内在病理变化所引起的组织结构与完整性缺失，其愈合过程通常包括止血、炎症、增殖和组织重塑等阶段，最终恢复皮肤屏障功能[1-2]。当这一愈合过程受到不良因素干扰时，创面愈合明显延缓，给患者身心及社会经济带来沉重负担[3]。目前临床上常采用负压吸引及各类敷料加速创面愈合，但治疗难愈性创面的效果并不理想。近年来再生医学兴起，脂肪干细胞(adipose-derived stem cells，ADSCs)因其来源丰富、获取方便、取材创伤小等优势，受到研究者的广泛关注[4]。下文通过阐述ADSCs及其衍生物在不同类型创面愈合中的应用，为干细胞疗法在创面治疗领域的后续研究提供新思路。

一、ADSCs的生物学特性

干细胞疗法是指利用干细胞的自我更新能力、多向分化潜力及旁分泌活性，以恢复组织或器官功能的治疗方法[5]。ADSCs作为间充质干细胞(mesenchymal stem cells，MSCs)的重要亚群，因其具备来源丰富、取材侵入性小、增殖能力强及免疫原性低等优势，成为创面修复领域极具应用前景的种子细胞[6]。ADSCs的表面标志物与MSCs谱系高度相似，呈CD29、CD90、CD105、CD44等阳性，但不表达CD45、CD31、CD79及HLA-DR等抗原[7-8]。研究证实，ADSCs具有较强的多向分化潜力，可诱导其分化为脂肪细胞、成骨细胞、神经细胞和软骨细胞等[9]，此外，ADSCs还能分化为创面修复所必需的角质形成细胞、血管内皮细胞和成纤维细胞等主要细胞[10-11]。ADSCs具备良好的旁分泌活性，可分泌血管内皮生长因子(vascular endothelial growth factor，VEGF)、胰岛素样生长因子-1(insulin-like growth factor-1，IGF-1)和成纤维细胞生长因子(fibroblast growth factor，FGF)等，从而促进创面修复相关细胞的增殖与迁移以及血管新生[12]。此外，ADSCs还具备免疫调节功能，可直接与T细胞、巨噬细胞等相互作用，调节免疫细胞的活化与极化，也可通过其旁分泌物质间接参与并维持创面局部免疫微环境的平衡[13-14]。

二、ADSCs相关衍生物

1.无细胞脂肪衍生物：无细胞脂肪衍生物是指通过物理、化学或酶学等方法去除脂肪组织中的细胞成分后获得的生物活性物质，主要包括脂肪干细胞来源的细胞外囊泡(adipose-derived stem cells extracellular vesicles，ADSCs-EVs)和脂肪干细胞条件培养基(adipose derived stem cells-conditioned medium，ADSCs-CM)。ADSCs-EVs是ADSCs在生理或病理条件下主动

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分泌的脂质双层膜结构囊泡，直径通常为30~1 500 nm，可根据大小细分为微囊泡、外泌体（exosomes，Exos）和凋亡小体。作为细胞间信号传递的重要媒介，ADSCs-EVs能将其携带的脂质、蛋白质、DNA、mRNA、miRNA等生物活性分子运输至受体细胞内，引发受体细胞增殖、分化及基因表达改变等一系列生物学变化[15-16]。ADSCs-CM是指经去细胞处理后，含有ADSCs在体外培养过程中分泌的各类生物活性物质的培养基，主要包括细胞因子、趋化因子、生长因子、多种酶和细胞外囊泡等[17]。ADSCs-EVs和ADSCs-CM不仅具备ADSCs的再生修复能力，还能较好地规避细胞移植的潜在风险（如免疫排斥、致瘤性等），且易于携带、运输和储存，因此在创面愈合、皮肤老化、瘢痕修复等治疗领域具有广阔的临床应用前景[18]。

2.工程化修饰的ADSCs：干细胞移植后常因处于炎症细胞浸润、促炎因子富集及缺血缺氧的微环境而无法存活，其实际应用受到限制，而基因工程的出现显著提升了ADSCs的应用潜力。工程化修饰的ADSCs是指采用基因编辑技术敲除或过表达特定基因、将靶向分子引入细胞表面或负载于生物可降解支架等方法，对ADSCs进行定向改造后获得的干细胞变体，使其具备更强的存活能力、靶向性、分化潜能及分泌功能[19-20]。

3. ADSCs生物材料复合物：ADSCs生物材料复合物是指将ADSCs与天然或合成材料结合形成的功能性三维结构，具有良好的生物相容性、可降解性及无细胞毒性等特点[21-22]。常见的生物材料包括合成聚合物（如水凝胶、聚己内酯）、天然聚合物（如胶原蛋白、透明质酸、壳聚糖）及金属纳米颗粒等，这些材料可作为ADSCs的干细胞生态位，为细胞提供支撑骨架，且可通过动态调节微环境中的生化及力学性质（如孔径大小、表面电荷、降解速率）促进ADSCs的成活与定植，还可诱导ADSCs定向分化、增强其旁分泌及免疫调节功能，最终促进组织稳态及再生[23]。目前，ADSCs生物材料复合物已被应用于烧伤瘢痕、慢性溃疡及软组织缺损修复等领域的研究，其安全性与有效性较高[24]。

三、ADSCs及其衍生物在不同创面愈合中的应用

1.烧伤创面：严重烧伤创面愈合困难，是临床治疗中的一大挑战。烧伤创面局部常出现活性氧（reactive oxygen species，ROS）、促炎细胞因子等物质的异常增多，使免疫系统过度激活，导致创面修复延迟、过度瘢痕增生及皮肤挛缩等问题[25]。目前，修复烧伤创面的主要手段包括敷料应用和皮肤移植等，其中敷料和非自体皮肤移植（如人工皮肤替代物、异种皮肤等）存在与创面不能完全贴合、抗感染能力较弱、生物活性差等问题，而自体皮肤移植虽被视为治疗金标准，但也面临供区有限、二次创伤等挑战[26]。因此，干细胞疗法旨在通过减轻炎症反应和刺激血管生成[27-28]，以避免创面不良修复、减少瘢痕形成、防止皮肤挛缩，并促进皮肤及其附属器的再生[29]。

有研究者在大鼠全层皮肤热损伤模型建立后当天及第4天分别向创缘处注射ADSCs，观察发现ADSCs通过增加Ⅲ型胶原蛋白沉积、减少淋巴管数量及瘢痕面积，显著改善烧伤创面的愈合质量[30]。Li等[31]采用α-酮戊二酸预处理ADSCs，以延长细胞在创面内的存活时间，并增强其迁移能力和旁分泌功能，使酸烧伤创面组织的胶原沉积和微血管密度均高于对照组，且皮肤结构更接近正常状态。Wu等[32]利用3D生物打印技术构建了整合ADSCs和一氧化氮的水凝胶支架，研究发现该支架能通过VEGF信号通路增强内皮细胞迁移与血管生成能力，并促进上皮化和胶原沉积，从而明显改善严重烧伤创面的修复与再生。另一研究将ADSCs和锰纳米颗粒共同负载于聚己内酯/明胶电纺纳米纤维支架，用于治疗大鼠Ⅱ度烧伤，结果显示该支架能降低肿瘤坏死因子-α、白细胞介素-1β等促炎因子含量，抑制纤维化，促进胶原合成与表皮再生，显著提升烧伤创面愈合率及修复效果[33]。此外，一项单中心Ⅰ期随机对照双盲临床试验结果显示，在深Ⅱ度烧伤后10~48 d，ADSCs治疗组的创面再上皮化程度较安慰剂组提高1.5~5.5倍，且治疗安全性良好，未出现不良反应[34]。

2.糖尿病创面：长期高血糖会破坏皮肤微环境，造成微血管功能障碍、周围神经病变和持续的炎症反应，显著延缓糖尿病患者的创面愈合进程，并增加感染和截肢风险。糖尿病足（diabetic foot ulcer，DFU）是糖尿病最常见的并发症之一[35-36]，在糖尿病患者中发生率为19%~34%[37]，给患者和社会带来沉重负担。目前，传统治疗手段主要包括采取手术清创、负压吸引及皮瓣移植等，但这些方法无法实现糖尿病创面的完全愈合，且存在一定局限性[38]。相比之下，ADSCs在糖尿病创面治疗中展现出良好的应用前景。

大量研究表明，ADSCs通过参与糖尿病创面愈合过程中的多个关键环节来调控局部微环境，在加速创面愈合的同时提高组织修复质量。ADSCs具有免疫调节和减轻氧化应激的作用。Xu等[39]研究发现过表达缺氧诱导因子-1α的ADSCs可促进VEGF、FGF和趋化因子CXCL12的表达，同时抑制细胞内ROS产生和DNA损伤，有效促进糖尿病小鼠创面愈合。Ouyang等[40]证实过表达造血前列腺素D合成酶的ADSCs可减少DFU中中性粒细胞和$CD8^+$T细胞募集、抑制促炎细胞因子释放，并促进巨噬细胞向M2型极化，加速糖尿病创面愈合。Yin等[41]发现ADSCs-Exos通过circ-Rps5/miR-124-3p轴调控巨噬细胞向M2极化，减少促炎细胞因子释放，并抑制长期高糖诱导的巨噬细胞过度自噬，有利于胶原合成及糖尿病创面愈合。同时，ADSCs可促进组织血管新生和细胞外基质重塑。Xie等[42]证实ADSCs通过KLF5/CXCL12途径招募并激活内皮祖细胞，增强其增殖、迁移和血管形成能力，改善高糖环境下内皮祖细胞的功能，从而促进糖尿病创面修复。Li等[43]发现采用CRISPRa系统内源性激活血小板源性生长因子受体-β的ADSCs，能通过增强VEGF及细胞外基质相关分子的分泌，促进内皮细胞管腔形成和胶原沉积，提高糖尿病创面愈合率。Song等[22]研发了一种温敏性细胞外基质水凝胶用于包裹ADSCs-Exos，结果表明持续缓慢释放的ADSCs-Exos显著促进创面血管生成、胶原沉积以及表皮细胞增殖，减轻炎症反应，有效加速糖尿病创面愈合。ADSCs还具备多向分化潜力，可分化成为角质形成细胞、血管内皮细胞和成纤维细胞等，直接参与组织的修复与再生[10-11]。研究表明，长期高糖小鼠体内的ADSCs分化能力显著下降，而外源性补充VEGF和IGF-1可一定程度上恢复其分化能力；将正常ADSCs移植到糖尿病创面后，可显著促进组织再上皮化进程并提高创面愈合率[44]。

此外，多项临床试验均证实了ADSCs在DFU治疗中的有效性[45]。一项随机对照试验将46例DFU患者分为2组，其中实验组采用ADSCs移植联合纤维蛋白凝胶治疗，对照组仅接受纤维蛋白凝胶治疗。结果显示，与单纯纤维蛋白凝胶治疗相比，联合ADSCs治疗可加快患者创面愈合速度，且治疗期间未出现严重不良反应，安全性良好[46]。Uzun等[47]采用随机对照单盲法对20例DFU患者实施同种异体ADSCs局部注射治疗，并进行长达48个月的随访。结果表明该治疗联合标准方案不仅安全有效，还能显著缩短DFU愈合时间，改善患者生存质量。

3.其他慢性难愈性创面：慢性难愈性创面是指经临床治疗1个月后，仍未能恢复正常解剖结构和功能的创面，具有病因复杂、病程长、致残率高等特点[48]。除上述DFU及严重烧伤创面外，难愈性创面还包括压力性损伤、血管性溃疡和放射性皮肤损伤等[49]。

压力性损伤是指身体骨性隆起部位因长期或强烈压力与剪切力作用引起的组织破溃、感染甚至坏死，常见于长期卧床或老年患者[50]。压力性损伤不仅易增加患者并发症或合并症风险，还会延长住院时间，造成医疗资源的大量消耗[51-52]。Jin等[53]研究证实ADSCs-CM可促进成纤维细胞的胶原分泌，并能刺激内皮细胞管腔形成；同时还发现，ADSCs联合透明质酸凝胶可通过激活PPARβ/δ通路调节脂质代谢并促进皮肤再生。Su等[54]研究发现miR-21-5p修饰的ADSCs-Exos通过抑制NF-κB信号通路，诱导巨噬细胞向M2型极化并减少炎症因子释放，进而促进上皮细胞再生及胶原沉积，提高压力性损伤的愈合率。

血管性溃疡好发于下肢，主要分为静脉性溃疡和动脉性溃疡。静脉性溃疡多见于静脉曲张患者，因静脉回流障碍所致静脉高压而引发皮肤破溃，具有较高的复发率[55-56]。动脉性溃疡常见于闭塞性动脉硬化、血栓性闭塞性脉管炎等存在动脉管腔狭窄或阻塞的患者，因下肢灌注不良引起局部组织缺血缺氧，最终形成创面。该类型溃疡诊疗难度较大，病情严重时可导致截肢[57]。Elsharkawi等[58]分析发现ADSCs能够促进下肢静脉性溃疡愈合，且安全性良好。另有研究通过对比9项临床研究和14项注册试验得出结论，认为ADSCs治疗相对安全，在促进慢性溃疡愈合、缓解疼痛等方面效果较好[59]。

放射性皮肤损伤（radiation-induced skin injury，RISI）是肿瘤放射治疗或核事故后出现的并发症，表现为皮肤红斑、干性或者湿性脱屑、溃疡及坏死等症状，严重影响患者健康与生存质量[60]。电离辐射可造成细胞DNA损伤，阻碍细胞修复过程，进而引发细胞衰老和凋亡；同时，还能导致水分子电离形成ROS，激活氧化应激反应，诱导受损细胞释放大量炎症因子，加重组织炎症；此外，辐射还会过度激活成纤维细胞，导致细胞外基质异常沉积及组织纤维化[61]。由于RISI发病机制复杂，传统治疗手段（如局部护理、药物治疗）无法达到理想效果。Lin等[62]利用人真皮成纤维细胞构建体外RISI模型，发现ADSCs-CM和ADSCs-EVs均可显著抑制促炎因子白细胞介素-6的表达，促进胶原合成并减少细胞凋亡，有利于辐射损伤修复。Yao等[63]通过制备携带ADSCs来源的线粒体富集EVs的水凝胶微针贴片，使其在创面逐步释放线粒体富集EVs，研究发现该贴片可改善组织细胞线粒体功能，降低氧化应激水平，促进巨噬细胞向M2型极化，显著促进辐射所致小鼠皮肤创面的愈合。另有研究采用20 Gy β射线构建小鼠背部慢性放射性皮炎模型，将ADSCs注射至皮肤受损区域，观察到移植的ADSCs通过凋亡释放旁分泌因子，促进真皮胶原基质重塑，改善辐射导致的胶原萎缩与断裂，从而缓解慢性放射性皮炎症状[64]。

四、总结与展望

随着糖尿病、烧伤、压力性损伤、血管性溃疡和放射性皮肤损伤等疾病发病率的增加，皮肤难愈性创面修复已成为临床亟待解决的关键难题。ADSCs及其衍生物能够有效促进难愈性创面愈合，其核心作用机制是通过旁分泌作用调节局部免疫微环境，介导巨噬细胞向M2型极化，从而逆转创面的炎症失衡状态，打破愈合停滞的恶性循环，进而促进血管新生及胶原沉积，重新启动并加速组织修复及再生进程。然而ADSCs及其衍生物的作用机制尚未完全阐明，其长期疗效与安全性仍需进一步验证。因此，未来研究方向可着眼于开发标准化的制备工艺，使所获ADSCs及其衍生物保持均一，并优化载体材料的靶向递送效率与降解速率，以实现疗效最大化；结合单细胞分析与组学技术，完善ADSCs及其衍生物治疗不同类型创面的分子机制和细胞相互作用网络，为精准治疗提供有力支撑；开展大样本、多中心的随机对照临床试验，为其临床转化提供坚实的理论基础与实践依据。

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