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Hans汉斯

间充质干细胞源外泌体对糖尿病慢性创面愈合过程的作用

路　婕[1]，李　毅[2*]

[1]青海大学临床医学院，青海　西宁
[2]青海大学附属医院烧伤整形外科，青海　西宁

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摘　要

随着全球糖尿病患病率逐年上升和人口老龄化加重，糖尿病足溃疡、压疮等慢性创面对人类健康问题造成了潜在威胁，使外科治疗难度增加。慢性创面是指伤口不能有序、及时地进行正常的愈合过程，且时间超过1个月。目前治疗方式包括清创、负压吸引、高压氧治疗、药物治疗、生物敷料和皮瓣移植等，可在一定程度上缓解疾病进展，减少患者痛苦，但总体治愈率低，复发率高。近年来利用间充质干细胞及其衍生物治疗慢性创面已经成为医学研究的重要领域。外泌体作为间充质干细胞分泌的一种细胞外囊泡，除了向靶细胞递送物质以促进细胞间通讯外，在细胞增殖和分化、血管生成、应激反应和细胞信号传导等过程中也发挥作用，本综述的目的是阐述常见间充质干细胞来源外泌体及其在糖尿病慢性创面愈合过程中的作用机制。

关键词

间充质干细胞，外泌体，慢性创面

Effect of Mesenchymal Stem Cell Derived Exosomes on the Healing Process of Chronic Diabetic Wound

Jie Lu[1], Yi Li[2*]

[1]School of Clinical Medicine, Qinghai University, Xining Qinghai
[2]Department of Burn Plastic Surgery, Affiliated Hospital of Qinghai University, Xining Qinghai

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*通讯作者。

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Abstract

With the increasing prevalence of diabetes in the world and the aging of the population, the chronic creation of diabetic foot ulcers and pressure sores has caused a potential threat to human health problems and increased the difficulty of surgical treatment. Chronic wound is a normal healing process that can not be ordered and timely, and more than one month. The treatment of the present treatment includes the development of the result, the pressure of negative pressure, the treatment of hyperbaric oxygen, the treatment of drugs, the material of the biological dressing and the flap transplantation, which can alleviate the progress of the disease in a certain degree, reduce the pain of the patient, but the overall cure rate is low and the recurrence rate is high. In recent years, the use of mesopress stem cells and their derivatives to treat chronic wound have become an important area of medical research. In addition to intercellular communication of the intercellular cells, the exosomes are used to promote intercellular communication, and in the process of cell proliferation and differentiation, angiogenesis, stress response and cellular signal conduction, the purpose of this paper is to explain the mechanism of the common mesolytic stem cell source and its mechanism in the healing process of chronic wound healing in diabetes.

Keywords

Mesenchymal Stem Cells, Exosome, Chronic Wound

1. 背景

糖尿病是一种以高血糖为特征的代谢性疾病，可引起多种组织的慢性损伤和功能障碍，严重危及健康，给社会经济和医疗卫生增加负担[1]。慢性创面愈合是创面修复领域的难点，糖尿病并发症是其主要病因。糖尿病慢性创面(diabetic chronic wound, DCW)难以封闭是糖尿病患者生存率降低的原因之一，主要原因是由于严重高血糖，致使创面愈合能力下降，从而引起 DCW 及其严重并发症，DCW 的主要特征是炎症反应失衡、感染风险增加、血管生成不足，通常受免疫缺陷、功能障碍、局部感染等复杂因素的影响。伤口愈合时间延长，复发可能性增加，可能导致 15%~25%的糖尿病患者需要截肢，对其身心造成极大伤害[1] [2]。目前临床治疗手段及方案取得了很大的进展，包括清创、负压吸引、高压氧治疗、药物治疗、生物敷料和皮瓣移植等，但在部分 DCW 患者中仍然无效[2]。

间充质干细胞(Mesenchymal stem cells, MSCs)是最重要的成体干细胞之一，具有可塑性、粘附性及多向分化潜能，MSCs 可以从不同组织中获得，如脐带、骨髓、脂肪组织、骨骼肌组织等[3]，在 DCW 治疗中发挥作用[4]。但是直接应用 MSCs 存在很多限制和困难，如致瘤性、免疫排斥等[5]。

近年来认为 MSCs 来源的外泌体(MSCs-derived exosomes, MSCs-exo)具有再生和免疫调节特性[6] [7] [8]。外泌体是一种直径约为 30~150 nm 的由蛋白质、脂质和核酸组成的细胞外囊泡[9]，通过核－溶酶体途径中的多泡体内陷形成[10]。外泌体含有多种蛋白质、核酸和必需的细胞通讯介质。MSCs-exo 不仅具有与 MSCs 相似的生物学功能，同时也具有体积小、易穿透生物膜、易储存、免疫原性低、不发生肿瘤等优点[11]。近年来大量基础及临床实验表明 MSCs-exo 可以通过调节炎症反应、促进血管生成、促进细

胞增殖和迁移、加速细胞外基质重塑等多个过程，从而加速创面愈合[12]。

2. 常见间充质干细胞源外泌体

2.1. 脂肪间充质干细胞源外泌体

脂肪源间充质干细胞(Adipose-derived stem cells, ADSCs)是一种具有自我更新和多向分化能力的间充质干细胞。ADSCs 来源的外泌体(Adipose-derived stem cells exosomes, ADSC-exos)是细胞间通讯所必需的细胞外囊泡，广泛可用且容易获取，它们主要通过促进创面修复的各个阶段，包括调节炎症反应、促进创面血管生成、加速细胞增殖和创面重塑，释放多种生物活性分子，恢复组织稳态，加速创面愈合，在 DCW 中应用广泛[13]。与 ADSCs 相比，ADSC-exos 具有避免伦理问题、易于储存、稳定性高等优点。

2.2. 骨髓间充质干细胞源外泌体

骨髓间充质干细胞(Bone marrow mesenchymal stem cells, BMSCs)是一种起源于中胚层的成熟干细胞，可以分化为各种间质组织，如骨、软骨、脂肪和骨髓[14]。与 ADSCs 相比，BMSCs 的分离相对困难，但是它们的作用机制及疗效不一致，不能被完全替代[15]，既往研究大多集中在骨再生和相关疾病上[16]。近来有研究证实(Bone marrow mesenchymal stem cells exosomes, BMSCs-exos)能促进创面愈合[17]，这使得骨髓间充质干细胞成为治疗 DCW 的可能选择。在多种实验中证明 BMSCs-exos 是通过抗凋亡、抗氧化、抗炎等作用改善组织纤维化，促进组织再生[18] [19] [20]。

2.3. 人脐带间充质干细胞源外泌体

临床研究中应用最广泛的干细胞是人脐带间充质干细胞(human umbilical cord mesenchymal stem cell, HUCMSCs)，在特定条件下，HUCMSCs 可以分化为构成人体组织和器官的细胞类型[21]。HUCMSCs 具有广泛的临床应用，因为它们不仅具有 BMSCs 的基本特性，还具有增殖迅速、分化潜力大和免疫原性低等特性[22]，这使 BMSCs 多用于药物输送系统[23] [24]。此外，HUCMSCs 衍生的外泌体(HUCMSC-exos)显示出与 HUCMSCs 相似的作用，如抗凋亡、抗炎、促进组织再生等[25] [26] [27]，具体见下文描述。

3. 间充质干细胞源外泌体在 DCW 愈合过程中的作用

伤口愈合是一个动态的病理生理过程，大致可分为四个阶段:止血期、炎症期、增殖期和重塑期[28]。DCW 的主要特征是炎症反应失衡、感染风险增加、血管生成不足，通常受免疫缺陷、功能障碍、局部感染等复杂因素的影响[29]。MSCs-exo 在伤口愈合的各个阶段都能发挥重要作用[30]，它可以通过增强或抑制某些生物活性来促进伤口愈合，包括止血、调节炎症、促进血管生成、促进细胞增殖与迁移和细胞外基质(ECM)重建[30]，基于这些作用，MSCs-exo 可能在 DCW 治疗中具有相当重要的意义。

3.1. 止血

组织因子(Tissue factor, TF)是外源性凝血系统激活的启动剂，存在于外泌体的质膜中，TF 可以转移到血小板，启动外源性凝血级联，使凝血酶原转化为凝血酶并形成纤维蛋白凝块[31]。将 BMSC-exos 应用于大鼠出血肝模型的出血部位，表现出减少出血量和缩短出血时间的效果，显示出其优异的止血性能[32]。然而，外泌体在皮肤伤口愈合中促凝的相关研究尚未开展，需要进一步的研究来证明外泌体在伤口愈合止血阶段的潜在作用。

3.2. 调节炎症

过度炎症刺激是 DCW 形成的主要原因，巨噬细胞异常极化和细胞因子过度表达导致持续炎症状态，

可以引起继发性组织损伤[33]。MSC-exos 可以抑制 T 细胞的分化、活化和增殖，并减少 IFN-γ 的释放，下调促炎因子 TNF-α、IL-1β 和 IL-6 的浓度[16]，上调抗炎因子 IL-10 的表达[34]。在糖尿病小鼠模型中应用 BMSC-exos 观察到巨噬细胞 M1 极化降低、M2 极化升高，而褪黑素联合 BMSC-exos (MT-exos)的作用更强，MT-exos 可通过激活 PTEN/PI3K/AKT 信号通路，促进巨噬细胞向 M2 极化、血管生成和胶原合成，从而促进创面愈合[35]。在感染的 DCW 中使用缺氧预处理的 HUVMSC-exos 后，HUVEC 也降低了促炎因子(TNF-α、IL-1β 和 IL-6)水平，诱导巨噬细胞向 M2 极化，减少细菌在创面部位的定植，氧化应激产物水平下降，抗氧化酶活力增高或者是抗氧化能力增强表明其可以发挥抗氧化作用促进伤口愈合[36]。BMSC-exos 与羧乙基壳聚糖－二醛羧甲基纤维素水凝胶的联合使用证实巨噬细胞从 M1 向 M2 极化，显著抑制细菌生长增强抗菌作用[37]。BMSC-exos 在调节炎症方面占据一定优势，在基础研究中广泛应用，且具有一定阶段临床应用。

3.3. 促进血管生成

高血糖会阻碍血管生成及创面愈合过程。ADSC-exos 过度表达 Nrf 不仅促进内皮祖细胞的增殖和血管生成，还增加了糖尿病小鼠创面的肉芽组织量及生长因子水平，加速血管化，同时降低炎症和氧化应激相关蛋白表达水平[38]。ADSC-exos 还可以促进血管内皮细胞的增殖和迁移，从而促进血管生成。通过下调 PTEN 并激活 PI3K/AKT 信号通路中的 miR-126，促进血管生成，同时刺激成纤维细胞、角化细胞和内皮细胞参与细胞增殖，与对肿瘤的双重调节作用不同，MSC-exos 通过刺激上述细胞的增殖和分化，同时促进损伤部位的血管生成，直接影响创面愈合的增殖阶段[14]。ADSC-exos 通过激活 AKT/HIF-1α 和 Wnt/β-catenin 通路，可以增强角质形成细胞的增殖和迁移能力，抑制角质形成细胞的凋亡[39]。在体内和体外实验中，ADSC-exos 均能诱导血管生成，通过转染 miR-125a 抑制血管生成抑制剂 delta-like 4 (DLL4)表达，同时上调促血管生成基因(Ang1 和 Flk1)，下调抗血管生成基因(Vash1 和 TSP1)，从而促进内皮细胞的血管生成[40]。多项研究表明 ADSC-exos 促血管生成作用明显，且有一定会促进细胞增殖和迁移作用。

3.4. 促进细胞增殖、迁移和成管

在 MSC-exos 中常见的机制是 Wnt/β-catenin 信号通路，它在创面愈合过程中起着关键作用，能促进 DCW 的细胞增殖和血管生成[41]。Wnt4 从 HUCMSC-exos 向内皮细胞的转移可以激活 Wnt/β-catenin 通路，增加包括增殖细胞核抗原(PCNA)、细胞周期蛋白 D3 和 N-cadherin 在内的血管生成相关因子的数量，促进血管生成，从而促进慢性创面愈合[42]。HUCMSC-exos 将血管生成素-2 (Ang2)转运到人脐静脉内皮细胞(HUVEC) [43]，从而增强其增殖、迁移和成管能力。Hu [44]等人发现 HUCMSC-exos 将 miR-21-3p 转运给 HUVEC，通过抑制磷酸酶及张力蛋白同源物(PTEN)和侧枝发芽因子同源物 1 (SPRY1)蛋白，从而增加血管生成和细胞增殖。在另一项研究中发现，将 miR-125a 从 ADSC-exos 转移到内皮细胞中，通过阻断 DLL4 的作用来增加血管生成[45]。BMSC-exos 能促进成纤维细胞增殖和迁移，增强生长因子分泌能力。HUCMSC-exos 可以通过抑制 AIF 核易位和 PARP-1 的过度激活来调节人永生化角质形成细胞(HaCaT 细胞)的功能，促进再上皮化和血管生成来治疗全层皮肤缺损[46]。AMSC-exos 通过促进细胞增殖、抑制细胞凋亡和促进血管生成，加速糖尿病小鼠全层皮肤缺损模型的创面愈合[38]。目前，用于修饰 MSC-exos 以增强成纤维细胞增殖和血管生成的方法明显增加。例如将 lncRNA h19 转染的 BMSC-exos 与糖尿病足溃疡患者足部组织中提取的成纤维细胞共同培养发现，过表达的外泌体通过竞争性结合 miR-152-3p 调节 PTEN 介导的 PI3K/AKT 信号通路，增强成纤维细胞的增殖和迁移，抑制细胞凋亡和炎症[47]；在糖尿病全层皮肤缺损大鼠模型中，阿托伐他汀预处理的 BMSC-exos 促进 HUVEC 的增殖、迁

移和血管内皮生长因子(VEGF)的表达，加速创面愈合[48]；经吡格列酮预处理的 BMSC-exos 用于治疗糖尿病大鼠全层皮肤缺损创面愈合速度更快，再上皮化更充分，胶原沉积更广泛，创面灌注显著增强，VEGF 和 CD31 水平显著上调[49]；皮下注射 mmu_circ_0000250 修饰的 AMSC-exos 能促进糖尿病小鼠的创面愈合，并且通过促进内皮细胞的增殖和迁移以及减少内皮细胞的凋亡，使毛细血管和肉芽组织的生成增加[50]。预处理后的 MSC-exos 可能在细胞增殖和迁移过程中起到促进作用，加速糖尿病慢性创面愈合。

3.5. 细胞外基质重塑

在创面愈合的最后阶段，细胞外基质(ECM)的产生和重塑是决定创面愈合时间和瘢痕形成程度的关键因素。近年来，一些研究报道了 exo 对 ECM 重塑的影响。已经证实 BMSC-exos 可以使全层皮肤缺损的大鼠皮肤形态恢复正常，这依赖于通过抑制转化生长因子-β (transforming growth factor-β, TGF-β)/Smad 信号通路下调 TGF-β1、上调 TGF-β3 含量[51]，TGF-β 与成纤维细胞上的受体结合，激活 Smad3 复合物，促进核转录，启动胶原和 α-SMA 合成[52]。在创面愈合和组织修复过程中，肌成纤维细胞过度累积及胶原沉积导致疤痕的形成，MSC-exos 有可能通过控制成纤维细胞转化和 ECM 重塑，从而抑制疤痕形成[53]。在创面愈合微环境中，巨噬细胞分泌 TGF-β1，促使成纤维细胞向肌成纤维细胞分化，破坏 TGF-β/Smad 通路阻止 TGF-β1 诱导的成纤维细胞分化为肌成纤维细胞，从而减少纤维化和瘢痕形成[54]。有证据表明，HUCMSC-exos 通过高表达 miR-21-5p 和 miR-125b-5，同时通过 TGF-β2/Smad2 途径抑制 TGF-β 受体，促进组织再生，减少瘢痕形成[43]。ECM 由多种蛋白质组成，其中最常见的是胶原蛋白。胶原蛋白在伤口愈合的不同阶段具有双重作用。在创面愈合早期，刺激胶原合成对创面强度的恢复至关重要，但在创面愈合后期，胶原过多会导致瘢痕形成[55]。有报道称，除了促进肌成纤维细胞的形成外，TGF-β/Smad 通路还参与了胶原合成的调节，TGF-β/Smad 通路的上调会在创面愈合早期增强 COLI2 基因的表达，而在创面愈合后期减少 I 型胶原的沉积[43]。基质金属蛋白酶(Matrix metalloproteinases, MMPs)可以降解过量胶原。有研究表明，ADSC-exos 可以触发 ERK/MAPK 通路，同时增强 MMP-3 的表达[56]。此外，Yang 等人发现，ADSC-exos 中的 miR-21 能调节 PI3K/AKT 通路并提高 MMP-9 的产生，从而加速 HaCaT 细胞的增殖和迁移[53] [57]。MSC-exos 通过在创面愈合不同时期调控肌成纤维细胞的形成和 TGF-β/Smad 通路减少瘢痕形成，提高患者生活质量。

4. 总结

MSCs 具有自我更新能力和多向分化潜能，是最常用、最有前景的成体干细胞之一，可从大多数成体组织如骨髓、脂肪和脐带组织中提取[3] [5]。MSC-exos 具有同源细胞的遗传信息，将其生物活性物质传递到靶细胞参与细胞间通讯，从而调控靶细胞功能，在创面愈合各个阶段均起着关键的促进作用[29]。虽然不同来源的外泌体具有相同的生物活性因子，其生物学功能大致相似，但它们的生物学特性取决于各自特异性表达的分子[14]。ADSC-exos 来源相对丰富，可以通过无痛微创手术轻松获得;它们具有多能性、可塑性、易于储存性，并且在血液和体液中稳定存在[13]。ADSC-exos 所携带的分子主要与血管生成有关，一些蛋白仅在 ADSCs-exo 中表达，如 Wnt 和 Ang1，Wnt 通路与促血管生成活性有关，从而促进创面愈合；Ang1 可以恢复受损的内皮蛋白通透性。而 BMSC-exos 的含量主要与角质形成细胞的增殖和迁移有关，但作用不足以保证治疗效果[3] [58]。BMSC-exos 具有生物稳定性，免疫原性低，移植后具有良好的增殖和存活能力，且最常用于临床试验，在各种疾病，特别是骨相关疾病中发挥突出作用[16]。近年来，HUVEC 因其易于分离、免疫原性低，自我更新和增殖能力强的特点，在许多临床领域得到应用，但在维持生物活性和临床治疗方面存在局限性[22]。一些研究表明，HUVEC 可以促进新血管形成，增强组织再生能力[42]。考虑到不同的生物学特性，一些研究也报道了 MSC-exos 在自身免疫性疾病[59]、缺

血性损伤[60]和代谢性疾病[61]中均发挥治疗作用，并且还与动态调节肿瘤生物学功能[11]、促进受损骨软骨、神经和肌腱组织的修复及再生有关[16]。

5. 讨论

间充质干细胞衍生的外泌体在糖尿病慢性创面治疗中具有很大的研究价值，但仍存在一些问题：间充质干细胞易受缺血和缺氧微环境的影响，而外泌体的分离和纯化仍然具有挑战性。因此，目前大部分研究都处于基础及临床试验阶段，未来还需要更多的研究来探索间充质干细胞来源的外泌体在临床中的广泛应用和可行性。

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