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骨髓间充质干细胞在韧带损伤腱骨愈合中的研究进展

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摘　要

韧带损伤作为运动系统常见损伤，显著影响关节稳定性并降低患者生活质量。良好的腱骨愈合是韧带重建手术成功以及术后早期康复的关键，其复杂愈合过程涉及炎症调控、纤维软骨再生及胶原重塑等生物学阶段。骨髓间充质干细胞(Bone Marrow Mesenchymal Stem Cells, BMSCs)凭借多向分化潜能、免疫调节功能及旁分泌活性，在促进腱骨愈合过程中展现出巨大潜力。本文主要对BMSCs从不同方面治疗韧带损伤以促进腱骨的研究进展进行综述。

关键词

骨髓间充质干细胞，腱骨愈合，韧带损伤，外泌体，生物支架材料

Advances in Bone Marrow Mesenchymal Stem Cells for Tendon-Bone Healing in Ligament Injuries

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Abstract

Ligament injuries, as prevalent disorders of the musculoskeletal system, significantly compromise joint stability and diminish patients' quality of life. Optimal tendon-to-bone healing is pivotal for successful ligament reconstruction and postoperative rehabilitation, involving a complex biological

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cascade encompassing inflammatory modulation, fibrocartilage regeneration, and collagen remodeling. Bone marrow mesenchymal stem cells (BMSCs), leveraging their multipotent differentiation capacity, immunomodulatory functions, and paracrine activity, exhibit substantial therapeutic potential in enhancing tendon-to-bone integration. This article mainly reviews the research progress of BMSCs in treating ligament injuries from different aspects to promote tendon-bone healing.

Keywords

Bone Marrow Mesenchymal Stem Cells, Tendon-Bone Healing, Ligament Injury, Exo-Somes, Biological Scaffold Materials

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1. 引言

韧带损伤是日常生活及运动中常见的损伤，尤其是在参与高强度运动的个体中更为普遍，例如常见的前交叉韧带(Anterior Cruciate Ligament, ACL)损伤、肩袖损伤和距腓前韧带损伤等，通常伴有长期的疼痛和功能障碍[1]。根据统计韧带和肌腱的损伤占所有运动损伤的 30%至 40%，这种高发病率使得韧带损伤的治疗成为运动医学领域的重要研究方向[2]。韧带损伤的治疗主要分为非手术和手术两类。非手术治疗包括物理治疗、药物治疗以及休息等，但治疗效果有限[1] [3]。而对于韧带的严重撕裂或断裂，手术治疗被认为是更有效的方法[4]。手术治疗通常涉及韧带重建，将肌腱移植物插入骨隧道中以重建受损的韧带，而手术成功的关键在于移植肌腱与骨骼的愈合程度[5]。许多患者韧带重建手术后面临再损伤或功能不全的风险，原因与韧带及其周围组织的复杂结构和生物学特性有关[6]。骨髓间充质干细胞(Bone Marrow Mesenchymal Stem Cells, BMSCs)是一类重要的多能干细胞，不仅在骨、软骨、脂肪等多种组织的再生中发挥关键作用，还在免疫调节、炎症反应和组织修复中扮演着重要角色[7] [8]。BMSCs 的研究为韧带损伤和腱骨愈合提供了新的治疗思路。

2. 腱骨愈合过程

腱骨界面结构复杂，是由韧带、非矿化的纤维软骨、矿化的纤维软骨和骨组织组成的一个特殊结构[9]。腱骨界面的主要功能是将肌腱的机械负荷有效地传递给骨骼，从而实现运动功能的稳定和协调[10]。然而肌腱和骨骼在组成、结构和机械性能上存在显著差异，这使得它们之间的机械负荷的转移变得复杂。Liu 等人[11]的研究表明，肌腱和骨骼拉伸的弹性模量沿着肌肉力的方向相差近百倍，这种差异使得腱骨界面在运动过程中容易产生应力集中，从而导致韧带损伤和韧带重建失败。Genin 等人[12]的研究发现，腱骨界面存在纤维网状结构，这种纤维网状结构可以增强机械负荷传递能力，使腱骨界面在承受高负载时能够局部变形，从而有效地分散应力，减少腱骨界面处的应力集中，进而提升了韧带–骨附着部位的韧性。健康的肌腱在急性过载(如高速或高冲击事件)和割伤时可能发生撕裂，过度使用或内在组织退化也可导致肌腱损伤，而年龄、新陈代谢和血压等其他因素也会加剧肌腱损伤[13] [14]。腱骨愈合是一个复杂的生物过程，Liu 等人[15]早期通过兔子模型观察腱骨愈合的过程，术后 1 周腱骨界面以炎症反应为主，术后 2 周瘢痕组织形成，术后 4 周后瘢痕组织逐步分化为致密结缔组织，胶原纤维沿力学方向排列，至术后 6 周时，Sharpey 纤维(III 型胶原)跨越肌腱与骨，形成类似间接插入的结构。Ishibashi 等人[16]通过对人体进行 ACL 重建术，发现腱骨愈合过程在移植后数月仍在持续进行，术后超过 1 年的肌腱组织则表现得更

接近正常韧带，原始的腱骨交界逐渐消失，形成了与正常韧带及腱骨界面相似的特征。Robert 等人[17]对12 名患者进行 ACL 重建术的研究中观察到，术后 3 个月腱骨界面表现为纤维血管组织及未钙化骨质，术后 5~6 个月时出现类 Sharpey 纤维及未成熟编织骨，10 个月后 Sharpey 纤维形成连续性界面，建立成熟的间接锚定。Xue 等人[5]将腱骨愈合过程总结为以下四个阶段，炎症期炎性细胞及骨髓干细胞募集，形成纤维血管瘢痕界面；增殖期干细胞分化并释放细胞因子，促进血管神经生成；基质合成期新的细胞外基质合成伴随骨组织长入；重塑期 Sharpey 纤维形成，胶原连续性重建，机械强度递增。近年来，BMSCs 的研究为韧带损伤腱骨愈合提供了新的治疗思路，具有广泛的应用前景。

3. BMSCs 在韧带损伤腱骨愈合中的作用

BMSCs 可以促进骨、软骨、肌肉、韧带和肌腱愈合，在腱骨愈合过程中发挥着重要的作用[18]。BMSCs 具有调节损伤部位附近生长因子和细胞因子的表达和释放的能力，从而促进伤口愈合和受损组织再生的过程[19]。BMSCs 能够分泌多种生长因子，包括血小板源性生长因子、转化生长因子 β (Transforming Growth Factor Beta, TGF-β)、成纤维细胞生长因子等，这些因子在调节细胞增殖、迁移和分化方面发挥着关键作用[20]。Lim 等人[21]和 Ouyang 等人[22]最早将 BMSCs 用于韧带损伤腱骨愈合的研究。Lim 等人[21]使用 BMSCs 涂覆腱移植物对兔子 ACL 进行重建，术后 2 周时观察到大量未成熟的软骨细胞，术后 4 周时软骨细胞的排列更加有序，并开始产生软骨基质，术后 8 周腱与骨之间形成了类似正常 ACL 插入的成熟软骨区域，且失效负荷和刚度方面显著优于对照组，得出结论，涂覆 BMSCs 的肌腱腱移植物通过形成介于腱骨之间的软骨组织来促进腱骨愈合。Ouyang 等人[23]采用新西兰白兔模型，将腓肠长肌腱移植到 2.5 毫米直径的跟骨骨隧道中，并对骨隧道进行 BMSCs 处理，术后 4 周出现垂直于界面的胶原纤维排列及软骨样细胞增殖，研究表明 BMSCs 在早期通过形成类似纤维软骨的附着结构来增强腱骨愈合效果。Canseco 等人[24]研究从约克夏猪分离的自体 ACL 细胞与 BMSCs 在不同细胞比例下直接接触共培养对韧带标志物表达的影响，结果显示 50% ACL 细胞与 50% BMSCs 共培养组显著促进了韧带修复关键标志物 I 型胶原和 Tenascin-C 的基因表达，这种效果在其他组中并未观察到，其 I 型胶原与 III 型胶原比值(5.8)最接近天然韧带水平(9:1)，而 III 型胶原在 BMSCs 单独培养组中表达最高，这表明，50% ACL 细胞与 50% BMSCs 共培养够促进韧带相关标志物的表达，从而可能增强韧带的愈合能力。现有研究证实骨 BMSCs 通过多种途径促进治疗韧带损伤促进腱骨愈合，为临床构建细胞治疗策略提供理论依据。

4. 刺激因素对 BMSCs 的影响

BMSCs 的功能受到多种刺激的影响，这些刺激可以促进腱骨愈合。He 等人[25]的研究发现，适度机械拉伸结合促红细胞生成素可以显著提高 BMSCs 的细胞周期进程，促进 BMSCs 的细胞增殖和成骨分化，这一作用可能是通过激活 ERK1/2 信号通路实现的，ERK1/2 通路激活主要作用于细胞周期调控。Teng 等人[26]通过对富血小板血浆与 BMSCs 结合影响兔子 ACL 重建后的腱骨愈合效果的研究，发现富血小板血浆共同培养的 BMSCs 在 I 型胶原蛋白、骨钙素和骨桥蛋白的表达上显著增加，体内实验腱骨界面更加成熟，骨隧道中新形成的骨量更多，且在生物力学测试中表现出显著更高的失败负荷，富血小板血浆效应侧重细胞外基质合成。Setiawati 等人[27]在兔子 ACL 重建后，向关节腔内注射 BMSCs 和血管内皮生长因子，研究结果显示经过 BMSCs 和血管内皮生长因子处理的兔子在 MRI 成像、III 型胶原纤维表达以及生物力学分析方面均表现出更好的愈合情况，特别是在术后 3 周和 6 周的评估中，表现出更高的 III 型胶原纤维含量和更强的最大拉伸强度，该研究主要聚焦于血管－基质耦合机制。现有研究表明，机械刺激、富血小板血浆干预和血管化调控三类策略均可通过不同分子机制增强 BMSCs 的腱骨愈合效能，但其作用方式存在显著差异。了解不同刺激对 BMSCs 的影响机制，对于优化腱骨愈合的治疗策略具有重要

意义。通过合理调控这些刺激，可以促进 BMSCs 的功能，从而提高腱骨愈合的成功率。

5. 骨髓间充质干细胞来源的外泌体(BMSCs-Exo)

外泌体是来源于多泡体的细胞内小体，是直径约为 30 至 150 nm 的细胞外小泡，密度在 1.1 至 1.2 g/ml 之间[28] [29]，能够携带多种生物活性分子，包括 miRNA、蛋白质和脂质等，是细胞间的信号传递和信息交换的媒介[2]。外泌体存在于各种细胞和细胞外液中，如血浆、滑液、尿液、羊水、唾液、脊髓液和母乳[30]-[32]。BMSCs 来源的外泌体(Bone Marrow Mesenchymal Stem Cells-derived Exosomes, BMSCs-Exo)广泛用于神经系统、呼吸系统、内分泌系统等多种疾病的治疗，随着研究的深入，BMSCs-Exo 也可用来治疗韧带损伤腱骨愈合[33]-[35]。Tan 等人[36]的研究发现 BMSCs-Exo 通过促进腱骨界面的成骨分化、软骨形成及纤维血管瘢痕组织的有序化，显著增强小鼠肩袖损伤模型的愈合效果，BMSC-Exo 可激活骨髓间充质基质细胞的增殖、迁移能力，并上调成骨标志物(如 RUNX2、ALP、Osteocalcin)和软骨相关基因(如 SOX9、Col2A1、Aggrecan)的表达。Huang 等人[37]研究发现 BMSCs-Exo 通过双重机制显著促进大鼠肩袖腱骨愈合，首先通过激活血管内皮生长因子和 Hippo 信号通路，增强人脐静脉内皮细胞的增殖、迁移及血管管腔形成能力，并提升体内肌腱–骨界面血管密度，另外 BMSCs-Exo 可抑制 M1 型巨噬细胞极化及炎性因子的分泌，降低局部炎症反应，从而促进大鼠肩袖损伤的腱骨愈合。该研究表明 BMSC-Exo 对增强血管生成具有广泛而有益的影响。巨噬细胞具有两种表型，M1 型巨噬细胞为促炎表型，M2 型巨噬细胞为抗炎表型，巨噬细胞在韧带损伤腱骨愈合的发生发展中起着不可忽视的作用[38] [39]，加速巨噬细胞从 M1 型向 M2 型极化可以加速组织修复，这可能是促进腱骨愈合的关键[40]。Shi 等人[41]的研究证实 BMSCs-Exo 可以通过促进 M2 型巨噬细胞极化，增加抗炎因子以及减少促炎因子产生，还促进了纤维软骨的再生，最终提高了腱骨愈合的生物力学特性。Wu 等人[42]的研究证实低强度脉冲超声预处理的 BMSCs-Exo 通过调控细胞分化微环境，显著促进腱骨界面纤维软骨再生并抑制肩袖脂肪浸润，提升修复部位的生物力学强度、组织成熟度评分及纤维软骨层面积与厚度，并验证了 miR-140 是介导该效应的关键分子。BMSCs-Exo 携带的 miRNA 通过靶向调控关键信号通路抑制炎症因子并促进组织修复。以上研究表明，BMSCs-Exo 可同时作用于炎症、凋亡、血管生成等多种途径，形成协同治疗效应，促进韧带损伤修复以及腱骨愈合。

BMSCs-Exo 与 BMSCs 直接移植相比，BMSCs-Exo 具有低免疫原性、良好的生物相容性，以及能够通过携带多种生物活性分子(如抗炎因子、促修复蛋白等)调节炎症微环境，例如促进 M2 巨噬细胞极化、减少炎症因子(IL-1β, IL-6)释放，从而抑制细胞凋亡、增强细胞增殖并促进纤维软骨再生，最终改善韧带组织修复[20] [41]。另外 BMSCs-Exo 在冻存后仍可保持生物活性，可通过预处理或基因编辑等技术增强其功能特异性[43]。然而目前 BMSCs-Exo 分离纯化过程复杂、生产成本较高，且促进韧带损伤修复与腱骨愈合的作用机制尚未完全阐明，长期临床应用的安全性和稳定性也有待进一步验证。BMSCs-Exo 通过多种机制促进腱骨愈合，展现出其在韧带损伤治疗上的巨大应用价值。

6. 生物支架材料

由于组织工程学的快速发展，BMSCs 与生物支架材料的结合在腱骨愈合中发挥着重要作用。生物支架不仅为细胞提供了生长的基础，还能通过物理和化学特性促进细胞的附着、增殖和分化[44]。使用复合生物支架可以有效促进 BMSCs 的定向分化和细胞外基质的合成，从而加速腱骨愈合的过程[45]。Yokoya 等人[46]采用聚乙醇酸作为生物可吸收支架材料，将体外扩增的自体 BMSCs 接种于聚乙醇酸材料表面形成细胞–聚合物复合体，聚乙醇酸的快速降解特性(16 周完全吸收)与 BMSCs 的协同作用通过优化胶原纤维排列、增加 I 型胶原比例，有效模拟天然腱骨界面的纤维软骨过渡结构，从而增强再生组织的生物力

学性能，显著提高其组织成熟评分和极限抗拉强度。Liu 等人[47]采用工程化肌腱–纤维软骨–骨复合物作为脱细胞多层支架，其结构模拟天然腱骨界面异质性组织层级，将 BMSCs 通过细胞片技术整合至该复合物支架中来修复狗的肩袖损伤，研究结果表明，整合了 BMSCs 的复合物支架材料组在组织学评分、纤维软骨形成、胶原纤维组织方面均显著优于对照组，且最大失效载荷(286.80 ± 45.02 N)和极限应力(4.50 ± 1.11 MPa)明显高于其他组，证实该体系通过力学支撑与生物活性协同机制有效增强腱骨愈合。Micalizzi 等人[48]通过结合电纺丝和 3D 生物打印技术开发了一种梯度支架，选用聚乳酸–羟基乙酸共聚物和聚己内酯分别模拟肌腱/韧带和骨组织的结构，在该支架上接种 BMSCs 进行生物相容性测试，结果显示 BMSCs 在支架上能够有效附着、增殖和分化为肌腱样和骨样细胞，其在拉伸测试中的表现与体内肌腱和韧带相当。然而该研究尚未进行体内实验验证，未来需开展临床前动物模型测试以推动临床应用转化。Tang 等人[49]设计了一种质量比为 1:5 的聚(D,L-丙交酯–共–乙交酯)/聚(ε-己内酯)支架材料，在大鼠 ACL 损伤模型下与来源于人的 BMSCs 共培养，动态培养的结果显示其力学性能(极限抗拉强度 58.3 ± 7.4 MPa，断裂伸长率 67%)和降解速率(8 周后质量保留 91%)与天然 ACL 匹配，该支架不仅可以促进 BMSCs 的增殖和粘附，而且诱导了 BMSCs 向成纤维细胞的分化，从而形成类似韧带的结构。除此以外，脱矿骨基质[50]、电纺聚己内酯纳米纤维[51]等生物材料治疗韧带损伤促进腱骨愈合方面都有显著的效果。通过与生物支架材料的结合，BMSCs 能够在腱骨愈合中发挥更为显著的作用，促进组织再生和功能恢复。现有研究显示，BMSCs 与生物支架材料的协同作用在腱骨愈合中具有多维调控潜力，但支架设计与生物学功能的整合仍需进一步优化。

7. 结语

韧带损伤作为日常生活和运动中常见的疾病，其导致的疼痛以及关节不稳定显著降低患者生活质量。临床治疗中，韧带重建术后腱骨愈合质量直接决定手术预后，BMSCs 凭借其多向分化潜能、免疫调节作用及旁分泌活性，在促进腱骨愈合中展现出独特优势。随着研究不断深入，探索出 BMSCs 在腱骨愈合方面不同的作用机制以及特性。目前大多数关于 BMSCs 治疗韧带损伤腱骨愈合的研究基于动物实验，未来需寻找更加安全、有效的方法将 BMSCs 应用于临床，并且进一步深入探索促进腱骨愈合的机制。未来研究可聚焦于开发靶向递送系统以提升 BMSCs 或其外泌体在损伤部位的富集效率与功能稳定性，优化生物支架设计并协同细胞因子诱导细胞定向分化及胶原有序重塑，探索多模态联合治疗策略调控炎症微环境、细胞内信号通路及血管生成方面协同增效，同时需建立大型动物模型的长期安全性评估体系，推动 BMSCs 治疗从基础研究向高效、安全、可推广的临床应用转化。

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