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骨髓间充质干细胞在骨科疾病中的临床应用与研究进展

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摘　要

骨髓间充质干细胞(BMSCs)因其多向分化潜能、自我更新能力及旁分泌特性，已成为骨科疾病再生治疗的研究热点。近年研究聚焦于BMSCs在骨缺损、股骨头坏死、骨关节炎、脊髓损伤等难治性疾病中的应用机制与临床转化。BMSCs可通过分化为成骨细胞、软骨细胞及神经细胞，结合生物支架材料、基因修饰或药物干预，促进组织再生与功能恢复。本文系统综述了BMSC在骨折与骨缺损修复、股骨头坏死、骨关节炎、脊髓损伤等骨科难治性疾病中的研究进展，总结BMSCs在骨科疾病治疗中的应用现状，分析现存挑战，并展望其未来发展方向，以期为临床转化提供理论依据。

关键词

骨髓间充质干细胞，骨科疾病，临床应用，研究进展

Clinical Applications and Research Progress of Bone Marrow Mesenchymal Stem Cells (BMSCs) in Orthopedic Diseases

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Abstract

Bone marrow mesenchymal stem cells (BMSCs) have emerged as a pivotal research focus in regenera-

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tive therapy for orthopedic diseases due to their multipotent differentiation capacity, self-renewal ability, and paracrine properties. Recent studies have concentrated on elucidating the mechanistic roles and clinical translation of BMSCs in refractory conditions such as bone defects, osteonecrosis of the femoral head (ONFH), osteoarthritis (OA), and spinal cord injury (SCI). BMSCs facilitate tissue regeneration and functional recovery through differentiation into osteoblasts, chondrocytes, and neural cells, combined with biomaterial scaffolds, genetic modification, or pharmacological interventions. This article systematically reviews advances in BMSC-based strategies for treating orthopedic refractory diseases, including fracture and bone defect repair, ONFH, OA, and SCI. It summarizes the current applications of BMSCs in orthopedic therapeutics, analyzes existing challenges, and proposes future directions to inform clinical translation with robust theoretical foundations.

Keywords

Bone Marrow Mesenchymal Stem Cells, Orthopedic Diseases, Clinical Applications, Research Progress

1. 引言

BMSCs 作为一类具有多向分化能力的成体干细胞，因其易于获取、低免疫原性及强组织修复能力，成为骨科领域的研究焦点[1]。BMSCs 的核心特性为多谱系分化能力，在特定诱导条件下，可分化为成骨细胞、软骨细胞、脂肪细胞及神经细胞，直接参与骨、软骨及神经组织的再生修复[2]。骨科疾病如骨折与骨缺损、股骨头坏死、骨性关节炎、脊髓损伤等常导致患者功能障碍，传统治疗手段如手术修复、药物干预等存在创伤大、疗效局限及复发率高等问题。骨缺损修复常依赖自体骨移植或金属植入物，但面临供区并发症、免疫排斥及力学适配性不足等问题[3]；股骨头坏死晚期多需关节置换，而假体寿命限制导致青中年患者面临二次手术风险[4]；脊髓损伤因神经元再生能力低下，尚无有效干预措施逆转神经功能障碍[5]。此类疾病不仅严重降低患者生活质量，亦为社会医疗资源带来沉重负担。近年来，再生医学的兴起为这类疾病的治疗提供了新思路，探索高效、持久的再生医学策略成为骨科领域亟待突破的科学命题。

2. 骨髓间充质干细胞的分离鉴定与生物学特性

BMSCs 广泛分布于骨髓、脂肪组织及脐带血中，其中骨髓来源的细胞因提取便捷成为研究主流[6]。分离方法以密度梯度离心法及全骨髓贴壁法为主，前者通过细胞沉降速度差异筛选目标群体，后者依赖细胞贴壁特性实现初步纯化，尽管流式分选或免疫磁珠法可提高 BMSCs 纯度，但因其操作复杂、成本较高且易损伤细胞活性，临床应用中仍以前两种方法为主导[7]。BMSCs 缺乏特异性表面抗原，目前依据国际细胞治疗协会标准，其鉴定需满足三项条件：塑料黏附性、特定表面标志物表达(CD105、CD73、CD90 阳性，CD34、CD45 等造血标志物阴性)及体外多向分化潜能[8]。流式细胞术联合免疫荧光染色是常用鉴定 BMSCs 的手段，但标准化流程仍待完善。

3. BMSCs 在骨科领域各类疾病中的应用与研究进展

3.1. BMSCs 在骨折愈合与骨缺损修复中的应用与研究进展

骨再生是修复创伤、感染或代谢性骨病的关键过程，但传统治疗方法存在供体不足、免疫排斥及修

复效率低等局限性。近年来，BMSCs 因其多向分化潜能与旁分泌特性成为骨再生研究的热点。BMSCs 通过外泌体介导细胞间通讯、结合 3D 生物打印技术构建仿生支架，以及线粒体动态调控能量代谢与信号传递，为骨缺损修复提供了新策略[9]。BMSCs-Exos 可以携带蛋白质、miRNA、mRNA 等生物活性物质，通过旁分泌途径调控骨微环境，研究表明 BMSCs-Exos 可激活 Wnt/β-catenin、MAPK 等信号通路，上调成骨相关蛋白如 Runx2、骨钙素的表达，促进成骨细胞分化与矿化[10]。BMSCs-Exos 还能通过传递 miR-196a、miR-29b 等调控靶基因如 Dkk1 和 Notch，抑制破骨细胞活性并减轻炎症反应[11]。药物预处理可以增强 BMSCs-Exos 的成骨诱导能力，这表明它们作为药物载体的潜力。然而，外泌体内容物的具体作用机制及其在体内的长期安全性仍需深入探索。3D 生物打印技术通过整合 BMSCs 与仿生支架材料，实现骨缺损的个性化修复[12]。支架材料需要具备生物相容性、孔隙连通性和力学适配性，例如，羟基磷灰石、壳聚糖等天然高分子与聚乳酸等合成材料的复合应用可以优化成骨微环境[13]。研究显示，锶取代硅酸钙支架联合 BMSCs-Exos 能够显著促进血管生成与骨整合[14]。在打印技术方面，熔融沉积成型(FDM)与光固化(SLA)技术因其高精度和操作便捷而成为主流，但仍需解决细胞存活率与动态力学适配的问题[15]。未来的研究方向包括开发抗菌复合支架、优化血管化策略以及推动临床转化。线粒体作为 BMSCs 的能量工厂，其结构与功能的动态调控对骨修复至关重要。在骨损伤的初期，线粒体通过融合(Mfn1/2 介导)增强 ATP 合成，以支持 BMSCs 的增殖，而持续的损伤则会触发分裂(Drp1 调控)与自噬(PINK1/Parkin 通路)，以清除受损的线粒体[16]。线粒体的转移与迁移体的释放进一步维持细胞的稳态，例如，通过调控 Mfn2 的表达来改善铁过载导致的 BMSCs 功能障碍[17]。此外，此外，低氧预处理结合姜黄素可以增强线粒体自噬，提升 BMSCs 在缺氧环境下的修复效能[18]。线粒体代谢产物如 ROS 和 mtDNA 的信号传递作用及其与成骨分化的关联仍需深入解析[19]。尽管 BMSCs 在骨再生中展现出多维度的潜力，但仍面临一些挑战，包括外泌体成分复杂，需要明确关键活性分子及其递送靶点；3D 打印支架的长期生物降解性与力学性能需进一步优化；线粒体调控网络的分子机制尚未完全阐明。未来的研究可以通过多组学技术解析 BMSCs 的功能调控网络，结合人工智能优化支架设计，并开展大规模临床试验以验证其安全性。通过跨学科的协作，BMSCs 联合新技术有望为骨代谢疾病提供革新性的治疗方案。

3.2. BMSCs 在骨性关节炎中的应用与研究进展

骨关节炎(Osteoarthritis, OA)是一种以关节软骨退行性改变为核心的慢性疾病，临床表现为疼痛、活动受限及关节畸形，传统治疗手段多聚焦于症状缓解，难以逆转病理进程[20]。近年来，BMSCs 因其多向分化潜能、旁分泌活性及免疫调节特性，成为 OA 治疗的研究热点，而自体 BMSCs 因免疫排斥风险低、安全性高，成为临床首选[21]。BMSCs 可以通过分泌血管内皮生长因子 VEGF、胰岛素样生长因子-1 (IGF-1)等生物活性分子，促进软骨细胞增殖并抑制凋亡，同时刺激细胞外基质的合成[22]。研究证实，BMSCs 条件培养基可以通过显著降低 IL-6、MMP-3 等炎症因子水平延缓软骨退化[23]。BMSC-Exos 作为细胞间通讯载体，通过传递 miRNA 调控靶基因表达，研究发现 miR-140-5p 通过抑制 Wnt5a 信号通路，上调 SOX9 和 II 型胶原蛋白表达，增强软骨修复能力[24]。BMSCs 还可以可抑制 NF-κB 信号通路的激活，减少促炎因子 TNF-α、IL-1β 的释放，促进 M2 型巨噬细胞极化，改善关节微环境炎症状态[25]。动物实验表明，关节腔内注射 BMSCs 可显著降低滑膜炎症细胞浸润，延缓 OA 进展[26]。多项随机对照试验显示，关节腔内注射自体 BMSCs 可显著改善患者视觉模拟量表(VAS)和 WOMAC 评分[27]。有相关研究通过开展的 4 年期 I/II 期临床试验表明，自体 BMSCs 联合富血小板血浆 PRP 注射后，患者关节功能及疼痛缓解效果优于单一 PRP 治疗[28]。软骨下注射 BMSCs 在长期随访中展现出与全膝关节置换术相当的疗效，且并发症发生率更低[29]。异体 BMSCs 具有操作便捷、无需二次取材等优势，但其免疫原性及宿主排斥反应仍需关注，有研究发现异体 BMSCs 注射治疗后患者软骨质量显著改善，但不良反应发生

率高于自体移植，未来需进一步验证其长期安全性[30]。BMSC-Exos 因稳定性高、易储存运输，成为无细胞治疗的新策略，动物实验表明 BMSC-Exos 能够有效促进 OA 大鼠软骨修复和细胞外基质合成，减轻膝关节疼痛，BMSC-Exos 还可以促进滑膜巨噬细胞从 M1 到 M2 的表型转化来缓解骨关节炎[31] [32]。尽管 BMSCs 治疗 OA 前景广阔，仍面临较多挑战现有研究在细胞剂量、外泌体提取方法及动物模型选择上存在显著差异，导致数据可比性不足。异体移植的免疫排斥风险、体外扩增细胞的遗传稳定性及潜在成瘤性需更严格的临床前评估，不同来源外泌体如脐带、滑膜的疗效差异仍需系统比较。联合生物支架、基因编辑技术或信号通路靶向调控可能进一步提升 BMSCs 的软骨修复能力。

3.3. BMSCs 在脊髓损伤中的应用与研究进展

脊髓损伤(SCI)是一种因创伤、肿瘤或炎症等因素导致的中枢神经系统严重疾病，常引发损伤平面以下运动、感觉及内脏功能障碍。传统治疗手段通过药物、手术及康复训练虽能缓解症状，但难以恢复神经功能。近年来，BMSCs 因其多向分化潜能、免疫调节特性及神经营养功能，成为 SCI 治疗的研究热点[33]。研究显示，BMSCs 移植途径可以显著影响疗效，蛛网膜下腔注射可使 BMSCs 随脑脊液扩散至损伤区，效果优于局部或静脉注射，移植时机也是影响疗效的关键，损伤后 3 天内的急性期静脉注射与局部注射效果相近，损伤后 7 天的亚急性期局部注射更具优势[34]。基因工程改造可提升 BMSCs 的治疗效能，过表达胶质细胞源性神经营养因子或 miR-200a 的 BMSCs，能通过激活抗氧化通路 Nrf2 或抑制凋亡信号 Keap1 显著改善神经功能，Bel-2 基因修饰则通过抑制线粒体凋亡途径，增强细胞存活率[35]。BMSC-EXOs 可以携带 miRNA、蛋白质等生物活性物质穿透血脊髓屏障，抑制神经元凋亡并促进轴突再生[36]。相关研究表明，BMSC-EXOs 可以上调损伤区脑源性神经营养因子表达，抑制少突胶质细胞凋亡，达到保护神经髓鞘的目的[37]。BMSCs 还可以联合施万细胞或嗅鞘细胞，通过协同作用增强髓鞘再生与抗凋亡效应[38]。水凝胶或明胶支架为 BMSCs 提供三维生长微环境，引导神经定向再生，同时抑制胶质瘢痕形成[39]。动物实验表明在两个不连续节段的亚急性脊髓压迫损伤后静脉注射人脐带血来源的间充质干细胞可以通过分化为特定细胞类型以及增强抗炎、抗星形胶质细胞增生、抗凋亡和轴突保存作用，每隔三天重复注射细胞恢复更为明显[40]。目前 BMSCs 用于治疗脊髓损伤还面临着挑战，部分研究报道了异位迁移或肿瘤形成的潜在风险，提示需严格把控移植剂量与时机。损伤区微环境的缺氧、炎症及抑制性分子也限制了 BMSCs 存活与功能发挥。目前最佳移植途径、剂量及时间窗尚未统一，个体化治疗策略亟待建立。BMSCs 致瘤性、免疫排斥及生物分布问题需通过长期随访与机制研究进一步阐明。

3.4. BMSCs 在股骨颈坏死中的应用与研究进展

研究表明，股骨头坏死(ONFH)的病理核心在于微循环障碍与骨重建失衡，而 BMSCs 通过促进血管生成、抑制骨吸收及增强成骨分化，可有效修复坏死区域[41]。其作用机制涉及调控成骨－成脂分化平衡、激活自噬通路如 LC3II、Beclin-1 及信号通路如 Wnt/β-catenin、BMP/Smad，从而改善骨内高压并延缓股骨头塌陷[42]。髓芯减压术通过降低骨内压缓解疼痛，但单纯减压难以阻止坏死进展，结合 BMSCs 移植可显著提升疗效：经减压通道注入 BMSCs 可促进新骨生成，减少塌陷风险[42]。临床数据显示，联合治疗组的 Harris 髋关节评分较单纯减压组提高 30%，且 5 年髋关节置换率降低至 15%以下[43]。有相关研究探讨了自体干细胞移植联合核心减压术治疗早期股骨头缺血性坏死 ONFH 的疗效及其与干细胞活力的关系，在术后 9 个月的随访中患者的 Harris 髋关节评分和磁共振成像结果均有明显改善[44]。有学者通过内侧旋股动脉进行自体骨髓单核细胞(BMMCs)靶向输送治疗股骨头坏死，探讨其有效性和安全性，发现早期进行 BMMCs 的输送可以有效延缓 ONFH 的进展，尤其是在未发生塌陷的早期阶段[45]。有相关研究使用一种多孔的纳米锂羟基磷灰石/明胶微球/红细胞生成素复合材料作为支架，通过提供生物相容性及

促进骨再生的环境来修复由糖皮质激素引起的股骨头缺血性坏死，研究发现此支架还能同时激活 Wnt 和 HIF-1/VEGF 信号通路，显著改善成骨和血管生成，对治疗 ONFH 具有较大潜力[46]。尽管 BMSCs 治疗 ONFH 前景广阔，仍存在以下瓶颈：(1) 干细胞来源受限，自体 BMSCs 易受病理微环境影响，活性降低；(2) 移植后存活率不足，局部缺氧及炎症微环境限制其功能；(3) 基因修饰的长期安全性未明，潜在致癌风险需进一步评估。未来研究需聚焦于优化干细胞递送系统如外泌体载药、开发仿生支架材料，并结合多组学技术解析中药–干细胞互作网络，以推动个体化治疗方案的实现。

4. 结语

骨髓间充质干细胞(BMSCs)在骨科疾病治疗中展现出潜力。BMSCs 可通过分化为成骨、软骨及神经谱系细胞直接参与受损组织再生，其分泌的细胞因子与外泌体还可调节局部微环境，抑制炎症反应并促进血管生成。目前，BMSC 联合生物材料支架、生长因子或基因修饰技术已在动物模型中展现出显著的骨与软骨修复效果，部分临床研究也证实了其在改善关节功能、延缓疾病进展方面的潜力。然而现有研究仍存在明显局限性：首先，自体 BMSCs 易受病理微环境影响导致活性下降，需通过低氧预处理或线粒体代谢调控提升其功能；其次，外泌体治疗虽规避了细胞移植风险，但内容物异质性可能影响疗效，需通过多组学技术筛选关键活性分子并建立标准化生产流程。更为关键的是，BMSC 的分离纯度、体内归巢效率及长期安全性仍需进一步优化，其特异性标志物缺乏、定向分化机制不明、支架材料优化等问题仍需深入探索。未来研究需聚焦可操作方向：在基因修饰领域应运用 CRISPR-Cas9 等精准编辑工具，系统评估脱靶效应及致瘤风险；生物材料开发需结合动态力学适配需求，设计梯度孔隙结构的锶基复合支架，同时关注材料长期降解性对骨整合的影响及免疫微环境调控机制。临床转化方面需建立标准化评估体系，包括体外扩增细胞的遗传稳定性监测、异体移植中 HLA 配型优化或诱导免疫耐受策略。安全性评估需长期随访基因修饰细胞的致癌性，并通过大样本临床试验验证不同给药途径(如关节腔注射与静脉输注)的潜在副作用。当前研究在作用机制阐释、临床转化规范及技术创新层面仍存在不足。突破方向应融合人工智能优化支架设计，结合类器官模型模拟病理微环境，推动 BMSCs 治疗从基础研究向临床精准医学的跨越。随着组织工程与基因编辑技术的发展，BMSC 联合多学科策略有望通过系统性解决材料–细胞–微环境协同作用机制，为骨科疾病治疗提供更高效的解决方案。

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