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·综述·

间充质干细胞来源外泌体促进软骨再生的研究进展

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【摘要】 关节软骨(AC)通常被认为是一种含有大约80%的水的组织，它没有血管、神经和淋巴管，只有一种细胞类型，即软骨细胞。关节软骨损伤是肌肉骨骼医学中最具挑战性的问题之一。关节软骨自身再生能力有限，损伤AC最终会导致骨关节炎(OA)的发生和发展。目前对受损的关节软骨的治疗方法如理疗、改变生活方式、使用药物以及外科手术等均只能短期缓解症状，且治疗过程中关节软骨的再生能力有限，因此对于骨-软骨界面和软骨损伤的修复仍然是一个挑战。间充质干细胞来源外泌体(mesenchymal stem cells-derived exosomes，MSC-EXO) 以其再生和免疫调节能力被广泛应用于骨关节炎和软骨损伤的治疗。本文就MSC-EXO对OA和软骨损伤的治疗效应及可能的作用机制的研究进展进行阐述，以期为后续研究提供参考。

【关键词】 骨关节炎；间充质干细胞；外泌体；软骨再生；机制

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Progress of mesenchymal stem cell-derived exosomes for cartilage regeneration. *HUANG Rui[1], ZHU Shu-min[1], MO Jing-xin[1], HUANG Zhi-li[2], LAI Ren-fa[1], LI Ze-jian[1], LI Ze-jian[1]. 1. School of Stomatology, Jinan University, Guangzhou 510630, Guangdong, CHINA; 2. Guangzhou Medical University Affiliated Hospital of Traditional Chinese Medicine, Guangzhou 510145, Guangdong, CHINA*

【**Abstract**】 Articular cartilage (AC) is commonly thought as a tissue containing approximately 80% water. It has only one cell type (the chondrocyte) and has no blood vessels, nerves or lymphatic vessels. Articular cartilage injury is one of the most challenging problems with musculoskeletal medicine. Articular cartilage has a limited ability to regenerate itself, and damage to AC eventually leads to the development and progression of osteoarthritis (OA). Current treatments for damaged articular cartilage such as physical therapy, lifestyle changes, use of medications, and surgical procedures provide only short-term relief and have limited ability to regenerate articular cartilage during treatment, so repair to the bone-chondral interface and cartilage damage remains a challenge. Mesenchymal stemmed cells-derived exosomes (MSC-EXO) have been widely used in the treatment of osteoarthritis and cartilage damage due to their regenerative and immunomodulatory abilities. In this paper, we describe the therapeutic effects of MSC-EXO on OA and cartilage injury and the possible mechanisms of action, in order to provide a reference for subsequent studies.

【**Key words**】 Osteoarthritis; Mesenchymal stem cells (MSCs); Exosomes; Cartilage regeneration; Mechanism

间充质干细胞(mesenchymal stem cells，MSCs) 是具有自我更新和分化为多种细胞类型能力的多系细胞，在组织修复和再生医学中起着关键作用[1]。在动物模型和人体临床试验中，间充质干细胞在修复各种退行性疾病的受损组织方面显示出巨大潜力，其通过介导旁分泌的方式发挥作用，调控损伤组织的微环境，达到减少炎症、促进血管生成等效果[2-4]。同时，MSCs可以迁移到损伤部位并分化为损伤部位的局部成分，分泌有助于组织再生的生长因子[4-6]。近年来，众多实验室和临床试验表明，利用间充质干细胞治疗骨性关节炎和软骨病变具有良好的前景[7-8]。例如，从骨髓中分离的骨髓间充质干细胞(BMSCs)已在动物模型和临床实践中证明了其形成软骨的能力[8]。随着研究的深入，有人认为外泌体的旁分泌可能在关节组织的修复以及基于间充质干细胞的其他疾病的治疗中发挥作用[9]。

目前已知细胞会分泌各种类型的细胞外囊泡(EVs)，根据其大小、含量和形成机制进行区分，EVs又主要分为凋亡小体、微囊泡以及外泌体[10]。外泌体是内吞起源的，直径30~150 nm的囊泡，它们可以运送各种不同的DNA、RNA、蛋白质和脂质[11-12]。有相关研究证明绝大多数类型的细胞在生理和病理条件下都能分泌它们，这表明外泌体是一种非常重要的临床诊断和治疗工具[10,12]。随着研究的深入，有人发现外泌体存在于多种细胞外液中，包括血液[13]、羊水[14]、唾液[15]、脑脊液[16]等。近年来，越来越多的研究结果表明外泌体在各种生理过程中起着重要作用，例如炎症[17]、免疫反应[18]、神经元功能[19]等。不仅如此，它们还在一些疾

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病不同的发展阶段中起作用，例如肝病[20]、神经退行性疾病[21]、与癌症相关的疾病[22]等。

1 不同间充质干细胞来源外泌体在软骨再生中的应用

1.1 滑膜间充质干细胞来源外泌体 滑膜间充质干细胞具有较好的分化潜能，其旁分泌产生的外泌体与软骨修复密切相关。滑膜间充质干细胞来源外泌体(synovial mesenchymal stem cell-derived exosomes，SMSC-Exos)可以明显促进软骨细胞的增殖和迁移。最近的一项研究表明，在OA的治疗中只有从过表达miR-140-5p的MSCs中分离出的外泌体才对软骨细胞的增殖和迁移明显具有促进作用[23]。miR-140-5p过表达SMSC-Exos来源的外泌体对大鼠OA模型关节软骨的成功修复，并在一定程度上延缓OA发展进程，表明通过技术手段对外泌体进行改造，使得分泌的外泌体具有治疗OA的潜力是今后研究的方向。

1.2 骨髓间充质干细胞来源外泌体 间充质干细胞释放的外泌体在细胞间通讯和组织修复中发挥着重要的作用。MSC-Exos在大鼠皮肤创伤模型和大鼠骨-软骨缺损模型中已被证明具有免疫调节作用，并具有一定的再生能力[24-25]。骨髓间充质干细胞来源的外泌体(bone marrow mesenchymal stem cell-derived exosomes，BMMSC-Exos)在体外和首例人体实验中也显示出免疫调节特性[26-27]。VONK等[28]首次证明了BMMSC-Exos在人类OA软骨中既具有再生特性又具有免疫调节特性。当BMMSC-Exos与OA软骨细胞共培养时，BMMSC-Exos不仅可以抑制TNF-α介导的COX2和促炎性白细胞介素的上调，还能抑制TNF-α诱导的胶原酶活性。同时BMMSC-Exos还可诱导软骨细胞、蛋白多糖和II型胶原的细胞外基质成分的产生[28]。BMMSC-Exos所展现出的潜力使它可能成为治疗OA的最佳疗法之一，该疗法不仅可以促进软骨修复，而且还能抑制软骨的退变。BMMSC-Exos有希望在OA早期阶段使病变关节改善并防止OA进一步发展。

1.3 脂肪间充质干细胞来源外泌体 早在2002年，已有研究证实脂肪组织也是间充质干细胞的重要来源[29]。与骨髓间充质干细胞(BMMSCs)相比，脂肪间充质干细胞(AMSCs)在分化为脂肪细胞、软骨、骨骼和骨骼肌等中胚层来源的细胞和组织方面具有同等的潜力[30]。大量研究表明，AMSCs高表达成软骨所必需的CD73、CD90、CD105和CD106[30-31]。WU等[32]通过在小鼠OA模型中连续数周于关节腔内多次注射MSCIPFP-Exos证明MSCIPFP-Exos可以进入关节软骨的受损区域，促进软骨细胞合成。同时，MSCIP-FP-Exos可以抑制IL-1β诱导的软骨细胞凋亡，促进IL-1β处理的软骨细胞的合成代谢并抑制其分解代谢。由于ROCKEL等[33]发现自噬在维持软骨稳态中起着重要作用，WU等[32]进一步研究得出MSCIP-FP-Exos保护软骨免受伤害的机制可能与miR100-5p介导的抑制mTOR信号通路提高自噬水平有关。由于mTOR/自噬信号通路在OA的发展中起着关键作用，因此以该通路为基础治疗OA可能是一个可行的方法。同时还需要更多的研究来阐明机制，以优化MSC-Exos对OA的治疗效果。

1.4 胚胎间充质干细胞来源外泌体 近年来，成人间充质干细胞(MSCs)已经在实验室和临床研究中用于软骨修复[28,34-35]。然而，成人间充质干细胞的临床应用受到供体来源和个体身体条件的限制，随着供体年龄的增加，细胞增殖和分化等能力逐渐下降[36]。而由多能胚胎干细胞(embryonic stem cell-mesenchymal stem cells，ESC-MSCs)来源的MSCs已逐渐展现出自己的潜力。ESC的自我更新能力和多能性确保了细胞批次间的可变性更小，这使得ESC-MSC的供应更加稳定[37]。此外，有研究认为ESC-MSCs有与成人MSCs相似的免疫调节特性和再生潜能[38]。WANG等[39]在已建立OA模型的小鼠关节内注射源自ESC-MSCs的外泌体，发现可以减轻软骨破坏和基质降解。ZHANG等[25]也得出相似的研究结果，骨-软骨缺损处显示出软骨和软骨下骨的完全恢复，且具有良好的表面规则性、与相邻软骨完全结合等特点。这些研究表明ESC-MSCs可以通过在软骨基质的合成和降解二者之间达到平衡而缓解OA，外泌体在这之中起到重要作用。同时，上述研究还表明利用人类胚胎间充质干细胞来源的外泌体进行软骨修复比目前的细胞疗法更有优势。

2 不同间充质干细胞来源外泌体成软骨的潜在机制

2.1 激活AKT、ERK、Wnt等信号通路促进软骨细胞增殖、迁移 CD73是目前已知的能将细胞外单磷酸腺苷(AMP)转化为腺苷的细胞外5'-核苷酸酶，腺苷又能通过与腺苷受体的相互作用引发促存活的AKT和ERK信号传导。据报道，外泌体激活AKT和ERK促生存信号是外泌体介导的组织修复和再生的重要途径，并已被证明在创伤愈合[24]、骨修复[40]中起重要作用。正是由于外泌体CD73介导的AKT和ERK信号传导的腺苷激活，使得在软骨修复过程中实现了细胞的快速增殖和迁移。ZHANG等[41]证明由外泌体介导的软骨细胞增殖和迁移增加现象可被AKT或ERK磷酸化抑制剂所抑制，但基质合成不受其影响。同时，TAO等[23]研究发现，MSC-EXO所携带的Wnt5a和Wnt5b通过Wnt信号通路激活YAP来促进软骨细胞增殖和迁移，但ECM的分泌明显减

少。据报道miR-92a-3p过表达的MSC-EXO在软骨形成和退变过程中对Wnt5a起着积极的调节作用，这增强了软骨细胞的聚集蛋白聚糖、COMP和COL2A1的表达[42]。

2.2 通过调节外泌体包含的miRNA谱促进软骨组织再生 迄今为止，有关外泌体miRNA的研究表明，miR-30d-5p、miR-199b和miR-133b-3p会阻止RUNX2基因表达，从而抑制成骨细胞分化[43]。研究发现miR-140-3p通过抑制BMP-2的表达而降低成骨细胞活性，另一方面，miR-885-5p负性调控BMP-2的表达，从而促进成骨细胞的分化和矿化[44]。据报道，miR-140-5p过表达的SMSC-EXO可有效促进软骨细胞的增殖和迁移，并可通过RALA阻断ECM分泌明显减少的副作用，而SMSC-Exos的作用有限[23]。WU等[32]研究证明，MSCIPFP-Exos中过表达的miR-100-5p可能通过mTOR/自噬信号通路参与关节软骨的维持。而最近的一项研究也表明miR-92a-3p过表达的MSC-EXO在软骨形成和退变过程中通过Wnt5a促进软骨细胞的合成[42]。如果特定的miRNA可以减轻OA中的炎症或组织破坏，则可以将它们包装在外泌体或纳米颗粒中来治疗OA。

2.3 通过增加抗炎性因子、减弱促炎性因子的表达改善炎症使软骨细胞存活 滑膜炎症现在被认为是OA症状和进展的一个重要特征[45]。在骨关节炎的早期，有一些独特的趋化因子信号与滑膜炎症有关[46]。例如，来自白细胞介素-1β(IL-1β)刺激的滑膜成纤维细胞(SF)的外泌体已被证明能诱导软骨细胞的骨关节炎改变[47]。DOMENIS等[48]的研究表明在外泌体的作用下，巨噬细胞产生一系列促炎细胞因子和趋化因子，包括CCL8、IL-1β、MMP12、CCL15、MMP7和CCL20，导致关节软骨的炎症和退化。而通过抗炎干预可以促进软骨细胞存活并降低发生创伤后骨关节炎的风险[49]。ZHANG等[41]发现，MSC-EXOs在软骨损伤处诱导再生M2巨噬细胞的浸润，同时伴有促炎滑膜细胞因子的减少，这与ZHANG等[27]研究发现的MSC-EXOs免疫调节特性相一致。这表明MSC-EXOs可以通过调控巨噬细胞等免疫细胞以增加抗炎因子如IL-10的表达，减弱促炎性因子如IL-1β、TNF-α表达，从而促进软骨细胞存活。

3 小结

由于具有修复受损组织的能力，MSC-EXOs在再生医学中得到了广泛关注，目前已经在MSC-EXOs实验中研究了不同的疾病模型。现有研究结果表明，不同间充质干细胞来源的外泌体在修复各种退行性疾病的受损组织方面显示出巨大潜力。但是，EXO疗法应用于临床实际仍存在一些难题，还需大量其他研究以证明MSC-EXOs在治疗OA中的有效性和可行性。

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