·专家论坛·

间充质干细胞移植治疗膝关节软骨损伤及骨关节炎的现况与未来

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【摘要】 关节软骨损伤、骨关节炎（OA）的患病率高，波及人群广。软骨组织自身修复能力差，一旦损伤将不可逆转地发展为OA。间充质干细胞在再生医学领域扮演重要角色，被认为是实现软骨的修复与再生中最具希望的种子细胞之一。本文结合国内外最新临床研究成果，对临床中应用间充质干细胞治疗软骨损伤或OA的理论依据，治疗目的、意义，间充质干细胞的来源、特点，临床实施方案及疗效进行论述，同时对间充质干细胞临床应用中面临的问题，以及未来需要攻克的方向进行论述和探讨。

【关键词】 膝关节；　关节软骨；　骨关节炎；　间充质干细胞

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The current status and future prospects of mesenchymal stem cell transplantation for the treatment of knee articular cartilage injuries and osteoarthritis

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【Abstract】 The prevalence of articular cartilage injuries and osteoarthritis (OA) is high, affecting a wide range of individuals. The self-repair ability of cartilage tissue is poor, and once damaged, it will irreversibly progress to OA. Mesenchymal stem cells (MSCs) play an important role in the field of regenerative medicine and are considered one of the most promising seed cells for cartilage repair and regeneration. In this article, based on the latest clinical research findings from both domestic and international sources, the theoretical basis, treatment goals, significance, sources, characteristics, clinical implementation plans, and efficacy of using MSCs for the treatment of cartilage injuries or osteoarthritis are reviewed. The article also discusses the challenges faced and future directions that need to be addressed in the clinical application of MSCs.

【Key words】 Knee joint;　Articular cartilage;　Osteoarthritis;　Mesenchymal stem cell

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关节软骨损伤、骨关节炎（OA）的治疗一直是骨科领域的难点和热点。近年来，随着运动理念的推崇和社会老年化的进程加快，关节软骨损伤和OA的发病率明显增高[1-2]。由于关节软骨有限的

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自愈能力，随着病情进展，最终发展为OA[3-4]，需进行人工关节置换以改善关节功能[5]。OA发病患者基数增长较快，截至2020年已成为全球第四大致死或致残的重大疾病[6]。因此，关节软骨损伤后，及时治疗促进软骨修复与再生，对阻止OA的发生至关重要。间充质干细胞（MSCs）具有多向分化潜能，营养和免疫调节作用，在软骨损伤、OA方面，MSCs实现了从基础研究逐步走向临床治疗[7-9]。本文聚焦在临床中MSCs移植治疗关节软骨损伤、OA的临床研究内容，分别从其治疗理论依据，MSCs的来源及其特点，应用方案和治疗效果，以及面临的困境和未来需要突破的难点等方面进行总结论述，并进行深入探讨。

一、MSCs治疗OA的依据，细胞来源和特性

（一）MSCs具有分化成软骨细胞，控制炎症和免疫调节作用

在一定条件下，MSCs能够被诱导分化成软骨细胞实现软骨再生，如添加转化生长因子（TGF）-β3、骨形态发生蛋白（BMP）等软骨分化诱导因子，低氧环境、三维立体（支架或微载体）[10-11]。MSCs也可分泌大量细胞因子或生长因子，通过旁分泌作用于软骨细胞促进细胞增殖，并分泌更多软骨细胞外基质[12-14]。

MSCs具有炎症或免疫调节作用，有研究发现，关节腔内注射骨髓MSCs（BMSCs）治疗OA，膝关节内炎性细胞和白细胞介素（IL）-12水平明显更低，这与MSCs分泌一些生长因子或细胞因子发挥炎症或免疫调节作用密切相关，如干扰素γ（IFN-γ）、IL-10、肝细胞生长因子（HGF）、前列腺素E2（PGE2）、TGF-β1、一氧化氮等[15-16]，通过这些因子缓解局部炎症反应，维持微环境稳态，从而达到缓解疼痛等症状的目的。

（二）MSCs来源丰富

用于治疗OA的MSCs来源丰富，按组织来源可分为BMSCs[16-21]、脂肪MSCs（ADMSCs）[22-26]、滑膜MSCs（SMSCs）[27]、外周血MSCs（PBMSCs）[28-29]以及脐带MSCs（UCMSCs）和胎盘MSCs（PMSCs）等[30-31]。根据是否为同种异体来源，又分为自体或同种异体MSCs[7,11]。

临床中用于治疗软骨损伤或OA的MSCs以自体细胞为主，多为骨髓血和脂肪组织来源，少量报道来自同种异体骨髓血[32-33]、脂肪组织[26,34]或围产期组织[31,35-37]。不同组织来源的MSCs具有各自的优缺点。自体MSCs不会带来疾病传播的风险，患者接受程度好，安全性好。但是，获取比较麻烦，从分离到获取治疗量的MSCs用时较长（约20 d），供体损伤，且细胞的活性可能受到健康状态及年龄的影响[7,38]。研究认为，MSCs的特性和再生潜能会受到心血管疾病的影响[39]，体外多次传代扩增后，细胞的代谢、分化和分泌功能会发生改变[40]。由于MSCs低表达HLA-Ⅰ型抗原，不表达HLA-Ⅱ型抗原，具有免疫源逃避的能力，同种异体MSCs多为商业化产品（如Stempeucel[32]、Allojoin[26]、ELIXCYTE[41]），随用随取，使用方便、经济。尽管MSCs免疫原性更低，但并不具有免疫豁免能力[42]。一项研究发现，在马的关节腔内注射等量的自体和同种异体BMSCs，第一次临床治疗效果无明显差异，而在第二次注射时出现了明显的不良反应和严重的炎症反应[43]。

对于不同组织来源的MSCs也各具特点。骨髓来源MSCs是临床中较常见的细胞来源，但对有血液系统或骨髓疾病的患者是不适合的，且常需要多个穿刺点方可获取足量骨髓血，否则会混合较多的外周血，导致获取效率下降。脂肪来源MSCs具有脂肪组织来源丰富，单次可获取足量MSCs，同样供区也会带来新的损伤或不良并发症，如伤口感染等。滑膜组织来源自体MSCs被证实具有很好的软骨再生潜能且不易分化成骨[27,44]。外周血中提取MSCs比较方便，获取部位损伤小，但是MSCs获取率低[28]。围产期组织，如胎盘、羊膜或脐带，来源丰富，为产后废弃组织，为临床提供很好的MSCs资源，也被认为较成体组织更年轻，分离的MSCs具有更高的活性和多项分化潜能[31,45-48]。但是，目前尚未建立个人围产期组织库，临床中围产期组织来源干细胞均为同种异体细胞，具有潜在的疾病传播风险。

因此，细胞的来源选择除了考虑细胞自身特性外，还需根据患者的健康状况综合考虑，进行个体化权衡。对于年轻患者，无其他基础疾病，自体来源的原代MSCs可能是更好的选择。对于老年患者，且合并有心血管或其他系统疾病，应用同种异体MSCs，可以减少对患者自身带来的损害，同时规避自身来源干细胞生物学特性不佳的顾虑。合并有血液系统疾病的患者，不宜从骨髓或外周血中提取MSCs。至于，不同组织来源的MSCs在治疗软骨损伤或OA的潜能缺乏全面系统的比较，很难判断优劣，需要进一步研究证实。

二、MSCs在治疗关节软骨损伤或OA的临床研究设计

（一）临床研究设计类型及样本特征

关于MSCs治疗软骨损伤或OA的临床研究多

以随机对照设计为主，还涉及队列研究或回顾性研究等，遍布全球近20个国家，其中以来自美国、意大利、韩国、中国的文章居多，其中美国开展较早。纳入样本量多为15~50例，50例以上研究约占29%，患者年龄平均在50岁左右（18~80岁），无未成年人参与[49]。患者不宜过胖，体质指数（BMI）约25 kg/m^2，不超过35 kg/m^2。膝关节病损情况以轻中度为主，以Kellgren-Lawrence（K-L）Ⅱ~Ⅲ级患者为主，少量纳入K-L Ⅳ级OA患者[50]。

（二）MSCs的临床干预方案

1. 细胞剂量和频次：主要以混悬液注射到关节腔内。单次注射为主，仅4项临床研究在2个时间点分别注射[17, 51-53]。MSCs的混悬剂以生理盐水、磷酸盐缓冲溶液或细胞培养基为主。单次注射细胞剂量多数为（20~50）×10^6[50]，低至3.4×10^{4}个原代自体细胞[54]，高达400×10^{6}个扩增细胞[55]，悬液一般在5 ml，最多不超过10 ml。对于MSCs的单次注射剂量或注射次数对治疗效果是否有明显依赖关系，不同研究结果不一。有研究认为，治疗效果与细胞数量的增多无明显相关性，甚至高浓度的细胞悬液会引起更多的不良反应，如关节肿痛。在两项应用同种异体BMSCs的研究中，均为低剂量组（分别为25×10^{6}和50×10^6）获得更好的疼痛缓解和软骨修复，且高剂量组（150×10^6）发生更多的不良反应[32, 56]。在两项应用同种异体ADMSCs的研究中，低剂量组（分别3.9×10^{6}和10×10^6）获得更好的疼痛和关节功能改善[26, 57]。而在自体MSCs的研究中获得的结果差异更大。在6项研究中2项得出高剂量组（分别为自体BMSCs>400×10^{6}和ADMSCs 100×10^6）获得更好的疼痛缓解和软骨修复[55, 58]，1项研究得出低剂量组（ADMSCs 2×10^6）观察到明显的疼痛缓解和功能改善[59]，1项研究在中等剂量组（ADMSCs 20×10^6）观察到最好的软骨修复和膝关节的功能改善[53]，另外2项研究发现，高剂量和低剂量组均获得很好的膝关节功能评分，如自体血管基质组分剂量为15×10^{6}和30×10^{6}的治疗效果无明显差异[60]，自体BMSCs剂量为10×10^{6}和100×10^{6}在12个月随访时，高剂量组影像学改善更明显，在4年随访时低剂量组疼痛缓解更佳[61]。

可见，对于同种异体MSCs来说，低剂量可获得更好的临床治疗效果，高剂量的异体细胞可能带来更多不良反应。对于自体MSCs来说最佳剂量差异较大，影响这些结果的原因可能是多方面的，包括细胞的组织来源不同，制备处理工艺不统一，还有患者自身基础健康状况等。

2. 细胞注射部位：除了关节腔内注射，也有学者进行软骨下骨注射。一项研究将骨髓浓聚成分（MSCs、骨髓造血干细胞和细胞因子、生长因子等）注射在膝关节软骨下骨位置，与关节腔内注射相比，其能够很好地修复软骨下骨髓损伤，随访15年，软骨下骨组全膝关节置换率更低（20% 比70%），较对照组平均延迟10年进行全膝关节置换术[62]。另一项将PBMSCs联合透明质酸（HA）进行软骨下骨注射治疗膝关节股骨髁软骨损伤，随访24个月，获得更明显的临床症状缓解和影像学改善[29]。如果关节腔内注射MSCs能够不同程度地修复损伤的软骨，软骨下骨注射是对损伤的软骨下骨进行修复，可见关节软骨或软骨下骨的修复均能一定程度上缓解OA临床症状，延迟关节置换时间。

3. 附加干预措施：除了关节腔内注射MSCs，根据患者具体病情会相应增加针对性的干预措施。如关节腔注射MSCs前，应用关节镜进行关节腔清理[63-66]，韧带重建或修复治疗膝关节韧带损伤，胫骨高位截骨纠正关节外畸形[38, 67-68]，半月板成型或缝合术治疗半月板损伤[69]，软骨损伤处行微骨折处理[24-25]。有研究将MSCs与HA或富血小板血浆（PRP）混合后进行关节腔注射，结果发现MSCs联合其他成分较单独治疗获得更好的治疗效果[20, 28-29, 61, 68, 70-73]。

4. 术后康复措施：关节腔注射MSCs的治疗当天限制活动，以后可进行正常日常活动。但避免过度或剧烈的负重活动，以避免修复软骨的进一步损害。关节的非负重活动可促进软骨组织内部营养物质的交换，促进细胞的代谢活动，有利于软骨的修复[74]。若联合其他外科操作，如韧带重建、微骨折术及高位胫骨截骨等，需要根据具体操作调整康复计划，通常术后4~6周内行非负重等张股四头肌肌力和活动范围训练，4~6周后开始部分负重和本体感觉训练，以后逐渐恢复全部负重和基本生活[25, 63, 67-68]。

三、临床疗效评价

（一）随访时间及评价工具

临床随访多在术后1~2年结束随访，仅少量研究随访至5年以上[47, 62, 75-76]。数据内容包括功能评分和影像学检查，个别研究包含二次关节镜探查或组织学染色。具体内容包括：疼痛评分、Lysholm评分、Tegner运动评分、国际膝关节文献委员会（IKDC）评分、健康状况调查简表（SF-36）、膝关节

损伤与骨关节炎评分(KOOS)、下肢功能量表(LEFS)评分和WOMAC评分,以及X线、MRI检查和关节镜探查取材活检等。

(二)临床疗效

1.临床症状有效缓解:从现有的临床研究证据可见,与口服NSAID类非甾体抗炎药,关节腔注射糖皮质激素,生理盐水,HA,或PRP相比,关节腔内注射MSCs能够很好地减轻关节疼痛,改善关节活动度,提高患者生活质量[10, 18, 47]。

2.损伤软骨的修复与再生证据不足:对于MSCs到达关节腔内能否实现软骨修复或再生的证据不足[5, 77]。在纳入的60项临床研究中,只有不到1/3的研究随访中观察到软骨损伤处有明显的组织填充或软骨生成。Kuroda等[64]将自体BMSCs与胶原水凝胶混合后移植在1位运动员的内侧股骨髁全层软骨缺损处,术后7个月关节镜观察及组织学染色可见透明样软骨再生。Jo等[58]纳入18例患者行关节腔内注射自体ADMSCs,术后半年行关节镜二次探查和组织学染色,发现高剂量组(1×10^8)软骨缺损处部分被透明样软骨填充。Koh等[24]报道,将ADMSCs联合微骨折术治疗膝关节软骨缺损,2年后行关节镜和组织学染色发现软骨缺损处有较好的修复,组织学染色评分更优。Park等[47]将同种异体UCMSCs与HA混合关节腔注射治疗K-LⅢ级OA患者,术后1年组织学观察可见透明样软骨生成。Kim等[67]通过胫骨高位截骨(HTO)术联合关节腔注射自体ADMSCs治疗OA,术后2年关节镜检查发现获得明显的软骨再生。

关节腔注射MSCs是否能够获得软骨的修复与再生是个很重要的问题,需要更多客观严谨的评价手段。二次关节镜探查和(或)组织学染色能够提供很好的证据,但是迫于临床研究伦理问题,这方面的证据稀缺,这些研究多联合其他治疗手段联合干预,很难定量MSCs在软骨修复与再生方面做出多大贡献。MRI技术检测简单无创,患者接受度高。但是,不同次MRI检测参数前后很难一致,不同级别机器的精度也有差异,层面很难前后严格匹配,不同的阅片医师读片也存在差异,它们所带来的误差不可忽略,影像学证据强度较弱。缺损处的新生组织是通过MSCs的营养作用促进自体细胞增殖修复,或是MSCs分化为软骨细胞实现的再生,也需要更深入的研究。

3.不良反应少,安全性高:关节腔内注射MSCs多无明显不良反应,少数报道注射部位疼痛和关节肿胀为主,其中疼痛发生率为2%~82%,关节肿胀为2%~53%[37]。有少数报道,术后出现关节僵硬,腰疼,深静脉血栓和髌前滑囊炎等[28, 57, 70, 78]。分析关节痛和肿胀的原因,可能与穿刺技术,MSCs剂量或浓度高,或关节腔内细胞死亡而引起的炎症反应相关[32]。而关节僵硬和深静脉血栓形成可能因合并胫骨截骨矫形或微骨折等,导致术后关节制动时间较长,局部加压包扎过紧所致。总之,关节腔内注射MSCs治疗软骨损伤,安全性好,无严重不良反应。

四、展望

1.MSCs治疗关节软骨损伤或OA临床应用前景:MSCs治疗关节软骨损伤或OA具有明确的基础研究理论依据,在临床试验中,也证实能够很好地缓解关节疼痛,改善膝关节功能,但缺乏有力证据能够获得透明软骨的再生。在细胞来源方面,以自体骨髓和脂肪为主,围产期组织来源的MSCs在细胞生物特性上更具优势,资源更丰富,未来具有更大的开发应用前景。在给药剂量和频次上变异较大,一般来说同种异体MSCs单次剂量不宜过大,单次注射为宜,大剂量或多频次可能带来更多的不良反应。而自体MSCs因受患者健康状况等多种因素影响,最佳治疗剂量波动范围较大。除关节腔内注射MSCs,软骨下骨注射也被证实具有良好的治疗作用,并能够明显延缓关节置换时间,但相关研究较少,需要更多研究加以证实。术后康复中,关节腔内注射MSCs后,多以休息为主,避免过度负重或剧烈运动。对于合并其他手术操作的需要根据具体术式制定个性化康复计划,以保证良好的治疗效果。在不良反应方面,主要为局部关节肿胀、疼痛,但多能自我康复,无需其他干预措施。

2.MSCs治疗关节软骨损伤或OA的挑战:未来关节腔内注射MSCs治疗软骨损伤或OA仍面临诸多挑战。需要系统地比较,选择最佳的MSCs来源。探索和制定出应用于临床的安全的规范的MSCs提取、扩增和培养操作标准。MSCs应用于临床治疗软骨损伤或OA的标准方案,包括适应证的选择、注射部位、剂量和频次、术后康复计划、不良反应的处置、科学客观的临床疗效评价技术等。另外,需要深入研究和明确关节腔内MSCs的生物学行为,如何将关节腔内注射的MSCs从无目的、随性的,转向定向迁移至软骨损伤处进行靶向修复的高效治疗轨道上,实现自主修复和再生透明软骨。

3.MSCs的衍生成分或生物材料的临床应用前

景：关于MSCs的衍生成分或生物材料辅助治疗OA或修复软骨损伤方面也开展了大量的基础研究，并展现了较好的应用前景。MSCs来源的细胞因子、生长因子或外泌体发挥治疗效应，能够促进软骨细胞增殖、迁移，或抑制软骨细胞退变、凋亡等作用，同时能避免细胞带来的免疫排斥等不良反应，对软骨修复具有很重要的应用价值。但是，由于细胞分泌的活性成分与细胞本身活性和代谢状态紧密相关，如不能很好地控制细胞良好的生理状态，其分泌或产生的活性成分也受到极大的影响，影响生物效应的发挥。生物材料在再生医学中扮演着重要的角色，能够作为细胞或外泌体的载体，或提供一定的空间结构和力学支持，将它们定向移植至软骨损伤处，促进细胞的增殖和黏附，同时能够延长有效的作用时间[79]，有望将MSCs或其衍生成分在OA的治疗上推向更高水平。

综上，随着对干细胞研究的逐渐深入，渐渐揭开更多OA的发病机制，结合分子生物学、生物材料学、计算机及生物医学工程等多学科的发展，未来对OA的治疗策略应该是多维度、多层次、多手段的个性化体系。在软骨损伤或OA患者的临床治疗中，仍以最大限度推迟或避免关节置换手术为阶段性的推进举措，以实现软骨修复和再生为永不止歇的追求目标。

利益冲突　所有作者声明不存在利益冲突

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