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间充质干细胞对骨关节炎修复机制的研究进展及应用

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【摘要】 骨关节炎是一种以软骨退化和软骨下骨改变为特征的慢性退行性疾病,其患病率随着人口老龄化的加剧而迅速增长。目前仍没有合适的药物和手术可以完全治疗骨关节炎。随着细胞疗法的出现,间充质干细胞的独特优势被不断发现,其治疗骨关节炎的研究也越来越多。本文就间充质干细胞对骨关节炎的修复机制进行综述。本文描述了间充质干细胞的特性和功能,以及它们在骨关节炎动物模型和临床中的治疗机制。

【关键词】 骨关节炎;间充质干细胞;修复机制;动物模型
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Research progress and application of stem cells in the repair of osteoarthritis

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【Abstract】 Osteoarthritis is a chronic degenerative disease characterized by cartilage degeneration and subchondral bone changes, and its prevalence has increased rapidly along with the aging of the population. There is still no drug or surgical treatment that completely resolves osteoarthritis. With the advent of cell therapy, the unique advantages of stem cells have been gradually uncovered, and their use in the treatment of osteoarthritis is increasingly studied. In this article, we review the mechanisms by which stem cells repair osteoarthritis. We describe the properties and function of mesenchymal stem cells and their therapeutic mechanisms of action in osteoarthritis in animal models and in the clinic setting.

【Keywords】 osteoarthritis; mesenchymal stem cells; mechanisms; animal model
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骨关节炎(osteoarthritis,OA)是一种以软骨下骨改变和软骨退化为特征的慢性退行性疾病。据世界卫生组织(World Health Organization,WHO)统计,60 岁及以上的患者中,男性大约占 10%,女性大约占 18%,在患病的人群中大约有 80%的患者会伴有关节活动障碍[1]。作为常见的慢性退行性疾病,OA 不仅因功能障碍导致关节疼痛,还会影响睡眠进而影响着患者的生活质量[2]。目前的常规治疗

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主要是药物控制,包括非甾体抗炎药(NSAIDs)、透明质酸(HA)、简单止痛药和皮质类固醇,但这些治疗虽然起到了缓解症状的作用,减轻了因活动障碍引发的疼痛,并能控制炎症,但并不能减缓关节的进行性退化[3]。当常规治疗无法缓解症状时,则需要进行关节清创术等外科手术治疗,这些治疗虽然有一定疗效,但并不会产生长期效果[4]。终末期患者最常用的治疗手段就是关节置换术,虽然能使关节恢复活动能力,但置换的关节存在使用年限的问题,并且由于手术创伤会造成感染甚至形成血栓。伴随着研究的逐渐深入,将新的细胞移植到组织损伤部位进行修复的细胞疗法越来越受到人们的重视[5]。近代组织工程发展的自体软骨细胞移植(autologous chondrocyte implantation, ACI)和基质诱导的关节软骨细胞移植(matrix-induced articular chondrocytes implantation, MACI)已被证实对 OA 有一定的疗效[6]。但是软骨细胞的培养以及移植细胞时的手术创伤仍是难以避免的难题。该方法的局限性促进了细胞疗法的进展,因此多项潜能的间充质干细胞(mesenchymal stem cells, MSCs)成为了研究者的选择。在这里,将进一步描述关于 MSCs 的特性和功能,以及它们在 OA 动物模型和临床中的治疗机制。

1960 年末,Friedenstein 等[7]首次发现了 MSCs。它是中胚层来源的成体干细胞,可以从如骨髓、脂肪等多种组织中分离出来,同时也具有分化为如软骨细胞、成骨细胞等多种细胞的能力[8]。国际细胞治疗学会(International Society for Cellular Therapy, ISCT)对 MSCs 的定义有三个标准:(1)能贴壁生长;(2)表达 CD105、CD73、CD90,不表达 CD45、CD34、CD14 或 CD11b、CD79a 或 CD19 和 HLA-DR;(3)能多向分化[9]。目前 MCSs 修复 OA 的机制主要包括:分化为软骨细胞、分泌抗炎因子、调节免疫系统、降低炎症因子释放[10]。但越来越多的研究证实 MSCs 来源的外泌体(MSC-Exos)也对延缓 OA 进展起到一定的作用[11]。这些观察激起了人们对 MSCs 修复关节软骨的浓厚兴趣。

1　MSCs 对 OA 的修复机制

1.1　MSCs 的成软骨特性

有研究显示,在特定的诱导条件下,在体外培养的 MSCs 可向软骨细胞分化,且软骨的形成模拟了胚胎软骨的发育和生长[12]。不同的细胞因子或生长因子,如胰岛素样生长因子(IGF),骨形态蛋白(BMP),转移生长因子 β(TGF-β),均已被证明对软骨组织的修复起着促进作用[13]。最近有研究发现维生素 D 可以促进骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)的增殖和迁移,并在 BMSCs 的定向软骨分化中发挥潜在的作用。TGF-β1 通过调控 ERK/JNK 信号通路参与维生素 D 的功能作用[14]。Sox9 是软骨发育的关键转录因子,卓群豪等[15]通过向小鼠膝关节内注射 Sox9 基因转染的 BMSCs,观察到转染后的细胞可促进小鼠膝关节的软骨修复。以上研究显示 MSCs 的成软骨特性是修复 OA 软骨损伤的一种重要机制。

1.2　MSCs 的抗炎和免疫调节作用

OA 患者的关节因炎性因子的浸润呈现一种低度炎症的状态,软骨基质分解代谢产物可引发巨噬细胞和免疫细胞释放炎性因子,进而通过改变软骨细胞功能加速软骨损伤[16]。有研究报道 MSCs 通过分泌多种生长因子促进血管生成,例如血管内皮生长因子(vascular endothelial growth factor, VEGF)、成纤维细胞生长因子 2(fibroblast growth factor 2, bFGF)、胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)、肝细胞生长因子(hepatocyte growth factor, HGF)等。VEGF、bFGF、HGF、IGF-1、TGF-β 还可防止细胞凋亡,HGF、bFGF 也有抵抗纤维化的能力[17]。其次 MSCs 在免疫调节方面通过抑制树突细胞(dendritic cells, DCs)、自然杀伤细胞(natural killer cells, NKs)、T 细胞、B 细胞的增殖发挥作用,还能分泌可溶性因子如吲哚胺 2,3-二氧合酶(indoleamine2,3-dioxigenase, IDO)、TNF 刺激基因 6(TNF-stimulated gene 6, TSG6)、一氧化氮(nitric oxide, NO)、白介素 10(interleukin-10, IL-10)、CC-趋化因子配体 2(CC-chemokine ligand 2, CCL2)、前列腺素 E2(prostaglandin E2, PGE2)进而对调节免疫系统起着关键作用[18-20]。综上所述,MSCs 分泌的抗炎因子以及抑制免疫细胞的增殖对 OA 炎症修复起着重大作用。

1.3　MSCs 的细胞外囊泡的作用

MSCs 衍生的细胞外囊泡(EVs),已被证明在介导组织再生和免疫调节方面发挥作用[21]。EVs 可由多种类型的细胞产生,如免疫细胞、内皮细胞、MSCs 等,并且存在于各种生物液体中,包括血液、尿液、滑液等[22]。EVs 根据其大小、组成和来源分为外泌体(Exosomes),微囊泡(microvesicles)和凋亡

小体(apoptotic bodies),其中 Exosomes 研究最为广泛[23]。所有的 EVs 都富含蛋白质、脂质和核酸(DNA、mRNA、miRNA、tRNA),可以传递给受体细胞,从而有助于细胞间的交流[24]。

最近有证据表明,MSC-Exos 可促进软骨再生。2016 年,Zhang 等[25]首次证明关节内注射 EMSC-Exos 可使缺损处软骨和软骨下骨恢复。随后在 2017 年,Cosenza 等[26]发现 Exos 或 MPs 均能再现 MSCs 的治疗作用。且通过基因载体或化学合成修饰的 MSC-Exos 也可改变某些 miRNA 或 LncRNA 的表达,从而影响 OA 的治疗[27-29]。与 MSCs 的细胞治疗相比,MSC-Exos 代表了一种更安全、更有效的治疗方式。

2 MSCs 在动物模型研究和人类临床研究中的疗效

2.1 MSCs 在 OA 中的应用

MSCs 无论在大型动物还是小型动物 OA 模型中的应用表明单独或协同其他因素关节内注射自体或同种异体 MSCs 均可改善 OA 症状(见表 1)。动物模型的成功极大地促进了临床研究,并为今后的临床研究提供了一定的科学依据[30-31]。根据表 2 可知无论是 MSCs 移植或是关节内注射都可修复 OA 损伤,但 MSCs 注射的剂量仍没有一个固定的标准,所以仍需要我们进行大量的临床研究加以确定和完善。

表 1 MSCs 在 OA 动物模型中的应用

Table 1 Application of MSCs in animal models of OA

细胞类型 Cell type	动物类型 Animal type	治疗效果 Treatment effect
骨髓间充质干细胞 BMSCs	山羊 Goat	受损关节显示内侧半月板明显再生、关节软骨退变、骨赘重塑和软骨下硬化均减轻[32] Damaged joints showedmarked regeneration of the medial meniscus, degeneration of the articular cartilage, osteophytic remodeling, and subchondral sclerosis were reduced[32]
富血小板血浆+ 脂肪间充质干细胞 PRP+ADSCs	比格犬 Beagle dog	PRP+ADSCs 通过促进细胞外基质合成和软骨细胞增殖,进而抑制炎症,延缓 OA 进展[33] PRP and MSCs treatments have a beneficial effect on OA via the stimulation of ECM synthesis and chondrocyte proliferation and via the inhibition of inflammatory reaction[33]
脂肪间充质干细胞 ADSCs	小鼠 Mice	单次注射 ADSCs 可以抑制滑膜增厚和软骨破坏[34] A single injection inhibits synovial thickening and cartilage destruction[34]
骨髓间充质干细胞 BMSCs	兔 Rabbit	关节表面受损软骨丢失和磨损减少,组织学评分和软骨含量明显改善[35] Joint surface showed less cartilage loss and surface abrasion, and significantly better in histological scores and cartilage content[35]

表 2 MSCs 在 OA 中的临床研究

Table 2 Clinical studies of MSCs in OA

细胞类型 Cell type	治疗方式 Treatment mode	治疗效果 Treatment effect
骨髓间充质干细胞 BMSCs	MSCs 移植 Transplantation	证明了 MSCs 移植用于软骨修复的长期安全性和有效性[36-37] Demonstrated the long-term safety and efficacy of MSCs transplantation for cartilage repair[36-37]
骨髓间充质干细胞 BMSCs	关节腔内注射 Intra-articular injection	4 名患者注射 8 ~ 9 × 10^6 个自体 BMSCs 后患者的疼痛和功能均有所改善,其 5 年随访表明 4 名患者的临床参数虽有所下降,但仍好于基线[38-39] Four patients showed improvement in pain and function after injection of 8 ~ 9 × 10^6 autologous BMSCs, and their subsequent 5-year follow-up indicated that the clinical parameters of the four patients, although decreased, were still better than those at baseline[38-39]
脂肪间充质干细胞 ADSCs	关节腔内注射 Intra-articular injection	关节腔内注射 1.0 × 10^8 个 ADSCs 可改善膝关节功能和疼痛,且无不良反应,并可通过透明样关节软骨的再生减少软骨缺损[40] Intra-articular injection of 1.0 × 10^8 ADSCs into the osteoarthritic knee improved function and pain of the knee joint without causing adverse events, and reduced cartilage defects by regeneration of hyaline-like articular cartilage[40]

2.2　MSCs 在血友病性关节病(hemophilic arthropathy, HA)中的应用

MSCs 在治疗 OA 中发挥了极大的作用,因此也为治疗其他疾病提供了思路。目前 HA 仍没有较好的治疗办法,终末期患者接受手术的风险也很大,因此 MSCs 对 HA 动物模型的治疗的有效性吸引了研究者的目光,通过对动物进行干预,针刺基因缺陷动物或通过自体血输注的方式构建 HA 动物模型,随后进行关节内注射 MSCs,观察疗效,结果证明 MSCs 的治疗是有一定的作用的[41-42]。动物模型的成功刺激了其在临床上的应用,2013 年 Ebihara 等[43]研究证明了自体血清培养自体 BMSCs 治疗 HA 的可行性。随后 Buda 的报告也指出,BMSCs 移植联合滑膜切除术和踝关节镜清创术,并使用自体富血小板纤维蛋白治疗血友病踝关节软骨病变。平均随访 2 年后,软骨修复、关节功能均得到改善[44]。

2.3　MSCs 在类风湿性关节炎(rheumatoid arthritis, RA)中的应用

MSCs 不仅在 OA、HA 的治疗上有一定的作用,在治疗 RA 上也有一定体现,通过输注Ⅱ型胶原构建小鼠胶原性关节炎(collagen-induced arthritis, CIA)。进而使用该动物模型进行一系列的实验研究表明 MSCs 对治疗 CIA 小鼠有一定的疗效[45-46],最近一项实验也证明 ADSCs 关节内注射可使 RA 小鼠滑膜炎症和关节软骨明显改善,这进一步为开发 RA 患者的局部治疗提供了新的途径[47]。但目前在临床研究中 MSCs 治疗 RA 的结果仍存在分歧,Jun 等[48]的研究证明 MSCT 是治疗难治性 RA 的一种安全方法,但其有效性需要进一步研究。而在 2019 年一项 I/II 期临床实验中也提示 BMSCs 治疗的 RA 可明显改善症状但疗效不能维持 12 个月,此外,BMSCs 还有助于减少甲氨蝶呤和泼尼松龙的使用[49]。

3　展望与不足

众所周知,OA 是一种慢性退行性的骨关节病,给中老年人及社会带来了巨大的经济负担。目前的治疗方法仍有很多限制与不足,MSCs 疗法提供了一种新的治疗途径。以上研究证明 MSCs 在治疗 OA、HA、RA 都显示出了极好的治疗效果。它主要通过分泌营养因子,调节免疫应答,以及其外泌体的作用来修复受损的软骨。在多项动物实验中已经展现了其治疗效果,并且在临床实验中也有一定的体现。因此该技术对软骨修复的效果是令人鼓舞的。但也仍然存在一些问题,如 MSCs 的治疗剂量、更优化的治疗方式、理想细胞的来源以及定向分化的各种潜在分子机制仍不明确。因此,仍需要大量的实验来研究 MSCs 治疗 OA 的诸多问题。随着交叉学科的开展与成熟,相信 MSCs 能够为 OA 提供更多的选择和帮助。

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