

# 骨关节炎间充质干细胞治疗进展

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**摘要:**骨关节炎(Osteoarthritis, OA)是最常见的骨科疾病,传统的治疗方法包括非手术法和手术法,但在恢复骨关节炎软组织的正常结构与机能方面并不理想,因此,急需建立新的高效的治疗骨关节炎的方法.以干细胞疗法为研究方向的再生医学为关节软组织的修复提供了新的治疗方向.对可用于治疗骨关节炎的间充质干细胞(Mesenchymal Stem Cells, MSCs)的来源、作用机理和治疗方法的研究进展进行了阐述.

**关键词:**骨关节炎;间充质干细胞;关节软骨;再生;免疫调节

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骨关节炎(Osteoarthritis, OA)是最常见的骨科疾病,与老龄化密切相关.骨关节炎以关节软骨退变、硬化、血管新生和滑膜炎为特征,最终导致关节僵硬,疼痛和关节活动的丧失,是排在首位的致残性疾病,长期影响病人的生活质量,加重患者和社会的负担<sup>[1-2]</sup>.随着全球老龄化的加剧,骨关节炎也成为世界上增长最快的人类疾病之一.

## 1 骨关节炎治疗的发展历程

骨关节炎(OA)被认为是衰老和关节损伤的必然结果.目前已有许多相应的治疗方法,如服用阿司匹林或使用非甾体类抗炎药以缓解疼痛;使用糖皮质激素迅速减轻关节疼痛与肿胀等;人工关节的出现使病人可以通过关节置换手术取代严重受损的关节,但其构造也存在不能自然旋转或弯曲膝盖的缺陷,最终导致许多患者的移植体在手术后不久开始松动.尽管这些传统理疗或药物治疗可暂时缓解临床症状,但难以恢复关节相应的功能,因此并不能根治.另外全膝关节置换存在较高失败风险,同时费用高、恢复周期长等弊端严重影响患者的身心治疗舒适度.迄今为止,还没有可以治愈骨关节炎的好方法<sup>[2]</sup>.因此,亟须开发新型实用的治疗方法,以提高关节软组织的修复效率,有效地缓解骨关节炎.

随着关节软骨在 OA 中的关键作用以及软骨可以修复的发现,使移植培养的自体软骨细胞可用于修复膝关节的深层软骨缺损得以成功<sup>[3-4]</sup>.早期研究表明,软骨修复可以通过软骨细胞的增殖作用得以完成,然而软骨细胞来源的软骨活组织样本须来源于供体,而软骨细胞在有限的扩张期间会出现去分化现象<sup>[5]</sup>;再有关节软骨的大部分是由软骨细胞产生,而软骨细胞是驻留细胞系,只占关节软骨的 5% 以下.这些现象和关节软骨的无血管状态导致软骨细胞几乎没有再生能力的条件<sup>[6]</sup>.间充质干细胞(MSCs)是具有自我更新和分化成多种类型细胞潜能的特殊细胞.MSCs 所具有的向软骨细胞分化的能力为 OA 治疗提供了新的途径.人们在培养扩增 MSCs 上已经积累了大量的经验和资料,其中一些 MSCs 正在用于 OA 的治疗的试验中<sup>[7-11]</sup>.本文在以上研究和最新的研究进展基础上论述,为探讨 MSCs 在 OA 中的临床治疗策略提供新的科学思路.

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## 2 可用于骨关节炎治疗的间充质干细胞的类型

间充质干细胞(MSCs)是具有分化、释放再生生长因子和免疫调节等功能且高度存在于多种组织中的成体干细胞<sup>[3]</sup>。虽然MSCs与胚胎干细胞(Embryonic Stem Cells, ESCs)和造血干细胞(Hematopoietic Stem Cell, HSCs)一样具有高速增殖、多重分化能的性质,但它们之间有很多不同。研究表明成年人体内存在多种能够分化成软骨细胞的MSCs,可能在骨关节炎的修复中发挥作用。实际上关节周围就存在多种参与软骨细胞的干细胞。

### 2.1 骨髓间充质干细胞

骨髓间充质干细胞(Bone marrow mesenchymal stem cells, BMSCs)是从骨髓抽吸物或骨髓浓缩物中分离的间充质干细胞。在骨小梁的骨髓腔内的含量较高。BMSCs在OA和骨折的修复中扮演着重要角色。骨髓MSCs与骨外MSCs相比,BMSCs在表型、形态、功能及潜在的治疗应用等方面更为优越。BMSCs在晚期OA中起着重要作用<sup>[12-13]</sup>。BMSCs也可以与造血干细胞共存,两种类型的细胞通过彼此间的调控,使其功能达到动态平衡。独特的微环境似乎对骨髓间充质干细胞的生理功能具有深刻的影响;BMSCs不仅控制宿主组织重塑、脂肪组织内平衡和骨折后的骨修复,还支持HSCs的功能成熟和循环排出。换言之,由于HSCs的协助,BMSCs比没有HSCs的MSCs(例如关节的其他组织)更具“多功能”<sup>[14-17]</sup>。

### 2.2 软骨驻留干细胞

对软骨驻留干细胞的理解主要来自于动物模型,因此软骨驻留干细胞与OA患者的相关性还有待进一步考察。关于软骨再生或周转始于软骨的深层区域的观点似乎已经过时,因为损伤通常表现在早期软骨的浅表区<sup>[18-19]</sup>。研究显示人刚出生时,存在于骨头末端的深层软骨区域会被骨头替代,同时在邻近关节腔内长出新的关节软骨<sup>[19]</sup>。事实上,只有浅层软骨不受重塑过程的影响;在重塑之后,浅层软骨包含具有双向有丝分裂活性(水平或垂直)的细胞群,并且通过组织的横向和垂直扩展来补充软骨细胞<sup>[20-21]</sup>。

### 2.3 关节驻留间充质干细胞

关节驻留间充质干细胞在滑膜中的自发性软骨形成(软骨瘤病)是众所周知的现象。为了适应关节内局部高压,关节纤维软骨在韧带或肌腱处压迫相邻骨的部位以复杂结构排列在骨表面。在动物模型中植入滑膜内或邻近滑膜的软骨分裂素会引发局部滑膜软骨的形成<sup>[22-23]</sup>。这些观察表明,关节环境在反向关节软骨表面会支持软骨形成,关节驻留的软骨细胞包括3类。

#### 2.3.1 滑膜驻留间充质干细胞

在小鼠中,表达生长/分化因子5(Growth differentiation factor 5, GDF5)的细胞产生于关节软骨、韧带和内滑膜衬里。但是这些细胞和形成相邻的长骨软骨轴或生长板的形成并无关系,说明软骨和滑膜之间有非常紧密的胚胎学联系<sup>[24-25]</sup>。关节腔相关的间充质干细胞最初见于滑膜<sup>[26]</sup>,但目前尚不清楚这些细胞是起源于浅层滑膜衬里还是起源于滑膜下层,或两者兼而有之。事实上,滑膜是软骨源性间充质干细胞有效和丰富的来源,其占比约为1%<sup>[27]</sup>。在兔模型中,滑膜覆盖浅层软骨,并且该滑膜有助于软骨修复<sup>[28]</sup>。在小鼠软骨损伤模型中,并没有发生自发性软骨修复,但在关节边缘处有明显的软骨生成<sup>[29]</sup>。

#### 2.3.2 关节脂肪组织的间充质干细胞

关节脂肪组织,包括滑膜下脂肪和髌下脂肪,像其他关节结构,包括韧带,也是MSCs的来源<sup>[30]</sup>。但是相比于其他脂肪组织,滑膜的脂肪组织能释放出更多的间充质干细胞<sup>[31]</sup>。

#### 2.3.3 滑液驻留的间充质干细胞

从软骨损伤患者的滑液中分离表达CD 90/CD 105,具有多种分化功能,被证实是MSCs<sup>[32]</sup>。在OA患者的滑液中发现每百万个单核细胞中包含40个细胞滑液驻留间充质干细胞,而在类风湿性关节炎患者的滑液中发现每百万个约1~2个驻留间充质干细胞。在对伴有软骨缺损的早期膝关节骨性关节炎患者的研究中发现,与伴有膝关节疼痛和无此类病变的个体相比,滑液驻留MSCs的比率增加<sup>[33]</sup>。另一项研究则直接将滑液驻留的间充质干细胞的数量与软骨病的程度(如关节镜所确定的)和放射损伤联系起来<sup>[34]</sup>。

研究表明,滑膜、关节脂肪组织、滑液和浅层软骨等关节内都存在MSCs群体,这一发现对“骨髓驻留

MSCs 在软骨修复中是绝对必要的”这一观点形成挑战.事实上,很多研究未能在健康或创伤的关节中观察到循环 MSCs<sup>[35-36]</sup>,在小鼠模型的损伤关节表面中也仅观察到骨髓源性 MSCs,几乎没有证据显示“骨髓驻留 MSCs 可以通过全身循环达到软骨修复的目的”<sup>[37-38]</sup>,来源于关节周围组织的 MSCs 为骨关节炎的治疗提供了新的路径.

#### 2.4 脂肪干细胞(Adipose stem cell, ADSCs)

脂肪干细胞是一类来源于脂肪的间充质干细胞.由于其来源广泛,易于提取,成为现在研究的热点.由于 ADSCs 位于脂肪组织中血管外膜和大血管周围外膜,普遍被认为是来源于周细胞<sup>[39]</sup>.脂肪干细胞具有和骨髓 MSCs 相似的表现型和形态,已经被证明具有分化成软骨细胞的能力<sup>[40-42]</sup>,同时还具有治疗骨关节炎的效果<sup>[43-46]</sup>.虽然另外一些研究对此持相反意见<sup>[47-48]</sup>.

### 3 间充质干细胞治疗 OA 的分子机制

最初, MSCs 用于骨关节炎的治疗被认为是由于其向软骨细胞分化,诱导软骨再生而完成的.但后来的研究发现, MSCs 的软骨再生能力不是减缓骨关节炎的唯一因素,并且可能不是主要因素.现在关于 MSCs 对骨关节炎治疗作用的机制分为 3 个方面.

#### 3.1 MSCs 向软骨细胞的分化

自体培养的软骨细胞被移植使软骨再生已经成功地被使用并超过 10 年.而使用 MSCs 的原因之一是 MSCs 可以分化成软骨细胞,从而达到软骨修复和膝盖软骨再生的目的.关于这点前面已经论述过,在此不再重复.

#### 3.2 MSCs 的免疫调节活性

尽管很多研究报道移植 MSCs 到关节内并没有观察到新的软骨产生<sup>[49-50]</sup>,但它们确实显示出具有软骨保护作用,该作用被认为是通过减少炎症来延缓软骨破坏的进程实现的.在小鼠关节炎模型中, MSCs 未能诱导软骨的再生,但减轻了骨关节炎的发展<sup>[51]</sup>;在兔关节炎模型中, MSCs 治疗的关节降低了肿瘤坏死因子 TNF- $\alpha$  和基质金属蛋白酶 MMP-1 的表达, MMP-1 具有降解软骨中的蛋白多糖的功能<sup>[50]</sup>;在马关节炎模型中, MSCs 对骨关节炎软骨病变没有显著修复作用,但是减轻关节炎症状<sup>[52]</sup>.这些结果进一步强调了 MSCs 的抗炎症作用.

研究发现 MSCs 的一个重要的性质是由于缺乏人的白细胞抗原(Human leukocyte antigen, HLA)而保持免疫调节的活性<sup>[53-54]</sup>,具有出色的免疫调节和抗炎机能.间充质干细胞能够以两种不同的方式与多种免疫细胞相互作用,调节它们的功能.首先,由于细胞表面分子的作用,间充质干细胞可以通过细胞与细胞的接触直接与免疫系统的细胞相互作用.其次,它们可以通过释放可溶性分子如细胞因子、生长因子、免疫调节因子等发挥其免疫调节特性<sup>[55-56]</sup>.此外,它们还具有黏附到炎症部位的能力,从而阻止炎症的进展和修复受损的细胞<sup>[55]</sup>. MSCs 在抑制树突状细胞(Dendritic Cells, DC)、自然杀伤细胞(Natural killer Cells, NK)和巨噬细胞(macrophage)等的先天性免疫细胞的活化等方面发挥作用.例如, MSCs 抑制未成熟 DC, NK 细胞的增殖,抑制细胞因子产生细胞毒性,诱导巨噬细胞从促炎 M1 分化为抗炎表型 M2,通过分泌 IL-10 和营养因子来减少炎症和促进组织修复<sup>[57-58]</sup>.另外,在适应性免疫方面,间充质干细胞能够抑制 T 细胞和 B 细胞的增殖.通过这些作用, MSCs 的免疫调节特性明显减弱 OA 的进展<sup>[59]</sup>.

#### 3.3 MSCs 防止软骨细胞凋亡

间充质干细胞可分泌多种生长因子,如 IGF-1, TGF- $\beta$  和 IL-6 以及抗氧化分子,促红细胞生成素和血红素氧化酶(Heme Oxygenase, HO)-1,从而阻止由于创伤、氧化应激和其他类型损伤诱导的细胞凋亡.同时它们还具有抗纤维化的特性,可能通过分泌 HGF、肾上腺调节素和 FGF $\beta$  发挥作用<sup>[60-61]</sup>.

### 4 MSCs 治疗 OA 的方法

#### 4.1 无支架注射

大多数情况下,在动物模型和临床试验中都没有用任何载体, MSCs 被直接通过关节内注射<sup>[62-66]</sup>.直接

注射由于其简单易行,为临床应用提供了巨大的优势,同时避免了手术给它们带来的副作用<sup>[67]</sup>。然而,由于在注射过程中 MSCs 悬浮液泄漏及操作过程中造成的细胞损伤,导致其存活率降低,被直接输送到关节损伤部位的数量是有限的<sup>[68]</sup>。在许多情况下,只有少于 5% 的被移植细胞在细胞注射后几天内留在应用部位。因此,提高细胞移植率和存活率是提高 MSCs 治疗成功率的一个关键因素。为解决这一问题并提高上述细胞活力,有人将 MSCs 嵌入保护性载体(支架和水凝胶)中,不仅保护细胞并有助于将它们保持在适当的位置,促进软骨再生和透明软骨形成<sup>[68-69]</sup>。

#### 4.2 MSCs 的支架/水凝胶的载体移植

MSCs 在目标组织中的存活是细胞疗法的主要挑战之一<sup>[57]</sup>。为了解决这个问题,MSCs 被载入到先进的载体系统中,旨在改善 MSCs 的驻留、活力、生长和分化。生物材料被用作制造大孔结构(支架)的初级材料,用于细胞嵌入目的以将 MSCs 接种在孔内或水合聚合物网络(水凝胶)中<sup>[70]</sup>。与天然软骨细胞的几何结构相似的 3D 支架的发展可促进关节软骨的再生<sup>[70]</sup>。近年来,支架生物材料受到广泛关注,其优点在于从 ECM 和机械性能等方面模拟天然软质的性质,从而提高体内 MSCs 的有效性。明胶显示良好的细胞黏附能力,生物相容性,支持软骨形成的能力<sup>[71]</sup>。纤维蛋白胶作为一种产生新软骨的细胞载体已得到广泛应用<sup>[72]</sup>。总之,水凝胶对再生医学具有特别的吸引力,因为它们为 MSCs 提供了高度水合的 3D 环境,类似于在体内的软骨细胞所在的环境<sup>[73]</sup>。许多研究表明去分化软骨细胞在许多水凝胶中再分化。此外,水凝胶被认为是 MSCs 输送的理想生物材料载体,因为它们能够重现天然软骨组织的许多重要特征<sup>[70]</sup>。

迄今为止,MSCs 已被证明对缓解骨关节炎具有良好的效果。MSCs 具备许多优点,如可进行软骨再生、易于培养、扩增、具有抗炎和免疫调节特性,可进行异体移植等,表明 MSCs 是 OA 治疗的一种的理想选择。虽然现在还处于细胞治疗的早期阶段,但可以预见不久的将来 MSCs 将成为 OA 的重要治疗方法,从而大大改善骨关节炎患者的生活质量。

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## Progress in the treatment of osteoarthritis with mesenchymal stem cells

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**Abstract:** Osteoarthritis (OA) is the most common orthopaedic disease. Traditional therapeutic methods including non-surgical and surgical methods are not ideal in restoring the normal structure and function of articular cartilage in osteoarthritis. Therefore, it is necessary to establish new and effective methods for the therapy of osteoarthritis. Regenerative medicine represented by stem cell therapy provides a novel treatment direction for the repair of articular cartilage. In this paper, the origin, mechanism and application of mesenchymal stem cells (MSCs) in osteoarthritis treatment are reviewed.

**Keywords:** : osteoarthritis; mesenchymal stem cells; articular cartilage; regeneration; immunomodulation

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