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间充质干细胞治疗银屑病关节炎的应用进展

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Advances of mesenchymal stem cell therapy for psoriatic arthritis ZHANG Hui, DONG Bo, YUAN Pu-wei, LIU De-yu, KANG Wu-lin. The First School of Clinical Medicine, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China

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【 Abstract 】 Psoriatic arthritis is an inflammatory musculoskeletal disease that affects multiple organs of the body, primarily involving peripheral joints, axial bones, attachment points and finger ends. At present, the main treatment methods for psoriatic arthritis include non-steroidal anti-inflammatory drugs, glucocorticoids, anti-rheumatic drugs, biological inhibitors, etc., but there are certain limitations. Mesenchymal stem cells provide a new method for the treatment of psoriatic arthritis because of their differentiation ability and immune regulation ability. In this paper, the pathogenesis of psoriatic arthritis immune factors, mesenchymal stem cells targeted regulation, and research progress were explored.

【 Key words 】 Arthritis, psoriatic; Stem cells; Immunomodulation; Review

【 关键词 】 银屑病关节炎; 干细胞; 免疫调节; 综述

银屑病关节炎 (psoriatic arthritis, PsA) 是一种慢性免疫介导的炎症性疾病, 其特征是关节肿胀、压痛、附着点炎和指关节炎, 会导致身体功能受损或长期残疾^[1]。目前已知的病因包括环境因素、遗传因素、免疫因素^[2]。鉴于免疫因素是 PsA 的重要致病因素, 以及针对性治疗的可实现性, 免疫系统的重建对于 PsA 的治疗以及病情延缓甚至逆转具有重要意义。目前临床中应用的方法多为缓解症状, 对于关节破坏的进程并没有显著影响。间充质干细胞 (mesenchymal stem cell, MSC) 具有强大的分化能力以及免疫学特性, 已经被证明具有较好的抗炎效果和免疫抑制能力^[3]。笔者就 MSC 免疫调节途径治疗 PsA 进行探究, 同时对临床应用的最新进展作一综述。

一、MSC 疗法

MSC 是一种具有干细胞特性和免疫调节作用的特殊细胞, 广泛来源于异体或者自体的骨髓、脂肪组织、脐带、胎盘和牙髓等多处^[4]。其具备分化为骨细胞、软骨细胞、脂肪细胞等多种细胞的强大能力, 同时能够促进血管生成、防止细胞凋亡、抑制炎症反应和调节细胞外基质动态, 可以在组织或细胞受损后, 通过免疫调节的方式来控制整个组织的再生过程^[5-6]。研究表明 MSC 诱导的免疫耐受性, 对于异体 MSC 不仅没有被排斥, 而且它们较好地保留了分化的能力^[7]。MSC 的上述特性使其目前被广泛地应用于治疗炎症性、组织的修复与再生和免疫性疾病中, 如系统性红斑狼疮 (systemic lupus erythematosus, SLE)、移植抗宿主病 (graft-versus-host disease, GVHD)、克罗恩病、多发性硬化 (multiple sclerosis, MS)、1 型糖尿病等^[8]。

二、PsA 的免疫性发病机制

树突状细胞 (dendritic cell, DC) 是固有免疫细胞的一种, 被认为是 PsA 的重要致病因素^[9]。DC 作为第一道免疫防线, 具有强大的抗原提呈能力, 在识别到危险信号后 DC 会释放抗菌肽、趋化因子和细胞因子等^[10], 并且通过 Toll 样受体 (toll like receptor, TLR) 的表达促进炎症反应^[11]。研究发现银屑病患者外周血中的 DC 相较于健康人群浓度明显降低, 并且 DC 亚群的表型不成熟。而未成熟的 DC 会产生高水平的干扰素- α (interferon α , IFN- α) 和肿

瘤坏死因子- α (tumor necrosis factor α , TNF- α), IFN- α 能促进局部的 DC 活化, TNF- α 则在适应性免疫过程中发挥重要作用^[12]。同时 DC 是将固有免疫和适应性免疫连接起来的重要桥梁, 其将抗原呈递给适应性免疫系统的细胞, 从而导致 T 细胞亚群的分化和扩增^[13]。

适应性免疫方面, T 细胞释放的细胞因子在 PsA 的发病中具有重要作用。CD4 + T 细胞在皮肤和关节中明显升高, 而在附着点中的 CD8 + T 细胞水平则更高^[14]。Leijten 等^[15]发现 PsA 患者的关节及关节滑液中 CD8 + T 细胞和 CD4 + T 细胞大量存在。而类似的研究结果显示, CD8 + T 细胞在 PsA 患者体内出现大规模的扩增^[16]。这些都被认为 T 淋巴细胞在 PsA 的疾病过程中广泛参与。

TNF- α 以及白介素 (interleukin, IL) -23 / IL-17 轴被认为是 PsA 的致病核心^[17]。TNF- α 导致浆细胞分化产生 IL-23, 并且使得 DC 募集^[18]。而 IL-23 则主要由 DC 产生^[19], 由辅助性 T 细胞 (T helper, Th) 17 亚群扩增和维持, Th17 淋巴细胞转录因子视黄酸受体相关孤儿受体- γ t (related orphan receptor- γ t, ROR- γ t) 的表达会产生细胞因子 IL-17^[20]。其中 IL-17A 被普遍认为是 IL-17 特征最好的成员^[21]。IL-17A 在 PsA 致病过程中的主要作用机制为: (1) 骨重塑, 通过上调成骨细胞表达的核因子 κ B (nuclear factor κ B, NF- κ B) 配体的受体激活因子 (receptor activator of NF- κ B ligand, RANKL) 和抑制 Wnt 信号, 从而抑制成骨细胞活性^[22], 导致破骨细胞活化和骨破坏的发生^[23], 同时抑制成骨细胞的增殖^[24]; (2) 增强炎症反应, IL-17 使得银屑病关节炎患者的炎症反应放大^[25], 同时促进血管生成, 增加血流量, 并增加炎症细胞流入已经存在炎症反应的关节^[26]。此外, IL-23 / IL-17 轴的激活会促进粒细胞集落刺激因子、粒细胞巨噬细胞刺激因子和趋化因子的产生, 促进中性粒细胞的募集和迁移到关节组织^[27]; 使滑膜成纤维细胞和巨噬细胞进一步产生炎症细胞因子, 如 IL-1b、IL-6 和 TNF- α ; 并最终导致骨软骨破坏^[28]。有学者在 PsA 患者的滑膜组织发现有较高水平的 IL-23、IL-17A 及其受体存在^[29]。另一项研究发现 PsA 患者较健康人群血清中 IL-23 和 IL-12 的共享亚基 p40 蛋白水平明显升高,

并且同 TNF- α 表现出正相关的特点^[30]。

三、PsA 的治疗现状

目前 PsA 的治疗选择较为多样。抗风湿类药物 (disease-modifying anti-rheumatic drug, DMARD) 依然是 PsA 的首选用药, 同时非甾体抗炎药 (nonsteroidal anti-inflammatory drugs, NSAIDs) 和糖皮质激素对于症状的缓解也具备一定的效果。随着生物制剂研究的不断深入, 也为 PsA 的临床治疗增加了一种选择。

现阶段的 DMARD 主要有氨甲蝶呤 (methotrexate, MTX)、柳氮磺吡啶、来氟米特和环孢素, MTX 是最常见的 DMARD, 低剂量的 MTX 被认为是 PsA 的一线用药^[31]。它通过刺激腺苷, 使其释放增强, 达到抑制炎症的目的^[32]。对于 PsA 的治疗而言, 能够缓解症状、减轻疾病活动度和预防疾病进展^[33], 并且不会增加 PsA 的常见并发症——糖尿病的患病风险^[34]。有研究发现 MTX 与磺胺嘧啶或 MTX 与环孢素联合使用的治疗效果可能会优于单独使用^[35]。但有学者认为, MTX 单独使用和联合其它疗法的有效性并没有明显差异^[36]。MTX 在临床应用中的主要风险为肝毒性, 易引发肝硬化甚至肝癌^[37], 这在一定程度上增加了临床管理的难度。

NSAIDs 在治疗 PsA 方面被作为症状药, 主要用于轻度的外周关节炎、末端炎和手指炎, 但在预防关节破坏进展方面作用较小^[38]。糖皮质激素存在停药后有复发风险等诸多问题, 因此相关指南建议在病情需要时最短时间内使用最低剂量^[39]。

现阶段主要的生物抑制剂主要有 TNF- α 抑制剂、IL-17 抑制剂、Janus 激酶 (janus kinase, JAK) 抑制剂。TNF- α 抑制剂目前在欧洲被用作 PsA 的一线生物制剂^[40]。常见的 TNF- α 抑制剂有 5 种, 分别为阿达木单抗、伊那西普、戈利单抗、英利昔单抗、培塞利珠单抗。一项针对除培塞利珠单抗之外的 4 种抑制剂差异性研究发现: 4 种药物对于 PsA 的有效性不存在明显差异; 6 个月内治疗持续性没有显著的差异, 但 6 个月后英利昔单抗明显低于其它 3 种。并且联合使用 DMARD 对于改善治疗并没有明显的效果^[41]。也有研究显示, TNF- α 抑制剂对于疼痛症状缓解作用较弱, 并不能降低阿片类药物的用量^[42]。目前国内用于治疗 PsA 的 IL-17 抑制剂主要为司库奇尤和伊奇珠两种, 它们对于 PsA 的治疗具有良好的表现。由于 IL-17 单抗对于心脑血管系统存在不错的治疗效果, 因此被推荐用于合并有心脑血管疾病的患者^[43]。赛库单抗和乌司奴单抗是 IL-23 抑制剂, 赛库单抗具备良好的耐受性, 感染的风险不高^[44], 乌司奴单抗则被用于 PsA 晚期发展阶段。IL-12/23 抑制剂为古西单抗, 其对于改善疼痛和改善睡眠质量具有良好的效果^[45]。乌达西替尼是一种 JAK1 抑制剂, 改善附着点炎和指端炎的效果良好, 对免疫功能并不会产生较大的不良影响, 被证实存在不错的安全性和可耐受性^[46]。不过有学者认为生物疗法虽然能够控制非关节症状, 较好地减缓运

动系统中破坏性过程的进展, 但并不能改变已经存在的关节系统的病变, 也不会抑制骨形成过程^[47]。

四、MSC 治疗 PsA 的基础研究

1. 免疫调节: MSC 通过产生趋化因子和细胞因子 (如 IL-6、IL-12 和 IL-15), 在慢性炎症中具有积极作用^[48]。并且在治疗炎症性疾病时通过调节炎症可以促进组织再生^[49]。MSC 能够使巨噬细胞由增强炎症反应的 M1 向促进表达抗炎作用的 M2 极化^[50]。来自芬兰的一项研究发现, MSC 及其来源的细胞外囊泡 (extracellular vesicle, EV) 通过抑制 IL-22 和 IL-23 的产生来增强巨噬细胞的抗炎能力, 且能够增加具有免疫特性的前列腺素 E2 (prostaglandin E2, PGE2) 的产生^[51]。

2. 调节 T 细胞: MSC 促进 T 细胞分化或诱导具有免疫抑制功能的调节性 T 细胞 (regulatory T cell, Treg) 产生^[52]。Treg 能够产生抗炎细胞因子, 如转化生长因子- β (transforming growth factor- β , TGF- β) 和 IL-10, 并具有耐受性^[53]。就现阶段研究而言, MSC 对 PsA 的关键免疫因子 Th17 的调节主要通过两种途径。第一, 分泌的抗炎因子 IL-10 不仅抑制 CD4+ T 细胞分化为 Th17 细胞, 而且能够抑制 DC 介导的 Th17 分化^[54]。第二, 产生的 IL-6 会降低 Th17 细胞的频率, 并抑制 IL-17 和 IL-22 的产生^[55]。当然, MSC 通过分泌一氧化氮^[56]、肝细胞生长因子 (hepatocyte growth factor, HGF)^[57] 等也会对 T 细胞的增殖产生抑制作用。Vellasamy 等^[58] 研究发现 MSC 并不会诱导 T 细胞凋亡, 而是抑制 T 细胞活化, 使其处于 G0/G1 期, 丧失 S 期 T 细胞存在的免疫功能。一项来自 Minhwa 的体外实验发现: 扁桃体来源的间充质干细胞能够有效抑制原始 T 细胞向 Th17 细胞的分化, 使得 RANKL 的表达降低, 从而抑制破骨细胞的生成, 改善骨破坏的发生^[59]。Ghannam 等^[60] 证实 MSC 能够将促炎性 T 细胞转化为抗炎, 同时可以特异性诱导 FOXP3 转录物的表达, 实现免疫调节的作用。

3. 调节 DC 细胞: MSC 可以抑制 DC 的分化、成熟和活化并损害其抗原提呈能力。已经证实 MSC 通过分泌 IL-6, 增强 MHC-II 类分子——HLA-DR, 抑制单核细胞和 CD1a、CD4 等分子的表达来影响 DC 的分化^[61-62]。MSC 还可下调 DC 中 CD80、CD86 和 IL-12 的表达, 从而抑制 DC 的成熟和激活^[63]。MSC 通过抑制 CCR7 和 CD38 的表达, 从而阻止 DC 向淋巴结中的回流^[64], 这导致幼稚 T 细胞的启动受损^[65]。MSC 通过下调炎症因子 TNF- α 、IL-12 和上调抗炎因子, 将细胞因子分泌从促炎性转向抗炎性^[66]。

五、MSC 治疗 PsA 的临床研究

1 例有两年半关节症状史的 PsA 患者在陆续接受 NSAIDs、糖皮质激素 (泼尼松)、MTX 以及 TNF- α 抑制剂未收到明显效果后改用人脐带来源的 MSC 治疗, 初次给予 200 000 个细胞, 静脉注射。注射后 1 周皮肤症状开始缓解, 关节疼痛减轻。初次治疗后 2 个月据不完整的

实验室检查显示:红细胞沉降率(erythrocyte sedimentation rate, ESR)变为 85, C 反应蛋白(C-reactive protein, CRP)和类风湿因子增加 1 倍。治疗后 3 个月再次接受静脉注射和关节注射 5×10^7 脐带血干细胞(cord blood stem cell, CBSC), 频次为每月 1 次, 共 3 次。此次治疗结束后患者皮肤症状基本消失, ESR 及 CRP 指标回到正常范围, 治疗后 18 个月虽略高于正常值, 但较治疗前降低明显。治疗期间出现的不良反应是为期 2 天的轻度发热和肌肉、关节疼痛^[67]。

1 例使用自体脂肪 MSC 的 PsA 患者的病例报道显示, 该患者共接受了 2 次治疗, 给药方式为静脉注射, 间隔 40 天, 最后一次治疗结束后银屑病面积与严重程度指数较治疗前降低了 12.7, 但关节疼痛没有显著缓解, 治疗后 10 个月使用依那西普治疗后各种症状明显改善, 可以进行体育锻炼。遗憾的是 2 年后确诊肺结核后症状复发^[68]。

就现有的报道而言, 使用 MSC 治疗 PsA 的临床治疗效果优于其它疗法, 症状改善的持久性也较为喜人, 同时没有出现明显的不良反应。但是不得不承认, 这仅为低级别证据的病例报道, 且数量极少, 缺乏大样本的临床随机对照试验进行安全性和有效性验证。

值得注意的是, 目前 MSC 在临床应用中的给药方式主要有静脉输注、腹膜注射和局部注射 3 种。虽然有研究显示, 静脉输注表现出更强于其它方法的免疫调节效果^[69], 却也会增加血栓形成的风险^[70]。现有的文献报道中, 在治疗 PsA 时多采用静脉注射和关节腔注射, 且都有一定疗效, 但究竟何种方式更佳, 仍有待研究。

六、小结

PsA 作为一种难治性疾病, 对于患者的身体危害较大, 且长期缺乏行之有效的治疗方法。MSC 由于具备良好的免疫调节特性, 尤其是针对 PsA 发病相关的 DC、IL-23 / IL-17 轴等有很好的调控作用, 能够有效地抑制炎症反应和骨破坏的发生。就现有的临床报道而言, MSC 有相较于其它疗法的明显优势, 这些都使得其成为治疗 PsA 的新希望。但是此类研究多以理论为主, 现有的临床研究较少, 缺乏说服力, 需要进一步的临床研究论证其治疗 PsA 的有效性、安全性等问题。

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