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骨髓间充质干细胞治疗激素性股骨头缺血性坏死的研究进展

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摘　要

糖皮质激素所导致的股骨头缺血性坏死，被认为是长期或过量使用类固醇治疗中最严重的副作用。糖皮质激素可以破坏骨髓间充质干细胞的正常分化，导致骨量的减少和骨髓脂肪组织的增加。然而，其潜在的发病机制仍不明确。尽管全髋关节置换术是治疗晚期股骨头缺血性坏死最有效的方法，但在年轻患者或活跃人群中，因为一些与假体相关的并发症，全髋关节置换术的效果往往不佳。骨髓间充质干细胞具有自我更新和多向分化的能力，包括分化为成骨细胞和内皮细胞，从而介导骨修复和血管生成。此外，骨髓间充质干细胞还可以通过旁分泌作用提供生长因子，从而促进坏死区的血液供应。因此，骨髓间充质干细胞治疗可以作为激素性股骨头缺血性坏死的保髋方案之一。

关键词

糖皮质激素，股骨头缺血性坏死，骨髓间充质干细胞，干细胞治疗

Research Progress of Bone Marrow Mesenchymal Stem Cells in the Treatment of Glucocorticoid-Induced Osteonecrosis of Femoral Head

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Abstract

Glucocorticoid (GC)-induced osteonecrosis is the most serious effect in long-term or over-dose steroid therapy. GC can destroy the normal differentiation balance of bone marrow mesenchymal stem cells (BMSCs), resulting in a decrease bone mass and an increase marrow fat tissue. However, its underlying pathogenesis is still unclear. Although total hip arthroplasty (THA) is the most effective treatment for patients with osteonecrosis of femoral head (ONFH) in the terminal stages, the outcomes of THA in young adults or active populations are often not excellent, due to some complications related to the prosthesis. BMSCs have been shown to have the ability to self-renew and to differentiate into multiple cell types including differentiate into osteoblasts and endothelial cells to affect bone repair and angiogenesis, and can produce growth factors to promote the blood supply to necrotic regions by paracrine effects. Therefore, BMSCs therapy can be used as one of the hip-saving programs for GC-induced ONFH.

Keywords

Glucocorticoid, Osteonecrosis of Femoral Head, Bone Marrow Mesenchymal Stem Cells, Stem Cell Therapy

1. 引言

糖皮质激素所导致的股骨头缺血性坏死是长期或过量使用类固醇激素最严重的副作用，其特征是血液供应中断，软骨下骨坏死，最终股骨头塌陷，导致严重的髋关节疼痛和功能障碍，严重影响患者生活质量[1]。一旦被确诊为股骨头缺血性坏死，如果不及时治疗的话，大约80%的患者会在1~5年的时间进展为股骨头塌陷[2]。尽管全髋关节置换术是治疗晚期股骨头缺血性坏死最有效的治疗方法，但是在年轻患者或活跃患者中，全髋关节置换术的效果并不尽如人意[3]。假体松动，聚乙烯假体的过度磨损以及假体周围感染都会导致全髋关键置换术的失败[4] [5] [6]。因此，保髋治疗股骨头缺血性坏死成为了我们目前面临的挑战。

2. 骨髓间充质干细胞治疗激素性股骨头缺血性坏死的理论依据

骨髓间充质干细胞已经被证明具有非凡的自我更新和多系分化能力，在股骨头缺血性坏死的病理生理过程中发挥着重要的作用，由于缺乏法律和伦理限制，易于获取，是一种很有前途的细胞治疗和组织再生医学方法[7]。尽管糖皮质激素诱导的股骨头缺血性坏死的病理生理机制尚不明确，但普遍认为与骨髓间充质干细胞有关，包括细胞凋亡、细胞数量减少、细胞生长能力减弱、干细胞代谢异常、成骨分化能力下降、成脂分化能力增强[8]。骨髓间充质干细胞可以分化为成骨细胞和内皮细胞，影响骨修复和血管生成，还可以通过旁分泌效应产生生长因子，促进坏死区的血液供应[9] [10]。因此，成骨修复和血管生成是干细胞治疗股骨头缺血性坏死最重要的机制之一。

骨髓是治疗股骨头缺血性坏死最常用的干细胞来源。在合适的条件下，骨髓间充质干细胞可以分化为骨骼肌肉系统细胞，如松质骨、关节软骨、肌腱等。目前，促进骨髓间充质干细胞成骨分化的研究受生长因子、糖皮质激素、小分子药物和基因多态性等多种因素影响。例如，骨形态发生蛋白-2 (BMP-2)，血管内皮生长因子(VEGF)和碱性成纤维细胞生长因子(BFGF)可以促进骨髓间充质干细胞的成骨分化[11]。大剂量地塞米松会促进骨髓间充质干细胞成脂分化，但小剂量地塞米松可以通过上调碱性磷酸酶的表达来促进骨髓间充质干细胞成骨分化[12]。淫羊藿苷可以通过增加 P-糖蛋白的表达促进骨髓间充质干细胞成骨分化[13]。戴等人[14]的研究表明，miRNA-217 过表达可以通过抑制 DKK1，促进 β-catenin 的核转位，显著促进骨髓间充质干细胞的增殖和成骨分化。

3. 骨髓间充质干细胞治疗激素性股骨头缺血性坏死的植入方法

3.1. 髓芯减压联合骨髓间充质干细胞移植治疗

髓芯减压术是早期治疗股骨头缺血性坏死最经典的方法，它可以降低骨内压力，去除坏死组织，刺激新生骨的形成[15]。然而只有在小的坏死性病变的患者中行髓芯减压术才能观察到良好的结果[16]。因此，髓芯减压术联合骨髓间充质干细胞移植成为治疗股骨头缺血性坏死的有效方法之一。简而言之，就是在髓芯减压术后，将骨髓间充质干细胞注入股骨头坏死区。Tebatabaee 等人[17]研究了髓芯减压术联合骨髓间充质干细胞移植治疗股骨头缺血性坏死的预后效果，通过西安大略大学和麦克马斯特大学骨关节炎评分(WOMAC)、疼痛视觉模拟评分(VAS)和磁共振(MRI)对患者愈合进行评估。结果显示，使用髓内减压联合骨髓间充质干细胞移植治疗的患者 WOMAC、VAS 以及 MRI 结果都有明显改善。同样，Rastogi 等人[18]的研究也表明了，髓芯减压联合骨髓间充质干细胞治疗在 2 年的随访中能够显著改善患者的髋关节 HARRIS 评分，同时 MRI 也显示病灶较前明显缩小。Sen 等人[19]进行了一项随机对照研究，结果显示使用髓芯减压联合骨髓间充质干细胞移植治疗的患者临床评分和平均髋关节存活率要明显优于仅接受髓芯减压的患者。

3.2. 骨髓间充质干细胞动脉灌注治疗

骨髓间充质干细胞动脉灌注是治疗股骨头缺血性坏死的另一种方法，其目的是改善股骨头的血液供应。Kinnaird 等人[20]的研究表明，干细胞可以通过诱导血管内皮生长因子(VEGF)和碱性成纤维细胞生长因子(BFGF)的释放，从而促进动脉生成，改善微循环。基于这一理论，在临床前和临床试验中探讨了骨髓间充质干细胞动脉灌注治疗股骨头坏死的疗效。金等人[21]通过建立比格犬股骨头缺血性坏死模型，进行了骨髓间充质干细胞动脉灌注治疗。他们发现，骨髓间充质干细胞动脉灌注治疗后，促进了血管内皮生长因子(VEGF)的表达，增加了微血管密度(MVD)，促进了股骨头的血管生成和修复，从而改善了坏死区的血液供应和重建。毛等人[22]在一项 5 年的随访研究中讨论了骨髓间充质干细胞动脉灌注治疗的效果，结果表明经旋股内侧动脉灌注自体骨髓间充质干细胞可以缓解股骨头坏死的临床症状，改善髋关节功能，延缓股骨头坏死进展。

3.3. 基因修饰的骨髓间充质干细胞移植

随着基因工程技术的快速发展，基因修饰的骨髓间充质干细胞在临床前试验中已经被广泛用作治疗股骨头缺血性坏死的种子细胞。Ma 等人[23]探讨了血管内皮生长因子-165 (VEGF-165)和骨形态发生蛋白-2 (BMP-2)基因修饰的骨髓间充质干细胞对兔股骨头缺血性坏死的治疗效果。结果表明，转染 VEGF-165/BMP-2 基因后增强了骨髓间充质干细胞的成骨作用，提高了新骨的数量和质量，加速了股骨头缺血性坏死的修复。另外，彭等人[24]将骨形态发生蛋白-2 (BMP-2)和碱性成纤维细胞生长因子(BFGF)

基因转染的骨髓间充质干细胞与脱钙骨基质(DBM)复合，修复比格犬股骨头缺血性坏死模型。他们发现，将 BMP-2 和 BFGF 基因转染的骨髓间充质干细胞与 DBM 联合移植可以增加成骨和血管生成，成功促进坏死区的修复。

3.4. 骨髓间充质干细胞移植与骨组织工程技术

目前，骨组织工程技术是骨科研究的主要领域，其特点是种子细胞、载体和支架。骨髓间充质干细胞分化能力强、增殖活性强、免疫原性低，是骨组织工程最理想的种子细胞。载体和支架不仅可以整合细胞和受体，还可以为股骨头坏死区提供生物力学支持，从而调节细胞功能。因此，骨髓间充质干细胞与载体或支架的结合已成为治疗股骨头缺血性坏死的新途径。自体骨组织是临床上骨髓间充质干细胞治疗股骨头缺血性坏死常用的支架材料。Kang 等人[25]使用自体髂骨松质骨联合自体骨髓间充质干细胞移植治疗股骨头缺血性坏死，并进行了 5 年的随访。他们认为，这种手术更适合中等大小病变的患者。此外，具有与正常骨组织相似的空间结构和力学支持的合成支架已被应用于股骨头缺血性坏死的治疗，包括脱钙骨基质(DBM)、异种抗原提取松质骨(XACB)、钽棒、双相磷酸钙(BCP)陶瓷支架、聚丙交酯－乙交酯仿生合成支架(PLGA)、PLGA 磷酸钙(CPC)复合支架以及掺锶聚磷酸钙(SCPP)。Kang 等人[26]研究了 SCPP 与自体骨髓间充质干细胞治疗兔激素性股骨头缺血性坏死中的协同作用，结果发现 SCPP 与骨髓间充质干细胞复合植入可增强 VEGF 的表达，促进成骨，从而在不削弱力学强度的情况下促进血管生成，并使其与新生的松质骨结合和重塑。

4. 不足与展望

糖皮质激素所导致的股骨头缺血性坏死是一种发病机制上不明确的进展性疾病，尤其对于年轻患者，缺乏最佳的治疗方法。随着生物技术的发展，骨髓间充质干细胞治疗股骨头缺血性坏死成为了当前研究的热点。然而，在实际应用中，仍有许多问题和挑战尚未解决，如患者的选择[27]，标准化程序[28]，安全性评估[29]，体内移植细胞的命运[30]等。因此需要更多的研究来寻找骨髓间充质干细胞的最佳移植方式、最佳剂量和浓度、最佳的注射时间以及系统的安全性评估和体内干细胞追踪也是必要的。随着上述问题的解决，可以肯定的是，骨髓间充质干细胞可能成为治疗股骨头缺血性坏死最有效的保留髋关节的替代方案。

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