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间充质干细胞治疗糖尿病肾病的研究进展

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摘 要

糖尿病是目前危害人类健康的重大疾病，并且会引发一系列严重的并发症，其中糖尿病肾病是一种严重的微血管并发症，是各种终末期肾病的主要原因之一，缺乏相应治疗靶点，治疗效果不佳。间充质干细胞(MSCs)是一类具有自我复制和多向分化能力的细胞，MSCs移植具有直接修复肾细胞损伤、调节炎症和免疫反应、抗纤维化等功能，其对糖尿病肾病的治疗展现出了令人欣喜的成果。本文对间充质干细胞对糖尿病肾病的治疗进行综述，为间充质干细胞治疗糖尿病治疗提供新的策略。

关键词

糖尿病肾病，间充质干细胞，旁分泌，外泌体

Development of Mesenchymal Stem Cells for Treatment of Diabetic Kidney Disease

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Abstract

Diabetes is a major disease endangering human health, and it will cause a series of serious complications. Diabetic kidney disease (DKD) is a serious microvascular complication, which is one of the main causes of various end-stage renal diseases (ESRD). It lacks corresponding therapeutic

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targets and has poor therapeutic effect. Mesenchymal stem cells (MSCs) are a kind of cells with the ability of self-replication and multi-directional differentiation. MSCs transplantation can directly repair renal cell injury, regulate inflammation and immune response, and anti-fibrosis. The treatment of diabetic nephropathy has shown gratifying results. This paper reviews the treatment of diabetic nephropathy by MSCs, and provides a new strategy for the treatment of diabetes mellitus with MSCs.

Keywords

Diabetic Kidney Disease (DKD), Mesenchymal Stem Cells (MSCs), Paracrine, Exosomes

1. 引言

2000 年全世界糖尿病患者为 1.51 亿人，到 2019 年这一数字达到了 4.63 亿人，占世界成人人口的 9.3% [1]，故糖尿病是危害公众健康的主要疾病之一。随着糖尿病进行性加重，常常会伴发糖尿病并发症，如其中糖尿病肾病(diabetic kidney disease, DKD)是糖尿病病人主要的并发症之一。早期糖尿病肾病以肾小球高滤过、微量的白蛋白尿(30~300 mg/d)、肾小球肥大、基底膜增厚、系膜扩张、细胞外基质(extracellular matrix, ECM)蛋白如 I 型或 IV 型胶原、纤维连接蛋白、层粘连蛋白等积聚为主，晚期糖尿病肾脏病变的特征是肾小球滤过率(glomerular filtration rate, GFR)进行性下降，肌酐清除率下降，大量蛋白尿(>300 mg/天)，肾小球硬化和间质纤维化。通过对血糖和血压的严格控制可以减缓 DKD 进展为终末期肾病，但是对于 DKD 的发展不能完全阻止；目前对 DKD 的治疗仍缺乏有效的治疗措施。

随着过去二十年再生医学领域的快速发展，干细胞在临床治疗上的应用为 DKD 患者带来了新的希望。在预防或调节糖尿病并发症的过程，MSCs 相对于胚胎干细胞以及组织特异性成体干细胞具有许多优点。它们更容易获得，可以从患者(自体 MSCs)以及健康供体(同种异体 MSCs)的骨髓，脂肪抽吸物，脐带和其他可获得的组织中获得，可以在组织培养瓶或生物反应器中大量扩增。它们在体内通过在损伤部位定植，旁分泌作用及分泌的外泌体来促进肾脏病理损伤的修复，调节炎性和免疫性反应。MSCs 的这些特性对改善 DN 的症状发挥了非常有益的作用[2]。

2. 糖尿病肾病的发病机制

DKD 主要是由于血糖的升高引起肾脏的微血管损伤，其一部分发病机制通过实验被阐明，例如高血糖会激活肾血管紧张素－醛固酮系统(RAAS) [3] [4]。这会导致血管紧张素 II 水平升高，从而导致促炎信号增加，肾小球系膜和肾小管上皮细胞肥大，转化生长因子-β (transforming growth factor-β, TGF-β) [5] [6]和单核细胞趋化蛋白-1 (Monocyte chemoattractant protein-1, MCP-1) [7] [8]的增加，并产生活性氧(reactive oxygen species, ROS)，高浓度的 ROS 使蛋白激酶 C 过度活化，可使半胱氨酸的天冬氨酸蛋白水解酶(cysteinyl aspartate specific proteinase, caspase)依赖的凋亡通路活化，促细胞凋亡[9]。MCP-1 的诱导导致单核细胞进入肾脏增加，浸润的单核细胞随后被转化为巨噬细胞，释放出促炎因子，包括白介素 6 (interleukin-6, IL-6)，肿瘤坏死因子 α (Tumour necrosis factor-α, TNF-α)和 ROS [10]。在这种炎症过程中，巨噬细胞和淋巴细胞还在组织水平上产生了额外的血管紧张素 II [11]，这形成了促炎信号的正反馈放大效应。

高血糖会诱导促纤维化细胞因子 TGF-β、ECM 基质蛋白中纤维连接蛋白和 IV 型胶原增多、一氧化氮失调、内皮功能障碍以及丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)和转录因子－核因子 κB (nuclear factor kappa-B, NF-κB)信号通路激活，进而使肾实质细胞蛋白激酶 C (protein kinase C, PKC)异常激活[12] [13]。高血糖症还与高水平的晚期糖基化终产物(advanced glycationend products, AGEs)有关，后者进一步刺激 TGF-β 的产生。而 TGF-β 进一步加重了肾小球结构的改变。例如葡萄糖水平升高会诱导血小板源性生长因子-β (PDGF-β)的早期活化，从而导致 TGF-β1 表达增加[14]。

由于 DKD 引起的系统性动脉高压和局部血流动力学功能障碍，可能会进一步加重肾内炎症、TGF-β 和 ECM 蛋白的产生。

由以上可见，由于代谢失调使肾脏处于一个慢性炎症环境中，而促使肾脏结构和功能发生改变。另外，DKD 并不是由于某一单一因素引起，而是各种细胞因子及细胞间的相互作用和不同信号通路的激活所导致的。因此单一靶向某一种信号分子或信号通路来逆转 DKD 的进展非常困难。细胞疗法，特别是 MSCs 因为能够提供同时作用于多种致病机制并积极促进组织修复和再生的潜力而显示出其独特的治疗优势[15]。

3. 间充质干细胞治疗 DKD 的机制

MSCs 具有多种特性，包括免疫调节、调节炎性反应、抑制凋亡和促进血管生成。这些特性使其在 DKD 的治疗中发挥了独特作用。MSCs 主要通过在组织损伤部位定植、旁分泌作用、分泌外泌体三种途径发挥作用[16] [17]。既往认为 MSCs 会在组织损伤的部位定植，修复和替代受损组织，但研究发现其在受损组织中定植是非常少量的，通过此途径发挥其作用亦很微弱[18] [19]。因此，MSCs 主要通过分泌的营养因子和外泌体改善 DKD、促进肾细胞增殖、减少纤维化、抑制氧化应激、抑制细胞凋亡、减轻炎症和免疫反应[20] [21] [22]。

3.1. MSCs 通过旁分泌作用改善 DKD

MSCs 对 DKD 的治疗通过其释放的各种营养因子的旁分泌效应被证明是其主要的作用机制[23] [24]，主要分为三种类型：包括细胞因子，生长因子和趋化因子[25]，其对细胞的生长，迁移，分化，凋亡，炎症，分裂和信号传导等起着重要作用。其中骨形态发生蛋白 7 (bone morphogenetic protein-7, BMP-7)可以拮抗 TGF-β1 [26] [27]。MSC 来源的 BMP-7 通过在体内和体外抑制 TGF-β/Smad 信号通路，改善肾小球纤维化和足细胞损伤($p < 0.05$) [28]。肝细胞生长因子(hepatocyte growth factor, HGF)通过抑制单核细胞趋化蛋白 1 (MCP-1)的表达来减少巨噬细胞浸润，下调糖尿病大鼠肾脏组织中促炎细胞因子如 IL-1β，IL-6 和 TNF-α 的表达，减轻炎症反应；HGF 还会通过下调葡萄糖转运蛋白 1 (GLUT1)的膜定位来抑制氧化应激，从而进一步减轻高血糖刺激的肾小球损伤($p < 0.05$) [29]。上皮细胞生长因子(epithelial growth factor, EGF)通过减少足细胞 caspase-3 的表达减少足细胞的凋亡和损伤($p < 0.05$) [30]。

3.2. MSCs 通过外泌体改善 DKD

MSCs 除了分泌的营养因子外，还可以分泌外泌体(exosomes, Exo)，后者通过转运 mRNA、miRNA、DNA 和蛋白质与目标细胞进行信号传导[31] [32]。MSCs 所分泌的外泌体可以通过抑制足细胞凋亡和通过哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路增强自噬而缓解 DKD。已经证明给大鼠静脉注射尿液源性干细胞外泌体(USCs-Exo)会降低尿微量白蛋白排泄，抑制 caspase-3 过表达而防止足细胞和肾小管上皮细胞凋亡，并促进了糖尿病大鼠肾小球内皮细胞的增殖；此外，USCs-Exo 可以减少高糖诱导的足细胞凋亡而改善 DKD ($p < 0.05$) [33]。Jing 等人证实了 miR-486 可以直接调控 Smad1

的表达，进而增加 mTOR 介导的自噬通量，在高糖诱导的 MPC5 细胞和 DN 小鼠中，脂肪 MSCs 来源外泌体(ADSCs-Exo)携带的 miR-486 可以转移至足细胞，并发挥自噬激活剂作用，促进自噬减轻细胞损伤($p < 0.01$) [34]。Nagaishi 等人证明 MSC-Exos 抑制 STZ 诱导的糖尿病大鼠肾小管上皮细胞(tubular epithelial cells, TECs)的凋亡和变性从而改善 DKD [35]。Ebrahim 等人研究了 MSC 来源的外泌体对增强自噬活性及其对 DN 影响的潜在作用，结果显示自噬标志分子 LC3 和 Beclin-1 显著增加，肾组织 mTOR 和纤维化标志物表达显着降低，外泌体显著改善肾功能，促进肾组织恢复，这些结果提示外泌体诱导的自噬可以减轻链脲佐菌素诱导的糖尿病大鼠模型的 DKD 预后($p < 0.05$) [36]。

3.3. MSCs 通过在组织损伤的部位定植改善 DKD

MSCs 在体内和体外具有多元分化能力，Wong 等人研究了 MSCs 在体外与氧化损伤的系膜细胞共培养时具有分化为肾小球系膜细胞的能力[37]。MSCs 目前的治疗应用，已知这些细胞可以归巢于一些组织，特别是在受伤或病理状态下，尽管有证据表明趋化因子及其受体和粘附分子都参与其中，但 MSCs 迁移的机制仍有待澄清[38]。对干细胞归巢于受损肾脏并转分化为肾细胞的能力还有待进一步确认，但普遍认为这种转分化事件是十分罕见的，不足以代表组织修复的主要机制。

4. 间充质干细胞的临床应用

DKD 的临床前研究表明，基于 MSCs 的治疗可能是治疗 DKD 的一种有效的治疗方法，对 DKD 模型动物的肾脏病理损伤都有不同程度的缓解，但这些研究的实验设计因输入的细胞来源(骨髓来源[39]、脂肪来源[40]、尿液来源[33]、自体细胞或异体细胞)、剂量、给药途径(静脉输入[33]、心内灌注[39]、左肾动脉注射[41])、糖尿病病程等方面的不同而不同，另外，由于 MSCs 在肾脏的归巢量少，在肾脏环境中的存活率亦有限。加之，MSCs 体外扩增能力差，易衰老，影响细胞复制和分化能力，MSCs 在体外长时间扩增可导致染色体不稳定而增加恶性转化的风险[42]。Kunter U 等人的研究 MSCs 可以分化为目的细胞之外的谱系，研究显示移植入肾小球内的 MSCs 会分化为脂肪细胞而加重了肾小球硬化[43]，因此将其应用于临床仍存在很多问题需要明确和克服。目前对于 MSCs 应用于 DKD 的临床实验项目十分有限，对于在动物模型中的实验结果是否可以应用于临床治疗还应该进行对 DKD 患者的随机、双盲、对照实验等以确定间充质干细胞治疗 DKD 的安全性、可行性和耐受性，并确保其有效性。

5. 小结

MSCs 主要通过其旁分泌及其分泌的外泌体来促进肾脏病理损伤的修复，调节炎性和免疫性反应，在各种 DKD 模型中展现了十分巨大的潜力，应用 MSCs 治疗 DKD 变得越来越可行，但其应用于临床时的安全性，移植的 MSCs 在体内存活和维持功能的时间、最佳给药方案、多次注射的长期效果等仍需进一步评估。间充质干细胞由于其具有恶性转化的潜能，因此，接受这种治疗的患者应密切监测是否有肿瘤发生。在接下来的研究中通过 DKD 动物模型进一步研究其发病机制及 MSCs 的应用效果，并且确定其对于 DKD 患者应用的安全性，并在此基础上进一步确认其有效性，这些因素如果能够被明确，干细胞治疗将成为 DKD 患者的另一种选择。

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