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间充质干细胞外泌体在糖尿病肾病治疗中的研究进展

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摘　要

糖尿病肾病(Diabetic Nephropathy, DN)易进展为终末期肾病，目前对其的治疗主要以降血糖、对症支持治疗及肾脏替代治疗等为主，缺乏有效的干预疾病进展的手段。间充质干细胞(mesenchymal stem cells, MSCs)因其具有免疫抑制作用和易再生的特性，被视为免疫、炎症性疾病的新治疗剂，其对糖尿病肾病的有效治疗得到许多实验和临床研究证明，而大多数MSCs介导的有益作用归因于源自MSCs的外泌体(mesenchymal stem cells' exosomes, MSC-exos)的作用。我们综述了MSC-exos在治疗DN的研究进展。

关键词

糖尿病肾病，间充质干细胞，外泌体

The Research Progress of Mesenchymal Stem Cells' Exosomes in the Treatment of Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is easy to progress to end-stage renal disease. At present, the treatment of DN is mainly based on controlling blood glucose, symptomatic and supportive treatment and renal replacement therapy. There is a lack of effective means to intervene the progression of

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DN. Mesenchymal stem cells (MSCs) are regarded as new therapeutic agents for immune and inflammatory diseases because of their immunosuppressive effects and regenerative properties, and their effective treatment for DN has been demonstrated by many experimental and clinical studies, while most MSCs mediated beneficial effects are attributed to the effects of exosomes (MSC-exos) derived from MSCs. We review the research progress of MSC-exos in the treatment of DN.

Keywords

Diabetic Nephropathy, Mesenchymal Stem Cells, Exosomes

1. 引言

随着 DN 发病率和死亡率的增加，其已成为危害世界各国的重要卫生问题[1]。目前针对 DN 的主要治疗措施包括药物治疗、肾脏替代治疗和肾脏移植[1]。然而，由于药物治疗的局限性、肾脏替代治疗的不便和肾移植供体的稀缺，寻找新的治疗方法迫在眉睫。近年来，干细胞作为一种新的再生疗法，被用于治疗包括肾脏疾病在内的众多疾病[2]。MSCs 逐渐成为治疗 DN 的新手段。MSC 衍生的外泌体 MSC-exos 由于其较低的免疫原性、致瘤性，且更容易制备及储存，与 MSCs 相比更具优势[3]。

2. MSCs 及 MSC-exos 概述

MSCs 是一种可自我更新的成体干细胞，遍布于所有出生后的组织和器官中，其主要尤以骨髓来源为主[4]。MSCs 除了具有较强的分化能力外，还具有调节固有和适应性免疫细胞的免疫调节潜力[4]。大量证据表明，MSCs 可通过抑制活化、增殖和分化为效应细胞，作用于各种炎症细胞及免疫细胞[5] [6]。在炎症因子刺激后，MSCs 表现出通过分泌各种免疫调节因子减少炎症反应、改善组织修复和避免感染的特性[7]。MSCs 现能广泛应用于神经、心血管、肝脏、肾脏和骨骼疾病以及皮肤伤口、炎症性肠病、癌症、不育症等多种疾病[3]。MSCs 通过旁分泌途径发挥其免疫调节功能，尤其是通过外泌体[7] [8]。MSC-exos 是 MSC 分泌的脂质膜囊泡，能携带丰富的蛋白质、核酸和其他生物活性物质。来自不同供体的间充质干细胞，其分泌的外泌体能够运载各种不同的生物活性分子[9]。这些货物通过内吞作用或与受体表面的蛋白质结合而转移到受体细胞，从而介导不同细胞类型之间的细胞间通讯并影响受体细胞的功能[9]。

3. MSC-exos 治疗 DN 的研究进展

MSC-exos 作为 DN 的一种新兴治疗手段，目前基于动物实验的许多研究表明其能够延缓肾功能的进展，但机制尚不明确，处于不断探索中的阶段。MSC-exos 可通过多种方式保护肾足细胞和其他肾细胞，包括控制高血糖、抗凋亡、抗纤维化、抗炎和促自噬等。

3.1. 控制高血糖

高血糖可诱导级联事件，导致肾小球和肾小管－间质纤维化，伴足细胞损伤或丢失和系膜细胞肥大，

这是糖尿病肾病的标志[10]。MSC-exos 可能通过转移血管内皮生长因子减轻胰岛细胞死亡并改善胰岛存活及功能[11]，这将有利于控制高血糖。脂肪组织间充质干细胞的外泌体(ADSCs-Exos)通过上调白细胞介素 IL-4、IL-10 和转化生长因子 b 及下调 IL-17 和干扰素-γ，改善 1 型糖尿病小鼠炎症免疫反应，能控制其血糖水平[12]。Qin He 等揭示了骨髓间充质干细胞来源的外泌体通过自噬相关的 AMPK 通路抑制参与葡萄糖稳态，他们研究发现 MSC 外泌体处理后糖酵解酶和脂解酶的表达增加，而肝糖异生酶减少；这表明 MSCs 来源的外泌体参与葡萄糖代谢下调高血糖[13]。Gallo S 等人证实了骨髓及人肝脏干细胞的外泌体可以通过转移 miR-222 对暴露于高血糖的系膜细胞具有治疗潜力[14]。并且，血糖水平较高本身可致足细胞损伤，加剧 DN 的发展。

3.2. 抗凋亡

在 I 型 DN 小鼠中，有研究发现骨髓间充质干细胞外泌体(BMSCs-Exos)可发挥抗凋亡作用，下调 TGF-β1 表达，维持紧密连接蛋白表达，抑制肾小管上皮细胞的上皮间质转化，能够抑制尿白蛋白的进展[15]。Mao 等发现 BMSCs-Exos 的 miR-let-7a 的升高和其靶向泛素特异性蛋白酶 22 (USP22)的沉默可以降低血尿素氮(BUN)、血肌酐(Scr)，抑制肾脏细胞凋亡和氧化应激，并下调 DN 大鼠肾组织中 N-钙粘蛋白表达，从而对 DN 起保护作用[16]。Jiang 等在链脲佐菌素注射诱导的糖尿病肾病大鼠模型，利用尿源性干细胞外泌体(USCs-Exos)处理高糖培养基培养的足细胞，测试 USCs-Exos 对足细胞凋亡的保护作用，结果显示其能阻止足细胞和肾小管上皮细胞凋亡[17]。Duan 等人揭示了 USCs-Exos 分泌的 miRNA-16-5p 可抑制血管内皮生长因子 A 的表达，并且通过下调 TLR4 和 NF-κB/VEGFA 信号通路抑制高血糖诱导的小鼠足细胞凋亡，进而缓解 DN [18]。除此，Jin 等人也证实了 ADSCs-Exos 可以通过上调 miR-486 的表达，逆转高血糖诱导的 MPC5 细胞活力下降和细胞凋亡增加，抑制足细胞凋亡[19]。上述两项实验均可通过降低小鼠 BUN、Scr、尿蛋白，改善 DN 的症状。

3.3. 抗纤维化

Grange 等设计了一个实验，对链脲佐菌素诱导的糖尿病肾病小鼠给予骨髓间充质干细胞和人肝干细胞样细胞(HLSCs)外泌体持续 4 周的治疗，与对照组相比，予以外泌体治疗的小鼠组肾组织纤维化和 I 型胶原表达显著降低，肾功能指标(BUN、Scr 及尿白蛋白/尿肌酐排泄率 UACR)明显改善，这表明 MSC-exos 可通过阻止和部分逆转 DN 的纤维化来改善肾功能[20]。在最近的一项研究中，研究人员将血管紧张素转换酶 II 修饰后的间充质干细胞移植到糖尿病大鼠体内，发现与单独的 MSC 治疗相比，MSC-ACE2 更有利于降低 AngII 和增加 Ang1-7，从而通过下调 I 型胶原和纤维连接蛋白(FN)表达，抑制转化生长因子(TGF-β)/Smad 通路，减少肾小球纤维化，对 DN 具有更好的治疗效果[21]。有研究发现 MSC-exos 能通过 miRNA-451a 负调控抑制细胞周期的抑制剂 P15 和 P19，重新开始被阻断的细胞周期，逆转上皮间质转化(EMT)和肾纤维化[22]。还有研究人员证明 ADSCs-Exos 能将 miRNA-215-5p 能抑制 ZEB2 的基因转录来削弱足细胞的 EMT [23]。同时，miR-26a5p 通过靶向 TLR4 也参与了这一过程。miR-26a-5p 的过表达使 NF-κB 通路失活，下调血管内皮生长因子 a [24]。在肾纤维化小鼠模型中，miR-let7c 能通过 MSC-exos 转运到受损的肾脏，通过抑制 1 型 α1 和 IV 型 α1 胶原、TGF-β1 型受体和 α 平滑肌肌动蛋白(α-SMA)，改善肾脏结构和减少细胞外基质(ECM)沉积[25]，这有助于延缓肾纤维化的进展[26]。另一项研究也有提到，小鼠脐带间充质干细胞(UCMSC)衍生的旁分泌因子通过抑制 TGF-β1 诱导的肌成纤维细胞转分化、PI3K/Akt 及 MAPK 信号通路介导的细胞增殖，上调基质金属蛋白酶 2、9 来减少 ECM 蛋白的沉积[27]。在小鼠模型中，有研究发现人脐带间充质干细胞外泌体(UCs-Exos)通过抑制 ROS 介导的 P38MAPK/ERK 通路，从而能缓解肾间质纤维化[28]。

3.4. 抗炎及促自噬

Xiang 等人揭示 UCMSC 可减轻 DN 大鼠肾小球内皮细胞和肾小管上皮细胞的炎症反应。实验观察到 MSCs 给予组中的 IL-6、IL-1b、TNF-a 的 mRNA 表达比对照组显著降低($P < 0.05$)。为进一步验证，研究者将 MSCs 来源的外泌体与高糖处理的肾细胞共培养，其中包括 HK2 细胞、NRK-52E 细胞和 hRGE 细胞；结果显示 MSCs 来源的外泌体以剂量依赖的方式抑制高糖诱导的 TGF-b、IL-6、IL-1b 和 TNF-a 的产生。而且，在 MSCs 来源的外泌体中检测到表皮生长因子、肝细胞生长因子、血管内皮生长因子等几种因子，这表明抗炎作用是由 MSCs 来源的外泌体介导的[29]。Ebrahim 等人在链脲佐菌素诱导的糖尿病大鼠模型中证实了 MSC-exos 能增强自噬，使自噬标记物 Beclin-1、轻链-3 (LC3)显著增加，然后通过雷帕霉素(mTOR)信号通路显著恢复肾功能和结构，减缓 DN 的进展[30]。Jin 等人更进一步地发现 ADSCs-Exos 可以通过 miRNA-486 靶向抑制 Smad1 的表达，抑制 mTOR 的激活，促进足细胞自噬，抑制其凋亡，从而改善 DN [19]。

4. 目前遇到的困难

目前，许多在动物模型的研究实验均能证实 MSC-exos 可作为治疗 DN 的一种潜力手段，但现仍需要去解决的问题有：1) 探究最佳的 MSC-exos 处理和储存方式，不同方式可能影响其功能活性；2) 研究肾细胞摄取 MSC-exos 的潜在机制，并确定临床试验的首选给药途径；3) 确定 MSC-exos 给药的最佳时间窗及确定 MSC-exos 的持续时间、长期效应和最佳方案；4) 探究最佳的 MSC 来源：比如 ADSCs-Exos 比 BMSCs-Exos 能更好地促进伤口愈合[31]；与骨髓来源的 MSCs 相比，肝来源的人 MSCs 产生更多的促血管生成、抗炎和抗凋亡细胞因子[32]；5) 研究 MSC-exos 潜在的长期有害影响；6) 关于 MSC-exos 治疗 DN 的强有力的安全性和有效性临床实验。

5. 总结

多种动物模型实验及临床前试验表明不同来源的 MSC-exos 可能通过控制高血糖、抗凋亡、抗纤维化、抗炎和促自噬等多种机制延缓 DN 的进展，显现出其作为 DN 治疗新手段的巨大前景，但目前治疗机制尚未完全明确，且仍面临着不少挑战，其有效性及安全性需要更多实验去证明。MSC-exos 在 DN 中的治疗可能还有漫长的路要走，但我们期待其广泛应用于临床的一天。

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