

间充质干细胞及其外泌体在慢性肾脏病中的研究进展

石文杰¹, 郑佳新^{2*}

¹黑龙江省中医药科学院, 肾病一科, 黑龙江 哈尔滨

²黑龙江中医药大学附属第二医院肾病二科, 黑龙江 哈尔滨

收稿日期: 2025年11月25日; 录用日期: 2025年12月19日; 发布日期: 2025年12月29日

摘要

慢性肾脏病(chronic kidney disease, CKD)是一个复杂的病理生理过程, 肾脏微血管内皮细胞损伤、炎症反应、纤维化是发生CKD的主要原因, 间充质干细胞(mesenchymal stem cells, MSCs)及其外泌体(MSCs-exosomes, MSCs-EXO)因其具有免疫调节和促生存的特性, 现已成为治疗CKD的一种新兴治疗方式。它们可以通过分泌多种抗炎因子来抑制炎症的发生, 促进疾病的缓解。近年来也被广泛应用于临床。但其中许多机制尚不清楚, 需要我们进一步探索和研究。因此本文就MSCs及MSCs-EXO在CKD中的作用机制及研究进展作一综述, 供临床医师参考。

关键词

间充质干细胞, 外泌体, 治疗, 慢性肾脏病, 研究进展

Research Progress on Mesenchymal Stem Cells and Their Exosomes in Chronic Kidney Disease

Wenjie Shi¹, Jiaxin Zheng^{2*}

¹First Department of Nephrology, Heilongjiang Academy of Traditional Chinese Medicine, Harbin Heilongjiang

²Second Department of Nephrology, The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin Heilongjiang

Received: November 25, 2025; accepted: December 19, 2025; published: December 29, 2025

*通讯作者。

文章引用: 石文杰, 郑佳新. 间充质干细胞及其外泌体在慢性肾脏病中的研究进展[J]. 临床个性化医学, 2026, 5(1): 102-109. DOI: 10.12677/jcpm.2026.51016

Abstract

Chronic kidney disease (CKD) is a complex pathophysiological process, with renal microvascular endothelial cell injury, inflammatory responses, and fibrosis being the main causes of CKD. Mesenchymal stem cells (MSCs) and their exosomes (MSCs-exosomes, MSCs-EXO), due to their immunoregulatory and pro-survival properties, have become an emerging therapeutic approach for CKD. They can inhibit inflammation and promote disease remission by secreting various anti-inflammatory factors. In recent years, they have also been widely applied in clinical practice. However, many of the underlying mechanisms remain unclear and require further exploration and research. Therefore, this paper reviews the mechanisms and research progress of MSCs and MSCs-EXO in CKD, providing a reference for clinical physicians.

Keywords

Mesenchymal Stem Cells, Exosomes, Therapy, Chronic Kidney Disease, Research Progress

Copyright © 2026 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

慢性肾脏病(CKD)被定义为肾脏结构或功能异常,持续>3个月,对健康有影响。最常用的诊断标准是尿白蛋白:肌酐比值 $\geq 30 \text{ mg/g}$ 或估计肾小球滤过率(eGFR) $< 60 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ [1]。其病因复杂且存在显著地域差异与人群差异。根据 KDIGO 指南,CKD 病因可归纳为以下几类,涵盖遗传、代谢、免疫、感染及环境等多维度因素。目前慢性肾脏病的治疗目标是延缓疾病进展、控制并发症、改善生活质量并降低心血管事件风险。传统的基础和药物治疗,虽然能延缓疾病进展,但不免会有并发症的可能,迫切寻求一种新兴疗法,早期干预来改善预后。间充质干细胞(mesenchymal stem cells, MSCs)是可以从各种人体组织和器官中获得的多能基质细胞,可以自我更新并分化为多谱系细胞。MSCs 可从多种人体组织和器官获得,例如骨髓、脂肪组织、脑、肺和胰腺[2],具有多向分化潜能、高增殖能力、免疫调节和自我复制能力[3]。间充质干细胞衍生的外泌体(MSCs-exosomes, MSCs-EXO)不仅具有外泌体的优点,而且通过转移功能性货物,主要是 microRNA (miRNA)和蛋白质,复制了 MSCs 的生物学特性。MSCs-Exo 将多种生长因子和非编码 miRNA 转移到受伤的肾细胞,通过促进增殖、自噬和血管生成,抑制炎症、氧化应激、细胞凋亡、EMT 和肾小管间质纤维化来减轻肾损伤并恢复肾功能[4], MSCs-Exo 诱导的肾脏保护机制尚且不清楚,仍需进一步探索。因此本文主要总结了 MSCs-EXO 的作用机制以及 CKD 的发病机制,并且对它们的研究进展作一综述。

2. 概述

2.1. MSCs

间充质干细胞(MSCs)具有向骨、软骨、脂肪、肌肉等多种组织器官增殖能力。他们分布于身体不同的组织,如骨髓,脂肪,脐带,以及胎盘[5]。MSC 可以根据它们的来源分化为脂肪细胞、成骨细胞、软骨细胞和肌细胞。MSC 还可以产生许多生长因子和细胞因子,这些生长因子和细胞因子可调节免疫反应、

抗炎、帮助愈合、改变宿主增强反应,并在组织修复中充当成熟的功能细胞。MSC 还可以产生和释放微泡,外泌体包裹着与 MSC 功能非常相似的细胞因子/生长因子/RNA/miRNA [6]。MSC 具有免疫调节特性,取决于细胞间接触和旁分泌信号传导,特别是通过外泌体发挥免疫调节,并促进靶细胞某些功能的作用[7]。

2.2. 外泌体

外泌体也称为腔内囊泡(ILV),被包裹在单个外膜内,直径通常为 30~150 nm,由所有细胞类型分泌,存在于血浆、尿液、精液、唾液、支气管液、脑脊液(CSF)、母乳、血清、羊水、滑液、泪液、淋巴液、胆汁和胃酸中[8]。外泌体中包含多种分子,包括蛋白质、脂质、DNA、mRNA 和 miRNA [9],在这些分子中,miRNA 因其在基因表达中的调节作用而引起关注,被广泛用作生物标志物、疫苗、药物载体和治疗工具等。研究表明,外泌体不仅参与多种生理过程,例如炎症反应、皮肤创伤修复、血管生成、免疫反应和免疫监视,而且在数种疾病的病理状态中也起着重要作用[10]。另外有研究表明,来自骨髓衍生的间充质基质细胞的外泌体诱导巨噬细胞组织修复极化并促进小鼠肌腱血管生成和愈合[11];HUCMSC-EXO 已被证明在体外和体内对顺铂诱导的肾毒性具有治疗作用。顺铂是一种抗癌药物,通过氧化应激诱导肾小管上皮细胞凋亡引起肾毒性,HUCMSC-EXO 治疗降低肌酐(Cr)水平、血尿素氮(BUN) [12];hAD-MSC 利用外泌体通过 Sox9 的肾小管上皮细胞依赖性激活来减轻 AKI-CKD 转变[13]。

3. 慢性肾脏病的发病机制

慢性肾脏病(CKD)是一种全球性的公共卫生问题,是对人类健康造成严重威胁的常见疾病,发病率呈逐年上升趋势。CKD 不仅仅是一个单一的疾病状态,而是一个复杂的病理生理过程,肾脏微血管内皮细胞损伤、炎症反应、纤维化是发生 CKD 的主要原因,但在 CKD 的发展过程中,肾脏纤维化起着关键作用。现在普遍认为,肾纤维化不仅是一个静态的“疤痕”,而是一个动态过程[14],其核心特征是在持续损伤和炎症背景下,肌成纤维细胞活化并大量合成异常的细胞外基质(ECM),同时伴随肾实质细胞(肾小管、肾小球、肾血管)的损伤、萎缩和丢失,导致正常肾组织逐渐被无功能的瘢痕组织取代,肾脏结构破坏和功能进行性、不可逆性丧失。其中 ECM 过度沉积、肌成纤维细胞活化(α -SMA)以及促纤维化 TGF- β_1 的核心作用是最关键的病理特征[15]。纤维化基质沉积在慢性损伤中不受控制,破坏器官结构、功能和血流,这与丢失的肾单位一起,损害机体而最终导致肾衰竭。众多刺激因子(TGF- β_1 、WNT、CTGF)和致病因子(损伤、糖尿病、高血压)可以启动这一过程,触发机体不适应修复和炎症信号级联反应,促进间质纤维化[16]。大量研究表明,TGF- β_1 是肾脏纤维化的主要调节因子,TGF- β_1 主要由损伤组织中的炎症反应相关巨噬细胞分泌,通过与特定受体结合,可激活 STAT3、EGFR 及 JNK/Notch2 等多条信号通路,进而刺激细胞外基质(ECM)中胶原蛋白等成分的异常积聚[17]。另外,表观遗传学调控在肾脏纤维化的发生和发展中起关键作用。表观遗传修饰是指在不改变 DNA 序列的前提下,通过可遗传的机制调控基因表达或细胞表型,主要包括染色质重塑、DNA 甲基化、组蛋白乙酰化/去乙酰化以及非编码 RNA 的调控作用。这些修饰能够上调促炎和促纤维化因子(如 MCP-1、C3 和 TGF- β_1)的表达,从而延长炎症反应、促进上皮-间质转化(EMT),最终驱动肾脏纤维化的进程[18]。

4. MSCs 及 MSCs-EXO 在治疗 CKD 中的作用机制

4.1. MSCs 的作用机制

间充质干细胞(MSCs)在治疗 CKD 中主要通过多靶点、多途径的调控机制发挥作用,凭借其独特的自我更新能力、多向分化潜能以及强大的组织再生和免疫调节特性,在慢性肾脏病(CKD)治疗中展现出广

阔的应用前景。MSCs 在调控肾脏炎症反应中展现出独特的免疫调节能力,其可通过抑制树突状细胞(DC)的成熟过程来发挥关键作用。研究表明, MSCs 能够显著降低肾脏组织中 CD103 + DCs (一种具有强抗原提呈能力的 DC 亚群)的表达水平[19]。MSCs 可以通过分泌 PGE2 和 TSG-6 激活巨噬细胞中 cAMP/PKA 通路,促进 Arg1 和 IL-10 表达,抑制 iNOS 和 TNF- α [20]。此外, MSCs 的旁分泌效应是发挥抗纤维化作用的主要机制,其通过分泌多种生物活性因子(如生长因子、细胞因子等)调节肾脏微环境,抑制纤维化进程[21]。其中, HGF (肝细胞生长因子)是 MSCs 分泌的关键抗纤维化因子,可抑制肾小管上皮细胞向肌成纤维细胞转化(EMT),减少胶原沉积,并促进血管生成,改善肾脏血流灌注[22]。转化生长因子- β (TGF- β)调控: TGF- β 是纤维化的核心驱动因子, MSCs 通过分泌抗纤维化因子(如 BMP-7、Smad7)或抑制 TGF- β 信号通路,阻断其促纤维化作用[23]。其他因子:如血管内皮生长因子(VEGF)、成纤维细胞生长因子(FGF)等,可促进血管新生和肾小管修复,减轻缺血缺氧导致的纤维。

4.2. MSCs-EXO 在肾纤维化治疗中的作用机制

MSC 释放的细胞外泌体能够促进肾内皮细胞增殖并抑制细胞凋亡。BMSC-Exos 装载 CDC6、CDK8、CCNB1 mRNA,同步启动肾小管上皮细胞周期并抑制凋亡[24]; BMSC-EVs 递送抗凋亡 mRNA 或 IGF1 mRNA,在体外与体内均显著提升肾细胞存活率并加速增殖[25]。hWJMSC-Exos 通过抑制 NOX/ROS-Nrf2/ARE 轴减轻氧化损伤[26]; hUCMSC-EVs 携带线粒体靶向 Mn-SOD,直接清除自由基[27]; ADMSC-Exos 下调促凋亡蛋白、降低血肌酐和 BUN,并同步抑制 Smad3、TGF- β 及促炎因子,重塑抗炎微环境[28]。细胞外泌体还可以通过过度促进血管生成和细胞迁移来保护肾脏。例如, GDNF 高表达的 ADMSC-Exos 激活 SIRT1 信号,驱动肾小管周毛细血管再生与细胞迁移,防止微血管稀疏[29]; MSC-EXos 将足细胞凋亡率降低 70%,提升 CD31⁺/Ki-67⁺内皮面积,恢复血管生成因子表达,阻断缺血-纤维化恶性循环[30]。MSC-EXos 下调肾静脉 TNF- α 、IL-6,上调 IL-10;招募修复性 M2 巨噬细胞,使促血管生成因子表达回升,髓质氧合改善,纤维化面积减少 12%,GFR 随之提升[31]。MSC-Exos 通过 CK1 δ / β -TRCP 轴抑制 YAP,阻断 ROS-p38MAPK/ERK-RhoA/ROCK 级联,遏制纤维化进程[32];同时减少巨噬细胞聚集与 CX3CL1 表达,抑制上皮-间质转化(EMT)及毛细血管稀疏,阻止肾损伤向终末期 CKD 演变[33]。另外,已有研究表明 MSC-exos 携带的多种 miRNAs 发挥肾脏保护作用。miR-24 抑制血管炎症,加速缺血后修复[34]; miR-34c-5p 破坏 CD81-EGFR 复合物,逆转肾间质纤维化[35]; miRNA-215-5p 靶向抑制 ZEB2,改善 DN [36]; miR-451a 通过沉默 P15、P19 下调 α -SMA、上调 E-cadherin,逆转 EMT 并减轻 DN [37]。

5. MSCs 及 MSCs-EXO 在 CKD 中的研究进展

5.1. MSCs 在治疗 CKD 中的研究进展

MSCs 在合适微环境下可跨谱系分化为肾小管上皮、系膜或足细胞等多种肾脏细胞,可直接参与组织修复[38]。Morigi 等的研究进一步证实,骨髓来源 MSCs 回输后能显著改善肾功能,是促进肾小管再生与功能恢复的主力群体;相比之下,造血干细胞仅产生有限的修复效应,突出显示 MSCs 在肾脏再生中的独特优势[39]。其中糖尿病是 CKD 的主要原因,具有复杂的发病机理,在损伤的早期阶段, MSCs 可以减少对肾脏组织的免疫和炎症反应。MSCs 通过 PI3K/AKT 信号通路促进了胰岛 β 细胞增殖,并通过减轻 IL-1 和 TNF- α 的影响来改善胰岛的生长[40]。UC-MSCs 还可以通过 MAPK/ERK 信号通路介导的旁分泌作用来保护内皮细胞免受高葡萄糖损伤[41]。大量研究表明, MSCs 作为肾间质纤维化的保护介质,通过其抗纤维化活性和旁分泌机制,在 EMT 过程中发挥重要的调节作用,延缓小管 EMT,改善肾纤维化[42]。例如, Tang 等人发现 BMMSCs 治疗通过阻断腺嘌呤诱导的 CKD 中 Akt/GSK3 β /Snail 信号通路来

预防肾间质纤维化[43]。另一项研究证实, 神经胶质细胞系来源的神经营养因子修饰的 ADMSCs 通过抑制 CKD120 的 PI3K/Akt 通路抑制 EMT 和肾纤维化[44]。

5.2. MSCs-EXO 在治疗 CKD 中的研究进展

外泌体在糖尿病肾病和肾纤维化等慢性肾脏病的疾病发生发展过程中发挥着重要作用。研究表明, BMSC-Exo 的抗纤维化效应与其下调肾脏组织中多个促纤维化基因的表达密切相关[45]。其中, Exo-miR-let-7a 在 BMSCs 对糖尿病肾病(DN)的保护机制中发挥重要作用[46], 该 miRNA 通过靶向泛素特异性肽酶 22 (USP22), 参与调节 TGF- β 的表达, 进而影响 DN 的病理进展[47]。值得注意的是, TGF- β 不仅是肾纤维化的关键调控因子, 还能在肾小球硬化过程中诱导足细胞凋亡[48]。在 DN 患者模型、DN 大鼠肾组织以及高糖(HG)条件下培养的足细胞和系膜细胞中, 均一致观察到 miR-let-7a 的表达下降及 USP22 的过度表达[49]。此外, BMSC-Exo 来源的 miR-125b 可通过靶向 TRAF6/AKT 信号轴, 显著抑制高糖诱导的人胚肾上皮细胞凋亡, 并增强其自噬活性[50]。另一项体外实验证明, BMSC-Exo 中的 miR-let-7c 能够特异性地转移至受损的肾小管上皮细胞, 通过抑制 TGF- β 1 信号通路, 下调包括 I α 1 和 IV α 1 型胶原及 α -平滑肌肌动蛋白(α -SMA)在内的细胞外基质(ECM)分子表达[51]。综上所述, BMSCs 来源的外泌体可通过递送 miR-125b、miR-let-7a 和 miR-let-7c 等保护性 miRNA, 有效减轻肾小管上皮细胞的损伤, 从而抑制间质纤维化进程。

MSCs 外泌体通过多维度机制协同作用, 成为肾纤维化治疗的潜在突破方向。其优势包括低免疫原性、高稳定性和可规模化生产。目前的研究表明, 单细胞测序技术能精细解析肾脏损伤后的细胞异质性和微环境变化, 而间充质干细胞(MSCs)来源的外泌体(MSC-Exo)在修复过程中扮演着关键角色。损伤肾脏的不同细胞亚型通过表达特定的表面分子, 为 MSC-Exo 提供了精确的“地址码”。例如, 损伤的肾小管上皮细胞高表达 VCAM-1 和 ICAM-1, 它们会与 MSC-Exo 表面上相应的整合素(如 VLA-4 和 LFA-1)结合, 介导外泌体在特定部位的富集。单细胞测序揭示的 iPT 细胞高表达 VCAM1, 正印证了这一点。然而, 目前研究多基于动物模型, 临床转化仍需解决外泌体标准化制备、靶向递送效率及长期安全性等问题。未来可探索工程化改造外泌体(如过表达特定 miRNA 或蛋白), 以增强其抗纤维化效果, 并结合基因编辑技术优化治疗策略。

参考文献

- [1] Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2024 Clinical Practice Guideline. *Annals of Internal Medicine*, **178**, 705-713. <https://doi.org/10.7326/annals-24-01926>
- [2] Lin, Z., Wu, Y., Xu, Y., Li, G., Li, Z. and Liu, T. (2022) Mesenchymal Stem Cell-Derived Exosomes in Cancer Therapy Resistance: Recent Advances and Therapeutic Potential. *Molecular Cancer*, **21**, Article No. 179. <https://doi.org/10.1186/s12943-022-01650-5>
- [3] Chen, F., Chen, N., Xia, C., Wang, H., Shao, L., Zhou, C., et al. (2023) Mesenchymal Stem Cell Therapy in Kidney Diseases: Potential and Challenges. *Cell Transplantation*, **32**, 1-23. <https://doi.org/10.1177/09636897231164251>
- [4] Cao, Q., Huang, C., Chen, X. and Pollock, C.A. (2022) Mesenchymal Stem Cell-Derived Exosomes: Toward Cell-Free Therapeutic Strategies in Chronic Kidney Disease. *Frontiers in Medicine*, **9**, Article ID: 816656. <https://doi.org/10.3389/fmed.2022.816656>
- [5] Haque, N., Kasim, N.H.A. and Rahman, M.T. (2015) Optimization of Pre-Transplantation Conditions to Enhance the Efficacy of Mesenchymal Stem Cells. *International Journal of Biological Sciences*, **11**, 324-334. <https://doi.org/10.7150/ijbs.10567>
- [6] Yan, L., Li, J. and Zhang, C. (2023) The Role of MSCs and CAR-MSCs in Cellular Immunotherapy. *Cell Communication and Signaling*, **21**, Article No. 187. <https://doi.org/10.1186/s12964-023-01191-4>
- [7] Wang, S., Xu, M., Li, X., Su, X., Xiao, X., Keating, A., et al. (2018) Exosomes Released by Hepatocarcinoma Cells Endow Adipocytes with Tumor-Promoting Properties. *Journal of Hematology & Oncology*, **11**, Article No. 82.

- <https://doi.org/10.1186/s13045-018-0625-1>
- [8] Doyle, L. and Wang, M. (2019) Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. *Cells*, **8**, Article 727. <https://doi.org/10.3390/cells8070727>
 - [9] Zhang, J., Li, S., Li, L., Li, M., Guo, C., Yao, J., *et al.* (2015) Exosome and Exosomal MicroRNA: Trafficking, Sorting, and Function. *Genomics, Proteomics & Bioinformatics*, **13**, 17-24. <https://doi.org/10.1016/j.gpb.2015.02.001>
 - [10] Li, W., Pang, Y., He, Q., Song, Z., Xie, X., Zeng, J., *et al.* (2024) Exosome-Derived MicroRNAs: Emerging Players in Vitiligo. *Frontiers in Immunology*, **15**, Article ID: 1419660. <https://doi.org/10.3389/fimmu.2024.1419660>
 - [11] Zhang, M., Johnson-Stephenson, T.K., Wang, W., Wang, Y., Li, J., Li, L., *et al.* (2022) Mesenchymal Stem Cell-Derived Exosome-Educated Macrophages Alleviate Systemic Lupus Erythematosus by Promoting Efferocytosis and Recruitment of IL-17⁺ Regulatory T Cell. *Stem Cell Research & Therapy*, **13**, Article No. 484. <https://doi.org/10.1186/s13287-022-03174-7>
 - [12] Yaghoubi, Y., Movassaghpour, A., Zamani, M., Talebi, M., Mehdizadeh, A. and Yousefi, M. (2019) Human Umbilical Cord Mesenchymal Stem Cells Derived-Exosomes in Diseases Treatment. *Life Sciences*, **233**, Article 116733. <https://doi.org/10.1016/j.lfs.2019.116733>
 - [13] Zhu, F., Chong Lee Shin, O.L.S., Pei, G., Hu, Z., Yang, J., Zhu, H., *et al.* (2017) Adipose-Derived Mesenchymal Stem Cells Employed Exosomes to Attenuate AKI-CKD Transition through Tubular Epithelial Cell Dependent Sox9 Activation. *Oncotarget*, **8**, 70707-70726. <https://doi.org/10.18632/oncotarget.19979>
 - [14] Nastase, M.V., Zeng-Brouwers, J., Wygrecka, M. and Schaefer, L. (2018) Targeting Renal Fibrosis: Mechanisms and Drug Delivery Systems. *Advanced Drug Delivery Reviews*, **129**, 295-307. <https://doi.org/10.1016/j.addr.2017.12.019>
 - [15] Humphreys, B.D. (2018) Mechanisms of Renal Fibrosis. *Annual Review of Physiology*, **80**, 309-326. <https://doi.org/10.1146/annurev-physiol-022516-034227>
 - [16] He, L., Wei, Q., Liu, J., Yi, M., Liu, Y., Liu, H., *et al.* (2017) AKI on CKD: Heightened Injury, Suppressed Repair, and the Underlying Mechanisms. *Kidney International*, **92**, 1071-1083. <https://doi.org/10.1016/j.kint.2017.06.030>
 - [17] Nie, L., Liu, Y., Zhang, B. and Zhao, J. (2020) Application of Histone Deacetylase Inhibitors in Renal Interstitial Fibrosis. *Kidney Diseases*, **6**, 226-235. <https://doi.org/10.1159/000505295>
 - [18] Rodríguez-Romo, R., Berman, N., Gómez, A. and Bobadilla, N.A. (2015) Epigenetic Regulation in the Acute Kidney Injury to Chronic Kidney Disease Transition. *Nephrology*, **20**, 736-743. <https://doi.org/10.1111/nep.12521>
 - [19] Zhang, F., Wang, C., Wen, X., Chen, Y., Mao, R., Cui, D., *et al.* (2020) Mesenchymal Stem Cells Alleviate Rat Diabetic Nephropathy by Suppressing Cd103⁺ DCS-Mediated Cd8⁺ T Cell Responses. *Journal of Cellular and Molecular Medicine*, **24**, 5817-5831. <https://doi.org/10.1111/jcmm.15250>
 - [20] Choi, H., Lee, R.H., Bazhanov, N., Oh, J.Y. and Prockop, D.J. (2011) Anti-Inflammatory Protein TSG-6 Secreted by Activated MSCs Attenuates Zymosan-Induced Mouse Peritonitis by Decreasing Tlr2/NF-κB Signaling in Resident Macrophages. *Blood*, **118**, 330-338. <https://doi.org/10.1182/blood-2010-12-327353>
 - [21] Villanueva, S., Ewertz, E., Carrión, F., Tapia, A., Vergara, C., Céspedes, C., *et al.* (2011) Mesenchymal Stem Cell Injection Ameliorates Chronic Renal Failure in a Rat Model. *Clinical Science*, **121**, 489-499. <https://doi.org/10.1042/cs20110108>
 - [22] Florquin, S. and Rouschop, K.M.A. (2003) Reciprocal Functions of Hepatocyte Growth Factor and Transforming Growth Factor-B1 in the Progression of Renal Diseases: A Role for Cd44? *Kidney International*, **64**, S15-S20. <https://doi.org/10.1046/j.1523-1755.64.s86.4.x>
 - [23] Wang, J., Lin, Y., Chen, X., Liu, Y. and Zhou, T. (2022) Mesenchymal Stem Cells: A New Therapeutic Tool for Chronic Kidney Disease. *Frontiers in Cell and Developmental Biology*, **10**, Article ID: 910592. <https://doi.org/10.3389/fcell.2022.910592>
 - [24] Bruno, S., Tapparo, M., Collino, F., Chiabotto, G., Deregibus, M.C., Soares Lindoso, R., *et al.* (2017) Renal Regenerative Potential of Different Extracellular Vesicle Populations Derived from Bone Marrow Mesenchymal Stromal Cells. *Tissue Engineering Part A*, **23**, 1262-1273. <https://doi.org/10.1089/ten.tea.2017.0069>
 - [25] Bruno, S., Grange, C., Collino, F., Deregibus, M.C., Cantaluppi, V., Biancone, L., *et al.* (2012) Microvesicles Derived from Mesenchymal Stem Cells Enhance Survival in a Lethal Model of Acute Kidney Injury. *PLOS ONE*, **7**, e33115. <https://doi.org/10.1371/journal.pone.0033115>
 - [26] Zhang, G., Zou, X., Miao, S., Chen, J., Du, T., Zhong, L., *et al.* (2014) The Anti-Oxidative Role of Micro-Vesicles Derived from Human Wharton-Jelly Mesenchymal Stromal Cells through Nox2/gp91(Phox) Suppression in Alleviating Renal Ischemia-Reperfusion Injury in Rats. *PLOS ONE*, **9**, e92129. <https://doi.org/10.1371/journal.pone.0092129>
 - [27] Yao, J., Zheng, J., Cai, J., Zeng, K., Zhou, C., Zhang, J., *et al.* (2019) Extracellular Vesicles Derived from Human Umbilical Cord Mesenchymal Stem Cells Alleviate Rat Hepatic Ischemia-Reperfusion Injury by Suppressing Oxidative Stress and Neutrophil Inflammatory Response. *The FASEB Journal*, **33**, 1695-1710. <https://doi.org/10.1096/fj.201800131rr>

- [28] Lin, K., Yip, H., Shao, P., Wu, S., Chen, K., Chen, Y., *et al.* (2016) Combination of Adipose-Derived Mesenchymal Stem Cells (ADMSC) and Admsc-Derived Exosomes for Protecting Kidney from Acute Ischemia-Reperfusion Injury. *International Journal of Cardiology*, **216**, 173-185. <https://doi.org/10.1016/j.ijcard.2016.04.061>
- [29] Chen, L., Wang, Y., Li, S., Zuo, B., Zhang, X., Wang, F., *et al.* (2020) Exosomes Derived from GDNF-Modified Human Adipose Mesenchymal Stem Cells Ameliorate Peritubular Capillary Loss in Tubulointerstitial Fibrosis by Activating the SIRT1/eNOS Signaling Pathway. *Theranostics*, **10**, 9425-9442. <https://doi.org/10.7150/thno.43315>
- [30] Jiang, Z., Liu, Y., Niu, X., Yin, J., Hu, B., Guo, S., *et al.* (2016) Exosomes Secreted by Human Urine-Derived Stem Cells Could Prevent Kidney Complications from Type I Diabetes in Rats. *Stem Cell Research & Therapy*, **7**, Article No. 24. <https://doi.org/10.1186/s13287-016-0287-2>
- [31] Eirin, A., Zhu, X., Ebrahimi, B., Krier, J.D., Riester, S.M., Van Wijnen, A.J., *et al.* (2015) Intrarenal Delivery of Mesenchymal Stem Cells and Endothelial Progenitor Cells Attenuates Hypertensive Cardiomyopathy in Experimental Renovascular Hypertension. *Cell Transplantation*, **24**, 2041-2053. <https://doi.org/10.3727/096368914x685582>
- [32] Shi, Z., Wang, Q., Zhang, Y. and Jiang, D. (2020) Extracellular Vesicles Produced by Bone Marrow Mesenchymal Stem Cells Attenuate Renal Fibrosis, in Part by Inhibiting the Rhoa/rock Pathway, in a UUO Rat Model. *Stem Cell Research & Therapy*, **11**, Article No. 253. <https://doi.org/10.1186/s13287-020-01767-8>
- [33] Zou, X., Zhang, G., Cheng, Z., Yin, D., Du, T., Ju, G., *et al.* (2014) Microvesicles Derived from Human Wharton's Jelly Mesenchymal Stromal Cells Ameliorate Renal Ischemia-Reperfusion Injury in Rats by Suppressing Cx3cl1. *Stem Cell Research & Therapy*, **5**, Article No. 40. <https://doi.org/10.1186/scrt428>
- [34] Maegdefessel, L., Spin, J.M., Raaz, U., Eken, S.M., Toh, R., Azuma, J., *et al.* (2014) miR-24 Limits Aortic Vascular Inflammation and Murine Abdominal Aneurysm Development. *Nature Communications*, **5**, Article No. 5214. <https://doi.org/10.1038/ncomms6214>
- [35] Hu, X., Shen, N., Liu, A., Wang, W., Zhang, L., Sui, Z., *et al.* (2022) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-34c-5p Ameliorates RIF by Inhibiting the Core Fucosylation of Multiple Proteins. *Molecular Therapy*, **30**, 763-781. <https://doi.org/10.1016/j.ymthe.2021.10.012>
- [36] Jin, J., Shi, Y., Gong, J., Zhao, L., Li, Y., He, Q., *et al.* (2019) Exosome Secreted from Adipose-Derived Stem Cells Attenuates Diabetic Nephropathy by Promoting Autophagy Flux and Inhibiting Apoptosis in Podocyte. *Stem Cell Research & Therapy*, **10**, Article No. 95. <https://doi.org/10.1186/s13287-019-1177-1>
- [37] Zhong, L., Liao, G., Wang, X., Li, L., Zhang, J., Chen, Y., *et al.* (2018) Mesenchymal Stem Cells-Microvesicle-miR-451a Ameliorate Early Diabetic Kidney Injury by Negative Regulation of P15 and P19. *Experimental Biology and Medicine*, **243**, 1233-1242. <https://doi.org/10.1177/1535370218819726>
- [38] Frescaline, G., Boudierlique, T., Huynh, M.B., Papy-Garcia, D., Courty, J. and Albanese, P. (2012) Glycosaminoglycans Mimetics Potentiate the Clonogenicity, Proliferation, Migration and Differentiation Properties of Rat Mesenchymal Stem Cells. *Stem Cell Research*, **8**, 180-192. <https://doi.org/10.1016/j.scr.2011.09.005>
- [39] Morigi, M., Imberti, B., Zoja, C., Corna, D., Tomasoni, S., Abbate, M., *et al.* (2004) Mesenchymal Stem Cells Are Renotropic, Helping to Repair the Kidney and Improve Function in Acute Renal Failure. *Journal of the American Society of Nephrology*, **15**, 1794-1804. <https://doi.org/10.1097/01.asn.0000128974.07460.34>
- [40] Gao, X., Song, L., Shen, K., Wang, H., Qian, M., Niu, W., *et al.* (2014) Bone Marrow Mesenchymal Stem Cells Promote the Repair of Islets from Diabetic Mice through Paracrine Actions. *Molecular and Cellular Endocrinology*, **388**, 41-50. <https://doi.org/10.1016/j.mce.2014.03.004>
- [41] Zang, L., Li, Y., Hao, H., Liu, J., Cheng, Y., Li, B., *et al.* (2022) Efficacy and Safety of Umbilical Cord-Derived Mesenchymal Stem Cells in Chinese Adults with Type 2 Diabetes: A Single-Center, Double-Blinded, Randomized, Placebo-Controlled Phase II Trial. *Stem Cell Research & Therapy*, **13**, Article No. 180. <https://doi.org/10.1186/s13287-022-02848-6>
- [42] Zhuang, Q., Ma, R., Yin, Y., Lan, T., Yu, M. and Ming, Y. (2019) Mesenchymal Stem Cells in Renal Fibrosis: The Flame of Cytotherapy. *Stem Cells International*, **2019**, 1-18. <https://doi.org/10.1155/2019/8387350>
- [43] Tang, H., Zhang, P., Zeng, L., Zhao, Y., Xie, L. and Chen, B. (2024) Retraction Note: Mesenchymal Stem Cells Ameliorate Renal Fibrosis by Galectin-3/Akt/GSK3 β /snail Signaling Pathway in Adenine-Induced Nephropathy Rat. *Stem Cell Research & Therapy*, **15**, Article No. 52. <https://doi.org/10.1186/s13287-024-03668-6>
- [44] Li, S., Wang, Y., Wang, Z., Chen, L., Zuo, B., Liu, C., *et al.* (2021) Enhanced Renoprotective Effect of GDNF-Modified Adipose-Derived Mesenchymal Stem Cells on Renal Interstitial Fibrosis. *Stem Cell Research & Therapy*, **12**, Article No. 27. <https://doi.org/10.1186/s13287-020-02049-z>
- [45] Grange, C., Tritta, S., Tapparo, M., Cedrino, M., Tetta, C., Camussi, G., *et al.* (2019) Stem Cell-Derived Extracellular Vesicles Inhibit and Revert Fibrosis Progression in a Mouse Model of Diabetic Nephropathy. *Scientific Reports*, **9**, Article No. 4468. <https://doi.org/10.1038/s41598-019-41100-9>
- [46] Mao, R., Shen, J. and Hu, X. (2023) Retraction Notice to "BMSCs-Derived Exosomal MicroRNA-Let-7a Plays a Protective

- Role in Diabetic Nephropathy via Inhibition of USP22 Expression” [Life Sci. 268 (2021) 118937]. *Life Sciences*, **318**, Article 121422. <https://doi.org/10.1016/j.lfs.2023.121422>
- [47] Huang, K., Chen, C., Hao, J., Huang, J., Liu, P. and Huang, H. (2015) Ages-Rage System Down-Regulates Sirt1 through the Ubiquitin-Proteasome Pathway to Promote FN and Tgf-B1 Expression in Male Rat Glomerular Mesangial Cells. *Endocrinology*, **156**, 268-279. <https://doi.org/10.1210/en.2014-1381>
- [48] Wu, J., Zheng, C., Fan, Y., Zeng, C., Chen, Z., Qin, W., *et al.* (2014) Downregulation of Microrna-30 Facilitates Podocyte Injury and Is Prevented by Glucocorticoids. *Journal of the American Society of Nephrology*, **25**, 92-104. <https://doi.org/10.1681/asn.2012111101>
- [49] Yan, N., Wen, L., Peng, R., Li, H., Liu, H., Peng, H., *et al.* (2016) Naringenin Ameliorated Kidney Injury through Let-7a/tgfb1 Signaling in Diabetic Nephropathy. *Journal of Diabetes Research*, **2016**, Article ID: 8738760. <https://doi.org/10.1155/2016/8738760>
- [50] Cai, X., Zou, F., Xuan, R. and Lai, X. (2021) Exosomes from Mesenchymal Stem Cells Expressing Microribonucleic Acid-125b Inhibit the Progression of Diabetic Nephropathy via the Tumour Necrosis Factor Receptor-Associated Factor 6/Akt Axis. *Endocrine Journal*, **68**, 817-828. <https://doi.org/10.1507/endocrj.ej20-0619>
- [51] Wang, B., Yao, K., Huuskes, B.M., Shen, H., Zhuang, J., Godson, C., *et al.* (2016) Mesenchymal Stem Cells Deliver Exogenous Microrna-Let7c via Exosomes to Attenuate Renal Fibrosis. *Molecular Therapy*, **24**, 1290-1301. <https://doi.org/10.1038/mt.2016.90>