中国临床研究 Chin J Clin Res, September 2025, Vol.38, No.9
Cite as: Liu YX, Tang W. Mesenchymal stem cell therapy for diabetic kidney disease [J]. Chin J Clin Res, 2025, 38(9):1301-1305.

DOI: 10.13429/j.cnki.cjcr.2025.09.001

Mesenchymal stem cell therapy for diabetic kidney disease

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Abstract: Diabetic kidney disease (DKD) is a common and rapidly progressing microvascular complication in patients with diabetes, and it can develop to end-stage renal disease (ESRD) in severe cases. The current treatment mainly focuses on controlling blood sugar and blood pressure and using kidney - protecting drugs, which it can delay the progression of the disease, but it is difficult to prevent its progression. In recent years, mesenchymal stem cells (MSCs) have emerged as a novel approach for DKD treatment due to their low immunogenicity, multipotent differentiation potential, and rich paracrine functions. Researches indicate that MSCs can exert renoprotective effects through a multi-target mechanism, including regulating macrophage polarization, inhibiting the transforming growth factor (TFG) -β/ small mother against decapentaplegic (Smad) and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) signaling pathways, upregulating the nuclear factor erythroid 2 - related factor 2 (Nrf2) antioxidant pathway, maintaining mitochondrial function, restoring autophagy activity, and reversing the renal tubular epithelial-mesenchymal transition (EMT) process. In particular, MSCs-derived exosomes, characterized by stability, low immunogenicity, and easy storability, may offer a new direction for cell-free therapy. In animal models and early clinical studies, MSCs have demonstrated significant efficacy in improving proteinuria, alleviating renal tubulointerstitial fibrosis, and delaying renal function decline. Although the preliminary results are encouraging, further research and optimization are needed to address long-term safety, standardization of treatment protocols, and individualized delivery strategies. With the understanding of the mechanisms deepens and clinical techniques improve, MSCs and their derived exosomes hold promise for providing more precise and controllable treatment options for DKD.

Keywords: Diabetic kidney disease; Mesenchymal stem cells; Exosomes; Immunomodulation; Mitochondrial function

Diabetic kidney disease (DKD) is the most common and severe microvascular complication of diabetes, and a major cause of end-stage renal disease (ESRD). The pathogenesis of DKD involves multiple mechanisms, including chronic inflammation, oxidative stress, accumulation of advanced glycation end products (AGEs), autophagy dysfunction, and renal fibrosis [1]. Current treatments mainly rely on controlling blood glucose, blood pressure, and blood lipids, as well as the use of renin-angiotensin system (RAS) inhibitors and sodium-glucose linked-transporter-2 (SGLT2) inhibitors [2]. However, most treatments only delay disease progression rather than prevent it. Mesenchymal stem cells (MSCs), which have multi-target effects, show promising potential in DKD therapy due to their roles in immune regulation, antioxidation, and anti-fibrosis [4-5].

1 MSCs Source and Biological Characteristics

MSCs are a type of adult stem cell with broad sources, self-renewal ability, and multi-lineage differentiation potential, and they are widely found in bone marrow, adipose tissue, umbilical cord, placenta, and other tissues [6-7]. MSCs from different sources have distinct characteristics in terms of proliferation ability, immunogenicity, and methods of collection:

(1) Bone marrow-derived MSCs were the first studied and have anti-apoptotic and anti-fibrotic effects [4], but their collection process is highly invasive and the quality

depends on the donor's condition.

(2) Adipose-derived MSCs are abundant, easily accessible, and have strong in vitro expansion ability. They can protect renal function by inhibiting oxidative stress and inflammation [8].

(3) Umbilical cord-derived MSCs are simple to obtain and have low immunogenicity. They can significantly reduce inflammation and fibrosis in DKD models [9].

(4) Non-conventional sources of MSCs, such as urine and dental pulp, can be obtained with less invasiveness and also show certain renal protective effects [10-11].

The diverse sources of cells provide potential for personalized cell therapy for DKD.

2 MSCs Mechanisms of Improving DKD

Although the application of MSCs in treating DKD is promising, its mechanisms of action are complex and not fully elucidated. MSCs primarily exert their therapeutic effects through two main pathways: homing differentiation and paracrine signaling. However, the homing efficiency in kidney tissues is limited, so the therapeutic effects are more dependent on their paracrine functions, including immune regulation, anti-inflammatory, antioxidant, and regenerative effects [12]. Various growth factors, cytokines, and exosomes secreted by MSCs play key roles in regulating the pathological processes of DKD, influencing aspects such as apoptosis, autophagy, inflammation, and fibrosis. In particular, exosomes secreted by MSCs are considered important mediators of intercellular communication, as they can carry mRNA, microRNA (miR), and proteins, stably transmitting information and regulating the function of recipient cells [13]. Exosomes, as acellular therapeutic carriers, offer advantages such as small size, easy storage, and low immunogenicity, and are currently regarded as one of the important "substitutes" through which MSCs exert their effects. Overall, current research focuses on the following aspects to explore the protective mechanisms of MSCs in DKD.

2.1 Anti-inflammatory Effects and Immune Regulation

The onset of DKD is accompanied by chronic inflammation. Dysregulated glucose metabolism and hemodynamic abnormalities can activate kidney resident cells to release pro-inflammatory mediators, such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), which lead to immune cell (macrophages, T cells, etc.) infiltration into kidney tissues, exacerbating kidney damage [12]. In this inflammatory environment, MSCs exhibit potent immune-regulatory capabilities. On one hand, MSCs, when stimulated by inflammation, secrete a variety of anti-inflammatory cytokines and growth factors, thereby reducing local and systemic levels of inflammation [14]. An experimental study has confirmed that in type 2 diabetic rats, the infusion of adipose-derived MSCs can suppress pro-inflammatory factors, such as IL-6, IL-1β, and TNF-α, in kidney tissues, while inducing the production of the anti-inflammatory factor IL-10, significantly improving the kidney's inflammatory microenvironment [15]. On the other hand, MSCs can also influence immune cell functions through intercellular interactions, such as inhibiting the activation of M1-type (pro-inflammatory) macrophages and promoting their polarization toward the M2-type (anti-inflammatory, reparative). One study reported that miR-146a-5p in MSC-derived exosomes could downregulate tumor necrosis factor receptor-associated factor 6 (TRAF6) and signal transducer and activator of transcription 1 (STAT1) signaling in macrophages, thereby promoting M2 polarization and alleviating inflammatory damage in DKD mice [9]. Moreover, MSC therapy can reduce the infiltration of activated $CD8^+$T lymphocytes in kidney tissues and may modulate the Th17/Treg balance via the programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway. For example, placenta-derived MSCs in diabetic rats have been found to increase the Treg population and decrease the proportion of pathogenic Th17 cells, thereby protecting kidney function [16]. It is noteworthy that exosomes secreted by MSCs also play a significant role in immune regulation. Human umbilical cord MSC-derived exosomes are rich in miR-22-3p [17] and miR-342-3p [18], which can target and inhibit the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in podocytes and kidney tissues under hyperglycemic conditions, reducing the damage caused by inflammatory cell death (pyroptosis) to the kidneys [19]. Overall, MSCs alleviate the inflammatory response in DKD through multiple pathways, including the secretion of anti-inflammatory factors, induction of macrophage polarization, and modulation of T cell subsets, thereby exerting therapeutic effects from an immune perspective.

2.2 Antioxidant Stress and Mitochondrial Protection

In a hyperglycemic state, excessive reactive oxygen species (ROS) production and insufficient antioxidant defense lead to a significant increase in kidney oxidative stress levels, which is one of the key drivers of DKD progression. The sources of ROS include glucose metabolism disorders, accumulation of advanced glycation end products (AGEs), activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and mitochondrial dysfunction. The body's antioxidant transcription factor, nuclear factor-erythroid 2-related factor 2 (Nrf2), plays a critical role in kidney protection, as it can induce the expression of various antioxidant enzymes to alleviate oxidative damage [20]. Studies have found that MSCs treatment can reduce ROS accumulation in the kidney tissues of diabetic mouse models and upregulate Nrf2 pathway activity [21]. For example, exosomes derived from adipose MSCs activate the Nrf2/Kelch-like ECH-associated protein 1 (Keap1) pathway by downregulating the family with sequence similarity 129 member B (FAM129B), thereby reducing oxidative stress damage in mesangial cells and podocytes [8]. In addition to clearing excessive ROS, MSCs can also improve mitochondrial dysfunction caused by oxidative stress. MSCs have been shown to reduce kidney damage and inflammation by transplanting healthy mitochondria

into damaged renal tubular epithelial cells [22]. Furthermore, MSCs can upregulate mitochondrial biogenesis-related proteins, such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), to reverse mitochondrial dysfunction in diabetes [23]. It has been reported that exosomes secreted by MSCs carry miR-204, which can inhibit the activity of key methyltransferases and repair mitochondrial dysfunction at the epigenetic level [24]. In conclusion, MSCs not only directly clear and combat ROS but also protect DKD kidneys from oxidative damage through the activation of endogenous antioxidant pathways and maintenance of mitochondrial function.

2.3 Autophagy Regulation, Anti-apoptosis, and Anti-fibrosis

Autophagy is an essential protective mechanism for cells to clear damaged proteins and organelles. In the diabetic environment, autophagy is often impaired, thereby exacerbating kidney cell damage. In DKD models, abnormal autophagy has been observed in both podocytes and renal tubular epithelial cells, contributing to disease development. MSCs exert kidney protective effects by regulating the autophagy process [25]. Additionally, components in MSC exosomes can influence autophagy signaling: studies have reported that MSC exosomes alleviate DKD renal fibrosis through the miR-99b-5p/mammalian target of rapamycin (mTOR)/autophagy axis [26]. It is noteworthy that the balance between autophagy and apoptosis is crucial for cell survival. When autophagy is insufficient, cells are more likely to undergo apoptosis. MSCs have been shown to have anti-apoptotic effects in multiple studies: they can secrete epidermal growth factor (EGF) to protect podocytes, reduce high-glucose-induced podocyte apoptosis, downregulate pro-apoptotic proteins (such as Bax, Caspase-3), and upregulate anti-apoptotic proteins such as B-cell lymphoma-2 (Bcl-2), thus maintaining the survival of glomerular and renal tubular cells [27]. At the same time, MSCs can resist high-glucose-induced apoptosis through the activation of the Akt/Nrf2 pathway [20,28]. MSC exosomes also play a role in anti-apoptosis: for example, miR-16-5p in human urine-derived stem cell exosomes can protect podocytes, reduce their apoptosis, and improve the glomerular filtration barrier; exosomes derived from MSCs carrying miR-424-5p can simultaneously inhibit high-glucose-induced renal tubular epithelial cell apoptosis and epithelial-to-mesenchymal transition (EMT), thus preventing progressive injury in DKD [30-31]. Renal fibrosis is a core and irreversible pathological change in the late stage of DKD, caused by excessive extracellular matrix (ECM) deposition and tissue sclerosis. Hyperglycemia and inflammatory mediators can induce renal EMT, promote myofibroblast generation, and drive fibrosis development. The mechanisms of MSCs in anti-fibrosis mainly involve the inhibition of pro-fibrotic signaling pathways. The transforming growth factor (TGF)-β/small mother against decapentaplegic (Smad) pathway plays a key role in DKD fibrosis: overexpression of TGF-β1 activates Smad2/3, leading to the synthesis of large amounts of collagen and fibronectin. Animal experiments by Rafiee *et al.* [32] showed that MSC treatment can downregulate TGF-β1 levels in the kidneys of DKD rats and reduce Smad3 phosphorylation, significantly improving renal tissue fibrosis. In addition to the classical TGF-β pathway, MSCs and their exosomes can influence other fibrosis-related pathways. For instance, recent studies have found that exosomes from human umbilical MSCs can inhibit the Hedgehog/Smoothened signaling pathway, reducing renal tubular epithelial cell EMT, and alleviating kidney fibrosis in diabetic mice [33]. Furthermore, exosome miRs (such as miR-424-5p, miR-16-5p) mentioned above, through multi-target synergy, directly reduce the formation of myofibroblast phenotypes such as α-smooth muscle actin (SMA) and restore the expression of epithelial markers such as E-cadherin [30]. Thus, MSCs intervene in the pathological process of DKD through multiple mechanisms, including enhancing autophagy, inhibiting apoptosis, and blocking pro-fibrotic signaling [31].

2.4 Promoting Angiogenesis and Renal Tissue Repair

Kidney microcirculation damage is a key characteristic of DKD, and promoting the regeneration of damaged blood vessels is crucial for improving renal function. MSCs and their secreted products show great potential in promoting angiogenesis. Studies have shown that conditioning MSC culture medium can protect damaged vascular endothelial cells. In a DKD rat model, after umbilical MSC treatment, vascular endothelial growth factor (VEGF), platelet endothelial cell adhesion molecule-1 (PECAM-1), von Willebrand factor (vWF), and other angiogenesis-related indicators in renal tissue were significantly upregulated, and capillary density increased, suggesting an improvement in blood supply [34]. In-depth mechanistic studies revealed that MSC-derived exosomes play a key role in promoting vascular regeneration: they are rich in VEGF and other angiogenic signals that can stimulate endothelial cell proliferation and angiogenesis. For example, high levels of VEGF were detected in exosomes from human urine-derived stem cells, which are believed to be related to their function in promoting vascular reconstruction in damaged tissues [35]. In contrast, some studies noted that miR-15b-5p in MSCs protects against abnormal neovascularization by downregulating the VEGF-pyruvate dehydrogenase kinase 4 (PDK4) axis in DKD podocytes [36]. Therefore, MSCs and their exosomes have a bidirectional regulatory effect on angiogenesis in DKD kidneys: they can promote beneficial vascular regeneration by providing angiogenic stimuli to maintain the renal microvascular network; at the same time, components like miR can inhibit abnormal pathological angiogenesis and endothelial dysfunction, ultimately protecting the kidney vascular system.

3 Challenges and Clinical Translation Prospects

MSCs offer new approaches and possibilities for the treatment of DKD due to their multiple functions,

including immune modulation, antioxidant properties, and regenerative promotion. In numerous animal studies and preliminary clinical trials (such as the NEPHSTROM study), MSCs therapy has shown positive effects in reducing urinary protein, improving renal function, and alleviating tissue lesions. However, MSC therapy still faces numerous challenges in terms of routine clinical application. First, MSCs have a low survival and engraftment rate in the recipient's body, and improving their efficiency in reaching and staying at the lesion site is a key challenge. Second, MSCs from different sources exhibit functional differences, and factors such as the donor's disease status and age may affect cell quality. Therefore, optimizing the cell source and *in vitro* culture conditions is necessary to achieve the best therapeutic effect. Third, allogeneic MSCs transplantation may induce immune rejection. Although MSCs themselves have low immunogenicity, safety concerns still need to be addressed. Future studies should focus on determining the optimal administration route, dose, and timing of MSCs therapy through more clinical trials, as well as long-term follow-up on its efficacy and safety. Notably, MSCs-derived exosomes and other acellular therapies are rapidly developing and may help overcome some of the limitations of live cell therapies. In conclusion, with further research into the mechanisms of MSCs and the accumulation of clinical experience, MSC therapy is expected to become more effective and feasible, providing safer and more efficient personalized treatment strategies for DKD patients.

Conflict of Interest None

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Submission received: 2025-08-06/ **Revised:** 2025-08-23

·学术前沿·

间充质干细胞治疗糖尿病肾病

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摘要：糖尿病肾病（DKD）是糖尿病患者常见且进展迅速的微血管并发症，严重者可发展至终末期肾病（ESRD）。现有治疗以控制血糖、血压及使用肾脏保护药物为主，虽能延缓病情，但难以阻断疾病进展。近年来，间充质干细胞（MSCs）因其低免疫原性、多向分化潜能及丰富的旁分泌功能，成为DKD治疗的新兴候选手段。研究表明，MSCs可通过多靶点机制发挥作用，包括调节巨噬细胞极化、抑制转化生长因子（TGF）-β/果蝇母本抗生存因子（Smad）及核苷酸结合寡聚化结构域样受体蛋白3（NLRP3）信号通路、上调核因子E2相关因子2（Nrf2）抗氧化通路、维持线粒体功能、恢复自噬活性以及逆转肾小管上皮-间质转化（EMT）过程。尤其是MSCs分泌的外泌体（exosomes），因其稳定、免疫原性低、易储存等特点，为无细胞治疗提供了新方向。在动物模型和早期临床研究中，MSCs已显示出改善蛋白尿、减轻肾小管间质纤维化和延缓肾功能下降的显著疗效。尽管前期成果令人鼓舞，其长期安全性、治疗方案标准化及个体化递送策略仍需进一步研究与优化。随着对其机制认识的深入和临床技术的改进，MSCs及其来源的外泌体有望为DKD提供更精准、可控的治疗选择。

关键词：糖尿病肾病；间充质干细胞；外泌体；免疫调节；线粒体功能
中图分类号：R587.2　**文献标识码：**A　**文章编号：**1674-8182（2025）09-1301-05

Mesenchymal stem cell therapy for diabetic kidney disease

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Abstract: Diabetic kidney disease (DKD) is a common and rapidly progressing microvascular complication in patients with diabetes, and it can develop to end-stage renal disease (ESRD) in severe cases. The current treatment mainly focuses on controlling blood sugar and blood pressure and using kidney-protecting drugs, which can delay the progression of the disease, but it is difficult to prevent its progression. In recent years, mesenchymal stem cells (MSCs) have emerged as a novel approach for DKD treatment due to their low immunogenicity, multipotent differentiation potential, and rich paracrine functions. Researches indicate that MSCs can exert renoprotective effects through a multi-target mechanism, including regulating macrophage polarization, inhibiting the transforming growth

DOI:10.13429/j.cnki.cjcr.2025.09.001
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出版日期：2025-09-20

QR code for English version

factor (TFG)-β/ small mother against decapentaplegic (Smad) and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) signaling pathways, upregulating the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway, maintaining mitochondrial function, restoring autophagy activity, and reversing the renal tubular epithelial-mesenchymal transition (EMT) process. In particular, MSCs-derived exosomes, characterized by stability, low immunogenicity, and easy storability, may offer a new direction for cell-free therapy. In animal models and early clinical studies, MSCs have demonstrated significant efficacy in improving proteinuria, alleviating renal tubulointerstitial fibrosis, and delaying renal function decline. Although the preliminary results are encouraging, further research and optimization are needed to address long-term safety, standardization of treatment protocols, and individualized delivery strategies. With the understanding of the mechanisms deepens and improvement of clinical techniques, MSCs and their derived exosomes hold promise for providing more precise and controllable treatment options for DKD.

Keywords: Diabetic kidney disease; Mesenchymal stem cells; Exosomes; Immunomodulation; Mitochondrial function

糖尿病肾病(diabetic kidney disease,DKD)是糖尿病最常见且严重的微血管并发症,也是终末期肾病(end-stage renal disease,ESRD)的主要原因,其发病涉及慢性炎症、氧化应激、晚期糖基化终产物(advanced glycation end products,AGEs)积聚、自噬障碍及肾脏纤维化等多重机制[1]。现有治疗主要依赖血糖、血压、血脂控制及肾素-血管紧张素系统(renin-angiotensin system,RAS)抑制剂、钠-葡萄糖协同转运蛋白2(sodium-glucose linked transporter-2, SGLT2)抑制剂等药物[2-3],但大多只能延缓而难以阻止病情进展。而具有多靶点作用的间充质干细胞(mesenchymal stem cells,MSCs)因其在免疫调节、抗氧化、抗纤维化等方面的作用,可成为DKD治疗中前景广阔的新策略[4-5]。

1 MSCs的来源与生物学特性

MSCs是一类来源广泛、具有自我更新和多向分化潜能的成体干细胞,广泛存在于骨髓、脂肪、脐带、胎盘等组织[6-7]。不同来源的MSCs在增殖能力、免疫原性及获取方式上各有特点:骨髓来源MSCs研究最早,具备抗凋亡和抗纤维化作用[4],但其获取过程侵入性强且供者条件影响质量;脂肪来源MSCs数量丰富、易获取、体外扩增能力强,可通过抑制氧化应激和炎症保护肾功能[8];脐带来源MSCs取材简便、免疫原性低,在DKD模型中可显著减轻炎症和纤维化[9]。尿液、牙髓等非常规来源MSCs获取更微创,也显示一定肾脏保护作用[10-11]。多样化的细胞来源为DKD的个体化细胞治疗提供了可能。

2 MSCs改善DKD的作用机制

虽然MSCs治疗DKD的应用前景令人期待,但其作用机制复杂多样,尚未完全阐明。MSCs主要通过归巢分化和旁分泌两大途径发挥疗效,但在肾组织中的归巢效率有限,因此更多依赖其旁分泌作用,包括免疫调节、抗炎、抗氧化、促再生等[12]。MSCs分泌的多种生长因子、细胞因子以及外泌体在调节DKD病理过程中发挥关键作用,可影响细胞凋亡、自噬、炎症和纤维化等环节。特别是MSCs分泌的外泌体被认为是细胞间通讯的重要媒介,能够携带信使RNA(messenger RNA, mRNA)、微小RNA(micro-RNA,miR)和蛋白质等,稳定地传递信息并调控受体细胞功能[13]。外泌体作为无细胞治疗载体具有体积小、易储存、免疫原性低等优势,目前被视为MSCs发挥疗效的重要"替身"之一。总体而言,当前研究重点聚焦于以下几个方面来探讨MSCs对DKD的保护作用机制。

2.1 *抗炎作用与免疫调节* DKD的发生伴随着慢性炎症反应,血糖代谢紊乱和血流动力学异常可激活肾脏固有细胞释放促炎介质[如白细胞介素(interleukin,IL)-1β、IL-6、肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)和单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)],导致免疫细胞(巨噬细胞、T细胞等)浸润肾组织,加重肾损伤[12]。MSCs在这种炎症环境中展现出强大的免疫调控能力。一方面,MSCs受炎症刺激可分泌多种抗炎细胞因子和生长因子,从而降低局部和系统性炎症水平[14]。实验研究证实,在2型糖尿病大鼠中,输注脂肪MSCs可抑制肾组织中IL-6、IL-1β、TNF-α等促炎因子,同时诱导抗炎因子IL-10的产生,明显改善了肾脏炎症微环境[15]。另一方面,MSCs还能通过细胞间相互作用影响免疫细胞的功能,例如抑制巨噬细胞M1型(促炎型)活化并促进其向M2型(抗炎修复型)极化。有研究报道,MSC来源外泌体中的miR-146a-5p可下调巨噬细胞内的肿瘤坏死因子受体相关因子6(TNF receptor-associated factor 6,TRAF6)/信号转导及转录激活因子1(signal transducer and activator of transcription 1, STAT1)信号,从而促进M2型极化,减轻DKD小鼠的炎症损伤[9]。此外,MSCs治疗还能降

低肾组织中活化的$CD8^+$T淋巴细胞浸润，并可能通过程序性死亡蛋白1（programmed cell death protein-1，PD-1）/程序性死亡配体1（programmed cell death-ligand 1，PD-L1）途径调整辅助性T细胞17型（T helper 17，Th17）/调节性T细胞（regulatory T，Treg）。例如，胎盘来源MSCs在糖尿病大鼠中就被发现可提高Treg比例、降低致病性Th17细胞比例，从而保护肾功能[16]。值得一提的是，MSCs分泌的外泌体在免疫调节中也功不可没。人脐带MSCs外泌体富含miR-22-3p[17]、miR-342-3p[18]，可靶向抑制高糖环境下足细胞和肾组织中的核苷酸结合寡聚化结构域样受体蛋白3（nucleotide-binding oligomerization domain-like receptor protein 3，NLRP3）炎症小体，减少炎症性细胞死亡（焦亡）对肾脏的损害[19]。总体而言，MSCs通过多途径协同减轻DKD的炎症反应，包括分泌抗炎因子、诱导巨噬细胞极化以及影响T细胞亚群，从免疫层面发挥了治疗效应。

2.2 抗氧化应激与线粒体保护 高血糖状态下过量活性氧（reactive oxygen species，ROS）的产生和抗氧化防御不足导致肾脏氧化应激水平显著升高，是推动DKD进展的重要驱动力之一。ROS的来源包括葡萄糖代谢紊乱、AGEs积累、还原型烟酰胺腺嘌呤二核苷酸磷酸（reduced nicotinamide adenine dinucleotide phosphate，NADPH）氧化酶激活以及线粒体功能障碍等多条途径。机体抗氧化转录因子核因子E2相关因子2（nuclear factor-erythroid 2-related factor 2，Nrf2）在肾脏保护中发挥关键作用，它可诱导多种抗氧化酶表达来减轻氧化损伤[20]。研究发现，MSCs治疗能够减轻糖尿病模型小鼠肾组织的ROS积累并上调Nrf2通路活性[21]。例如，脂肪MSC来源的外泌体可通过靶向下调序列相似性129家族成员B（family with sequence similarity 129 member B，FAM129B）而激活Nrf2/Kelch样ECH关联蛋白1（Kelch-like ECH-associated protein 1，Keap1）途径，减轻系膜细胞和足细胞的氧化应激损伤[8]。除了清除过多ROS，MSCs还可以改善氧化应激导致的线粒体功能紊乱。MSCs被证明可通过移植健康线粒体至受损肾小管上皮细胞，从而减轻肾损伤及炎症状态[22]。此外，MSCs还能上调线粒体生物发生相关蛋白，如腺苷酸活化蛋白激酶（AMP-activated protein kinase，AMPK）、过氧化物酶体增殖物激活受体-γ辅激活因子1-α（peroxisome proliferator-activated receptor gamma coactivator 1-alpha，PGC-1α）等的水平，逆转糖尿病状态下线粒体功能低下的状况[23]。有报道指出，MSCs分泌的外泌体携带的miR-204能够抑制关键甲基转移酶的活性，从表观遗传层面修复线粒体功能障碍[24]。总之，MSCs一方面直接清除和对抗ROS，另一方面通过激活内源性抗氧化通路和维护线粒体功能，从多个层面保护DKD肾脏免受氧化损伤。

2.3 自噬调控、抗凋亡及抗纤维化作用 自噬是细胞清除损伤蛋白和细胞器的重要保护机制。在糖尿病环境中，自噬功能往往受损，从而加剧肾脏细胞损伤。在DKD模型中，足细胞和肾小管上皮细胞均观察到自噬异常，参与疾病发生。MSCs可以通过调控自噬过程来发挥肾保护作用[25]。此外，MSCs外泌体中的成分也能影响自噬信号：有研究报道，MSCs外泌体通过miR-99b-5p/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）/自噬轴缓解DKD的肾纤维化[26]。值得关注的是自噬与细胞凋亡的平衡对细胞存活至关重要。当自噬不足时，细胞更易走向凋亡。MSCs在抗凋亡方面的作用已在多个研究中体现：它们可分泌表皮生长因子（epidermal growth factor，EGF）保护足细胞，减少高糖诱导的足细胞凋亡，还可下调促凋亡蛋白（如Bax、Caspase-3）的表达，上调B淋巴细胞瘤-2基因（B-cell lymphoma-2，Bcl-2）等抗凋亡蛋白水平，从而维持肾小球和肾小管细胞的存活[27]。同时，MSCs还能通过激活Akt/Nrf2通路抵抗高糖环境下氧化应激所致的细胞凋亡[20,28]。MSCs外泌体在抗凋亡中同样发挥作用：例如，人尿源性干细胞外泌体中的miR-16-5p能够保护足细胞，减少其凋亡并改善肾小球滤过屏障[29]；来自MSCs的外泌体携带miR-424-5p，可同时抑制高糖诱导的肾小管上皮细胞凋亡和上皮–间充质转化（epithelial-to-mesenchymal transition，EMT）过程，从而对DKD造成进行性损伤[30-31]。肾脏纤维化是DKD后期病理变化的核心和不可逆环节，由大量细胞外基质（extracellular matrix，ECM）沉积和组织硬化所致。高血糖和炎症介质可诱导肾脏EMT，促进肌成纤维细胞产生，推动纤维化发展。MSCs在抗纤维化方面的作用机制集中于抑制致纤维信号通路。尤其是转化生长因子（transforming growth factor，TGF）-β/果蝇母本抗生存因子（small mother against decapentaplegic，Smad）通路在DKD纤维化中起关键作用：TGF-β1过度表达会激活Smad2/3，诱导大量胶原和纤连蛋白合成。Rafiee等[32]的动物实验证明，MSCs治疗可下调DKD大鼠肾脏中TGF-β1水平并减少Smad3磷酸化，从而显著改善肾组织纤维化。除经典TGF-β途径外，MSCs及其外泌体还能影响其他纤维化相关通路。

例如，研究发现，人脐带 MSCs 来源的外泌体可抑制 Hedgehog/Smoothened 信号通路，减少肾小管上皮细胞 EMT，从而减轻糖尿病小鼠肾脏纤维化[33]。此外，上文提到的外泌体 miR（如 miR-424-5p、miR-16-5p 等）通过多靶点协同，直接减少α-平滑肌肌动蛋白（smooth muscle actin，SMA）等肌成纤维表型的形成并恢复上皮标记物 E-钙黏蛋白的表达[30]。可见，MSCs 通过增强自噬、抑制凋亡以及阻断致纤维信号等多重机制，全面干预了 DKD 的病理过程[31]。

2.4　促血管生成与肾组织修复　肾脏微循环损伤是 DKD 的重要特点，促进损伤血管的再生对于改善肾功能至关重要。MSCs 及其分泌产物在促进血管新生方面展现出巨大潜力。研究表明，给予 MSCs 条件培养基可保护受损血管内皮。在 DKD 大鼠模型中，脐带 MSCs 治疗后肾组织内血管内皮生长因子（vascular endothelial growth factor，VEGF）、血小板内皮细胞黏附分子-1（platelet endothelial cell adhesion molecule-1，PECAM-1）、血管性血友病因子（von Willebrand factor，vWF）等血管生成相关指标均显著上调，小血管密度增高，提示血供改善[34]。深入机制研究揭示，MSCs 来源的外泌体在促血管再生过程中发挥关键作用：其富含 VEGF 等促血管生成信号，能够刺激内皮细胞增殖和血管新生。例如，人尿源性干细胞外泌体中检测到高水平的 VEGF，被认为与其促进损伤组织血管重建的功能相关[35]。而一些研究注意到 MSCs 中的 miR-15b-5p 通过下调 VEGF-丙酮酸脱氢酶激酶 4（pyruvate dehydrogenase kinase 4，PDK4）轴减少 DKD 足细胞中异常新生血管形成[36]。因此，MSCs 及其外泌体对 DKD 肾脏内的血管生成具有双向调节作用：既能通过提供促血管生成刺激促进有益的血管再生，维护肾组织微血管网络；又可通过 miR 等成分抑制异常的病理性血管新生和内皮功能紊乱，最终发挥对肾脏血管系统的保护作用。

3　研究挑战与临床转化前景

MSCs 凭借免疫调节、抗氧化、促再生等多重功效，为 DKD 的治疗提供了新的思路和可能。在大量动物研究以及初步临床试验（如 NEPHSTROM 研究）中，MSCs 疗法已显示出降低尿蛋白、改善肾功能和组织病变的积极效果。然而，MSCs 治疗要真正走向临床常规应用仍面临诸多挑战。首先，MSCs 在受体内的存活和定植率较低，如何提高其到达和滞留病灶部位的效率是关键难题。其次，不同来源的 MSCs 在功能上存在差异，供者疾病状态和年龄等因素也会影响细胞质量，需要优化细胞来源和体外培养条件以获得最佳治疗效应。再者，异体 MSCs 移植可能引发免疫排斥反应，虽然 MSCs 本身免疫原性低，但仍需警惕安全性问题。未来应通过更多临床试验来确定 MSCs 治疗的最佳给药途径、剂量和时机，并长期随访其疗效和安全性。值得关注的是，MSCs 来源的外泌体等无细胞疗法正快速发展，有望规避活细胞治疗的一些限制。总之，随着对 MSCs 作用机制的深入研究和临床经验的积累，未来有望进一步提升 MSCs 疗法的有效性和可行性，为 DKD 患者提供更安全高效的个体化治疗策略。

利益冲突　无

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收稿日期:2025-08-06 **修回日期**:2025-08-23 **编辑**:许煜晗

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对医学名词及术语的一般要求

医学名词应使用全国科学技术名词审定委员会公布的名词。中医临床诊疗术语、经穴部位、耳穴名称与部位等应遵循相应的国家标准。对于没有通用译名的名词术语,在文内第一次出现时应注明原词。中西药名以最新版《中华人民共和国药典》和《中国药品通用名称》(均由中国药典委员会编写)为准。英文药物名称则采用国际非专利药名。在题名及正文中药名不得使用商品名,确需使用商品名时应先注明其通用名称。冠以外国人名的体征、病名、试验、综合征等,人名可以用中译文,但人名后不加“氏”(单字名除外,例如福氏杆菌);也可以用外文,但人名后不加“’s”。文中尽量少用缩略语。已被公知公认的缩略语可以不加注释直接使用,例如:DNA、RNA、HBsAg、PCR、CT、MRI等。不常用的、尚未被公知公认的缩略语以及原词过长在文中多次出现者,若为中文可于文中第一次出现时写出全称,在圆括号内缩略语境若为外文可于文中第一次出现时写出中文全称,在圆括号内写出外文全称及其缩略语。不超过4个汉字的名词不宜使用缩略语,以免影响论文的可读性。西文缩略语不得拆开移行。

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