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REVIEW

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Mechanism of mesenchymal stem cells in treating diabetic kidney disease

Lingqian Zheng[1], Wenmin Chen[1], Kaijin Yao[1], Yongda Lin[1], Chunling Liao[1] and Tianbiao Zhou[1*]

Abstract

Diabetic kidney disease (DKD) is a serious microvascular complication of diabetes, with symptoms of progressive kidney dysfunction, proteinuria, and fibrosis, ultimately causing end-stage renal disease. Mesenchymal stem cells (MSCs) represent a promising therapeutic approach for DKD, primarily through their paracrine effects. In this review, we concluded the mechanism of MSCs in treating DKD, including the inhibition of inflammation, fibrosis, oxidative stress, and modulate vascular endothelial growth factor (VEGF). Additionally, we discuss strategies to enhance MSC efficacy, such as preconditioning, genetic engineering, and combination therapies with pharmacological agents. Furthermore, we provide an overview of completed clinical trials assessing the effectiveness and safety of MSCs transplantation in DKD patients. The purpose of this review is to highlight the MSCs' potential as an innovative treatment for DKD and to guide future research toward optimizing their therapeutic applications, ultimately improving DKD patients' quality of life.

Keywords Mesenchymal stem cells, Diabetic kidney disease, Diabetic nephropathy, MSCs, DKD

Introduction

Diabetic kidney disease (DKD) is a severe microvascular complication of diabetes mellitus, clinically diagnosed based on persistent albuminuria and/or a decline in estimated glomerular filtration rate (eGFR) [1, 2]. It is the leading cause of end-stage renal disease (ESRD) and chronic kidney disease (CKD) worldwide [3]. The histopathological changes observed in diabetic nephropathy (DN) include glomerular basement membrane (GBM) thickening, extracellular matrix accumulation, mesangial expansion, glomerulosclerosis, podocyte loss, interstitial inflammation, renal fibrosis, and tubular atrophy with reduced peritubular capillary density [4, 5]. Despite advancements in therapeutic strategies targeting hyperglycemia, hypertension, dyslipidemia, and dietary factors, the incidence of DKD continues to rise. Approximately 40% of individuals with diabetes worldwide are at risk of developing DKD, which remains a leading cause of kidney failure and significantly elevates the risk of cardiovascular diseases [6, 7].

Currently, traditional management of DKD primarily focuses on controlling the risk factors associated with the disease, such as hyperglycemia, hypertension, and dyslipidemia [2, 8]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are commonly used to slow the progression of DKD by reducing glomerular pressure and mitigating renal fibrosis [9, 10]. However, these treatments only provide partial protection and often fail to halt the disease progression entirely. The introduction of sodium-glucose cotransporter 2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists (such as finerenone), and GLP-1 receptor agonists (such as semaglutide) has been shown to significantly reduce major cardiovascular

*Correspondence:
Tianbiao Zhou
zhoutb@aliyun.com
[1]Department of Nephrology, The Second Affiliated Hospital of Shantou, Shantou University Medical College, No. 69 Dongsha Road, Shantou 515041, China

events and mortality in DKD patients [11–14]. While these drugs have shown significant renal protective effects, particularly in slowing the progression of kidney dysfunction and reducing hospitalization rates for heart failure, their long-term use may be associated with adverse effects, such as increased risk of hyperkalemia (in the case of finerenone) and genital infections (for SGLT2 inhibitors) [15–18]. Moreover, these treatments primarily address the symptoms of DKD rather than targeting the underlying pathological processes. In this regard, mesenchymal stem cells (MSCs) offer a promising alternative, as they have the potential to directly intervene in the key mechanisms of DKD, such as inflammation, fibrosis, and tissue repair, without the associated risks of long-term drug therapy.

MSCs represent a promising therapeutic avenue for DKD owing to their regenerative, immunomodulatory, and anti-fibrotic characteristics. Multipotent adult stem cells can be sourced from various tissues, including kidney, bone marrow, placenta, umbilical cord, and adipose tissue [19–21]. MSCs exert their therapeutic effects primarily through the release of cytokines and other bioactive molecules via a paracrine mechanism, which can promote tissue repair, modulate immune responses, and mitigate fibrosis [22–25]. Research has shown that MSC-based treatments are effective in managing fibrosis-related disorders in various organs, including the kidneys, liver, heart, and blood [26–29]. Given their unique biological properties, MSCs represent a promising approach for slowing or reversing DKD progression. This review summarizes the mechanism of MSCs in treating DKD. By synthesizing current insights into these mechanisms, we aim to provide valuable guidance for future investigations, to promote the further development and clinical application of MSC-based therapies for DKD.

Mechanism

Inhibit inflammation

Inflammation has been increasingly recognized as a significant factor in the pathogenesis and progression of DKD. Persistent hyperglycemia not only triggers oxidative stress but also activates NF-κB, toll-like receptors (TLRs), and the NLRP3 inflammasome, leading to sustained production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [30–33]. Chronic inflammation further promotes fibroblast activation and extracellular matrix deposition through the TGF-β/Smad pathway, thereby linking inflammatory injury to irreversible renal fibrosis [34, 35]. Importantly, recent studies have demonstrated that MSCs and MSC-derived exosomes exert anti-inflammatory effects by releasing IL-10, TSG-6, and regulatory microRNAs (e.g., miR-146a-5p), which suppress inflammasome activation and enhance M2 macrophage polarization, ultimately alleviating fibrosis progression [36–38]. The systemic immune-inflammation index (SII) has also been identified as a novel biomarker associated with DKD, indicating that higher SII levels correlate with increased risk and severity of the disease [32, 39]. Furthermore, MSCs have shown efficacy in reducing inflammation in acute lung injury, inflammatory bowel disease, and other inflammatory conditions by modulating immune responses and enhancing tissue repair [40].

MSCs inhibit inflammation and relieve DKD through the following mechanisms:

1) Reduction of pro-inflammatory cytokines levels.

MSCs or MSCs-derived exosomes (MSC-Exo) can down-regulate pro-inflammatory cytokines levels (such as IL-1β, TNF-α, IL-6), thereby improving renal function and mitigating inflammation in DN rats [36, 41]. To investigate the specific anti-inflammatory mechanism of MSCs or MSC-Exo, basic experimental studies were conducted. Wang et al. (2023) [37] discovered that hUMSCs-Exo can alleviate DKD by reducing inflammatory responses through the inhibition of pro-inflammatory cytokines, including IL-1β and IL-18, via the NLRP3 signaling pathway. Notably, miR-22-3p derived from exosomes may play a key role in suppressing NLRP3 expression. Additionally, hUMSC-Exo improves glomerular podocyte morphology, enhances podocyte viability, and reduces urinary albumin excretion, thereby contributing to the delay of DKD progression (Table 1; Fig. 1). Another group of researchers found that MSC-Exo can inhibit inflammation through the NOD2 signaling pathway, protecting high-glucose (HG)-induced podocytes from injury and improving cell viability in vitro. Consistently, in vivo studies have demonstrated that MSC-Exo primarily localizes in the glomeruli of DKD mice, where it alleviates glomerulosclerosis and improves basement membrane thickening, thereby mitigating DKD progression [42] (Table 1). Wang et al. (2021) [43] discovered through cell experiments that hUMSCs can alleviate HG-induced podocyte injury and inflammatory responses by secreting HGF, which inhibits the TLR2 and TLR4 signaling pathways. In vivo experiments further demonstrated that hUMSCs can reduce glomerulosclerosis and renal fibrosis in DN mice (Table 1).

2) Promote M2 macrophage polarization.

Macrophage polarization is essential in disease development. Macrophage polarization refers to the process by which macrophages undergo activation in response to a variety of stimuli, such as pathogenic microorganisms, inflammatory cytokines, or specific physicochemical conditions [85]. This activation triggers their

Table 1 Summary of mechanisms of MSCs in treating DKD

Author, year	MSCs type	Cell model	Animal model	Mechanism (pathway)	Results
Inhibit Inflammation					
Yuan et al. [44]	Mice-BMSCs	HG-stimulate-RAW 264.7cells	STZ-induced DN rats; male BALB/c mice	mTOR/TFEB pathway	BMSCs activate transcription factor EB (TFEB) signals in the macrophages to promote M2 macrophage polarization, leading to enhance autophagy and reduce inflammation, which contributes to protect renal function.
Wang et al. [43]	hUMSCs	HG-induced MPC5 cells	Male type 2 diabetic db/db mice	TLR2 and TLR4 pathway	hUMSCs can secrete HGF decrease inflammation and inhibit TLR2 and TLR4 signaling pathways in podocytes under high glucose.
Zhang et al. (2022) [36]	hUMSCs	RAW264.7 cells and THP-1 cells	STZ-induced DN; male Sprague-Dawley rats	MicroRNA-146a-5p/TRAF6-STAT1 pathway	MicroRNA-146a-5p plays a key role in mitigating renal injury in DN rats by targeting TRAF6, thereby suppressing STAT1 pathway. This regulation promotes M2 macrophage polarization, reduces inflammation, and enhances kidney tissue repair.
Rafiee et al. (2022) [45]	Kidney stem cells	NA	STZ-induced DN rats; Sprague-Dawley rats	TGF-β/Smad pathway	Kidney stem cells can reduce inflammatory cytokines and improve kidney function through the TGF-β/Smad pathway to ameliorate diabetic nephropathy.
Wang et al. (2023) [37]	hUMSCs-Exo	HG-induced human podocytes	db/db mice	NLRP3 pathway	MicroRNA-22-3p derived from hUMSCs-exo can target NLRP3 mRNA and inhibit its expression, thereby reducing inflammation and protecting podocytes from damage.
Liu et al. (2023) [46]	Rat-BMSCs-Exo	NA	STZ-induced DN rats; Sprague-Dawley rats	NA	BMSCs-Exo can inhibit apoptosis and inflammation to alleviate diabetic kidney disease in Rats.
Wang et al. (2024) [42]	hUMSCs-Exo	HG-induced human podocytes	High-fat diet and STZ-induced C57BL/6J male mice	NOD2 pathway	MSCs-Exo can reduce inflammation and suppress the activation of the NOD2 pathway and reduce apoptosis, increasing cell ability to protect renal function in DN rats and HG-induced podocytes.
Su et al. (2024) [38]	hUMSCs-Exo	THP-1 cells	db/db mice	PI3K/Akt pathway	1.MiR-486 derived from hUMSCs-exo plays an important part in promoting macrophage polarization by targeting PIK3R1 via the PI3K/AKT pathway.
Li et al. (2024) [47]	hUMSCs-Exo	RAW264.7 cells	db/db mice	M2 macrophage polarization	hUMSCs-Exo can alleviate diabetic nephropathy by promoting M2 macrophage polarization.
Inhibit Fibrosis					
Xiang et al. (2020) [41]	hUMSCs; hUMSCs-Exo	HG-induced HK2, NRK-52e, hrGECs cells	STZ-induced DN rats; Sprague-Dawley rats	NA	hUMSCs and hUMSCs-Exo can significantly enhance renal function by suppressing inflammation and fibrosis.
Lin et al. (2020) [48]	Rat-BMSCs	HG-induced glomerular mesangial cell line (HBZY-1 rat cell)	STZ-induced DN rats; Sprague-Dawley rats	TLR-4/NF-κB pathway	BMSCs can down-regulate TLR-4/NF-κB expression to inhibit inflammation and fibrotic to protect renal function.
Li et al. (2020) [49]	Mice-UCMSCs	HG-induced mesangial cells (SV40-MES-13 cell line)	STZ-induced DN mice; C57BL/6 mice	Myofibroblast transdifferentiation (MFT); PI3K/Akt pathway; MAPK pathway	Mice-UCMSC inhibits TGF-β1-triggered myofibroblast transdifferentiation (MFT) to ameliorate fibrosis through the paracrine pathway.
Chen et al. (2022) [50]	hUMSCs; hUMSCs-Exo	HG-induced HK2 cells	C57BL/KsJ-db/db mice	miR-424-5p target YAP1 reduces apoptosis and EMT	hUMSCs-exo-miR-424-5p can target Yes-associated protein 1 (YAP1) and inhibit YAP1 expression to inhibit EMT and cell apoptosis in HG-induced HK2 cells.

Table 1 (continued)

Author, year	MSCs type	Cell model	Animal model	Mechanism (pathway)	Results
Ji et al. (2024) [51]	MSCs-EVs	HG-induced macrophages and cocultured with primary mesangial cells	STZ-induced DN rats; Sprague-Dawley rats	TGF-β1/Smad2/3/YAP signaling axis; Ubiquitin-Proteasome System	MSC-sEVs transport CK1δ/β-TRCP to promote YAP ubiquitination and degradation, thereby alleviating DKD progression.
Zhang et al. (2024) [52]	hUMSCs-Exo	HG-induced NRK-52e cells	STZ-induced DN rats; Sprague-Dawley rats	Hedgehog/SMO pathway	hUMSCs and hUMSCs-Exo can protect against renal injury and reduce HG-induced EMT in kidney tubular epithelial cells through the Hedgehog/SMO signaling pathway.
Bai et al. (2024) [53]	Rat-BMSCs	HG-induced HK-2 cells	STZ-induced C57BL/6 male mice	Smad2/3/WTAP/m6A/ENO1 axis	BMSCs can alleviate DN progression through Smad2/3/WTAP/ENO1 pathway.
Li et al. (2024) [54]	hUMSCs-sEV	HG-induced HK-2 cells	C57BLKS/J db/db	KLF3/STAT3	hUMSCs-SEV-miR23a-3p can reduce inflammation and renal fibrosis by blocking KLF3/STAT3 in diabetic nephropathy.
Regulation of Oxidative Stress					
Jin et al. (2019) [55]	Mice-ADSCs-Exo	HG-induced MPC5 cells	C57BL/KsJ db/db	Smad1/mTOR pathway	ADSCs-Exo could enhance the expression of miR-486 to inhibit Smad1/mTOR pathway promote autophagy and reduce podocyte apoptosis to ameliorate DN.
Lee et al. (2019) [56]	hUMSCs; hADSCs	HK-2 cells; LPS-induced RAW264.7 cells	STZ-induced male CD1 mice	Cytokine-mediated mitochondrial dysfunction	(1) hUMSCs can improve the Arg-1 level in M2 macrophages to improve mitochondrial dysfunction to alleviate diabetic nephropathy. (2) hADSCs cannot reduce mitochondrial dysfunction compared to hUMSCs.
Yuan et al. (2021) [57]]	Mice-BMSCs	HG-induced RAW264.7 cells	STZ-induced DN mice; C57BL/6 mice	PGC-1α/TFEB-mediated autophagy	BMSCs can transfer mitochondria to macrophages to inhibit inflammation and alleviate kidney injury via PGC-1α-mediated mitochondrial biogenesis and PGC-1α/TFEB-mediated autophagy in diabetic nephropathy mice.
Nie et al. (2021) [58]	hUMSCs	HG and palmitate-induced human GMCs	High-fat diet and STZ-induced male Sprague-Dawley rats	PI3K/Akt pathway	hUMSCs activate the PI3K/Akt pathway to regulate Nrf2, thereby ameliorating oxidative damage and apoptosis in DN rat models and in vitro systems.
Sávio-Silva et al. (2021) [59]	mice-BMSCs	HG-induced-immortalized GMCs. Hydrogen peroxide-induced GMCs	BTBR ob/ob Mice	Mitophagy and mitochondrial biogenesis	BMSCs protected HG-induced GMCs against apoptosis-related cell death, reduced ROS generation and maintained mitochondrial membrane potential.
Yue et al. (2022) [60]	hUMSCs	NA	STZ-induced DN rats; Sprague-Dawley rats	NA	Intrarenal arterial administration of hUMSCS significantly preserved residual renal function in diabetic kidney disease rats.
Han et al. (2023) [61]	hPMSCs	HG-induced MPC5 cells	STZ-induced DN rats; Sprague-Dawley rats	SIRT1-PGC-1α-TFAM pathway	PMSCs can reduce podocyte injury and promote mitophagy through the SIRT1-PGC-1α-TFAM pathway.
Ren et al. (2023) [62]	ADSCs-Exo	HG-induced-MPC5 mouse podocyte cell line	C57BL/KsJ db/db mice	Keap1/Nrf2/ARE pathway	ADSCs-Exo can upregulate its FAM129B expression to regulate the keap1/Nrf2-HO-1 pathway to reduce oxidative stress and inflammation in both HG-induced podocytes and kidney tissues of DN mice.
Li et al. (2023) [63]	hUMSCs	HG-induced rat podocytes	STZ-induced DN rats; Sprague-Dawley rats	AMPK/mTOR	hUMSCs ameliorate HG-induced podocyte damage through promoting autophagy and alleviating cellular senescence via the AMPK/mTOR pathway.
Khamis et al. (2023) [64]	Rat-BMSCs	NA	STZ-induced DN rats; Sprague-Dawley rats	NA	BM-MSCs mitigate diabetic nephropathy in rats by modulating endoplasmic reticulum stress, oxidative stress, inflammation, and apoptotic pathways.

Table 1 (continued)

Author, year	MSCs type	Cell model	Animal model	Mechanism (pathway)	Results
Lv et al. (2023) [65]	hBMSCs-Exo	HG-induced HK-2 cell	NA	Inhibit pyroptosis	hBMSC-Exo-miR-30e-5p targeting ELAVL1 and reduce its expression to inhibits caspase-1-mediated pyroptosis in high glucose-induced HK-2 cells.
Zheng et al. (2023) [66]	hUMSCs	HG-induced NRK-52e cells	STZ-induced DN rats; Sprague-Dawley rats	MiR-342-3p/Caspase1 pathway	hUMSCs can inhibit pyrotosis through miR-342-3p/Caspase 1 signaling pathway in HG-induced NRK-52e cells and DN rats.
Liu et al. (2024) [67]	hPMSCs	HG-induced HPC5 cells	STZ-induced DN rats; Sprague-Dawley rats	SIRT1/FOXO1 pathway	hPMSCs can upregulate the autophagy-mediated SIRT1/FOXO1 pathway to promote podocytes autophagy to improve cell health and reduce damage in DN rats.
He et al. (2024) [68]	hUMSCs	NA	High-fat diet and STZ-induced C57BL/6 male mice	promote autophagy	hUMSCs can restore autophagy and repair renal injury in DN mice.
Zhang et al. (2024) [69]	hUMSCs	NA	High-fat diet and STZ-induced T2DM rat model; Sprague-Dawley rats	IGF1R-CHK2-p53 signaling axis	hUMSCs can repair DNA damage through the IGF1R-CHK2-p53 signaling axis to reduce diabetic nephropathy.
Barutta et al. (2024) [70]	human MSCs; mice-BMSCs	HG-induced human podocytes	STZ-induced C57BL/6 ale mice	M-Sec-TNT-meditate mitochondria transfer	MSCs can form heterotypic tunneling nanotubes (TNTs) with podocytes through an M-sec-dependent mechanism to transfer mitochondria, which can improve mitochondrial function and reduce podocyte apoptosis, providing a new therapy direction for diabetic nephropathy.
Zhu et al. (2024) [71]	hUMSCs	HG and palmitate-stimulated HK-11 cells	High-fat diet and STZ-induced T2DM rat model; male C57BL/6J mice	JNK/KEAP1/NRF2 signaling pathway	hUMSCs can inhibit ferroptosis through JNK/KEAP1/NRF2 Signaling pathway to alleviate diabetic nephropathy.
Modulate VEGF level					
Duan et al. (2020) [72]	Mice-ADSCs-Exo	HG-induced mouse glomerular podocytes (MP5 cells)	C57BL/KsJ db/db mice	TLR-4/NF-κB / VEGFA pathway	ADSCs-Exo-miR-26a-5p target TLR4 and inhibit the expression of TLR4 to inactivation of TLR4/NF-κB pathway to regulate inflammation and downregulate VEGFA levels to protect diabetic nephropathy.
Duan et al. (2021) [73]	Human urine-derived stem cells (hUSCs)-Exo	HG-treated human podocytes (HPDCs)	STZ-induced DN; male Sprague-Dawley rats	Inhibition of VEGFA	hUSCs deliver miR-16-5p to HG-treated podocytes via exosomes. This process targets VEGFA, downregulating its expression, which in turn reduces podocyte apoptosis, enhances cell viability, and mitigates podocyte injury in DN rats.
Zhao et al. (2022) [74]	hADSCs-Evs	HG-induced MPC5 cells	NA	VEGF/PDK4 axis	hADSCs-Evs-miR15b-5p can protect HG-induced podocyte injury via the VEGF/PDK4 pathway.
Other mechanisms participate in DKD					
Zhang et al. (2020) [75]	Rat-BMSCs	CD103 + DCs, CD8 + T-cells	STZ-induced DN rats; Sprague-Dawley rats	Modulate the activity of $CD103^+$ DCs and $CD8^+$T cells	BMSCs suppress the maturation and function of $CD103^+$ dendritic cells while reducing $CD8^+$ T cell activation and cytotoxicity, thereby exerting a protective effect against diabetic nephropathy.
Wang et al. (2023) [76]	hPMSCs	NA	STZ-induced DN rats; male Sprague-Dawley rats	PD-1/PDL1 pathway	PMSCs modulate the balance between Th17 cells and regulatory T cells (Treg) through the PD-1/PDL1 pathway to ameliorate diabetic kidney disease.
Optimizing MSC Therapy					

Table 1 (continued)

Author, year	MSCs type	Cell model	Animal model	Mechanism (pathway)	Results
Liu et al. (2020) [77]	ACE2-modified-MSCs;	Ang II stimulated rat glomerular mesangial cell line (HBZY-1 rat cell)	STZ-induced DN rats; female Wistar rats	Modulate renin-angiotensin system (RAS) and inhibit TGF-β/smad pathways	MSCs modified with ACE2 can effectively reduce glomerular fibrosis and improve kidney function via inhibiting the TGF-β/Smad pathway and modulating RAS.
Habib et al. (2020) [78]	Rat-ADSCs; Rat-ADSCs + exenatide	NA	STZ-induced DN rats; male Wistar rats	NA	ADSCs combined with exenatide therapy have significant renal protective effects by improving renal function, reducing oxidative stress, and inflammation, and modulating apoptotic.
Ozkan et al. (2022) [79]	Deferoxamine (DFS)-preconditioned hUMSCs	NA	STZ-induced DN rats; Sprague-Dawley rats	NA	Deferoxamine-preconditioned hUMSCs produced conditioned medium (DFS-CM) enriched with beneficial factors, including VEGF-α, NGF, and GDNF. DFS-CM demonstrated enhanced renal protection in diabetic nephropathy rat models.
Wang et al. (2024) [80]	Fe3O4 coated polydopamine nanoparticle (NP)-labeled human-PLMSCs	NA	High-fat diet and STZ-induced C57BL/6 male mice	Endocytosis of Nanoparticle	Fe3O4-coated NP-labeled PL-MSCs can more effectively target PLMSCs to mitigate injury kidney issues in DN models.
Yang et al. (2024) [81]	Rat-ADSCs + EMPA(empagliflozin)	NA	STZ-induced DN; Sprague-Dawley rats	NA	ADSCs enhance the protective effects of EMPA in preserving residual renal function and maintaining kidney architecture integrity in DKD rats.
Meng et al. (2024) [82]	hUMSCs + irbesartan	NA	High-fat diet and STZ-induced T2DM rat model; Sprague-Dawley rats	NA	The combination of UC-MSCs and irbesartan is believed to have a synergistic effect on reducing inflammation and protecting kidney function in diabetic nephropathy.
Wang et al. (2024) [83]	hUMSCs-Exo load with Ex-4 (hUCMSCs-Exo@Ex-4)	NA	STZ-induced T2DM rat model; male C57BL/6J mice	Induction of CD4 + Treg Cells; Gut Microbiota Interaction	Ex-4-loaded hUMSCs-Exo can promote CD + Treg cell induction and modulate gut microbiota and immune to alleviate diabetic nephropathy in DN rats.
Wang et al. (2025) [84]	Engineered mice-ADSCs-Exo with high HOXB3OS	HG-induced MPC5 cells	Mice C57BL/KsJ db/db	Inhibition of YHOXB3OS disrupts the binding of Ythdc2 to SIRT1 mRNA, thereby inhibiting its degradation.	Engineer ADSCs-Exo with lnc HOXB3OS can improve HG-induced podocytes injury by Ythdc2-mediated SIRT1 mRNA degradation.

MPC5 cells: mouse conditionally immortalized podocyte cell line; LPS: lipopolysaccharides; HG: high glucose; SD rats: Sprague-Dawley rats; DN rats: diabetic nephropathy rats; RAW 264.7 (a mouse mononuclear macrophage cell line); HK2 cells: (human kidney proximal tubular epithelial cell line); HK-11cells (human renal tubular epithelial cells); hADSCs: human adipose-derived mesenchymal stem cells; STZ: Streptozotocin; hrGECs: human renal glomerular endothelial cell line; NRK-52e: rat renal tubular epithelial cells; Exo: Exosomes; Evs: extracellular vesicles; BMSCs: bone marrow mesenchymal stem cells; hUMSCs: human umbilical cord-derived mesenchymal stem cells; Mice-UCMSCs: mice umbilical cord-derived mesenchymal stem cells; hPMSCs: human-placental mesenchymal stem cells; GMCs: glomerular mesangial cells; EMT: epithelial-to-mesenchymal transition; TRAF6: tumor necrosis factor receptor-associated factor 6

differentiation into distinct phenotypic states, each associated with different functional roles [86]. Macrophages can be broadly categorized into two distinct phenotypes: the classically activated M1 macrophage, which is typically associated with pro-inflammatory responses, and the alternatively activated M2 macrophage, which is linked to tissue repair and anti-inflammatory functions [87, 88]. Li et al. [47] found that MSCs and MSC-Exo promote M2 macrophage polarization to alleviate inflammation, and studies also demonstrated that MSCs and MSC-Exo improve renal function by reducing blood glucose levels, lowering urinary albumin excretion and serum creatinine (Scr) levels. Additionally, they help ameliorate renal pathological features, such as alleviating tubular vacuolar degeneration, reducing glomerular matrix thickening, and improving glomerular interstitial expansion (Table 1). Zhang et al. [36] discovered that hUMSCs-Exo-miRNA-146a-5p can inhibit the TRAF6/

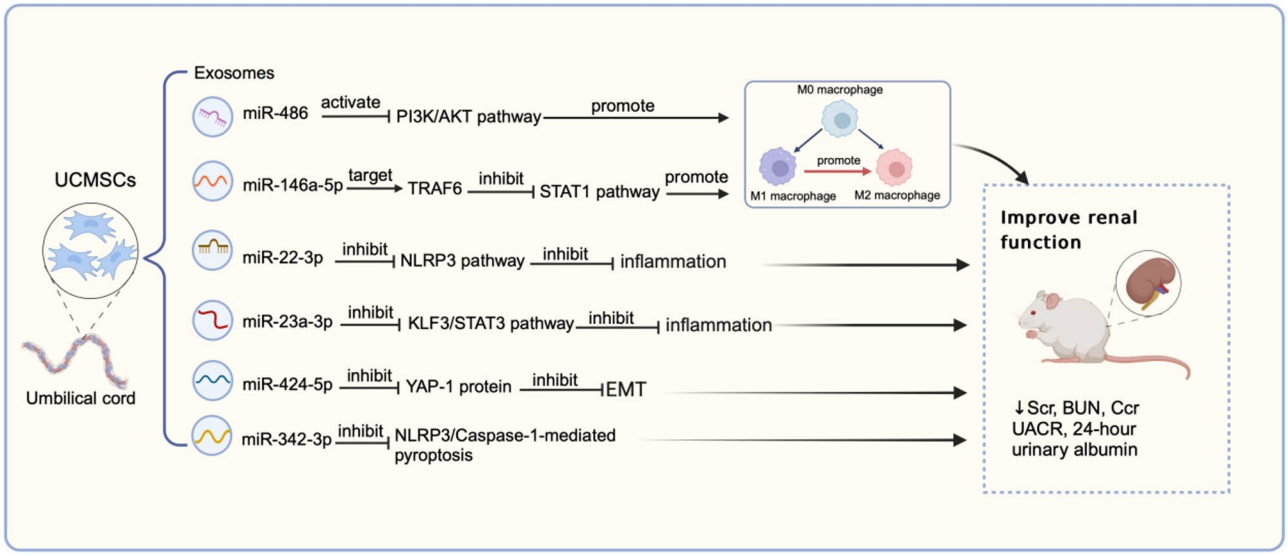

Fig. 1 Mesenchymal stem cells derived from umbilical cord can secrete exosomes to alleviate diabetic nephropathy, and microRNAs in the exosomes might play a crucial role in this process. Created in https://BioRender.com

STAT1 signaling pathway, facilitating the transition of M1 macrophages to M2 macrophages, which reduces inflammation and improves renal function (Table 1; Fig. 1). Su et al. [38] demonstrated that miR-486-5p from hUMSCs-Exo promotes M2 macrophage polarization via the PI3K/Akt pathway, thereby alleviating tubular injury, glomerulosclerosis, and interstitial fibrosis (Table 1; Fig. 1). In addition, researchers found that BMSCs (bone marrow-derived mesenchymal stem cells) alleviate diabetic nephropathy by promoting M2 macrophage polarization through TFEB-mediated autophagy, thereby inhibiting inflammation and reducing mesangial cell proliferation and matrix expansion in DN mice [44] (Table 1; Fig. 2). Current DKD therapies increasingly focus on inflammation modulation. Drugs such as metformin, finerenone, and SGLT2 inhibitors exhibit anti-inflammatory effects and show promise in reducing renal damage [32]. MSCs offer a promising approach due to their ability to suppress pro-inflammatory cytokines, promote M2 macrophage polarization, and secrete exosomes and other cytokines through the paracrine pathway to modulate inflammation. These mechanisms emphasize the potential of MSCs as an innovative therapeutic approach for DKD, showcasing their capacity to mitigate inflammation and facilitate kidney repair.

Inhibit fibrosis

MSC or MSCs-Exo have been shown to not only reduce the levels of pro-inflammatory cytokines but also inhibit the expression of pro-fibrotic factors in DN rat models [41]. The mechanisms involved in the progression of MSCs or MSC-Exo in treating fibrosis in DKD are complex and multifaceted.

1) MSCs can inhibit fibrosis through different signaling pathways.

Li et al. [54] found that miR-23a-3p derived from MSCs-EV (MSC-derived extracellular vesicles) can mitigate inflammation and kidney fibrosis by inhibiting the KLF3/STAT3 pathway in DN mice and HG-induced HK2 cells (Table 1). Similarly, Lin et al. [48] discovered that BMSCs can reduce collagen deposition and extensive interstitial fibrosis through the TLR4/NF-κB in DN rat models (Table 1; Fig. 2). In addition, another researcher investigated that mice-UCMSCs (mice umbilical cord-derived mesenchymal stem cells) can inhibit TGF-β1-triggered myofibroblast transdifferentiation (MFT) to ameliorate fibrosis through paracrine pathway in STZ (Streptozotocin)-induced DN mice models [49] (Table 1). A recent study using single-cell sequencing to analyze 27,424 kidney cells has identified a previously unknown subset of fibrosis-associated macrophages, characterized by the expression of TGF-β1 and Arg1. This subset, which is expanded and polarized in DKD, exhibits significant profibrotic activity by activating the TGF-β1/Smad2/3/YAP signaling pathway, contributing to the progression of kidney fibrosis. Furthermore, transcriptome sequencing and LC-MS/MS analysis revealed that intervention with MSC-sEV can mitigate renal interstitial fibrosis in DKD. This effect is achieved by restoring the kinase ubiquitin system and delivering CK1δ/β-TRCP to mesangial cells, facilitating the ubiquitination and degradation of YAP [51] (Table 1). The Smad2/3 signaling pathway, which is frequently upregulated in DKD, plays an important role in the pathogenesis of the disease by promoting fibrosis and inflammation [34]. Studies have

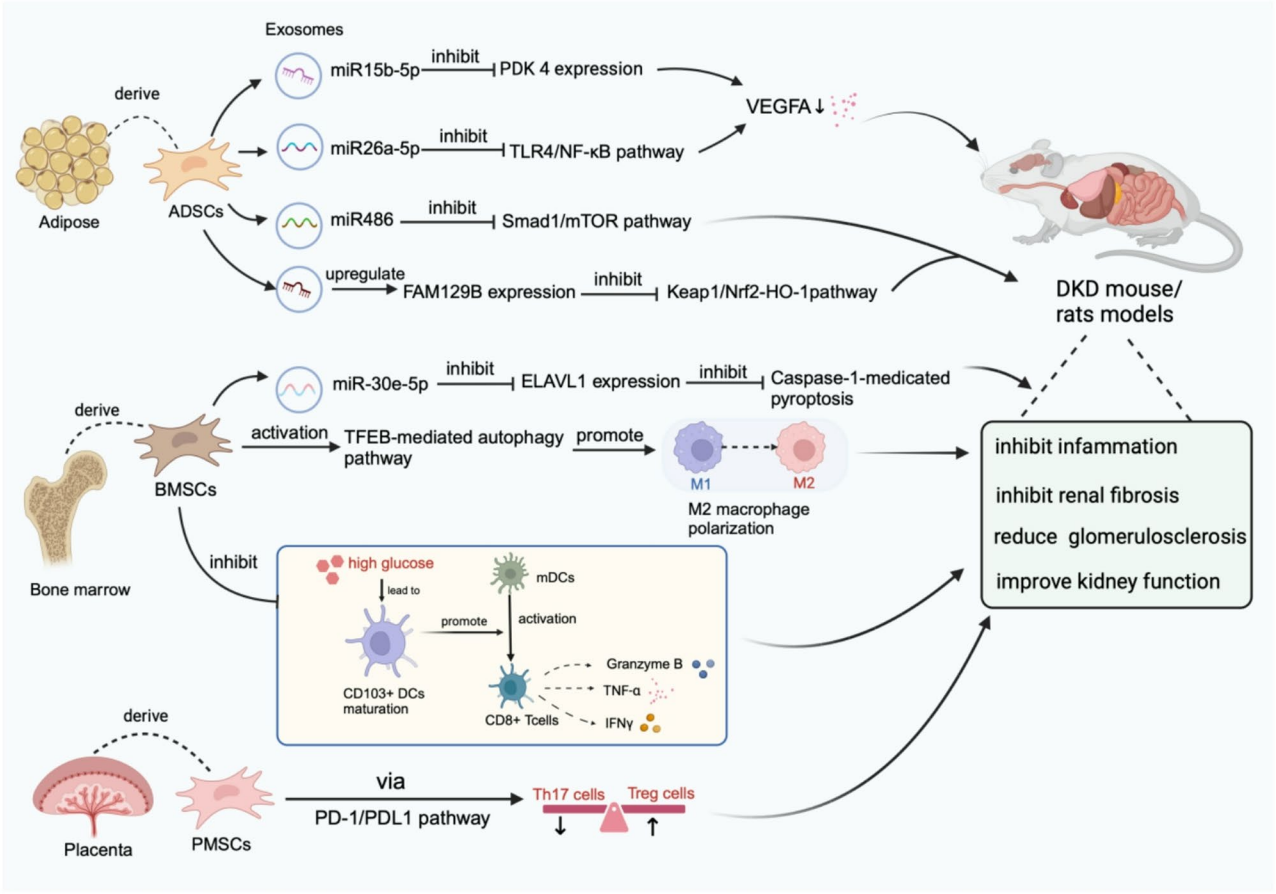

Fig. 2 Different sources of mesenchymal stem cells via different signaling pathways to alleviate diabetic nephropathy in animal models. Created in https://BioRender.com

demonstrated that MSCs can influence the activity of the Smad2/3 pathway, thus modulating renal fibrosis and other aspects of DKD [89]. Bai et al. [53] revealed that BMSCs can modulate DKD progression via the Smad2/3/WTAP/m6A/ENO1 axis, offering new insights into the molecular pathways involved in MSC-based therapeutic strategies for DKD (Table 1). In summary, MSCs exert protective effects against renal fibrosis through a variety of mechanisms, including the Hedgehog/SMO pathway, KLF3/STAT3 axis, Smad2/3/WTAP/m6A/ENO1 axis and TLR4/NF-κB pathway, while also restoring the kinase ubiquitin system in DKD.

2) The role of EMT in the process of fibrosis.

Early studies suggested that epithelial-to-mesenchymal transition (EMT) plays a central role in renal fibrosis by directly generating myofibroblasts, leading researchers to explore methods to inhibit fibrosis based on this mechanism. For instance, Zhang et al. [52] demonstrated that hUMSCs and hUMSCs-Exo can inhibit EMT-associated signaling through the Hedgehog/SMO pathway, thereby reducing renal fibrosis (Table 1). Similarly, Chen et al. [50] found that MSC-Exo-miR-424-5p prevents YAP1 activation in HK2 cells, reversing HG-induced EMT-like phenotypic changes and apoptosis (Table 1; Fig. 1). However, recent lineage tracing and single-cell sequencing studies have challenged the traditional EMT hypothesis, showing that pericytes and resident fibroblasts, rather than tubular epithelial cells, are the primary precursors of myofibroblasts in fibrotic kidneys [35]. Consequently, the notion that tubular epithelial cells are the primary source of myofibroblasts through EMT is now under scrutiny. It is crucial to acknowledge the diverse origins of fibroblasts, including pericytes and resident fibroblasts, in the context of renal fibrosis. Furthermore, the perspective that MSCs mitigate fibrosis by inhibiting EMT warrants critical evaluation. While previous studies have suggested that MSCs can regulate changes in mesenchymal markers such as α-SMA and vimentin, these alterations may not fully represent the occurrence of EMT. Instead, they may reflect partial phenotypic changes or EMT-like alterations, where epithelial cells transiently acquire migratory properties under stress but retain their epithelial identity. This partial EMT-like state does not necessarily equate to true transdifferentiation into myofibroblasts [90].

Moreover, we propose that MSCs likely mitigate fibrosis through multiple mechanisms, including paracrine signaling to secrete anti-inflammatory factors and immune modulation, rather than relying solely on inhibiting EMT. This broader view of MSC-mediated therapeutic effects underscores the complexity of fibrosis and the need to move beyond the exclusive focus on EMT as the principal mechanism driving renal fibrosis.

Regulation of oxidative stress

Oxidative stress plays a pivotal role in triggering multiple forms of programmed cell death (PCD), including apoptosis, ferroptosis, and pyroptosis. Excessive reactive oxygen species (ROS) production leads to lipid peroxidation, mitochondrial dysfunction, DNA damage, and activation of various death pathways, exacerbating disease progression. Researchers have investigated that MSCs serve as a potential therapeutic option that can alleviate DKD through regulation of oxidative stress [46, 64].

MSCs regulate oxidative stress-induced programmed cell death

Ferroptosis, an iron-dependent form of regulated cell death characterized by the accumulation of lipid peroxides, plays a pivotal role in the pathogenesis of DKD. Zhu et al. [71] demonstrated that hUMSCs could inhibit ferroptosis via the JNK/KEAP1/NRF2 signaling pathway in type 2 DN mice and in vitro experiments. Treatment with hUMSCs significantly improved kidney function and reduced tubular injuries, as evidenced by decreases in blood glucose levels, urinary albumin-to-creatinine ratio (uACR), Scr, and BUN (Table 1). Apart from ferroptosis, another type of programmed cell death that contributes significantly to the development of DKD is pyroptosis, which enhances renal inflammation and results in additional cellular damage. Characterized by rapid cell swelling, membrane rupture, and the release of pro-inflammatory cytokines, pyroptosis amplifies the inflammatory response in the kidneys [91, 92]. Lv et al. [65] revealed that exosomal miR-30e-5p derived from BMSCs could inhibit caspase-1-mediated pyroptosis in HG-induced HK-2 cells by targeting ELAVL1 (Table 1; Fig. 2). Similarly, Zheng et al. [66] demonstrated that hUMSCs-Exo-miR-342-3p inhibits pyroptosis via the NLRP3/caspase-1 signaling pathway, and ameliorates vacuolar degeneration in renal tubular epithelial cells and reduces extracellular deposition in DN rats (Table 1; Fig. 1). Both studies highlight the potential of MSC or MSC-derived exosomal microRNAs in regulating pyroptosis and ferroptosis to mitigate kidney damage in DN rat models, indicating a potential therapeutic mechanism for treating DKD in the future.

MSCs restore mitochondrial function to alleviate oxidative stress

Mitochondrial dysfunction is a hallmark of diabetes mellitus and plays a pivotal role in the progression of DKD. Under hyperglycemic conditions, impaired electron transport chain activity and defective mitochondrial dynamics lead to excessive reactive oxygen species (ROS) generation, triggering a state of chronic oxidative stress [93]. This redox imbalance creates a self-perpetuating cycle: surplus ROS not only damages mitochondrial DNA (mtDNA), disrupts membrane potential, and oxidizes critical mitochondrial proteins, but also impairs antioxidant defense systems, further exacerbating mitochondrial deterioration [94, 95]. In renal cells, this vicious cycle is amplified by persistent hyperglycemia, which drives pathological ROS overproduction that directly damages podocytes, tubular epithelial cells, and mesangial cells, ultimately accelerating glomerulosclerosis and renal fibrosis [96]. Recent studies highlight MSCs as a promising therapeutic approach for disrupting this cascade through two key mechanisms. First, MSCs enhance mitophagy to remove dysfunctional mitochondria. Second, they directly transfer healthy mitochondria to recipient cells, restoring redox homeostasis and improving renal cellular function. The following sections will explore these mechanisms in detail.

1. Promote autophagy.

Autophagy, a critical cellular process, plays a pivotal role in maintaining cellular integrity by degrading damaged organelles and misfolded proteins [97, 98]. Under normal conditions, autophagy operates at a basal level to sustain cellular homeostasis, which is particularly essential for maintaining podocyte stability in the kidneys [99]. Mitophagy, a specialized and highly conserved autophagic mechanism, specifically targets and eliminates damaged or superfluous mitochondria, thereby ensuring intracellular environmental stability [100]. Disrupted autophagy in podocytes contributes to glomerular filtration barrier (GFB) dysfunction, macroalbuminuria, and severe glomerulosclerosis [101]. Studies have shown that autophagy is suppressed in DN rat models, suggesting that restoring autophagy could be a promising therapeutic approach for DKD. For example, Han et al. [61] revealed that high glucose exposure aggravates mitochondrial damage and inhibits PINK1/Parkin-mediated mitophagy in podocytes, while treatment with p-MSCs (placenta-derived MSCs) activates the SIRT1-PGC-1α-TFAM pathway, mitigating HG-induced podocyte injury and enhancing mitophagy (Table 1). Similarly, Jin et al. [55] demonstrated that ADSCs-Exo alleviates DN by upregulating miR-486 expression, which targets Smad1 to reduce its expression and suppress mTOR activation.

This regulation enhances podocyte autophagy, decreases apoptosis in vitro, and provides renal protection by reducing urinary protein levels, Scr, and blood urea nitrogen (BUN) (Table 1; Fig. 2). Li et al. [63] reported that hUMSCs ameliorate HG-induced podocyte damage through promoting autophagy and alleviating cellular senescence via the AMPK/mTOR pathway (Table 1). Additionally, Liu et al. [67] discovered that p-MSCs improve DKD by enhancing autophagy via the SIRT1/FOXO1 signaling pathway, which in turn reduces renal tubular injury, glomerular mesangial matrix deposition, and podocyte damage in DKD rats (Table 1). In conclusion, autophagy is dysregulated in diabetic nephropathy, contributing to podocyte damage and kidney dysfunction. MSCs offer a promising therapeutic approach by modulating autophagy to regulate oxidative stress, improving renal function, alleviating pathological changes, and protecting podocytes in animal models.

2) Promote mitochondrial transfer.

Mitochondrial transfer is a therapeutic approach that involves the transfer of healthy mitochondria from donor cells into recipient cells with impaired or dysfunctional mitochondria. This procedure aims to restore the normal cellular functions that are compromised due to mitochondrial deficiencies. It is considered a potentially universal remedy for treating mitochondrial deficiencies of various etiologies [102–104]. Various studies have shown that the transfer of healthy mitochondria from stem cells to damaged or dysfunctional cells significantly improves ATP production, restores mitochondrial integrity, and offers protection to the recipient cells against apoptosis [103]. This therapeutic effect has been observed in conditions such as ischemic stroke [105], spinal cord injury [106], and respiratory system injury [107].

As a result, mitochondrial transfer is increasingly being considered as a key mechanism for MSCs-based therapies aimed at treating a wide range of mitochondrial-related diseases. Additionally, researchers have identified several mechanisms by which mitochondria are transferred from stem cells to damaged cells, including tunneling nanotube (TNT) formation [108], extracellular microvesicle release [109], cellular fusion, and mitochondrial extrusion [110]. Among these, the M-Sec-TNT system, which involves the formation of long cellular channels facilitating mitochondrial exchange, has been identified as a critical pathway for MSC-mediated mitochondrial transfer. A study by Kubat et al. [111] established a doxorubicin-induced nephrotoxicity rat model and performed mitochondrial transfer from MSCs into the renal cortex of rats. The results revealed that mitochondrial transfer significantly mitigated oxidative stress within the renal cells, promoted the regeneration of tubular cells following renal injury, reduced the accumulation of proteins in the damaged tubular structures, as well as effectively restored renal function (Table 1). Similarly, Barutta et al. [70] developed DKD cell and animal models to evaluate the effects of MSCs. They found that MSCs form heterotypic TNTs with podocytes, facilitating mitochondrial transfer through an M-Sec-dependent process. This procedure decreased cell apoptosis, enhanced nephrin expression, and improved mitochondrial function in recipient podocytes (Table 1). Additionally, Yuan et al. [57] demonstrated that MSC-derived mitochondria were transferred into macrophages, which promoted M2 macrophage polarization and restored mitochondrial function in DN mice. This process was mediated through PGC-1α-driven mitochondrial biogenesis and PGC-1α/TFEB-regulated lysosome-autophagy pathways (Table 1). In summary, mitochondrial transfer is a promising therapeutic approach for diseases related to mitochondrial dysfunction. Transferring healthy mitochondria from various sources of stem cells into injured cells has the potential to enhance cellular energy production, thereby improving health outcomes. This innovative strategy offers a novel avenue for exploring treatments for DKD. But mitochondrial transfer would face several challenges that require resolution. A key issue is ensuring the survival of transplanted mitochondria in high-calcium environments, which can induce dysfunction [112]. While it enhances acute bioenergetics, achieving long-term functional recovery, as observed in spinal cord injury models, remains difficult [113]. Additionally, ensuring mitochondria specifically migrate to and integrate into damaged tissues is crucial for therapeutic efficacy. Continued research and refinement of transplantation techniques are vital for advancing this promising treatment strategy.

MSCs mitigate DNA damage to alleviate oxidative stress

Diabetic nephropathy is characterized by excessive oxidative stress, which leads to DNA damage and contributes to kidney dysfunction. Zhang et al. [69] demonstrated that insulin-like growth factor 1 receptor (IGF1R) interacts with checkpoint kinase 2 (CHK2) to mediate DNA damage in the kidneys under high-glucose conditions. Their team showed that hUMSCs could mitigate DNA damage in DN rats by modulating the IGF1R-CHK2-p53 signaling pathway. This suggests that hUMSCs may offer a promising therapeutic approach to reduce oxidative stress-induced DNA damage in DKD, providing new insight into potential therapeutic interventions targeting the IGF1R-CHK2-p53 axis (Table 1).

Does Nrf2 pathway activation have real benefits for DKD?

Researchers found that nuclear factor erythroid 2-related factor 2 (Nrf2) is a crucial transcription factor that

regulates oxidative stress, a key contributor to the pathogenesis of diabetes [114]. Recent studies have emphasized the therapeutic potential of modulating Nrf2 in DKD. For example, Nie et al. [58] found that hUMSCs can upregulate Nrf2 expression and activate the PI3K/Akt pathway, leading to Nrf2 nuclear translocation and subsequently reducing renal oxidative stress and apoptosis in DN rats (Table 1). Similarly, Ren et al. [62] discovered that ADSCs-Exo can target FAM129B to modulate the Nrf2/Keap1 pathway, contributing to reducing oxidative stress and inflammation in DN mice (Table 1; Fig. 2). However, a study by Zoja et al. [115] found that bardoxolone methyl, a potent pharmacological Nrf2 activator, failed to confer renal protection and instead exacerbated DN pathology, leading to worsened dyslipidemia, proteinuria, glomerulosclerosis, tubular damage, and increased blood pressure. These findings underscore the importance of critically evaluating the potential of Nrf2 pathway activation as a therapeutic strategy for DKD. Notably, there may be significant differences between MSC-mediated Nrf2 activation and pharmacological activation using bardoxolone methyl. While bardoxolone methyl induces systemic Nrf2 activation, often resulting in off-target effects such as sodium retention and fluid overload, MSCs and their exosomes may provide a more localized and context-dependent modulation of Nrf2, reducing oxidative stress at the cellular level without inducing adverse effects observed in clinical trials. Given the adverse outcomes of bardoxolone methyl trials, it is essential to critically assess the therapeutic relevance of MSC-mediated Nrf2 activation. More study is needed to discover whether MSC-driven Nrf2 activation has particular advantages over pharmaceutical methods and to understand its possible limitations in DN treatment.

Modulate VEGF level

VEGF-A (vascular endothelial growth factor A) is a signaling protein that stimulates angiogenesis. VEGF is pivotal in the pathogenesis of DKD and CKD. Research indicates that dysregulation of VEGF, particularly VEGF-B, is associated with lipid deposition and inflammation in the kidneys, contributing to DKD progression [116]. Elevated VEGF levels may serve as a non-invasive biomarker for early detection of kidney dysfunction, particularly in CKD patients [117] VEGF-A expression is often upregulated by the activation of inflammatory pathways, particularly the NF-κB pathway. This upregulation can lead to increased vascular permeability and contribute to kidney damage, including podocyte injury and glomerulosclerosis [118]. Several studies have investigated the molecular mechanisms behind VEGF regulation in DKD. Duan et al. [73] observed that high glucose exposure in human podocytes led to the suppression of microRNA-16-5p expression, accompanied by an increase in VEGFA production. Interestingly, microRNA-16-5p, originating from human urine-derived stem cells, could be transferred to hyperglycemia-induced podocytes, thereby reducing VEGF-A expression and alleviating podocyte injury in DKD rat models (Table 1). Furthermore, ADSC-derived exosomes containing miR-26a-5p have been shown to target and inhibit TLR4, thereby inactivating the TLR4/NF-κB pathway, which leads to reduced inflammation and lower VEGF-A levels. Animal studies have demonstrated that ADSC-Exo can alleviate glomerular damage in the kidney tissue of diabetic mice, including reducing extracellular matrix accumulation and basement membrane thickening [72] (Table 1, Fig. 2). Additionally, Zhao et al. [74] found that miR-15b-5p derived from ADSCs-Exo can protect against HG-induced injury in mouse podocytes by down-regulating the VEGF/PDK4 axis. This miRNA directly binds to the 3' UTR region of the PDK4 gene, suppressing its expression, which results in reduced VEGF levels and, consequently, less apoptosis and inflammation (Table 1; Fig. 2).

Interestingly, another study presented opposite results. Benigni et al. constructed adriamycin-induced nephropathy rat models found that MSC-derived VEGF promoted podocyte survival, increased glomerular VEGF expression and limited microvascular rarefaction. This difference likely arises from the distinct pathological mechanisms of DKD and adriamycin-induced nephropathy. Adriamycin-induced kidney injury is characterized by glomerular basement membrane damage, podocyte injury, and capillary rarefaction. In this context, the pro-angiogenic effects of VEGF play a beneficial role by promoting the repair of damaged microvascular networks, improving renal perfusion, and restoring oxygen supply. MSCs, through the secretion of appropriate levels of VEGF, can enhance angiogenesis, protect podocytes, and reduce glomerulosclerosis, ultimately leading to improved renal function. In contrast, DKD presents distinct pathological features, including glomerular hyperfiltration, inflammation, and tubulointerstitial fibrosis. Under hyperglycemic conditions, excessive VEGF expression can lead to abnormal angiogenesis and increased capillary permeability, worsening glomerular hyperfiltration and proteinuria. Furthermore, VEGF can exacerbate inflammation and fibrosis, accelerating renal damage in DKD. Therefore, VEGF exhibits different effects across various types of kidney injuries. MSCs, through their complex regulatory mechanisms, can modulate VEGF levels to exert therapeutic effects in different diseases. Rather than simply correlating high or low VEGF levels with disease severity, it is essential to adopt a more critical perspective, conducting a nuanced analysis that considers the specific pathophysiological state of each kidney disease (Table 1).

Other mechanisms participate in DKD

CD103⁺ dendritic cells (DCs)

Studies have shown that CD103⁺ dendritic cells (DCs) contribute to pathogenesis in mouse models of CKD [119]. These DCs are known to migrate to injury sites, where they upregulate the expression of chemokines, cytokines, and co-stimulatory molecules, subsequently influencing kidney cells and innate immune cells [120, 121].

Consistently high levels of glucose in the blood can cause kidney damage and inflammation, which can result in accumulation and maturation of CD103⁺ DCs. Additionally, CD103⁺ DCs have the ability to regulate the proliferation and activation of CD8⁺ T cells. Granzyme B, TNFα, and IFNγ are released by activated CD8⁺ T cells, which results in kidney dysfunction, structural damage, local inflammation, and fibrosis in DKD rats. Zhang et al.'s study [75] found that MSC transplantation dramatically decreased the amount of CD103⁺ DCs and downregulated important transcription factors such Batf3, Id2, and Flt3 that are linked to their differentiation. Additionally, after receiving MSC treatment, there was a decrease in the infiltration of CD8⁺ T cells and a decrease in the expression of inflammatory cytokines. The results suggest that MSCs may be able to eliminate DKD by specifically targeting CD103⁺ DCs (Table 1; Fig. 2).

PD-1/PD-L1 signaling pathway

The programmed cell death protein 1 (PD-1) and its ligand PD-L1 play critical roles in regulating immune responses, particularly in maintaining immune tolerance. In DKD, the balance between pro-inflammatory Th17 cells and regulatory T cells (Tregs) is crucial for disease progression [122, 123]. Wang et al. [76] discovered that p-MSCs enhanced renal function and mitigated pathological damage in DKD rat models. The study revealed that p-MSCs modulate the balance between Th17 and Treg cells through the PD-1/PD-L1 signaling pathway. Specifically, p-MSCs enhanced PD-1 expression while downregulating PD-L1, leading to a reduction in Th17 cell proportions and an increase in Treg cells. This shift in immune cell populations resulted in a reduction in inflammation and kidney injury, suggesting that MSC-based therapies may be able to restore immune homeostasis in DKD via the PD-1/PD-L1 pathway (Table 1; Fig. 2).

Optimizing MSC therapy

Preconditioning and genetic engineering

Researchers discovered that under the high glucose environment of pre-treated hUMSCs, the treating function of exosomes can be more effective than the nature culture environment of hUMSCs in treating the rat models of DKD. High-glucose treatment of hUMSCs-exo can dramatically reduce M1 macrophage numbers while increasing M2 macrophage numbers [38]. Wang et al. [80] found that Fe3O4-coated polydopamine nanoparticle (NP)-internalized p-MSCs can notably improve p-MSCs homing to injured kidney tissues resulting in enhanced renal function and decreased tubulointerstitial fibrosis compared to the traditional transplantation of p-MSC alone in DKD rat models (Table 1). Ozkan et al. [79] discovered that deferoxamine-preconditioned MSC-derived conditioned media (DFS-CM) is more effective than normal conditioned media in treating DN rats. DFS-CM improved albumin/creatinine ratio, renal mass index, podocyte damage, and tubular apoptosis, with enhanced levels of key growth factors and reduced autophagic activity. These findings highlight DFS-CM's superior therapeutic potential for diabetic nephropathy due to its enriched secretome content (Table 1). Researchers compared the effects of MSCs modified with ACE2 (angiotensin-converting enzyme 2) to unmodified MSCs in DN rats. They found that MSC-ACE2 treatment more effectively reduced albuminuria, improved glomerulosclerosis, and decreased glomerular fibrosis. This was characterized by decreasing Ang II levels, raising Ang1-7, and blocking the TGF-β/Smad pathway. The study concluded that MSCs modified with ACE2 provide superior therapeutic benefits in DKD by suppressing renal RAS activation and mitigating fibrosis [77] (Table 1).

Long non-coding RNAs (lncRNAs) are non-coding RNAs longer than 200 nucleotides, and they play a critical role in podocyte injury and the progression of DKD [124]. For instance, lncRNA ENST00000436340 is found to be upregulated in DKD. It exacerbates podocyte injury by promoting the interaction between PTBP1 and RAB3B, which results in cytoskeletal rearrangement and disrupted GLUT4 translocation, ultimately leading to the progression of DKD [124]. Wang et al. [84] identified lncRNA HOXB3OS as a potential therapeutic target in DKD. HOXB3OS has been shown to reduce HG-induced podocyte damage, and when incorporated into engineered ADSC-derived exosomes, it improved kidney function in type 2 DKD mouse models. The protective effect of HOXB3OS was attributed to its ability to combine with Ythdc2, inhibiting the binding of Ythdc2 to SIRT1 mRNA and thus preventing m6A-dependent SIRT1 mRNA degradation (Table 1). In addition to lncRNAs, immune regulatory mechanisms also play a critical role in DKD. For instance, CD4⁺CD25⁺FoxP3⁺ regulatory T cells (Tregs) exert an immunosuppressive effect, which is beneficial in inflammatory conditions. In STZ-induced DN mice, researchers have shown that loading Ex-4 into hUMSCs-derived exosomes via electroporation significantly induces Treg expansion, ultimately alleviating kidney injury [83] (Table 1). These findings

highlight the therapeutic potential of targeting both lncRNAs and immune cell regulation to mitigate the progression of DKD.

Combination with drug therapy

Yang et al. [81] found that combining ADSCs and empagliflozin (EMPA) can protect renal function superior to just one therapy in DN rats (Table 1). Meng et al. [82] observed that hUMSCs plus irbesartan can greatly improve renal function indices and the expression of proteins associated with glomerular podocyte injury in rats, compared to MSCs or irbesartan alone (Table 1). Researchers examined the renal protective effects of combining ADSCs with exenatide in diabetic rats, the results showed that this combination therapy significantly improved kidney function and renal architecture by restoring the balance of inflammatory, fibrotic, and apoptotic markers, in comparison to ADSCs alone [78] (Table 1). In conclusion, the combination of MSCs with drugs like empagliflozin and exenatide offers a synergistic approach to treating DKD. MSCs' anti-inflammatory, antioxidative, and regenerative properties complement these drugs' mechanisms, enhancing therapeutic effects. Empagliflozin reduces glucose toxicity and oxidative stress, while exenatide improves glycemic control and reduces inflammation, both aligning with MSCs' reparative actions. This combined approach can significantly enhance renal function and offer optimism for the management of diabetic nephropathy.

Clinical trials

Packham et al. [125] conducted a multicenter, randomized, double-blind, dose-escalation, placebo-controlled trial to evaluate the safety and efficacy of allogeneic bone marrow-derived mesenchymal precursor cells (rexlemestrocel-L) in DKD. The study demonstrated that rexlemestrocel-L exert anti-inflammatory effects by reducing IL-6 levels in DKD patients. Intravenous administration was well-tolerated, with no acute or treatment-related adverse events, and no participants developed persistent donor-specific anti-HLA antibodies, highlighting its strong immunological safety. Notably, treatment with 300 × 10^6rexlemestrocel-L led to improvements in mGFR and eGFR. These findings suggest that rexlemestrocel-L is safe and may support renal function, presenting a promising therapeutic option for patients at risk of requiring kidney transplantation (Table 2).

Pericoet al. [126] conducted a randomized, double-blind, placebo-controlled phase 1b/2a clinical trial to investigate the potential therapeutic effects of MSCs therapy in patients with type 2 diabetes and progressive DKD. The study enrolled 16 participants and employed bone marrow-derived, anti-CD362 antibody-selected allogeneic MSCs (ORBCEL-M) as the intervention. The study found that a single intravenous infusion of ORBCEL-M was safe and well-tolerated and observed a significantly lower rate of decline in eGFR compared with placebo, although mGFR did not differ significantly. The research suggests that ORBCEL-M may exert its effects through immunomodulatory mechanisms, including the preservation of circulating regulatory T cells (Tregs), lower natural killer T cells, and stabilization of inflammatory monocyte subsets. Correlative analyses also indicated significant relationships between Treg proportions and eGFR, as well as inverse correlations between inflammatory biomarkers and GFR, supporting a potential anti-inflammatory/immune-modulating effect of ORBCEL-M. While both the Packham et al. and Pericoet et al. studies explored the potential of allogeneic MSCs for diabetic kidney disease, they differed significantly in their approaches. Packham et al.'s phase 1 study investigated the safety and tolerability of rexlemestrocel-L (STRO-3 selected MPCs) using a dose-escalation design with a 60-week follow-up, observing short-term trends

Table 2 Overview of clinical studies of MSCs in the treatment of DKD

Author, year	Patients	Research type	Stem cell type	Group	Handling methods	Treatment effect
Packham et al. (2016) [125]	Adults with DKD ($n=30$)	Multicenter, randomized, double-blind, dose-escalating, sequential, placebo-controlled trial	Adult allogeneic bone-marrow-derived mesenchymal precursor cell (MPC)	T1: treated with MPC 150×10^6 ($n=10$) T2: treated with MPC 300×10^6 ($n=10$) C: placebo group ($n=10$)	Randomized received intravenous (IV) infusion either MPC (150×10^6 or 300×10^6 cells) or placebo	Treatment with MPC can decrease IL-6 levels and stabilize or improve eGFR and mGFR.
Perico et al. (2023) [126]	Type 2 diabetes and progressive DKD patients ($n=16$)	Randomized, double-blind, placebo-controlled phase 1b/2a trial	Next-generation human bone marrow-derived, anti-CD362 antibody–selected allogeneic MSCs (ORBCEL-M)	T: treated with ORBCEL-M, ($n=12$) C: placebo group ($n=4$)	Randomized to receive a single intravenous infusion of ORBCEL-M (80×10^6 cells) or placebo and followed-up for 18 months	MSC therapy significantly slowed eGFR decline while preserving regulatory T cells, reducing natural killer T cells, and stabilizing inflammatory monocyte subsets compared to placebo.

eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate; DKD: diabetic nephropathy disease; IL-6: Interleukin-6

of stabilized or improved eGFR and mGFR. In contrast, Remuzzi et al.'s phase 1b/2a trial focused on a single low dose of ORBCEL-M (CD362 selected MSCs) over 18 months, finding a significant reduction in eGFR decline rate but no difference in mGFR. The former study's mechanistic exploration was more focused on general anti-inflammatory properties and IL-6, whereas the latter provided a more in-depth immunological profile, highlighting the preservation of Tregs and stabilization of monocyte subsets. Future research should focus on larger, longer-term trials to validate these preliminary efficacy signals, directly compare the effectiveness of different MSC products and selection markers and further elucidate the optimal dosing regimens and specific mechanisms of action, especially regarding the divergent eGFR and mGFR results observed between the studies (Table 2).

Limitations & challenges

Potential risks of MSC therapy

1) Tumorigenicity: MSCs exhibit tumorigenic properties. Research indicates that their immunomodulatory effects and uncontrolled proliferative activity can promote tumor growth, angiogenesis, and metastasis. These effects are mediated through the secretion of cytokines, growth factors, and tumor-regulating factors [127]. Additionally, MSCs can differentiate into cancer-associated fibroblasts (CAFs), contributing to a supportive tumor microenvironment that facilitates proliferation and metastasis. [128].
2) Contribution to Fibrosis: MSCs may contribute to fibrosis in various organs or differentiate into unintended cell types, potentially leading to off-target effects. One mechanism by which MSCs promote fibrosis is their differentiation into myofibroblasts, which are key effector cells in the fibrotic process. In the liver, MSCs derived from adult and pediatric bone marrow have been shown to differentiate into myofibroblasts, resulting in collagen deposition and fibrotic tissue development [129]. Bonzo et al. transplanted human bone marrow-derived mesenchymal stem cells (hBMSCs) into non-obese diabetic severe combined immunodeficient (NOD/SCID) mice via tail vein injection, and found that hBMSCs have the potential to migrate into both normal and injured liver parenchyma, but differentiation into hepatocyte-like cells was rare, with a significant number of hBMSCs of human origin exhibiting a myofibroblast-like morphology [130].
3) Immunosuppressive Effects: MSCs are often considered immune-privileged due to their ability to prolong graft survival and reduce immune rejection by promoting regulatory T-cell expansion and suppressing inflammatory cytokines, making them promising for transplantation and immune-related therapies [131, 132]. However, despite these immunosuppressive effects, MSCs are not entirely immune-privileged. They can induce immune memory, leading to rejection upon re-exposure, which highlights their potential to trigger specific immune responses [133, 134]. Therefore, while MSCs offer significant therapeutic benefits, their immunogenicity must be carefully considered in clinical applications. Strategies such as optimizing cell sources, immune-matching, or genetic modifications may be required to enhance their safety and efficacy.

Challenge of MSCs in treating disease

The application of MSCs in therapeutic settings faces several challenges, primarily due to the variability in MSC sources, culture conditions, and preconditioning methods. First, MSCs can be obtained from a range of tissues, such as bone marrow, umbilical cord, and adipose tissue. Each of these sources possesses unique phenotypic and functional traits. This variation leads to differences in therapeutic outcomes, as MSCs derived from different tissues may display distinct gene expression profiles and functional properties [135–137]. Second, the culture conditions, such as media composition, growth factor presence, and serum supplements, significantly affect MSC characteristics. Differences in these culture conditions can lead to variations in cell morphology, physiology, and functionality, thereby contributing to the overall heterogeneity of MSCs [138, 139]. Furthermore, the passage number during the culture process also influences the properties of MSCs. Research has demonstrated that MSCs from different passages, specifically passages 1 through 7, exhibit varying degrees of therapeutic efficacy [136]. Finally, preconditioning approaches, such as chemical induction and genetic modifications, are employed to improve the therapeutic potential of MSCs. However, variations in both the source of the cells and the preconditioning methods used present additional challenges when attempting to compare outcomes across different studies [139, 140]. These variations underscore the difficulties in standardizing MSC-based therapies and highlight the need for well-defined protocols to optimize their use in clinical applications.

Proposed solutions and future directions

To improve the safety and efficacy of MSC-based therapies, several key strategies should be implemented.

(1) Standardizing the source of MSCs is crucial to reduce variability and ensure consistent therapeutic

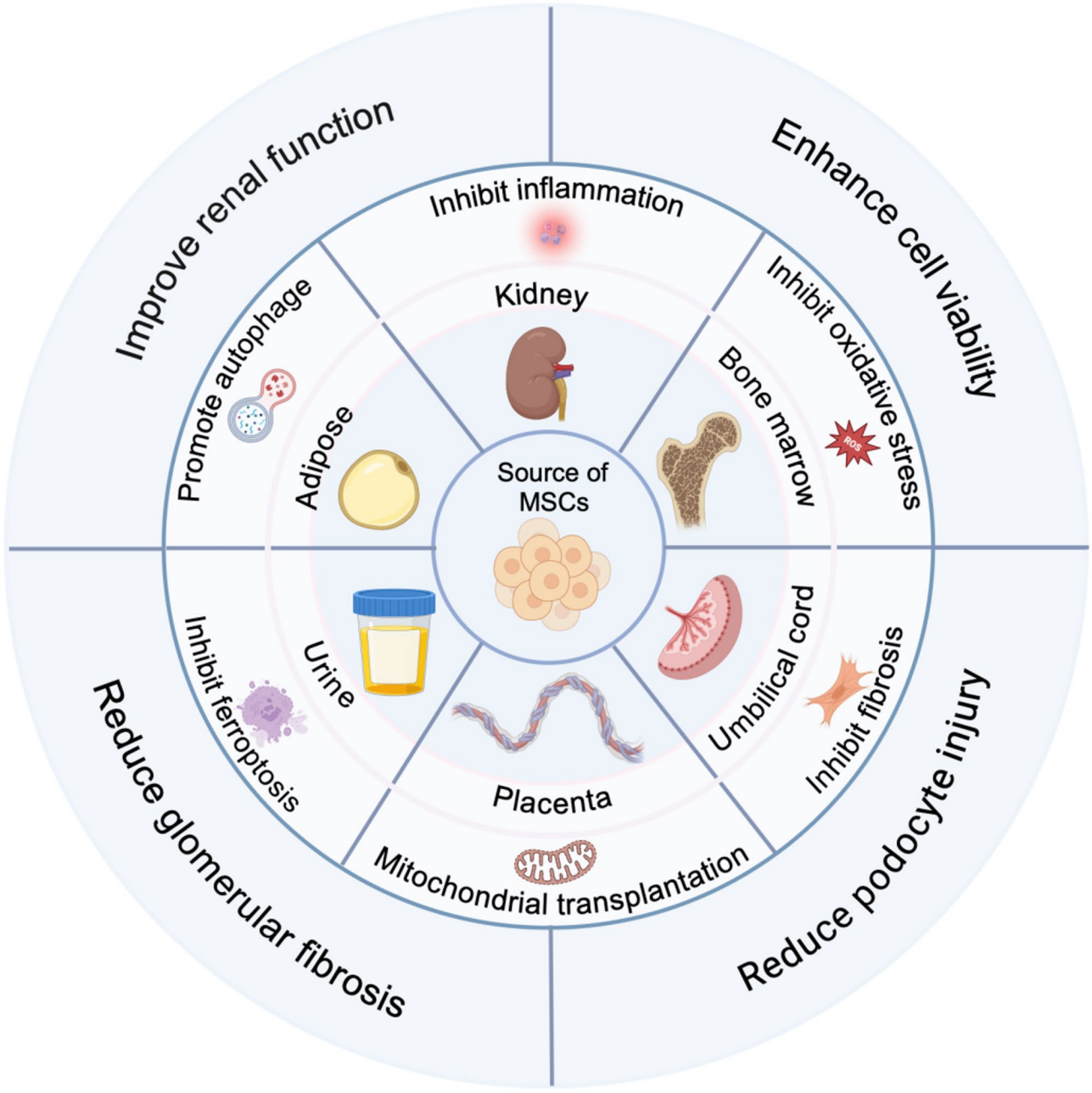

Fig. 3 Outline of the mechanism of mesenchymal stem cells in treating diabetic nephropathy. Created in https://BioRender.com

outcomes. (2) Optimizing culture conditions, including media composition and growth factors, will enhance MSC homogeneity and therapeutic potential. (3) Preconditioning methods and genetic modifications must be carefully regulated to minimize risks like tumorigenicity and fibrosis, while standardizing these techniques across studies will facilitate comparisons. (4) Managing MSC immunogenicity through immune matching or genetic engineering is necessary to prevent rejection, and long-term safety monitoring is essential to track potential adverse effects. In conclusion, addressing these challenges through standardized protocols and rigorous clinical trials will be essential for the successful integration of MSC therapy into clinical practice.

Conclusion

In this review, we have outlined the mechanisms by which MSCs treat DKD, including the inhibition of inflammation, fibrosis, oxidative stress, apoptosis, ferroptosis, and pyroptosis, as well as the promotion of autophagy, mitochondrial transfer, and VEGF-targeted effects. Preconditioning or genetic engineering strategies may

enhance the therapeutic efficacy of MSCs compared to unmodified MSCs, while combination therapy with pharmacological agents has shown the potential to yield superior outcomes. Clinical trials suggest that MSC-based therapies are generally safe and well-tolerated, with serious adverse events being rare. To provide a clear overview of the current research landscape, we have compiled key mechanisms and clinical trial findings in two tables (Tables 1 and 2) and three figures (Figs. 1, 2 and 3), helping readers better grasp recent advancements.

Despite its promise, MSC therapy for DKD still faces significant challenges. These include the heterogeneity of MSCs due to variations in donor sources, isolation techniques, and expansion protocols, which can lead to inconsistent therapeutic outcomes. Additionally, concerns regarding MSC survival, engraftment, and functional stability after transplantation remain unresolved. The long-term safety and potential tumorigenicity of MSC-based therapies also require further investigation. Moreover, logistical hurdles such as large-scale production, storage, and transport limit the widespread clinical application of MSC therapy. Looking ahead, future research should focus on optimizing MSC preparation methods to enhance consistency and therapeutic efficacy. Advances in biomaterials and three-dimensional culture systems may provide solutions for improving MSC viability and function. Furthermore, integrating MSC therapy with novel drug delivery systems, gene editing technologies, and artificial intelligence-driven approaches for patient stratification could refine treatment strategies. Large-scale, well-designed clinical trials with standardized protocols are crucial to validating the long-term safety and effectiveness of MSC therapy. Addressing these challenges will be key to unlocking the full clinical potential of MSCs in DKD treatment.

Abbreviations

BMSCs	Bone marrow mesenchymal stem cells
CKD	Chronic kidney disease
DCs	Dendritic cells
DN rats	Diabetic nephropathy rats
DKD	Diabetic kidney disease
Evs	Extracellular vesicles
Exo	Exosomes
EMT	Epithelial-to-mesenchymal transition
ESRD	End-stage renal disease
GBM	Glomerular basement membrane
GMCs	Glomerular mesangial cells
HK-11 cells	Human renal tubular epithelial cells
HK2 cells	Human kidney proximal tubular epithelial cell line
hrGECs	Human renal glomerular endothelial cell line
HG	High glucose
iNOS	Inducible nitric oxide synthase
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
LPS	Lipopolysaccharides
LncRNAs	Long non-coding RNAs
MPC5 cells	Mouse conditionally immortalized podocyte cell line
MSCs	Mesenchymal stem cells
NF-κB	Nuclear factor kappa B
NRK-52e	Rat renal tubular epithelial cells
Nrf2	Nuclear factor erythroid 2-related factor 2
p-MSCs	Placenta-derived MSCs
RAW 264.7	A mouse mononuclear macrophage cell line
SD rats	Sprague-Dawley rats
STZ	Streptozotocin
TNF-α	Tumor Necrosis Factor-alpha
TLRs	Toll-like receptors
UCMSCs	Umbilical cord-derived mesenchymal stem cells
VEGF	Vascular endothelial growth factor
hADSCs	Human adipose-derived mesenchymal stem cells
hPMSCs	Human-placental mesenchymal stem cells
hUMSCs	Human umbilical cord-derived mesenchymal stem cells

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