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Mesenchymal Stem Cell Therapy in Kidney Diseases: Potential and Challenges

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Abstract

Kidney disease (KD) is a life-threatening disease characterized by high morbidity and mortality in clinical settings, which can be caused by many reasons, and the incidence increases with age. However, supportive therapy and kidney transplantation still have limitations in alleviating KD progression. Recently, mesenchymal stem cells (MSCs) have shown great potential in repairing injury through their multidirectional differentiation and self-renewal ability. Of note, MSCs serve as a safe and effective therapeutic strategy for treating KD in preclinical and clinical trials. Functionally, MSCs ameliorate KD progression by regulating the immune response, renal tubular cell apoptosis, tubular epithelial–mesenchymal transition, oxidative stress, angiogenesis, and so on. In addition, MSCs exhibit remarkable efficacy in both acute kidney injury (AKI) and chronic kidney disease (CKD) through paracrine mechanisms. In this review, we outline the biological characteristics of MSCs, discuss the efficacy and mechanisms of MSCs-based therapy for KD, summarize the completed and ongoing clinical trials, as well as analyze limitations and new strategies, aiming to provide new ideas and approaches for the preclinical experiments and clinical trials of MSCs transplantation for KD.

Keywords

kidney diseases, mesenchymal stem cell, regeneration, paracrine

Introduction

Kidney disease (KD) is a global public health problem that affects more than 750 million of the global population and causes 5 to 10 million deaths each year[1,2], with the main common diseases being acute kidney injury (AKI) and chronic kidney disease (CKD). Previous studies have shown that the development and progression of KD were associated with obesity[3], diabetes[4], hepatitis B virus infection[5], and so on. Meanwhile, KD progression is a risk factor for cardiovascular diseases[6]. In addition, clinical studies have found that the high incidence and poor prognosis of KD were relevant to clinical care and huge economic costs[7], with approximately $10 billion spent annually on treating AKI[8] and more than $80 billion spent on caring for CKD without kidney replacement therapy[9] in the United States. Currently, the common therapeutic methods for KD include drugs, hemodialysis and peritoneal dialysis, and renal transplantation[10]. However, the expected efficacy was still not achieved due to the irreversibility of kidney injury, the toxic effects of drug therapy, the inconvenience of dialysis, and the shortage and high cost of kidney transplant donors[11]. Therefore, there is an urgent need to explore new therapeutic strategies to slow down the progression of KD.

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In recent years, stem cells have been used as a new regenerative therapy for a variety of diseases, including KD[12]. Mesenchymal stem cells (MSCs), as one of the important members of the stem cell family, can be obtained from a variety of tissues such as bone marrow, adipose, umbilical cord, and peripheral blood and have powerful biological properties of immunomodulation, anti-inflammation, and tissue repair[13]. Preclinical and clinical trials have shown that MSCs possess reparative and protective effects on kidney injury[14,15]. Functionally, MSCs exert anti-apoptotic, antioxidant, anti-inflammatory, anti-fibrotic, and immunomodulatory activities through secreting trophic factors and delivering extracellular vesicles (EVs)[16,17]. Overall, MSCs are considered to be the most promising stem cell population for the treatment of KD.

In this review, we will focus on the current research advances and challenges in the use of MSCs for the treatment of KD. Preliminarily, this review provides an overview of the origin and biological properties of MSCs. Subsequently, we summarize the underlying mechanisms and clinical translational applications of MSCs in the treatment of KD. Finally, we analyzed the obstacles encountered in the use of MSCs for the treatment of KD and proposed corresponding strategies to cope with the limitations of MSCs in KD. Of note, this review aims to provide new ideas and directions for the treatment of KD with MSCs in preclinical experiments and clinical trials.

Biological Characteristics of MSCs

Mesenchymal stem cells are a class of adult stem cells with self-renewal and differentiation potential[18]. They have become a new means of treating KD because of their multidirectional differentiation potential, high proliferative capacity, immune regulation, and self-replication[19]. They can be obtained from a variety of tissues, including bone marrow, adipose tissue, umbilical cord, placenta, amniotic fluid, and dental pulp[20] (Fig. 1). Although MSCs are derived from different sources [eg, bone marrow mesenchymal stem cells (BMMSCs), adipose-derived mesenchymal stem cells (ADMSCs), and umbilical cord mesenchymal stem cells (UCMSCs)], they have similar differentiation and biological functions[21]. Numerous studies have confirmed that MSCs can differentiate a variety of cells (eg, osteoblasts, myoblasts, cardiomyocytes, and renal parenchymal cells) with different functional characteristics under different induction conditions[22]. Previous studies have shown that MSCs regulated immune activity and enhanced the expansion and differentiation potential of host cells through direct cell–cell contact or paracrine mechanisms, thus promoting the recovery of injured tissues[23]. Importantly, preclinical experiments and clinical trials have confirmed that treatment with MSCs significantly improved the progression of KD[24,25]. Functionally, the main regulatory roles of MSCs are as follows: (1) The recruited MSCs differentiate into functional cells to replace damaged cells, and (2) as a response to inflammatory cytokines, MSCs produce large amounts of cytokines, chemokines, growth factors, and exosomes, which stimulate angiogenesis, prevent cell apoptosis and epithelial–mesenchymal transformation (EMT) process, block oxidative stress, promote extracellular matrix (ECM) remodeling, and induce differentiation of tissue stem cells[26]. In recent years, several studies have proved that MSCs-secreted exosomes (MSCs-Exo) via paracrine mechanisms not only have the same effects as MSCs but also have the advantages of low transplantation risk, easy storage management, high controllability, low immunogenicity, high safety, high repairability, and so on[27]. The above studies suggest that MSCs exhibit great therapeutic effects on injury repair and immune-characterized diseases, and serve as shining stars of stem cells in the field of cell therapy and regenerative medicine.

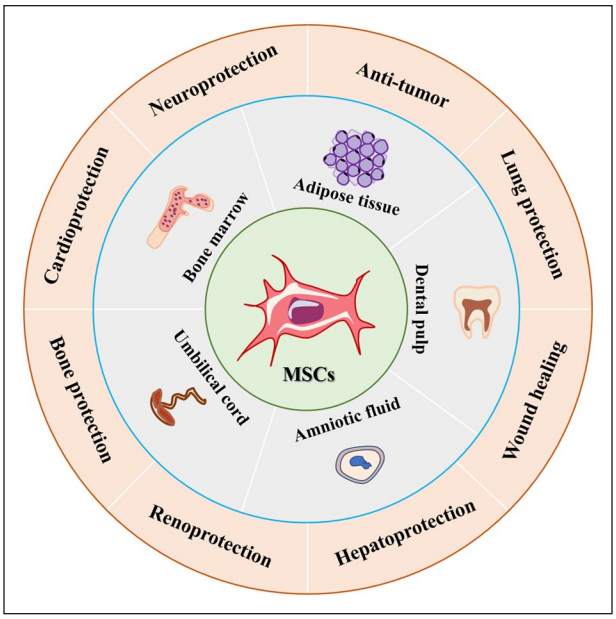

Figure 1. Sources and application of MSCs. MSCs: mesenchymal stem cells.

Efficacy and Mechanisms of MSCs Therapy in KD

Currently, MSCs are considered as new therapeutic tools for the treatment of KD because of their multidirectional differentiation, migration and homing, and paracrine effects[17,28]. Previous studies have shown that MSCs are effective and safe when used to treat organ injury[29,30]. Importantly, MSCs therapy promoted the recovery of renal function after renal pathogenesis through various mechanisms[31] (Fig. 2) such as anti-inflammation, anti-apoptosis, angiogenesis, anti-oxidative stress, anti-fibrosis, regulating autophagy, and senescence (Table 1).

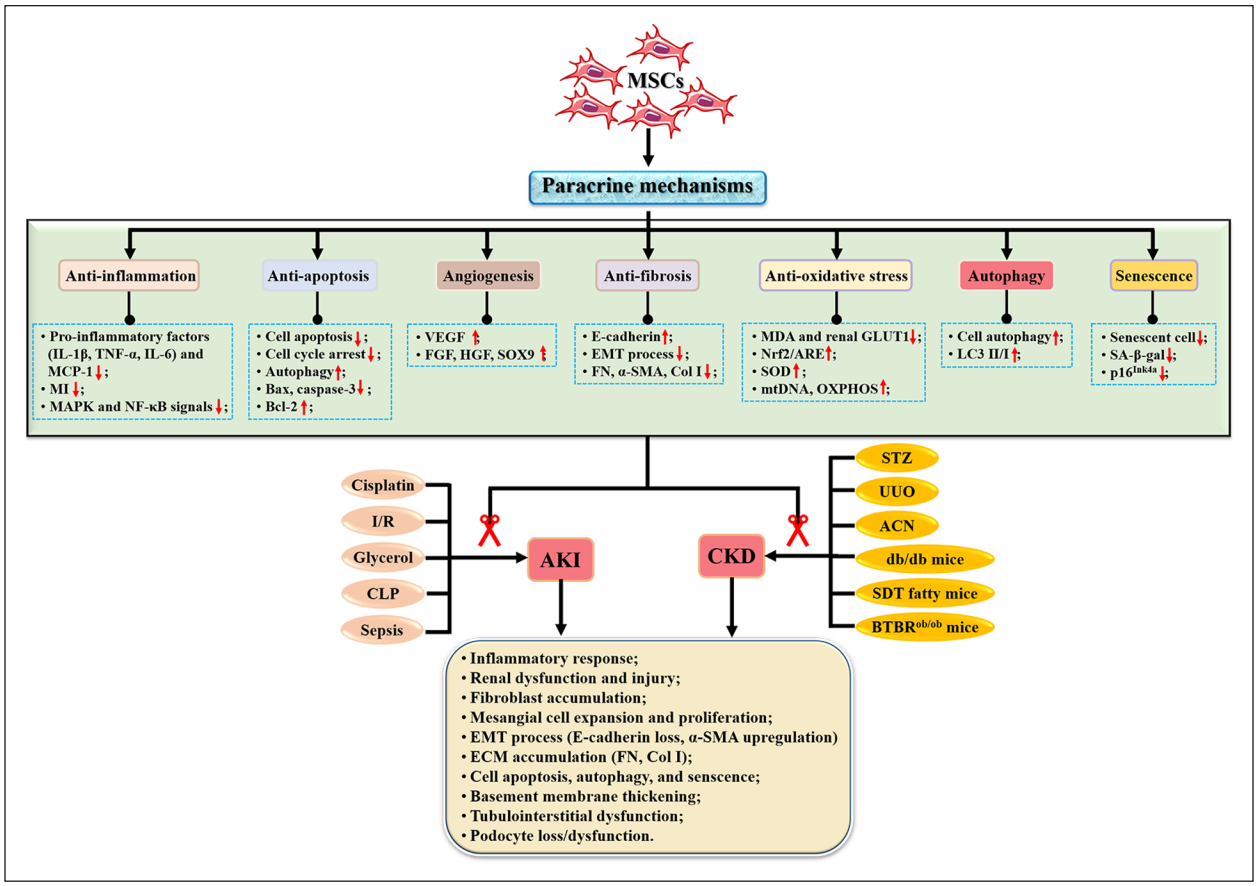

Figure 2. Mechanisms of MSCs in the treatment of kidney diseases. ACN: aristolochic acid nephropathy; AKI: acute kidney injury; BTBR$^{ob/ob}$: Black and Tan Brachyury (BTBR) leptin deficiency; CKD: chronic kidney disease; CLP: cecal ligation and puncture; Col I: type I collagen; ECM: extracellular matrix; EMT: epithelial–mesenchymal transformation; FGF: fibroblast growth factor; FN: fibronectin; GLUT1: glucose transporter type 1; I/R: ischemia–reperfusion; HGF: hepatocyte growth factor; IL-1β: interleukin-1β; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; MI: macrophage infiltration; mtDNA: mitochondrial DNA; NF-κB: nuclear factor–kappa B; Nrf2/ARE: nuclear factor erythronid 2-related factor 2/antioxidant response elements; OXPHOS: oxidative phosphorylation; SDT: Spontaneously Diabetic Torii; α-SMA: alpha-smooth muscle actin; SOD: superoxide dismutase; SOX9: sex-determining region Y-box 9; STZ: streptozotocin; TNF-α: tumor necrosis factor–alpha; UUO: unilateral ureteral obstruction; VEGF: vascular endothelial growth factor.

Anti-Inflammation

Previous studies have proved that activation of inflammation was an important part of the pathogenic process of KD, and macrophage infiltration and aggregation contribute to the acceleration of KD progression[83]. For example, a study by Heerspink et al.[84] showed that high plasma levels of tumor necrosis factor (TNF) receptor 1 and IL-6 were associated with the progression of diabetic KD. Martos-Rus et al.[85] found that the serum levels of inflammatory cytokines/chemokines were upregulated in patients with end-stage KD and activated the nuclear factor–kappa B (NF-κB) pathway, as well as increased peripheral monocytes and inflammatory polarization of macrophages were detected in the kidney tissue of mice with uremia model. In addition, macrophages play an important role in immune surveillance and maintaining the stability of the renal internal environment[86], and macrophages derived from bone marrow can directly transform into myofibroblasts in the damaged kidney, accelerating the progression of pathogenic fibrosis[87,88]. Of note, MSCs can ameliorate kidney injury by inhibiting inflammation and promoting kidney repair[89]. For instance, treatment with UCMSCs significantly prevented the progression of diabetic nephropathy (DN) by reducing pro-inflammatory cytokines and secreting abundant epidermal growth factor and vascular endothelial growth factor (VEGF)[52].

Recently, several studies have confirmed that MSCs-derived EVs play a major role in treating KD[15]. For example, MSCs-Exo treatment slowed the progression of ischemic–reperfusion injury (IRI) by inhibiting expressions of inflammatory factors [eg, IL-6, TNF-α, NF-κB, and interferon (IFN)-γ][51]. Gao et al.[41] showed that ADMSCs-Exo inhibited inflammation of sepsis-related AKI by blocking the NF-κB pathway. Another study found that BMMSCs-Exo was a promising therapeutic approach for preserving CKD progression via reducing inflammation and degeneration[69].

Table 1. Mechanisms of MSCs and Extracellular Vesicles in the Treatment of KD According to Published Studies From 2017 to 2022.

No.	Type of source	Model & doses	Treatment effect	Mechanism	Ref.
AKI					
1	BMMSCs	◆ *In vitro*: NRK-52E cells subjected to H/R ◆ Dose: co-culture (BMMSCs:NRK-52E) ratio 1:1 ◆ *In vivo*: I/R-induced AKI mice model ◆ Dose: 5×10^5 BMMSCs	✓ Renal macrophage infiltration and inflammation, and tubular apoptosis ↓; ✓ Tubular proliferation ↑; ✓ Superoxide formation, DNA damage, and lipid peroxidation ↓; ✓ Increased antioxidant expression ↑; ✓ Expression of IL-1β, Bax, and caspase 3 ↓; ✓ Expression of autophagy-related LC3B, Atg5 and Beclin 1 ↑;	Anti-oxidative stress Anti-apoptosis	Tseng et al.[32]
2	BMMSCs	◆ *In vitro*: HK-2 cells treated with LPS ◆ Dose: 1×10^4 BMMSCs ◆ *In vivo*: sepsis-induced AKI rat model ◆ Dose: 1×10^6 BMMSC	✓ Tubular injury score ↓; ✓ Levels of serum creatinine and nitrogen ↓; ✓ Levels of TNF-α, IL-6, and IL-1β ↓; ✓ Mitophagy in RTECs of kidney tissues and HK-2 cells ↑; ✓ Cell apoptosis and pyroptosis ↓; ✓ Expression of NLRP3, ASC, Caspase-1 ↓; ✓ SITR1/Parkin pathway ↑;	Anti-apoptosis	Guo et al.[33]
3	BMMSCs	◆ *In vivo*: I/R-induced AKI rat model ◆ Dose: 5×10^5 BMMSCs	✓ Expression of α-SMA, collagen I/III ↓; ✓ Interstitial fibrosis and infiltration of inflammatory cells ↓; ✓ Levels of VEGF, HGF, and PGE2 ↑;	Anti-fibrosis	Ishiuchi et al.[34]
4	BMMSCs	◆ *In vivo*: I/R-induced AKI ◆ Dose: 1×10^6 BMMSCs	✓ Levels of serum creatinine and nitrogen ↓; ✓ Levels of TNF-α, IL-1β, and IL-6 ↓; ✓ Cell apoptosis ↓;	Anti-inflammation Anti-apoptosis	Wang et al.[35]
5	BMMSCs	◆ *In vivo*: I/R-induced AKI ◆ Dose: 1×10^6 BMMSCs	✓ Macrophages infiltration and pro-inflammatory cytokines (TNF-α and IL-1β) ↓; ✓ C5a and C5aR expression ↓; ✓ NF-κB pathway ↓;	Anti-inflammation	Tang et al.[36]
6	BMMSCs	◆ *In vivo*: adriamycin-induced AKI ◆ Dose: 5×10^6 BMMSCs	✓ Tubular fibrosis, serum creatinine, and nitrogen ↓; ✓ Profibrotic PECs ↓;	Anti-fibrosis	Aslam et al.[37]
7	ADMSCs	◆ *In vivo*: gentamicin-induced AKI ◆ Dose: 1×10^6 ADMSCs	✓ Levels of serum creatinine and nitrogen ↓; ✓ Expression of Grp78, Atf6, Ire1, Perk, Chop, Caspase12, and Xbp1 ↓; ✓ ER stress ↓;	Anti-ER stress	He et al.[38]
8	ADMSCs	◆ *In vivo*: I/R-induced AKI ◆ Dose: 2×10^6 ADMSCs	✓ Number of apoptotic cells ↓; ✓ Levels of total urinary protein and serum creatinine, pro-inflammatory cytokines (eg, IL-6, TNF-α, IL-1β, IFN-γ, IFN-γ, and TGF-β), and the inflammation-associated proteins (eg, HGF and SDF1) ↓; ✓ Expression of the anti-inflammatory cytokine (IL-10) and Bcl-2 ↑;	Anti-inflammation Anti-apoptosis	Zhang et al.[39]

(continued)

Table 1. (continued)

No.	Type of source	Model & doses	Treatment effect	Mechanism	Ref.
9	ADMSCs	◆ *In vivo*: cisplatin-induced AKI ◆ Dose: 2.5 × 10^7 ADMSCs	✓ Necrosis or epithelial cells damage ↓; ✓ Levels of serum creatinine and nitrogen ↓; ✓ Expression of TNF-α and TGF-β1 ↓;	Anti-inflammation Anti-apoptosis	Begum et al.[40]
10	ADMSCs-Exo	◆ *In vivo*: sepsis-induced AKI ◆ Dose: 100 μg ADMSCs-Exo	✓ Levels of BUN and Scr ↓; ✓ Levels of MCP-1, IL-6, TNF-α ↓; ✓ NF-κB pathway ↓;	Anti-inflammation	Gao et al.[41]
11	ADMSCs-Exo	◆ *In vivo*: sepsis-induced AKI ◆ Dose: 2 mg/kg body weight ADMSCs-Exo	✓ Levels of AST, ALT, BUN ↓; ✓ Levels of IL-6, IL-1β, TNF-α, MCP-1 ↓; ✓ circ_0001295 expression ↑;	Anti-inflammation	Cao et al.[42]
12	ADMSCs-Exo BMMSCs-Exo	◆ *In vivo*: LPS-induced AKI ◆ Dose: 1 × 10^5 and 5 × 10^5 BMMSCs-Exo	✓ Renal function ↑; ✓ Oxidative stress and inflammation ↓;	Anti-oxidative stress Anti-inflammation	Zhang et al.[43]
13	BMMSCs-Exo	◆ *In vitro*: H/R-induced HK-2 cells ◆ Dose: unknown ◆ *In vivo*: IRI mice model ◆ Dose: 5 × 10^{10} BMMSCs-Exo	✓ Cell apoptosis ↓; ✓ Expression of cleaved caspase-3 and Bax ↓; ✓ miR-199a-3p expression ↑; ✓ AKT and ERK pathway ↑;	Anti-apoptosis	Zhu et al.[44]
14	BMMSCs-Exo	◆ *In vivo*: IRI mice model ◆ Dose: 100 μg/mouse BMMSCs-Exo	✓ Levels of BUN and Scr ↓; ✓ Renal tubular cell apoptosis ↓; ✓ Renal fibrosis ↓; ✓ M1 macrophages infiltration and levels of IL-1β, IL-6 and TNF-α ↓; ✓ M1 macrophage to M2 macrophage ↑;	Anti-inflammation	Xie et al.[45]
15	UCMSCs-Exo	◆ *In vivo*: I/R-induced AKI ◆ Dose: 50 and 100 μg UCMSCs-Exo	✓ Renal tubules injury ↓; ✓ Cell cycle arrest and apoptosis of TECs ↓; ✓ miR-125b-5p expression ↑;	Anti-apoptosis	Cao et al.[46]
16	UCMSCs-Exo	◆ *In vivo*: I/R-induced AKI ◆ Dose: 4 × 10^8 UCMSCs-Exo	✓ Apoptosis and necroptosis ↓; ✓ Pro-inflammatory cytokines/chemokines and infiltration of macrophages ↓; ✓ NF-κB pathway ↓;	Anti-apoptosis Anti-inflammation	Huang et al.[47]
17	UCMSCs-Exo	◆ *In vivo*: I/R-induced AKI ◆ Dose: unknown	✓ Pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and oxidative stress (malondialdehyde) ↓; ✓ Levels of BUN, Scr, urinary albumin and CR, 8-isoprostane ↓; ✓ IL-10 level ↑;	Anti-inflammation	Zhang et al.[48]
18	UCMSCs-Exo	◆ *In vivo*: sepsis-induced AKI ◆ Dose: 120 μg UCMSCs-Exo	✓ Levels of BUN and Scr ↓; ✓ Level of cleaved caspase-3 protein ↓; ✓ Levels of IL-1β and TNF-α ↓; ✓ NF-κB pathway ↓; MiR-146b ↑;	Anti-inflammation	Zhang et al.[49]
19	UCMSCs-Exo	◆ *In vitro*: cisplatin-induced NRK-52E cells ◆ Dose: 200 μg/mL UCMSCs-Exo ◆ *In vivo*: cisplatin-induced AKI ◆ Dose: 200 μg UCMSCs-Exo	✓ Cell proliferation ↑; ✓ Levels of Scr and BUN ↓; ✓ The protein levels of caspase-3 and Bax ↓; ✓ Expression of LC3B, ATG5 and ATG7 ↑; ✓ Levels of TNF-α, IL1-β, and IL6 ↓;	Autophagy Anti-apoptosis	Wang et al.[50]

(continued)

Table 1. (continued)

No.	Type of source	Model & doses	Treatment effect	Mechanism	Ref.
20	MSCs-Exo	◆ *In vivo*: I/R-induced AKI ◆ Dose: 1.5 × 10^5 MSCs-Exo	✓ Levels of IL-6, TNF-α, IFN-γ ↓; ✓ Levels of caspase-9, cleaved caspase-3, and Bax ↓;	Anti-inflammation Anti-apoptosis	Li et al.[51]
CKD					
1	UCMSCs	◆ *In vitro*: HK2 and NRK-52E cells treated with high glucose ◆ Dose: 25, 50, and 100 μg/mL UCMSCs ◆ *In vivo*: STZ-induced DN ◆ Dose: 2 × 10^6/500 μL UCMSCs	✓ Serum urea nitrogen and CR ↓; ✓ The 24-hour urinary protein and urinary albumin/CR ratio ↓; ✓ Kidney weight/kidney weight index ↓; ✓ Levels of IL-6, IL-1β, TNF-α, and TGF-β ↓; ✓ Expression of EGF, FGF, HGF, and VEGF ↑;	Anti-inflammation Anti-fibrosis	Xiang et al.[52]
2	UCMSCs	◆ *In vitro*: HK2 cells treated with high glucose and rhTNF-α ◆ Dose: co-culture at a 5:1 ratio (HK2: UCMSCs) ◆ *In vivo*: STZ-induced rhesus macaque model of DN ◆ Dose: 2 × 10^6 UCMSCs	✓ Blood glucose level and daily insulin requirement ↓; ✓ Expression of FN, SGLT2, IL-1β, TNF-α ↓; ✓ Interstitial fibrosis ↓; ✓ NF-κB pathway ↓;	Anti-inflammation Anti-fibrosis	An et al.[53]
3	UCMSCs	◆ *In vitro*: HK2 cells treated with LPS ◆ Dose: RAW264.7 plus MSCs at a ratio of 2:1 (MSCs: RAW264.7 cells) ◆ *In vivo*: STZ-induced mice model of DN ◆ Dose: 5 × 10^5 UCMSCs	✓ Plasma CR and BUN ↓; ✓ Levels of desmin, α-SMA, FN1, Kim-1, and Lcn2 ↓; ✓ Expression of arginase-1 ↑; ✓ Expression of IL-1β, TNF-α, IL-6 ↓;	Anti-inflammation	Lee et al.[54]
4	UCMSCs	◆ *In vivo*: STZ-induced DN rat model ◆ Dose: 2 × 10^6 UCMSCs	✓ 24-hour urinary total protein, urinary albumin to CR ratio, Scr, and blood urea nitrogen ↓; ✓ Renal cell apoptosis ↓; ✓ Apoptosis signal-regulating kinase 1 and P38 MAPK ↑;	Anti-apoptosis	Chen et al.[55]
5	ADMSCs	◆ *In vivo*: SDT fatty rat ◆ Dose: 6.0 × 10^6 cells/mL ADMSCs	✓ Kidney engraftment ↑; ✓ Glomerular injury ↓; ✓ Urinary levels of TNF-α and IL-6 ↓;	Anti-inflammation 31622047	Takemura et al.[56]
6	BMMSCs	◆ *In vitro*: LPS-induced peritoneal macrophages ◆ Dose: 3 × 10^4 BMMSCs ◆ *In vivo*: STZ-induced rat model of DN ◆ Dose: 5 × 10^6 BMMSCs	✓ Renal macrophage infiltration and inflammatory cytokine secretion ↓; ✓ Serum anti-inflammatory cytokines IL-10 and EGF ↑; ✓ Levels of IL-6, MCP-1, TNF-α, and IL-1β ↓;	Anti-inflammation	Li et al.[57]
7	BMMSCS	◆ *In vitro*: HG-induced glomerular mesangial cells ◆ Dose: co-culture at a 1:5 ratio (BMMSCs: glomerular mesangial cells) ◆ *In vivo*: $BTBR^{ob/ob}$ mice ◆ Dose: 1 × 10^6 BMMSCs	✓ Mitochondrial ROS accumulation ↓; ✓ Cell apoptosis ↓; ✓ Mesangial expansion ↓; ✓ Renal cleaved caspase-3 ↓;	Anti-oxidative Anti-apoptosis 33557007	Sávio-Silva et al.[58]

(continued)

Table 1. (continued)

No.	Type of source	Model & doses	Treatment effect	Mechanism	Ref.
8	BMMSCs	◆ *In vitro*: LPS-induced peritoneal macrophages ◆ Dose: 3 × 10^4 BMMSCs ◆ *In vivo*: STZ-induced rat model of DN ◆ Dose: 5 × 10^5 BMMSCs	✓ Expression of FN, α-SMA, Bax ↓; ✓ Lysosome-autophagy, M2 polarization, IL-10 and TFEB expression ↑; ✓ Levels of MCP-1, IL-1β, and TNF-α ↓; ✓ AMPK pathway ↑;	Anti-inflammation	Yuan et al.[59]
9	BMMSCs	◆ *In vitro*: rat glomerular mesangial cells treated with high glucose ◆ Dose: 400,000 cells/well BMMSCs ◆ *In vivo*: STZ-induced rat model of DN ◆ Dose: 5 × 10^6 BMMSCs	✓ Lipoxin A4 expression ↑; ✓ Renal fibrosis ↓; ✓ Levels of TNF-α, IL-6, IL-8, and IFN-γ ↓; ✓ TGF-β/Smad pathway ↓;	Anti-inflammation	Bai et al.[60]
10	BMMSCs	◆ *In vivo*: STZ-induced DN rat model ◆ Dose: 100 μg BMMSCs	✓ BUN and Scr, blood lipid–related indicators of total cholesterol and triglyceride ↓; ✓ Cell apoptosis ↓; ✓ Expression of USP22, caspase-3, and Bax ↓; ✓ miR-let-7a ↑;	Anti-apoptosis	Mao et al.[61]
11	BMMSCs	◆ *In vivo*: UUO mice model ◆ Dose: 2 × 10^6 BMMSCs	✓ CD68-positive macrophage, renal tubulointerstitial injury and fibrosis ↓; ✓ Proliferation of myofibroblasts ↓;	Anti-inflammation Anti-fibrosis	Xing et al.[62]
12	BMMSCs	◆ *In vivo*: UUO mice model ◆ Dose: 1 × 10^6 BMMSCs	✓ Expression of E-cadherin ↑; ✓ Expression of TGF-β1, α-SMA and TNF-α ↓;	Anti-fibrosis	Saberi et al.[63]
13	UCMSCs	◆ *In vivo*: STZ-induced DN mice model ◆ Dose: 1.0 × 10^4 MuMSCs	✓ Levels of glomerular volume ↓; ✓ Expression of FN, α-SMA, vimentin ↓; ✓ TGF-β1/Smad2/3 pathway ↓;	Anti-fibrosis	Li et al.[64]
14	ADMSCs-Exo	◆ *In vitro*: hypoxia/serum deprivation injury models ◆ Dose: 100 μg/mL ADMSCs-Exo ◆ *In vivo*: UUO mice model ◆ Dose: 1 × 10^3 ADMSCs-Exo	✓ Peritubular capillary rarefaction and renal fibrosis ↓; ✓ Cell migration and angiogenesis ↑; ✓ SIRT1/eNOS signaling pathway ↑;	Angiogenesis	Chen et al.[65]
15	ADMSCs-Exo	◆ *In vitro*: high glucose–induced MPC5 cells ◆ Dose: 25 μg/mL of ADMSCs-Exo ◆ *In vivo*: C57BL/KsJ db/db ◆ Dose: unknown	✓ Levels of Scr, BUN, and podocyte apoptosis ↓; ✓ Cell viability and autophagy flux ↑; ✓ Cell apoptosis and podocyte injury ↓; ✓ miR-486 and mTOR pathway ↑;	Autophagy Anti-apoptosis	Jin et al.[66]
16	ADMSCs-Exo	◆ *In vivo*: adenine-containing diet to induce CKD ◆ Dose: 50 and 100 μg ADMSCs-Exo	✓ Pro-inflammatory cytokines, BUN, and Scr ↓; ✓ Aquaporin 2 and 5 levels ↑; ✓ Renal fibrosis ↓;	Anti-fibrosis Anti-inflammation	Yea et al.[67]
17	BMMSCs-Exo	◆ *In vitro*: TGF-β1-induced HK-2 cells ◆ Dose: 100 μg/mL BMMSCs-Exo	✓ EMT process ↓; ✓ Cell autophagy ↑;	Anti-fibrosis	Yin et al.[68]

(continued)

Table 1. (continued)

No.	Type of source	Model & doses	Treatment effect	Mechanism	Ref.
18	BMMSCs-Exo	◆ *In vivo*: postmenopausal CKD ◆ Dose: 100 μg/mL BMMSCs-Exo	✓ Body weight, drastic reduction of estrogen and progesterone levels ↓; ✓ MDA levels and pro-inflammatory cytokines ↓; ✓ GPx SOD, and CAT in kidney tissue ↑;	Anti-inflammation	Alasmari et al.[69]
19	BMMSCs-Exo	◆ *In vivo*: isogenic/allograft kidney transplantation mouse model ◆ Dose: 100 μg/mL BMMSCs-Exo	✓ Treg cell differentiation in kidney transplantation mice ↑; ✓ Inflammatory response, $CD4^+$ T-cell infiltration, SCr, and plasma rejection–related factors' expression ↓; ✓ lncRNA DANCR expression ↑;	Anti-inflammation	Wu et al.[70]
20	BMMSCs-Exo	◆ *In vivo*: STZ-induced DN mice model ◆ Dose: 100 μg BMMSCs-Exo	✓ Levels of LC3 and Beclin-1 ↑; ✓ Fibrotic marker expression ↓;	Autophagy	Ebrahim et al.[71]
21	BMMSCs-Exo	◆ *In vivo*: UUO mice model ◆ Dose: 1 mg/kg BMMSCs-Exo ◆ *In vitro*: TGF-β1-induced NRK-52E cells ◆ Dose: 20 μM BMMSCs-Exo	✓ ECM deposition and renal fibrosis ↓; ✓ EMT process ↓; ✓ let-7i-5p ↓; ✓ TSC1/mTOR pathway ↑;	Anti-fibrosis	Jin et al.[72]
22	BMMSCs-Exo	◆ *In vitro*: TGF-β1-induced HK-2 cells ◆ Dose: 1×10^5 BMMSCs-Exo ◆ *In vivo*: UUO mice model ◆ Dose: 1×10^6 BMMSCs-Exo	✓ Expression of α-SMA, collagen 1α1, and fibronectin ↓; ✓ mTOR signaling and autophagy ↓; ✓ Renal fibrosis ↓; ✓ miR-122a ↑;	Anti-fibrosis Autophagy	Li et al.[73]
23	BMMSCs-Exo	◆ *In vivo*: 5/6 nephrectomy + high phosphate diet-induced CKD mice model ◆ Dose: 75 μg BMMSCs-Exo	✓ Cellular apoptosis ↓; ✓ Levels of Bax and caspase-3 ↓; ✓ Levels of Scr and BUN ↓; ✓ miR-381-3p expression ↑;	Anti-apoptosis	Liu et al.[74]
24	BMMSCs-Exo	◆ *In vivo*: 5/6 subtotal nephrotomy rat model ◆ Dose: 150 μg/week BMMSCs-Exo ◆ *In vitro*: TGF-β1-induced human renal proximal tubular epithelial cells ◆ Dose: 100 μg/mL BMMSCs-Exo	✓ Renal fibrosis ↓; ✓ Expression of fibronectin, collagen I, α-SMA ↓;	Anti-fibrosis	Liu et al.[75]
25	BMMSCs-Exo	◆ *In vivo*: UUO mice model ◆ Dose: 30 μg BMMSCs-Exo	✓ Levels of α-SMA and fibronectin ↓; ✓ Levels of BUN and Scr ↓; ✓ Number of $F4/80^+CD86^+$ and $F480^+/CD206^+$ macrophages ↓;	Anti-inflammation	Lu et al.[76]
26	BMMSCs-Exo	◆ *In vivo*: postmenopausal chronic kidney damage ◆ Dose: 100 μg BMMSCs-Exo	✓ Levels of CR and BUN ↓; ✓ Levels of GPx, CAT, SOD ↑; ✓ Renal fibrosis, levels of α-SMA, caspase-3, and TGF-β1 ↓; ✓ Cell apoptosis ↓;	Anti-fibrosis Anti-apoptosis	Alasmari et al.[77]

(continued)

Table 1. (continued)

No.	Type of source	Model & doses	Treatment effect	Mechanism	Ref.
27	BMMSCs-Exo	◆ *In vivo*: UUO mice model ◆ Dose: 50 μg and 100 μg BMMSCs-Exo	✓ Expression of fibronectin and collagen I ↓; ✓ miR-21a-5p expression ↑;	Anti-fibrosis	Xu et al.[78]
28	UCMSCs-Exo	◆ *In vitro*: TGF-β1-induced NRK-52E cells ◆ Dose: 100 μg UCMSCs-Exo ◆ *In vivo*: UUO mice model ◆ Dose: 200 μg UCMSCs-Exo	✓ Levels of BUN and Scr ↓; ✓ Cell apoptosis and oxidative stress ↓; ✓ ROS level ↓; ✓ Renal fibrosis ↓; ✓ p38MAPK/ERK1/2 pathway ↑;	Anti-apoptosis Anti-oxidative stress	Liu et al.[79]
29	UCMSCs-Exo	◆ *In vitro*: γ-irradiation-induced renal tubular epithelial cell senescence ◆ Dose: 2.6×10^5 UCMSCs-Exo	✓ Senescence markers (CDKN2D, $p16^{INK4a}$) and senescence-associated secretory phenotype factors ↓; ✓ Expression of IL-6 and CCL7 ↓; ✓ SA-β-gal activity ↓;	Senescence	Liao et al.[80]
30	UCMSCs-Exo	◆ *In vitro*: high glucose–induced HK-2 cells ◆ Dose: 50 μg UCMSCs-Exo ◆ *In vivo*: C57BL/KsJ-db/db DN mice ◆ Dose: 10 mg/kg body weight UCMSCs-Exo	✓ Levels of ALB, BUN, Scr ↓; ✓ Protein levels of Bax and cleaved caspase-3 ↓; ✓ Cell apoptosis ↓; ✓ Levels of N-cadherin, Snail, α-SMA ↓; ✓ Levels of E-cadherin ↑; ✓ miR-424-5p expression ↑;	Anti-apoptosis Anti-fibrosis	Cui et al.[81]
31	MSCs-Exo	◆ *In vitro*: TGF-β1-induced NRK-52E cells ◆ Dose: 4×10^4 MSCs-Exo ◆ *In vivo*: UUO mice model ◆ Dose: unknown	✓ Level of ECM and EMT process ↓; ✓ Renal injury and fibrosis ↓; ✓ miR-186-5p expression ↑;	Anti-fibrosis	Yang et al.[82]

ADMSCs: adipose-derived mesenchymal stem cells; AKI: acute kidney injury; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMMSCs: bone marrow mesenchymal stem cells; BUN: blood urea nitrogen; CR: creatinine; DN: diabetic nephropathy; ECM: extracellular matrix; EGF: epidermal growth factor; EMT: epithelial–mesenchymal transformation; ER: endoplasmic reticulum; FGF: fibroblast growth factor; FN: fibronectin; HGF: hepatocyte growth factor; H/R: hypoxia/reoxygenation; I/R: ischemia–reperfusion; IFN: interferon; IL: interleukin; KD: kidney disease; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MCP-1: monocyte chemoattractant protein-1; MDA: malondialdehyde; MSCs: mesenchymal stem cells; NF-κB: nuclear factor–kappa B; PGE2: prostaglandin E2; ROS: reactive oxygen species; Scr: serum creatinine; SDT: Spontaneously Diabetic Torii; α-SMA: alpha-smooth muscle actin; SOD: superoxide dismutase; STZ: streptozotocin; TGF: transforming growth factor; TNF-α: tumor necrosis factor–alpha; UCMSCs: umbilical cord mesenchymal stem cells; UUO: unilateral ureteral obstruction; VEGF: vascular endothelial growth factor.

Similarly, Song et al.[90] stated that MSCs-derived EVs serve as effective therapeutic strategies for CKD via upregulating anti-inflammatory M2 macrophages and regulatory T-cell numbers. In addition, it is well recognized that EV activity mainly involves the horizontal transfer of genetic materials[91,92]. For example, MSCs-EVs secrete insulin-like growth factor (IGF-1) receptor mRNA directly to renal tubular epithelial cells, as well as directly secreting IGF-1 and carrying IGF-1 receptors to promote kidney repair in AKI[93]. Several studies have confirmed that MSCs-derived exosomes enriched with miRNAs (eg, miR-15a, miR-15b, and miR-16[90]) and/or chemokine receptors (eg, CCR2[94] and CXCR4[95]) could ameliorate inflammation and kidney injury by reducing chemokines (eg, CX3CL1[96] and CCL2[97]).

Anti-Apoptosis

Cell apoptosis is closely related to kidney injury and KD progression. Previous studies have shown that renal tubular epithelial cell apoptosis was detected in both animal AKI models and human kidney tissues of AKI[98], and the expression of pro-apoptotic genes (Bax and caspase-3) was increased, while the expression of anti-apoptotic gene Bcl-2 was reduced. Of note, numerous studies have confirmed that MSCs implantation can inhibit apoptosis of renal tubular epithelial cells and thus restore renal function[99,100]. Guo et al.[33] confirmed that BMMSCs alleviated sepsis-induced AKI by inhibiting apoptosis and promoting mitophagy of renal tubular epithelial cells. Another study by Tseng et al.[101]

found that hypoxic MSCs significantly reduced cell apoptosis in renal tubular NRK-52E cells exposed to hypoxia-reoxygenation as well as promoted renal tubular autophagy in acute renal IRI rats.

Of note, MSCs play a therapeutic role in KD through paracrine mechanisms. For example, HuMSC-Exo inhibited apoptosis of NRK-52E cells induced by cisplatin via activation of the ERK1/2 pathway[102]. Alasmari et al.[77] illustrated that exosomes derived from BMMSCs impeded the progression of CKD by interfering with fibrosis and apoptosis. Moreover, MSCs-Exo exhibited anti-apoptotic effect on KD progression by transferring miRNAs (eg, miR-199a-3p[44] and miR-424-5p[81]). What's more, exosomes released from MSCs preconditioned with melatonin blocked apoptosis by decreasing the levels of caspase-3[67], which had a protective effect against CKD.

Pro-Angiogenesis

It has been reported that sparse peritubular capillaries, accompanied by reduced blood perfusion, limit the supply of interstitial oxygen to the kidney, ultimately leading to adverse consequences such as renal fibrosis and tubular atrophy, which accelerate KD progression[103]. Previous studies have shown that MSCs can survive for a long time after implantation into the injured kidney, promote renal interstitial capillary neovascularization, improve renal microcirculation, and inhibit renal fibrosis progression[104]. Meanwhile, MSCs derived from the kidney facilitated angiogenesis, vasculogenesis, and endothelial repair[105]. Numerous studies have demonstrated that MSCs transplantation increased the expression of VEGF mRNA in kidney tissues along with endothelial cell proliferation, reduced the loss of peritubular capillaries, and improved kidney function[106].

In addition, MSCs-derived EVs ameliorated AKI progression by promoting angiogenesis (enhancing renal VEGF levels) *in vivo* and *in vitro*[107]. Eirin et al.[108] proved that the autologous ADMSCs-EVs improve the renal microvascular system in pigs with metabolic renal vascular diseases. Another study found that melatonin-stimulated MSCs-Exo isolated from patients with CKD promoted angiogenesis in ischemic diseases through the upregulation of miR-4516[109]. Mechanistically, MSCs promote angiogenesis through paracrine secretion of some bioactive substances related to angiogenesis [such as VEGF, hypoxia-inducible factor 1-alpha (HIF-1α), platelet-derived growth factor-BB (PDGF-BB), stromal cell-derived factor 1 (SDF-1), and angiogenin][34,52,110], as well as differentiation to vascular endothelial cells[111] and smooth muscle cells[112]. For example, ADMSCs transplantation significantly increased peritubular vascular density and the number of CD31- and vWF (von Willebrand factor)-positive cells in renal interstitium and peritubular area of mice with IRI injury, as well as improved blood perfusion in the kidney of mice[113]. The above studies suggest that MSCs have beneficial effects against KD progression by promoting renal angiogenesis and preventing peritubular capillary loss.

Anti-Fibrosis

Renal interstitial fibrosis is the common pathological hallmark of CKD progression, and eventually inevitably develops into end-stage KD[114], causing a huge socioeconomic burden. Increasing evidence has confirmed that EMT of renal tubular cells is a key event in renal interstitial fibrosis, characterized by fibroblast proliferation and an imbalance between ECM production and degradation[115,116], and inhibition of renal tubular EMT may be a potential therapeutic strategy for the treatment of CKD[117]. Numerous studies have shown that MSCs, as a protective mediator of renal interstitial fibrosis, can play an important regulatory role in the process of EMT through their anti-fibrotic activity and paracrine mechanisms, delaying tubular EMT and improving renal fibrosis[118]. For example, Tang et al.[119] showed that BMMSCs treatment prevents renal interstitial fibrosis by blocking the Akt/GSK3β/Snail signaling pathway in adenine-induced CKD. Another study proved that glial cell line–derived neurotrophic factor–modified ADMSCs suppressed EMT and renal fibrosis via inhibition of the PI3K/Akt pathway in CKD[120].

As the research progresses, subsequent studies have shown that MSCs-Exo exerts anti-fibrotic and EMT-suppressive effects by delivery of genetic information to target cells, thereby alleviating renal fibrosis in CKD. For instance, Grange et al.[121] found that EVs of MSCs can inhibit and reverse the progression of glomerular and tubule-interstitial fibrosis in the DN mouse models by downregulating fibrosis-related genes (eg, Serpia1a, TIMP1, MMP3, collagen I, and Snail). The MSCs-Exo inhibited the EMT process of transforming growth factor (TGF)-β1–treated renal tubular epithelial cells and renal fibrosis in a unilateral ureteric obstruction (UUO)–induced renal fibrosis mouse model via delivery of miRNA-122a[73] and miR-186-5p[82]. Liu et al.[79] found that UCMSCs-Exo exhibits anti-fibrotic effects in CKD through the inactivation of the reactive oxygen species (ROS)–mediated p38 mitogen-activated protein kinases/extracellular signal-regulated kinase (MAPK/ERK) pathway.

Anti-Oxidative Stress

Oxidative stress is involved in the development and progression of KD, including AKI[122] and CKD[123]. Several studies have confirmed that oxidative stress induces renal tubular inflammation, fibrosis, and renal tubular epithelial cell apoptosis, and resulted in promoting the progression of KD[124,125]. Meanwhile, the kidney acts as an essential organ for the production of reactive oxygen species (ROS), and oxidative stress is a mediator of CKD progression[126]. In recent years, numerous studies have proved that MSCs were reported to be used as an antioxidant therapeutic drug in the treatment of KD[98,127,128]. Therefore, the regulation of oxidative stress is the essential mechanism of MSCs-based treatment in KD. Recently, Song et al.[129] showed that MSCs alleviated adriamycin-induced nephropathy by inhibiting

oxidative stress and NF-κB-mediated inflammation. Another study showed that valsartan- and melatonin-modified MSCs improved renal architecture and function in CKD by diminishing oxidative stress[130].

In addition, several preclinical studies demonstrate that MSCs-derived EVs promote tissue repair and reduce oxidative stress in KD[131]. For instance, Zhang et al.[132] revealed that human Wharton's jelly MSCs-EVs could protect the kidney against IRI by mitigating oxidative stress. Another study confirmed that exosomes derived from UCMSCs prevented AKI progression via suppressing renal oxidative stress and inflammation as well as improving kidney function of kidney failure[48]. Cao et al.[133] showed that human placenta MSCs-Exo reduced oxidative stress and mitochondrial fragmentation in a renal IRI model through activation of the Nrf2/keap1 pathway.

Regulating Autophagy

Autophagy is a type II programmed cell death[134] that can be activated to promote cell survival[135] or resulted in cell death[136] by stimulating various physiological and pathological factors. A basal level of autophagy occurs as a self-eating cellular process to degrade cytosolic proteins and subcellular organelles in lysosomes, recycle the cytoplasmic components, and regenerate cellular building blocks and energy, thus maintaining cellular and tissue homeostasis in all eukaryotic cells[137,138]. Recently, transplantation of MSCs has emerged as an effective strategy in regenerative medicine to repair injured organ function via regulating autophagy[139]. For instance, hypoxic MSCs alleviate AKI progression by promoting renal tubular autophagy[32]. Feng et al.[140] found that transplantation of sirtuin3-overexpression amniotic fluid stem cells serves as promoting therapeutic strategies for DN through activation of mitophagy and inhibition of apoptosis. Other studies confirmed that UCMSCs enhanced autophagy in advanced oxidation protein products–treated HK-2 cells through inactivation of the PI3K/Akt/mTOR pathway[141,142]. Intriguingly, upregulation of autophagy remarkably increased the secretion of TGF-β1 from MSCs and suppressed the proliferation of $CD4^+$ T lymphocytes[143], whereas inhibition of autophagy reduced the responsiveness of T cells to mitogen IL-2 and increased the production of immunosuppressive prostaglandin E2[144]. For example, Yuan et al.[25] showed that MSCs ameliorate kidney injury in DN via eliciting macrophages into anti-inflammatory phenotype and elevating PGC-1α (peroxisome-proliferator-activated receptor-γ coactivator-1alpha)/TFEB (transcription factor EB)-mediated lysosome-autophagy. In addition, autophagy is active in the physiological state or can be activated by cellular stresses such as oxidative stress[145]. Gergin et al.[146] demonstrated that transplanted MSCs inhibited oxidative stress in colistin-induced nephrotoxicity by modulating autophagy. Autophagy and oxidative stress are correlated, and the underlying mechanisms of MSCs-based treatment have not been fully explored.

At the same time, some researchers demonstrated that MSCs-Exo has become a research focus for targeted therapy of KD[147]. Wang et al.[50] discovered that UCMSCs-Exo preprocessing can prevent cisplatin-induced AKI *in vivo* and *in vitro* by activating autophagy. Jia et al.[148] identified that UCMSCs-Exo can prevent cisplatin-induced AKI by activating autophagy. Ebrahim et al.[71] confirmed that MSCs-Exo enhances autophagy and then slows the progression of DN via activating the mTOR pathway.

Senescence

Cellular senescence is a specialized cell state of permanent cell cycle arrest caused by the accumulation of cellular damage due to a variety of stressors such as telomere shortening, DNA damage, oxidative stress, and activation of oncoproteins[80,149]. Senescent cells are known to be present at increased levels in KD, and accumulation of senescent cells is thought to facilitate renal fibrosis, DN, severe AKI, and decay in renal function[150,151]. Several studies have shown that the removal of senescent tubular cells in the kidney by transgenic or pharmaceutical approaches reduced features of tissue aging and efficiently ameliorated glomerulosclerosis, inflammation, and renal function[152–154]. Of note, ADMSCs transplantation can alleviate ischemia–reperfusion (I/R)-induced kidney injury through reducing renal senescence[155]. Rodrigues et al.[156] found that UCMSCs can prevent IRI-induced renal senescence in AKI.

In addition, several studies have demonstrated that MSCs-derived exosomes exhibit therapeutic effects on KD by regulating cell senescence[157,158]. For example, Wang et al.[159] showed that MSCs-derived exosomal let-7b-5p ameliorates cisplatin-induced AKI by reducing renal senescence and cell apoptosis. Another study confirmed that treatment with exosomes derived from MSCs efficiently reduced senescence in renal tubular epithelial cells by diminishing the transcription of senescence markers and senescence-associated secretory phenotype factors[80]. In addition, the paracrine effects of MSCs were enhanced after pretreated with metformin and inhibited MSCs senescence by suppressing SA-β-gal activity, $p16^{Ink4a}$ expression, and p53 and NF-κB activation, thus effectively reducing CKD inflammation and fibrosis[160]. Taken together, the above studies have proven that MSC-EVs are effective in treating KD.

Clinical Trials of MSCs Therapy in KD

In the last decade, the beneficial efficacy of MSCs in the treatment of KD has been confirmed in multiple cellular and animal experimental models. For example, MSCs-base therapy was first shown to promote renal tubular regeneration and improve renal function in cisplatin-induced AKI mice models in 2004[161]. Subsequent studies have also confirmed that MSCs alleviate other animal models of AKI induced by ischemia–reperfusion, glycerol, sepsis, cecal ligation and puncture[162,163], and so on. In addition, MSCs transplantation

significantly alleviated CKD progression by inhibiting renal tubular epithelial cell apoptosis, EMT process, and inducing cell autophagy[15,164]. For example, Liu et al.[165] showed that treatment with BMMSCs restricted inflammation and renal damage in the IRI model. Of note, several clinical studies are completed or ongoing to evaluate the safety and efficacy of MSCs for the treatment of KD according to ClinicalTrials.gov (Table 2). For example, a phase I/II clinical trial by Swaminathan et al.[166] showed that BMMSCs alleviated inflammatory response in patients with AKI by secreting anti-inflammatory factors. Two other clinical trials (NCT00698191 and NCT01741857) confirmed that UCMSCs transplantation for refractory systemic lupus erythematosus improved disease activity and renal function, and reduced proteinuria, as well as no adverse events occurred. Currently, a total of seven and nine clinical trials are ongoing to evaluate the safety and efficacy of MSCs in patients with DN and CKD. However, MSC-based therapy is limited by the low survival rate of MSCs when used to treat severe KD[167]. Several factors such as poor control of the disease, cellular microenvironment, anoikis, ischemia, inflammation, and ROS production reduce the efficacy of MSC-based therapies[168,169]. Some preclinical studies have suggested that the preconditioning or cotreatment of MSCs protects them from the harmful environment at the site of damage and improves their function[23], including cytokines or natural/chemical compounds. In addition, as several clinical trials are in recruiting status, it is worthwhile to further consider and explore whether there are safety issues and insignificant efficacy of MSCs for the treatment of KD. Therefore, we will further explore multiple treatment strategies based on MSCs for KD after obtaining the results of the existing clinical trials to prolong the survival of patients and delay the progression of KD.

Current Challenges of MSCs Therapy in KD

Selection of MSCs Source

Interestingly, the results of animal models and clinical trials have confirmed that MSCs have shown positive results for the treatment of various KD, and no adverse effects or serious adverse complications have been observed. Currently, MSCs are widely available in clinical trials, but the ultimate goal is to use MSCs to delay KD progression and avoid its progression to end-stage renal disease. Therefore, the choice of autologous or allogeneic MSCs for transplantation should be considered in clinical applications. Autologous MSCs have low immunogenicity and no risk of infection, but the longer time required for autologous cell preparation may limit their practical application in clinical treatment. Allogeneic MSCs can be selectively derived from young healthy donors and have the potential to be produced rapidly and in large quantities *in vitro* culture, significantly reducing costs[118], while the use of allogeneic MSCs includes a higher risk of immunological reactions and shorter cell survival times following injection[170]. Although transplantation with autologous MSCs is safer and more ethical than allogeneic MSCs, there are still some problems in clinical applications. First, after autologous MSCs are extracted, the *in vitro* culture cycle is long, which may not fully meet the needs of the body. Second, there is a significant difference between the secretion and immune regulation of autologous MSCs[171]. However, a clinical study reported that injections of allogeneic or autologous BMMSCs were both associated with low rates of treatment-emergent serious adverse events (such as immunologic reactions) in patients with ischemic cardiomyopathy[172]. Further studies to overcome the immune rejection caused by allogeneic MSCs during the treatment process are necessary. Owing to the many sources of allogeneic MSCs and the high efficiency of *in vitro* culture, the treatment of immune rejection caused by allogeneic MSCs is still receiving widespread attention[173]. On the contrary, an obvious solution is to immediately use autologous MSCs as a ready-made product. In addition, new products such as acellular exosomes and MSCs derived from human pluripotent stem cells are exciting developments that are attracting significant attention[174].

Transplantation Protocol of MSCs

Currently, MSCs are mostly transplanted in animal experiments by intravenous, arterial, intraperitoneal, and local injections for KD, whereas clinical transplantation of MSCs includes arterial and intravenous injections. Previous studies have shown that MSCs transplantation via arterial injection was more effective than intravenous injection in promoting renal regeneration[175]. Moreover, local injection of MSCs also plays a positive role in renal repair[176], but this route was less commonly used in clinical practice. Importantly, different transplantation modalities have a significant impact on the survival and homing rate of MSCs, and the optimal implantation modality needs to be determined[177]. Furthermore, the timing of MSCs injection, the number of injections, the number of cells per injection, exploring the optimal strategy for MSCs migration to the damaged site, understanding the interactions between MSCs and other tissue cells, and the adverse effects of MSCs after transplantation (eg, low differentiation *in vivo* and tumorigenesis)[178], all of which pose challenges for MSCs to move from basic experiments to clinical applications.

Migration and Survival of MSCs

A prerequisite for the efficacy of MSCs is the ability to migrate to damaged tissues. Previous studies have found that MSCs can localize to diseased sites[179], but only a small fraction of MSCs[180]. Several studies found that the migration of

Table 2. The Ongoing Clinical Trials of MSCs Therapy in KD.

No.	Estimated enrollment	Phase	MSCs source	Status	Sponsor	Clinical trial ID
AKI						
1	80	I/II	UCMSCs	Not recruiting	Chinese PLA General Hospital, China	NCT04194671
2	15	I	ADMSCs	Recruiting	Tambi Jarmi, USA	NCT04388761
3	15	I	BMMSCs	Completed	AlloCure Inc., USA	NCT00733876
4	24	I/II	MSCs	Not recruiting	Sentien Biotechnologies, Inc.	NCT03015623
CKD						
1	7	I	BMMSCs	Completed	Royan Institute, Iran	NCT02195323
2	44	I/II	UCMSCs	Recruiting	Tongji Hospital, Tongji Medical College, Huazhong University of Science & Technology, China	NCT05512988
3	20	I	BMMSCs	Recruiting	Mayo Clinic Florida, USA	NCT05362786
4	31	I/II	ADMSCs	Recruiting	Bangladesh Laser & Cell Surgery Institute & Hospital, Bangladesh	NCT03939741
5	116	II	UCMSCs	Unknown	Zhujiang Hospital, China	NCT02966717
6	40	I	ADMSCs	Recruiting	Mayo Clinic Florida, USA	NCT04869761
7	6	I	BMMSCs	Completed	Royan Institute, Iran	NCT02166489
8	10	I	BMMSCs	Recruiting	Pharmicell Co., Ltd., Korea	NCT05042206
9	20	I	UCMSCs	Recruiting	The Foundation for Orthopaedics and Regenerative Medicine, Antigua, and Barbuda	NCT05018845
10	7	I	BMMSCs	Completed	Royan Institute, Iran	NCT02195323
11	20	I/II	MSCs	Unknown	Fuzhou General Hospital, China	NCT00659620
12	30	II	ADMSCs	Recruiting	Mayo Clinic in Rochester, USA	NCT03325322
13	31	I/II	ADMSCs	Recruiting	Bangladesh Laser & Cell Surgery Institute & Hospital, Bangladesh	NCT03939741
14	42	I	ADMSCs	Completed	University of Alabama, USA	NCT02266394
15	60		Urinary MSCs	Not recruiting	Hospices Civils de Lyon, France	NCT04998461
16	100	Not applicable	ADMSCs	Unknown	The Affiliated Hospital of Xuzhou Medical University, China	NCT03321942
17	30	I/II	MSCs	Unknown	Nanjing Medical University, China	NCT03460223
18	100	Not applicable	ADMSCs	Unknown	The Affiliated Hospital of Xuzhou Medical University, China	NCT03321942
DN						
1	30	I	ADMSCs	Recruiting	Mayo Clinic in Rochester, USA	NCT03840343
2	54	I/II	UCMSCs	Unknown	Shanghai East Hospital, China	NCT04216849
3	15	Early I	UCMSCs	Recruiting	Yan'an Affiliated Hospital of Kunming Medical University, China	NCT04125329
4	38	Not applicable	UCMSCs	Unknown	Renmin Hospital of Wuhan University, China	NCT04562025
5	48	I/II	BMMSCs	Recruiting	Mario Negri Institute for Pharmacological Research, Ireland	NCT02585622
6	20	I/II	Wharton Jelly MSCs	Unknown	University of Jordan, Jordan	NCT03288571
7	15	I	ADMSCs	Recruiting	Albert Hakaim, USA	NCT04392206
Lupus nephritis						
1	16	I	Human amniotic MSCs	Completed	Yan'an Affiliated Hospital of Kunming Medical University, China	NCT04318600
2	230	II	UCMSCs	Unknown	The Affiliated Drum Tower Hospital of Nanjing University Medical School, China	NCT03580291
3	20	I/II	BMMSCs	Unknown	Fuzhou General Hospital, China	NCT00659217
4	30	Not applicable	UCMSCs	Unknown	The First Affiliated Hospital of Dalian Medical University, China	NCT03458156
5	36	II	BMMSCs	Not recruiting	Hanyang University Hospital, Korea	NCT03673748
6	7	I	BMMSCs	Completed	Corestem, Inc., Korea	NCT03174587
7	25	II	UCMSCs	Unknown	Second Affiliated Hospital & SLE Research Centre, Kunming Medical University, China	NCT01539902
8	7	I	BMMSCs	Completed	Hanyang university hospital, Korea	NCT03174587

ADMSCs: adipose-derived mesenchymal stem cells; AKI: acute kidney injury; BMMSCs: bone marrow mesenchymal stem cells; CKD: chronic kidney disease; DN: diabetic nephropathy; KD: kidney disease; MSCs: mesenchymal stem cells; UCMSCs: umbilical cord mesenchymal stem cells.

Table 3. Current Approved in South Korea, Europe, Japan, and Other Countries With MSCs for Diseases.

Sources	Clinical condition	Trade name	Approving country (year)
ADMSCs	Subcutaneous tissue defects	Queencell	South Korea (2010)
BMMSCs	Acute myocardial infarction	Cellgram-AMI	South Korea (2011)
ADMSCs	Crohn's fistula	Cupistem	South Korea (2012)
UCMSCs	Knee articular cartilage defects	Cartistem	South Korea (2012)
BMMSCs	Graft-versus-host disease	Prochymal	Canada (2012)
BMMSCs	Graft-versus-host disease	Remestemcel-L	New Zealand (2012)
BMMSCs	Amytrophic lateral sclerosis	Neuronata-R	South Korea (2014)
BMMSCs	Graft-versus-host disease	Temcell HS Inj	Japan (2015)
BMMSCs	Critical limb ischemia	Stempeucel	India (2016)
BMMSCs	Spinal cord injury	Stemirac	Japan (2018)
ADMSCs	Complex perianal fistulas in Crohn's disease	Darvastrocel (Alofisel)	Europe (2018)

ADMSCs: adipose-derived mesenchymal stem cells; BMMSCs: bone marrow mesenchymal stem cells; MSCs: mesenchymal stem cells; UCMSCs: umbilical cord mesenchymal stem cells.

MSCs *in vivo* was regulated by various surface adhesion molecules (eg, CD44, VLA-4/VCAM1, SDF-1/CXCR4, and CXCL5/CXCR2)[181–183]. Importantly, pretreatment with cytokines or active substances can improve the localization/migration ability of MSCs. For example, MSCs modified by CXC chemokine receptors (such as CXCR3[184] and CXCR4[185]) exhibited better migration and localization abilities. In addition, enhanced migration and anti-inflammatory activities of MSCs mediated by the transient ectopic expression of CXCR4 and IL-10 or IL-35[186,187]. However, the source, culture, and amplification methods of MSCs may affect the expression of their localized surface molecules[188], as well as the cell activity, therapeutic effects, and safety of modified MSCs were difficult to control. Meanwhile, there is a lack of effective strategies to precisely localize MSCs to damaged tissues.

Safety of MSCs Transplantation

With the gradual increase of studies on the application of MSCs in clinical practice, the safety of MSCs has received widespread attention. In the phase I clinical trial by Liu et al.[189], no physical abnormalities were found in healthy volunteers after receiving BMMSCs infusion at a 2-month follow-up. Wang et al.[190] conducted a toxicity study of UCMSCs transplantation in 32 macaques and no adverse reactions were observed. Ra et al.[191] evaluated the safety of ADMSCs preparations using an animal model of ulcerative colitis and no toxicity or tumorigenicity was found in immunodeficient mice. Hu et al.[192] showed that no severe adverse reactions or tumorigenicity was observed in clinical trials with either autologous or allogeneic transplantations of MSCs. These results indicated that MSCs were relatively safe in the treatment of diseases. Currently, no US Food and Drug Administration (FDA)-approved MSCs on market for disease treatment, whereas some MSCs-approved products for human disease are in other countries (Table 3). Meanwhile, most clinical studies of MSCs are still in the early stage, as well as the source, isolated, purified methods, and injection route of MSCs are different. Therefore, the safety of MSCs needs to be summarized and improved with continuous clinical trials.

Others

Except for the current challenges mentioned above, clinical applications of MSCs have other limitations. For example, tissue sources and isolation methods can influence MSC proliferation and differentiation potential[193,194]. In addition, microenvironment, donor age, and environmental factors affect the genetic stability of MSCs. No consensus on the standard properties (eg, phenotype, differentiation potential, physiological functions, and biological properties) of MSCs has been developed[195]. Of note, MSCs can only proliferate for a limited number of passages *in vitro* and will eventually enter a senescence state[196]. Progressively slow growth and lack of differentiation of high-passaged MSCs have been reported in several studies[197,198]. Other important challenges are the isolation and culturing of MSCs using xenofree conditions[199] as cells grown in media containing fetal bovine serum and other animal or bacterial products cannot be used for clinical purposes. Thus, a better understanding of the origin, biological properties, and function of MSCs derived from different tissues could provide insight into what truly is an "MSC."

Improvement of MSCs' Therapeutic Effect in KD

MSC-based therapy has been widely studied for KD therapy and has been shown to result in improved renal function and the recovery of damaged renal tissues in animal studies and clinical trials[200]. However, the limited effects of the current therapy for KD drive the need for the development of novel

strategies such as preconditioning, genetic modifications, and strategies for scalability. For instance, several cytokines and natural/chemical compounds have been shown to have protective effects by enhancing cell survival and proliferation[201]. Docosahexaenoic acid (DHA) is a necessary omega-3 fatty acid found in the blood and the kidney. The 14S,21R-dihydroxy-doxosa 4Z,7Z19Z,12E,16Z,19Z-hexaenoic acid (14S,21R-dHDHA) has been identified as a new DHA-derived lipid mediator, and treatment with this compound has been shown to enhance the function of MSCs. *In vitro* and IRI mouse models, MSCs treated with 14S,21R-dHDHA show reduced apoptosis and inflammatory responses, and improved renal function[202]. Other studies have shown that the pharmacological agent, S-nitroso N-acetyl penicillamine (SNP), a nitric oxide donor associated with cytoprotective and tissue-protective effects, promoted MSCs functionality by increasing cell proliferation and survival in renal IR model[203]. Moreover, administration of SNP-treated MSCs resulted in a significant improvement in renal function and increased the expression of pro-survival and pro-angiogenic factors in ischemic renal tissue. Darbepoetin-α is an erythropoietic agent that shows similar protective and hematopoietic effects and reduces kidney damage in an animal model of renal IRI[204]. In a mice model of renal ischemia, the administration of melatonin-pretreated MSCs increased the secretion of angiogenic cytokines and the survival of engrafted MSCs in CKD-associated ischemic sites. Moreover, miRNAs (eg, miR-146a-5p[205], miR-19a-3p[206], miR-374a-5p[207], and miR-34a[208])-modified MSCs ameliorated KD progression via reducing inflammation, oxidative stress, renal fibrosis, cell apoptosis, and so on.

Conclusion

Numerous studies have confirmed the safety and tolerability of MSCs transplantation for the treatment of KD[209–212]. Given the increasing incidence of KD worldwide, MSCs-based therapy appears to be an innovative intervention approach with tremendous potential for the management of KD, but there is still much work to be done before MSCs can be used for clinical treatment on a large scale. First, the issues of donor heterogeneity, mass production, immunogenicity, and cryopreservation of MSCs need to be addressed. Second, how to make MSCs with more efficient targeting ability, more precise immunomodulatory function, and safer application effect by artificial means need to be studied. Existing studies have provided several strategies, including genetic engineering, microparticle engineering, and preculture, which theoretically improve the efficiency of MSCs application. Third, the detailed underlying mechanisms of MSCs for the treatment of KD and the functional role of targeting kidney-related injury need to be further explored. Fourth, the therapeutic safety of MSCs (eg, carcinogenic) remains controversial. With the advancement of novel biotechnology, there are many strategies to enhance the efficacy and safety of MSCs (such as drug conjugation, hypoxia condition, cytokine pretreatment, and genetic modification), but long-term efficacy has not been proven and standardized clinical trial protocols are still needed. Currently, the treatment of KD is limited to drug therapy, dialysis, and renal transplantation, whereas MSCs transplantation has emerged as a promising alternative therapy and has been supported by evidence from relevant clinical studies[213,214]. From the perspective of functional improvement and clinical parameters, the results of clinical trials are more favorable, and the development of new technologies is expected to overcome current barriers to the clinical application of MSCs therapy. In conclusion, with the continuous innovation of treatment protocols and more and larger scale clinical trials in the future, MSCs-based therapy is expected to become a major "tool" for the treatment of KD.

Author Contributions

F.C. and N.C. are responsible for the acquisition, analysis and interpretation of the data, and drafting of the manuscript. Others contributed to the critical revision of the manuscript.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

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