



OPEN ACCESS

EDITED BY
Chee-Yin Wong,
Universiti Tunku Abdul Rahman,
Malaysia

REVIEWED BY
Carlo Tremolada,
Manchester Metropolitan University,
United Kingdom
Yu Meng,
Jinan University, China

*CORRESPONDENCE
Tianbiao Zhou,
zhoutb@aliyun.com

SPECIALTY SECTION
This article was submitted to Stem Cell
Research,
a section of the journal
Frontiers in Cell and Developmental
Biology

RECEIVED 01 April 2022
ACCEPTED 12 September 2022
PUBLISHED 04 October 2022

CITATION
Wang J, Lin Y, Chen X, Liu Y and Zhou T
(2022), Mesenchymal stem cells: A new
therapeutic tool for chronic
kidney disease.
Front. Cell Dev. Biol. 10:910592.
doi: 10.3389/fcell.2022.910592

COPYRIGHT
© 2022 Wang, Lin, Chen, Liu and Zhou.
This is an open-access article
distributed under the terms of the
[Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is
permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original
publication in this journal is cited, in
accordance with accepted academic
practice. No use, distribution or
reproduction is permitted which does
not comply with these terms.

Mesenchymal stem cells: A new therapeutic tool for chronic kidney disease

Jiali Wang, Yongda Lin, Xiutian Chen, Yiping Liu and
Tianbiao Zhou*

Department of Nephrology, the Second Affiliated Hospital, Shantou University Medical College,
Shantou, China

Chronic kidney disease (CKD) has a major impact on public health, which could progress to end-stage kidney disease (ESRD) and consume many medical resources. Currently, the treatment for CKD has many flaws, so more effective treatment tools are urgently required for CKD. Mesenchymal stem cells (MSCs) are primitive cells with self-renewal and proliferation capacity and differentiation potential. Extensive preclinical and clinical data has shown that cell-based therapies using MSCs can modulate immunity, inhibit inflammatory factors, and improve renal function in CKD, suggesting that MSCs have the potential to be a new, effective therapeutic tool for CKD. In this review, we will describe different kinds of MSCs and MSCs products for the treatment of CKD in experimental models and clinical trials, potential signaling pathways, therapeutic efficacy, and critical issues that need to be addressed before therapeutic application in humans.

KEYWORDS

mesenchymal stem cells, mesenchymal stem cell-derived extracellular vesicles, chronic kidney disease, diabetic nephropathy, lupus nephritis, autosomal dominant polycystic kidney disease

Introduction

Chronic kidney disease (CKD) refers to chronic kidney structure and function obstacles for three or more months for any causes. CKD may lead to many complications, such as hyperkalemia (Gennari and Segal, 2002), metabolic acidosis (Uribarri et al., 1995), hypertension (Stefanski et al., 1996), anemia (Eschbach, 1991), and sexual dysfunction (Procci et al., 1981). Complications of CKD have a major impact on the quality of life of patients and can increase the risk of mortality (Webster et al., 2017). According to Global Burden Assessment Report, the number of people dying of CKD has increased in recent years (Xie et al., 2018; Wong, 2021). The prevalence of CKD is rising as the incidences of the main risk factors for CKD, including DM and hypertension, are sharply increasing, leading to a rising prevalence of CKD. Therefore, CKD has been putting pressure on medical resources as a critical cause of global mortality (Ene-Iordache et al., 2016; Simeoni et al., 2021).

Common causes of CKD include poorly controlled diabetes mellitus (DM), hypertension, glomerular disease, glomerulonephritis, and autosomal dominant

polycystic kidney disease (Webster et al., 2017). Statins, antiplatelet agents, renin-angiotensin system inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, lifestyle changes, and other treatments are used to slow the progression of CKD (Heerspink et al., 2018; Simeoni et al., 2021). However, new therapies are limited. When CKD progress cannot be prevented, it will evolve into end-stage renal disease (ESRD). Those with ESRD, compared with patients with CKD, had a significantly higher frequency of vascular disease, cognitive impairment, and depression (Murali et al., 2020). The current treatment approaches for ESRD are dialysis and kidney transplantation, which consume a lot of health care resources (Webster et al., 2017). Moreover, dialysis may lead to deterioration of the quality of life and kidney transplantation may carry the risk of severe complications (Ene-Iordache et al., 2016; Webster et al., 2017). Therefore, novel therapies for CKD are required.

A hallmark of CKD is renal fibrosis. Renal fibrosis includes glomerulosclerosis and tubulointerstitial fibrosis, which can be divided into four phases, including cellular injury, fibrogenic signaling activation, fibrogenic execution, and destruction (Genovese et al., 2014). Endothelial damage and dysfunction, mesangial cell proliferation, podocyte destruction, and tubular atrophy are essential contributors to CKD progression (Webster et al., 2017). During the CKD progression, epithelial-mesenchymal transition (EMT) is a crucial process. The key inducer of EMT is transforming growth factor- β 1 (TGF- β 1) (Wu et al., 2014) and the important symbols of EMT are E-cadherin loss and overexpression of α -smooth muscle actin (α -SMA). Extracellular matrix (ECM) deposition, including overexpression of fibronectin, collagen I, and collagen IV is an important feature of kidney fibrosis. In addition, macrophage aggregation, myofibroblast activation, and loss of peritubular capillary are imperative factors in CKD progression (Webster et al., 2017). Some signaling pathways, such as TGF- β , Mitogen-activated protein kinase (MAPK), Wnt/ β -catenin, PI3K/Akt, JAK/STAT, and Notch pathways, are closely related to CKD (Edeling et al., 2016; Liu et al., 2017; Hu et al., 2018). Therefore, regenerating specific renal cells and blocking the pathway of CKD progression is vital for CKD treatment.

In many previous studies, mesenchymal stem cells (MSCs) have been found to be safe and feasible for treating cardiomyopathy (Chin et al., 2010; Chin et al., 2011; Chin et al., 2021), multiple myeloma (Teoh et al., 2016), and DM (Li et al., 2021). It is also reported as an effective treatment for fibrosis diseases, like liver fibrosis (Eom et al., 2015), lung fibrosis (Barczyk et al., 2015), as well as myocardial fibrosis (Jin et al., 2020). MSCs are attractive candidates for kidney repair therapy because they can promote recovery and prevent kidney failure (Wong et al., 2014).

This review includes the role of different kinds of MSCs and MSCs products such as d extracellular vesicles from MSCs (MSCs-EVs) for treating CKD in preclinical and clinical

research and possible mechanisms, along with prospects and challenges in clinical application.

Characteristics of different kinds of MSCs

MSCs are plastic-adherent cells and can be expanded to yield many cell numbers. However, there is no specific marker found to characterize MSCs better so far. The International Society of Cell Therapy (ISCT) has proposed the minimal criteria for MSCs definition, which includes: adherence to plastic, tri-lineage, and differentiation potential; positive for CD105, CD73, and CD90 marker expression while being negative for CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR expression on the cell surface; the ability to differentiate into osteoblasts, adipocytes, and chondroblasts *in vitro* culture conditions (Dominici et al., 2006). MSCs include bone marrow mesenchymal stem cells (BMMSCs), adipose-derived MSCs (ADMSCs), umbilical cord blood mesenchymal stem cells (UCMSCs), human placenta-derived MSCs (PDMSCs), Wharton's jelly-derived MSCs (WJMSCs), dental mesenchymal stem cells (DMSCs), and so on (Pittenger et al., 1999).

The most commonly used cell types for CKD are BMMSCs. BMMSCs have low expression of MHC I and MHC II, and thus can avoid attack by allogeneic T cells. Studies have shown that BMSCs can differentiate into glomerular mesangial cells. However, BMMSCs are difficult to purify efficiently and quickly. As a result, researchers examined different types of MSCs for kidney regeneration.

Among the various sources, ADMSCs derived from adipose tissue have become promising candidates. They have characterized surface markers including CD44/CD90 or CD34/kinase insert domain receptor (Zhu et al., 2013). ADMSCs, like BMMSCs, may differentiate into distinct lineages and have the potential to be used therapeutically to restore tissues that have been injured. In addition, like BMMSCs, ADMSCs also have minimal immunogenicity and operate as immunomodulators (Puissant et al., 2005). ADMSCs exhibit more stronger immunomodulatory effects than BMMSCs due to variations in cytokine production. ADMSCs had a greater degree of cytokine release, particularly interleukin-6 (IL-6) and TGF- β 1, which have been linked to the immunomodulatory actions of MSCs. This is due to ADMSCs having increased metabolic activity when compared to BMMSCs. In addition, ADMSCs are more effective than BMMSCs at suppressing the proliferation of peripheral blood mononuclear cells and preventing the development of dendritic cells (Melief et al., 2013). Besides, ADMSCs have other advantages, including widely available sources, easy access, minimal injury, rapid proliferation, easy purification, and a lack of ethical concerns (Katsuno et al., 2013). Adipose tissue is an excellent source of

MSCs, but ADMSCs are not as effective at restoring kidney function as BMMSCs (Ashour et al., 2016).

UCMSCs also provide an alternative source of MSCs. UCMSCs could transform medical waste into a valuable product with clinical applications (Musiał-Wysocka et al., 2019). Immune rejection in allogeneic transplants is unlikely because UCMSCs are less immunogenic than MSCs from other sources (Li et al., 2014). In addition, UCMSCs proliferate more rapidly than BMMSCs or ADMSCs (Fazzina et al., 2016). Moreover, UCMSCs show no signs of senescence despite multiple passages, suggesting they can be manufactured in large numbers without losing potency (La Rocca et al., 2009).

In contrast to ADMSCs and BMMSCs, where MSCs are affected by the donor's age, the placenta is an excellent source for cell therapy (Shigeno and Ashton, 1995). Additionally, PDMSCs can be collected, cultured, and evaluated after childbirth and the placenta removed from the uterus. PDMSCs could offer numerous sources, have low immunogenicity, and have no ethical concerns, making them a promising cell therapy source. Therefore, the proliferative potential of PDMSCs is greater than that of BMMSCs (Liu et al., 2019).

In conclusion, BMMSCs are the cell types that are most frequently used for CKD, however, BMMSCs are challenging to purify quickly and effectively. ADMSCs, UCMSCs, and PDMSCs have consequently emerged as promising options. ADMSCs have several advantages over BMMSCs, such as easy purification, quick proliferation, high cell viability, and convenient supply and more potent immunomodulatory effects (Katsuno et al., 2013; Melief et al., 2013). Compared to BMMSCs or ADMSCs, UCMSCs multiply more quickly, and they can be produced in enormous quantities without losing their effectiveness (La Rocca et al., 2009). PDMSCs have a wide range of sources, minimal immunogenicity, and no ethical issues. Additionally, PDMSCs have a higher proliferative potential than BMMSCs (Liu et al., 2019).

MSCs and MSCs-EVs with CKD in preclinic study

MSCs and CKD in preclinic study

Animal models have been widely used to better understand the pathogenesis and underlying mechanisms of CKD. Mice and rats are the most commonly used models for studying CKD and potential therapeutic targets. Typical animal models for glomerular disease include the COL4A3 gene knockout model, 5/6 NPX (nephrectomy) model, diabetic mellitus model, and Lupus nephritis (LN) model. Common models for tubule-
interstitial fibrosis include unilateral ureteral obstruction (UUO) model, albumin-overloaded model and polycystic kidney disease (PKD) model. We reviewed the studies in

those fields. Also, the safety and efficacy of MSCs in various CKD models are discussed in this section.

One of the most commonly used experimental models of CKD is the remnant kidney model. In rats, 5/6 NPX is typically used to mimic human CKD. Villanueva S et al. transplanted ADMSCs to 5/6 NPX rats and found that the group treated with ADMSCs had a higher level of protecting factors, such as epitheliogenic, bone morphogenetic protein 7 (BMP-7), and vascular endothelial-derived growth factor (VEGF). Also, the levels of damage markers in renal fibrosis, including ED-1 and α -SMA are decreased. Additionally, the study showed that Oct-4, a marker of renal ADMSCs, increased after ADMSCs therapy (Villanueva et al., 2013).

MSCs also exert protective effects in diabetic mellitus models in mice. In order to test the effectiveness of a single dose of BMMSCs in the experimental model of type 1 diabetic mice, Ezquer et al. injected 0.5×10^6 BMMSCs into Streptozotocin (STZ) induced type 1 diabetes C57BL/6 mice. The kidneys treated by BMMSCs showed a more normal appearance. Besides, BMMSCs were found to revert hyperglycemia, glycosuria, and microalbumin (Ezquer et al., 2008). By contrast, Lee et al. used a larger number of BMMSCs in a type 2 diabetes model. It was observed that human BMMSCs prevented further blood glucose increases but did not revert hyperglycemia. One possible implication of this is that MSCs exert therapeutic effects in a type 1 diabetic animal model but have preventive effects in a type 2 diabetic animal model induced by STZ. The study also showed that human BMMSCs decrease mesangial thickening and macrophage infiltration, which are important stages in CKD. Single cells were found both in pancreatic islets and glomeruli, indicating that BMMSCs are selective homing (Lee et al., 2006). In another study, STZ-induced DN rats were infused with 2×10^6 human UCMSCs via the tail vein at week 6. The study shows that UCMSCs increase the level of growth factors, fibroblast growth factor (FGFs), HGF, and VEGF but decrease levels of IL-6, interleukin-1 β (IL-1 β), tumor necrosis factor alpha (TNF- α) and TGF- β , thus improving the renal function (Xiang et al., 2020).

Murine models are used in the majority of LN research. MRL and CD95 mutants are widely used to develop proteinuria, lymphoproliferation, and other features similar to human LN (McGaha and Madaio, 2014). The inflammatory microenvironment of SLE patients increases NF- κ B expression in glomerular endothelial and mesangial cells, while NF- κ B overexpression can induce the expression of inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes, creating a vicious cycle (Liu et al., 2019). NF- κ B signaling pathway activation could be downregulated in MRL/lpr mice after infusion of human PDMSCs by reducing the level of NF- κ B mRNA and phospho-NF- κ B p65. Also, TNF- α , plasminogen activator inhibitor-1 (PAI-1), and ICAM-1 expression in MRL/lpr mouse kidneys was observed to

decrease (Liu et al., 2019). In a study by Ruan et al., human UCMSCs were given *via* intravenous injections for 4 weeks to B6.Fas mice. The results showed decreased levels of antinuclear, anti-histone, and anti-dsDNA antibodies within the MSCs treatment group. In the MSCs group, the 24-h urine protein level was lower than in the lupus group, indicating that renal function improved. Compared to the lupus group, renal pathology was ameliorated by UCMSCs treatment, such as glomerular mesangial cell proliferation, tubulointerstitial fibrosis reduction, and diminished immune complex deposition in the glomeruli (Ruan et al., 2014).

The COL4A3 gene knockout mouse is a model for analyzing the pathogenesis of Alport syndrome. In a model of COL4A3-deficient mice, BMMSCs injections to COL4A3-deficient mice can prevent peritubular capillary loss through the production of VEGF mRNA. Hepatocyte growth factor (HGF) and tumor necrosis factor stimulated gene-6 (TSG-6), as paracrine factors of BMMSCs, may contribute to this positive result, while BMMSCs differentiation is unimportant in this process (Ninichuk et al., 2006).

The UUO model is used to mimic tubulointerstitial fibrosis. Obstruction of the urinary tract causes hydronephrosis, interstitial inflammatory infiltration, and tubular cell death caused by apoptosis and necrosis (Docherty et al., 2006). Many studies have proved the effectiveness of the BMMSCs by the UUO model. In a UUO model in mice, cultured BMMSCs transplanted through the tail vein can attenuate cell death, macrophage infiltration, and renal fibrosis. In addition, Ki67, a marker used to evaluate cell proliferation was increasing while CD68-positive macrophage infiltration was decreasing (Xing et al., 2019). In another UUO model, the UUO + BMMSCs + melatonin (MT) group had the lower gene and protein expressions of TGF- β 1, α -SMA, and TNF- α but higher expression of E-cadherin (Saber et al., 2019). In conclusion, BMMSCs infusion can increase cell proliferation, and decrease peritubular capillary loss and macrophage infiltration in the UUO model. BMMSCs were injected into the UUO rat through the cava vein and da Silva et al. reported that both BMMSCs and their conditioned medium could decrease levels of collagen I, TNF- α , caspase 3, α -SMA, and proliferating cell nuclear antigen (PCNA) and finally decrease EMT and fibrosis area (Da Silva et al., 2015).

BMMSCs could also reduce tubular EMT and renal fibrosis in albumin-overloaded mice. A study reported that BMMSCs can decrease levels of tubular CCL-2, CCL-5, TNF- α , α -SMA, fibronectin (FN), and collagen IV and finally reduce tubular EMT and renal fibrosis in albumin-overloaded mice. Also, research has shown that BMMSCs delivered *via* the renal artery can lower BUN and UACR (Wu et al., 2014).

Genetically engineered murine models are widely used to mimic human PKD. Franchi et al. were the only researchers to use allogeneic MSCs in a PKD rat model. They demonstrated the beneficial effect of a single intravenous infusion of allogeneic

MSCs on systolic blood pressure and fibrosis. Although the infusion had no effect on cyst size or number, it did improve cortical and parenchymal vasculature density, which resulted in better tubular function and creatinine clearance in the intervention group in the autosomal recessive PKD (ARPKD) model (Franchi et al., 2015). Furthermore, 4 weeks after transplantation, some of the MSCs that remained in the kidney developed endothelial or tubular characteristics (Franchi et al., 2015). While it is a genetic model of ARPKD, its features are quite similar to autosomal dominant polycystic kidney disease, the most common form of PKD affecting adults (Lager et al., 2001).

In conclusion, MSCs exert renal protective effects in 5/6 NPX rats, diabetic mellitus models in mice, MRL/lpr mice, COL4A3-deficient mice, UUO mice, albumin-overloaded mice, and PKD rat models by increasing levels of BMP-7, VEGF, FGFs, and HGF. Also, the levels of damage markers in renal fibrosis, including ED-1 α -SMA, IL-6, IL-1 β , TNF- α , TGF- β , NF- κ B mRNA, CCL-2, CCL-5, collagen I, FN, collagen IV, and PCNA are decreased (Ninichuk et al., 2006; Ezquer et al., 2008; Villanueva et al., 2013; Da Silva et al., 2015; Franchi et al., 2015; Liu et al., 2019; Xiang et al., 2020). Despite promising results in animal models, studies in CKD cats have not replicated the efficacy of MSCs treatment reported in experimentally induced CKD models (Quimby et al., 2016). A study in eight CKD cats suggested that allogeneic MSCs from cryopreserved adipose had no improvement after administration (Quimby et al., 2016). One possible explanation for the disparate outcomes in cats is that uremia impairs the function of allogeneic MSCs. Zhu et al. transplanted ADMSCs into pigs with renal artery stenosis and found that ADMSCs could raise the levels of growth factors HGF, VEGF, and their receptors, Flk-1, and Flt-1, in the pigs' bodies. The transmural cortical microvascular density is also increasing in the therapy group. These data confirm that ADMSCs can attenuate kidney injury in the setting of renal artery stenosis (Table 1) (Zhu et al., 2013).

MSCs-EVs and CKD in preclinical study

EVs (extracellular vesicles) are alternative to MSCs. Compared with MSCs, treating CKD with MSCs-EVs may have the advantage of lower immunogenicity, tumorigenicity, and easier management (Abbaszadeh et al., 2020). EVs carry complex cargoes of biological molecules including cytokines, chemokines, growth factors, and nucleic acids. The content of the EVs cargo is related to the state of their cells of origin and can reflect the phenotype of the releasing cell. Many preclinical trials have revealed that MSCs-EVs are effective in treating CKD (Table 1).

In a mouse model, single MSCs-MVs enriched with miR-451a were injected into STZ-induced diabetic nephropathy (DN) animals. The study found that MSCs-MVs enriched with miR-

TABLE 1 Summary of preclinical data of MSCs in CKD.

Author, year	Stem cell type	Animal model	Groups	Handling methods	Treatment effect
Villanueva et al. (2013)	ADMSCs	5/6 NPX rats	1 Sham group 2 NPX group 3 NPX rats injected with 450 μ L of X-VIVO™ medium (without MSCs) 4 NPX rats injected in the tail vein with 450 μ L (0.5×10^6 cells) of ADMSCs in X-VIVO™ medium	0.5×10^6 ADMSCs or MSCs CM alone	↓plasma creatinine, damage markers ED-1 and α -SMA ↑Pax-2, BMP-7, and VEGF, Oct-4
Ezquer et al. (2008)	BMMSCs	STZ-induced type 1 diabetes C57BL/6 mice	1 Sham group 2 MSCs group	0.5×10^6 MSCs <i>via</i> the tail vein	↓ blood glucose levels ↑normal beta-pancreatic islets Reversion of hyperglycemia and glycosuria remained for 2 months at least More normal glomeruli appearance Reverts microalbuminuria and precludes renal structural damage
Lee et al. (2006)	BMMSCs	STZ-induced diabetic NOD/scid mice	1 control mice (Normal) 2 STZ 3 STZ + hMSCs	2.5×10^6 MSCs <i>via</i> left cardiac ventricle	↓mesangial thickening and macrophage infiltration BMMSCs prevented further blood glucose increases but did not revert hyperglycemia Single cells were found both in pancreatic islets and glomeruli
Xiang et al. (2020)	UCMSCs	STZ-induced DN rats	1 LG group: D-glucose 5.5 mmol/L 2 HG group: D-glucose 30 mmol/L 3 HG + 25% UCMSCs-CM group 4 HG + 50% UCMSCs-CM group 5 HG + 100% UCMSCs-CM group 6 HG + 25 μ g/ml UMSCs-Exo group 7 HG + 50 μ g/ml UCMSCs-Exo group 8 HG + 100 μ g/ml UCMSCs-Exo group	2×10^6 MSCs <i>via</i> the tail vein	↓proteinuria, Scr, BUN, IL-6, IL-1 β , TNF- α and TGF- β ↑Ccr, FGFs, HGF, and VEGF
Liu et al. (2019)	PDMSCs	a model of LN: MRL/lpr mice	1 the control group, age-matched BALB/C mice 2 the vehicle group, untreated MRL/lpr mice 3 the LEF group 4 the MSCs group	1×10^6 MSCs/300 μ L of saline IV	↓NF- κ B mRNA, phospho-NF- κ B p65, TNF- α , PAI-1, and ICAM-1 expression
Ruan et al. (2014)	UCMSCs	B6.Fas mice	1 normal control (C57BL/6 mice) group 2 model (B6.Fas mice) group 3 low-treatment (B6.Fas mice) groups 4 medium-treatment (B6.Fas mice) groups 5 high-dose treatment (B6.Fas mice) groups	Mice in the B6.Fas mouse high-dose group were injected with 2×10^6 labeled cells, mice in the B6.Fas mouse medium-dose group were injected with 1×10^6 labeled cells, and mice in the B6.Fas mouse low-dose group were injected with 0.5×10^6 labeled cells	↓antinuclear, anti-histone, anti-dsDNA antibodies, tubulointerstitial fibrosis and immune complex deposition in the glomeruli ↑glomerular mesangial cell proliferation

(Continued on following page)

TABLE 1 (Continued) Summary of preclinical data of MSCs in CKD.

Author, year	Stem cell type	Animal model	Groups	Handling methods	Treatment effect
Ninichuk et al. (2006)	BMMSCs	COL4A3-deficient mouse (Alport disease model)	1 Wild type group 2 Collagen4A3 $-/-$ + saline group 3 Collagen4A3 $-/-$ + MSCs group	MSCs (1×10^6) or vehicle <i>via</i> tail vein	↓BUN, Scr, glomerulosclerosis and renal fibrosis →EVGF, BMP
Xing et al. (2019)	BMMSCs	UUO mice	1 MSCs group 2 DMEM group 3 UUO group	500 μ L MSCs (10^6 cells/mL) <i>via</i> the tail vein	↓CD68-positive macrophage, PTC loss, renal tubulointerstitial injury and fibrosis ↑Ki67, α -SMA
Saberi et al. (2019)	BMMSCs	UUO rats	1 Sham group UUO group 2 UUO + BMMSCs group 3 UUO + BMMSCs + MT group	$1 \times 10^6/1$ ml PBS MSCs <i>via</i> lateral tail vein	↑E-cadherin ↓TGF- β 1, α -SMA and TNF- α MT enhance homing effect and survival of transplanted BMMSCs
Saberi et al. (2019)	BMMSCs BMMSCs-CM	UUO rats	1 Sham group 2 UUO group 3 UUO + MSCs group 4 UUO + CM group	1×10^6 MSCs or MSCs-CM (500 μ L) <i>via</i> the cava vein	↓Col1a I, TNF- α , caspase 3, PCNA, α -SMA, EMT and fibrosis area
Wu et al. (2014)	BMMSCs	albumin-overloaded mice	1 UNX group 2 UNX + MSCs group 3 UNX + BSA group 4 UNX + BSA + MSCs group	1×10^6 cells/mouse	↓BUN, UACR, collagen IV and α -SMA message RNAs, tubular CCL-2, CCL-5, TNF- α over expression, α -SMA, FN and collagen IV, tubular EMT
Franchi et al. (2015)	BMMSCs	ARPKD rat model (PCK model)	1 control 2 PCK 3 PCK + MSCs	2.5×10^5 MSCs intrarenal infusion	↑cortical and parenchymal vasculature density →cyst size or number
Quimby et al. (2016)	ADMSCs	CKD cats	1 MSCs 2 Placebo MSCs crossover 3 Placebo	2×10^6 MSCs/kg IV	→Scr, BUN, potassium, phosphorus, GFR by nuclear scintigraphy No adverse effects
Zhu et al. (2013)	EPC ADMSCs	RAS pigs of renal artery stenosis	1 Intrarenal infusion of vehicle 2 EPC (RAS + EPC) 3 MSCs (RAS + MSC) 4 normal controls	Vehicle or 10×10^6 EPC or 10×10^6 MSCs intra-renal infusion	Both EPC and MSCs →renovascular hypertension, PRA, creatinine, and urine protein, Cleaved caspase3 ↑GFR, post stenotic RBF, transmural cortical microvascular density EPC
Kholia et al. (2020)	BMMSCs- EVs	a mouse model of AAN	1 control group 2 AA group 3 AA + BMMSCs-EVs group	1×10^{10} EV/ml/mouse IV	↓ α -SMA, Col1a1, pro-fibrotic genes, blood creatinine and BUN, tubular necrosis, interstitial fibrosis, infiltration of CD45 positive immune cells, fibroblasts, and pericytes →weight loss
Grange et al. (2019)	EVs from bone marrow or liver	NOD SCID gamma mice with STZ-induced T1DM	1 control group 2 STZ-diabetic mice group 3 HLSC EV group 4 MSCs EVFIBRO 5 EV-treated mice group	Multiple dose of 1×10^{10} (IV)	↓ collagen I, MMP3, TIMP1, FasL, Serpina1a, SNAI1, CCL3, BUN, creatinine, fibrosis, EMT, recruitment of macrophages, T cells
Ramirez-Bajo et al. (2020)	BMMSCs EVs	An aggressive mouse model of chronic CsA nephrotoxicity	1 control group 2 CsA group 3 CsA + BMMSCs group 4 CsA + EVs group	BMMSCs, EVs and dCM groups were administered as prophylaxis or as treatment of CsA nephrotoxicity	BMMSCs therapy ↓tubular vacuolization, casts, and cysts rate, BUN ↑body weight EVs therapy ↓ the number of cysts

(Continued on following page)

TABLE 1 (Continued) Summary of preclinical data of MSCs in CKD.

Author, year	Stem cell type	Animal model	Groups	Handling methods	Treatment effect
	EVs-depleted CM		5 CsA + dCM group		EVs decreased the BUN levels but without statistical significance ↑body weight dCM therapy: ↑body weight →histological injury
Ishiy et al. (2020)	ADMSCs	2 K-1C rats (model of renal chronic hypoxia)	1 Sham group 2 Stenotic group	The ADMSCs were injected at a density of 2×10^5 cells diluted in 200 μ L of PBS. The EV-treated groups received 100 μ g of MVs or EVs diluted in 200 μ L of PBS	ADMSCs or MV- and EX-treated ↑SDF1- α (a stem cell homing marker), Col I and TGF- β , IL-10 ↓ HIF1- α , a stabilization of blood pressure ADMSCs and MVs ↓proteinuria ADMSCs ↑IL-1 β
	ADMSCs-MVs		3 Stenotic + ADMSCs group		
	ADMSCs-EVs		4 Stenotic + MVs group		
			5 Stenotic + EVs group		
Liu et al. (2018)	UCMSCs-CM	UUO rats	1 sham group 2 UUO group 3 UUO + CM group	The CM group received UCMSCs-CM (500 μ L) <i>via</i> left renal artery	↓ malondialdehyde (MDA), reactive oxygen species (ROS), the expression of TGF- β 1, α -SMA, TNF- α and Collagen-I, RTEs apoptosis ↑activity of glutathione (GSH), proliferation of RTEs, expression of E-cadherin
Wang et al. (2016)	BMMSCs- EVs	UUO mice	1 sham group 2 NTC MSCs group 3 miR-let7c MSCs group	EVs released from 1×10^6 MSCs intravenously	↓ fibrosis, collagen, MMP-9, α -SMA, TGF- β R1 its receptor
Liu et al. (2021)	UCMSCs -EVs	UUO rats	1 sham operation group 2 sham operation transplanted with UCMSCs -EVs group 3 UUO group 4 UUO transplanted with UCMSCs -EVs group	<i>via</i> the left renal artery after total ligation of the left ureter	↓apoptosis of NRK-52 E cells, Scr, BUN, oxidative stress, the renal tubular injury and tubulointerstitial fibrosis

CKD, chronic kidney disease; MSCs, mesenchymal stem cells; BMMSCs, bone marrow mesenchymal stem cells; ADMSCs, adipose-derived mesenchymal stem cells; UCMSCs, umbilical cord blood mesenchymal stem cells; PDMSCs, placenta-derived mesenchymal stem cells; EPC, endothelial progenitor cells; CM, conditioned medium; dCM, exosomes depleted conditioned medium; UCMSCs-Exo, exosomes from umbilical cord mesenchymal stem cells; MVs, microvesicles; SLE, systemic lupus erythematosus; LN, lupus nephritis; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; 5/6 NPX, nephrectomy; UUO, unilateral ureteral obstruction; RAS, renal artery stenosis; AAN, aristolochic acid nephropathy; UNX, uninephrectomy; STZ, streptozotocin; CsA, cyclosporine; 2K-1C, 2 kidneys, 1 clip model; IV, intravenous; α -SMA, α -smooth muscle actin; BMP-7, bone morphogenetic protein 7; BUN, blood urea nitrogen; VEGF, vascular endothelial-derived growth factor; Ccr, creatinine clearance rate; FGFs, fibroblast growth factor; HGF, hepatocyte growth factor; PAI-1, plasminogen activator inhibitor-1; IL-6, interleukin 6; TGF- β 1, transforming growth factor- β 1; TNF- α , tumor necrosis factor alpha; IL-1 β , interleukin-1 β ; PTC, peritubular capillary; HIF-1 α , hypoxia induction factor-1 α ; IL-10, interleukin 10; PCNA, proliferating cell nuclear antigen; PBS, phosphate-buffered saline; Scr, serum creatinine; UACR, urine albumin creatinine ratio; eGFR, estimated glomerular filtration rate.

451a decreased the level of α -SMA and increased E-cadherin expression, finally reducing fibrosis (Kholia et al., 2020). BMMSCs-EVs delivered miRNA to mice with STZ induced T1DM and downregulated the expressions of collagen I, metalloproteinase 3 (MMP3), and tissue inhibitor of matrix metalloproteinase-1 (TIMP1). Also, the apoptotic gene expressions such as FasL and Serpina1a (α -1-antitrypsin) were suppressed (Grange et al., 2019). In the mouse model of chronic cyclosporine (CsA) nephrotoxicity, EVs can improve the prognosis of kidney diseases (Ramírez-Bajo et al., 2020).

EVs exert anti-fibrotic activity through the transfer of miRNA targeting predicted pro-fibrotic genes. Multiple studies have demonstrated that MSCs-EVs exert a therapeutic effect by

downregulating pro-fibrotic gene expression, inhibiting EMT, reducing tubular atrophy and inflammation, and promoting vascular regeneration. The mechanism of renoprotection of MSCs-EVs was attributed to the downregulation of phosphorylated Smad2, Smad3, and p38 MAPK signaling and upregulation of E-cadherin (Table 1) (Ishiy et al., 2020; Liu et al., 2021).

In a UUO model, the conditional medium (CM) of UCMSCs significantly reduced expressions of pro-fibrogenic factors, such as malondialdehyde, reactive oxygen species, TGF- β 1, α -SMA, TNF- α , and Collagen I. Besides, CM increased E-cadherin expression. These data reflect that CM of UCMSCs effectively improves renal interstitial fibrosis induced by UUO by pro-

proliferation, anti-apoptosis, and anti-fibrosis (Liu et al., 2018). Similarly, a single injection of exosomes enriched with miR-let7 was given to mice with UUO in a study. It found that exosomes with miR-let7 could travel to the kidneys of mice with UUO and downregulate collagen, metalloproteinase-9 (MMP-9), α -SMA, TGF- β type 1 receptor (TGF- β R1) (Wang et al., 2016).

Using MSCs-EVs instead of MSCs would have many advantages in clinical applications, like addressing safety issues such as tumorigenicity, embolisms, and infection transmission through injected cells, as well as making it easier to store them (Vizoso et al., 2017). However, the transition of MSCs-EVs into therapeutically effective drugs offers various hurdles, including determining the optimal method for isolating and characterizing the vesicles in the absence of particular biomarkers. It will be challenging to apply it to future studies due to the lack of an assessment of the complexity of exosome cargo and the possibility of interference by unknown secreted substances. The rules for large-scale manufacturing and quality control are also expected. Moreover, mechanistic studies should also be included in efficacy trials of MSCs-EVs therapy.

MSCs and CKD in clinical study

MSCs and DN in clinical study

DM affects millions of people worldwide. Hyperglycemia in DM can affect several major organs. DN is one of the most severe microvascular consequences for both type 1 and type 2 diabetics. Also, DN is still progressing rapidly and is the primary cause of ESRD. Currently, DN is treated by blocking the renin-angiotensin system and controlling glucose, lipids, and blood pressure (Webster et al., 2017). Renal replacement therapy is an effective treatment option for patients with DN who have progressed to ESRD, but it is associated with significant medical and socioeconomic burdens (Tang and Lai, 2012). Therefore, regenerative approaches are urgently needed.

Numerous preclinical trials have indicated that MSCs-based therapy can slow the progression of DN. However, research on MSCs therapy for DN remains limited to preclinical models, and there is very little human data available. Only one clinical trial has been completed so far. In this completed trial, two doses of allogeneic BMMSCs were given to 30 patients with DN. No acute adverse events occurred with the administration of the drug and no patients developed enduring donor-specific anti-HLA antibodies in this study. It is likely that BMMSCs infusion is safe in patients with DN. In addition, the MSCs-treated group showed a more stable or improved eGFR (estimated glomerular filtration rate) at week 12, which may provide a clue to how MSCs act in this disease. In conclusion, this multicenter, randomized, double-blind, dose-escalating, sequential, and placebo-controlled trial suggests that it is feasible and safe to use MSCs in subjects with DN (Table 2) (Packham et al., 2016).

MSCs and LN in clinical study

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that involves multiorgan damage, including kidneys. LN is a main cause of morbidity and overall mortality in SLE (Almaani et al., 2017). Currently, the efficacy of MSCs in treating LN was controversial.

An RCT study showed that the clinical symptoms and serological markers in the IV type of LN improved with no significant difference after the infusion of MSCs (Deng et al., 2017). However, in a clinical trial involving eighty-one patients with severe and drug refractory SLE, MSCs were safe and resulted in long-term clinical remission in SLE patients. Moreover, at follow-up after 1, 2, 3, 4, and 5 years, 24-h proteinuria was significantly reduced after MSCs treatment (Wang et al., 2018). In another clinical study, a single injection of allogeneic BMMSCs was given to patients with refractory SLE. Although two patients had a relapse of proteinuria, the remaining 11 patients showed a significant decrease in proteinuria and also an improvement in serological markers. Increased levels of circulating CD4⁺ Foxp3⁺ Tregs induced by BMMSCs may contribute to these positive findings (Liang et al., 2010). However, the exact mechanism was unclear. Allogeneic UCMSCs might suppress inflammation in SLE patients by up-regulating tolerogenic CD1c⁺ dendritic cells, suppressing T cells proliferation and differentiation (Yuan et al., 2019). Despite the *in vivo* evidence for the therapeutic efficacy of MSCs in LN treatment, the underlying mechanisms remain unclear. Therefore, future advances can explore specific mechanisms of MSCs behaviors in LN patients (Figure 1 and Table 2).

MSCs and ADPKD in clinical study

ADPKD is the most common genetic cause of CKD with chronic nonproteinuric nephropathies (Patel et al., 2009). Current management for ADPKD includes blood pressure control, dietary sodium restriction, and increasing fluid intake. Potential treatments for ADPKD include tolvaptan, octreotide, cystic fibrosis transmembrane conductance regulator protein (CFTR) inhibitors, pioglitazone, etanercept, and triptolide (Patel et al., 2009). A safety assessment of autologous BMMSCs has been conducted in a phase 1 clinical trial including six patients with ADPKD. This report indicated that no cell-related adverse events were observed following a single-cell infusion of MSCs during the 12-months follow-up. This trial demonstrated that the mean serum creatinine (SCr) level of the patients gradually increased from 2 ± 0.3 mg/dl to 2.5 ± 0.4 mg/dl before MSCs infusion and remained stable at 2.5 ± 0.6 mg/dl after 12 months of BMMSCs treatment. However, BMMSCs infusion did not significantly affect eGFR or kidney length,

TABLE 2 Summary of clinical data of MSCs in CKD.

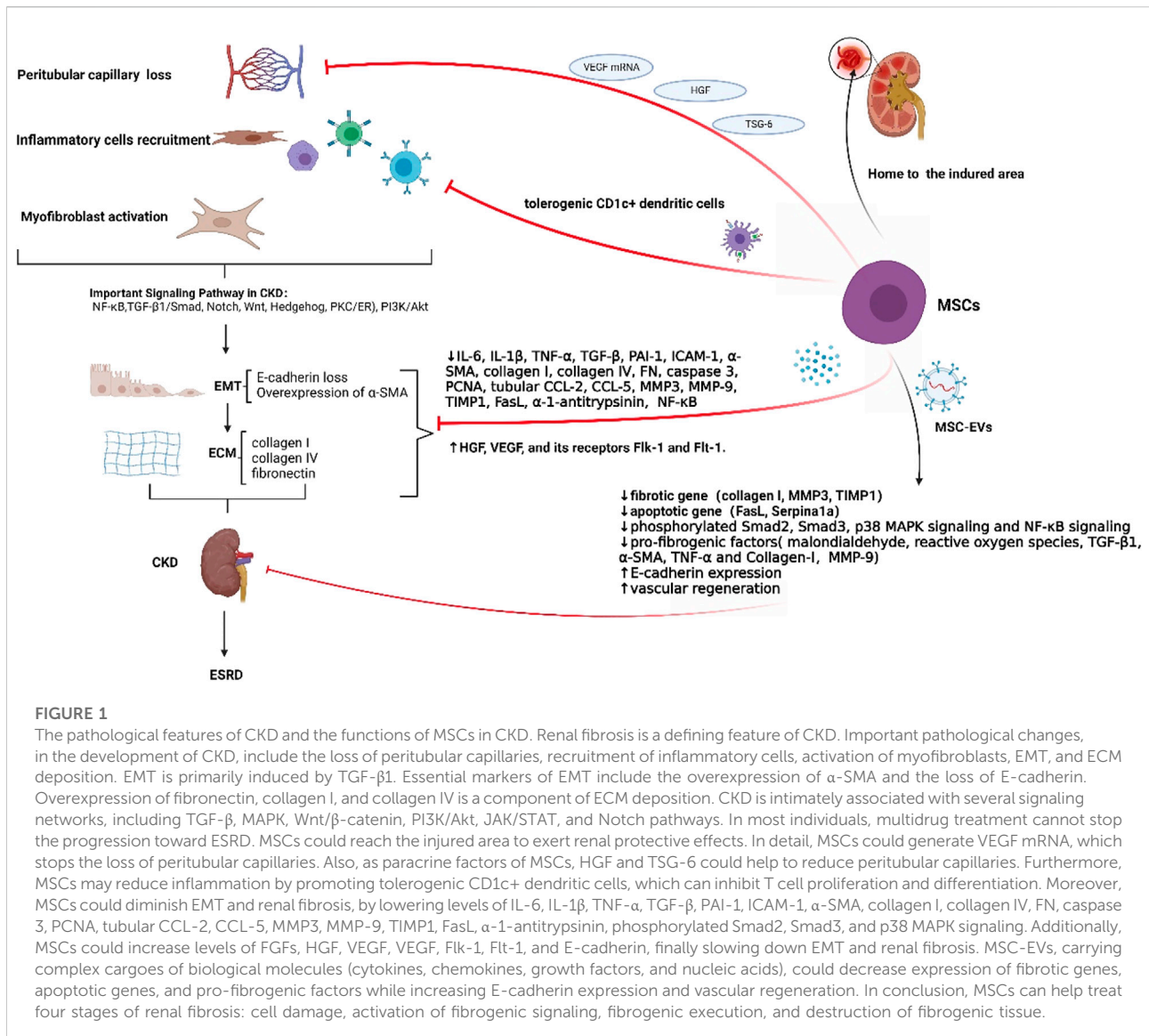
Author, year	Stem cell type	Patients	Study type	Handling methods	Treatment effect
Packham et al. (2016)	BMMSCs	13 patients at three Australian centers with moderate to severe DN	A multicenter, randomized, double-blind, dose-escalating, sequential, placebo-controlled trial	150×10 ⁶ or 300×10 ⁶ MSCs IV	No acute adverse events No patients developed persistent donor specific anti-HLA antibodies
Deng et al. (2017)	UCMSCs	12 among 18 patients were randomized to UCMSCs arm	A randomised double-blind, placebo-controlled trial	2×10 ⁸ MSCs IV	No significant difference after the infusion of MSCs
Wang et al. (2018)	BMMSCs UCMSCs	81 patients with severe and drug-refractory SLE	A long-term follow-up study	Of the 81 patients, 22 received allogeneic BMMSCs. Four were treated a second time with UCMSCs. Two other patients received two additional doses of UCMSCs and one patient received three additional doses of UCMSCs. Among the 59 patients first treated with UC-MSCs, 7 received a second UCMSCs, 1 received two additional doses of UCMSCs, and 1 received three additional doses of UCMSCs	MSCs transplantation is safe and resulted in long-term clinical remission in SLE patients
Liang et al. (2010)	BMMSCs	15 patients with refractory SLE	A pilot clinical study	13×10 ⁶ /kg IV	All patients: no serious adverse events, non-renal-related manifestations improved significantly, increase 2 patients: relapse of proteinuria 11 patients ↓SLEDAI score, 24-h proteinuria, anti-dsDNA levels
Yuan et al. (2019)	UCMSCs	21 among 166 SLE patients refractory to conventional therapies were enrolled in UCMSCs therapy	Clinical Trial.gov (identifier: NCT01741857)	2×10 ⁷ /kg IV	↓Peripheral tolerogenic CD1c+ DCs, serum FLT3L ↑peripheral blood CD1c+DCs and serum FLT3L
Makhlough et al. (2017)	BMMSCs	6 eligible ADPKD patients	A single-arm phase I clinical trial	2×10 ⁶ /kg IV	Safe and well tolerated →eGFR, BUN, Calcium, Phosphorus, Dipstick proteinuria, Alkaline phosphatase, Total cholesterol, Triglycerides, SCr, Kidney length

BMMSCs, bone marrow mesenchymal stem cells; UCMSCs, umbilical cord blood mesenchymal stem cells; SLE, systemic lupus erythematosus; LN, lupus nephritis; SLEDAI, systemic lupus erythematosus disease activity index; DN, diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; IV, intravenous; DCs, dendritic cells; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

an index of kidney growth. These non-significant findings may be associated with the small number of patients, the short follow-up period, the single cell infusion, or the unexplored possible dysfunction of autosomal MSCs derived from patients with ADPKD (Makhlough et al., 2017). There is still relatively little research on MSCs therapy for ADPKD. More research is expected to validate the therapeutic effects of MSCs (Table 2).

Challenges and future perspectives for MSCs therapy

MSCs might be an attractive treatment for CKD. However, low cell survival after transplantation restricts the efficiency of cell therapy. We cover the major barriers to successful cell engraftment as well as the solutions that have been investigated to increase the therapeutic benefits of cell therapy.



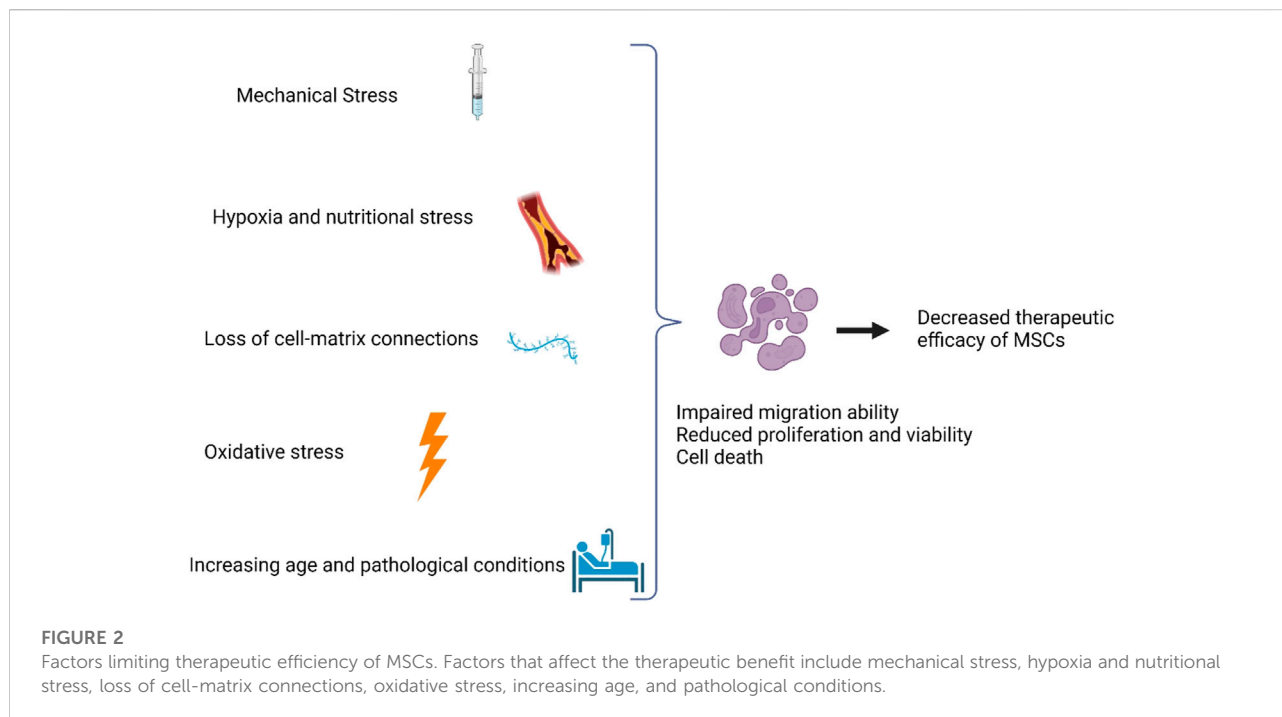
The number of given cells that reach the target area, their vitality, and their potential to promote tissue regeneration will ultimately decide the cell therapy efficacy. Several variables influence long-term transplanted cell survival, including mechanical stress during implantation, extracellular matrix loss during delivery, nutrition and oxygen deprivation at the recipient site, increasing age, and pathological circumstances.

Cell membranes are easily ruptured by the mechanical stresses during injection, in particular the stretching and shearing forces created by the extensional and linear flow into the syringe needle or catheter (Aguado et al., 2012). Cell injection techniques usually result in a loss of living cells, with viabilities ranging from 1 to 32% post-transplantation (Zhang et al., 2001). Therefore, improvement of the delivery techniques may greatly enhance the vitality and function of the injected cells. Hydrogels

may aid in increasing the viscosity of the cell suspension, hence lowering the mechanical forces during injection (Foster et al., 2017).

ECM facilitates cell adherence and engraftment (He et al., 2015). However, therapeutic applications of MSCs are based on single cell suspension, which results in the loss of cell-matrix connections and the downregulation of adhesion signals, leading to cell death (He et al., 2015).

Oxygen and nutrition deprivation caused by delayed revascularization at the implantation site is a key cause of early cell death (Rouwkema et al., 2010). Several preconditioning procedures have been devised to increase the resistance of transplanted cells to death triggers after transplantation. One technique is to stimulate a wide prosurvival response in cells by subjecting them to a physical



or environmental shock, such as high temperature, nutritional restriction, hypoxia, or anoxia (Fulda et al., 2010). Sub-lethal settings enable cells to progressively adapt to environmental changes, generating an anti-stress response and activating pathways that facilitate survival (Fulda et al., 2010).

The proliferation and differentiation abilities of MSCs significantly decline with increasing age (Li et al., 2014). The poor health of the patient may also limit the function of MSCs derived from CKD patients for the use of autologous MSCs. Furthermore, diabetes also creates an unfavorable microenvironment for MSCs, making it harder to survive, migrate to infected tissue, and perform their functions. *In vivo*, MSCs show reduced proliferation and viability with a reduced level of proteoglycans and glycosaminoglycans in the surrounding tissue (Bi et al., 2005). The production of advanced glycosylated end products also triggers apoptosis and the generation of reactive oxygen species, inhibiting MSCs proliferation. Oxidative stress can also affect the paracrine effects of MSCs under hypoxic conditions in diabetics. Superoxide levels in hypoxic MSCs rise a lot, which makes them less likely to make angiogenic growth factors like hypoxia-induced factor-1 α , VEGF-A, and platelet-derived growth factor B (PDGF-B) (Kume et al., 2005; Ishizuka et al., 2011). MSCs are also impaired in their migration ability in high glucose conditions (Secchiero et al., 2008). As a result, novel approaches are required to improve the therapeutic efficacy of MSCs in pathophysiological conditions. Several studies have shown that preconditioning of MSCs extends their lives and improves their function. Pretreatment can be achieved by using

specific compounds such as MT and fucoidan. Pretreatment with MT ameliorated oxidative stress and senescence in a model of ischemic disease associated with CKD (Han et al., 2019). Additionally, fucoidan-treated MSCs can enhance cell proliferation, angiogenesis, and regeneration in a model of hind limb ischemia associated with CKD in mice (Han et al., 2015).

In conclusion, reduced cell survival after transplantation limits the efficacy of cell treatment, which is caused by a combination of mechanical, cell, and human factors. Many techniques have been developed to promote the survival of MSCs after transplantation in preclinical studies, such as hydrogel microcarriers, biomaterials, preconditioning, and so on. However, before these strategies can be successfully used in the clinic, more studies are needed to find out if and how they affect the biological activity of transplanted cells *in vivo* (Figure 2).

Discussion

Various studies have proposed that MSCs can reduce the development and progression of CKD by modulating immunity, inhibiting inflammatory factors, and improving renal function (Ruan et al., 2014; Ishiy et al., 2020; Xiang et al., 2020). MSCs could reduce tubular EMT and renal fibrosis by decreasing levels of IL-6, IL-1 β , TNF- α , TGF- β , PAI-1, ICAM-1, α -SMA, collagen I, collagen IV, FN, caspase 3, PCNA, tubular CCL-2, CCL-5, MMP3, MMP-9, TIMP1,

FasL, α -1-antitrypsin, phosphorylated Smad2, Smad3, NF- κ B expression, and p38 MAPK signaling. However, levels of FGFs, HGF, VEGF, Flk-1, Flt-1, and E-cadherin were increased in this process.

Using MSCs for CKD therapy has been demonstrated to be feasible and safe based on many experimental evidence and clinical trials. Concerns about an increase in the risk of opportunistic infections have been alleviated by reassuring safety data from a large kidney transplant program (Reinders et al., 2013). The reassuring safety profile of MSCs in patients with kidney disease is consistent with other published information (Casiraghi et al., 2013), but long-term monitoring of MSC-treated patients with nephropathy is still essential, especially for the potential risk of developing anti-HLA antibodies and cancer.

Data on efficacy are promising, however, the results have not been replicated in the clinic (Bao et al., 2018). In STZ-induced DN rats, MSCs were able to migrate to the kidneys and repair renal dysfunction effectively, such as lowering proteinuria, Scr, and urea nitrogen levels and increasing creatinine clearance rate (Ccr) (Xiang et al., 2020). However, in 30 DN patients, no functional parameters were improved except a more stable or improved eGFR at week 12 after using MSCs (Packham et al., 2016).

Differences in animal models and human physiology preclude the direct translation of promising results from animal experiments into clinical applications. In animal models, kidney diseases are typically induced artificially. Generally, induced injury is acute, unphysiological, and does not illustrate the complex pathophysiology of the human kidney (Pesenti et al., 1990; Hewitson et al., 2015). Thus, it is difficult to predict precisely how a disease will respond to treatment using an animal model. Because other factors like age, gender, and comorbidities are not considered in animal experiments, CKD animal experiments are not sufficiently reflective of the conditions of the disease. Additionally, CKD patients may suffer from comorbidities affecting multiple organs and functions, further triggering the pathological processes underpinning CKD (Togoe et al., 2014). These complications have not been considered in animal models.

The potential use of EVs as an alternative to live MSCs should also be explored. Considering the complexity of exosome cargo and the possibility of interference by unknown secreted substances, future studies will be challenging to apply. Nevertheless, quality control and large-scale manufacturing rules remain unclear. The hurdles above will require effort and attention, but they are not unimprovable.

Conclusion

There has been extensive preclinical and clinical data showing that cell-based therapies using MSCs can modulate immunity, inhibit inflammatory factors, and improve renal function in CKD, suggesting the possibility of MSCs as a new, effective therapeutic tool for CKD. However, more well-designed studies in preclinical and clinical studies should be performed in the future to confirm it.

Author contributions

JW looked up a lot of pertinent papers and wrote the manuscript. YL, XC, and YL reviewed and checked the article. TZ modified and polished the article, and reviewed the article. The authors have read and approved the final manuscript.

Funding

This review was supported by Shantou Science and Technology Project (Shanfuke (2019) 106-4: 190606165268433), Guangdong Province Science and Technology Special Fund (shanfuke (2021) 88-28: 210714086900312) and Shantou Youth Talent Project (no. 2020023).

Acknowledgments

Figures are created with BioRender.com.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Abbaszadeh, H., Ghorbani, F., Derakhshani, M., Movassaghpour, A., and Yousefi, M. (2020). Human umbilical cord mesenchymal stem cell-derived extracellular vesicles: A novel therapeutic paradigm. *J. Cell. Physiology* 235, 706–717. doi:10.1002/jcp.29004
- Aguado, B. A., Mulyasmita, W., Su, J., Lampe, K. J., and Heilshorn, S. C. (2012). Improving viability of stem cells during syringe needle flow through the design of hydrogel cell carriers. *Tissue Eng. Part A* 18, 806–815. doi:10.1089/ten.TEA.2011.0391
- Almaani, S., Meara, A., and Rovin, B. H. (2017). Update on lupus nephritis. *Clin. J. Am. Soc. Nephrol.* 12, 825–835. doi:10.2215/cjn.05780616
- Ashour, R. H., Saad, M. A., Sobh, M. A., Al-Husseiny, F., Abouelkheir, M., Awad, A., et al. (2016). Comparative study of allogenic and xenogeneic mesenchymal stem cells on cisplatin-induced acute kidney injury in Sprague-Dawley rats. *Stem Cell Res. Ther.* 7, 126. doi:10.1186/s13287-016-0386-0
- Barczyk, M., Schmidt, M., and Mattoli, S. (2015). Stem cell-based therapy in idiopathic pulmonary fibrosis. *Stem Cell Rev Rep* 11, 598–620. doi:10.1007/s12015-015-9587-7
- Bao, Y. W., Yuan, Y., Chen, J. H., Lin, W. Q., et al. (2018). Kidney disease models: tools to identify mechanisms and potential therapeutic targets. *Zool. Res.* 39, 72–86. doi:10.24272/j.issn.2095-8137.2017.055
- Bi, Y., Stuelten, C. H., Kilts, T., Wadhwa, S., Iozzo, R. V., Robey, P. G., et al. (2005). Extracellular matrix proteoglycans control the fate of bone marrow stromal cells. *J. Biol. Chem.* 280, 30481–30489. doi:10.1074/jbc.M500573200
- Casiraghi, F., Remuzzi, G., Abbate, M., and Perico, N. (2013). Multipotent mesenchymal stromal cell therapy and risk of malignancies. *Stem Cell Rev Rep* 9, 65–79. doi:10.1007/s12015-011-9345-4
- Chin, S. P., Maskon, O., Tan, C. S., Anderson, J. E., Wong, C. Y., Hassan, H. H. C., et al. (2021). Synergistic effects of intracoronary infusion of autologous bone marrow-derived mesenchymal stem cells and revascularization procedure on improvement of cardiac function in patients with severe ischemic cardiomyopathy. *Stem Cell Investig.* 8, 2. doi:10.21037/sci-2020-026
- Chin, S. P., Poey, A. C., Wong, C. Y., Chang, S. K., Tan, C. S., Ng, M. T., et al. (2011). Intramyocardial and intracoronary autologous bone marrow-derived mesenchymal stromal cell treatment in chronic severe dilated cardiomyopathy. *Cytotherapy* 13, 814–821. doi:10.3109/14653249.2011.574118
- Chin, S. P., Poey, A. C., Wong, C. Y., Chang, S. K., Teh, W., Mohr, T. J., et al. (2010). Cryopreserved mesenchymal stromal cell treatment is safe and feasible for severe dilated ischemic cardiomyopathy. *Cytotherapy* 12, 31–37. doi:10.3109/14653240903313966
- Da Silva, A. F., Silva, K., Reis, L. A., Teixeira, V. P., and Schor, N. (2015). Bone marrow-derived mesenchymal stem cells and their conditioned medium attenuate fibrosis in an irreversible model of unilateral ureteral obstruction. *Cell Transpl.* 24, 2657–2666. doi:10.3727/096368915X687534
- Deng, D., Zhang, P., Guo, Y., and Lim, T. O. (2017). A randomised double-blind, placebo-controlled trial of allogeneic umbilical cord-derived mesenchymal stem cell for lupus nephritis. *Ann. Rheum. Dis.* 76, 1436–1439. doi:10.1136/annrheumdis-2017-211073
- Docherty, N. G., O'Sullivan, O. E., Healy, D. A., Fitzpatrick, J. M., and Watson, R. W. (2006). Evidence that inhibition of tubular cell apoptosis protects against renal damage and development of fibrosis following ureteric obstruction. *Am. J. Physiology-Renal Physiology* 290, F4–F13. doi:10.1152/ajprenal.00045.2005
- Dominici, M., Le Blanc, K., Mueller, L., Slaper-Cortenbach, I., Marini, F., Krause, D., et al. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Int. Soc. Cell. Ther. position statement Cytotherapy* 8, 315–317. doi:10.1080/14653240600855905
- Edeling, M., Ragi, G., Huang, S., Pavenstädt, H., and Susztak, K. (2016). Developmental signalling pathways in renal fibrosis: The roles of Notch, Wnt and hedgehog. *Nat. Rev. Nephrol.* 12, 426–439. doi:10.1038/nrneph.2016.54
- Ene-Iordache, B., Perico, N., Bikbov, B., Carminati, S., Remuzzi, A., Perna, A., et al. (2016). Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-kddc): A cross-sectional study. *Lancet Glob. Health* 4, e307–e319. doi:10.1016/S2214-109X(16)00071-1
- Eom, Y. W., Shim, K. Y., and Baik, S. K. (2015). Mesenchymal stem cell therapy for liver fibrosis. *Korean J. Intern Med.* 30, 580–589. doi:10.3904/kjim.2015.30.5.580
- Eschbach, J. W. (1991). Erythropoietin 1991—an overview. *Am. J. Kidney Dis.* 18, 3–9.
- Ezquer, F. E., Ezquer, M. E., Parrau, D. B., Carpio, D., Yañez, A. J., and Conget, P. A. (2008). Systemic administration of multipotent mesenchymal stromal cells reverts hyperglycemia and prevents nephropathy in type 1 diabetic mice. *Biol. Blood Marrow Transplant.* 14, 631–640. doi:10.1016/j.bbmt.2008.01.006
- Fazzina, R., Iudicone, P., Fioravanti, D., Bonanno, G., Totta, P., Zizzari, I. G., et al. (2016). Potency testing of mesenchymal stromal cell growth expanded in human platelet lysate from different human tissues. *Stem Cell Res. Ther.* 7, 122. doi:10.1186/s13287-016-0383-3
- Foster, A. A., Marquardt, L. M., and Heilshorn, S. C. (2017). The diverse roles of hydrogel mechanics in injectable stem cell transplantation. *Curr. Opin. Chem. Eng.* 15, 15–23. doi:10.1016/j.coche.2016.11.003
- Franchi, F., Peterson, K. M., Xu, R., Miller, B., Psaltis, P. J., Harris, P. C., et al. (2015). Mesenchymal stromal cells improve renovascular function in polycystic kidney disease. *Cell Transpl.* 24, 1687–1698. doi:10.3727/096368914x684619
- Fulda, S., Gorman, A. M., Hori, O., and Samali, A. (2010). Cellular stress responses: Cell survival and cell death. *Int. J. Cell Biol.* 2010, 1–23. doi:10.1155/2010/214074
- Gennari, F. J., and Segal, A. S. (2002). Hyperkalemia: An adaptive response in chronic renal insufficiency. *Kidney Int.* 62, 1–9. doi:10.1046/j.1523-1755.2002.00350.x
- Genovese, F., Manresa, A. A., Leeming, D. J., Karsdal, M. A., and Boor, P. (2014). The extracellular matrix in the kidney: A source of novel non-invasive biomarkers of kidney fibrosis? *Fibrogenes. Tissue Repair* 7, 4. doi:10.1186/1755-1536-7-4
- Grange, C., Tritta, S., Tapparo, M., Cedrino, M., Tetta, C., Camussi, G., et al. (2019). Stem cell-derived extracellular vesicles inhibit and revert fibrosis progression in a mouse model of diabetic nephropathy. *Sci. Rep.* 9, 4468. doi:10.1038/s41598-019-41100-9
- Han, Y. S., Kim, S. M., Lee, J. H., Jung, S. K., Noh, H., and Lee, S. H. (2019). Melatonin protects chronic kidney disease mesenchymal stem cells against senescence via PrPC-dependent enhancement of the mitochondrial function. *J. Pineal Res.* 66, e12535. doi:10.1111/jpi.12535
- Han, Y. S., Lee, J. H., Jung, J. S., Noh, H., Baek, M. J., Ryu, J. M., et al. (2015). Fucoidan protects mesenchymal stem cells against oxidative stress and enhances vascular regeneration in a murine hindlimb ischemia model. *Int. J. Cardiol.* 198, 187–195. doi:10.1016/j.ijcard.2015.06.070
- He, N., Xu, Y., Du, W., Qi, X., Liang, L., Wang, Y., et al. (2015). Extracellular matrix can recover the downregulation of adhesion molecules after cell detachment and enhance endothelial cell engraftment. *Sci. Rep.* 5, 10902. doi:10.1038/srep10902
- Heerspink, H. J. L., Kosiborod, M., Inzucchi, S. E., and Cherney, D. Z. I. (2018). Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int.* 94, 26–39. doi:10.1016/j.kint.2017.12.027
- Hewitson, T. D., Holt, S. G., and Smith, E. R. (2015). Animal models to study links between cardiovascular disease and renal failure and their relevance to human pathology. *Front. Immunol.* 6, 465. doi:10.3389/fimmu.2015.00465
- Hu, H. H., Chen, D. Q., Wang, Y. N., Feng, Y. L., Cao, G., Vaziri, N. D., et al. (2018). New insights into TGF- β /Smad signaling in tissue fibrosis. *Chemico-Biological Interact.* 292, 76–83. doi:10.1016/j.cbi.2018.07.008
- Ishiy, C., Ormanji, M. S., Maquigussa, E., Ribeiro, R. S., da Silva Novaes, A., and Boim, M. A. (2020). Comparison of the effects of mesenchymal stem cells with their extracellular vesicles on the treatment of kidney damage induced by chronic renal artery stenosis. *Stem Cells Int.* 2020, 1–13. doi:10.1155/2020/8814574
- Ishizuka, T., Hinata, T., and Watanabe, Y. (2011). Superoxide induced by a high-glucose concentration attenuates production of angiogenic growth factors in hypoxic mouse mesenchymal stem cells. *J. Endocrinol.* 208, 147–159. doi:10.1677/joe-10-0305
- Jin, L., Zhang, J., Deng, Z., Liu, J., Han, W., Chen, G., et al. (2020). Mesenchymal stem cells ameliorate myocardial fibrosis in diabetic cardiomyopathy via the secretion of prostaglandin E2. *Stem Cell Res. Ther.* 11, 122. doi:10.1186/s13287-020-01633-7
- Katsuno, T., Ozaki, T., Saka, Y., Furuhashi, K., Kim, H., Yasuda, K., et al. (2013). Low serum cultured adipose tissue-derived stromal cells ameliorate acute kidney injury in rats. *Cell Transpl.* 22, 287–297. doi:10.3727/096368912x655019
- Kholia, S., Herrera Sanchez, M. B., Cedrino, M., Papadimitriou, E., Tapparo, M., Deregibus, M. C., et al. (2020). Mesenchymal stem cell derived extracellular vesicles ameliorate kidney injury in aristolochic acid nephropathy. *Front. Cell Dev. Biol.* 8, 188. doi:10.3389/fcell.2020.00188
- Kume, S., Kato, S., Yamagishi, S., Inagaki, Y., Ueda, S., Arima, N., et al. (2005). Advanced glycation end-products attenuate human mesenchymal stem cells and prevent cognate differentiation into adipose tissue, cartilage, and bone. *J. Bone Min. Res.* 20, 1647–1658. doi:10.1359/jbmr.050514
- La Rocca, G., Anzalone, R., Corrao, S., Magno, F., Loria, T., Lo Iacono, M., et al. (2009). Isolation and characterization of oct-4+/HLA-G+ mesenchymal stem cells from human umbilical cord matrix: Differentiation potential and

- detection of new markers. *Histochem Cell Biol.* 131, 267–282. doi:10.1007/s00418-008-0519-3
- Lager, D. J., Qian, Q., Bengal, R. J., Ishibashi, M., and Torres, V. E. (2001). The pck rat: A new model that resembles human autosomal dominant polycystic kidney and liver disease. *Kidney Int.* 59, 126–136. doi:10.1046/j.1523-1755.2001.00473.x
- Lee, R. H., Seo, M. J., Reger, R. L., Spees, J. L., Pulin, A. A., Olson, S. D., et al. (2006). Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. *Proc. Natl. Acad. Sci. U.S.A.* 103, 17438–17443. doi:10.1073/pnas.0608249103
- Li, B., Cheng, X., Aierken, A., Du, J., He, W., Zhang, M., et al. (2021). Melatonin promotes the therapeutic effect of mesenchymal stem cells on type 2 diabetes mellitus by regulating TGF- β pathway. *Front. Cell Dev. Biol.* 9, 722365. doi:10.3389/fcell.2021.722365
- Li, X., Bai, J., Ji, X., Li, R., Xuan, Y., and Wang, Y. (2014). Comprehensive characterization of four different populations of human mesenchymal stem cells as regards their immune properties, proliferation and differentiation. *Int. J. Mol. Med.* 34, 695–704. doi:10.3892/ijmm.2014.1821
- Liang, J., Zhang, H., Hua, B., Wang, H., Lu, L., Shi, S., et al. (2010). Allogeneic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: A pilot clinical study. *Ann. Rheumatic Dis.* 69, 1423–1429. doi:10.1136/ard.2009.123463
- Liu, B., Ding, F. X., Liu, Y., Xiong, G., Lin, T., He, D. W., et al. (2018). Human umbilical cord-derived mesenchymal stem cells conditioned medium attenuate interstitial fibrosis and stimulate the repair of tubular epithelial cells in an irreversible model of unilateral ureteral obstruction. *Nephrology* 23, 728–736. doi:10.1111/nep.13099
- Liu, B., Hu, D., Zhou, Y., Yu, Y., Shen, L., Long, C., et al. (2021). Erratum: Exosomes released by human umbilical cord mesenchymal stem cells protect against renal interstitial fibrosis through ROS-mediated P38MAPK/ERK signaling pathway. *Am. J. Transl. Res.* 13, 3921–3922.
- Liu, J., Lu, X., Lou, Y., Cai, Y., Cui, W., Wang, J., et al. (2019). Xenogeneic transplantation of human placenta-derived mesenchymal stem cells alleviates renal injury and reduces inflammation in a mouse model of lupus nephritis. *BioMed Res. Int.* 2019, 1–11. doi:10.1155/2019/9370919
- Liu, M., Ning, X., Li, R., Yang, Z., Yang, X., Sun, S., et al. (2017). Signaling pathways involved in hypoxia-induced renal fibrosis. *J. Cell. Mol. Med.* 21, 1248–1259. doi:10.1111/jcmm.13060
- Makhlouf, A., Shekarchian, S., Moghadasali, R., Einollahi, B., Hosseini, S. E., Jaroughi, N., et al. (2017). Safety and tolerability of autologous bone marrow mesenchymal stromal cells in ADPKD patients. *Stem Cell Res. Ther.* 8, 116. doi:10.1186/s13287-017-0557-7
- McGaha, T. L., and Madaio, M. P. (2014). Lupus nephritis: Animal modeling of a complex disease syndrome pathology. *Drug Discov. Today Dis. Models* 11, 13–18. doi:10.1016/j.ddmod.2014.08.002
- Melief, S. M., Zwaginga, J. J., Fibbe, W. E., and Roelofs, H. (2013). Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts. *Stem Cells Transl. Med.* 2, 455–463. doi:10.5966/sctm.2012-0184
- Murali, K., Mullan, J., Roodenrys, S., and Lonergan, M. (2020). Comparison of health literacy profile of patients with end-stage kidney disease on dialysis versus non-dialysis chronic kidney disease and the influencing factors: A cross-sectional study. *BMJ Open* 10, e041404. doi:10.1136/bmjopen-2020-041404
- Musiał-Wysocka, A., Kot, M., and Majka, M. (2019). The pros and cons of mesenchymal stem cell-based therapies. *Cell Transpl.* 28, 801–812. doi:10.1177/0963689719837897
- Ninichuk, V., Gross, O., Segerer, S., Hoffmann, R., Radomska, E., Buchstaller, A., et al. (2006). Multipotent mesenchymal stem cells reduce interstitial fibrosis but do not delay progression of chronic kidney disease in collagen4A3-deficient mice. *Kidney Int.* 70, 121–129. doi:10.1038/sj.ki.5001521
- Packham, D. K., Fraser, I. R., Kerr, P. G., and Segal, K. R. (2016). Allogeneic mesenchymal precursor cells (MPC) in diabetic nephropathy: A randomized, placebo-controlled, dose escalation study. *EBioMedicine* 12, 263–269. doi:10.1016/j.ebiom.2016.09.011
- Patel, V., Chowdhury, R., and Igarashi, P. (2009). Advances in the pathogenesis and treatment of polycystic kidney disease. *Curr. Opin. Nephrol. Hypertens.* 18, 99–106. doi:10.1097/MNH.0b013e3283262ab0
- Pesenti, A., Rossi, G. P., Pelosi, P., Brazzi, L., and Gattinoni, L. (1990). Percutaneous extracorporeal CO₂ removal in a patient with bullous emphysema with recurrent bilateral pneumothoraces and respiratory failure. *Anesthesiology* 72, 571–572. doi:10.1097/00000542-199003000-00031
- Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., et al. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science* 284, 143–147. doi:10.1126/science.284.5411.143
- Procci, W. R., Goldstein, D. A., Adelstein, J., and Massry, S. G. (1981). Sexual dysfunction in the male patient with uremia: A reappraisal. *Kidney Int.* 19, 317–323. doi:10.1038/ki.1981.22
- Puissant, B., Barreau, C., Bourin, P., Clavel, C., Corre, J., Bousquet, C., et al. (2005). Immunomodulatory effect of human adipose tissue-derived adult stem cells: Comparison with bone marrow mesenchymal stem cells. *Br. J. Haematol.* 129, 118–129. doi:10.1111/j.1365-2141.2005.05409.x
- Quimby, J. M., Webb, T. L., Randall, E., Marolf, A., Valdes-Martinez, A., and Dow, S. W. (2016). Assessment of intravenous adipose-derived allogeneic mesenchymal stem cells for the treatment of feline chronic kidney disease: A randomized, placebo-controlled clinical trial in eight cats. *J. Feline Med. Surg.* 18, 165–171. doi:10.1177/1098612X15576980
- Ramírez-Bajo, M. J., Martín-Ramírez, J., Bruno, S., Pasquino, C., Banon-Maneus, E., Rovira, J., et al. (2020). Nephroprotective potential of mesenchymal stromal cells and their extracellular vesicles in a murine model of chronic cyclosporine nephrotoxicity. *Front. Cell Dev. Biol.* 8, 296. doi:10.3389/fcell.2020.00296
- Reinders, M. E., de Fijter, J. W., Roelofs, H., Bajema, I. M., de Vries, D. K., Schaapherder, A. F., et al. (2013). Autologous bone marrow-derived mesenchymal stromal cells for the treatment of allograft rejection after renal transplantation: Results of a phase I study. *Stem Cells Transl. Med.* 2, 107–111. doi:10.5966/sctm.2012-0114
- Rouwkema, J., Koopman, B., Blitterswijk, C., Dhert, W., and Malda, J. (2009). Supply of nutrients to cells in engineered tissues. *Biotechnol. Genet. Eng. Rev.* 26, 163–178. doi:10.5661/bger-26-163
- Ruan, G. P., Yao, X., Yang, S. J., Wang, J. X., Shu, F., Li, Z. A., et al. (2014). Transplanted human umbilical cord mesenchymal stem cells facilitate lesion repair in B6.Fas mice. *J. Immunol. Res.* 2014, 1–13. doi:10.1155/2014/530501
- Saberi, K., Pasbakhsh, P., Omidi, A., Borhani-Haghighi, M., Nekoonam, S., Omidi, N., et al. (2019). Melatonin preconditioning of bone marrow-derived mesenchymal stem cells promotes their engraftment and improves renal regeneration in a rat model of chronic kidney disease. *J. Mol. Hist.* 50, 129–140. doi:10.1007/s10735-019-09812-4
- Secchiero, P., Melloni, E., Corallini, F., Beltrami, A. P., Alviano, F., Milani, D., et al. (2008). Tumor necrosis factor-related apoptosis-inducing ligand promotes migration of human bone marrow multipotent stromal cells. *Stem Cells* 26, 2955–2963. doi:10.1634/stemcells.2008-0512
- Shigeno, Y., and Ashton, B. A. (1995). Human bone-cell proliferation *in vitro* decreases with human donor age. *J. Bone Jt. Surg. Br. volume 77-B*, 139–142. doi:10.1302/0301-620x.77b1.7822372
- Simeoni, M., Borrelli, S., Garofalo, C., Fuiano, G., Esposito, C., Comi, A., et al. (2021). Atherosclerotic-nephropathy: An updated narrative review. *J. Nephrol.* 34, 125–136. doi:10.1007/s40620-020-00733-0
- Stefanski, A., Schmidt, K. G., Waldherr, R., and Ritz, E. (1996). Early increase in blood pressure and diastolic left ventricular malfunction in patients with glomerulonephritis. *Kidney Int.* 50, 1321–1326. doi:10.1038/ki.1996.444
- Tang, S. C., and Lai, K. N. (2012). The pathogenic role of the renal proximal tubular cell in diabetic nephropathy. *Nephrol. Dial. Transplant.* 27, 3049–3056. doi:10.1093/ndt/gfs260
- Teoh, H. K., Chong, P. P., Abdullah, M., Sekawi, Z., Tan, G. C., Leong, C. F., et al. (2016). Small interfering RNA silencing of interleukin-6 in mesenchymal stromal cells inhibits multiple myeloma cell growth. *Leukemia Res.* 40, 44–53. doi:10.1016/j.leukres.2015.10.004
- Togoe, E. B., Silva, I. S., Cury, J. L., Souza, A. S., Borges, J. H., and Saturnino, K. C. (2014). Animal model of chronic kidney disease using a unilateral technique of renal ischemia and reperfusion in White New Zealand rabbits. *Acta Cir. Bras.* 29, 651–657. doi:10.1590/s0102-8650201400160005
- Uribarri, J., Douyon, H., and Oh, M. S. (1995). A re-evaluation of the urinary parameters of acid production and excretion in patients with chronic renal acidosis. *Kidney Int.* 47, 624–627. doi:10.1038/ki.1995.79
- Villanueva, S., Carreño, J. E., Salazar, L., Vergara, C., Strothoff, R., Fajre, F., et al. (2013). Human mesenchymal stem cells derived from adipose tissue reduce functional and tissue damage in a rat model of chronic renal failure. *Clin. Sci. (Lond)* 125, 199–210. doi:10.1042/cs20120644
- Vizoso, F. J., Eiro, N., Cid, S., Schneider, J., and Perez-Fernandez, R. (2017). Mesenchymal stem cell secretome: Toward cell-free therapeutic strategies in regenerative medicine. *Jims* 18, 1852. doi:10.3390/jims18091852
- Wang, B., Yao, K., Huuskos, B. M., Shen, H. H., Zhuang, J., Godson, C., et al. (2016). Mesenchymal stem cells deliver exogenous MicroRNA-let7c via exosomes to attenuate renal fibrosis. *Mol. Ther.* 24, 1290–1301. doi:10.1038/mt.2016.90
- Wang, D., Zhang, H., Liang, J., Wang, H., Hua, B., Feng, X., et al. (2018). A long-term follow-up study of allogeneic mesenchymal stem/stromal cell transplantation

- in patients with drug-resistant systemic lupus erythematosus. *Stem Cell Rep.* 10, 933–941. doi:10.1016/j.stemcr.2018.01.029
- Webster, A. C., Nagler, E. V., Morton, R. L., and Masson, P. (2017). Chronic kidney disease. *Lancet* 389, 1238–1252. doi:10.1016/s0140-6736(16)32064-5
- Wong, C. Y. (2021). Current advances of stem cell-based therapy for kidney diseases. *Wjsc* 13, 914–933. doi:10.4252/wjsc.v13.i7.914
- Wong, C. Y., Tan, E. L., and Cheong, S. K. (2014). *In vitro* differentiation of mesenchymal stem cells into mesangial cells when co-cultured with injured mesangial cells. *Cell Biol. Int.* 38, 497–501. doi:10.1002/cbin.10231
- Wu, H. J., Yiu, W. H., Li, R. X., Wong, D. W., Leung, J. C., Chan, L. Y., et al. (2014). Mesenchymal stem cells modulate albumin-induced renal tubular inflammation and fibrosis. *PLoS One* 9, e90883. doi:10.1371/journal.pone.0090883
- Xiang, E., Han, B., Zhang, Q., Rao, W., Wang, Z., Chang, C., et al. (2020). Human umbilical cord-derived mesenchymal stem cells prevent the progression of early diabetic nephropathy through inhibiting inflammation and fibrosis. *Stem Cell Res. Ther.* 11, 336. doi:10.1186/s13287-020-01852-y
- Xie, Y., Bowe, B., Mokdad, A. H., Xian, H., Yan, Y., Li, T., et al. (2018). Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int.* 94, 567–581. doi:10.1016/j.kint.2018.04.011
- Xing, L., Song, E., Yu, C. Y., Jia, X. B., Ma, J., Sui, M. S., et al. (2019). Bone marrow-derived mesenchymal stem cells attenuate tubulointerstitial injury through multiple mechanisms in UUO model. *J. Cell. Biochem.* 120, 9737–9746. doi:10.1002/jcb.28254
- Yuan, X., Qin, X., Wang, D., Zhang, Z., Tang, X., Gao, X., et al. (2019). Mesenchymal stem cell therapy induces FLT3L and CD1c+ dendritic cells in systemic lupus erythematosus patients. *Nat. Commun.* 10, 2498. doi:10.1038/s41467-019-10491-8
- Zhang, M., Methot, D., Poppa, V., Fujio, Y., Walsh, K., and Murry, C. E. (2001). Cardiomyocyte grafting for cardiac repair: Graft cell death and anti-death strategies. *J. Mol. Cell. Cardiol.* 33, 907–921. doi:10.1006/jmcc.2001.1367
- Zhu, X. Y., Urbieto-Caceres, V., Krier, J. D., Textor, S. C., Lerman, A., and Lerman, L. O. (2013). Mesenchymal stem cells and endothelial progenitor cells decrease renal injury in experimental swine renal artery stenosis through different mechanisms. *Stem Cells* 31, 117–125. doi:10.1002/stem.1263

Glossary

ADMSCs adipose-derived mesenchymal stem cells

ARPKD autosomal recessive polycystic kidney disease

ADPKD autosomal dominant polycystic kidney disease

BMSCs bone marrow mesenchymal stem cells

BMP-7 bone morphogenetic protein seven

CKD chronic kidney disease

Ccr creatinine clearance rate

CM conditional medium

CsA cyclosporine

CMV cytomegalovirus

CFTR cystic fibrosis transmembrane conductance regulator protein

DM diabetes mellitus

DMSCs dental mesenchymal stem cells

DN diabetic nephropathy

ESRD end-stage kidney disease

EMT epithelial-mesenchymal transition

ECM extracellular matrix

EVs extracellular vesicles

eGFR estimated glomerular filtration rate

FGF fibroblast growth factor

FGFs fibroblast growth factor

FN fibronectin

HGF hepatocyte growth factor

ISCT International Society of Cell Therapy

IL-6 interleukin six

IL-1 β interleukin-1 β

LN lupus nephritis

MAPK mitogen-activated protein kinase

MSCs mesenchymal stem cells

MT melatonin

MMP3 metalloproteinase three

MPC mesenchymal precursor cells

MMF mycophenolate mofetil

PCNA proliferating cell nuclear antigen

PDMSCs placenta-derived mesenchymal stem cells

PKD polycystic kidney disease

PDGF-B platelet-derived growth factor B

SGLT2 sodium-glucose cotransporter two

SCr serum creatinine

STZ streptozotocin

SLE systemic lupus erythematosus

TGF- β 1 transforming growth factor- β 1

TSG-6 tumor necrosis factor stimulated gene-6

TNF- α tumor necrosis factor alpha

TIMP1 tissue inhibitor of matrix metalloproteinase-1

UCMSCs umbilical cord mesenchymal stem cells

UUO unilateral ureteral obstruction

VEGF vascular endothelial growth factor

WJMSCs wharton's jelly-derived mesenchymal stem cells

α -SMA α -smooth muscle actin

5/6 NPX nephrectomy