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Immunomodulatory effects of mesenchymal stem cell therapy in chronic kidney disease: a literature review

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Abstract

Chronic kidney disease (CKD) has been a growing public medical concern in recent years which calls for effective interventions. Mesenchymal stem cells (MSCs) have garnered increased interest in past decades due to their potential to repair and regenerate damaged tissues. Many clinical trials have highlighted the safety and effectiveness of kidney disease with this novel cell therapy. MSC infusion can improve renal function indices such as glomerular filtration rate, urine protein, serum creatinine, and blood urea nitrogen, while inhibiting immune response by increasing regulatory T cells. The therapeutic mechanisms may be primarily attributed to a function combined with immunomodulation, anti-inflammation, anti-fibrosis, promoting angiogenesis, anti-oxidation, anti-apoptosis, or tissue healing produced by cell secretsome. However, CKD is a broad concept due to many pathological etiologies including diabetes, hypertension, heart disease, immunological damage, a family history of renal failure, and so on. Furthermore, the therapeutic efficacy of MSCs may be influenced by different cell sources, injection methods, medication dosage, or homing proportion. As a result, it is timely and essential to access recent advancements in the MSC application on CKD.

Keywords Mesenchymal stem cell, Chronic kidney disease, Diabetic nephropathy, Lupus nephritis, Immunomodulation

Introduction

Chronic kidney disease (CKD) is defined as an abnormal renal structure or function over 3 months and is becoming one of the most common risks for people [1]. Based on data in 2017, the global average incidence rate is 9.1%, with about 700 million patients registered [2] and, in the following 10 years, CKD will swiftly become the fifth leading cause of mortality globally [3]. In addition, end-stage renal disease (ESRD) has been a misery dilemma faced by more than 2 million patients with the exacerbation of renal function worldwide [4] and the number is still keeping a rapidly rising trend, resulting in a heavy burden on public health and medical care [5, 6]. The most recommended treatment strategies for CKD have been a comprehensive project consisting of early prevention, delaying the progression, and supporting treatment against complications [7]. DAPA-CKD and EMPA-KIDNEY have shown that sodium-dependent glucose transporters 2 (SGLT2) inhibitors can delay the progression of CKD [8, 9]. Accordingly, the KDIGO 2024 CKD guideline recommends SGLT2 inhibitors as a first-line treatment, regardless of whether patients have type 2 diabetes mellitus or not [10].

However, it is frustrating that conventional medications still have a substantial residual probability of disease progression. Many CKD patients in stages 3 to 5 exhibit not only poor efficacy but also noticeable side effects from drug combinations. Sustainable loss of renal function will inevitably lead to renal replacement therapy

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or transplantation, especially for cases of glomerular diseases [11]. Thus, more positive and effective interventions are urgently needed in clinical practice.

Mesenchymal stem cells (MSCs), derived from the mesoderm and possessing self-renewal ability, are a new attention in advanced cell-based therapy. MSCs, unlike hematopoietic stem cells derived from the blood system, can be found in the perinatal tissues of infants such as the placenta or umbilical cord, adult dental pulp, adipose, and other areas in the body [12]. MSCs have emerged as a viable clinical strategy in recent years due to their excellent properties, including easy separation, multipotent differentiation potential, and strong paracrine activity, which provide new opportunities for kidney disease therapy and prognosis. After long-term efforts, encouraging results have indicated that MSCs may potentially promote the regeneration of damaged renal tissue [13, 14], as well as a potential for alleviating or improving renal function in animal models [15, 16]. The safety and efficiency of MSC infusion were then evaluated by many clinical trials in patients with kidney diseases. These stem cells have shown promise in improving renal function and mediating immunity when administrated in CKD patients for different renal pathology. The therapeutic ability of the cells may contribute to homing [17], differentiation, and secretion [18]. This novel cell therapy may thereby provide an alternative and complementary approach to precious therapies to improve the long-term prognosis of CKD.

Clinical administration of MSCs in CKD

Although many pre-clinical studies have suggested that MSCs may have a broad application prospect to improve renal function [19–22], it is still uncertain about the specific effect in clinical utilization. Thus, aiming to find the answer and guide clinical practice, we reviewed 18 published studies (Table 1) involving MSCs in CKD since 2010. Up to now, attempts have been made to several pathological causes of chronic renal insufficiency in those studies including 11 in lupus nephritis (LN), 2 in diabetic nephropathy (DN), and other different causes. For better clinical practices of stem cell injection therapy in kidney diseases, we summarized the results of these clinical trials in renal function from cell sources, characteristics, and dosage, based on their therapy plans.

Sources

In the late 1960s, MSCs were first isolated from bone marrow [41]. MSC infused into patients with CKD were mainly derived from autologous or allogeneic interstitial tissues [42], generally including bone marrow, umbilical cord, and adipose. Regardless of resources, these cell products collected from human tissues are manufactured to take effect on patients, encompassing standard laboratory processes and quality inspection under Good Manufacturing Practice [43] (Fig. 1).

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are the most widely administered in all clinical trials [42, 44]. Autologous BM-MSCs have high genetic stability, strong multidirectional differentiation ability, and low immunogenicity [45]. The expression of cluster of differentiation (CD)133 is higher in BM-MSCs than cells from other sources, which may be related to stem cell regeneration, differentiation, and metabolic function [46]. For an aspect of differentiation, BM-MSCs possess a stronger potential for chondrocytes and osteoblasts driven by epigenetic memory [47].

Human umbilical cord-derived mesenchymal stem cells (UC-MSCs) can differentiate into adipocytes, osteocytes, or chondrocytes, and have been found to have stronger osteogenic differentiation capacity than BM-MSCs [48]. UC-MSCs are more convenient to collect, which used to be discarded medical waste, with fewer ethical concerns, adequate donors, and less deoxyribonucleic acid damage [49]. Additionally, human fetal tissue-derived MSCs may have a stronger potential to modulate the immune system [50] and grow rapidly in vitro culture [51].

Adipose-derived mesenchymal stem cells (AD-MSCs) are isolated from fat tissues in the body to obtain stromal vascular fraction, which requires an invasive operation, just like BM-MSCs [52]. Approximately 5 thousand MSCs can be isolated from one gram of fat tissue, much more than the number of cells obtained from bone marrow [53]. AD-MSCs were infused into the body during two studies with reduced blood perfusion in renal tissue [31, 40] and a trial involving LN [36].

MSCs from different sources vary in differentiating capacity, which may be due to the epigenetic memory from their lineage [54]. For example, BM-MSCs are more likely to differentiate into bone cells, while UC-MSCs have a stronger capacity to differentiate towards adipocytes due to their similar morphology to AD-MSCs and expression of CD29, CD44, CD105, and CD166 [55]. Cells from umbilical cord tissues or blood have a specific differentiation capacity to become endothelial-like cells, as opposed to those from bone marrow or adipose tissues [56].

Characteristics

Human MSCs are collected and isolated from biological samples of acquired donors or patients themselves, then expanded to cellular dosage in vitro as needed. Minimal criteria [57] of the definition must be met for the intermediate and final MSCs products which include: 1) plastic-adherent behavior in culture conditions, 2) expression of CD105, CD73, and CD90, and

Table 1 Clinical trials exploiting mesenchymal stem cells for infusion therapy of chronic kidney disease

Study	Design	Cell source	Patients MSCs/Control	Dose	Times / Method	Trial Registration
Sun et al., 2010 [23]	Single-arm	Allogeneic UC	16 SLE (15 LN)	1.0 $\times 10^6$/kg	Single IV	NCT 00698191
Liang et al., 2010 [24]	Open-label/ Single-arm	Allogeneic BM	15 SLE (15 LN)	1.0 $\times 10^6$/kg	Single IV	NCT 00698191
El-Ansary et al., 2012 [25]	Open-label/ Controlled	Autologous BM	10 / 10 (10 LN)	0.7 ~ 1.0 $\times 10^6$ /kg	Twice IV	NA
Wang et al., 2013 [26]	Open-label/ Single-arm	Allogeneic UC/BM	87 SLE (73 LN)	1.0 $\times 10^6$ /kg	Single IV	NA
Wang et al., 2014 [27]	Open-label/ Single-arm	Allogeneic UC	40 SLE (39 LN)	1.0 $\times 10^6$ /kg	Twice IV	NCT 01741857
Gu et al., 2014 [28]	Open-label/ Single-arm	Allogeneic UC/BM	81 LN	1.0 $\times 10^6$ kg	Single IV	NA
Packham et al., 2016 [29]	RCT	Allogeneic BM (MPC)	20 / 10 DN	150 ~ 300 $\times 10^6$	Single IV	NCT 01843387
Deng et al., 2017 [30]	RCT	Allogeneic UC	12 / 6 LN	100 $\times 10^6$	Twice IV	NCT 01539902
Saad et al., 2017 [31]	Open-label/ Dose-escalation	Autologous AD	14 / 14 IN / RVD	1.0 ~ 2.5 $\times 10^5$/kg	Single IA	NCT 02266394
Makhlough et al., 2017 [32]	Open-label/ Single-arm	Autologous BM	6 ADPKD	1.0 ~ 2.0 $\times 10^6$/kg	Single IV	NCT 02166489
Barbado et al., 2018 [33]	Open-label/ Single-arm	Allogeneic BM	3 LN	1.5 $\times 10^6$/kg	Single IV	EudraCT2017 –000391–28
Makhlough et al., 2018 [34]	Open-label/ Single-arm	Autologous BM	7 DE	1.0 ~ 2.0 $\times 10^6$/kg	Single IV	NCT 02195323
Yuan et al., 2019 [35]	Open-label/ Single-arm	Allogeneic UC	11 SLE (11 LN)	1.0 $\times 10^6$/kg	Single IV	NCT 01741857
Ranjbar et al., 2022 [36]	Open-label/ Single-arm	Allogeneic AD	9 LN	2.0 $\times 10^6$/kg	Single IV	IRCT201609 0729747N1
Chun et al., 2022 [37]	Open-label/ Single-arm	Allogeneic BM	7 LN	2.0 ~ 3.0 $\times 10^6$/kg	Single IV	NCT 03174587
Perico et al., 2023 [38]	RCT	Allogeneic BM	12/4 DN	80 $\times 10^6$	Single IV	NCT 02585622
Vivarelli et al., 2023 [39]	Open-label/ Single-arm	Autologous BM	16 NS	1.0 $\times 10^6$/kg	Twice IV	EudraCT2016 –004804–77
Carstens et al., 2023 [40]	Openlabel/Historical Controls	Allogeneic AD (SVF)	18 / 12 IN	50 ~ 200 $\times 10^6$	Single IA	NCT 05154591

a. Register details of these clinical trials involved in the review were stated in supplementary materials

b. Data are median [interquartile range], median (range), mean ± standard deviation, and *: data are mean (range)

c. *RCT* Randomized control trials, *LN* Lupus nephritis, *DN* Diabetic nephropathy, *IN* Ischemic nephropathy, *ADPKD* Autosomal dominant polycystic kidney disease, *NS* Nephrotic syndrome, *DE* Different etiologies, *RVD* Atherosclerotic renovascular disease, *CKDu* Chronic kidney disease of unknown cause or mesoamerican nephropathy, *M/F* Male/female, *IV* Intravenous infusion, *IA* Intra-arterial infusion, *mo* Month, *yr* Year, *NA* Not applicable, *Single* Single infusion on the first day, *Twice* The time interval between two infusions is 7 days

lack of CD45, CD34, CD14, or CD11b, CD79a or CD19 and HLA-DR, 3) in vitro differentiation ability. Besides, detecting bacteria, fungus, viruses, and mycoplasma is critical for confirming sterility and chromosome stability is tested after multiple generations of expansion and cultivation. Because of their various origins, available MSCs have immunophenotypic differences that explain some of the variances in their responses.

There is a diversity in cell markers expressed by MSCs. For example, CD146 is a key cell adhesion molecule expressed at the endothelial cell intercellular junction that influences a variety of activities such as MSCs differentiation, angiogenesis, signal transduction, and immune response [58]. However, CD146 expression in MSCs is heterogeneous. A study found that the UC-MSCs express a higher level of CD146 than BM-MSCs or AD-MSCs [59], which may explain why UC-MSCs can adhere and proliferate more effectively. Although both $CD146^+$ and $CD146^-$ MSCs have a consistent tri-lineage

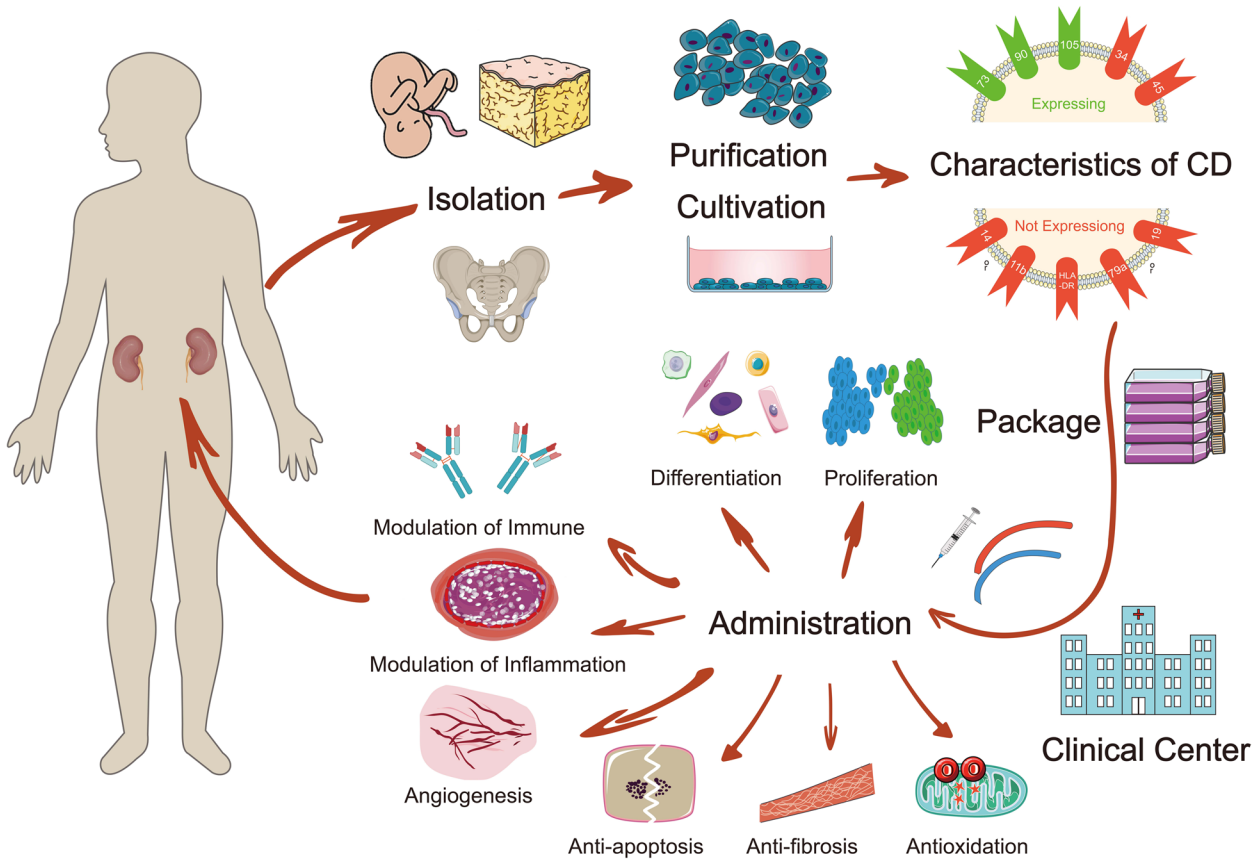

Fig.1 Mesenchymal stem cells for infusion therapy on chronic kidney disease: isolation, cultivation, characteristics, clinical administration and treatment mechanism

differentiation potential, $CD146^+$ MSCs are more prone to differentiate into vascular smooth muscle cells [60]. However, it is still unclear why MSCs from different tissues differ in tissue functional roles and immunomodulatory properties. One explanation would be that MSCs from different sources are influenced by dissimilar signal inputs.

Therefore, MSC products used in clinical practice must undergo strict identification. After being separated by the tissue block adhesion method, stem cells can be sporadically observed in the adherent tissue block about 7 days later, along with single spindle or triangular adherent cells. MSCs exhibit typical fibroblast-like morphology after prolonged culture time or passage. The characteristic of the surface marker on cells usually tests a positive expression (> 90 ~ 95%) of CD73, CD90, and CD105 in common, and CD29 and CD44 additionally by flow cytometry, while not expressing (< 1 ~ 2%) CD45, CD34, CD14, CD 79 and HLA-DR (Table 2). The results of cells from different sources may vary, but the minimum criteria must be met.

Dosage

MSC infusion administration is feasible because an inflammatory environment can facilitate MSCs homing to injured renal tissues [61], and these cells can transmigrate through the endothelial barrier and finally reach the targeted tissue [62]. A safety-depended dose was infused intravenously or intra-arterially in the majority of MSC-related clinical trials, which were in phase 1 or 2.

Since there is an obvious distinction in stem cell treatment – the amount of receiving cells in each patient may range from over 1 million to hundreds of millions at one time in clinical trials – the ideal dosage is still uncertain. Although single infusion was the most common method among all trials, 4 (22.2%) studies chose a double injection method, with half of the total dose administered intravenously for the first time and the remaining cells used after 7 days [25, 27, 30, 39]. Regarding the tolerance dose for CKD patients, a previous dose escalation study has demonstrated that intravenous MSC administration did not cause cell transplantation-related adverse events (AEs) or serious adverse events (SAEs), even when the total dose reached 300 million cells. Furthermore,

Table 2 Difference in cell surface markers from mesenchymal stem cells exploited in clinical trials

Trials	Positive					Negative					
	CD29	CD73	CD90	CD105	CD44	CD45	CD34	CD11b	CD14	CD79	HLA-DR
Bone Marrow											
Liang,2010 [24]	●	—	●	●	●	○	○	—	○	—	—
Wang,2013 [26]	●	●	●	●	—	○	○	—	○	○	○
Gu,2014 [28]	●	●	●	●	—	○	○	—	○	○	○
Makhlough, 2017 [32]	—	●	●	●	●	○	○	○	—	—	—
Makhlough, 2018 [34]	—	●	●	●	●	○	○	○	—	—	—
Chun,2022 [37]	●	●	●	●	●	○	○	—	—	—	○
Perico,2023 [38]	—	●	●	●	—	○	○	—	—	—	—
Umbilical Cord											
Sun,2010 [23]	●	●	●	●	—	○	○	—	○	○	○
Wang,2013 [26]	●	●	●	●	—	○	○	—	○	○	○
Wang,2014 [27]	●	●	●	●	—	○	○	—	○	○	○
Yuan,2019 [35]	●	●	●	●	—	○	○	—	○	○	○
Adipose											
Ranjbar,2022 [36]	—	●	●	●	●	○	○	—	○	—	○

●: positive expression, ○: negative expression, —: not tested

another study indicated that a single dosage of 150 million cells might slightly outperform 300 million cells in maintaining the stability of glomerular filtration rate (GFR) among patients with DN [29]. These previous investigations showed that the most common dose was a single infusion of one million cells per kilogram body weight for patients with kidney diseases.

It is worth noting that the tolerance of MSC therapy is associated with the concentration, speed, and uniformity of cell product suspension during infusion. Compared to the transvenous approach, intra-arterial injection can deliver cells directly into the renal artery and kidney through a femoral artery catheterization bypassing a clearance in the body, particularly in the pulmonary and splenic capillary network. However, this method has greater trauma and more complex procedures.

Drug combinations

Immunosuppressive, antiplatelet, or anticoagulant drugs are essential in kidney disease management [10, 63]. Almost previous MSCs-relevant clinical trials included LN [27, 28, 30, 33, 35, 36] or INS [39] patients with conventional immunosuppressants, such as cyclophosphamide, tacrolimus, mycophenolate mofetil (MMF), hydroxychloroquine, leflunomide, or glucocorticosteroids (GCs) (Table S1). However, the potential impact of co-medication should be more attention in MSC therapy when eligible patients are screened.

Lee et al. found that combining GCs or MMF did not affect MSC viability, migration, and immunomodulation capacity in lupus mice, as well as reducing the side effects of the immunosuppressants by lowering the dose [64]. A short-term cellular experiment revealed that although immunosuppressants, specifically GCs, may reduce some factor-relevant gene expression in MSCs, the immunosuppressive properties of MSCs were not restricted [65]. Aspirin interferes with the proliferation and survival of MSCs by downregulating miRNA145/cyclin D1, resulting in cell-cycle arrest [66]. According to Deng et al., aspirin may influence MSC survival by inducing apoptosis via the mitochondrial/caspase-3 pathway [67]. Besides, aspirin could promote osteogenic [68, 69] or cardiomyocyte [70] differentiation of MSCs, while inhibiting adipogenic differentiation [71].

In terms of immunosuppressive drugs, it seems to be appropriate to continue with the conventional strategy of adequate or lowered doses of immunosuppressants in immune-mediated kidney disease. Antiplatelet or anticoagulant medications should be used with caution when considering MSC therapy in patients with kidney diseases. Other drug combinations also require more critical scrutiny.

Effects of MSCs infusion in CKD

MSCs may prevent or reverse the progression of certain stages of experimental CKD, which can be demonstrated by improving renal function markers and serological indicators used clinically. Here, we mainly evaluate the efficacy of MSCs in CKD patients based on safety, renal function, and other laboratory parameters (Table 3 and 4). Major parameters include proteinuria, GFR, serum creatinine (SCr), and blood urea nitrogen

Table 3 Safety of mesenchymal stem cells in clinical outcomes

Trials	AEs, n (%)	Common AEs	SAE, n (%)	Death, n	Cause of death
LN					
Sun et al., 2010 [23]	0	no event reported	0	0	no death
Liang et al., 2010 [24]	—	upper respiratory tract infection	0	0	no death
Wang et al., 2013 [26]	8 (9.2)	diarrhea, agranulocytosis, infections, ACS	5 (5.7)	5	heart failure, pneumonia, pulmonary embolism, uncontrolled SLE
Wang et al., 2014 [27]	4 (10.0)	infections	3 (7.5)	3	heart failure, respiratory failure, uncontrolled SLE
Gu et al., 2014 [28]	4 (4.9)	diarrhea, enteritis, infections	4 (4.9)	4	heart failure, pneumonia, uncontrolled SLE
Deng et al., 2017 [30]	—	agranulocytosis, pneumonia,	2 (16.7)	1	pneumonia
Barbado et al., 2018 [33]	0	no event reported	0	0	no death
Ranjbar et al., 2022 [36]	1 (11.1)	transient hypertension	0	0	no death
Chun et al., 2022 [37]	2 (28.6)	diarrhea, toothache, Arthralgia	0	0	no death
DN					
Packham et al., 2016 [29]	17 (85.0)	infections, cough, heart failure, diabetic ulcer	5 (25.0)	0	no death
Perico et al., 2023 [38]	11 (91.7)	diarrhea, cough, chest pain	4 (33.3)	2	heart failure, multiple myeloma
IN					
Saad et al., 2017 [31]	0	no event reported	0	0	no death
CKDu					
Carstens et al., 2023 [40]	0	renal failure	6 (33.3)	3	cerebral hemorrhage, renal failure
ADPKD					
Makhlough et al., 2017 [32]	6 (100)	nausea, headache, dizziness	1 (16.7)	0	no death
NS					
Vivarelli et al., 2023 [39]	15 (94.0)	infections, oliguria, relapse of NS	6 (37.5)	0	no death
Muti-etiology					
Makhlough et al., 2018 [34]	7 (100)	headache, dizziness, cough, pruritus	3 (42.9)	0	no death

a. AE and SAE are presented by n (patient numbers with at least one event). % (a percentage of the total)

b. LN: lupus nephritis, DN: diabetic nephropathy, IN: ischemic nephropathy, CKDu: chronic kidney disease of unknown cause or mesoamerican nephropathy, ADPKD: autosomal dominant polycystic kidney disease, NS: nephrotic syndrome, AE: adverse event, SAE: serious adverse event, ACS: acute coronary syndrome, SLE: systemic lupus erythematosus

(BUN) while others involve immune or inflammatory responses consisting of complement, interleukins, and immune cells.

Safety and tolerance

In the past decade, the safety of MSC therapy has been verified in different populations [72]. Among all possible AE related to MSC application, no other serious safety events were found except for transient fever, side effects at the administration site, insomnia, or constipation. The occurrence of any AE may be related to age, analysis method, cell type, disease, gender, location, research stage, following-up period and administration method. All clinical studies showed both safety and tolerance of MSC infusion in patients with CKD.

However, it must be admitted that some AEs still occurred, even if identified by researchers as independent of injection (Table 3). Infections, especially upper respiratory tract infections, were among the most common AEs, irrespective of whether the studies have experienced a global COVID-19 pandemic. Other AEs were mentioned sometimes, such as fever, cough, headache, dizziness, diarrhea, or nausea, and SAEs mainly included hospitalization, ESRD, heart failure, death, etc. During and after infusion, patients were well tolerated with few adverse reactions or mild side effects. The highest incidence of SAE was 42.9% [34] in the study by Makhlough et al. and mainly consisted of hospitalization or ESRD without death. All cardiorenal outcomes and death events occurred during the late safety monitoring stage in reported clinical studies, most as a result of uncontrolled diseases and organ failure. Moreover, it should be noted that SCr may slightly and temporarily increase after infusion into the artery [31].

Malignant transformation is a significant safety issue for expanded progenitor or stem cells. Although tumor tropism has been found in murine MSCs [73], there has been no evidence of such an event in human MSC-based

therapies and it is not an obstacle to clinical application. First, there is no report about hematopoietic or solid tumors after systemic or local MSC infusion into patients during a long-term follow-up. Second, most experiments evaluating the impact of MSCs on tumor growth in animal models are conducted through co-injection or co-transplantation with cancer cells, which is inconsistent with the real world and does not apply to the prediction of clinical therapy. In addition, MSC treatment is not associated with an increased risk of malignant tumors in solid organ transplant recipients receiving long-term immunosuppressive drug therapy [74]. Hence, MSC infusion treatment is safe with a bare possibility of malignant transformation but is still not recommended to apply in patients with malignant disease for unpredictable outcomes by tumor microenvironment [75].

Clinical efficacy

Renal function

Proteinuria decreased in almost all LN trials (9/10), and the earliest follow-up period for the improvement ranged from 1 to 9 months. 5 of 9 (55.6%) trials [24, 26, 28, 33, 36] found a decline in proteinuria at the first-month follow-up, while 3 of them remained showing improvement for a full year. Quite interestingly, Wang et al. [26] observed that just a few of the patients had improvements in 24-h proteinuria over the course of the 36-month follow-up period as compared to baseline. There was no significant change in urine protein in DN, idiopathic nephrotic syndrome (INS), and ADPKD. MSCs may help the remission of proteinuria in LN, based on the research mentioned above, but there is currently insufficient evidence to determine the efficacy in CKD for other causes.

Perico et al. [38] showed that, in comparison to the placebo group, the mean GFR evaluated by different formulas was likely to keep steady in the MSC group during a long follow-up period for patients with DN. Similarly, receiving cells may be effective according to the results from two studies [31, 40] about atherosclerotic renovascular disease and mesoamerican nephropathy, respectively. It was noteworthy that patients with higher GFR (≥ 30 ml/min/m^2) got sustained improvement, whereas those with lower GFR (< 30 ml/min/m^2) only underwent temporal improvement. This could show that MSC treatment is more beneficial for patients with early-stage CKD. Although, some LN studies have reported disputed changes in GFR, others with larger sample sizes showed improvement or a positive trend. Therefore, in patients with kidney diseases, MSC therapy will be anticipated to bring out an encouraging effect on renal filtration function.

In these trials, the improvement in GFR was often accompanied by a decrease in creatinine or nitrogen. However, a different ADPKD study showed a decrease just in creatinine but not nitrogen [32]. BUN can be used as an indicator for renal function evaluation, and improvement in it might imply that MSCs are playing a part as well (Table 4).

Immune function of MSCs

Lymphocytes are essential components of the immune system. MSC transplantation can increase the percentage of $CD4^+FOXP3^+$ Tregs in peripheral blood mononuclear cells [23, 24, 38, 39], while a reducing in B cells [39]. In addition, Yuan et al. found that UC-MSCs could promote the proliferation and decrease the apoptosis of $CD1c^+$ dendritic cells(DCs) via FLT3L [35]. Natural killer T (NKT) cells exhibited significantly lower levels in the treatment group throughout the 18-month follow-up [38].

Cytokines mainly produced by immune cells, are the most dynamic components of the immune microenvironment and mediate cell-to-cell interactions. Transforming growth factor-β (TGF-β) and interleukin 10 (IL-10) are associated with the proliferation and differentiation of Tregs. The concentration of TGF-β increased after MSC treatment but the change in IL-10 was not significant [23]. Besides, there was a reduction in IL-4 [23], tumor necrosis factor-α (TNF-α) [35], and vascular endothelial growth factor (VEGF) [31] and an increase in complement C3 (C3) [24, 26, 27] and IL-6 [29], respectively. As for complement C4 (C4) and interferon-γ (IFN-γ), the two parameters showed no significant change.

Generally, the immunomodulation of MSCs can be effectively achieved in patients with kidney disease. MSCs can influence both the adaptive and innate immune systems by inhibiting the activation and proliferation of NKT cells, B cells, and DCs while promoting the production of Tregs. Despite the fact that changes in these immune indicators did not occur simultaneously in a specific experiment, cytokine levels are regulated in a manner consistent with immune cells.

Other parameters

Serum albumin (ALB) is closely related to proteinuria while eliminating a large amount of protein from urine in CKD patients will lead to low serum albumin levels. In all cases, ALB increased along with the recovery of renal function. For IN, renal blood perfusion parameters improved after MSC therapy, including renal blood flow, tissue oxygenation levels, and renal artery resistance [31, 40]. Intriguingly, the degree of improvement in cortical perfusion and renal blood flow (RBF) in the kidney that underwent intra-arterial renal artery injection of MSCs was comparable to that of the contralateral kidney. This

Table 4 Efficacy of mesenchymal stem cells in clinical outcomes

Trials	Renal function	Immune function & others
LN		
Sun et al., 2010 [23]	**PRO:** declined 58% at 3 mo (1.3 ± 0.9 vs 3.1 ± 1.2 g at BV) **SCr:** improved 43% at 3 mo (2.3 ± 1.1 vs 4.0 ± 2.2 mg/dl at BV) **BUN:** 6 (40%) patients improved at 3 mo	Tregs,C3,TGF-β ↑ IL-4 ↓ IFN-γ,IL-10 ↑↓ALB ↑
Liang et al., 2010 [24]	**PRO:** declined 64% at 1 yr (0.9 ± 0.8 vs 2.5 ± 1.3 g at BV) **SCr:** 4 (27%) patients improved within 3 mo **GFR:** 2 (13%) patients improved at 18 mo (45.5 vs 32.5 ml/min at BV) and 6 mo (49 vs 24 ml/min at BV), respectively	Tregs ↑
El-Ansary et al., 2012 [25]	**SCr:** a lower decrease at 6 mo (0.9 ± 0.3 vs 1.5 ± 0.5 mg/dl in controls) **GFR:** improved 41% at 6 mo (72.3 ± 25.1 vs 43.0 ± 17.6 ml/min in controls)	Hb ↑↓
Wang et al., 2013 [26]	**PRO:** declined 44% decline at 6 mo (1.5 ± 1.0 vs 2.7 ± 1.2 g at BV) **SCr:** declined 13% decline at 1 yr (2.0 [0.3] vs 2.3 [0.2] mg/dl at BV) **BUN:** declined 36% decline at 1 yr (11.7 [0.9] vs 18.3 [1.7] mmol/l at BV) **GFR:** improved 23% at 1 yr (63.4 ± 26.2 vs 51.5 ± 21.5 ml/min at BV)	C3 ↑ ALB, PLT, Hb ↑
Wang et al., 2014 [27]	**PRO:** declined 36% decline at 1 yr (1.4 ± 1.3 vs 2.2 ± 1.4 g at BV) **SCr:** a significant decline at 6 mo **BUN:** a significant decline at 6 and 9 mo	C3 ↑ ALB ↑
Gu et al., 2014 [28]	**PRO:** declined 44% at 1 yr (1.5 ± 1.0 vs 2.7 ± 1.2 g at BV) **SCr:** declined 18% at 1 yr (1.8 ± 1.1 vs 2.2 ± 1.1 mg/dl at BV) **BUN:** declined 36% at 1 yr (11.7 ± 4.7 vs 18.3 ± 9.5 mmol/l at BV) **GFR:** improved 19% at 1 yr (69.5 ± 27.9 vs 58.6 ± 19.2 ml/min at BV)	ALB ↑
Deng et al., 2017 [30]	**PRO, SCr and GFR:** no significant change in both arms during 6 mo	C3, C4 ↑↓ ALB ↑↓
Barbado et al., 2018 [33]	**PRO:** all patients substantially improved at 1 w **SCr:** 2 (67%) patients improved and another one kept at 9 mo **GFR:** 1 (33%) patient improved at 3 m and the other 2 (67%) kept at 9 mo	Tregs, C4 ↑↓
Yuan et al., 2019 [35]	**PRO:** improved 68% at 6 mo (2.1 ± 3.4 vs 6.6 ± 4.1 g at BV) **SCr and BUN:** no significant change during 6 mo	DCs,FLT3L ↑ TNF-α ↓ IL-10 ↑↓
Ranjbar et al., 2022 [36]	**PRO:** most substantially improved at 1mo (1.0 [0.3 to 2.5] vs 1.8 [1.0 to 5.3] g at BV) **GFR:** improved 46% at 3 mo (86.9 [50.2 to 107.4] vs 59.4 [38.3 to 83.0] ml/min/1.73m^2 at BV)	C3, C4 ↑↓
DN		
Packham et al., 2016 [29]	**PRO and GFR:** no significant change during 6 mo	IL-6 ↓ TNF-α,TGF-β↑↓ HbA1c ↑↓
Perico et al., 2023 [38]	**GFR:** improved significantly at 12 and 18 mo (35.0 ± 8.9 vs 23.2 ± 4.3 ml/min/1.73m^2 in placebo) **PRO:** no significant change during 18 mo (1.0 [0.4 to 1.3] vs 0.7 [0.3 to 3.2] g in placebo)	Tregs ↑ NKT cells↓ T cells ↑↓ HbA1c ↑↓
IN		
Saad et al., 2017 [31]	**SCr:** a transient increase in 1 w **GFR:** a significant improvement at 3 mo	VEGF ↓ Cortical Perfusion, RBF ↑ Hypoxia ↓
CKDu		
Carstens et al., 2023 [40]	**GFR:** a 25% improvement for stage 3a, 11% for 3b, −29% for 4 and −46% for 5 at 36 mo	Renal Volume ↑ RRI ↓
ADPKD		
Makhlough et al., 2017 [32]	**SCr and GFR:** no significant change at 12 mo	Kidney Size↑↓
NS		
Vivarelli et al., 2023 [39]	**SCr, BUN, PRO and GFR:** no significant change at 12 mo	B cells↓ Treg cells ↑ IgG,IgA,IgM,IL-10 ↑↓
Muti-etiology		
Makhlough et al., 2018 [34]	**SCr, BUN, PRO and GFR:** no significant change	ALB ↑↓

LN Lupus nephritis, *DN* Diabetic nephropathy, *IN* Ischemic nephropathy, *CKDu* Chronic kidney disease of unknown cause or mesoamerican nephropathy, *ADPKD* Autosomal dominant polycystic kidney disease, *NS* Nephrotic syndrome, *PRO* Urinary protein, *GFR* Glomerular filtration rate, *SCr* Serum creatinine, *BUN* Blood urea nitrogen, *ALB* Serum albumin, *CYS-C* Cystatin-C, *TG* Triglyceride, *C3* Complement C3, *C4* Complement C4, *Tregs* Regulatory T cells, *DCs* Dendritic cells, *Hb* Hemoglobin, *PLT* Platelet, *TGF-β* Transforming growth factor-β, *IFN-γ* Interferon-γ, *TNF-α* Tumor necrosis factor-α, *VEGF* Vascular endothelial growth factor, *RBF* Renal blood flow, *RRI* Renal resistive index

a. Values presented as mean ± standard deviation, mean [standard error of the mean], median [range, min to max]

b. The change in renal function parameters is presented as a percentage by mean or median. Immune function and others are shown by ↑ (increase), ↓ (decrease), or ↑↓ (no significant change)

may imply that MSCs can home to injured renal tissue and treat distal tissues via paracrine secretion.

The kidney size in CKD patients tends to become smaller with the progression of chronic fibrosis, along with renal atrophy and a loss of nephrons. Ultrasonography suggested an enlargement of kidney volume in another arterial AD-MSC intervention research. Besides, Wang et al. [26] found that after treatment with MSCs,

the peripheral blood hemoglobin and platelet levels increased in some LN patients with anemia or low platelet, respectively, and this improvement remained for 24 months.

In summary, previous clinical research indicated that MSCs can effectively reduce proteinuria, stabilizing GFR and increasing Tregs in kidney diseases.

Possible mechanisms of MSCs in CKD

MSCs can secrete a variety of exosomes, nanofilm bubbles with a diameter of 40–160 nm nanometers [76], interacting with different receptor cells. This interaction can effectively influence the different biological behaviors of target cells as well as those in the kidney, thereby playing a crucial role in maintaining physiological homeostasis and regulating the progression of human diseases. MSC-based therapy usually follows two major pathways.

Some MSCs can directly home to injured kidney tissue and proliferate. homing of MSCs is defined as retention in tissue vasculature and migration between endothelial cells, which can be divided into five phases: rolling, activation, arrest, transmigration or diapedesis, and migration [62]. First, MSC-expressed CD44 binds to selectins causing cells to roll along the vessel wall [77]. Secondly, stromal cell-derived factor (SDF)−1 expressed by MSCs, the ligand for the chemokine receptor (CXCR) 4, is essential for the activation step [78, 79]. Other chemokines and receptors are also involved, such as monocyte chemoattractant protein (MCP)−1/ C−C motif chemokine receptor (CCR) 2 pathway [80]. Integrins facilitate MSCs firmly adhere to endothelial cells, and MSC then secretes matrix metalloproteinase (MMP) to break down the endothelial basement membrane, allowing cells to migrate out of the vessel [81]. Finally, MSCs respond to and migrate toward various signals of tissue damage, such as platelet-derived growth factor (PDGF) -AB, insulin-like growth factor (IGF)−1, RANTES, macrophage-derived chemokine (MDC), SDF-1, IL-8 [82, 83].

Another pathway is that MSCs and their secretome, consisting of soluble factors and extracellular vesicles (EVs), can yield beneficial effects in kidney diseases through the paracrine release of over 1500 bioactive components, including functional peptides, proteins, mRNAs, microRNAs (miRs), and lipids [21, 84]. Until now, many previous investigations have confirmed that MSCs and their secretome can balance stimulatory and inhibitory signals in different diseases to affect immunomodulation, anti-inflammatory, promoting angiogenesis, anti-oxidation, anti-apoptosis, and anti-fibrosis [22, 85–88], with immunomodulation characteristic playing a major role in kidney diseases [89–91] (Fig. 2).

In kidney diseases, MCSs secretome can mediate innate and adaptive immune responses via cell–cell contact cytokines or regulating factors [92]. Up-regulating of miRNAs like miR-126-3p, miR-223-3p, miR-142-3p, as well as factors like indoleamine 2,3 dioxygenase (IDO), IL-10, prostaglandin E2 (PGE_2), hepatocyte growth factor (HGF), TGF-β, heme oxygenase-1 (HO-1), nitric oxide (NO), chemokine (C–C motif) ligand 2 (CCL2), contribute to immunomodulation and anti-inflammatory function. Down-regulating IL-6, TNF-α, and IFN-γ levels can inhibit excessive immune activation response in the kidney. Overall, MSCs do not possess antigen presentation ability and rely on inducing factors to influence the expression of cytokines, suppress T cells, reduce B cell activation and proliferation, or inhibit NK cell proliferation and cytotoxicity while promoting anti-inflammatory immune cells including Tregs, Bregs, $CD1c^+$ dendritic cells (DCs) and M2 macrophages (Fig. 3).

Some MCS-exosomal miRs, such as miR-126, miR-210, miR-21, miR-23a, miR-130a, are associated with angiogenesis and vascular development [93]. The MSC-induced changes in signal factors also have the properties of reducing fibrosis and stimulating angiogenesis which can lead to improvements in vascular structure and function, primarily including VEGF, fibroblast growth factor 2 (FGF-2), PDGF, SDF-1, chemokine (C-X-C motif) ligand 1 (CXCL-1), RANTES, MCP-1, macrophagecolony stimulating factor (M-CSF) [88, 92, 94]. The inhibition of cell apoptosis is an important mechanism by which MSCs alleviate kidney disease. Antiapoptotic mediators derived from MSCs inhibit three major pathways in target cells—endogenous pathways, exogenous pathways, and endoplasmic reticulum stress pathways, thereby preventing apoptosis [95]. These mediators include miR-29a-3p, miR-125b-5p, miR-93, miR-150-5p, lncRNA-UCA1, VEGF, HGF, IGF-1, FGF, TGF-β, Nrf2, HIF, HO-1, and PDGF [95–97]. In addition, HO-1 mediated by MSCs can protect cells against apoptosis and oxidative stress [98].

MSCs in DN

Diabetes is a major cause of CKD, with a complex pathogenesis [99]. Though DN is traditionally regarded as a non-inflammatory glomerular disease induced by metabolic and hemodynamic factors, increasing evidence indicates that the immune response is an important participant in the renal inflammation associated with DN, in which activated innate immune cells and kidney cells affect inflammation [100]. Therefore, inhibiting inflammatory signaling pathways, cytokines and chemokines, and immune cells contributes to the pathogenesis and progression of DN. Potential mechanisms of MSCs therapy may consist of tissue regeneration and repair, protection of podocytes, and resistance to oxidative stress.

MSCs may reduce the immune and inflammatory response to kidney tissues during the early stages of

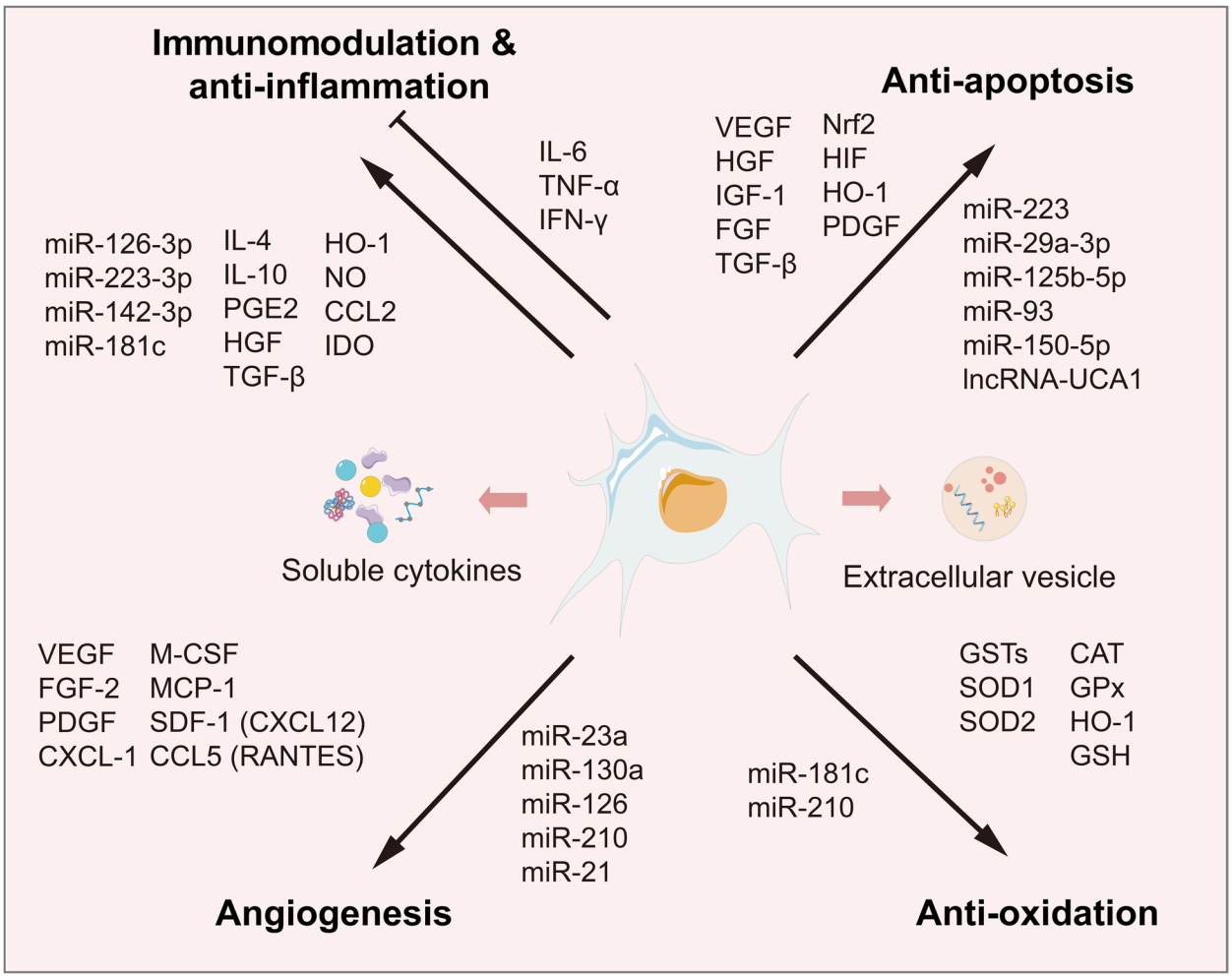

Fig.2 The common factors in MSCs secretome. MSCs secretome consists of soluble components (growth factors, cytokines, chemokines, and hormones) and non-soluble components in extracellular vesicles (EVs). The effects mediated by EVs depend on "cargo", including proteins, functional mRNAs, miRNAs, and lipids. CAT: catalase, CCL: chemokine (C–C motif) ligand, CXCL: chemokine (C-X-C motif) ligand, FGF: fibroblast growth factor, GPx: glutathione peroxidase, GSH: glutathione, GSTs: glutathione S-transferases, HGF: hepatocyte growth factor, HIF: hypoxia-inducible factor, HO-1: heme oxygenase-1, IDO: indoleamine 2,3 dioxygenase, IGF-1: Insulin-like growth factor 1, INF-γ: interferon γ, IL: interleukin, MCP-1: monocyte chemoattractant protein-1, M-CSF: macrophagecolony stimulating factor, miR: microRNA, NO: nitric oxide, Nrf2: nuclear factor erythroid 2-related factor 2, PDGF: platelet-derived growth factor, PGE_2: prostaglandin E2, SDF-1: stromal cell-derived factor-1, SOD: superoxide dismutase, TGF-β: transforming growth factor-β, TNF-α: Tumor Necrosis Factor-α, VEGF: vascular endothelial growth factor

injury [101]. Then the inflammatory effect may result in a lower glucose level, reducing the burden of high glucose on renal tissues [102]. Transcriptome analysis of human kidney biopsy samples found significant upregulation of C3 in the DN context [103]. MSCs can affect alternative pathways starting from C3, increasing serum complement concentration and preventing renal tissue from deposition. Besides, Toll-like receptors (TLR) play an essential role in renal inflammation and fibrosis in kidney disease [104]. The anti-inflammatory factor PGE_2 is key in inhibiting innate immune cells. MSCs can produce it and this expression of PGE_2 in MSCs is abolished after knocking out TLR4, along with its therapeutic effect in the sepsis model [105]. MSCs promoted islet β cell proliferation improved hyperglycemia via the PI3K/Akt signaling pathway [106], and facilitated pancreatic islet growth by mitigating the influence of IL-1 and TNF-α [107]. UC-MSCs can also improve blood glucose levels while protecting endothelial cells from high glucose injury via a paracrine effect mediated by the MAPK/ERK signaling pathway [108].

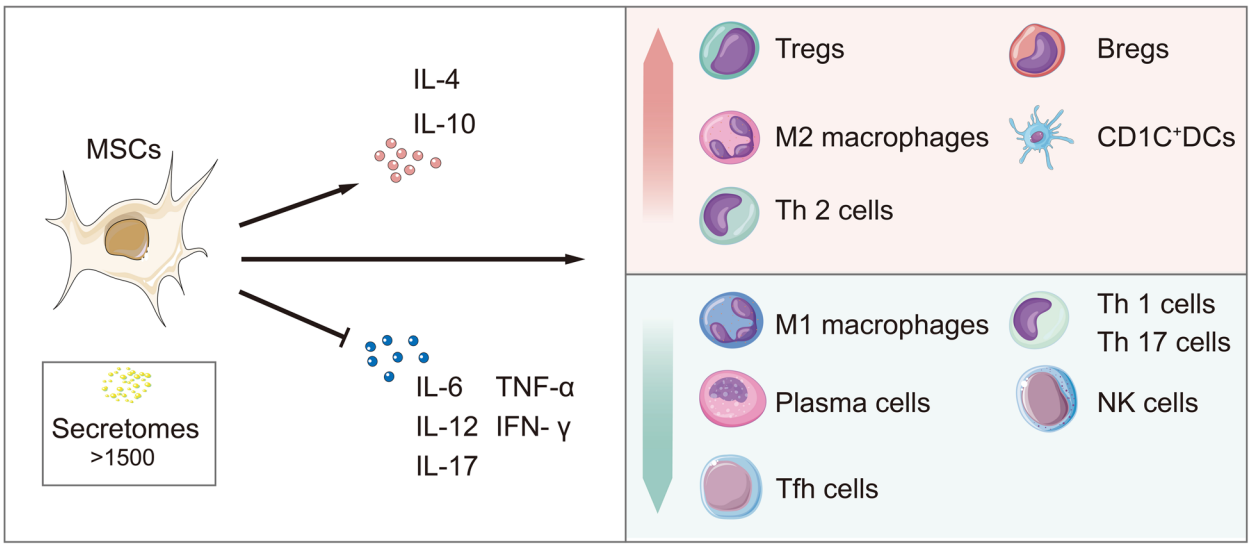

Fig.3 Immunomodulation of mesenchymal stem cells in chronic kidney disease. MSCs can influence many cytokines and immune cells by secreting exosomes with over 1500 secretomes. MSCs can increase interleukin-4 (IL-4) and IL-10, while decreasing IL-6, IL-12, IL-17, tumor necrosis factor –α (TNF-α) and interferon-γ (IFN-γ). MSCs can stimulate anti-inflammatory immune cells including regulatory T cells (Tregs), regulatory B cells (Bregs), M2-type macrophages, and $CD1c^+$ dendritic cells (DCs). MSCs can suppress pro-inflammatory immune cells including plasma cells, M1-type macrophages, natural killer (NK) cells, and follicular helper T (Tfh) cells. Besides, MSCs may change the balance of helper T (Th) cells by promoting Th2 cells, while inhibiting Th1 and Th17 cells

Furthermore, Kidney renovation cannot be achieved without tissue repair and angiogenesis. Podocytes are an important structure in the glomerular filtration membrane, and their damage is an obvious pathological change in DN. MSCs may alleviate the loss of podocytes [109] and endothelial cell injury in vivo by inhibiting apoptotic and reactive oxygen species [110]. Jiang et al. [111] revealed that MSCs isolated from the human embryonic pancreas can reduce podocyte fusion and defect in DN rats. Reducing podocyte loss will assist in maintaining the integrity of the glomerular filtration barrier.

MSCs in LN

LN is a serious complication of systemic SLE and a major cause of mortality in patients. Overactive T and B cells are criminals in SLE or LN, producing an excess of autoantibodies and pro-inflammatory cytokines without being constrained by Bregs and Tregs. Helper T (Th) cells are all $CD4^+$T cells that differentiate into subgroups with different functions when stimulated by antigens. A characteristic of LN is an imbalance of the Th1/Th2 ratio in peripheral blood [112]. IL-12 and IFN-γ are important factors inducing Th1 cell differentiation. A high IFN-γ level is parallel with the severity of renal injury. Previous clinical studies have found that IFN- γ and IL-4 decreased after MSCs infusion in patients with LN, indicating that MSCs can improve immune function by adjusting the Th1/Th2 ratio. Tregs can inhibit the activity of self-reactive T cells and maintain self-tolerance, hence the up-regulation of $FOXP3^+$Tregs after MSCs illustrates their immunomodulatory activity in LN. Yuan et al. found that UC-MSCs promoted the proliferation of $CD1c^+$DCs via an IFN-γ/FLT3L/FLT3 axis, suggesting that it may be an important subtype for improving immune dysfunction [35]. Additionally, MSCs interact with B cells. A co-culture study found that MSCs could inhibit B cell responses, manifested as cell cycle arrest, blocked differentiation, reduced immunoglobulin production, and defective chemotaxis [113]. Moreover, MSCs can promote the M2-type transformation of macrophages [114], reduce the proliferation and differentiation of follicular Th cells [115], and inhibit the proliferation and activity of NK cells [116].

Many cytokines make up the immune microenvironment of LN in the kidney. MSCs may slow down disease progression by regulating the secretion of certain cytokines. MSCs can increase serum IL-10 and IL-4 levels, while decreasing IL-17, IL-12, IL-6, TNF-α, IFN-γ, and expression of HMGB-1 [117], which is consistent with clinical trial findings. Thus MSCs can mediate the therapeutic effects of LN through immunoregulation of anti-inflammatory and anti-fibrosis properties [114, 117].

Conclusions

MSC infusion in CKD has now demonstrated good safety and tolerability, and previous trials appear to support the feasibility of this cell therapy for CKD patients. Those with LN primarily were more likely to have remission and improved renal function including, urine protein, SCr, and BUN, which was consistent with the preclinical results [118]. MSC treatment also showed a capacity to improve GFR in DN. In patients with kidney diseases, overactive immune responses can be suppressed by promoting Tregs and inhibiting adaptive immunity through MSC therapy.

However, clinical evidence is limited and biased based on current MSC trials, which most focus on phases 1–2, small sampled, single-arm, control-free studies. Although more randomized controlled trials are in progress, the results remain unknown. Moreover, the heterogeneity of cell products means that released secretomes differ in terms of differentiation potency and secretome profiles of subpopulations, as well as influences in on secretome by different pathophysiological microenvironments in vivo [119]. This makes it difficult to determine which cell product improves the outcome of CKD. It is also worth noting that the large-scale elimination of MSCs by the pulmonary capillary network may not allow sufficient time to exist and ideal cell number in the target organ or tissues, such as the kidney. As CKD causes are so heterogeneous, with diverse pathogenesis, including immune and non-immune-related conditions, it is impossible to draw general conclusions about the benefits of MSCs. With the subdivision of CKD causes, clinical efficacy was more obvious in LN patients, but not confirmed in DN or IN. Though INS had a common basis of abnormal immune activation as LN, a preliminary small-sampled study conducted less-than-perfect results. In CKD clinical applications, etiology needs more attention rather than renal function stage.

The clinical dilemma with MSCs in treating kidney diseases lies primarily from inefficient delivery and uncertainty in renal tissue regulation. To address the challenges faced by MSC therapy for kidney diseases, more effective and safe ways of MSC delivery must be developed in order to improve the efficiency and survival rate of stem cells reaching the therapeutic target area. For example, hydrogels and gold nanoparticles can help MSC exosomes target damaged kidney tissue. Engineered exosomes or pre-stimulated MSCs likewise may achieve targeted homing of damaged kidneys. Additionally, it is important to find key substances for targeted induction of differentiation which can help improve the efficiency and purity of MSCs. Developing MSCs that can maintain a steady state in vivo for a longer time is another way to improve the efficiency of future cell therapy.

In brief, MSCs therapy for kidney diseases has great potential and a broad spectrum of applications as an emerging treatment. For CKD, clinical practitioners must select the most suitable MSC type and treatment plan based on different types of renal pathologies and individual differences of patients. MSCs are expected to provide new hope to patients with kidney disease and revolutionize treatment as basic research and clinical translation continue to advance.

Abbreviations

AD-MSCs	Adipose-derived mesenchymal stem cells
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse events
BM-MSCs	Bone marrow-derived mesenchymal stem cells
BUN	Blood urea nitrogen
C3	Complement C3
C4	Complement C4
CAT	Catalase
CCL	Chemokine (C–C motif) ligand
CD	Cluster of differentiation
CKD	Chronic kidney disease
CXCL	Chemokine (C-X-C motif) ligand
DCs	Dendritic cells
DN	Diabetic nephropathy
ESRD	End-stage renal disease
FGF	Fibroblast growth factor
FLT3/FLT3L	FMS-like tyrosine kinase 3/ Fms-related tyrosine kinase 3 ligand
FOXP3	Forkhead box P3
GFR	Glomerular filtration rate
GPx	Glutathione peroxidase
GSH	Glutathione
GSTs	Glutathione S-transferases
HGF	Hepatocyte growth factor
HIF	Hypoxia-inducible factor
HO-1	Heme oxygenase-1
IDO	Indoleamine 2,3 dioxygenase
IGF-1	Insulin-like growth factor 1
IFN-γ	Interferon-γ
IL	Interleukin
IN	Ischemic Nephropathy
LN	Lupus nephritis
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophagecolony stimulating factor
miR	MicroRNA
MSCs	Mesenchymal stem cells
NKs	Natural killer cells
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2-related factor 2
PDGF	Platelet-derived growth factor
PGE_2	prostaglandin E2
PI3K	Phosphoinositide 3-kinase
RBF	Renal blood flow
RRI	Renal resistive index
SAE	Serious adverse events
SCr	Serum creatinine
SDF-1	Stromal cell-derived factor-1
SLE	Systemic lupus erythematosus
SOD	Superoxide dismutase
Tfh	follicular helper T cells
TGF-β	Transforming growth factor-β
Th	Helper T cells
TNF-α	Tumor necrosis factor-α
Tregs	Regulatory T cells
UC-MSCs	Umbilical cord-derived mesenchymal stem cells
VEGF	Vascular endothelial growth factor

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Lijie He contributed to the conception and design of the study, Jipeng Li organized the database and wrote the first draft of the manuscript, Mengting Wu checked and polished the revised manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Data availability
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Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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