Mesenchymal/stromal cell therapy in kidney diseases: an update

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Purpose of review
This review synthesizes advanced preclinical and clinical studies published over the past 18 months evaluating mesenchymal stromal cells (MSCs) and MSC-derived products in kidney diseases. We focused on the translational relevance of MSC-based therapies against ischemia–reperfusion injury (IRI) and toxic acute kidney injury (AKI), as well as chronic kidney disease (CKD) progression in diabetic kidney disease (DKD) and lupus nephritis (LN).

Recent findings
The renoprotective effects of MSC-based therapies are highly dependent on the timing of administration and the local pathological microenvironment. In IRI and AKI, therapeutic efficacy is confined to specific exposure windows and is driven by early modulation of mitochondrial dysfunction, inflammation and cell death. In DKD, MSCs from multiple sources consistently improve albuminuria, renal function and structural damage through anti-inflammatory, antifibrotic, autophagy-restoring and ferroptosis-inhibiting mechanisms. This nephroprotection appears to be largely independent of the glycaemic control. In LN, immune-contextual conditioning critically shapes the phenotypes of MSCs and MSC-derived extracellular vesicles (EVs), with optimized or engineered products outperforming the naïve approaches. In contrast, hypertension-related kidney disease illustrates how chronic ischemia and vascular remodelling limit MSC efficacy unless the underlying hemodynamic stress is corrected.

Summary
Across diverse settings of acute and chronic kidney injury, MSC-based therapies act primarily as modulators of early pathogenic cascades rather than curative interventions for advanced damage. Their efficacy critically depends on timing, disease context and micro-environmental conditioning. Increasingly, cell-free strategies based on EVs offer scalable and potentially safer alternatives, supporting the translational development of context-adapted and combinatorial strategies.

Keywords
acute kidney injury, cell therapy, chronic kidney disease, extracellular vesicles, kidney transplantation, mesenchymal stromal cells

INTRODUCTION

Renal ischemia–reperfusion injury (IRI) represents a central determinant in the pathophysiology of acute kidney injury (AKI), with a direct impact on both early and long-term outcomes of kidney recovery [1]. By initiating cascades of mitochondrial dysfunction, innate and adaptive immune activation, tubular epithelial cell death, endothelial injury and maladaptive repair, IRI frequently drives the transition toward acute kidney disease (AKD) and chronic kidney disease (CKD) [2]. Despite major advances in the understanding of the IRI pathophysiology [3,4] and in the development of immunomodulatory strategies, no targeted therapy is currently available to effectively and positively modulate the pathological processes interconnected along the IRI cascade.

Over the past decade, mesenchymal stromal cells (MSCs) and their cell-free derivatives, particularly extracellular vesicles (EVs), have emerged as promising therapeutic platforms owing to their pleiotropic immunomodulatory, cytoprotective and pro-regenerative properties. Rather than acting through direct tissue replacement, MSC-based approaches exert

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KEY POINTS

- Mesenchymal stromal cells (MSC)-based therapies primarily modulate early pathogenic processes in kidney injury rather than reversing established chronic damage.
- Therapeutic efficacy is critically dependent on timing of administration and the local microenvironment.
- In acute kidney injury and ischemia–reperfusion injury, MSCs and MSC-derived extracellular vesicles confer protection through early regulation of mitochondrial dysfunction, inflammation and regulated cell death.
- In diabetic kidney disease and lupus nephritis, MSC efficacy relies on context-specific immunomodulatory, antifibrotic and metabolic mechanisms, often independently of the systemic disease control.
- Cell-free strategies based on extracellular vesicles offer scalable, safer and more controllable alternatives to whole-cell MSC therapy, supporting their translational potential.

broad paracrine effects on mitochondrial homeostasis, inflammatory signalling, immune cell phenotyping, cellular senescence and fibrotic remodelling [5–7]. This review synthesizes recent preclinical and clinical evidence published over the past 18 months, highlighting how MSCs and MSC-derived products attenuate AKI in conditions of ischemic, toxic, metabolic, and/or immune-mediated insults, including kidney transplantation and how MSCs and MSC-derived products slow down CKD progression in cases of diabetic kidney disease (DKD) and lupus nephritis (LN). The therapeutic window and stage-dependent limitations of MSC-based strategies across the spectrum of kidney disease are summarized in Fig. 1.

ISCHEMIA–REPERFUSION INJURY AND KIDNEY TRANSPLANTATION

Preclinical studies provide mechanistic information to explain how MSC-based strategies mitigate both

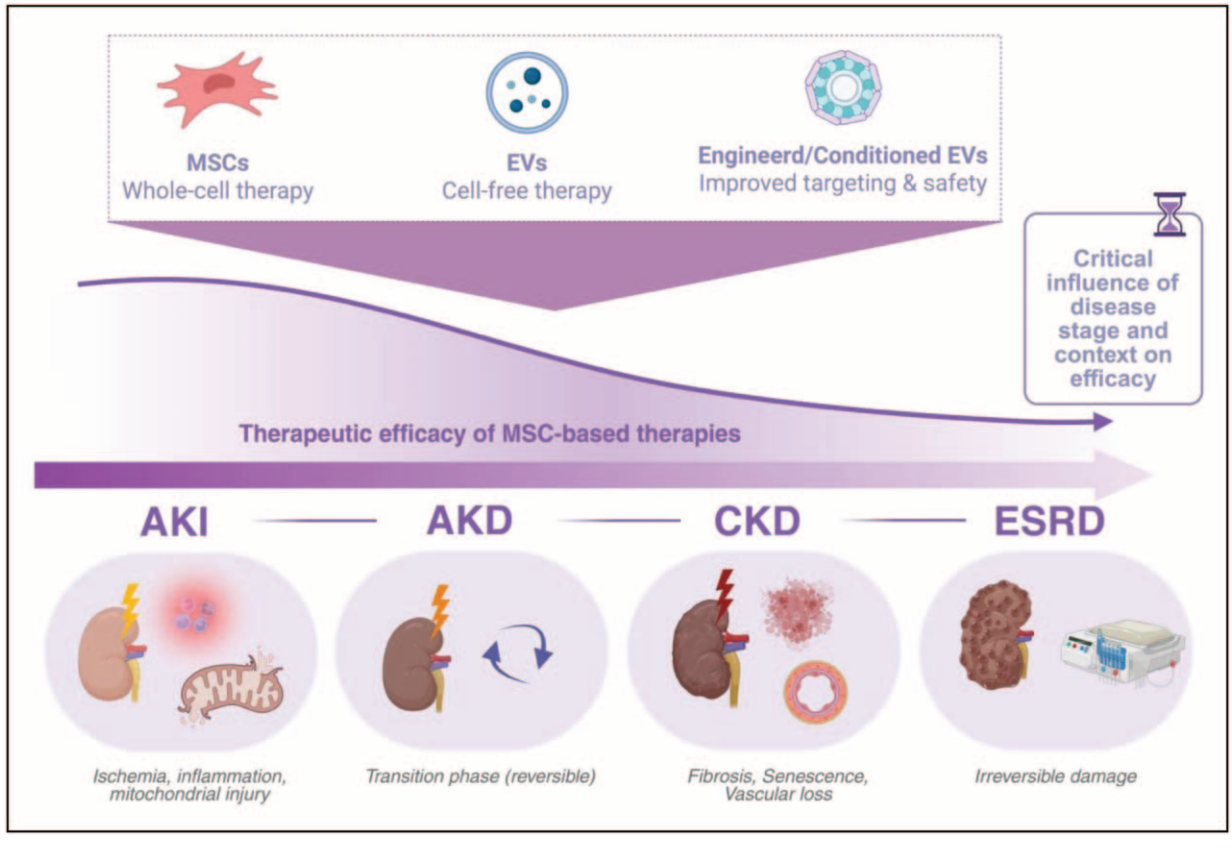

FIGURE 1. Disease stage and microenvironment shape the therapeutic efficacy of MSC-based strategies. MSC-based therapies show maximal efficacy at early stages of kidney injury, including acute kidney injury (AKI) and the reversible phase of acute kidney disease (AKD), where ischemia, inflammation and mitochondrial dysfunction predominate. As disease progresses toward chronic kidney disease (CKD) and end-stage renal disease (ESRD), increasing fibrosis, senescence and vascular loss impose irreversible constraints that limit therapeutic benefit, despite advances in cell-free and engineered MSC-derived products. MSC, mesenchymal stromal cell.

acute and chronic consequences of IRI. Exosomes derived from Wharton's jelly MSCs exert potent renoprotection by delivering high levels of miR-19b, which suppresses GSK3β signalling and stabilizes pyridoxine metabolism through PDXK preservation, thereby reducing tubular apoptosis in *in vivo* transplanted kidneys and *in vitro* ischemia–reoxygenation models. Optimization of MSC culture conditions further enhances therapeutic potential [8,9]. Hypoxia-preconditioned three-dimensional MSC spheroids produce exosomes enriched in miR-210, with increased vesicle yield and superior ability to reduce reactive oxygen species (ROS) accumulation, apoptosis and migration defects after hypoxia–reoxygenation [10].

Clinical studies provided essential insight into the feasibility, safety and immunological impact of MSC-based therapies in kidney transplantation [11,12]. In recipients with chronic active antibody-mediated rejection, repeated infusions of allogeneic bone marrow-derived MSCs were globally well tolerated, with no acute infusion reactions and only one opportunistic infection reported [13▪]. Importantly, renal functional decline was attenuated, as reflected by an improvement of the estimated glomerular filtration rate (eGFR) slope from a steep decline before treatment to near stability following MSCs therapy. This functional stabilization was accompanied by reductions in proteinuria and donor-specific antibody (DSA) mean fluorescence intensity, suggesting partial control of ongoing graft injury. Immunophenotyping revealed expansion of $CD4^+CD25^+CD127^{low}$ regulatory T cells and $CD8^+CD45RA^+CCR7^-$ effector cells, together with a reduction in $CD8^+CCR7^+$ memory subsets, consistent with early immunomodulatory effects [13▪]. A complementary study using mass cytometry further demonstrated that within hours of MSCs infusion, highly proliferative $CD11b^+CD11c^+CD38^+CD39^+Ki\text{-}67^+$ B- and T-cell subsets expand in the circulation, highlighting the rapid and dynamic immune reprogramming induced by MSCs therapy [14]. Conversely, donor-specific MSCs administered repeatedly in both human and nonhuman primate studies failed to induce durable tolerance and did not result in detectable chimerism. Furthermore, these cells were in some cases associated with *de novo* DSA formation or reversible rejection episodes [15]. Collectively, these findings indicate that MSCs are biologically active and generally safe in the transplant setting, but MSCs should not be considered as stand-alone tolerance-inducing agents [16].

Parallel advances in EV engineering highlight the importance of microenvironmental conditioning. EVs generated under hypoxic conditions display altered transcriptional and microRNA profiles that translate into enhanced antiapoptotic and pro-proliferative effects on renal tubular epithelial cells compared with normoxic EVs, both *in vivo* and *in vitro*[17]. Beyond the acute injury, several MSC-derived EVs specifically prevent the chronic sequelae of IRI (Fig. 1). Human umbilical cord MSC–derived exosomes enriched in miR-29a-3p protect against interstitial fibrosis and vascular rarefaction by directly targeting COL1A1 in fibroblasts and TNFR1 in endothelial cells [18]. Complementing these findings, MSC-derived EVs attenuate tubular epithelial senescence through coordinated regulation of Bax/Bcl-2-dependent apoptosis and Ras–pERK–Ets1–p53-mediated senescence pathways. When combined with senolytic agents such as dasatinib and quercetin, these EVs yield additive benefits in reducing tubular atrophy and chronic interstitial fibrosis [19].

Beyond EVs, innovative cell-free platforms have been developed to overcome limitations associated with whole-cell therapy. Mesenchymal membrane particles generated through controlled membrane extrusion reproduce key antifibrotic actions of MSCs while avoiding issues related to cell size, pulmonary trapping and viability. In murine unilateral IRI models and in human induced pluripotent stem cell-derived kidney organoids exposed to hypoxia and inflammatory stimuli, these particles significantly reduced TGF-β signalling, COL1A1 expression and α-SMA-positive myofibroblast activation without significantly altering immune cell infiltration, pointing toward a predominantly epithelial and stromal mechanism of action [20]. Combination strategies further amplify MSC efficacy by targeting complementary pathogenic pathways. In experimental renal IRI, adipose-derived MSCs combined with melatonin synergistically improved renal function, reduced histological injury, suppressed pro-apoptotic Bax and caspase-3 expression, and restored antiapoptotic Bcl-2 levels, illustrating the therapeutic value of pairing MSC-based products with agents targeting oxidative stress and mitochondrial dysfunction [21].

In line with these experimental observations, we had explored MSCs as a strategy of ischemic conditioning rather than as a primary immunosuppressive intervention [22]. Experimental studies demonstrated that MSCs administration prior to renal ischemia markedly attenuates AKI, reduces inflammatory infiltration and tubular apoptosis, and limits subsequent tissue damage. Transcriptomic analyses further revealed that MSCs pretreatment induces metabolic reprogramming toward lipid catabolism, with activation of the PPAR-α pathway and reduced lipid peroxidation, identifying metabolic modulation as a key mechanism underlying protection against renal IRI [23].

The translational potential of MSC- and EV-based strategies is further supported by the development of a porcine model of paired kidney *ex situ* normothermic machine perfusion [24▪]. The low intra-individual variability observed in this model enables one kidney to serve as a direct comparator for the other, providing a robust and clinically relevant platform to evaluate therapeutic interventions against IRI during machine perfusion prior to transplantation [25].

TOXIC ACUTE KIDNEY INJURY

In AKI models, mitochondrial safety consistently emerges as a central mechanism underlying MSC-mediated renoprotection. MSC therapy restores mitochondrial membrane potential, enhances PGC-1α-driven mitochondrial biogenesis, normalizes the balance between fusion and fission proteins, and reduces mitochondrial ROS accumulation. These effects converge on suppression of NLRP3 inflammasome activation and pyroptotic cell death, thereby limiting tubular injury. Importantly, mitochondrial stabilization is associated with long-term antifibrotic effects, demonstrating that MSCs influence both the acute and reparative phases of AKI [26▪▪].

EV-based strategies further refine these protective effects by improving tissue targeting and pharmacodynamics. Adipose-derived MSC small EVs (AMEVs), when surface-modified with ε-polylysine–PPD polymers, exhibit enhanced renal tropism and prolonged retention, attenuate epithelial–mesenchymal transition, inhibit mTOR signalling via miR-100 enrichment, and significantly reduce postischemic fibrosis [27▪]. The importance of model selection and MSC source is illustrated by strain-dependent differences in cisplatin-induced AKI severity, where CXCL1 emerged as a robust injury biomarker enabling comparison of MSC potency across sources. Notably, umbilical cord-derived MSCs displayed stronger anti-inflammatory activity than bone marrow or adipose-derived MSCs [28].

MSC-derived exosomes also exhibit substantial reparative capacity in human-relevant systems. In a three-dimensional microfluidic proximal tubule model subjected to hypoxic injury, bone marrow MSC-derived exosomes restored epithelial polarity, as evidenced by ZO-1 upregulation, improved barrier integrity, rebalanced nutrient transport and stimulated epithelial proliferation, albeit within a defined dosing window, underscoring the importance of pharmacodynamic precision [29]. Mechanistically engineered EVs provide even more targeted benefits. Exosomes enriched in miR-127-3p suppress aberrant autophagy by inhibiting ATG5 and ATG7 through modulation of the KIF3B–Hedgehog pathway, revealing a novel regulatory axis in AKI [30]. Similarly, hUCMSC-derived small EVs enriched in miR-13896 promote anti-inflammatory macrophage polarization by inhibiting the TRADD/NF-κB signalling axis, thereby limiting cisplatin-induced tubular apoptosis and inflammatory signalling [31].

Translational relevance is reinforced by large-animal studies. In a minipig model of cisplatin-induced AKI, ultrasound-guided subcapsular MSC injection improved renal functional recovery, and identified the kynurenine–aryl hydrocarbon receptor–NF-κB/NLRP3 axis as a key inflammatory pathway modulated by MSC therapy [32▪]. Complementarily, EVs released by hypoxia-preconditioned adipose-derived MSCs preserved mitochondrial function and redox homeostasis during IRI by maintaining mitochondrial membrane potential, respiratory capacity, ATP production and antioxidant defences through activation of the Nrf2/HO-1 pathway [33,34]. In infectious injury, MSCs complement antimicrobial therapy by enhancing ciprofloxacin's effect, reducing bacterial burden and suppressing TLR4/MyD88/TRAF6/NF-κB signalling in acute pyelonephritis [35]. In parallel, MSC-derived EVs enriched in tumour necrosis factor-α-induced protein 6 (TSG-6) exert potent immunomodulatory effects by promoting M2 macrophage polarization and regulatory T-cell induction, leading to marked suppression of renal inflammation and fibrosis and limiting AKI-to-CKD progression (Fig. 1) [36–38].

DIABETIC KIDNEY DISEASE

A large body of preclinical evidence supports the therapeutic potential of MSCs and MSC-derived products in DKD, where metabolic stress, chronic inflammation and progressive fibrosis converge to drive podocyte loss and CKD [39,40]. Furthermore, recent observations have highlighted the ambiguous role of hypoxia in the development and progression of DKD [41]. Multiple studies demonstrate that MSC therapy directly preserves podocyte integrity – an early and critical determinant of proteinuria – by reducing apoptosis, restoring slit diaphragm proteins such as nephrin and podocin, and limiting foot process effacement in both type 1 and type 2 diabetic models [42–44]. Accordingly, intravenous, intra-arterial or repeated systemic administration of bone marrow-, umbilical cord-, placenta- or adipose-derived MSCs consistently reduced albuminuria, improved renal function and attenuated mesangial expansion, glomerular basement membrane thickening and interstitial fibrosis, even in the absence of significant improvement in glycaemic control [43,45,46].

At the mechanistic level, multiple studies converge on the potent anti-inflammatory effects of MSCs in the diabetic kidney. MSC therapy suppresses the expression of key proinflammatory cytokines, including tumour necrosis factor-α, interleukin-6, interleukin-1β and interleukin-18, and inhibits major inflammatory signalling pathways implicated in DKD progression, such as NOD2, PKC/NF-κB/STAT3 and MAPK [45,47,48]. Immunomodulation further contributes to renoprotection, as MSCs promote macrophage polarization toward an anti-inflammatory M2 phenotype, thereby reducing glomerular inflammation and limiting podocyte injury in hyperglycaemic environments [45]. In parallel, fibrosis-specific mechanisms have been identified, with MSC therapy downregulating profibrotic mediators such as interleukin-11 and transforming growth factor-β, reducing collagen I and III deposition, α-smooth muscle actin expression and epithelial–mesenchymal transition, ultimately limiting renal scarring [49–51].

Beyond whole-cell therapy, several studies emphasize the central role of EVs as key mediators of renoprotection in DKD. These vesicles deliver bioactive cargos, including microRNAs and regulatory proteins, that inhibit mammalian target of rapamycin signalling, restore autophagic flux, stabilize cytoskeletal proteins such as Talin-1, and suppress podocyte epithelial–mesenchymal transition [52,53]. Restoration of autophagy emerges as a unifying mechanism across multiple DKD models, mediated through miR-99b-5p/mTOR, SIRT1/FOXO1 or SIRT1/TGF-β/Smad pathways, and is shown to be essential for limiting podocyte loss and renal fibrosis [43,46,50,52].

More recently, ferroptosis has been identified as a novel pathogenic process contributing to podocyte injury and progressive fibrosis in DKD. Several studies demonstrate that MSCs inhibit ferroptotic cell death by regulating SLC3A2 expression, suppressing Smad2/3-driven METTL3-dependent m6A modification, and preserving protective downstream targets such as sphingosine-1-phosphate receptor 1. Through these mechanisms, MSC therapy reduces lipid peroxidation, inflammatory activation and extracellular matrix accumulation in diabetic kidneys [48,54]. Additional complexity is introduced by evidence that MSCs can directly rescue mitochondrial dysfunction in injured podocytes via M-Sec–dependent tunnelling nanotubes, enabling the transfer of healthy mitochondria and restoration of cellular metabolism and survival [55].

Finally, combinatorial therapeutic strategies appear to further enhance MSC efficacy in DKD. Co-administration of MSCs with renin–angiotensin system blockers, sodium–glucose cotransporter 2 inhibitors, vitamin D supplementation, calorie restriction or brown and white adipose tissue transplantation resulted in improved glucose handling, reduced oxidative stress, reinforcement of renoprotective RAAS signalling, and superior preservation of podocyte structure and renal function compared with monotherapy [42,50,56]. Collectively, these studies depict MSC-based therapy as a multifaceted intervention in DKD, acting through coordinated modulation of inflammation, immunity, autophagy, fibrosis, ferroptosis, mitochondrial homeostasis and paracrine signalling, thereby providing a strong experimental rationale for its continued translational development.

LUPUS NEPHRITIS

Preclinical and translational studies investigating MSC-based therapies in systemic lupus erythematosus (SLE), particularly LN, revealed that their therapeutic efficacy is tightly linked to immune modulation, regulation of cell death and control of renal fibrosis. In this immune-driven context, optimized or "trained" MSC-based approaches consistently outperform naïve MSCs in controlling disease progression. In a pristane-induced murine lupus model progressing to end-stage kidney disease, treatment with a trained MSC-derived product significantly improved survival, stabilized proteinuria and halted glomerulosclerosis. These effects were associated with profound immune reprogramming, including reductions in Th17 polarization, plasmacytoid dendritic cells, interferon-γ, interleukin-17A, B-cell activating factor and anti-double-stranded DNA antibody levels, highlighting the importance of MSC functional optimization to overcome disease-associated immune dysregulation [57].

Metabolic and hypoxic preconditioning strategies further enhance MSC therapeutic efficacy in LN. Dimethyloxallyl glycine-pretreated human umbilical cord MSCs exhibited superior anti-inflammatory and antifibrotic effects compared with unconditioned cells, resulting in marked reductions in proteinuria, inflammatory cytokine expression and renal fibrosis. These benefits were mechanistically linked to inhibition of the transforming growth factor-β/Smad2/3 signalling pathway, a central driver of fibrotic remodelling in LN [58].

Beyond fibrosis, emerging evidence implicates inflammatory cell death pathways as key contributors to LN pathogenesis. Caspase-4/5/11–mediated noncanonical pyroptosis was shown to be activated in macrophages from patients with SLE and murine models of LN, directly contributing to podocyte injury and renal dysfunction. MSC administration effectively suppressed pyroptotic signalling through galectin-3 and interleukin-10–dependent mechanisms, resulting in significant protection of podocyte

structure and renal function in both experimental and clinical settings [59].

In parallel, ferroptosis has also emerged as a critical mechanism of podocyte loss in LN. MSC therapy reduced lipid peroxidation and restored antioxidant defences by activating the Nrf2/heme oxygenase-1/glutathione peroxidase 4 axis, stabilizing podocyte actin cytoskeleton organization and improving cell viability *in vivo* and *in vitro*[60]. Importantly, MSCs themselves can be functionally altered by the lupus microenvironment. Bone marrow–derived MSCs from lupus-prone mice exhibited a proinflammatory phenotype driven by aryl hydrocarbon receptor activation and Hippo–YAP signalling, leading to enhanced Th17 responses and exacerbation of renal pathology. These effects were reversible through pharmacological inhibition of the AhR or YAP pathways, underscoring the need for careful MSC characterization and conditioning prior to therapeutic use [61].

Cell-free approaches further refine MSC-based immunomodulation in LN. EVs derived from MSCs, particularly those primed with disease-conditioned immune cell media, significantly improved survival, reduced autoantibody production, normalized macrophage polarization toward anti-inflammatory phenotypes, and ameliorated renal histopathology in lupus-prone mice. These findings highlight the importance of immune-contextual conditioning of EVs cargo and support the development of tailored cell-free therapies for immune-mediated kidney disease [62].

HYPERTENSION-RELATED KIDNEY DISEASE

Hypertension-related kidney disease provides a complementary perspective on the context dependency of MSC efficacy. In this particular setting, chronic hemodynamic stress, vascular remodelling and ischemia impose intrinsic constraints on regenerative

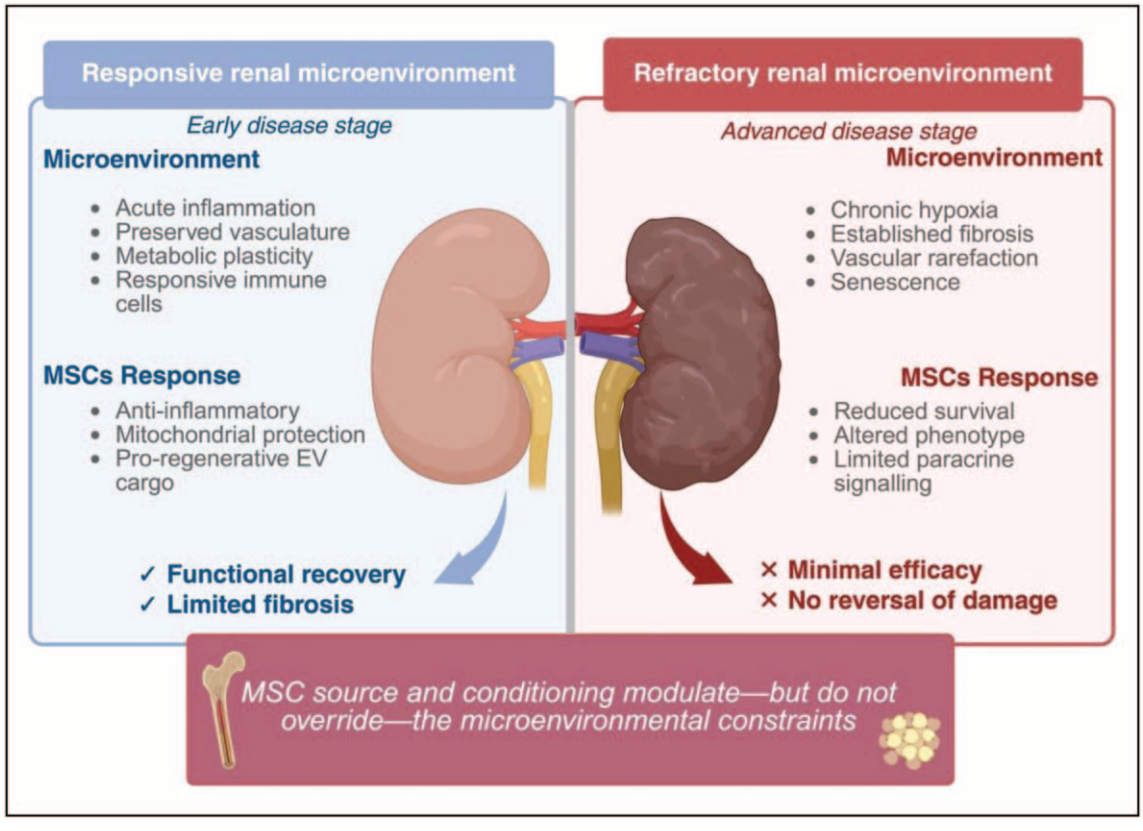

FIGURE 2. The responsiveness of the renal microenvironment shapes MSC therapeutic efficacy. MSC-based therapies are effective in biologically responsive renal microenvironments characterized by acute inflammation, preserved vasculature, metabolic plasticity and immune responsiveness, enabling anti-inflammatory, mitochondrial-protective and pro-reparative paracrine effects that support functional recovery and limit fibrosis. In contrast, refractory microenvironments dominated by chronic hypoxia, established fibrosis, vascular rarefaction and cellular senescence constrain MSC survival and function, resulting in minimal therapeutic benefit without reversal of established damage. The sources and conditioning approaches of MSCs may modulate their efficacy, but do not overcome the microenvironmental constraints. MSC, mesenchymal stromal cell.

therapies. Studies using human adipose-derived MSCs demonstrated that cells isolated from patients with advanced hypertensive kidney disease exhibit reduced responsiveness to hypoxic preconditioning, with only modest improvements in proliferation, angiogenic signalling and senescence markers compared with MSCs from healthy donors. These findings suggest that disease-induced intrinsic dysfunction may limit the efficacy of autologous MSC-based strategies in hypertensive nephropathy [63▪▪].

In experimental renovascular hypertension, MSC therapy alone failed to reverse established renal dysfunction or structural damage. In contrast, the combination of MSC administration with renal artery revascularization normalized renal function, reversed proteinuria, reduced the number of ischemic glomeruli and atrophic tubules, and improved overall parenchymal architecture [64]. These results underscore that correction of the underlying hemodynamic insult is a prerequisite for effective MSC-mediated renal repair and highlight the importance of integrating regenerative therapies into multimodal treatment strategies.

CONCLUSION

Across diverse models of renal injury – including ischemia–reperfusion, toxic exposure, DKD and immune-mediated nephropathies – a coherent therapeutic paradigm emerges in which MSC-based approaches act primarily as modulators of early pathogenic events rather than as curative interventions for advanced disease. Their efficacy depends critically on timing, disease context and microenvironmental conditioning, as well as on the choice between whole-cell and cell-free delivery platforms (Fig. 2). Increasingly, paracrine mechanisms mediated by EVs and other cell-free derivatives offer scalable and potentially safer alternatives to MSC transplantation. Continued refinement through preconditioning, molecular engineering and rational combination strategies will be essential to translate these promising approaches into effective clinical therapies for kidney diseases and kidney transplantation.

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Conflicts of interest

There are no conflicts of interest.

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