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Concise Review: Mesenchymal Stem Cell Treatment for Ischemic Kidney Disease

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Abstract

Ischemic kidney diseases are common clinical entities that bear high mortality and morbidity and may lead to irreversible loss of kidney function. Their pathophysiology is multifaceted, involves complex hormonal-immunological-cellular interactions, and leads to damage in multiple cell types, which is often resistant to conventional therapy. Thus, novel strategies are needed to repair the renal parenchyma and preserve kidney function. Mesenchymal stem cells (MSC) confer renal protection through paracrine/endocrine effects, and to some degree possibly by direct engraftment. Their anti-inflammatory and immune-modulatory properties target multiple cascades in the mechanisms of ischemic kidney disease. This review focuses on recent progress on the use of MSC to prevent kidney injury in ischemic kidney injury, with a focus on the chronic form.

Introduction

Ischemic kidney injury might result in fibrosis, irreversible renal dysfunction, and a need for renal replacement therapy. Acute kidney ischemia (AKI), which is associated with high mortality, involves a rapid decrease in glomerular filtration rate (GFR), often caused by vasoconstriction or loss of auto-regulation. Chronic ischemic kidney disease (CIKD) usually involves loss of renal parenchyma or reduction of GFR caused by gradual vascular obstruction. Clinically, the term “ischemic renal disease” most often describes CIKD, which contributes to 6–27%¹ of end-stage kidney disease, particularly among patients older than 50 years².

Atherosclerotic renal artery stenosis (ARAS) is the major cause of CIKD, and an independent risk factor for cardiovascular disease. Because revascularization of the stenotic renal artery often fails to restore renal function, effective therapeutic strategies to preserve the post-stenotic kidney by repairing its parenchyma directly are under intense investigation. However, intervention trials using atrial natriuretic peptide, insulin-like growth-factor-1, or erythropoietin have been rather disappointing.

In recent years, regenerative medicine has shown much promise for kidney repair. Mesenchymal stem cells (MSC) have become the preferred cell type, because a large number of MSC can be obtained relatively easily from adult sources like bone-marrow or adipose tissue, and because of their prominent anti-inflammatory properties. MSC seem to

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be uniquely suited to target multiple pathways contributing to ischemic kidney injury (Figure 1). Indeed, MSC have been applied for treatment for several forms of AKI^{3, 45, 6} in animals and humans. The rationale for MSC treatment in AKI has been reviewed recently⁷⁻⁹, while applications of MSC in CKD are still emerging. This review will briefly summarize MSC application in AKI, but will focus on recent progress in potential applications of MSC in CKD.

1. MSC in AKI

AKI might constitute an ideal target for MSC therapies. The self-renewal capabilities of MSC can benefit the kidney by their transdifferentiation into kidney cells. Because of the high regenerative capacity of renal cells, MSC can accelerate their repair by releasing cytokines/growth factors. Furthermore, MSC can target the entire cascade of mechanisms activated not only in ARAS, but also in AKI (Figure 1), by their paracrine, anti-inflammatory, and immuno-modulatory properties, thereby achieving kidney protection and repair.

MSC have been applied in AKI secondary to several common etiologies. Ischemia-reperfusion injury (IRI) contributes to early graft dysfunction during kidney transplantation. Ischemia and hypoxia cause metabolic disturbance, induce reactive oxygen species (ROS) formation and secretion of proinflammatory cytokines and chemokines. During reperfusion, restored oxygen supply initially enhances release of ROS and proinflammatory mediators, and triggers immune responses. MSC target oxidative stress and inflammation¹⁰ in both IRI phases to protect kidney. In rat kidney transplantation¹¹, MSC reduced inflammation in early acute allograft rejection. Furthermore, in a phase-II clinical trial¹², autologous MSC decreased the incidence of acute rejection in patients undergoing kidney transplantation, although their effects on graft survival and long-term outcomes require further studies.

Excessive systemic inflammation following sepsis or burn may lead to AKI. In a rat sepsis model, MSC protected major organs from damage¹³, and in systemic endotoxemia attenuated multi-organ injury, including the kidney, by reducing inflammatory cell infiltration and kidney cell apoptosis¹⁴. MSC have also exerted a paracrine-mediated renoprotective effect in rat cisplatin-nephrotoxicity at multiple target sites¹⁵.

Preliminary results in a phase-1 clinical trial¹⁶ using supra-renal aortic injection of allogeneic bone-marrow-derived MSC after cardiac surgery showed that post-operative AKI was reduced (20%) as were the length of stay and readmission (~40%) compared to historical controls. Importantly, this study showed that suprarenal, postoperative administration of allogeneic MSC has not led to adverse events.

Thus, the use of MSC to protect the kidney or to prevent AKI in high-risk patients seems to be feasible and safe. Yet, their benefits in AKI need to be established in larger clinical trials.

2. MSC in CKD

ARAS is the major cause for renovascular hypertension and may lead to CKD. Kidney damage distal to the stenosis is characterized by microvascular rarefaction and fibrosis, and when severe may lead to glomerulosclerosis. The hallmark of CKD is activation of the renin-angiotensin-aldosterone system, which when prolonged becomes maladaptive. Angiotensin-II (AngII) stimulates production of ROS, which decrease bioavailability of nitric oxide, thereby allowing vasoconstriction, endothelial dysfunction, microvascular loss, and decreased GFR. AngII and ischemia also increase the expression of monocyte chemotactic protein-1 and renal macrophage infiltration, thereby enhancing tissue inflammation. Increased oxidative stress and inflammation can both downregulate growth factors like VEGF, aggravating microvascular rarefaction^{17, 18}. Furthermore, AngII

increases the expression of TGF- β , resulting in accumulation of extracellular matrix and renal fibrosis. These pathogenic mechanisms activated in CIKD lend themselves to potential application of reparative cell-based therapy.

The mechanisms by which MSC achieve renal cellular repair are multifactorial. Upon infusion, MSC firstly home to injury sites. For this purpose, MSC express two major homing receptors^{19–21}: CXCR4 for stromal cell-derived factor (SDF)-1 and CD44 for hyaluronic acid. MSC then release growth factors or anti-inflammatory cytokines to the injury site. Furthermore, MSC release microparticles^{22, 23} carrying anti-inflammatory cytokines and growth factors that promote kidney repair by their internalization in tubular or other cells. All these actions tone down intra-renal inflammation and allow for vascular regeneration. Moreover, anti-apoptotic effects of MSC²⁴ can prevent cell loss. Genetic fate-mapping techniques have shown that kidney repair after AKI depends on proliferation of tubular epithelial cells, whereas few marrow-derived MSC trans-differentiate into kidney cells^{25–27}. However, other studies identified MSC engrafted in peritubular capillaries, nephrons, and tubular structure in AKI²⁸ or CIKD¹⁰. Therefore, MSC seem to have at least some capability for replacing injured cells, or possibly need to engraft in order to exert some paracrine effects.

Nonetheless, unlike acute alterations elicited in AKI, regression of longstanding structural remodeling, like fibrosis and lost microvessels, is difficult to attain with any therapeutic intervention. In order to evaluate the feasibility of MSC in decreasing renal injury in experimental CIKD, we isolated porcine adipose tissue-derived MSC, expanded them in vitro, and characterized them by surface markers (CD44 and CD90) and tri-lineage differentiation. CIKD was induced in pigs by unilateral renal artery stenosis, and DiI-labeled MSC (10×10^6) directly infused through the stenotic renal artery six weeks later. Four weeks later renal structure, function, and mechanisms of repair were assessed and compared to those achieved by similarly infused endothelial progenitor cells (EPC), isolated and expanded from the pig peripheral blood. MSC and EPC showed similar retention rates of around 4% of total injected cells in normal kidneys and 12% in stenotic kidneys, likely because of increased expression of homing and adhesion factors. MSC were commonly observed in the interstitium, while EPC tended to engraft in renal tubules and small microvessels. Interestingly, EPC and MSC engrafted preferentially into proximal tubules. Functionally, both cell types improved renal blood flow (RBF) similarly, but MSC induced a greater improvement in GFR (Figure 2). EPC prominently enhanced renal growth-factor expression and decreased oxidative stress, while MSC additionally attenuated renal inflammation, endoplasmic-reticulum stress, and apoptosis, possibly through mechanisms involving cell contact¹⁰. Thus, MSC and EPC achieve a comparable decrease of kidney injury in CIKD by different mechanisms, although MSC elicited slightly superior improvement of renal function. Importantly, it remains to be tested whether similar to MSC in AKI²⁹ and to EPC in experimental CIKD³⁰, MSC mobilize endogenous resident kidney stem cells in CIKD.

Their efficacy in resolving chronic ischemic injury provided the impetus to apply MSC to address clinical needs. Renal revascularization using percutaneous transluminal renal angioplasty and stenting (PTRA) is common employed to restore RBF and function in CIKD, clinical trials have not identified major benefits for this procedure³¹, likely due to lingering kidney tissue damage. To improve its efficiency, we replenished MSC as an adjunct to experimental PTRA in ARAS pigs³². CIKD pigs were also fed a high-cholesterol diet to simulate atherosclerosis, and PTRA performed 6 weeks after renal artery stenosis, with adjunct delivery of adipose tissue-derived-MSC (10×10^6 cells). Four weeks after successful PTRA, mean arterial pressure fell to similar levels in all revascularized pigs. MSC restored stenotic-kidney GFR and RBF, which remained low after PTRA alone.

Interstitial fibrosis, inflammation, microvascular rarefaction, and oxidative stress were also attenuated to a greater degree in PTR+ treated pigs. This study suggested a novel therapeutic potential for MSC in restoring renal function and blunting structural remodeling when combined with PTR in CIKD. However, longer duration of CIKD, preexisting renal disease or essential hypertension, and comorbidities, will likely decrease the efficacy of this approach in human subjects; clinical trials are urgently needed to assess its utility in patients with ARAS.

Patients with diabetes mellitus often develop chronic macro- and micro-vascular disease, including diabetic nephropathy (DN), arguably epitomizing a specific form of CIKD. Accumulation of advanced glycation-end-products and ROS, inflammation, and AngII activation play important roles in DN. The anti-inflammatory, antioxidant, and immune-modulating features of MSC may serve to attenuate DN. Indeed, MSC ameliorate streptozotocin-induced DN in rats by inhibiting ROS and pro-inflammatory cytokines³³. Alas, those models recapitulate the early stages of human DN, and the renoprotective potential of MSC in patients with advanced DN remains to be shown.

The route of MSC delivery, intravenous, intra-arterial, or intra-parenchymal, may affect their efficiency for kidney repair. When labeled MSC intravenously infused into baboons were observed for 9–21 months, estimated levels of engraftment in the kidney, lung, liver, thymus, and skin ranged from 0.1–2.7%³⁴. Indeed, the intravenous route lags in delivery efficiency, because MSC may initially be trapped in the lungs³⁵. Intra-arterial infusion of MSC was the most effective route to achieve immunomodulation in rat kidney transplantation³⁶, possibly by avoiding lodging in the pulmonary circulation, allowing MSC to home to the injured kidney. Indeed, we observed retention of 12–14% of intra-arterially injected MSC in experimental CIKD³². Contrarily, a recent study found similar functional efficacy, with most MSC label diminished within 7 days after either intravenous or intra-arterial infusion in rat IRI³⁷. Intra-parenchymal administration of MSC also reduces renal fibrosis and promoted functional recovery³⁸, but is impractical for clinical applications, especially when kidney pathology is diffuse.

Potential limitations of MSC in CIKD

One potential disadvantage of administration of large numbers of MSC is the possibility for these highly self-renewable cells to form teratoma or other tumors. So far, no direct evidence shows kidney tumor formation. A case-report describing formation of teratoma³⁹ did not elaborate on the type, dose, or administration route, and adverse effects are thus hard to evaluate. Nevertheless, longer follow-up times are mandatory to exclude detrimental effects of MSC in humans. To circumvent infusion of cells, researchers evaluated conditioned culture media of MSC, which contain MSC-derived cytokines or growth-factors necessary for kidney repair²⁸, and may confer similar renoprotective benefits to using MSC directly⁴⁰. More recently, the protective effects of conditioned media have been proposed to be mediated through MSC-derived proteins and RNA carried by exosome-like membrane microvesicles released in culture^{22, 41}, found to be effective in several renal disease models. Cell-free products offer exciting advantages, as they minimize safety concerns and limitations associated with transplantation of replicating cells or unnecessary proteins in the conditioned medium. So far microvesicles have only applied in small animals. Given that they mimic mostly paracrine action of MSC, it is critical to establish whether MSC replication and engraftment are not, in fact, essential for their long-term benefits and replacement of injured kidney cells. The potential clinical application of microvesicles for CIKD also requires further investigation in large pre-clinical models.

How long the effects of MSC on kidney protection can last remains unclear. In a pilot study¹⁰, ARAS pigs were studied 4 or 12 weeks after injection of MSC. Very few pre-labeled MSC were detectable in the kidney by 12 weeks, possibly because of dilution and decay of the label. Nevertheless, comparable improvements in RBF were observed at both time-points, suggesting that their beneficial effects are sustained for at least 3 months. Notably, the decrease over time in the paracrine/endocrine effects of MSC may be more important for CIKD than AKI, in which the injurious trigger might have been removed. Repeated weekly administration of MSC improves their protective effects in the rat remnant kidney, primarily via paracrine effects⁴². Whether CIKD would benefit from multiple MSC administration awaits further testing in CIKD models. Furthermore, hypoxic preconditioning enhances MSC recruitment and functional recovery from IRI¹⁹, but remains to be tested in CIKD.

In summary, MSC clearly show remarkable potential to treat ischemic kidney disease. Their anti-inflammatory and immune-modulatory properties target multiple cascades in the mechanisms of ischemic kidney disease, and several potential indications can be envisioned (Table 1). MSC exert renal protection through paracrine/endocrine effects and to some extent possibly by direct engraftment. Further studies are needed to discern the chief elements of their action, define the optimal type (tissue source, preconditioning), dose, and delivery route, and establish the cost/benefit associated with delivery of viable cells as opposed to cocktails shuttling their paracrine vectors. As this field is marching forward, innovative research continuously sheds light on the trophic mechanisms of MSC and on improving their safety profile. Cantaluppi et al⁹ recently summarized phase 1/2 trials of autologous or allogeneic MSC in various forms of kidney disease that are listed in ClinicalTrials.gov. Most of the primary end points are the safety and efficacy of MSC; once these are established, rapid clinical translation is warranted.

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Figure 1.

Mechanisms that contribute to the potential of mesenchymal stem cells (MSC) to treat ischemic kidney disease. Their anti-inflammatory and immune-modulatory properties target multiple cascades activated in ischemic kidney disease. MSC also exert renal protection through paracrine/endocrine effects and to some extent possibly by direct engraftment. AKI: acute kidney ischemia. ARAS: atherosclerotic renal artery stenosis. ROS: reactive oxygen species. TGF- β : transforming growth-factor-beta

EPC tracking

MSC tracking

Figure 2.

Top: Representative images of CM-DiI labeled (red) endothelial progenitor cells (EPC) or mesenchymal stem cells (MSC) in the post-stenotic kidneys of pigs with renal artery stenosis (RAS) 4 weeks after delivery. Green shows peanut agglutinin (PA, green arrow), a distal tubular marker, and cyan shows a proximal tubular marker phaseolus vulgaris erythroagglutinin (PHA-E, cyan arrow). EPC showed mainly tubular engraftment (yellow arrow), while MSC tended to integrate into both proximal tubules (yellow arrow) and interstitium (red arrow). Bottom: Both EPC and MSC improved RBF and GFR in pigs with RAS, yet MSC more effectively restored GFR. * $p < 0.05$ vs. Normal, † $p < 0.05$ vs. RAS. Scale bar=200 μ m. (Figure 2 from Stem Cells. 2013;31:117–125).

Table 1

Potential future uses of MSC in chronic ischemic kidney diseases.

<ul style="list-style-type: none">• Prevention of acute renal injury in patients with chronic kidney disease<ul style="list-style-type: none">– Major surgery– Nephrotoxic drugs• Adjuvant therapy for interventional procedure for renal artery stenosis• Bridge for kidney transplantation?