Mesenchymal Stem Cell-Based Therapy in Acute Kidney Injury

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Acute kidney injury (AKI) causes a lot of harm to human health but is treated by only supportive therapy in most cases. Recent evidence shows that mesenchymal stem cells (MSCs) benefit kidney regeneration through releasing paracrine factors and extracellular vesicles (EVs) to the recipient kidney cells and are considered to be promising cellular therapy for AKI. To develop more efficient, precise therapies for AKI, we review the therapeutic mechanism of MSCs and MSC-derived EVs in AKI and look for a better understanding of molecular signaling and cellular communication between donor MSCs and recipient kidney cells. We also review recent clinical trials of MSC-EVs in AKI. This review summarizes the molecular mechanisms of MSCs' therapeutic effects on kidney regeneration, expecting to comprehensively facilitate future clinical application for treating AKI.

Keywords: acute kidney injury ; mesenchymal stem cells ; extracellular vesicles

1. Mesenchymal Stem Cell-Based Therapy in Acute Kidney Injury

1.1. Different Stem Cell Sources in Acute Kidney Injury

Mechanisms involved in self-renewal, differentiation, and repair after kidney injury is still unclear. Evidence showed that stem cell therapies have protective effects on AKI [1]. It was found that the resident renal tubular cells in the injured denudated tissue expressed CD133, an important stem cell marker and a molecule for Wnt/beta-catenin signaling for cell proliferation and tissue repair. Embryonic renal cells express CD133 and maintain uneven expression on the scattered tubular cells in different segments. These resident scattered renal progenitor $CD133^+$ cells act like stem cells, capable of self-renewal and differentiation [2]. Besides, endothelial progenitor cells (EPCs) from bone marrow can also act as a source of regenerative progenitor cells for AKI via the surface protein expression of L-selectin, an adhesion molecule that promotes EPCs migration to injured tissue [3]. Different stem cell sources, such as EPCs [3][4], human liver stem cells (HLSCs) [5], and MSCs [6][7], had demonstrated protective effects in murine AKI models. Among different stem cell sources, MSCs have the most extensive preclinical evidence and can be harvested from variable tissues, e.g., bone marrow, umbilical cord, adipose tissue, etc. Herrera et al. found that exogenous MSCs migrated to the injured kidney through the interaction between MSC surface CD44 and its ligand, hyaluronic acid), which promoted kidney regeneration [8]. Ullah et al. summarized molecular mechanisms of MSC homing steps: (1) tethering by selectins, (2) activating by cytokines, (3) arresting by integrins, (4) transmigrating by matrix remodelers, (5) extravascular migrating by chemokine gradients [9]. Besides, human induced pluripotent stem cells (hiPSCs) and embryonic stem cells were both demonstrated to promote kidney regeneration [10]. Schubert et al. had demonstrated the MSC migration and homing by tracking the adipose-derived MSC (ADSC) with bioluminescence imaging (BLI) versus quantitative reverse transcription-polymerase chain reaction (qRT-PCR) in the cisplatin-induced AKI model [11]. They detected the labeled Luc-specific mRNA in the injured kidney tissue using qRT-PCR; however, they only detected Luc^+-ADSCs in the lung but not in the kidney, suggesting that Luc-based qRT-PCR might be a better tool than BLI to track the transplanted MSCs. In 2021, Chen et al. reported a novel therapy combined with plerixafor (AMD3100, as an immunostimulant) and granulocyte-colony stimulating factor (G-CSF). The combinative therapy of AMD3100 and G-CSF could mobilize bone marrow-derived mesenchymal stem cells (BM-MSCs) to the injured tissue and ameliorate kidney function deterioration in the cisplatin-induced AKI model [12].

2. Mesenchymal Stem Cells and MSC-Derived Extracellular Vesicles Protect from Acute Tubular Injury in Different Models

EV trafficking is multidirectional cell-to-cell communication in damaged tissues and has the effect of facilitating and reprogramming regenerative cells [13]. Additionally, the EVs contained various therapeutic mediators, including cytokines,

proteins, and miRNAs [14]. The application of EVs for clinical use relies on efficient EV isolation and characterization [15] [16].

Numerous studies in various experimental AKI models demonstrated that MSCs and MSC-derived EVs had the therapeutic activities to reverse AKI via cell-to-cell paracrine communication rather than MSCs per se transdifferentiation. Gatti et al. reported that human MSC-derived EVs could prevent AKI and CKD progression by inhibiting TEC-apoptosis while promoting TEC proliferation in the ischemia-reperfusion (I/R) AKI model [17]. A similar therapeutic effect for AKI prevention had also been observed by using EVs from renal glomerular and tubular progenitor $CD133^+$ cells [18]. Besides, Chen et al. found MVs extracted from Wharton's jelly MSCs of the umbilical cord could mitigate renal fibrosis, induce cell proliferation, and inhibit cell apoptosis via ERK1/2 signal pathway to initial G2/M cell cycle arrest in the I/R AKI model [19]. MSC-derived MVs administered in the cisplatin-AKI model have been found to upregulate anti-apoptotic genes, including Bcl2, Bcl-xL, and BIRC8. The down-regulation of apoptosis genes, e.g., Casp1, Casp8, and LTA, was also noted [20]. HLSC, with MSC surface markers but without hematopoietic/endothelial markers, and HLSC-derived EVs enhanced renal tubular regeneration in a murine glycerol-induced AKI model [5]. Furthermore, human MSC-conditioned media (MSC-CM) also possess regenerative properties for tissue injury due to MSC-secreted products, such as proteins, lipids, cytokines, or EVs, etc. Overath et al. found that MSC-CM from ADSCs preincubated in a hypoxic environment contains more protective factors and had better therapeutic effects for cisplatin-induced AKI mice than ordinary MSC-CM [21]. These studies show that MSC-derived EVs can be an innovative therapy for AKI.

3. MSCs and MSC-Derived EVs Protect from Acute Glomerular Injury in Different Models

The pathophysiology of AKI is multifactorial and complex. Definite diagnosis of AKI etiologies is sometimes challenging because multiple kidney injuries may coexist. The two major causes of acute tubular damage are ischemic and nephrotoxic [22]. Another important AKI etiology is glomerular damage, including primary rapidly progressive glomerulonephritis (RPGN), or glomerulonephritis secondary to systemic lupus erythematosus, or bacterial endocarditis [23][24]. The epidemiology, clinical phenotypes, and pathophysiology are different between acute tubular and glomerular injuries [25]. We summarized MSC-derived EVs in experimental AKI models of glomerular and tubular damage and listed the potential involved factors and main effects of EV-related kidney repair (**Table 1**).

Table 1. MSC-derived EVs in experimental models of AKI and the potential mechanisms of EV-induced renal tissue repair.

Histology	Authors/Year Reference	EV Sources	EV Types	Experimental Model	Species	EV Factors	Molecular Response	Functional Modulation
Acute Tubular Injury	Herrera et al., 2007 [8]	BM-MSCs	NM	In vitro/in vivo, glycerol-induced AKI	Mouse	NM	↑CD44 and hyaluronic acid (major ligand of CD44) interactions	↑exogenous MSC migration and homing
	Gatti et al., 2011 [17]	BM-MSCs	MVs	In vivo, I/R induced acute tubular injury	Rat	NM	NM	↓tubular cell apoptosis, ↑TEC proliferation
	Bruno et al., 2012 [20]	BM-MSCs	MVs	In vitro/in vivo, cisplatin-induced acute tubular injury	Mouse	Human POLR2E mRNA	↑anti-apoptotic genes, *Bcl-xL*, *Bcl2*, and *BIRC8*, ↓apoptosis genes, *Casp1*, *Casp8*, and *LTA*	↑renal function, morphology, and survival
	Mb et al., 2014 [5]	hLSCs	NM	In vitro/in vivo, intra-muscle glycerol induced AKI	Mouse	NM	↑PCNA expression	↑tubular cell proliferation, ↑renal function, ↑morphology
	Chen et al., 2017 [19]	hWJMSCs	MVs	In vitro/in vivo, I/R-induced renal fibrosis	Rat	NM	↑ERK1/2 signaling ↓EMT–related protein, TGF-β1 ↑cell cycle-related proteins, CDK 1 and CyclinB1	↑proliferation, ↓apoptosis, ↓collagen deposition, ↑cells in G2/M cell cycle, ↓fibrosis, ↓EMT

Histology	Authors/Year Reference	EV Sources	EV Types	Experimental Model	Species	EV Factors	Molecular Response	Functional Modulation
	Ranghino et al., 2017 [18]	Gl-MSCs T-CD133^{+} cells	Gl-MSC-EVs T-CD133^{+}-EVs	In vivo, I/R induced acute tubular injury	Mouse	62 group of miRNAs	NM	↑TEC proliferation
	Overath et al., 2016 [21]	ADSC-pCM	pCM	In vitro/in vivo, cisplatin-induced acute tubular injury	Mouse	64 expressed proteins	↓inflammatory cytokines, IL-1β, IL-6	↑ survival ↓ serum Cr and N-GAL
Acute Glomerular Injury	Tsuda et al., 2010 [26]	FM-MSCs	NM	In vitro/in vivo, anti-Thy1 nephritis	rats	NM	↓TNF and MCP-1 through a PGE2-dependent mechanism.	↓Proteinuria ↓mesangial matrix/cell proliferation, ↓glomerular monocyte/macrophage infiltration,
	Zoja et al., 2012 [27]	BM-MSCs	NM	In vitro/in vivo, Adriamycin-induced crescentic nephritis	rats	NM	↑VEGF expression ↑nephrin and CD2AP	↓monocyte infiltration, ↓podocyte apoptosis, ↓microvascular rarefaction
	Iseri et al., 2016 [28]	hMSC-CM	CM	In vitro/in vivo, anti-glomerular basement membrane nephritis	rats	NM	↓proinflammatory cytokines TNF-α, IL-1-β, MCP-1, and IL-6	↑M2 macrophage polarization, ↓proteinuria and crescent formation

Abbreviations: ADSC-pCM, adipose-derived MSC-preconditioned media; AKI, acute kidney injury; BM-MSCs, bone marrow-derived MSCs; CDK, cyclin-dependent protein kinase; EMT, epithelial-mesenchymal transition; EVs, extracellular vesicles; FM-MSCs, fetal membrane-derived MSCs; Gl-MSCs, MSCs derived from human glomeruli; I/R, ischemia/reperfusion; hLSCs, human liver stem cells; hMSC-CM, human MSC-conditioned media; hWJMSCs, human Wharton's jelly-MSCs; IGF-1R, insulin-like growth factor-1 receptor; MAC, membrane attack complex; MCP-1, monocyte chemoattractant protein 1; MSC, mesenchymal stem cell; MVs, microvesicles; N-GAL, neutrophil gelatinase-associated lipocalin; NM, not mentioned; PCNA, proliferating cell nuclear antigen; T-CD133^{+} cells, T-CD133^{+} progenitor cells from human renal tubules tissue.

An experimental glomerulonephritis rat model was created by intravenous infusion of anti-Thy1.1 antibody through complement-mediated mesangial cell damage, impairing glomerular angiogenesis. Tsuda et al. found that allogeneic fetal membrane-derived MSCs (FM-MSCs) decreased urinary protein excretion by inhibiting glomerular monocyte infiltration and mesangial matrix hyperplasia histologically in the rats with anti-Thy1 glomerulonephritis. The mechanism was evident by in vitro experiment showing that FM-MSC conditioned medium contributed to the healing process in injured kidney tissue by inhibiting prostaglandin E2-dependent expression of TNF-α and monocyte chemoattractant protein 1 (MCP-1; a key chemokine for monocyte activation) [26]. In another glomerulonephritis rat model induced by Adriamycin, Zoja et al. found that multiple administrations of BM-MSCs increased VEGF expression and reduced monocyte infiltration, podocyte apoptosis, and microvascular rarefaction and subsequently attenuated glomerular sclerosis [27]. Moreover, Iseri et al. reported that human MSC-CM treatment reduced TNF-α-related proinflammatory cytokine and modulated the glomerular macrophage polarization. The shift to anti-inflammatory M2 subsequently reduced proteinuria and crescent formation in the rat AKI model with anti-glomerular basement membrane RPGN [28]. These studies demonstrated the MSCs significantly decrease proteinuria and regain renal function through various immunomodulatory pathways.

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