

## Review Article

# The Regulation of Inflammatory Mediators in Acute Kidney Injury via Exogenous Mesenchymal Stem Cells

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Received 7 January 2014; Revised 7 March 2014; Accepted 20 March 2014; Published 15 April 2014

Academic Editor: Ronald Gladue

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Acute kidney injury (AKI) remains to be an independent risk factor for mortality and morbidity. Inflammation is believed to play a major role in the pathophysiology of AKI. Exogenous mesenchymal stem cells (MSCs) are now under extensive investigation as a potential therapy for AKI. Various preclinical studies indicated the beneficial effects of MSCs in alleviating renal injury and accelerating tissue repair. However the mechanisms responsible for these effects are incompletely understood. In the recent years, anti-inflammatory/immunoregulatory properties of MSCs have become one of the important issues in the treatment of AKI. This review will summarize the current literature on the regulation of inflammatory mediators via exogenous MSCs contributing to the recovery from AKI.

## 1. Introduction

Acute kidney injury (AKI) is defined as a rapid decrease in glomerular filtration rate (GFR) caused by both vascular and tubular factors, including increased renal vasoconstriction, loss of autoregulation, and tubular obstruction [1–3]. Although incidence rates are decreasing, AKI is still associated with a high mortality rate [4]. Inflammation is now believed to play a major role in the pathophysiology of AKI [5, 6]. Endothelial injury can increase microvascular permeability which may lead to inflammatory cells recruitment into the injured kidney during the initial process of AKI [7]. Proximal tubular cells under hypoxia-induced damage can produce proinflammatory and profibrotic factors that result in infiltration of inflammatory cells into the injured kidney [8]. In the recent years, some anti-inflammatory therapies, such as lymphocyte or macrophage depletion, have been used against inflammatory targets for prevention and treatment of AKI [9]. Exogenous mesenchymal stem cells (MSCs) have been considered as one of the new effective strategies for AKI recently. Although the mechanisms responsible for their

protective and regenerative effects are incompletely understood, anti-inflammatory/immunoregulatory properties of MSCs are recognized as one of the important mechanisms. The present brief review hopes to focus on the role of exogenous MSCs to ameliorate kidney injury and accelerate kidney repair in AKI through regulating inflammatory mediators.

## 2. Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, have been the focus of great interest in regenerative medicine for their potential therapeutic applications in AKI. Since nephrons are largely of mesenchymal origin and stromal cells are of crucial importance for signaling leading to the differentiation of both nephrons and collecting ducts, MSCs are undifferentiated adult cells and may be isolated from bone marrow, umbilical cord, adipose tissue, placenta, synovium, and skeletal muscle [10–14]. They are characterized by three main criteria: (a) the ability to

differentiate into osteoblasts, adipocytes, and chondroblasts *in vitro*; (b) the expression of surface markers CD73, CD90, and CD105; lack of expression of haematopoietic markers including CD34 and CD45; (c) plastic adherence in culture [15]. Recent studies suggested that administering exogenous MSCs could ameliorate renal injury and accelerate renal repair in AKI (Table 1). Exogenous MSCs appeared to make renoprotective effects by several mechanisms, including (a) engraftment and differentiation of MSCs into the host tissue or organ; (b) therapeutic fusion into one with existing host cells; (c) stimulation of endogenous repair by regenerating local resident SCs; and (d) release of paracrine and/or endocrine signals from MSCs. In the last decade, almost all the studies showed that the therapeutic effects of MSCs are mainly mediated through paracrine rather than differentiative mechanism. They have identified over forty growth factors, cytokines and chemokines secreted from MSCs, such as hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), interleukin-1 (IL-1), IL-4, IL-5, IL-6, KC, CXCL16, CCL2, CCL3, CX3CL1, and CCL5 [16, 17]. Some of them enhance cell proliferation, reduce cell apoptosis, modulate the inflammation, and are good candidates for therapeutic effects in AKI. Given the importance of inflammation in the pathophysiology of AKI, it is very imperative to discuss these anti-inflammatory/immunoregulatory properties of MSCs and the role they play in renoprotection [5].

### 3. Cytokines and Chemokines

Many cytokines and chemokines are released by leukocytes, renal tubular cells, mesangial cells, endothelial cells, and platelets into the injured tissue [29–33]. They are also important components for both the initiation and extension of inflammation. Exogenous MSCs would protect kidney from AKI by regulating the inflammatory-related cytokines and chemokines. Chemokine receptors may assist MSCs in migrating to sites of inflammation and participating in the regulation of inflammation.

**3.1. Cytokines.** Cisplatin-induced AKI is associated with increases in the cytokines IL-1 $\beta$ , IL-6, and IL-18 and neutrophil infiltration in the kidney [34]. The expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is increased in cisplatin-induced AKI [35]. TNFR2 also participates in cisplatin-induced AKI and may play an important role in TNF- $\alpha$  mediated inflammation in kidney [36]. In the model of ischemic AKI, some proinflammatory cytokines are increased in kidney [37–39]. In response to the stimulation with noxious stimuli, endotoxin, and hypoxia in AKI, administered MSCs would reduce the expression of proinflammatory cytokines and increase the expression of anti-inflammatory factors in kidney. In the model with ischemic AKI, MSCs significantly reduced the expression of proinflammatory cytokines IL-1 $\beta$ , TNF- $\alpha$ , interferon-gamma (IFN- $\gamma$ ), and inducible nitric oxide synthase (iNOS) and highly upregulated the expression of anti-inflammatory cytokines IL-10, basic fibroblast growth factor (bFGF), TGF- $\alpha$ , and Bcl-2 in kidney [18]. In another

study with ischemic AKI, the expression of IL-6 and TNF- $\alpha$  was significantly lower, while the expression of VEGF was significantly higher in kidney after MSCs treatment [40]. When cisplatin-treated mice were injected with MSCs, some cytokines in serum, such as MIP-2, IL-6, and IFN- $\gamma$ , were significantly lowered and renal injury was ameliorated [19]. Several growth factors released from MSCs, such as VEGF, fibroblast growth factor-2 (FGF-2), HGF, and IGF-1, would improve blood flow, promote cell growth, decrease cell apoptosis, and exert a beneficial effect on neovascularization and tissue remodeling [16, 41–44]. Some studies also found that MSC-conditioned medium (MSC-CM) might protect renal cells from apoptosis induced by cisplatin *in vitro* [17, 45].

**3.2. Chemokines.** Chemokines are a family of chemotactic cytokines that were initially identified on the basis of their ability to induce the migration of different cell types [46]. A large number of proinflammatory chemokines, for example, CCL2, CCL5, CXCL8, and CXCL12, are upregulated in kidney after ischemic AKI, and chemokine receptor expressing inflammatory cells are attracted by these chemokines. These results lead to marked neutrophil infiltration in kidney [47, 48]. Some proinflammatory chemokines are controlled at the transcriptional level by nuclear factor- $\kappa$ B (NF- $\kappa$ B) and activating protein-1 (AP-1), which are activated by the phosphorylation of p38 MAPK. And pharmacological inhibition of p38 MAPK might significantly reduce proinflammatory chemokines production, attenuate leukocyte infiltration, and prevent tubular necrosis in a mouse model of ischemic AKI [49].

MSCs express several chemokines and chemokine receptors (Table 2). The chemokine receptors may assist in their migration to the sites of inflammation and participate in the regulation of inflammation. Some chemokine receptor genes, such as CXCR3, CXCR5, CCR1, CCR7, and CX3CR1, were upregulated in human bone marrow-mesenchymal stem cells (hBM-MSCs), while human umbilical cord Wharton's jelly-mesenchymal stem cells (hUCWJ-MSCs) showed higher expression for CCR3 [50]. Short-term exposure of MSCs to low oxygen increased the expression of chemokine receptors CX3CR1 and CXCR4 and enhanced their engraftment *in vivo* [51]. Hypoxic preconditioning mesenchymal stem cells (HP-MSCs) enhanced the expression of CXCR4 and CXCR7, which not only improved MSCs' chemotaxis but also stimulated the secretion of proangiogenic and mitogenic factors [52].

In response to the stimulation with noxious stimuli, endotoxin and hypoxia in AKI, administered MSCs would reduce the expression of proinflammatory chemokines and ameliorate kidney injury. MSCs could decrease the expression of MIP-2, CCL2, and KC in plasma and reduce the toxicity of cisplatin on kidney *in vivo* [19]. MSCs could decrease mRNA levels of CXCL1, CXCL2, CXCL5, CCL2, and CCL3 in kidney in sepsis-associated mice AKI and improve the recovery of tubular function [20]. In ischemic AKI, MSCs could also decrease the expression of CCL2, CCL3, CCL5, and KC in kidney and reduce acute tubular necrosis in injured kidney [21].

TABLE 1: Preclinical studies using mesenchymal stem cells isolated from various sources to treat acute kidney injury. All the results showed that MSCs could ameliorate the kidney injury [18–28] (main mechanism involving inflammatory mediators).

MSC source	Type of AKI model	Route of MSC delivery	Main mechanism	Reference
Rat BM-MSCs	40 min bilateral IRI	Intra-aortic delivery via left carotid artery	↓IL-1 $\beta$ , TNF- $\alpha$ , IFN- $\gamma$ , iNOS in kidney ↑IL-10, bFGF, TGF- $\alpha$ in kidney	[18]
Human BM-MSCs	Cisplatin-induced kidney injury	i.p. injection	↓MIP-2, KC, CCL-2, IFN- $\gamma$ , IL-6 in serum ↑P-Akt in kidney	[19]
Mouse BM-MSCs	Sepsis-associated AKI.	Tail vein	↓IL-17, IL-6, IFN- $\gamma$ , TNF- $\alpha$ CXCL1, CXCL2, CXCL5, CCL2, CCL3 in kidney ↑IL-10 in kidney	[20]
Mouse AD-MSCs	45 min unilateral IRI	Tail vein	↓CCL3, IL-1b, CCL5, CXCL-10, IL-17 in serum; ↓CCL2, CCL3, CCL5, KC in kidney	[21]
Rat fetal membrane MSCs (FM-MSCs)	60 min unilateral IRI	Tail vein	↓infiltration of macrophages and T cells; ↓IL-6 and MCP-1 levels in kidney; ↑IL-10 levels in serum	[22]
Rat BM-MSCs	60 min bilateral IRI	i.v. injection	↓IL-1 $\beta$ , IL-6, TNF- $\alpha$ in kidney ↑IL-4 and IL-10 in kidney	[23]
Human umbilical cord-MSCs	60 min bilateral IRI	Intra-aortic delivery via left carotid artery	↓IL-1 $\beta$ , IL-6, TNF- $\alpha$ in kidney	[24]
Rat BM-MSCs	60 min bilateral IRI	i.v. injection	↓IL-1 $\beta$ in kidney ↑IL-4 in kidney	[25]
Rat BM-MSCs	Gentamicin-induced kidney injury	i.v. injection	↓IL6, INF- $\gamma$ and TNF- $\alpha$ levels in serum ↑IL-10 levels in serum	[26]
Human Wharton's jelly-MSCs	45 min unilateral IRI	Tail vein	↑IL-10, heme oxygenase (HO)-1 and HGF in kidney ↑p-Akt in kidney	[27]
Rat AD-MSCs	60 min bilateral IRI	Intrarenal injection and intravenous injection	↓oxidative stress ↓inflammatory response ↓bcl-2, eNOS in kidney ↑IL-10, TNF- $\alpha$ in kidney	[28]

TABLE 2: Comparative data on chemokines and chemokine receptors expressed in different human MSC populations [50, 53–60].

Human MSCs: tissue sources	Chemokines	Chemokine receptors
Bone marrow-MSCs	CXCL1, CXCL2, CXCL5, CXCL6, CXCL8, CXCL12, CXCL13 CCL2, CCL3, CCL13, CCL17, CCL18	CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6 CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCRL1, CCRL2 CX3CR1
Umbilical cord (Wharton's jelly)-derived MSCs	CXCL1, CXCL2, CXCL5, CXCL6, CXCL8, CXCL12, CXCL13 CCL2, CCL3, CCL13, CCL17, CCL18	CXCR3, CXCR5 CCR1, CCR3, CCR5, CCR6, CCR7, CCRL1, CCRL2 CX3CR1
Adipose tissue-MSCs	CXCL1, CXCL2, CXCL5, CXCL6, CXCL8, CXCL16 CCL2, CCL8,	CXCR2, CXCR4, CXCR5, CXCR6 CCR1, CCR7

#### 4. Adhesion Molecules

Adhesion molecules are required for leukocyte adhesion during inflammation. Leukocyte adhesion to endothelial cells leads to inflammation and extension of cellular injury [61]. Intercellular adhesion molecule-1 (ICAM-1) plays an important role in the pathophysiology of AKI [62]. The administration of a monoclonal ICAM-1 antibody or ICAM-1 deficient mice is protected against renal ischemia [63, 64]. In the model of kidney transplantation, MSCs could reduce the gene expression of proinflammatory cytokines/chemokines and ICAM-1 and ameliorate inflammation induced by prolonged cold ischemia [65]. In another study with ischemic AKI, kallikrein-modified mesenchymal stem cells (TK-MSCs) can provide enhanced protection against AKI by inhibiting apoptosis and inflammation. The expression of proinflammatory mediators CCL-2 and ICAM-1 was significantly reduced in the TK-MSCs group [66].

Selectins and their ligands are other important adhesion molecules that participate in the inflammatory response. P-selectin is expressed as part of the inflammatory stimulus in platelets and endothelial cells; L-selectin is expressed in leukocytes and lymphocytes; and E-selectin is expressed in endothelium. Renal ischemia has been shown to be associated with upregulation of endothelial P-selectin and enhanced adhesion of neutrophils [67].

Although there is no report about the expression of selectins in injured kidney after MSCs' treatment, P-selectin and its counter-ligand were found to be involved in the extravasation of MSCs [68]. Intravenously administered MSCs can roll along the walls of the blood vessels in the ear veins of mice, and this phenomenon was significantly decreased in mice genetically deficient of P-selectin. E-selectin and L-selectin have been reported to be absent or present only in low amounts on MSCs, and their significance in MSC trafficking, compared with P-selectin, may be unimportant.

#### 5. Inflammatory Cells

Inflammatory cells play a central role in the pathogenesis of AKI. Exogenous MSCs showed a beneficial effect on ameliorating kidney injury and accelerating kidney repair. Administered MSCs may decrease the infiltration of neutrophils and macrophages, inhibit the dendritic cells' differentiation and maturation, reduce the lymphocytes activities, and decline the cytotoxic activity of NK cells in injured kidney.

**5.1. Neutrophils.** Neutrophil recruitment is an important early step in controlling tissue infections or injury. Neutrophil chemoattractants CXCL1/CXCL2 produced by mast cells and macrophages initiate an early stage of neutrophil recruitment during tissue inflammation [69]. MSCs can decrease a panel of inflammatory cytokines and reduce the inflammatory infiltration of macrophages and neutrophils in kidney when following kidney injury [70]. The improvement of inflammatory responses in animal models was at least partially explained by the NF $\kappa$ B-dependent secretion of soluble tumour necrosis factor receptor-1 (sTNFR1) by MSCs. In a mouse model of

sepsis-associated AKI, MSCs would alleviate kidney injury and attenuate neutrophils' infiltration in kidney [20]. In another mouse model with cisplatin-induced AKI, infusion of MSCs ameliorated both renal function and tubular cell injury and prolonged survival. Transplanted MSCs might localize in peritubular areas and limit capillary alterations and neutrophils' infiltration [71]. Human MSCs, pretreatment with an antioxidant, might improve the efficacy of MSCs' transplantation [72]. Administration of these pretreated MSCs could decrease inflammation and fibrosis and reduce neutrophils' infiltration in injured tissue.

**5.2. Lymphocytes.** The role of lymphocytes in AKI is an ongoing area of study. Lymphocytes have been shown to be important modulators of innate and adaptive inflammatory responses in AKI models [73].

MSCs can regulate T cells function and make their therapeutic effects in AKI [74]. MSCs can inhibit T cells activities. They can inhibit the effector T cells both *in vitro* and *in vivo* [75, 76]. MSCs could also suppress AKI-induced T cells infiltrating in ischemic kidney. When cultured with T cells, MSCs either from the same donor or from different donor can induce a G0/G1 checkpoint arrest in T cells [77, 78]. The mechanisms by which MSCs are able to mediate immunosuppression of T cells are diverse and complex; several secreted effectors have been linked to this process. Among them, indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), TGF- $\beta$ , and HGF have been described to play major roles [79–81]. MSCs can also display potent immunosuppressive effects on lymphocyte responses. These effects included the prevention of lymphocyte activation as well as the suppression of T cells proliferation. These effects were mediated through the expression of COX1/COX2 enzymes and by the production of PGE2 [82]. Moreover, MSCs can stimulate the production of regulatory T cells (Tregs), leading to self-regulation of the immune response. Through interaction with splenocyte, MSCs may induce more Tregs and attenuate ischemic AKI. Coculture of splenocytes with MSCs could increase the number of Tregs *in vitro* [74]. Tregs are commonly identified by their expression of CD4 and CD25 on the cell surface and upregulation of the transcription factor FoxP3. MSCs could expand CD4+CD25<sup>high</sup>Foxp3+ regulatory T cells via HLA-G5 secretion in peripheral blood lymphocytes [83].

MSCs also have an important immunosuppressive action on suppression of B cells proliferation. Mice deficient in B cells are protected against ischemic AKI [84]. In a murine model of systemic lupus erythematosus, MSCs could inhibit the activation of B cells with IFN- $\gamma$  [85]. MSCs could also suppress the activation of B cells via inhibiting the production of B cell-activating factor (BAFF) [86].

**5.3. Natural Killer Cells.** Natural killer (NK) cells are a type of lymphocytes that mediates innate immunity against pathogens and inflammation via their ability to secrete cytokines [87]. NK cells are important participants in the early-stage innate immune responses in ischemia AKI. A recent study



demonstrated that NK cells could directly kill tubular epithelial cells. NK cells induced apoptosis in tubular epithelial cells and contributed to renal ischemia-reperfusion injury (IRI). NK cells depletion in wild-type mice was protective against AKI, while adoptive transfer of NK cells worsened kidney injury in NK cell, T cell, and B cell-null Rag2 (-/-) gamma(c)(-/-) mice with IRI [88]. MSCs could inhibit NK cells proliferation and cytotoxic activity. The inhibition was mediated by a soluble factor generated upon incubation with NK cells activated by IL-15 or IL-2 [89]. MSCs can inhibit NK cells function. Through human leukocyte antigen-G5 (HLA-G5), MSCs can affect innate immunity by inhibiting both NK cell-mediated cytotoxicity and IFN- $\gamma$  secretion [90]. MSCs can hamper the NK cells-mediated immune response by preventing their acquisition of lymphoblast characteristics, activation, and changing the expression profile of proteins with an important role in immune function [91]. Moreover, MSCs may inhibit the cytolytic functions of NK cells and have negative effects on the NK-mediated graft-versus-leukemia (GVL) [92].

**5.4. Macrophages.** Macrophages are important effector cells in both the adaptive and the innate immune response. They can mediate inflammation in the interstitium of the outer medulla, which has been described early in the course of ischemic AKI. Although the precise mechanisms of macrophage-mediated renal injury have yet to be determined, it is evident that macrophages can produce many molecules to cause renal damage. Some proinflammatory factors, for example, TNF- $\alpha$ , IL-1, TGF- $\beta$ 1, and PDGF secreted by macrophages, are thought to play important roles in the pathogenesis of the disease [93]. Apart from tissue destruction, macrophages can also play roles in tissue homeostasis, cellular replacement, and tissue repair [94]. Macrophages can phagocytose and remove apoptotic cells, deposited immune complexes, and fibrin. In addition, macrophages can secrete HGF and VEGF, which can promote the repair of damaged tubules and endothelium.

Some researchers reported that AKI induced kidney inflammation and fibrosis involving M1 and M2 macrophages, respectively [95, 96]. M1 macrophages predominate in the early stage of AKI and produce multiple cytokines and chemokines to recruit the immune cells and activate the innate host defense. M2 macrophages include M2a, M2b, and M2c subtypes. M2 macrophages predominate in the late stage of AKI. They are alternatively activated according to the defined stimulation and promote angiogenesis and mediate wound healing, extracellular matrix (ECM) deposition, and tissue remodeling. With ongoing injury, sustained macrophage infiltration may result in the continuous production of various wound-healing growth factors and ultimately lead to irreversible fibrosis, tissue destruction, and progressive chronic kidney disease [97]. In the recent years, some researchers proposed an alternative view to classify macrophage phenotypes as proinflammatory, anti-inflammatory, profibrotic, and fibrolytic macrophages according to their different microenvironments and functional characteristics [98]. As the injury and repair process

shifts from the initial inflammatory phase to that of remodeling phase, macrophages subsequently exhibit varying polarization states and exert a diverse range of functional activities.

Several studies have demonstrated that MSCs could inhibit the expression of macrophage in the initial period of AKI. In a mouse model with cisplatin-induced AKI, infusion of mesenchymal-like progenitors (MPs) derived from human embryonic stem cells (hESCs) reduced renal macrophage infiltration through regulating MCP-1 and promoted the recovery from AKI via paracrine mechanism [99]. In a rat model of ischemic AKI, intravenous administration of allogenic fetal membrane-derived mesenchymal stem cells (FM-MSCs) could significantly suppress macrophage infiltration and renal tubular apoptosis [22]. Recent studies have also demonstrated that, in ischemic AKI, anti-inflammatory macrophages were markedly increased in kidney in the late period when human umbilical cord-derived stromal cells (hUCSCs) were injected intravenously [100, 101].

**5.5. Dendritic Cells.** Dendritic cells (DCs) have a dual role and can induce tolerance or immunity. In the steady state, immature DCs (iDCs) situated in the renal interstitial microenvironment are affected by autophagy of proteins from dying cells, cell-to-cell contact, danger-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), humoral mediators, or filtered antigens [102]. Without tissue damage or local inflammation, these iDCs express low amounts of costimulatory molecules. During an infection or in the presence of maturation-inducing inflammatory signals, mature DCs will induce the development of effector T-cell responses. DCs may play an important role on the production of cytokines and chemokines that drive neutrophils' infiltration in ischemic AKI.

MSCs are able to alter the cytokine production of DCs, resulting in a more tolerant and/or anti-inflammatory phenotype. MSCs have also been known to interact with DCs, making them become regulatory DCs [103–105]. In the mouse model of ischemic AKI, MSCs are partially mediated via DCs to induce the immune tolerance and play an important role in alleviating kidney injury [102]. MSCs, treated with 14S, 21R-dihydroxy-docosahexaenoic acid, could enhance the efficiency in improving the renal function, reducing renal tubular cell death, and inhibiting infiltration of neutrophils, macrophages, and DCs in ischemic AKI [106]. *In vitro*, MSCs mediated a potent inhibition on DC differentiation, and the inhibition was restricted to the early stages of cytokine-induced progression from monocytes to iDCs. The inhibition affected both the expression of informative DC surface markers and the acquisition of DC functions, such as IL-12 production. The inhibitory effect is primarily mediated by PGE2 [107, 108].

## 6. Microvesicles Derived from MSCs in AKI

It has been suggested that MSCs can alleviate AKI by providing a paracrine support rather than replacing renal tubular cells to the repair. Further support for the paracrine action of MSCs is provided by the experiments showing that

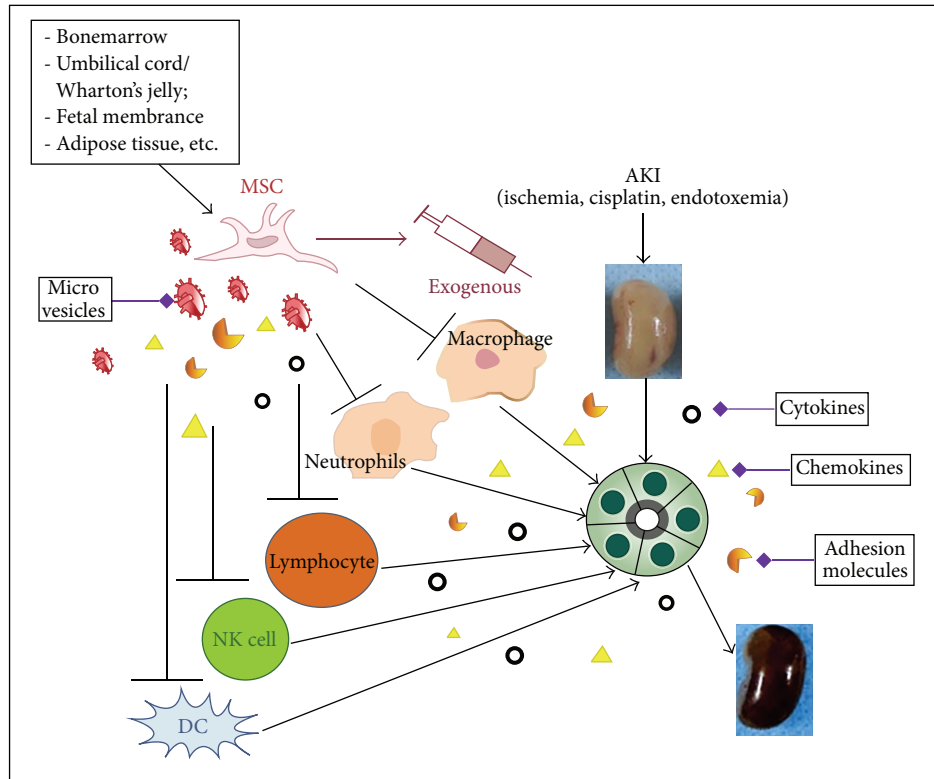


FIGURE 1: Exogenous MSCs likely involve paracrine effects in regulating the inflammatory mediators to ameliorate AKI. They exert protective and reparative effects in the treatment of AKI by regulating inflammatory mediators like cytokines, chemokines, neutrophils, lymphocytes, NK cells, DCs, and macrophages. MSCs ultimately improve the kidney's structure and function.

MSC-CM can mimic the beneficial effects as the cells of origin [16, 44, 45]. Microvesicles (MVs) from MSCs, as one of the components in the cell-to-cell communication network, are involved in tissue regeneration and therefore contribute to the paracrine action of MSCs [109, 110]. MVs are vesicles composed by exosomes, shedding vesicles, and apoptotic bodies. Exosomes range from 30 to 120 nm in size, and their release depends on cytoskeleton activation, while vesicles generated by direct budding of the plasma membrane, also known as shedding vesicles, are more heterogeneous in size and ranging from 100 nm to 1  $\mu$ m in size [111]. In our study, MVs derived from hUCWJ-MSCs were positive for some surface expressed molecules, such as CD9, CD44, CD63, and CD73, and negative for CD34 and CD45 [112]. MVs may influence the behavior of the target cells in several ways: (a) directly stimulate the cells by a surface interaction [113]; (b) transfer receptors from the cell of origin to the target cell [114]; (c) deliver proteins to target cells [115]; (d) mediate a horizontal transfer of mRNA and microRNA inducing epigenetic changes in the target cell [116–118]. Therefore, understanding the modulation of MVs' therapeutic effect upon AKI may provide insight into the molecular mechanisms. For example, MVs expressing ICAM1 at their surface can interact with the lymphocyte function-associated antigen 1 (LFA1) to activate T cells [119]. MVs expressing the delta-like 4 (Dll4) may activate angiogenesis and axon growth by interacting with Notch receptors expressed by endothelial or

nerve cells, respectively [120]. MVs derived from MSCs may activate a proliferative programme in tubular epithelial cells that survived injury both *in vitro* and in a glycerol-induced model of AKI in severe combined immunodeficiency (SCID) mice [121]. Several other studies also reported that MSCs-MVs might favor the kidney repair in nonlethal toxic and ischemic AKI. They were found to exert a prosurvival and antiapoptotic effect on renal tubular cells *in vitro* and *in vivo* [122–124].

## 7. Summary

Inflammation is now believed to play a major role in the pathophysiology of AKI. Inflammatory mediators are produced to regulate the inflammation in injured kidney. If tubular epithelial and endothelial injury exceeds over the regenerative potential, injured kidney might progress to interstitial fibrosis and even chronic kidney disease. Therefore, controlling kidney inflammation and promoting epithelial/endothelial repair are probably the best ways to target AKI and to maintain renal function. The role of MSCs in cell-based therapies for AKI is under intensive investigation. Preclinical studies indicate that administered MSCs can both ameliorate renal injury and accelerate renal repair. The mechanisms responsible for their protective and regenerative effects are incompletely understood. However, a

concept is now clearer that exogenous MSCs likely involve paracrine effects in regulating the inflammatory mediators to ameliorate kidney injury (Figure 1). Some researchers also found that MVs derived from MSCs can alleviate AKI. By regulating inflammatory mediators like cytokines, chemokines, neutrophils, lymphocytes, NK cells, DCs, and macrophages, MSCs could reduce the kidney inflammation, restore the healthy epithelium and endothelium, and ultimately improve the kidney structure and function.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Acknowledgments

This study is supported by Grants from the Research Program of Science and Technology Commission of Shanghai Municipality (10411967200) and the National Natural Science Foundation of China (81170642) and the fund of Shanghai First People's Hospital (12RC04).

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