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Mesenchymal Stromal Cell Uses for Acute Kidney Injury-Current Available Data and Future Perspectives: A Mini Review

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Abstract

There is growing evidence about the potential use of mesenchymal stromal cells (MSCs) for different tissue injuries. Initially, the intended physiological use of MSCs was due to their ability to differentiate and replace damaged cells. However, MSCs have been found to have multiple effects, including being able to significantly modulate immunological responses. MSCs are currently being tested for neurodegenerative diseases, graft versus host disease, kidney injury and other chronic unremitting tissue damage. Using MSCs in acute tissue damage is only now being studied. Acute kidney injury (AKI) is a common cause of morbidity and mortality. After the primary insult, overactivation of the immune system culminates in additional secondary potentially long-standing kidney damage. MSCs have the potential to ameliorate the secondary damage and recent studies have shed important light on their mechanisms of action. This article summarizes the basics of MSCs therapy, the newly discovered mechanisms of action and their potential application in the setting of AKI.

Keywords: Acute renal failure; AKI; Mesenchymal stem cells; MSC; Immune response

Introduction

Acute Kidney Injury (AKI) is a syndrome of rapid deterioration of renal functions over a period of hours or days [1]. AKI is a common cause of morbidity and mortality, complicating 20% of hospitalized patients, half of them needing renal replacement therapy [2]. This severe form of AKI is related to a 50% increase in mortality among other devastating long-term consequences, including end stage renal disease (ESRD) and dialysis dependence[2,3].

The etiologies of AKI are varied, with pre-renal AKI and acute tubular necrosis being the most common [4,5]. AKI's mechanism is often related to ischemia and reperfusion injury (IRI) [6]. In the last decade, cumulative evidence has shown the significant role that over activated immune responses play in the development of AKI [7]. This understanding paved the way to new therapeutic strategies for this relatively common and life-threatening acute kidney condition. Unfortunately, despite the progress in our understanding of AKI biology, treatment options for AKI in the daily clinical setting are still limited [1,3,4]. While dialysis can be relatively effective in handling the hazardous electrolytes and volume complications as a supportive therapy, there is need for a treatment that can eliminate the pathological cascade that may culminate in irreversible loss of renal tissue [1,4].

The Immune Response to Acute Kidney Injury

The immune system plays a crucial role in the mechanisms of AKI with both the innate and adaptive branches of the immune system involved [8]. Regarding the innate immune system, cytokines serve as major mediators while both increased production of cytokines and reduced clearance are reported during AKI [9] Interleukins (IL)-6, IL-8 and tumor necrosis factor (TNF)-α are usually elevated and are related to endothelial dysfunction and tubular injuy [10]. Conversely, IL-10 has an ameliorating effect by promoting immune tolerance [11].

The complement system, a part of the innate immune system, also has an important role in the pathogenesis of renal injury, and is involved in glomerular, tubulointerstitial and vascular kidney injuries [12]. The final common pathway of the complement system is the membrane attack complex that induces direct cellular damage, and causes activation and migration of neutrophils which further amplify the injury [13]. Suppressing the complement system in AKI has shown promising results in pre-clinical studies [14].

The cellular response to AKI includes both pro-inflammatory and anti-inflammatory characteristics. Dendritic cells, monocytes/macrophages, neutrophils, T lymphocytes, and B lymphocytes are all involved in AKI, and can be detected even as early as one hour after the acute insult [15]. The involvement of these cells can directly and indirectly induce apoptosis of the renal tubular cells [15]. In contrast, M2 macrophages and regulatory T cells are essential for suppression of the overactivated inflammatory response and for the regeneration of damage renal tissue and are detected while recovering from the acute insult [8].

The relation between the different arms of the immune system can either escalate or downgrade the final injury [10,13]. To veer the cells and factors towards a less devasting rout, new treatments are being investigated including the use of stem-cell therapy.

Mesenchymal Stromal Cells

Mesenchymal stromal cells (MSCs) are fibroblast-like multipotent cells that can differentiate into mesodermal-line cells including adipocytes, chondroblasts, osteoblasts and renal tubular cells [16,17].

These cells exhibit self-renewal properties, with a potential to replace damaged cells [18].

MSCs are defined by three main characteristics:

Plastic-adherent when maintained in standard culture conditions;

Expression of CD105, CD73 and CD90, with no expression of other CDs that are not mesenchyme related (including CD45, CD34, CD14 or CD11b, CD79-α or CD19 and HLA-DR) surface molecules.

The ability to differentiate into a mature mesoderm related cell-line *in vitro*.19 Unlike embryonic stem cells, MSCs can be found in many organs even in adults [17,19,20].

In the past two decades, MSCs from different origins are being used in different clinical trial settings [21]. For example, bone-marrow derived MSCs are used in children to treat graft-versus-host disease autologous marrow MSCs for heart disease [20] and both bone-marrow and adipose-derived MSCs are used in Crohn's-related enterocutaneous fistular disease [22]. In the neurodegenerative field, MSCs are being studied in amyotrophic lateral sclerosis, multiple system atrophy, Parkinson's disease, Alzheimer's disease and multiple sclerosis. While animal studies have been promising, clinical studies have demonstrated conflicting results [23,24]. The encouraging results obtained in the field of degenerative diseases can be related, among others, to the effect that MSCs have on the immune factors in these diseases setting [23,24].

The Biology of Mesenchymal Stromal Cells

MSCs can affect and be affected by other cells through different immune mediators. Cytokines, chemokines, and transcription factors can influence the differentiation of MSCs. Expression in MSCs of specific transcription factors, including Runx2, Sox9, PPARγ, MyoD, GATA4, and GATA6, may promote their differentiation into specific cell lineage [17].

The primary rational for using MSCs to rejuvenate damaged tissue was initially related to their ability to differentiate into the damaged tissue related cells. Following ischemic-reperfusion injury (IRI), MSCs migrate to the injured site and alleviate the damage [18]. Intriguingly, studies have demonstrated that MSCs have beneficial effects even at very early stages after their migration, before any differentiation and proliferation can be expected [25]. This observation has led to the understanding that early beneficial effects are related to their paracrine activity of the surrounding tissue [26,27].

Recent studies have demonstrated that MSCs can induce both local and remote anti-inflammatory effects [28]. The immunomodulatory effect of MSCs is broad and covers much of the innate and adaptive immune systems [16]. For example, MSCs can secrete factors such as insulin-like growth factor 1, vascular endothelial growth factor, angiopoietin 1, keratinocyte growth factor, and macrophage inflammatory protein 1α. These broad signaling factors are capable of promoting cell proliferation, angiogenesis, and wound healing [27].

MSCs can present both pro-inflammatory and anti-inflammatory profiles. These different phenotypes are related to their ability to sense the environment and respond to changes in the tissue. The effect is induced by activation of different macrophage populations.16 Macrophages are divided to two main groups, M1 and M2 macrophages. M1 macrophages are considered pro-inflammatory cells and secrete pro-inflammatory cytokines including IL-1, IL-6, TNF-α, and interferon-γ. M2 macrophages are anti-inflammatory cells that secret anti-inflammatory cytokines such as IL-10 and transforming growth factor (TGF)-β1 [16,29,30]. Thus, MSCs can induce differentiation of monocytes to one of the macrophage phenotype groups according to the inflammatory status of the damaged tissue [16].

MSCs can also affect T-cell activation and differentiation toward T-regulatory cells that have anti-inflammatory properties [31]. In addition to the paracrine effect on the immune system, MSCs can transfer mitochondria into the damaged cells, enabling better energy utilization, and restoration of the adenosine triphosphate (ATP) supply, thus promoting cellular recuperation [31]. MSCs might also assist in preserving tubular mitochondria thus preserving the functionality of these cells [32]. Since oxygen metabolism and energy utilization are improved, MSCs reduce the oxidative stress and induce anti-oxidant activity [33].

To conclude, MSCs can promote tissue regeneration even before differentiating into the damaged cell line of the injured tissue. This influence is related to their early multifaceted paracrine effects.

Treatment with Mesenchymal Stromal Cells in Acute Kidney Injury

In the setting of AKI, MSCs promote protective effects on the injured kidney and ameliorate tissue damage [31,33]. The beneficial effects of MSCs are noticeable early after their injection and can be attributed the following paracrine related mechanisms (Table 1 and Figure 1) [34-49].

Part of the immune system	Mechanism	Reference
Complement system	Amelioration of Complement system activation	Zilberman-Itskovich, et al. [25] Tang et al. [50]
Cytokines	Down regulation of pro-inflammatory cytokines: IL-1β, IL-6, IL-17, TNF-α, INF-γ, TGF-β	Tögel et al. [51], Zilberman-Itskovich, et al. [25]. Semedo et al. [52], Semedo, et al. [53] Cao, et al. [54], Furuichi, et al. [55] Sun, et al. [56]
	Upregulation of anti-inflammatory cytokines: IL-10, IL-4, bFGF, TGF-α, and Bcl-2	Tögel, et al. [51]. Zilberman-Itskovich, et al. [25]. Semedo, et al. [52], Luo, et al. [57], Tsuda et al. [58], Sun, et al. [56]
Macrophages	Proliferation and migration of M2 macrophages population	Zilberman-Itskovich, et al. [25], Geng, et al.[59], Sun, et al.[56].
	Inhibition of macrophages infiltration	Tsuda, et al. [58]

T-cells	Inhibition of T-cell infiltration	Tsuda, et al. [58], Sun, et al. [56].
	Differentiation to T-cell regulatory cells	Kilpinen, et al. [60], Semedo, et al.[53], Hu, et al.[61], Sun, et al.[56]
Neutrophils	Inhibition of neutrophils infiltration	Sun, et al. [56], Tian, et al. [62]
Abbreviation: IL: Interleukin; TNF: Tumor Necrosis Factor; INF: Interferon; TGF: Transforming Growth Factor; bFGF: basic Fibroblast Growth Factor; Bcl: B-cell lymphoma; MSC: Mesenchymal Stromal Cell		

Table 1: Immunomodulatory mechanisms of mesenchymal stromal cells in the setting of acute kidney injury.

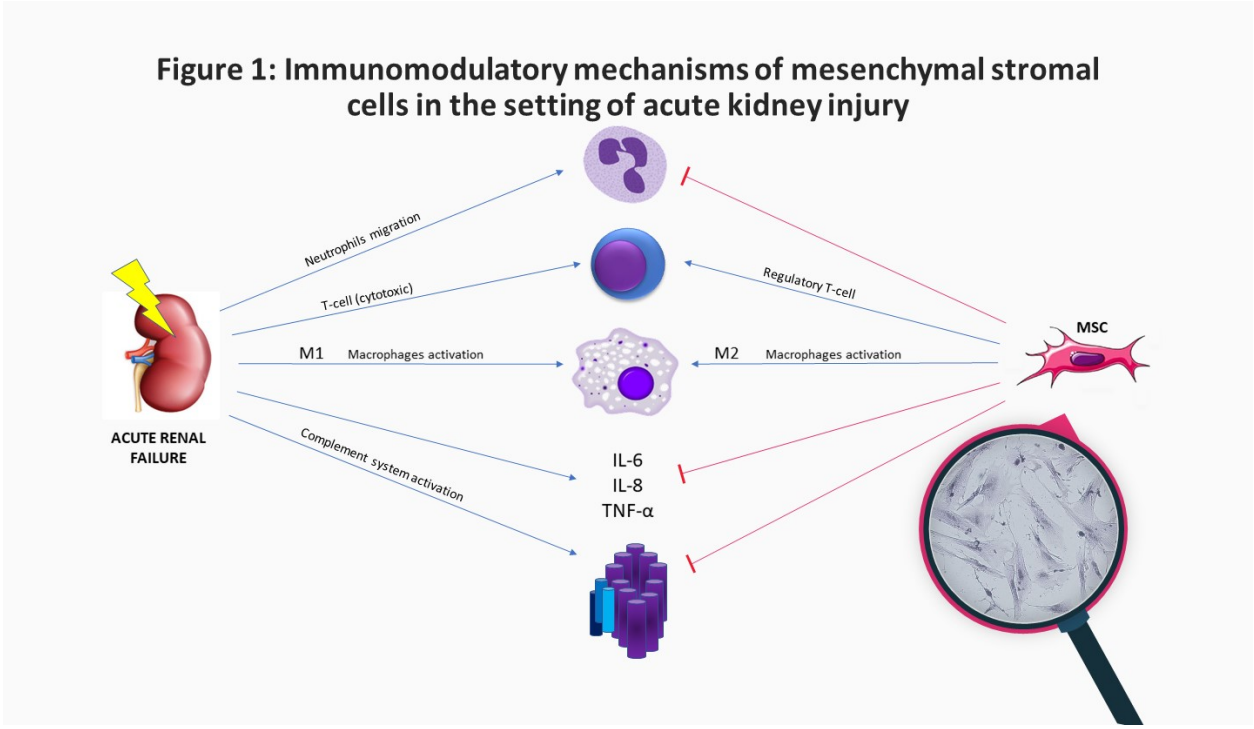

Figure 1: Immunomodulatory mechanisms of mesenchymal stromal cells in the setting of acute kidney injury.

Illustration of the immune mechanisms of acute kidney injury and the immunomodulatory effect of mesenchymal stromal cells. Acute kidney injury is accompanied by increase in inflammatory cytokines, complement activation and immune cell activation. Mesenchymal stromal cells inhibit cytokines release, complement system activation, and neutrophils migration, while promoting M2-anti-inflammatory macrophages and regulatory T-cells proliferation; in magnifying glass: microscopic picture of mesenchymal stromal cells- placenta origin; MSC= mesenchymal stromal cell; IL= Interleukin; TNF= tumor necrosis factor.

In magnifying glass: microscopic picture of mesenchymal stromal cells-placenta origin.

An increase of the M2 macrophage CD68/CD163 population. As discussed, these M2 macrophages have anti-inflammatory and pro-regenerative phenotypes [25,29].

A shift from the pro-inflammatory cytokines TNF-α, and IL-1β to the anti-inflammatory cytokine IL-10 with a favorable expression of homing adhesion molecules ICAM-1 and VCAM-1[34]

An inhibitory effect of the complement system's overactivation and the related cellular damage generated by the membrane attack complex [25].

Exosomes-One of the most exciting discoveries in intercellular communication is exosomes. Exosomes are membrane bound extracellular vesicles that can be produced by most eukaryotic cells. Their size is about 30 to 120 nanometers (nm) in diameter (around the size of lipoproteins) and they contain various molecular constituents of their cell of origin, including proteins, mRNA and miRNA or double-stranded DNA [35,36]. Recent studies have demonstrated that administration of exosomes derived from MSCs can ameliorate the expected renal damage in the setting of AKI [35]

Epigenetic effects a shift in gene expression. Xie et al. demonstrated that overexpression of the Klotho gene, which regulates apoptosis, can reinforce the protective effect of MSCs in the setting of AKI [37] Chen et al. demonstrated that the protective effect of MSCs in the setting of AKI can be related to TNF-inducible gene 6 protein expression. This protein, in addition to its anti-inflammatory effect, can promote renal tubular epithelial cell proliferation [38].

While there is growing body knowledge in pre-clinical studies, the available clinical data on MSCs in AKI is still scarce. A recent study using MSCs in post-cardiac surgery patients did not show beneficial effects regarding post-surgery AKI [39]. This unfortunate result can be attributed to time of MSCs administration. The optimal results are obtained if the administration of MSCs is closest to the initiation of IRI [34]. The detection of AKI, based on commonly used blood markers in humans (serum creatinine and urea) is usually late, after AKI and tubular necrosis is well established [6] In this scenario, while the damage is already well established, the potential immunological benefits of MSCs are probably negligible. In addition, the MSCs themselves can be injured by an overactivated complement system [40]

In addition to AKI, there is growing evidence of MSCs benefits in the setting of chronic kidney disease (CKD). Even though the clinical studies done so far included relatively a small number of patients, the evidence looks promising with regards to the ability of MSCs to prevent the expected kidney function deterioration over time [41-43]. In patients suffering from chronic diabetic nephropathy, allogeneic transplantation of MSCs demonstrated improvement of renal functions compared to placebo [43]. The effect might be attributed to the paracrine secretion of the vascular endothelial growth factor and insulin growth factor-1 by MSCs [42].

One of the relevant clinical settings where MSCs have the potential to have beneficial effects is in post-renal transplantation patients. In the immediate post-transplantation period, IRI is one of the main reasons for AKI [44]. Thanks to the above discussed immunomodulating effects of MSCs, there are promising results in pre-clinical trials, and clinical studies are currently ongoing [45].

Current Available Safety Data on MSCs

Several safety concerns are related to the use of MSCs in the clinical setting. The first concern is related to the administration technique. When the cells are administered intravenously (IV), most of the cells can be found within the lungs [25,46]. If the lung capillaries are blocked with these cells, ventilation and respiratory difficulties are expected. Therefore, higher dosage with high concentration of MSCs should be avoided. The second concern is related to exposing the immune system to foreign cells, when administering cells from a donor. Luckily, MSCs do not stimulate a profound immune response, since they only express the human leucocyte antigen (HLA)-DR but lack other HLA typings [26]. In a CKD trial, none of the patients developed persistent donor specific anti-HLA antibodies [43].

In particular, fetal MSCs have very low immunogenicity by nature, and those can be used to overcome this potential barrier [33].The last concern is related to the proliferation and differentiation of pluripotent cells injected to a living body, with the potential of transforming into malignant cells. This concern is probably irrelevant, since stromal cells need a special environment and signaling factors to act as stem cells and differentiate, and usually do not survive after administration [17,46]. In any case, to address this scenario, more research with long-term follow-up is needed.

Even though clinical trials with long-term follow-up are still lacking, some preclinical trials have addressed the safety issues. Till now, no serious adverse effects were reported in either preclinical [47,48] and clinical studies [18,39,43,49].

Conclusion

The ongoing cumulative data on the beneficial physiological effects of MSCs open new treatment opportunities for diseases that are currently being managed with only supportively therapy. While other types of stem cells, such as hematopoietic stem cells, are used in the clinical practice, the clinical data on MSCs is still scarce. In the setting of AKI, MSCs by way of their paracrine effects may modulate the hazardous results of an overactivated inflammatory response. MSCs hold the hope for future novel therapies, and a better understanding of the immune-biological effects of these cells will enable development of new treatment strategies.

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Author Declaration

All authors are in agreement with the content of the manuscript. Each author's contributed to the paper significantly.

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