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Rationale of Mesenchymal Stem Cell Therapy in Kidney Injury

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Numerous preclinical and clinical studies suggest that mesenchymal stem cells, also known as multipotent mesenchymal stromal cells (MSCs), may improve pathologic conditions involving different organs. These beneficial effects initially were ascribed to the differentiation of MSCs into organ parenchymal cells. However, at least in the kidney, this is a very rare event and the kidney-protective effects of MSCs have been attributed mainly to paracrine mechanisms. MSCs release a number of trophic, anti-inflammatory, and immune-modulatory factors that may limit kidney injury and favor recovery. In this article, we provide an overview of the biologic activities of MSCs that may be relevant for the treatment of kidney injury in the context of a case vignette concerning a patient at high immunologic risk who underwent a second kidney transplantation followed by the development of ischemia-reperfusion injury and acute allograft rejection. We discuss the possible beneficial effect of MSC treatment in the light of preclinical and clinical data supporting the regenerative and immunomodulatory potential of MSCs.

Background

Tissue damage with loss of parenchymal cells is a common final outcome of different pathologic conditions. The process of repair tends to counteract the loss of parenchymal cells and replace dead cells. However, in the kidney, this process frequently is hampered by evolution to fibrosis and long-term loss of function.1 Therapeutic strategies to optimize the repair therefore should inhibit the mechanisms involved in cellular loss and stimulate the proliferation of parenchymal cells.1 In the context of kidney transplantation, several immunologic and nonimmunologic factors contribute to the loss of transplant function.2 and 3 Among these factors, delayed graft function (DGF)4 and 5 due to ischemia-reperfusion injury, T-cell–mediated rejection,6 and 7 and antibody-mediated rejection8, 9 and 10 are recognized to significantly affect long-term allograft survival.

Bone marrow–derived stem cells have been proposed as an appealing therapeutic approach to avoid or at least limit allograft injury.11 In particular, mesenchymal stem cells, cautiously renamed multipotent mesenchymal stromal cells (MSCs) by the International Society for Cellular Therapy,12 have garnered great interest for their regenerative and immunomodulatory properties, mainly due to the release of paracrine factors.13

Case Vignette

A 46-year-old man with dialysis-treated end-stage renal disease (1986-1988, peritoneal dialysis; 1988-1989, hemodialysis) secondary to vesicoureteral reflux received a first kidney transplant from a deceased donor in 1989 (Box 1). T-Cell–mediated rejection was followed by the development of chronic transplant glomerulopathy, severe interstitial fibrosis, and vascular damage, and the patient experienced a progressive deterioration in kidney function and fluid overload. In 2007, he returned to hemodialysis therapy. In July 2011, he underwent a second kidney transplantation in the presence of a heightened immunologic profile with different subsets of anti-HLA antibodies (anti–HLA-A1, A2, A3, A9, A10, A11, A28, A36, A80; anti–HLA-B13, B27, B37, B40, B44, B47, B57; and anti–HLA-DR3-DR13) and panel-reactive antibody level of 97%. He received immunosuppressive therapy with basiliximab, 20 mg, at days 0 and 4; tacrolimus, 0.2 mg/kg, daily; mycophenolate mofetil, 1 g, twice daily; and steroids. In the first days after transplantation, a clinical picture of DGF characterized by oliguria and increase in serum creatinine level was observed, and dialysis was performed on days 1, 2, 3, and 5. Kidney biopsy showed tubular necrosis due to ischemic

damage. In the following days, urine output increased and serum creatinine level decreased. However, at day 12 posttransplantation, urine output again decreased and serum creatinine level increased. For this reason, he underwent a second biopsy showing the presence of T-cell–mediated rejection in association with congestion of tubulointerstitial and glomerular capillaries and mild positivity for C4d staining. He was treated with thymoglobulin (100 mg daily for a total of 1.1 g), withdrawal of mycophenolate mofetil therapy, and decreasing blood levels of tacrolimus. Kidney function improved and the patient was discharged 36 days after transplantation (serum creatinine, 2.4 mg/dL, corresponding to estimated glomerular filtration rate of 36 mL/min/1.73 m2 determined by the 4-variable Modification of Diet in Renal [MDRD] Study equation) on treatment with tacrolimus, mycophenolate mofetil, and steroids.

Box 1.

Clinical Course of the Patient Described in the Case Vignette

1986 – ESRD due to vesicoureteral reflux: start of peritoneal dialysis

1988 – Switch to hemodialysis

1989 – First kidney transplantation

1989 – T-cell–mediated rejection

1990 – Development of chronic transplant glomerulopathy

2004 – Progressive deterioration of kidney function

2007 – Fluid overload and return to hemodialysis (eGFR = 9 mL/min/1.73 m^2)

2011

July

– Second transplantation (anti-HLA antibody serum titer, 97%); immunosuppressive therapy: basiliximab, tacrolimus, mycophenolate mofetil, and steroids

– Delayed graft function: need for dialysis at days 1, 2, 3, and 5 after transplantation; kidney biopsy with tubular necrosis due to ischemic damage

– Serum creatinine increases to 7.54 mg/dL, corresponding to eGFR decrease to 6 mL/min/1.73 m^2

Aug

– Second kidney biopsy: T-cell–mediated rejection, mildly positive C4d staining; start thymoglobulin

– Discharge 36 days after transplantation with serum creatinine of 2.4 mg/dL (eGFR, 36 mL/min/1.73 m^2); treated with tacrolimus, mycophenolate mofetil, and steroids

2012

Jan

– Stable kidney function (serum creatinine, 2.3 mg/dL; eGFR, 39 mL/min/1.73 m^2).

Note: Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease.

Pathogenesis

DGF, a form of acute kidney injury (AKI), usually is defined as the need for dialysis in the first week after transplantation.4, 5 and 14 The incidence of DGF ranges from 2%-50% in kidney transplants from deceased donors, with the variation associated with the transplantation center. In

contrast, DGF has a lower incidence in living donor transplants, likely due to less ischemia-reperfusion injury (5%-15%).15 Although many factors may be responsible for DGF (urinary obstructions, artery/vein thrombosis, early acute rejection, drug nephrotoxicity, viral infections, volume depletion, etc), ischemia-reperfusion injury is known to contribute to the delay of cellular regeneration and functional recovery of grafted kidneys.4 and 5 The increase in cold ischemia time is considered the major determinant of DGF.5, 15 and 16 In addition, DGF may increase allograft immunogenicity, with a consequent increased risk of acute rejection and early occurrence of chronic allograft nephropathy.5 and 17 Several studies reported an association between DGF and decreased transplant survival.4 Others found a correlation of DGF with decreased transplant survival only when associated with acute rejection.4 and 18 These considerations are strengthened by changing clinical scenarios in kidney transplantation over recent years.17 Elderly patients increasingly are being considered for kidney transplantation.19 On this basis, several transplantation programs using non–heart-beating donors and in particular suboptimal deceased donors have been developed.19 and 20 Unfortunately, kidneys from such donors are exposed to increased ischemic injury and drug nephrotoxicity that deeply influence their regenerative potential and long-term transplant survival.19 and 20

The cellular and molecular mechanisms involved in tissue damage after kidney ischemia-reperfusion injury have been studied extensively.1 and 16 Ischemia can activate a complex sequence of events (release of oxygen free radicals, increased expression of major histocompatibility complex class I and II antigens, endothelial activation with consequent cytokine release, etc)21 that sustain kidney injury and favor DGF.16 and 21 Tubular epithelial cells are the main target of hypoxia within the kidney.1 and 16 Ischemia leads to the loss of tubular cell polarity and cytoskeleton and brush-border integrity, leading to mislocalization of molecules usually expressed at the apical/basolateral membrane or tight junctions.1 and 22 These events are responsible for the functional impairment of tubules that are not able to preserve distinct fluid-filled compartments with precise electrolyte concentrations.22

In the presence of a sustained ischemic injury, tubular cells not only show functional impairment, but also undergo necrosis and apoptosis through activation of the death receptor (tumor necrosis factor/tumor necrosis factor receptor and Fas/Fas-ligand) and the mitochondrial (the apoptosis regulator Bcl-2 family members) pathways.23 In the meantime, transplant metabolism shifts from an aerobic to anaerobic state, with consequent accumulation of lactate and oxygen free radicals that lead to the release of proinflammatory cytokines and activation of innate immunity.21

The final stage of ischemic injury occurs during the reperfusion period, characterized by reoxygenation, production of adenosine triphosphate, and generation of high concentrations of radical oxidants that cause hyperoxidation of cell membranes and synthesis of different types of chemokines.16, 21, 22 and 23 Moreover, different adhesion and antigenic molecules are upregulated on tubular cells, favoring T-lymphocyte adhesion.21 Tubular cells are immunologically active and in the presence of an inflammatory state may express surface adhesion molecules, chemokines, and costimulatory molecules such as CD40, able to directly bind to CD40-ligand present on activated T cells.23 and 24 These events may lead to amplification of the immune response and recruitment and activation of other inflammatory cells able to perpetuate tissue injury.21 and 24 Apart from its effects on tubular cells, ischemic injury also is known to affect the function and survival of endothelial cells within the kidney.24 Microvascular injury is one of the hallmarks of ischemia and is responsible for the extension phase of AKI, which involves enhanced coagulation and adhesion of inflammatory cells.24 Ischemia-reperfusion injury can be worsened by the nephrotoxic effect of immunosuppressive drugs such as calcineurin inhibitors, tacrolimus, and cyclosporine.25 The restoration of kidney function after DGF is related to replacement of necrotic cells with functional tubular epithelium.5, 26 and 27 Surviving tubular cells are able to

dedifferentiate, expressing mesenchymal (vimentin) and embryonic (Pax-2) markers; proliferate; migrate to cover the denudated basal membrane; and finally redifferentiate, restoring polarity and epithelial integrity to the cell.5, 26 and 27 These mechanisms are orchestrated by a series of growth factors able to promote tubular cell proliferation.23, 26 and 27

Triggering of the immune response against the allograft is based on antigen presentation to T lymphocytes by different cell types.28 Cells expressing class II HLA antigen molecules on their surface, including B cells, dendritic cells, and macrophages, may operate as professional antigen-presenting cells able to activate naive or memory T cells.28 and 29 Of interest, the existence of biologically active resident dendritic cells has been demonstrated within the kidney.28 and 29 Kidney dendritic cells may initiate allograft rejection by direct antigen presentation to infiltrating T cells.28 and 29 Moreover, recent investigations have shown a key role for innate immunity in the triggering of the adaptive immune response.28 The presence of an inflammatory microenvironment created by different causes may induce the maturation of kidney dendritic cells, allowing antigen presentation to activated T cells.28 and 29 Moreover, further studies showed that an influx of myeloid and plasmocytoid dendritic cells is a hallmark of allograft rejection that correlates with the development of tubular atrophy and interstitial fibrosis.28, 29 and 30 Tubular epithelial cells may deeply influence the biological behavior of infiltrating T cells because they may express class II HLA antigen and costimulatory molecules such as CD40, B7-H1, and inducible costimulator ligand.30 Furthermore, allorecognition also can occur through indirect T-cell–antigen presentation of HLA antigen molecules by antigen-presenting cells.28, 29 and 30 Regulatory T cells originating from the thymus or from T-cell conversion in the periphery may counteract the effector T cells.31 and 32 Recent studies showed a critical function of CD4+CD25+Foxp3+ regulatory T cells in the mechanisms of induction of transplant tolerance.31 and 32

Recent studies have highlighted the role of humoral rejection in the acute and chronic loss of function of kidney transplants.33 Humoral rejection is mediated by activation of different cell types, including B cells, plasma cells, and plasmoblasts, that may produce different classes of alloantibodies.10 and 33 In particular, immunoglobulin M (IgM) and IgG may activate the classical pathway of the complement system.10 Antibody-mediated rejection is recognized at present as the preeminent mechanism of loss of kidney transplant and is defined as a syndrome characterized by transplant dysfunction, microvascular damage (glomerulitis, capillaritis, and microthrombi formation) in the presence of donor-specific anti-HLA antibodies in the circulation and C4d deposition in peritubular capillaries.34 In antibody-mediated rejection, after antibody activation and triggering of the complement cascade, endothelial cells upregulate the expression of adhesion molecules, induce a procoagulant state, and finally undergo apoptosis, or programmed cell death.34 Recent studies show the involvement of natural killer cells in antibody-mediated rejection through the release of cytotoxic granules.35

Recent Advances

New MSC-Based Therapeutic Perspectives

Could a patient with DGF and acute rejection benefit from treatment with MSCs? Numerous preclinical and clinical studies provide evidence that MSCs ameliorate different organ pathologic conditions by modulating tissue regeneration and immunity. MSCs belong to a rare population of cells of mesenchymal origin first isolated from bone marrow and then from several tissues and organs. Because MSCs do not express specific cell markers, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy has suggested the following minimal criteria to define human MSCs12: adherence to plastic; cell positivity for CD90, CD73, and CD105 and negativity for CD34, CD14, CD45, CD19, CD79a, CD11b, and HLA-DR12; and in vitro osteo-, chondro-, and adipogenic differentiation capabilities. At molecular levels, it has been shown that

MSCs express 113 RNA transcripts and 17 proteins not expressed by the hematopoietic stem cells.36 Also, the microRNA (miRNA) present may provide a cell signature.37

The rationale for the use of MSCs in regenerative medicine is based on the following properties: (1) their ability to migrate to the site of injury; (2) the potential to differentiate in various mesenchymal tissues and, at least in vitro, into different cell lineages; (3) the ability to release factors that influence cell survival and proliferation; and (4) the modulation of immune response and inflammation. Are these properties applicable to kidney injury?

Migration of MSCs to the site of injury within the kidneys has been studied extensively. Using iron dextran–labeled MSCs that can be detected by magnetic resonance imaging, Lange et al38 demonstrated accumulation in the cortex of the injured kidney. Tögel et al39 and 40 showed early localization of MSCs in glomeruli and peritubular capillaries after ischemic AKI by 2-photon microscopy39 and observed by bioluminescence in living animals prompt homing to the injured kidney after intra-arterial administration of MSCs.40

The molecular mechanisms responsible for the recruitment of MSCs are only partially known (Fig 1). Although the chemokine receptor CXCR4 has low basal expression on the MSC surface,41 it has been suggested that its interaction with stromal derived factor (SDF-1) may induce migration of MSCs to the site of injury in the brain.42 Tögel et al43 demonstrated that SDF-1 favors homing of MSCs to the kidney after interaction with CXCR4, which is upregulated after kidney injury. The other SDF-1 receptor that could be involved in MSC migration is CXCR7.44 It has been shown that CXCR4 and CXCR7 act independently to regulate migration.45 In particular, CXCR7 is required to provide directional migration46; however, knockdown of CXCR7 has a minimal effect on MSC migration.44 The interaction between CD44 and hyaluronic acid also may guide MSCs to the site of injury. The relevance of this interaction for regulation of MSC migratory capacity has been shown both in vitro and in vivo.47 We found that pre-incubation of MSCs with an anti-CD44 blocking antibody or soluble hyaluronic acid inhibited in vitro migration of MSCs and that in vivo MSCs from knockout mice failed to home to the damaged kidney.48 The in vitro migration and in vivo homing of CD44 knockout MSCs was recapitulated after transfection with complementary DNA encoding wild-type CD44, but not with complementary DNA encoding a CD44 loss-of-function mutant that was unable to bind hyaluronic acid.48

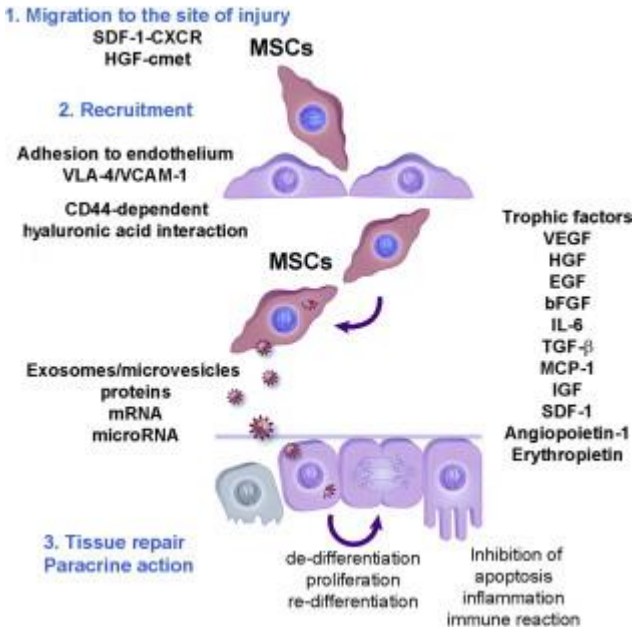

Figure 1.

Schematic representation of multipotent mesenchymal stromal cell (MSC) involvement in tubular repair. Three phases are represented. (1) Migration of MSCs to the site of injury after interaction between stromal derived factor 1 (SDF-1) ligand and CXCR chemokine receptor.[43] (2) Recruitment of MSCs to endothelium following the very late antigen 4 (VLA-4)/vascular cell adhesion molecule 1 (VCAM-1) interaction and the CD44-hyaluronic acid interaction.[48] (3) Paracrine action of MSCs favoring the proliferation of dedifferentiated epithelial cells surviving the injury by the release of exosomes/microvesicles that may reprogram the injured cells by delivering messenger RNAs (mRNAs) and microRNAs that induce the dedifferentiation.[73] The paracrine action also involves the production by MSCs of trophic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), hepatocyte growth factor (HGF), transforming growth factor β (TGF-β), epidermal growth factor (EGF), insulin-like growth factor (IGF), SDF-1, angiopoietin 1, macrophage inflammatory protein, keratinocyte growth factor, and erythropoietin.[13, 49 and 59] The cell cycle re-entry of the tissue-injured cells favors tissue repair.

After being localized in the kidney, do MSCs contribute to tissue repair by a direct substitution of dead cells or a mechanism of protection? This point has been debated extensively. In vitro, MSCs have the potential, after appropriate stimulation, to transdifferentiate into different cell lines, including epithelial and endothelial cells. It is not clear if this also may occur in vivo.

After kidney injury, it has been shown that bone marrow–derived stem cells and kidney resident stem cells may participate in kidney repair. However, it is widely accepted that the beneficial effect of bone marrow–derived stem cells in AKI is due to the generation of an environment that favors the proliferation of dedifferentiated epithelial cells surviving the injury rather than to direct transdifferentiation of stem cells into mature tissues.49

Preclinical studies have consistently shown that administration of ex vivo–expanded MSCs accelerates recovery in AKI induced by a toxic agent48, 50, 51 and 52 or ischemia-reperfusion38, 39 and 53 and induces functional improvement in chronic kidney disease.54 Although some tubular engraftment of MSCs was described in AKI induced by cisplatin50 and 51 and glycerol48 and 52 after systemic injection, this was not observed in the ischemia-reperfusion injury model of AKI.53 Moreover, at least in the model of glycerol-induced AKI, after early localization of exogenous MSCs to peritubular capillaries and glomeruli,48 most of them disappeared from the kidney after a few days.55 Similarly, no evidence of permanent MSC engraftment in the kidney was obtained in ischemia-reperfusion AKI.53 Thus, MSCs in the kidney function not by replacing kidney tubular cells, but by ameliorating injury by giving paracrine support to the repair process (Fig 1). This was confirmed in living animals by bioluminescence imaging, in which kidney localization of MSCs decreased after 24 hours.40

By means of genetic fate-mapping techniques, it has been shown that kidney repair after ischemic tubular injury depends on proliferation of tubular epithelial cells.56 Tubular regeneration has been ascribed to a mechanism defined as “epithelial-mesenchymal-epithelial cycling.”57 The concept of a paracrine/endocrine action of MSCs in kidney tissue repair has been strengthened by the study of Bi et al58 that showed that the conditioned medium of MSCs mimics the beneficial effects of the cells of origin. In addition, MSC homing does not seem to be an absolute requirement for therapy with MSCs because intraperitoneal administration of an MSC-conditioned medium to mice in which AKI has been induced by cisplatin is enough to reduce tubular cell apoptosis, increase tubular cell survival, and diminish kidney injury.58 These data suggest that the renoprotective effect of MSCs arises from the factors they secrete. MSCs are able to produce a number of trophic factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF-2), interleukin 6 (IL-6), monocyte chemoattractant protein 1, hepatocyte growth factor, transforming growth factor β, epidermal growth factor, insulin-like growth factor (IGF-1), SDF-1, angiopoietin 1,

keratinocyte growth factor, and erythropoietin.59 In particular, it has been shown that the effects of MSCs on tubular repair partially depend on the production of IGF-1.60 Tögel et al61 also reported that VEGF has a key role in the recovery of ischemia-reperfusion AKI because VEGF gene knockdown by short interfering RNA reduces the effectiveness of MSC infusion. Furthermore, other studies have indicated a possible role of MSCs in the mechanisms of angiogenesis and vascular remodeling through upregulation of prosurvival and proangiogenic factors such as VEGF-a, angiopoietins, IGF-1, and hepatocyte growth factor.59 This may be relevant in the setting of kidney regeneration after ischemia-reperfusion injury because the damage of peritubular endothelial cells has been involved in an "extension phase" of ischemic AKI that is characterized by sustained tissue hypoxia and an inflammatory and procoagulant state triggered by endothelial cell injury.62

MSCs have been shown to inhibit inflammatory and immune response through modulation of cytokine production, restraint of T-cell proliferation and dendritic cell maturation, modulation of B-cell function, and suppression of natural killer cell proliferation and cytotoxicity. The immune-modulatory action of MSCs is still a matter of extensive studies, but it is evident that both direct interactions of MSCs with dendritic or antigen-presenting cells and release of soluble factors are involved63, 64, 65, 66, 67 and 68 (Fig 2). Based on these properties, MSCs have been investigated as a new therapy for several immune-mediated diseases, such as graft-versus-host disease,69 and 70 Crohn disease,71 and rejection in organ transplantation.72

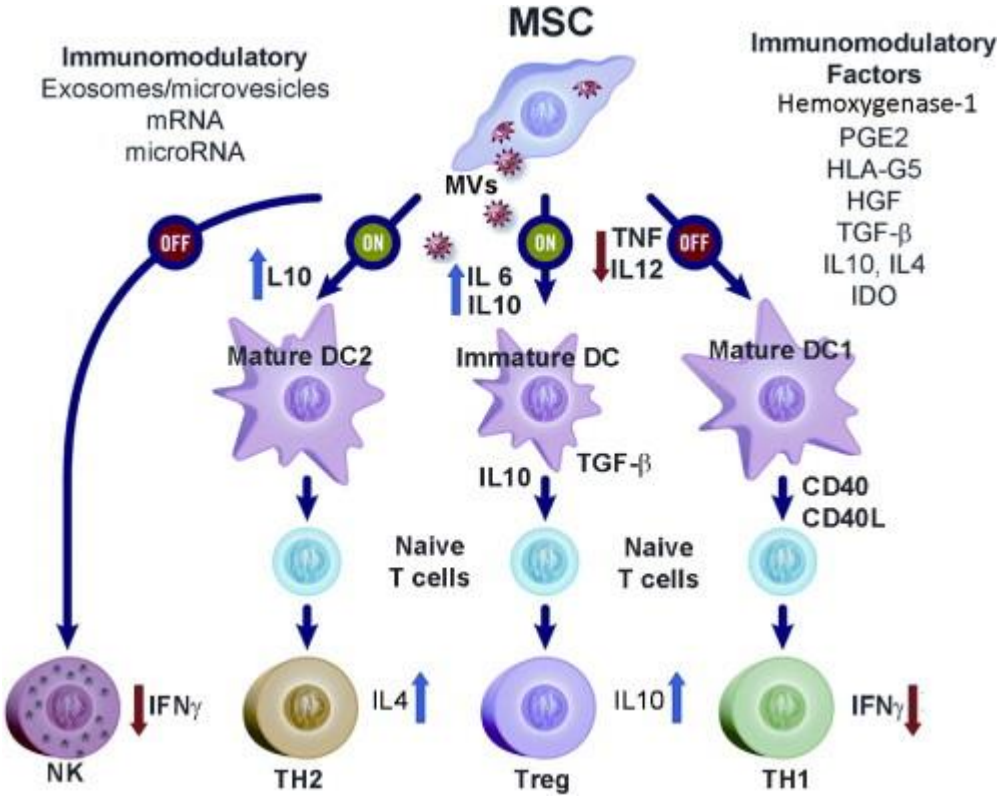

Figure 2.

Schematic representation of the multipotent mesenchymal stromal cell (MSC) modulatory action of immune response. MSCs inhibit immune response through modulation of cytokine production, suppression of T-cell proliferation and dendritic cell (DC) maturation, modulation of B-cell function, and suppression of natural killer cell (NK) proliferation and cytotoxicity.63, 64, 65, 66, 67 and 68 MSCs, through inhibition of cyclin D2, maintain T cells in the G0-G1 phase of the cell cycle. In addition, MSCs modify the cytokine expression profile of DCs, naive and effector T cells, and NKs and increase the number of regulatory T cells (Tregs). The immunomodulatory effects of MSCs are sustained by the production of several factors, such as hemoxygenase 1, prostaglandin E_2 (PGE2), human leukocyte antigen (HLA-G5), hepatocyte growth factor (HGF), transforming growth factor β (TGF-β), interleukin 10 (IL-10), IL-4, and indoleamine 2,3

deoxygenase (IDO). MSCs inhibit the upregulation of antigen presentation/costimulatory molecule expression, the ability to present defined antigens, and the capacity to migrate in response to chemokine CCL19 of DCs, at least in part due to MSC IL-6 secretion, which induces a less mature DC phenotype. TGF-β and PGE2 together with the cell contact also have a role in the expansion of Tregs from $CD4^+CD25^-$ precursors.[68] Moreover, human MSCs are able to secrete the soluble major histocompatibility complex (MHC) isoform of human HLA-G5 by a mechanism dependent on IL-10 and cell-to-cell contact. HLA-G may sustain Treg survival and its suppressor phenotype over time by favoring the expression of $CD4^+CD25^{high}FOXP3^+$ Treg cells. IDO, TGF-β, and PGE2 mediate MSC inhibition of NK functions.[68]

Recent studies also suggest that extracellular vesicles may participate in the paracrine/endocrine network involved in the MSC biologic action. Extracellular vesicles released by MSCs after receptor-ligand interaction are internalized in target cells, transferring proteins, bioactive lipids, and surface receptors.73 Extracellular vesicles released by MSCs also contain selected patterns of messenger RNA (mRNA) and miRNA74 and 75 and may be instrumental in the exchange of genetic information between cells.76, 77 and 78 We demonstrated a horizontal transfer of mRNA through extracellular vesicles released from endothelial progenitors, with consequent activation of an angiogenic program in quiescent endothelial cells.78 Extracellular vesicles derived from human MSCs mimic the beneficial effects of cells because they favor the recovery of AKI in severe combined immunodeficiency mice by inhibiting apoptosis and promoting kidney tubular epithelial cell proliferation74 and 79 (Fig 1). Administration of extracellular vesicles not only abated the acute injury, but also prevented the development of chronic kidney disease.79 The mechanism was ascribed to the transfer of specific MSC-derived miRNA and mRNA.74 and 75 The cargo of mRNAs and miRNAs shuttled by stem cell–derived microvesicles potentially may trigger the regeneration of injured tissues and modulation of the activities of different cells of the immune system, finally allowing transplant tolerance.

Clinical Trials and Potential Risks of MSC Therapy

MSCs have been used safely in several phase 1 and 2 clinical trials aimed to treat a broad range of inflammatory and degenerative diseases (Table 1). In the transplantation setting, a model of cotransplanting MSCs with purified human pancreatic islets has been developed with the aim to protect islets from inflammatory and immune-mediated damage and improve transplant vascularization.80

Table 1.

Nephrology-Related Trials of MSCs

Trial/Registration No.	Cell Type	Primary End Point	Design	Site
Induction therapy recipient of living kidney allograft;NCT00658073	Autologous MSCs	Safety and efficacy	Randomized, open-label, active control	Fuzhou General Hospital, China
Subclinical rejection;NCT00734396	Autologous MSCs	Safety and feasibility	Nonrandomized, open-label, uncontrolled	Leiden University Medical Center, the Netherlands
MSC under basiliximab; low-dose RATG; NCT00752479	Autologous MSCs	Safety and efficacy to induce kidney transplant tolerance	Randomized, open-label, active control	Mario Negri Institute, Italy
Chronic allograft nephropathy;NCT00659620	Autologous and allogeneic MSCs	Safety and efficacy	Treatment, open-label, historical control	Fuzhou General Hospital, China
Refractory systemic lupus erythematosus; NCT00698191	Allogeneic MSCs	Safety and efficacy	Treatment, nonrandomized, open-label	Nanjing Medical University, China
Cisplatin-induced AKI in patients with solid-organ cancers; NCT01275612	Allogeneic MSCs	Safety and efficacy	Treatment, open-label	Mario Negri Institute, Italy

Note: Listed are phase 1/2 trials available in ClinicalTrials.gov.

Abbreviations: AKI, acute kidney injury; MSC, multipotent mesenchymal stromal cell; RATG, rabbit antithymocyte globulin induction.

Perico et al81 recently reported a pilot study of safety and clinical feasibility of autologous MSC infusion in kidney transplantation. In this study, 2 recipients of kidneys from living related donors under rabbit antithymocyte globulin induction received MSCs on day 7 posttransplantation, demonstrating the feasibility of this approach, enlargement of regulatory T cells in the peripheral blood, and control of memory CD8+ T-cell function. However, in both patients, MSC infusion after kidney transplantation induced transplant dysfunction possibly related to intragraft recruitment of granulocytes, raising concerns about its safety. More recently, results of a large randomized prospective study of autologous MSC induction in living related kidney transplants were presented.82 Patients were inoculated with marrow-derived autologous MSCs at kidney reperfusion and 2 weeks later. MSC induction with standard or low-maintenance immunosuppression was compared with standard anti–IL-2 receptor antibody induction. By enrolling 159 patients divided into 3 arms of 53 patients each, this study is characterized by unprecedented statistical power in the field of stem cell research in solid-organ transplantation. Results showed that MSC induction compared with anti-IL-2 receptor antibody induction led to a lower incidence of acute rejection, reduced risk of opportunistic infection, and improved kidney function at 1 year. In addition, kidney function recovered faster in both MSC groups, with increased estimated glomerular filtration rates during the first month after surgery compared with the control group, suggesting a positive impact on ischemia-reperfusion injury. This study may represent a milestone in the field, but long-term monitoring is needed to provide more data about the efficacy and safety of this approach. However, this study seems to override at least the concern of compromising kidney function after infusion raised by the study of Perico et al.81 The dissimilarity can be explained by differences in MSC preparations, such as MSC growth in the absence of platelet lysates that may contain proinflammatory factors, use of cell preparations without freeze preservation, the timing of infusion, and induction without rabbit antithymocyte globulin.

MSCs may interfere with the pathogenetic mechanisms involved in DGF, T-cell recognition, antibody-mediated rejection, and chronic allograft nephropathy. First, MSCs may stimulate proliferation of injured tubular cells after ischemia-reperfusion injury by directing a correct regeneration, thus inhibiting the development and progression of chronic allograft nephropathy. Second, MSCs can affect solid-organ allograft survival by interfering with several cell types of the immune system, such as T and B cells, dendritic cells, and natural killer cells. In the field of kidney diseases, MSCs also sparked great interest in the prevention of AKI and progression toward the final stages of chronic kidney disease. In a phase 1 clinical trial, the prevention and treatment of AKI with infusion of allogeneic MSCs have been evaluated.83 The trial involved adult patients who underwent coronary artery bypass graft and/or major cardiac valve surgery; these patients then were infused through the suprarenal aorta with allogeneic MSCs. In analyzing outcomes in this group of patients, the investigators determined that postoperative suprarenal administration of allogeneic MSCs is feasible and safe. Moreover, efficacy data appeared promising, showing that MSC therapy prevented postoperative deterioration in kidney function and decreased durations of intensive care unit stay and hospitalization.

The ongoing clinical trials in the field of MSC-based therapies in AKI and solid-organ transplantation will be the platform for newly evolving pluripotent stem cell therapeutics in the near future. However, some notes of caution must be taken into account.84 The heterogeneity of the MSC population may generate some difficulties in the evaluation of their potency in different studies. Some potential complications may arise from MSC administration into the bloodstream, such as pulmonary emboli or infarctions. The possibility of tumorigenesis or maldifferentiation also should be considered. Myocardial calcifications85 and enhanced accumulation of fibroblasts and myofibroblasts in the lung have been reported86 in preclinical studies. In the experimental model of

mesangioproliferative anti-Thy1.1 glomerulonephritis, after an early beneficial effect, MSCs were shown in the long term to maldifferentiate in adipocytes, favoring the development of chronic kidney disease.87 However, in humans to date, no significant detrimental effects have been reported and MSC-based therapies raise significantly fewer concerns than embryonic stem cells or genetically modified cells. Additional studies are necessary to define the contexts in which MSCs could be beneficial in kidney disease and transplantation.

Summary

MSCs represent the new frontier for cell-based therapies of different inflammatory and degenerative diseases, and several phase 1 and 2 clinical trials currently are underway. The rationale for the use of MSCs is based on their ability to migrate to the sites of injury, differentiate into multiple cell types, and release trophic mediators and factors that modulate the immune and inflammatory response. In the field of kidney diseases, preclinical studies have suggested a beneficial effect of MSCs in various models of AKI and chronic kidney injury. Clinical trials with MSCs in AKI after cardiac surgery and kidney transplantation have been started. The mechanisms involved in regeneration are related mainly to the release of factors including extracellular vesicles from MSCs that promote tubular cell proliferation and survival.

The patient described in the case vignette experienced DGF due to ischemia-reperfusion injury and acute kidney transplant rejection. In light of preclinical and clinical studies, one might predict a beneficial effect of MSCs to prevent DGF or accelerate recovery from DGF. In addition, the anti-inflammatory and immunomodulatory properties of MSCs may interfere with the pathogenic mechanisms involved in kidney allograft rejection. In conclusion, MSCs may find potential therapeutic application in different pathologic conditions occurring in kidney transplant recipients.

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