

## Full Review

# Mesenchymal stem cells and kidney repair

Marina Morigi  
and Ariela Benigni

Correspondence and offprint requests to: Ariela Benigni;  
E-mail: ariela.benigni@marionegri.it

Mario Negri Institute for Pharmacological Research, Centro Anna  
Maria Astori, Science and Technology Park Kilometro Rosso,  
Bergamo, Italy

Keywords: acute renal failure, kidney, mesenchymal, stem cell

### ABSTRACT

Acute renal failure (ARF; acute kidney injury—according to the more recent classification) is emerging as a public health problem. Despite major advances in supportive therapy, the mortality and morbidity among patients remain dismally high. In the attempt to yield innovative interventions fostering the limited capability of regeneration of the kidney, several studies have tested stem cell-based technology mainly employing mesenchymal stem cells (MSC) of different origins. The results of this approach provide the exciting prospect of a powerful treatment to repair acutely damaged organs by virtue of the unique MSC tropism for the damaged tissue, as well as their paracrine action. In the present review, we discuss the mechanisms underlying the regenerative processes triggered by MSC therapy in preclinical models of ARF by analysing modalities of cell-to-cell communication through the release of soluble factors and microvesicles/exosomes by MSC into the damaged renal tissue. Key receptors involved in MSC homing, engraftment and survival at the sites of injury are also elucidated. A translation of basic discoveries of MSC biology into effective care is still limited to the preliminary data of a phase I clinical trial, and further studies are needed to definitively assess the efficacy of MSC-based therapy in humans.

### THE PERIL OF EARLY STEM CELL THERAPY

More than 12 years ago, ‘Science’ dedicated its breakthrough issue to the discovery of stem cell potential to cure diseases of multiple organs. So far, apart from haematopoietic stem cell (HSC) transplantation for the treatment of haematological disorders and some dermal and corneal indications, essentially all other approaches based on stem cells remained

experimental medical research. On the other hand, the desperation of patients who find no hope for the cure of their diseases allows the proliferation of institutions that perform unproven, probably ineffective, stem cell-based therapies. Sponsored websites promise a cure for diseases for which no effective treatments exist emphasizing the benefit of stem cells while playing down the potential risks of the procedure. The presumption of efficacy of stem cell-based therapy flaunted by different media leads to administering interventions outside of controlled clinical trials that threaten patients and undermine confidence in medical research [1]. The pressure of finding new therapeutic indications for stem cells together with the attraction on their regenerative potential has stimulated early practice in patients with cardiac injury and left ventricular dysfunction, which remain the major causes of morbidity and mortality worldwide [2]. Although the perspective of regeneration of cardiac tissue provided an initial challenge for cell-based therapies [3], subsequent studies in animals have questioned the ability of stem cells to effectively generate cardiomyocytes [4, 5]. More generally, the enthusiasm of the early trials in patients with heart failure was tempered somewhat by the modest size of the outcome [6]. Failure of clinical studies might derive from the lack of robust data in animal models that would have helped address a number of key issues including the underlying mechanism of protection. Before jumping into clinical practice, many questions remain unanswered regarding the best cell type, the source of cells, the route of delivery, the timing of the intervention and the number of cells needed. Despite the fact that human biology is only partially predictable from animal models, pre-clinical studies remain a key element in the scientific development of novel therapies such as stem cell treatment. The story of stem cells as a mean to cure acute kidney injury (AKI) started in the last decade from studies in experimental animals mainly carried out with mesenchymal

stem cells (MSC). The aim of the present review is to describe the key findings of protection from AKI achieved by stem cell therapy, the mechanism underlying the beneficial effect and the possible translation in therapeutic approaches for acute renal failure (ARF). The review will focus on ARF rather than AKI since cell therapy at present does apply to the former but not to minor abnormalities of the kidney encompassed by the high spectrum of renal injuries.

### WHY THE CHOICE OF MSC?

MSC represent an important component of the haematopoietic niche in the bone marrow (BM), where they contribute to regulating self-renewal, maturation and recruitment of HSCs to the vascular compartment, via cell-to-cell interaction and local release of specific cytokines, chemokines and growth factors [7, 8]. MSC comprise approximately 0.01% of BM cells and are operationally defined as plastic adherent. They represent a heterogeneous population of multipotent stem cells that can differentiate into mesodermal lineages such as adipocytes, chondrocytes and osteocytes, however, the evidence that they can transdifferentiate into tissue-specific cell types of ectodermal and endodermal lineages, both *in vitro* and *in vivo*, is still controversial. MSC, originally identified in the BM [9], were also found in other tissues including peripheral blood, connective tissue, adipose tissue, skeletal muscle, umbilical cord wall/blood and amniotic fluid [10, 11]. Recent studies indicated the presence of perivascular cells co-expressing the markers of both pericytes and MSC in multiple organs [12] including the kidney [13], suggesting their functional role in the regulation of vascular stability. Despite established functional differences among tissues of origin, there is general consensus that cultured human MSC express variable levels of CD105, CD73, CD44, CD90, CD271, CD166, Stro-1 and lack expression of haematopoietic markers, including CD14, CD11b and CD45 [7, 8]. MSC possess a powerful immunomodulatory activity highlighting the potential for clinical translation in solid organ transplantation [14]. Indeed, they strongly inhibit T-cell proliferation by cell-to-cell interaction, release of soluble factors in *in vitro* and *in vivo* settings and exert similar inhibitory effect on B cells, dendritic cells, natural killer cells and on cells of innate immunity [14].

### MSC CONTRIBUTE TO THE REPAIR OF AKI

Pioneering pre-clinical studies have described a role of BM-derived stem cells in renal physiological cell turnover and regeneration of several compartments of the kidney including tubular cells, podocytes [15], mesangial cells [16] and endothelial cells of the glomerular capillary [17]. Based on the biological properties of MSC in the BM niche, their regenerative ability and tropism for damaged tissues in a wide array of disorders [7, 18], the therapeutic use of MSC has been investigated in animal models of ARF in which the quest for effective treatments has been largely unsuccessful.

Our group was the first to document that an infusion of murine BM-MSC at the concentration of  $2 \times 10^5$  cells/mouse in mice with ARF induced by the nephrotoxic anti-cancer drug cisplatin protected animals from renal function impairment and tubular injury [19, 20]. The temporary low engraftment of BM-MSC to the site of injury in the proximity of peritubular areas and not within tubular epithelium reasonably ruled out that BM-MSC repair renal injury via transdifferentiation into renal cells. Finding that in mice with ARF, BM-MSC engrafted the kidney and markedly increased the number of resident tubular cells positive for Ki-67 indicates renal cell proliferation as a key step of kidney repair locally triggered by stem cells [19, 20]. In the clinical perspective, MSC obtained from human BM aspirates were tested in immunodeficient nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice with cisplatin-induced ARF [21]. Pilot experiments indicated the dose of  $5 \times 10^5$  human BM-MSC per mouse as the most effective quantity of cells that could be injected without adverse effects. Human BM-MSC reached the injured renal tissue, although in a limited number, where they preserved renal function and tubular integrity, leading to a prolongation of animal survival in respect to mice given saline (Table 1). Treatment with human BM-MSC promoted the proliferation and counteracted apoptosis of proximal tubular cells besides preserving microvascular integrity and contributing to ameliorating renal tissue oxygenation [21].

In search of new and more accessible sources of MSC for renal repair, cells derived from human adipose tissue (hAD) as an alternative to BM were investigated. The infusion of hAD-MSC isolated from two donors into NOD/SCID mice with ARF failed to improve renal function, evaluated as blood urea nitrogen at 4 days (hAD-MSC1,  $121 \pm 19$  and hAD-MSC2,  $125 \pm 17$  versus saline,  $100 \pm 17$  mg/dL). In parallel, hAD-MSC-treated mice showed tubular alterations consisting of casts [hAD-MSC1,  $4.8 \pm 3.6$  and hAD-MSC2,  $11.2 \pm 2$  versus saline,  $4.4 \pm 3.8$  number of casts/high power field (HPF)], nuclear fragmentation and necrosis (hAD-MSC1,  $8.1 \pm 3$  and hAD-MSC2,  $17.2 \pm 1.7$  versus saline,  $8 \pm 4$  number of necrotic tubuli/HPF) comparable with those observed in mice given saline.

Next, the efficacy of stem cells derived by human fetal tissues [22], including umbilical cord blood (hCB) and amniotic fluid (hAF), was evaluated. Human CB-MSC share morphological characteristics, immunophenotype and multipotency with MSC of BM origin [23, 24]; however, gene expression profile revealed higher expression of genes involved in matrix remodelling via metalloproteinases and in angiogenesis in hCB-MSC [23]. Systemic infusion of hCB-MSC ( $5 \times 10^5$  cells/animal) into NOD/SCID mice with ARF-protected animals from renal function impairment and tubular injury; however, the effects of hCB-MSC on animal survival were considerably stronger than that observed with human bone marrow (hBM) MSC (Table 1) [24]. Human AFS cells represent a type of stem cells described to possess high plasticity and expansion potential that share characteristics of both embryonic and adult stem cells [25]. Indeed, these cells immunisolated for c-Kit express embryonic

**Table 1. Comparative effect of stem cells of different origin in experimental ARF**

Treatment	Blood urea nitrogen (mg/dL)	Renal histology <sup>a</sup>	Survival <sup>b</sup>	Refs.
Saline	>140	Damaged	0	[21, 24, 26]
Bone marrow-MSc	63 ± 5	Preserved	50	[21]
Cord blood-MSc	58 ± 7	Preserved	86	[24]
Amniotic fluid-SC cKit+	81 ± 3	Preserved	56	[26]

<sup>a</sup>On day 4 from cisplatin injection.  
<sup>b</sup>On day 7 from cisplatin injection.

markers such as OCT4 and SSEA4 and several MSC markers including CD90, CD105, CD73 and CD44 [26]. Cisplatin NOD/SCID mice infused with hAFS cells exhibited improvement in renal function and decreased tubular damage. The effect on animal survival observed with human AFS cells was comparable with that of hBM-MSc (Table 1). These findings suggest that hCB-MSc and to a lesser extent hBM-MSc and hAFS cells, hold potential for successful application in human ARF.

#### PARACRINE MECHANISMS OF MSC THERAPY IN ARF

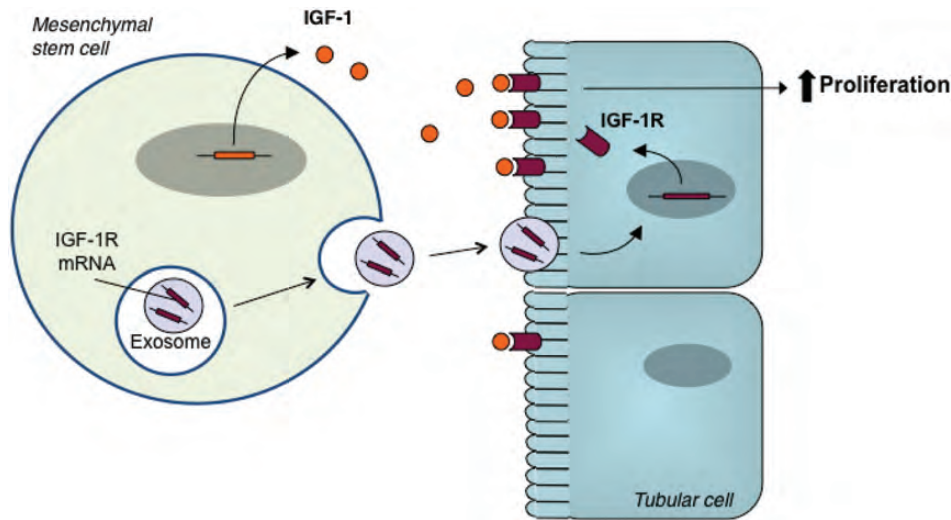
Complementary studies to those on survival have tried to better highlight the mechanisms possibly involved in regenerative processes evoked by MSC therapies in the injured kidney. In ischaemia-reperfusion (IR) injury, rat BM-MSc, which transiently engrafted the damaged renal tissue, exerted a beneficial effect on renal function and tubular damage via the production of anti-apoptotic, pro-mitogenic and vasculotropic factors [27, 28]. In these experiments, animals that received BM-MSc had decreased expression in the kidney of interleukin 1  $\beta$ , tumor necrosis factor  $\alpha$  and interferon  $\gamma$  coupled with the upregulation of anti-inflammatory cytokines and growth factors as IL10, basic fibroblast growth factor (bFGF) transforming growth factor  $\alpha$  and the anti-apoptotic Bcl-2 [27]. The concept that MSC exert renoprotection via a local paracrine action is supported by data that repeated injections of BM-MSc-conditioned medium in mice with cisplatin-induced ARF limited renal injury, apoptosis and increased animal survival [29]. That soluble factors are responsible for the renoprotective effect of MSC also rests on *in vitro* data showing that BM-MSc co-cultured, but physically separated, with cisplatin-damaged proximal tubular cells, elicited mitogenic and anti-apoptotic effects on tubular cells [20]. Among growth factors, insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) have been described to be responsible for the renal regenerative processes by BM-MSc in animals with ARF as documented by gene-silencing experiments [20, 30]. Knocking down IGF-1 expression in murine BM-MSc by siRNA before infusion limited cell-protective effects on renal function and tubular damage in mice with cisplatin-induced ARF [20]. Similarly, VEGF silencing reduced the effectiveness

of rat BM-MSc on renal functional recovery and survival in IR injury model [30].

Finding relatively few MSC engrafting the injured tissue in the face of robust functional recovery has raised the interest to investigate additional mechanisms that could act in concert with the release of soluble factors to explain MSC's renoprotective effect. MSC-derived microvesicles (MVs) and exosomes (Exo) have been indicated as a new mechanism of cell-to-cell communication that allows the transfer of functional proteins or genetic material via mRNAs and microRNAs upon cell activation [31, 32]. MVs released from the surface of activated cells are relatively large (100 nm to 1  $\mu$ m diameter) in respect to Exo, smaller membrane fragments (30–90 nm diameter), which originate from the endosomal compartment after fusion of secretory granules with the plasma membrane [31, 32]. A recent study compared the effect of a low number of human BM-MSc ( $7.5 \times 10^4$  MSC/mouse) with that of MVs generated by this very dose of BM-MSc (accounting for 15  $\mu$ g proteins) in mice with glycerol-induced ARF [33]. Systemic injection of either MVs or cells promoted a comparable regenerative programme in damaged renal tissue [33]. This study characterized the transcripts present in MVs and demonstrated the shuttling *in vitro* and *in vivo* of two mRNAs encoding proteins involved in proliferation. Furthermore, another report unravelled a new mechanism underlying the beneficial effect of BM-MSc-derived Exo on proximal tubular cells exposed to cisplatin. In these experiments,  $1 \times 10^6$  human BM-MSc released a smaller amount of Exo (0.5–2  $\mu$ g proteins) in respect to that previously described [33]. The repair of cisplatin-damaged proximal tubular cells resulted from a combined trophic effect of IGF-1 released by BM-MSc and the transfer of mRNA of the corresponding IGF-1 receptor via Exo, which potentiates tubular cell sensitivity to the growth factor [34] (Figure 1). The possibility to use MVs derived from MSC as strategy to enhance survival in ARF and to protect against IR injury has been proposed [35].

#### STRATEGIES TO ENHANCE MSC HOMING, SURVIVAL AND EFFICACY

Despite the fact that a large body of evidence substantiates the efficacy of MSC therapy in ameliorating the outcome of



**FIGURE 1:** Horizontal transfer of mRNA for IGF-1 receptor (R) via MSC-derived Exo and expression of the corresponding protein in damaged proximal tubular cells potentiate renal cell sensitivity to locally produced IGF-1.

ARF in different experimental models induced by cisplatin [19, 21], glycerol [33, 36] and IR injury [27, 37], one may wonder whether migration and the low survival of MSC in the damaged tissues might possibly hamper the potential benefit of cell transplantation. The process of MSC engraftment at the site of injury is regulated by numerous chemotactic receptors [38, 39]. In the kidney following acute damage, the expression of stromal cell-derived factor (SDF)-1 is up-regulated within the kidney and the axis SDF-1/CXCR4 has been proposed to play a pivotal role in MSC engraftment [40, 41]. CD44 represents another important candidate expressed by MSC that regulates their trafficking through the interaction with hyaluronic acid (HA), which is significantly up-regulated during ARF [42]. Data that BM-MSC isolated from CD44 knockout mice lost the ability to migrate into the renal injured tissue and did not accelerate morphological and functional recovery in mice with glycerol-induced ARF [42] clearly support a role of CD44/HA pathway in MSC migration.

Strategies are being developed to maximize the MSC capacity to migrate into the injured tissue, to survive and to enhance their regenerative activity through cell pre-conditioning with growth factors, cytokines and hypoxia [41, 43–45] or genetic modification [46–50], before *in vivo* cell infusion. *Ex vivo* pre-conditioning of BM-MSC with IGF-1 increased stem cell motility and engraftment in renal tissue of cisplatin mice with ARF, thus enhancing their protective effect on renal function and tubular injury [41]. **Stem cell exposure to IGF-1 increased IGF-1 production, enhanced the surface expression of CXCR4, one of the major players of BM-MSC mobilization, and reduced BM-MSC susceptibility to oxidative damage [41].** Another growth factor, glial cell line-derived neurotrophic factor (GDNF), a member of the TGF family, has been described to exert a cytoprotective activity against oxidative stress-induced apoptosis in cultured kidney-derived MSC [43]. Exposure of hAFS cells with GDNF markedly increased their engraftment in renal tissues

of mice with ARF fostering their paracrine activity and renoprotective effect [26]. Thus, cultured hAFS cells in response to GDNF expressed higher levels of CD44, CXCR4 and CX3CR1 on cell surface and further produced IL-6, and VEGF and SDF-1 [26]. Moreover, pre-treatment of rat BM-MSC with the pineal hormone melatonin improved their survival, proangiogenic/mitogenic activity and efficacy in rats with IR injury possibly by enhancing bFGF, hepatocyte growth factor (HGF) production and antioxidant enzyme expression [44]. Genetic modification of MSC with retroviral vectors encoding homing receptors such as CXCR4 or the VLA-4 subunit has been recently used to enhance migratory behaviour of MSC [46, 47]. Adenovirus transduction with the serine protease kallikrein rendered BM-MSC more resistant to oxidative stress-induced apoptosis and *in vivo* enhanced protection against ischaemic renal injury by inhibiting inflammation [48]. Treatment with genetically modified human embryonic MSC that produced four-fold higher levels of VEGF further enhanced renoprotection against cisplatin-induced ARF in respect to untransfected cells [49]. Furthermore, hCB-MSC overexpressing HGF showed enhanced therapeutic effects when infused to animals with IR injury as compared with untreated cells [50].

## CLINICAL STUDIES

Despite experimental data suggest that MSC promote renal recovery by acting on various pathways of injury operating in ARF more effectively than targeted pharmacological therapies, the translation of pre-clinical approaches into humans is still limited. In this context, a food and drug administration-approved phase I clinical trial (NCT00733876) is ongoing with the aim to investigate the safety and efficacy of escalating doses of allogeneic MSC administered to open-heart surgery patients at high risk of post-operative ARF due to underlying chronic kidney disease, advanced age, diabetes mellitus and



congestive heart failure. Preliminary data show that renal function was well preserved post-operatively for up to 16 months and none of the patients required haemodialysis, whereas 20% of case controls developed ARF. The length of hospital stay and readmission rates in study patients were reduced by 40%. Infusion of allogeneic MSC was safe as no adverse events were observed to be related to this novel therapy [51, 52].

Based on experimental studies on cisplatin-induced ARF, our group has designed an ongoing pilot, explorative study to test the feasibility and safety of systemic infusion of donor *ex vivo*-expanded MSC to repair the kidney and to improve function in patients with solid organ cancer who develop ARF after chemotherapy with cisplatin (ClinicalTrials.gov NCT 01275612). The effect of escalating three doses of donor *ex vivo*-expanded MSC given as a single intravenous infusion will be first tested in three patients. If the results show efficacy on renal function with any of the employed doses and the procedure is safe, the number of treated patients will be upgraded to eight subjects. One of the problems related to the identification of cisplatin-treated patients who are at increased risk of nephrotoxicity and might benefit most by cell-based intervention is the availability of early markers of renal/tubular injury. In this context, comparative analysis of serum and/or urinary neutrophil gelatinase-associated lipocalin (NGAL) levels as well as serum creatinine concentration in a cohort of patients administered cisplatin revealed that urinary NGAL is an early marker of renal dysfunction since its increase precedes the rise of serum creatinine [53].

Altogether the data on the safety of MSC therapy, although preliminary, are encouraging, however, further clinical trials devoted to testing the efficacy of this intervention are needed. The time is mature for the kidney to move to humans.

## ACKNOWLEDGEMENTS

Manuela Passera helped prepare the manuscript.

## FUNDING

The paper was supported by a grant from Ministero della Salute (Bando Cellule Staminali/Ricerca Sanitaria 2008—Conv. N.25—25/3/2011).

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

- Daley GQ. The promise and perils of stem cell therapeutics. *Cell Stem Cell* 2012; 10: 740–749
- Gerczuk PZ, Kloner RA. An update on cardioprotection: a review of the latest adjunctive therapies to limit myocardial infarction size in clinical trials. *J Am Coll Cardiol* 2012; 59: 969–978
- Orlic D, Kajstura J, Chimenti S *et al.* Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; 410: 701–705
- Murry CE, Soonpaa MH, Reinecke H *et al.* Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature* 2004; 428: 664–668
- Balsam LB, Wagers AJ, Christensen JL *et al.* Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature* 2004; 428: 668–673
- Rosenzweig A. Cardiac cell therapy—mixed results from mixed cells. *N Engl J Med* 2006; 355: 1274–1277
- Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 2008; 8: 726–736
- Le Blanc K, Mougiakakos D. Multipotent mesenchymal stromal cells and the innate immune system. *Nat Rev Immunol* 2012; 12: 383–396
- Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. *Science* 1997; 276: 71–74
- Edwards RG, Hollands P. Will stem cells in cord blood, amniotic fluid, bone marrow and peripheral blood soon be unnecessary in transplantation? *Reprod Biomed Online* 2007; 14: 396–401
- Flynn A, Barry F, O'Brien T. UC blood-derived mesenchymal stromal cells: an overview. *Cytotherapy* 2007; 9: 717–726
- Crisan M, Yap S, Casteilla L *et al.* A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell* 2008; 3: 301–313
- Bruno S, Bussolati B, Grange C *et al.* Isolation and characterization of resident mesenchymal stem cells in human glomeruli. *Stem Cells Dev* 2009; 18: 867–880
- Casiraghi F, Noris M, Remuzzi G. Immunomodulatory effects of mesenchymal stromal cells in solid organ transplantation. *Curr Opin Organ Transplant* 2010; 15: 731–737
- Poulsom R, Forbes SJ, Hodivala-Dilke K *et al.* Bone marrow contributes to renal parenchymal turnover and regeneration. *J Pathol* 2001; 195: 229–235
- Ito T, Suzuki A, Imai E *et al.* Bone marrow is a reservoir of repopulating mesangial cells during glomerular remodeling. *J Am Soc Nephrol* 2001; 12: 2625–2635
- Li B, Morioka T, Uchiyama M *et al.* Bone marrow cell infusion ameliorates progressive glomerulosclerosis in an experimental rat model. *Kidney Int* 2006; 69: 323–330
- Wise AF, Ricardo SD. Mesenchymal stem cells in kidney inflammation and repair. *Nephrology* 2012; 17: 1–10
- Morigi M, Imberti B, Zoja C *et al.* Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. *J Am Soc Nephrol* 2004; 15: 1794–1804
- Imberti B, Morigi M, Tomasoni S *et al.* Insulin-like growth factor-1 sustains stem cell mediated renal repair. *J Am Soc Nephrol* 2007; 18: 2921–2928
- Morigi M, Inrona M, Imberti B *et al.* Human bone marrow mesenchymal stem cells accelerate recovery of acute renal injury and prolong survival in mice. *Stem Cells* 2008; 26: 2075–2082
- Pappa KI, Anagnou NP. Novel sources of fetal stem cells: where do they fit on the developmental continuum? *Regen Med* 2009; 4: 423–433

23. Panepucci RA, Siufi JL, Silva WA, Jr *et al.* Comparison of gene expression of umbilical cord vein and bone marrow-derived mesenchymal stem cells. *Stem Cells* 2004; 22: 1263–1278
24. Morigi M, Rota C, Montemurro T *et al.* Life-sparing effect of human cord blood-mesenchymal stem cells in experimental acute kidney injury. *Stem Cells* 2010; 28: 513–522
25. De Coppi P, Bartsch G, Jr, Siddiqui MM *et al.* Isolation of amniotic stem cell lines with potential for therapy. *Nat Biotechnol* 2007; 25: 100–106
26. Rota C, Imberti B, Pozzobon M *et al.* Human amniotic fluid stem cell preconditioning improves their regenerative potential. *Stem Cells Dev* 2012; 21: 1911–1923
27. Togel F, Hu Z, Weiss K *et al.* Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms. *Am J Physiol Renal Physiol* 2005; 289: F31–F42
28. Togel F, Weiss K, Yang Y *et al.* Vasculotropic, paracrine actions of infused mesenchymal stem cells are important to the recovery from acute kidney injury. *Am J Physiol Renal Physiol* 2007; 292: F1626–F1635
29. Bi B, Schmitt R, Israilova M *et al.* Stromal cells protect against acute tubular injury via an endocrine effect. *J Am Soc Nephrol* 2007; 18: 2486–2496
30. Togel F, Cohen A, Zhang P *et al.* Autologous and allogeneic marrow stromal cells are safe and effective for the treatment of acute kidney injury. *Stem Cells Dev* 2009; 18: 475–485
31. Ratajczak J, Wysoczynski M, Hayek F *et al.* Membrane-derived microvesicles: important and underappreciated mediators of cell-to-cell communication. *Leukemia* 2006; 20: 1487–1495
32. Fevrier B, Raposo G. Exosomes: endosomal-derived vesicles shipping extracellular messages. *Curr Opin Cell Biol* 2004; 16: 415–421
33. Bruno S, Grange C, Deregibus MC *et al.* Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *J Am Soc Nephrol* 2009; 20: 1053–1067
34. Tomasoni S, Longaretti L, Rota C *et al.* Transfer of growth factor receptor mRNA via exosomes unravels the regenerative effect of mesenchymal stem cells. *Stem Cells Dev* 2012; [Epub ahead of print]
35. Biancone L, Bruno S, Deregibus MC *et al.* Therapeutic potential of mesenchymal stem cell-derived microvesicles. *Nephrol Dial Transplant* 2012; 27: 3037–3042
36. Herrera MB, Bussolati B, Bruno S *et al.* Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. *Int J Mol Med* 2004; 14: 1035–1041
37. Semedo P, Palasio CG, Oliveira CD *et al.* Early modulation of inflammation by mesenchymal stem cell after acute kidney injury. *Int Immunopharmacol* 2009; 9: 677–682
38. Honczarenko M, Le Y, Swierkowski M *et al.* Human bone marrow stromal cells express a distinct set of biologically functional chemokine receptors. *Stem Cells* 2006; 24: 1030–1041
39. Ponte AL, Marais E, Gallay N *et al.* The in vitro migration capacity of human bone marrow mesenchymal stem cells: comparison of chemokine and growth factor chemotactic activities. *Stem Cells* 2007; 25: 1737–1745
40. Togel F, Isaac J, Hu Z *et al.* Renal SDF-1 signals mobilization and homing of CXCR4-positive cells to the kidney after ischemic injury. *Kidney Int* 2005; 67: 1772–1784
41. Xinaris C, Morigi M, Imberti B *et al.* A novel strategy to enhance mesenchymal stem cell migration capacity and promote tissue repair in an injury specific fashion. *Cell Transplant*; [Epub ahead of print]
42. Herrera MB, Bussolati B, Bruno S *et al.* Exogenous mesenchymal stem cells localize to the kidney by means of CD44 following acute tubular injury. *Kidney Int* 2007; 72: 430–441
43. Shi H, Patschan D, Dietz GP *et al.* Glial cell line-derived neurotrophic growth factor increases motility and survival of cultured mesenchymal stem cells and ameliorates acute kidney injury. *Am J Physiol Renal Physiol* 2008; 294: F229–F235
44. Mias C, Trouche E, Seguelas MH *et al.* Ex vivo pretreatment with melatonin improves survival, proangiogenic/mitogenic activity, and efficiency of mesenchymal stem cells injected into ischemic kidney. *Stem Cells* 2008; 26: 1749–1757
45. Hung SC, Pochampally RR, Hsu SC *et al.* Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment in vivo. *PLoS One* 2007; 2: e416
46. Cheng Z, Ou L, Zhou X *et al.* Targeted migration of mesenchymal stem cells modified with CXCR4 gene to infarcted myocardium improves cardiac performance. *Mol Ther* 2008; 16: 571–579
47. Kumar S, Ponnazhagan S. Bone homing of mesenchymal stem cells by ectopic alpha 4 integrin expression. *FASEB J* 2007; 21: 3917–3927
48. Hagiwara M, Shen B, Chao L *et al.* Kallikrein-modified mesenchymal stem cell implantation provides enhanced protection against acute ischemic kidney injury by inhibiting apoptosis and inflammation. *Hum Gene Ther* 2008; 19: 807–819
49. Yuan L, Wu MJ, Sun HY *et al.* VEGF-modified human embryonic mesenchymal stem cell implantation enhances protection against cisplatin-induced acute kidney injury. *Am J Physiol Renal Physiol* 2011; 300: F207–F218
50. Chen Y, Qian H, Zhu W *et al.* Hepatocyte growth factor modification promotes the amelioration effects of human umbilical cord mesenchymal stem cells on rat acute kidney injury. *Stem Cells Dev* 2011; 20: 103–113
51. Gooch A, Doty J, Flores J *et al.* Initial report on a phase I clinical trial: prevention and treatment of post-operative acute kidney injury with allogeneic mesenchymal stem cell in patients who require on-pump cardiac surgery. *Cell Ther Transplant* 2008; 1: 31–35
52. Togel FE, Westenfelder C. Mesenchymal stem cells: a new therapeutic tool for AKI. *Nat Rev Nephrol* 2010; 6: 179–183
53. Gaspari F, Cravedi P, Mandala M *et al.* Predicting cisplatin-induced acute kidney injury by urinary neutrophil gelatinase-associated lipocalin excretion: a pilot prospective case-control study. *Nephron Clin Pract* 2010; 115: c154–c160

Received for publication: 2.7.2012; Accepted in revised form: 25.10.2012