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Review Article

Bone Marrow Stem Cell Therapy for Renal Regeneration After Acute Tubular Necrosis: A Dream or a Reality?

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Abstract

Bone marrow transplantation and organ transplantation studies suggest that bone marrow cells can differentiate into a variety of non-hematological tissues, including renal cells. The results of a number of experimental animal studies also showed that cell therapy (bone marrow cells (BMCs), hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs)) might have the potential to rescue animals from organ injuries. However, when BMCs or HSCs were injected into rodents subjected to ischemic or toxin-induced acute tubular necrosis (ATN), the results with regard to whether they could rescue rodents from ATN were inconsistent. The reasons for the conflicting results of BMC or HSC therapy in ATN are unknown, but may be due to the different types of cells injected, number of cells injected, route of injection, or injury model of acute renal failure. It is known that MSCs can contribute to renal tubular regeneration after ATN, although the exact mechanism, either transdifferentiation or effects of paracrine/cytokines, is uncertain. In the future, the most pertinent issue is to determine how MSCs protect the renal tubule from injury, and then to imitate this protective or reparative effect pharmacologically. (*Tzu Chi Med J* 2007;19(3):115–126)

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1. Introduction

Acute renal failure (ARF) is defined as a rapid decline in glomerular filtration rate (GFR) occurring within hours or days, resulting in the failure of the kidney to excrete nitrogen waste products, and failure to maintain extracellular fluid volume, electrolyte and acid-base homeostasis (1–4). Definitions of ARF range from a slight rise in serum creatinine concentration (e.g. of 0.5 mg/dL) to severe ARF status (i.e. that requiring dialysis). Although there is no universal laboratory definition, it is reasonable to define ARF as a rise in serum creatinine levels for 2 weeks or less of 0.5 mg/dL (44.2 μmol/L) if the baseline is less than 2.5 mg/dL, or a rise in serum creatinine levels by more than 20% if the baseline is more than 2.5 mg/dL (4).

ARF may occur in three clinical settings: (1) as a result of severe volume depletion and hypotension without compromising the integrity of renal parenchyma (prerenal ARF); (2) obstruction to the urinary

tract (postrenal ARF); and (3) diseases that directly affect renal parenchyma (intrinsic renal ARF). Prerenal ARF can be corrected if the extrarenal factors causing the renal hypoperfusion are reversed. In addition, an obstructive cause of ARF must be excluded because prompt intervention can lead to improvement or complete recovery of renal function. Acute tubular necrosis (ATN), resulting from prolonged renal hypoperfusion and renal ischemia or nephrotoxic substances, is a pathological diagnosis. Pathophysiologically, ATN is associated with tubular cell death and shedding into the tubular lumen, resulting in tubular blockage, further reducing glomerular filtration. Despite major advances in intensive care, renal replacement therapy, and exploration of cellular and molecular pathogenesis of ARF, no specific therapy is currently available. Consequently, the overall mortality rate of patients with ARF is still high, about 50% in a recent series [3,5,6], and has changed little during the past 30 years. Therefore, a more powerful therapeutic intervention for ATN to decrease mortality rate is imperative. Recently, a number of studies have provided evidence that bone marrow stem cells (BMSCs) may have a great potential to rescue people from organ injury. Here, we introduce the present studies on BMSCs in patients with renal diseases and discuss the future direction for applying BMSCs to renal regeneration.

2. Stem cells

2.1. *Totipotent, pluripotent and multipotent*

A stem cell is defined as a cell from the embryo, fetus, or adult that is capable of self-renewal over long periods and differentiation to one or more types of specialized cells under certain conditions [7]. Competent levels of stem cells can be classified as either totipotent (able to contribute to all three embryonic germ layers as well as extraembryonic tissues), pluripotent (giving rise to all three germ layers of the embryo), or multipotent (with the potential to differentiate into multiple cell types, but not derivatives of all three germ layers).

2.2. *Embryonic stem cells*

Embryonic stem (ES) cells are derived from the inner cell masses of the blastocysts and are pluripotent [8]. The pluripotent character of ES cells may provide therapeutic potential for many disorders. However, there are still several issues remaining unresolved about using ES cells from human embryos and applying them to clinical applications, including uncontrolled growth of inappropriate tissue types, rejection complications, and ethical issues.

2.3. *Adult stem cells*

In adult organisms, each tissue and organ are believed to contain a small subpopulation of cells, i.e. tissue-specific stem cells that remain committed to support their own family of descendants. Hematopoietic stem cells (HSCs) are the best characterized; this knowledge has allowed therapeutic grafting to make a tremendous impact on hematological malignancy and offers great promise for hemoglobinopathies and other genetic diseases [9]. A recent study showed *in vitro* expanded renal-derived $CD133^+$ cells homed into the injured kidney and integrated into tubules. However, it cannot be excluded that these $CD133^+$ cells might have been contaminated from the blood of renal microcirculation because these cells were directly obtained from the cortex without pre-infusion with isotonic sodium chloride solution [10]. Therefore, do renal stem cells exist in the adult kidneys? Most researchers agree that the kidney should contain organ-specific stem cells like other adult organs, but no researchers claim they can recognize functional renal stem cells either by location or by characteristic morphology or surface molecule expression [11,12].

3. BMSCs and their therapeutic potential

3.1. *Plasticity of BMSCs*

BMSCs are a many-faceted population and have been classified as HSCs, marrow stromal cells (or MSCs), multipotent adult progenitor cells (MAPCs), and side population (SP) cells [13]. Bone marrow transplantation (BMT) is an existing mode of stem cell therapy for patients with blood disorders such as leukemia. More than four decades of accomplished *in vivo* BMT studies have clarified the activities of a rare BMSC that is both self-renewing and multipotent in its ability to give rise to all blood cell types and provide recipients with long-term repopulating cells [9]. Traditionally, adult stem cells were believed to be lineage-restricted and organ-specific. Therefore, it was not thought possible that stem cells derived from bone marrow could not only rescue patients with hematological disorders but also extricate non-hematopoietic tissues from organ damage, i.e. the existence of stem cell plasticity had not been recognized. The first significant report alerting to the possibility of stem cell plasticity was published by Ferrari et al [14] who transplanted bone marrow cells (BMCs) into recipient mice and subsequently injured the muscles of these recipient

animals. Surprisingly, donor cell nuclei were found incorporated into the regenerated skeletal muscle at a frequency of approximately 0.01%. Now, a growing number of studies based on simple BMT protocols have claimed that adult BMSCs can differentiate into a variety of non-hematological tissues in rodents, such as skeletal muscle [14], astrocytes [15], osteoblasts [16], endothelial cells [17], cardiomyocytes [18], neuronal cells [19,20], hepatocytes [21], epidermal cells [22], pneumocytes [22,23], renal tubular epithelium and podocytes [24], and gut cells [22,25]. Likewise, in humans, bone marrow can apparently differentiate into hepatocytes [26,27], renal tubular cells [24], epithelium of the skin [27], skeletal muscle [28], cardiomyocytes [29], epithelia of gastrointestinal tract [27, 30], respiratory tract [31], and neurons [32,33].

3.2. *Cell fusion between BMCs and differentiated cells in engrafted organs*

Although some researchers have questioned stem cell plasticity and showed this is really the result of the fusion of BMCs with the differentiated cells in the engrafted organ including hepatocytes [34–36], Purkinje cells [36,37], cardiomyocytes [36] and skeletal muscle cells [38,39], a number of studies have demonstrated that cell fusion is not a major player in the transdifferentiation of BMCs into various specific cell types (reviewed in [40,41]).

4. Therapeutic potential of BMCs for extrarenal diseases

Through the establishment of bone marrow chimerism, a few successful cases of HSC transplantation *in utero* have rescued patients with severe combined immunodeficiency disease, β-thalassemia, and Bloom's syndrome [42,43]. Moreover, the results of a series of studies have shown the possibility that bone marrow grafting could act as cell therapy for non-hematological diseases, such as osteogenesis imperfecta [44–46]. Horwitz et al [44] showed that BMT improved certain parameters of patients with osteogenesis imperfecta, and stromal cell cultures from biopsies of recipient bones indicated that donor-derived cells were present. A subsequent study showed that further administration of mesenchymal cells cultured from the same donor gave some further improvement of clinical parameters due to the formation of functional wild-type osteoblasts from the donor mesenchymal cells, although gene-marked cells when detectable were $<1\%$ of cells in bone cultures [46]. Recently, experimental and early clinical studies have supported the concept that autologous bone marrow infusions were beneficial in chronic limb ischemia [47], ischemic heart disease [48], and myocardial infarction [49,50] in humans, although the benefits appeared to be related to preserving or re-establishing microvessels and limiting the extent and severity of the damage [51].

4.1. *Engraftment of BMCs as renal cells*

Table 1 [22,24,52–78] shows the potential of BMCs to transdifferentiate into renal cells according to the study results of cross-sex BMT and kidney transplantation.

4.2. *Engraftment of BMCs as renal vessels and interstitium*

Considering the renal vessels and interstitium, the results of early studies of renal vascular engraftment by Williams et al [52,53] and Sinclair [54] showed, based on cross-sex renal transplant studies, that repopulated endothelium of vessels may be derived from circulating cells when chronic rejection of allografts occurred. Williams et al reported that 10% of the endothelium in allografts of the kidney and aorta could be from the host marrow when chronic rejection of allografts occurred, and engraftment was less when rejection was attenuated by immunosuppression [52,53]. Sinclair [54] counted Barr bodies in 40 male patients with female renal transplants and showed donor endothelium persisted in 37 of 40 cases, but not in three patients with grafts that were very poorly functioning and severely damaged. However, Andersen et al [55] examined kidney specimens from 40 sex-mismatched transplant patients clinically suggested of developing acute rejection, and reported that there was no evidence of revascularization by recipient endothelial cells; furthermore, tubular and glomerular cells remained of donor origin in the transplanted kidneys with acute rejection, even 10 months after transplantation. Recently, the results of two studies showed that vascular endothelium [58,61] and tubulointerstitial cells [58] were of host origin when allografts of human kidneys show chronic rejection. The percentage of engraftment of vascular endothelium of host origin was more than 33% in the majority of patients (86%) with vascular rejection [58,61]. Similarly, the percentage of vascular endothelium of host origin was 34–76% in allografts with vascular rejection, and the percentage of interstitial cells of host origin was 30–77% in allografts with interstitial rejection [58]. These results suggest circulating mesenchymal precursors reside within the bone marrow and migrate to vessels or interstitial areas when allograft rejection occurs. However, the results from a study by Iwano et al showed that interstitial kidney

Table 1 — Summary of the potential of bone marrow cells to transdifferentiate into renal cells according to the studies of cross-sex bone marrow transplantation and kidney transplantation

Reference	Host	Donor cell	Number of cells	Route of administration	Injury	Cell type of renal cells	Outcome	Follow-up
Williams & Alvarez (1969) (52)	Human, sex-mismatch KT (male to female)	None	None	None	Acute rejection and chronic rejection	Endothelium	1. Acute rejection: 2–2.9% of Barr bodies in renal artery 3rd branch 2. Chronic rejection: 5.9% and 0.8% of Barr bodies in renal artery and vein individually 3. Endothelial cells of graft are destroyed and repopulated by host	Acute rejection: 2 wk Chronic rejection: 182 wk
Williams et al (1971) (53)	Rats, sex-mismatch aortic grafts	None	None	None	Acute rejection and chronic rejection	Endothelium	10% of endothelium is host marrow derived and engraftment was less when rejection was attenuated by immunosuppression	6 d to 4 mo after aortic grafts
Sinclair (1972) (54)	Human, sex-mismatch KT	None	None	None	Variable renal function	Endothelium	Extensive acute damage required repair by host cells while less severely damaged grafts was restored by endothelial continuity from surviving donor endothelial cells	4 d to 6.5 yr after KT
Andersen et al (1991) (55)	Human, sex-mismatch KT	None	None	None	Acute rejection	None of endothelium, glomerular and tubular cells derived from recipients	1. 40 patients suspected of developing acute rejection but no evidence of revascularization by recipient 2. Tubular and glomerular cells remained of donor origin in transplanted kidneys even 10 mo after KT	10 mo after KT
Imasawa et al (1999) (56)	HIGA mice (a murine model of IgA nephropathy), ddY strain	T-cell depleted BMCs of C57BL/6j mice	10^7	IV, 5–6 hr after TBI	None	Glomerular mesangial cells	1. Attenuation of glomerular lesion 2. Transplant with WT BMCs showed milder histology changes and lower serum IgA levels than those transplanted with HIGA BMCs	6–50 wk after BMT
Cornacchia et al (2001) (57)	ROP +/+ mice	BMCs of ROP OS/+; ROP OS/+ mice is a non-diabetic model of GS	5×10^7	IV, after TBI	None	Glomerular mesangial and endothelial cells	Glomerular mesangial and endothelial cells are derived from BM and can deliver a disease phenotype to normal glomeruli	8 wk after BMT
Grimm et al (2001) (58)	Human, sex-mismatch KT	None	None	None	Chronic rejection	Circulating mesenchymal precursor cell has the potential to migrate to areas of inflammation	1. Six male recipients with female donor showed Y positive/SMA+ cells around 30–40% in neointima, adventitia, interstitium 2. Four female recipients with male donor showed Y positive/SMA+ cells around 20–40% in neointima, adventitia, interstitium	1–12 mo after KT

Imasawa et al (2001) (59)	C57BL/6j mice	T-cell depleted GFP(+) BMCs	10^7	Tail vein, 5–6 hr after TBI	None	Glomerular mesangial cells	BMCs may differentiate into glomerular mesangial cells	2–24 wk after BMT
Ito et al (2001) (60)	SD rats	Enhanced GFP BMCs	2×10^7	Tail vein, 4 hr after TBI	Anti-Thy1.1 Ab mediated nephritis	Glomerular mesangial cells	BMCs can give rise to mesangial cells	24–77 d after BMT
Krause et al (2001) (22)	B6D2/F1 mice	Sorted HSCs ($Fr25lin^-$) from male C57BL/6 CD34 knockout mice, primary and secondary BMT	Primary BMT: 10^7 cells Secondary BMT: single cell	IV	None	None	HSC did not transdifferentiate into glomerular epithelial and tubular cells	5 and 11 mo after BMT
Lagaaij et al (2001) (61)	Human, sex-mismatch KT	None	None	None	Kidney rejection	Endothelium	1. Six of 7 grafts affected by vascular rejection showed 33% recipient-derived endothelial cells 2. Two of 13 without rejection showed extensive endothelial recolonization	6 mo after KT
Poulsom et al (2001) (24)	Human, sex-mismatch KT	None	None	None	Poor renal function after KT	Tubular epithelium	8–20% Y positive tubular cells were seen	5–1144 d after KT
Poulsom et al (2001) (24)	Female C57/B mice	Male BMCs	Three male donor mice BMCs for 10 recipient female mice	Tail vein, post TBI	None	Tubular epithelium and podocytes	1. Around 3.8–7.9% Y positive tubular cells were observed 2. Marrow-derived cells that appeared to be podocytes	7–13 wk after BMT
Gupta et al (2002) (62)	Human, sex-mismatch KT	None	None	None	Acute tubular necrosis after KT	Tubular epithelium	1. Total 6 patients, 1 positive control, 1 negative control 2. Subjects with ATN showed 1% of tubules contained Y chromosome and the other 2 subjects without ATN did not	10–515 d after KT
Imasawa & Utsunomiya (2002) (63)	High serum level IgA (HIGA) ddY mice	T-cell depleted BMCs of C57BL/6j (B6) mice	10^7	IV, 5–6 hr after TBI	None	Glomerular mesangial cells	BMT from normal mice may not only replace recipient's immune cells with donor's BMCs, but also regenerate glomerular cells in HIGA mice	26 wk after BMT
Iwano et al (2002) (64)	Balb/c mice	T-cell depleted BMCs	2×10^7	Tail vein, after TBI	Unilateral ureteral obstruction was done, 30 d after BMT	Interstitial fibroblast	Evidence showed interstitial kidney fibroblasts derived from 2 sources: BM and local tubular epithelium	10 d after unilateral ureteral obstruction
Xu et al (2002) (65)	Rats, sex-mismatch KT	None	None	None	Ischemia and rejection	Endothelium	Endothelial chimerism demonstrated in rats after KT may be caused by endothelial damage induced by vascular rejection or ischemia	10–20 d after KT

(*Continued*)

Table 1 — (*Continued*)

Reference	Host	Donor cell	Number of cells	Route of administration	Injury	Cell type of renal cells	Outcome	Follow-up
Kale et al (2003) (66)	C57BL/6J mice	BMCs of LacZ gene expressing mice (Rosa 26 mice)	10^6 whole BMCs or 5×10^3 Lin(–) Sca-1(+)c-kit(+) cells	Retro-orbital sinus, after TBI	I/R for 25 min, 16 wk after BMT	Tubular epithelium	I/R induces mobilization of BMCs and repopulation of the S3 segment of the renal tubule	7 d after I/R
Masuya et al (2003) (67)	C57BL/6 mice	Enhanced GFP(+)-Lin(–)Sca(+) c-Kit(+), $CD34^-$ BMCs	Viable clusters of cells derived from a single cell or 100 non-cultured cells	Tail vein, after TBI	None	Glomerular mesangial cells	1. High levels (60–90%) of multilineage hematopoietic reconstitution 2. A single HSC can differentiate into glomerular mesangial cells and that process does not involve cell fusion	2–6 mo after BMT
Rookmaaker et al (2003) (68)	BN rats	BMCs of WR rats	5×10^7	IV, 5 hr after TBI	Anti-Thy1.1 GN, 5 wk after BMT	Glomerular endothelial and mesangial cells	BMCs participate in glomerular endothelial and mesangial cell turnover and contribute to microvascular repair	7–28 d after anti-Thy1.1 mAb injection
Mengel et al (2004) (69)	Human, sex-mismatch KT (36 patients)	None	None	None	Variable chronic rejection	Tubular epithelial chimerism is 2.4–6.6%	1. 88% of patients had epithelial chimerism and 72% had stable chimerism in sequential biopsy samples 2. Chimerism did not show correlation with allograft function	8 d to 8 yr after KT
Fang et al (2005) (70)	Female FVB/N mice	Male FVB/N BMCs	2×10^7	Tail vein, 4 hr after TBI	Folic acid, 6 wk after BMT	Tubular epithelium	BMC contributed to renal tubular epithelial cell population, although most (90%) renal tubular regeneration came from female indigenous cells	7 d after folic acid
Iwasaki et al (2005) (71)	BALB/c mice	Enhanced GFP BMCs	3×10^7	Intra BM-BMT, 1 d after TBI	Cisplatin, 1 mo after BMT	Tubular epithelium	BMCs mobilized by G-CSF accelerate improvement in renal function and prevent renal tubular injury	4 d after cisplatin
Iwatani et al (2005) (72)	SD rats	Rat kidney-derived Hoechst low/side population cells	3000–8000	IV, 1 d after TBI	Anti-Thy1.1 GN, 5 wk after BMT; gentamicin-induced ATN (8 wk after BMT)	Negative for renal cells, especially mesangial and tubular cells	Kidney side population cells may have potential for hematopoietic and non-hematopoietic lineages, but are not stem cells for renal cells	10 wk after BMT
Duffield & Bonventre (2005), Duffield et al (2005) (73,74)	C57BL/6J mice	Male, or β-gal-, or enhanced GFP C57BL/6J BMSCs	10^7	IV, 2 hr after TBI	I/R for 30–45 min, 6 wk after BMT	None	1. The injured tubule is repopulated by daughter cells of surviving tubular cells 2. No evidence of transdifferentiation of these injected cells into tubular cells	21 d after I/R

Stokman et al (2005) [75]	Female C57BL/6 mice	Enhanced GFP BMCs (plus 2×10^5 female WT spleen cells and cytokine [SCF and human G-CSF])	5×10^5	IV, immediately after TBI	I/R for 45 min 6 wk after BMT	None	Cytokine treatment improved renal function rapidly after I/R, and the mechanism is not stem cell transdifferentiation but rather altered inflammatory kinetics	1–28 d after I/R
Yokoo et al (2005) [76]	SD rats and Fabry mice	Human MSC	Not mentioned	Local injection at site of ureteric bud sprouting of whole embryonic culture	None	Functional complex structures of new kidney	Human MSC in rodent whole embryo culture reprogrammed to contribute to kidney tissues	48 hr after MSC injection
Sugimoto et al (2006) [77]	COLA4A3-/- mice, Alport mice	BMCs from ROSA26/ LacZ+mice	$2–5\times10^6$	IV, 24 hr after irradiation	None	Podocytes	BM-derived podocytes can offer viable strategy for repairing basement membrane defects	13 wk after BMT
Guo et al (2006) [78]	WT1 heterozygous mice (K-mice), WT1+/– mice	Enhanced GFP(+) WT BMCs	$0.1–17\times10^6$	Tail vein, after TBI	No injury, but K-mice are a model of mesangial sclerosis	Mesangial cells	Transplantation of WT BM attenuates progression of mesangial sclerosis in the WT1+/– model of renal disease	200 d after BMT

ATN = acute tubular necrosis; BM = bone marrow; BMC = bone marrow cell; BMSC = bone marrow stem cell; BMT = bone marrow transplant; G-CSF = granulocyte-colony stimulating factor; GFP = green fluorescent protein; GN = glomerulonephritis; GS = glomerulosclerosis; HSC = hematopoietic stem cell; I/R: ischemia–reperfusion; IV = intravenous; KT = kidney transplant; MSC = mesenchymal stem cell; TBI = total body irradiation; WT = wild type.

fibroblasts were derived not only from bone marrow but also from local tubular epithelium [64].

4.3. *Engraftment of BMCs as glomerular mesangial cells and podocytes*

Turning to glomerular mesangial cells and podocytes, Poulsom et al and Sugimoto et al demonstrated that BMCs contributed to podocyte regeneration and amelioration of renal disease in a mouse model of Alport syndrome [24,77,79]. Regarding mesangial cells, Cornacchia et al demonstrated that mesangial cell progenitors may carry a disease genotype and that the phenotype can be transmitted after BMT [57]. Several studies also showed that BMCs differentiated into glomerular mesangial cells in rodents with and without glomerular injury [59,60,63,68,78]. Moreover, Masuya et al reported that transplantation of a single HSC could generate numerous glomerular mesangial cells [67].

4.4. *Engraftment of BMCs as renal tubular epithelium*

Considering renal tubular epithelium, Poulsom et al demonstrated that BMSCs contributed to both normal turnover of renal epithelium in mice and the level of engraftment in renal tubular cells was 3–8%, and regeneration after damage in humans where the level of engraftment in renal tubular cells was 1.8–20% [24]. Animal studies from our group and other groups also showed that BMCs contributed to renal regeneration after ATN [70,71]. However, not all reports were compatible with these studies. Krause et al showed that no donor-derived renal tubule epithelial cells were seen in any of the five mice transplanted with a single highly selected HSC, perhaps ineffective due to the use of a sorted HSC rather than the whole bone marrow [22]. However, it is unknown whether epithelial chimerism is an incidental by-product of cross-gender BMT and renal allografts without biological meaning or whether alternatively the process plays a role in kidney repair. For example, Gupta et al reported that 1% of tubules contained male epithelial cells in two male patients with female kidney allografts and ATN, however, no male epithelial cells were noted in two cases without ATN, suggesting that recipient-derived cells do not routinely repopulate the transplanted kidney [62,80]. These findings contrast with recent observations by Mengel et al who showed that chimeric tubular epithelial cells (2.4–6.6%) occurred regularly in allografts, and was not correlated with outcome [69]. The results of our recent study demonstrated that BMCs contributed to the renal tubular epithelial cell population and regenerated renal tubular epithelium after ARF via cell proliferation [70].

5. Therapeutic potential of BMC therapy for ATN

Table 2 (66,73,81–88) shows the conflicting results of BMC therapy for acute renal injury. The reasons for the conflicting results of BMC therapy in acute renal injury are unknown, but may be due to the different types of injected cells, number of injected cells, route of injection, or injury model of ARF.

5.1. Whole BMC therapy for ATN

It is still conflicting whether whole BMCs can contribute to tubular regeneration after ATN (66,85). For example, Kale et al demonstrated that the engraftment of renal tubular cells of the outer medulla from BMCs increased from 3.0 ± 0.1% to 20.9 ± 1.6% after ischemia–reperfusion (I/R) renal injury (66), suggesting a major contribution of BMCs to functional repair of the ischemically injured tubule. However, the results of another study showed that BMCs did not improve renal function after I/R renal injury, although a rise in engraftment of tubular epithelial cells, glomerular cells and interstitial cells was seen (85).

5.2. HSC therapy for ATN

With regard to HSC therapy for ATN, it is still uncertain. For example, Lin et al studied female non-transgenic mice subjected to 11 Gray γ-irradiation 2 hours before the left renal artery was clamped for 15 minutes, and 2000 $Rh^{lo}Lin^{-}Sca\text{-}1^{+}ckit^{+}$ HSCs from male ROSA26 mice were injected into the female mice within hours after the unilateral renal I/R injury (81). Four weeks after I/R renal injury, HSC-derived tubular epithelium was seen only with ischemic damage, and the percentage of Y chromosome-positive cells in the regenerating renal proximal tubules was 8.3±3.2%. However, Dekel et al showed that human BM $CD34^{+}$ HSCs when injected into NOD/SCID mice subjected to I/R renal injury via renal pelvis could not improve renal function and these cells could not acquire a tubular phenotype (87).

5.3. MSC therapy for ATN

With regard to MSC therapy for ATN, it is established that MSCs can contribute to regeneration of renal tubules after ATN, although the exact mechanism is controversial. There are at least two possible mechanisms for MSCs to rescue ATN: transdifferentiation of MSCs into renal tubule cells and paracrine and/or angiogenic effects of MSCs. However, it is not known which one is more important. For example, two studies demonstrated that MSCs, when injected into non-irradiated mice subjected to cisplatin-induced or glycerol-induced ATN, could rescue mice from acute tubular damage and differentiate into renal tubular epithelium (82,83). However, the results of other studies showed that the administration of MSCs via carotid artery either immediately or 24 hours after renal ischemia (73,84,86) or via either tail veins or left renal artery 1 day after anti-Thy1.1 nephritis induction (88), significantly improved renal function through a change in the cytokine milieu or paracrine growth factor release, but not because of their transdifferentiation into renal tubular cells. The reason for the discrepant results of MSC transdifferentiation into renal epithelial cells between these two kinds of studies is unclear.

In fact, MSCs not only release angiogenic (vascular endothelial growth factor) and anti-inflammatory cytokines (transforming growth factor β1), but MSCs also have strong immunosuppressive activity (89). However, it is still conflicting if administration of MSCs to people subjected to ATN can develop a neo-expressing protein and may induce an immune response. For example, several studies demonstrated that MSCs had shown strong immunosuppressive activity (89), and modulated the immune response via modifying the cytokine response of dendritic cells and T cells, via interfering with the development of immunocompetent dendritic cells, and via favoring the development of regulatory T cells (90,91). In contrast, one recent study showed that the administration of allogeneic donor MSCs primed naïve T cells and hastened rejection of the bone marrow, whereas recipient autologous MSCs promoted tolerance and acceptance of transplants (92).

6. Conclusion

Studies of tissue from recipients of BMT or organ allografts suggest that BMCs can differentiate into a variety of non-hematological tissues, including renal cells. However, it is uncertain whether BMCs or HSCs, when injected into rodents subjected to ischemic or toxin-induced ATN, could rescue rodents from ATN. The reasons for the conflicting results of BMC or HSC therapy in ATN are unknown, but may be dependent on the different types of injected cells, number of injected cells, route of injection, or injury model of ARF. MSCs could contribute to renal tubular regeneration after ATN, although the exact mechanism, either transdifferentiation of MSCs or effects of paracrine/cytokines, is uncertain. In the future, the most pertinent issue is to determine exactly how MSCs protect the renal tubule from injury, and then to imitate this protective or reparative effect pharmacologically. If the primary role of MSCs is to secrete a cytokine or growth factor in response to injury, then the cells themselves

Table 2 — Results of bone marrow stem cell therapy for renal injury

Reference	Host	Injury	Donor cell phenotype	Number of cells	Route of administration	Timing of cell injection after injury	Outcome	Follow-up
Kale et al (2003) (66)	C57BL/6J mice	I/R for 30 min, 12 hr after TBI	Lin(–) BMCs	5×10^3	Retro-orbital sinus	2.5 hr after reperfusion	BMCs contribute to functional repair of the ischemically injured tubule	7 d after I/R
Lin et al (2003) (81)	Female B6-Ly5.2/Cr mice	I/R for 15 min, 2 hr after TBI	HSC from BM of male Rosa26 mice	2000 HSC plus 2×10^5 Lin(–) BMCs	Tail vein	2–4 hr after reperfusion	HSC can differentiate into renal tubular cells after I/R injury	4–12 wk after I/R
Herrera et al (2004) (82)	C57/BL6 mice	Intramuscular injection of glycerol	GFP(+) MSCs	10^6	IV	Day 3 after glycerol	22% of tubular cells were GFP-positive after injury and promoted recovery of morphological and functional alterations	21 d after glycerol injury
Morigi et al (2004) (83)	Female C57ML6/J mice	CP	Male CD45(–) MSCs or Lin(–) c-kit(+) HSCs	MSCs, 2×10^5; HSCs, 2×10^5	IV	1 d after CP	MSCs contribute to tubular regeneration after CP-induced ATN, but HSCs cannot	4–29 d after CP
Duffield et al (2005) (73)	C57BL/6J mice	I/R for 30–45 min	MSC	0.5×10^6	IV	Immediately and 24 hr after I/R injury	Improvement of renal function, but no evidence of transdifferentiation	15 d after I/R
Lange et al (2005) (84)	SD rats	I/R for 40 min	Iron-dextran-labeled cultured MSCs	1.5×10^6	Thoracic aorta	Cell injection after reflow	1. MSCs had better renal function after ATN 2. MSCs were predominantly located in glomerular capillaries, and no transdifferentiation of MSCs into tubular cells	72 hr after I/R
Lin et al (2005) (85)	Female C57BL/6NC mice	I/R for 45 min, on the day of TBI	Enhanced GFP BMCs	10^6	Tail vein	2 hr after I/R	1. BMCs consisted of tubular epithelial cells (8.4%), glomerular cells (10.6%), and interstitial cells (81%) 2. No renal function improvement	28 d after I/R
Togel et al (2005) (86)	SD rats	I/R for 40 min	Fluorescence-labeled MSCs	10^6	Intracarotid	Immediate or 24 hr	MSCs have significant renoprotection through paracrine actions not by differentiation into target cells	24–72 hr after I/R
Dekel et al (2006) (87)	NOD/SCID mice	I/R for 40 min	Human $CD34^+$ HSC (from BM)	4×10^6	Local injection through renal pelvis	Immediately after removal of vascular clamp	Human BM $CD34^+$stem cell cannot acquire tubular phenotype	24 hr after I/R
Kunter et al (2006) (88)	Wistar or Lewis rats	Anti-Thy1.1 mAb induced anti-Thy1.1 glomerulonephritis	Fluorescence-labeled MSCs	2×10^6	Left renal artery or IV	2 d after anti-Thy1.1 mAb injection	MSCs can markedly accelerate glomerular recovery from mesangiolytic damage possibly related to paracrine growth factor release and not differentiation into resident glomerular cells	6 d after disease induction

ATN = acute tubular necrosis; BM = bone marrow; BMC = bone marrow cell; CP = cisplatin; GFP = green fluorescent protein; HSC = hematopoietic stem cell; I/R = ischemia–reperfusion; IV = intravenous; MSC = mesenchymal stem cell; TBI = total body irradiation.

might not be essential, and we should be able to recognize the factor or factors and either administer it directly or establish pharmacological policy to stimulate its production by endogenous cells.

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