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REVIEW

Kidney repair and stem cells: a complex and controversial process

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Abstract Over the last decade, stem cells have been the topic of much debate and investigation for their regenerative potential in the case of renal injury. This review focuses on bone marrow stem cells (BMSC) for renal repair and the potential origins of the controversial results between studies. Some authors have shown that BMSC can differentiate into renal cells and reverse renal dysfunction while others obtained contradictory results. One significant variation between these studies is the choice of BMSC used. According to the literature and our own experience, unfractionated bone marrow cells and hematopoietic stem cells are able to lead to long-term cell tissue engraftment and repair, whereas mesenchymal stem cells have a short-term paracrine effect. Detection of the bone-marrow-derived cells is also an important source of error. However, the major difference between studies is the model of kidney injury used. Two categories of models have to be distinguished: acute and chronic kidney disease. However, variation within these categories also exists. The outcomes of various strategies for BMSC transplantation after injury to the kidney must be compared within a single model and cannot be transposed from one model to another.

Keywords Bone marrow stem cells · Kidney injury · Repair · Acute kidney disease · Chronic kidney disease

Introduction

Regeneration of kidney tissue in mammals in response to injury is limited but can occur under certain circumstances [1–3]. Three major origins for this regeneration include: (1) re-entry of renal parenchymal cells into cell cycle of differentiated cells, (2) direct transdifferentiation of one cell type into another (i.e., tubular cells into interstitial cell and vice versa), and (3) differentiation of a stem cell population from the kidney or the bone marrow [2]. This review will focus on bone marrow stem cell differentiation for kidney regeneration in response to injury.

Over the last decade, stem cells have been the topic of much debate and investigation for their regenerative and potential therapeutic properties for renal injury and disease. Both organ-specific renal stem cells and circulating multipotent bone marrow stem cells (BMSC) have been studied as sources for stem-cell-based renal repair.

Bone marrow stem cells are an attractive therapy for renal tissue regeneration due to their pluripotency, and because they can be easily isolated, modified in vitro by vector-mediated gene delivery, and reintroduced as an autologous cell transplant reducing the risk of an immunogenic reaction. The use of adult stem cells also avoids the ethical ambiguities of using embryonic stem cells. In clinical trials, BMSC have already been used to treat cardiac, genetic, hematological, metabolic, and neurologic diseases [4–8]. Regarding the kidney, BMSC have been shown to be involved in repair by engraftment within the kidney after both acute and chronic injury [9–13], and restoration of normal renal function [13–16]. In contrast, other studies showed that bone marrow cells could not generate renal cells or impact kidney injury [17–20]. In order to understand the discrepancies existing in the field of using bone marrow stem cell for kidney repair, we will review the potential sources of these differences.

Origin of stem cells: a major source of controversies

Four different types of stem cells have to be considered for kidney repair: unfractionated bone marrow cells, hemato-

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poietic stem cells, mesenchymal stem cells, and intrinsic renal progenitors. The two major philosophies emerging from the studies are regenerative mechanisms based on paracrine effects of the stem cells or systemic effects. In terms of the systemic effects, it is worth noting the ongoing research in identifying whether the stem cells transdifferentiate into and/or fuse with renal cells. These mechanisms are currently the topic of much debate [21–23] but will not be included in this discussion.

Unfractionated bone marrow cells

Early evidence for the participation of BMSC in renal cell generation was published by Poulsom et al. who showed the presence of Y chromosome-positive renal cells in female kidneys after transplantation of male BMC into irradiated female mice or transplantation of a female kidney into male patients [9]. Y-chromosome-positive cells were observed within the tubules, co-expressing epithelial markers, as well as in the glomeruli with podocyte phenotype. A similar study by Gupta et al. suggested that BMSC only invade injured kidney [24]. Thus, tubular cells carrying a Y-chromosome were found only in female donor kidney biopsies of male patients that developed tubular necrosis post-transplant. In contrast, no Y-chromosome-positive cells were detected with normal renal function after transplantation. By transplanting unfractionated bone marrow cells expressing green fluorescent protein (GFP) into rats and inducing anti-Thy1 antibody-mediated glomerulonephritis, Ito et al. showed that 7-8% of mesangial cells were bone-marrow-derived cells expressing Thy1 [11]. A study by Cornacchia et al. demonstrated that wild-type mice transplanted with bone marrow cells from $ROP^{Os/+}$ mice, which have glomerular hypertrophy and glomerulosclerosis, developed the same lesions than the $ROP^{Os/+}$ mice [25]. Mesangial cells in the transplanted animals exhibited the $ROP^{Os/+}$ genotype, suggesting that the disease phenotype was transmitted by engraftment of the transplanted cells in the recipient kidney. Rookmaaker and colleagues showed that BMSC could also give rise to endothelial cells in the glomeruli [26]. After induction of anti-Thy1-glomerulonephritis, bone-marrow-derived glomerular endothelial cells and mesangial cells were observed as soon as 7 days after transplantation of allogeneic unfractionated bone marrow cells and remained elevated at 28 days, contributing to glomerular microvascular repair.

In contrast, others did not obtain bone-marrow-derived cells differentiated into renal cells after systemic injection of unfractionated bone marrow cells in irradiated mice and ischemic or folic acid-induced renal injury [17, 27]. These investigators showed that bone-marrow-derived cells within the kidney after injury were mostly lymphoid lineage cells. Thus, the outcome of bone marrow cell transplantation for kidney repair can be highly variable between studies, reasons for which will be discussed later in this review.

Hematopoietic stem cells

Following a systemic injection of human hematopoietic stem cells (HSC) 24 h post-injury in immunodeficient mice, Li et al. showed selective recruitment and localization of bone-marrow-derived cells to the kidney vasculature resulting in the improvement of the structural and functional recovery as well as increased survival [14]. Kale and colleagues illustrated that transplantation of murine $Sca1^{+}$ HSC after acute renal ischemia resulted in their differentiation into renal tubular epithelium, and in the repair of the previously necrotic tubules [28]. In a study to distinguish the contribution of HSC and mesenchymal stem cells (MSC) to regenerate renal tubules, Fang et al. transplanted female GFP^{+} HSC together with male GFP^{-} MSC into lethally irradiated female mice and then induced acute tubular damage by HgCl2 injection 4 weeks later [29]. The results showed that GFP^{+} HSC and MSC could engraft into the bone marrow and spleen, but only HSC-derived cells were found in the renal tubules after injury.

Stokman and colleagues showed that renal failure after ischemia is improved by HSC mobilization using cytokines. However, the authors showed that the improvement was due to the cytokines altering the underlying inflammatory processes triggered by kidney injury and not due to the involvement of the mobilized HSC [19]. Many of the bone-marrow-derived cells detected in the kidney in the first few days after acute kidney disease were leukocytes and T-cells located in the renal interstitium, which many researchers believe actually exacerbate the injury rather than heal it [30–33].

Mesenchymal stem cells

MSC provide stromal support for HSC in the bone marrow compartment as well as give rise to various different cell types such as osteoblasts, adipocytes, chondroblasts, and myoblasts [34, 35]. Studies comparing MSC and HSC fractions by Morigi et al. exhibited that MSC, but not HSC, contributed to the therapeutic benefit, differentiated into tubular cells and accelerated the structural recovery after cisplastin-induced acute kidney injury [15]. However, several investigators have shown evidence that MSC function through paracrine effects rather than engraftment and proliferation to mediate renal repair [36–38]. Kunter et al. showed that after 6 days, the vast majority of transplanted MSC failed to differentiate into other cell types by immunostaining for endothelial, mesangial, or monocyte/macrophage lineages [37]. Using BrdU analysis, they also indicated that the majority of MSC did not proliferate

either. The MSC did, however, release large amounts of vascular endothelial growth factor (VEGF) in vitro, which has been shown to be a critical factor for glomerular function and stimulates proliferation of peritubular capillaries essential to tubular regeneration [39]. Further studies on VEGF in kidney repair by Togel et al. established that VEGF is a critical factor mediating renal recovery after ischemia/reperfusion acute renal injury [38]. This was accomplished by knocking down VEGF using small-interfering RNA, which reduced the effectiveness of MSC significantly and decreased survival. Using a cisplatin model for renal damage, Bi et al. showed that a regenerative response was elicited by intraperitoneal injection of MSC-conditioned culture media, indicating that a paracrine response is the mechanism for MSC-induced repair [40].

A study looking at the effects of transplanting both HSC and MSC versus HSC alone, after kidney transplantation in human showed that the combination of HSC and MSC was more effective in achieving immune hypo-responsiveness to the donor with stable graft function and reduced rejection [41]. As alluded to in the previous study, an advantage of using whole bone marrow is that supporting cells are transplanted as well, which may contribute to better engraftment and transplantation outcomes [42]. We addressed this question using the murine model for cystinosis, $Ctns^{-/-}$ mice, which develop chronic kidney disease. We performed syngeneic unfractionated bone marrow cells, HSC, or MSC transplantation [13]. Our strategy was to take advantage of stem cells obtained from wild-type GFP-transgenic mice that express both a GFP reporter gene and a functional Ctns gene. All recipient animals were lethally irradiated before transplantation. We showed that in mice receiving whole bone marrow cells, bone-marrow-derived cells could efficiently engraft in the kidney tissue compartment 4 months post-transplantation and lead to significant decreases in tissue levels of cystine in multiple compartments (from 57% decrease in brain to 94% in liver). In the kidney, 12.9% of the total renal cells, as determined by quantitative PCR, were derived from the transplanted wild-type bone marrow cells and kidney cystine levels were decreased by 70% compared to untreated animals. Moreover, the progression of kidney dysfunction was prevented. The GFP-positive bone-marrow-derived cells within the kidney were predominately interstitial cells and non-lymphoid lineage but some also co-localized with distal and proximal tubular and endothelial cells (Fig. 1). We obtained the same resulted with wild-type Sca 1^{+} HSC but with a little less efficacy, 8.7% of the total renal cells and 43% cystine decrease in the kidney. However, MSC transplantation resulted in only short-term improvements of renal function and tissue cystine content levels in the $Ctns^{-/-}$ mice and MSC did not integrate efficiently and stably in any organ. Therefore, from our experience, we concluded that a long-term therapeutic effect for kidney injury would require bone-marrow-derived cells to stably engraft within the kidney, and either unfractionated bone marrow cells or HSC would be the cells of choice.

Intrinsic renal stem cells

Renal stem cells comprise the alternative to bone marrow cells for stem-cell-based regeneration of the kidney. Identification of renal stem cells was based on identifying

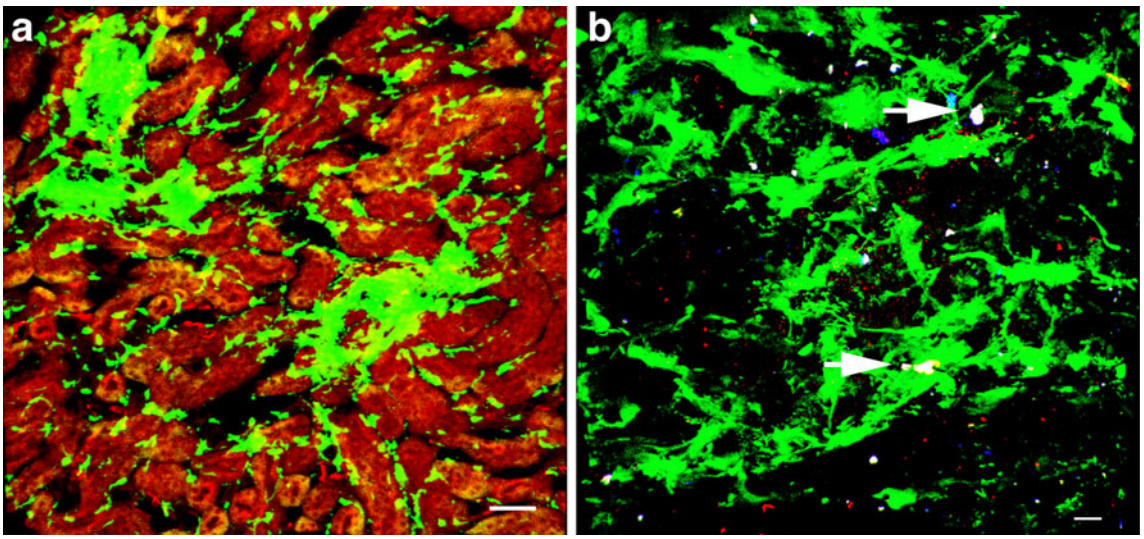

Fig. 1 Representative confocal microscopy pictures of kidney from $Ctns^{-/-}$ mice treated by bone marrow cell transplantation [13] (used with permission). Transplanted, bone-marrow-derived GFP-positive cells are seen in *green*. **a** Abundant interstitial bone-marrow-derived cells can be observed. Some GFP-positive cells are co-localized with distal tubular cells seen in *red* after staining by Dolichos Biflorus Agglutinin (*yellow cells*). **b** F4/80-positive macrophages are stained in *blue* and CD45-positive leukocyte lineage cells are stained in *red*. Few GFP-positive cells are macrophages (*white*, *arrows*)

cells in the kidney expressing CD24 and CD133, and sharing functional properties of stem cells such as their characteristically slow cycling time shown by BrdU labeling. Renal progenitors have been located in several sites within the kidney including the proximal tubuli, glomeruli, peritubular capillaries, and the papilla [43–45]. CD133-expressing renal cells isolated from the tubular fraction of the cortex-enhanced recovery from glycerol-induced tubulo necrosis by integrating into proximal and distal tubules [46]. Studies also showed CD133 and CD24-expressing cells are actively differentiating into podocytes [47]. Duffield and colleagues' research supports the hypothesis that intrinsic renal cell proliferation accounts for the functional recovery of the kidney after ischemia [17]. They showed that 99% of the bone-marrow-derived cells engrafted in the kidney were from lymphoid lineage origin and thus do not restore the epithelial integrity. Similarly, Lin et al. concluded that intrarenal stem cells (not bone-marrow-derived cells) were responsible for the regeneration of kidney tissue after ischemic injury. Thus, following ischemia/reperfusion, most of the epithelial cells were derived from the host and not from the transplanted BMSC [18]. Sequeira Lopez and colleagues showed that blood vessels and red blood cells derive from common precursors during hemo-vasculogenesis in multiple regions in the embryo including the kidney; these precursors may be reactivated after kidney injury as a method of repair [48]. These studies indicate that there are interstitial renal stem cells present in adult kidney that play a part in the regeneration process but the extent of their role and mechanism of action still require extensive investigation.

Other possible origins for the discrepancies in transplantation outcomes

A major issue concerning the present state of determining the role of stem cells in kidney regeneration is the wide variability of cell identification techniques and kidney injury models used.

Detection methodology

Some early studies using fluorescent in situ hybridization (FISH) identified what were thought to be bone-marrow-derived tubules in males with female kidney transplants [9, 24]. In contrast, other studies also using FISH were unable to find any bone-marrow-derived tubules [17], raising the question of whether detection of Y-chromosome-positive epithelial cells had been a technical artifact. Tissue analysis after FISH necessitates immunofluorescent staining and rigorous three-dimensional imaging to avoid the possibility of confusing intraepithelial bone-marrow-derived lymphocytes with bone-marrow-derived epithelial cells. Spyridonidis and colleagues showed that bone-marrow-derived $CD45^+$ hematopoietic stem cells in close contact with epithelial cells could be falsely identified as epithelial cells unless FISH was coupled with staining for anti-CD45 and an epithelial cell-specific marker and imaged by three-dimensional confocal microscopy [49]. Another detection method, using β-galactosidase-positive cells to track bone-marrow-derived cells in the kidney, can also be technically unreliable. Indeed, either pH-dependent detection of endogenous β-galactosidase activity or the leak of the β-galactosidase enzyme/or product from infiltrating BMSC and its local uptake by injured tubular cells might result in the false-positive detection of bone-marrow-derived epithelium [17, 50]. Currently, GFP-positive cell detection seems to be the most effective and sensitive method for identifying stem cell incorporation [11, 13, 17, 51]. GFP has been regarded as a simple marker system to directly trace distribution of donor cells after transplant [52]. However, in some cases, identification of GFP-positive cells can also be problematic due to the tendency of some tissues to demonstrate significant levels of auto-fluorescence with similar emission profiles [29, 53]. Nonetheless, GFP detection in conjunction with lineage-specific antibody staining to unequivocally identify the tubular epithelial cells by three-dimensional confocal microscopy is an effective and specific method.

Renal injury models

The two main categories of renal injury are acute and chronic, though significant differences also exist within these categories. We believe that the kinetics and mechanisms of cell death in the kidney are important to generate the necessary stimuli driving bone marrow stem cell mobilization, migration, and integration into the kidney. Thus, we propose that both differences in the mechanisms and pace of kidney injury can impact experimental outcomes and contribute to the discrepancies observed in the field.

Acute kidney injury in animal models is commonly induced by decreasing blood supply to create ischemia/reperfusion injury (IRI), or via toxins such as folic acid, cisplatin, mercuric chloride, and glycerol. The impact of bone marrow cell transplantation has been studied in one model or another with often different results. Given the fact that even differences in one particular model can lead to different results, this could explain some of these discrepancies. For example, Broekema et al. reported that tubular engraftment of bone-marrow-derived cells depend on the extent and severity of renal damage after ischemia/reperfusion injury [54]. Thus, the quantity of bone-marrow-derived tubular epithelial cells increased with longer ischemic time. What is missing is a systematic

comparison of essentially identical bone marrow transplant protocols across multiple models to determine the impact of the acute renal injuries in each model on the final results reported.

It is our belief that chronic kidney injury is important to obtain abundant and stable bone marrow cell engraftment within the kidney. Support for this hypothesis is found in studies done in a model of Hepatorenal Tyrosinemia Type 1 (HT1) that is characterized by the accumulation of fumarylacetoacetate (FAA) due to the lack of fumarylacetoacetate hydrolase (*FAH*) expressed in liver and proximal tubular cells [55]. Affected human patients develop both chronic liver injury and renal Fanconi syndrome [56]. The mouse model, $Fah^{-/-}$ mice, is neonatal lethal but animals can survive quite well if treated from birth with cyclohexanedione [57]. In this case, renal tubule repopulation by Fah^{+} bone marrow stem cells did not occur presumably due to the minimal renal disease in this successfully drug-treated mouse model [58]. Similarly, no renal tubule repopulation was observed after induction of acute tubular necrosis. Therefore, the investigators modified the HT1 model to induce chronic renal injury by backcrossing the $Fah^{-/-}$ mice to the homogentisic acid dioxygenase-deficient mice, an enzyme upstream of *Fah* in the pathway, leading to the accumulation of the toxic FAA substrate in the proximal tubules. As a consequence, there was a dramatic increase in the repopulation of renal tubules (up to 50%) by Fah^{+} transplanted bone marrow cells and correction of the kidney dysfunction.

However, in chronic kidney disease also, differences in a particular model can lead to different outcomes of BMSC transplantation on renal injury. For example, the genetic background of a particular mouse model can influence the extent and severity of the renal injury and thus, the engraftment of bone-marrow-derived cells within the kidney. The mouse model for Alport syndrome, which develops progressive glomerulonephritis due to a mutation in the Col4A3 gene, illustrates this statement. Col4A3 gene encodes the α3(IV) chain of the collagen protomer in the glomerular basement membrane (GBM) and the mutation closely recapitulates the loss of α3α4α5 type IV collagen protomer found in human Alport's disease [59]. Several investigators demonstrated that wild-type bone marrow-derived cells in C57BL/6J Col4A3 knock-out mice specifically targeted the diseased glomeruli and allowed the reconstitution of the α3(IV) chain resulting in the restoration of the collagen protomer in the GBM [60, 61]. Other studies on 129x1/SvJ Col4A3 knock-out mice showed that Alport mice receiving wild-type or $Col4a3^{-/-}$ BMC exhibited the same prolonged survival benefits, suggesting that irradiation alone was responsible for the therapeutic effects of bone marrow cell transplantation [62]. The progression of the kidney disease in Col4A3 knock-out mice has been shown to be influenced by the genetic background, C57BL/6 J versus 129x1/SvJ [63] and could explain these outcome discrepancies. The mouse model for cystinosis is another example showing the importance of the mouse genetic background in the development of renal

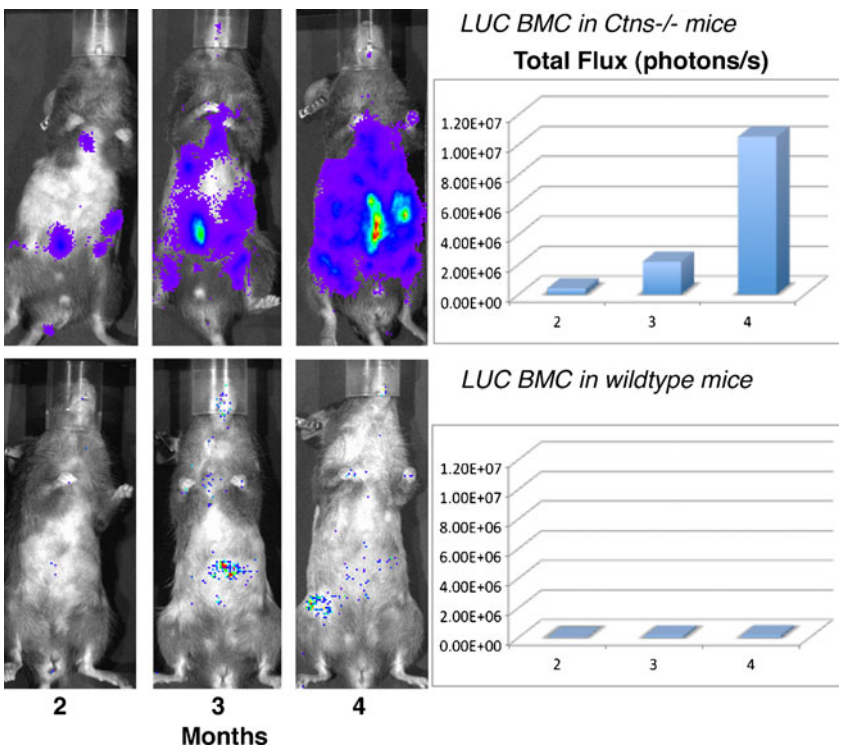

Fig. 2 In vivo luciferase imaging in $Ctns^{-/-}$ mice treated with BMC as a function of time [13] (used with permission). BMC isolated from luciferase transgenic mice were transplanted into lethally irradiated $Ctns^{-/-}$ mice (*upper panel*) and wild-type mice (*lower panel*). These are representative pictures taken in live animals with the IVIS imaging system after luciferin injection at 2, 3, and 4 months post-transplant. The luminescence signal intensities were quantified and are represented in the matching histograms

disease. Indeed, *Ctns*$^{-/-}$ mice on a mix of C57BL/6J and 129×1/SvJ or FVB-N backgrounds did not develop any renal defects [64, 65]. In contrast, *Ctns*$^{-/-}$ mice develop a progressive chronic renal failure on a pure C57BL/6J genetic background [65]. Thus, the mouse model for cystinosis, C57BL/6J *Ctns*$^{-/-}$ mice, is an excellent model for chronic kidney disease and the levels of bone-marrow-derived cells we have observed stably engrafted in the kidney and other organs are impressive by both GFP reporter gene and quantitative PCR analysis (Fig. 1). Moreover, the dynamics of bone marrow cells engrafting in tissue increased rapidly over time as observed using serial measurements in live animals of luciferase reporter gene activity from luciferase-expressing bone marrow cells transplanted in *Ctns*$^{-/-}$ mice (Fig. 2) [13]. In contrast, wild-type mice did not exhibit any stable bone-marrow-derived cell engraftment (Fig. 2), which was consistent with our hypothesis that bone marrow cell migration and integration is actively driven by tissue injury. We also showed that *Ctns*$^{-/-}$ mice transplanted under otherwise identical conditions with Ctns$^{-/-}$ BMSC still accumulated cystine and developed renal dysfunction, proving that these therapeutic benefits came from the transplanted bone marrow cells expressing a functional *Ctns* gene and not from the irradiation. Finally, we showed that transplantation of bone marrow stem cells expressing a functional *Ctns* gene could provide long-term protection to the kidney in *Ctns*$^{-/-}$ mice (up to 15 months post-transplant; data not shown).

Thus, we propose that another reason for discrepancies might be differences in the extent and chronicity of the renal injury, particularly as many of the studied models represent dramatic acute injury. However, even within these models, the genetic backgrounds can influence the extent and pace of the kidney disease and consequently the bone marrow cell transplantation response.

Conclusions

We believe that kidney repair by stem cells is a complex process involving intrarenal stem cells and bone marrow stem cells. For long-term stem cell tissue engraftment and repair, unfractioned bone marrow cells and hematopoietic stem cells are the most suitable compared to mesenchymal stem cells, which have a short-term paracrine effect. The origin of the injury that drives cell death is important and bone marrow stem cell responses will be different according to the model chosen. We believe that the chronicity of the injury is a determinant factor to obtain efficient and abundant bone marrow stem cell mobilization and tissue integration. We also believe that the outcome of bone marrow cell transplantation on kidney disease has to be compared within a unique and identical model and cannot be transposed from one kidney disease to another.

The fate of the cells and the mechanism of action after tissue integration are under investigation. Do the stem cells fuse with or transdifferentiate into renal cells? Do they exchange factors or genetic material that will allow the survival of the surrounded cells? The answers to these questions will be critical in understanding the actual signals regulating and mechanisms resulting in kidney repair by stem cells, local or bone marrow-derived.

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