Contribution of Stem Cells to Kidney Repair

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Key Words

Stem cells • Models of renal disease • Renal injury • Renal repair • Mesenchymal stem cells

Abstract

The potential role of stem cells in the repair of glomerular and tubular injury is under intensive investigation. Several studies have addressed the role of endogenous bone-marrow (BM)-derived stem cells (SC) in the repair of renal injury. Some reports indicate that BM-derived SC are capable of engraftment into damaged nephrons, although the lineage of SC recruited has not been established. However, this issue remains highly controversial, and several studies point to a paracrine/endocrine action of endogenous SC rather than a direct repopulation of the injured nephron. Administration of exogenous mesenchymal SC in experimental acute kidney injury suggests that an SC-based therapy may improve functional and structural recovery of both glomerular and tubular compartments. A contribution of renal resident SC has also been postulated in the recovery after damage. However, several points still need to be clarified regarding the signals regulating homing of SC to injured tissue, the secreted factors underlying the paracrine/endocrine mechanisms, and in particular the long-term in vivo behavior of the administered SC. This review summarizes the current literature on the physiological role of endogenous SC in renal regeneration and on the potential therapeutic strategies based on the administration of exogenous SC.

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Introduction

Acute kidney injury (AKI) is one of the most enigmatic syndromes in nephrology, with reported incidence rates varying from 0.9 to 20% with overall mortality rates between 25 and 80% [1–3]. A significant proportion of patients with AKI requires dialysis [4]. The mortality rate of patients requiring dialysis for AKI (50–60%) is nearly twice as high as that of patients without AKI [5–7]. Although the clinical management of AKI patients has significantly improved in recent years, we still lack specific therapies to enhance kidney repair. Recovery after acute injury is critical for patient morbidity and mortality in the hospital setting. The kidney is the target of several injurious stimuli such as sepsis-associated cytokines, endogenous or exogenous toxins and ischemia. In this context, the renal tubular cells may undergo apoptosis and/or necrosis and loss of tubular epithelial cells [8]. The susceptibility to develop AKI and the recovery of renal function following AKI depend on the ability of renal tubules to regenerate and to replace necrotic tubular cells with functional tubular epithelium [9]. The response to renal injury involves the dedifferentiation of tubular cells that acquire a mesenchymal phenotype. Dedifferentiated cells then migrate into the regions where tubular cells underwent necrosis, apoptosis and detachment with denudation of the tubular basement membrane. This process is followed by cell proliferation and eventually by their subsequent differentiation into functional epithelial cells and restoration of tissue integrity [9]. The absence or re-

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duction of epithelial regeneration may predispose to tubulointerstitial scarring and chronic kidney disease.

Although the tubular epithelium is the target of ischemic and nephrotoxic insults, it has become increasingly clear that renal endothelial cells in AKI undergo early damage and swelling [10] causing narrowing of the vascular lumen, followed by impaired microvasculature perfusion [11]. The most important consequence of this 'no-reflow' phenomenon is a delayed functional recovery of the damaged kidney due to prolonged hypoperfusion. Therefore, the renal microvasculature is of significant importance for tissue regeneration in AKI.

Taken together these considerations have stimulated research to develop stem-cell (SC)-based therapy for treatment of AKI. In the last 10 years, huge steps have been taken in research into SC, including progress towards the identification and understanding of embryonic kidney precursor cells and adult renal progenitor cells. However, the limited access to embryonic tissues as well as the complex ethical issues involved with the use of embryonic cells have led to more attention being placed on adult SC.

SC in the adult are critical for self-renewal in tissues such as the hematopoietic system, the intestine and the skin that require a high cell turnover to maintain their homeostasis. Other tissues have a much lower rate of cell turnover such as the kidney, the lung, the skeletal muscle and the liver. However, following injury, it has been suggested that repair also in these tissues may involve the recruitment, proliferation and differentiation of SC. SC are characterized by their ability to self-renew and to differentiate into a variety of cell types [12]. Several studies have established the plasticity of bone-marrow (BM)-derived SC as they have the ability to cross lineage boundaries forming components of different tissues [12, 13]. Moreover, resident adult SC have been isolated from several tissues, including the central nervous system [14], retina [15], skeletal muscle [16], liver [17] and kidney [18]. Tissue SC preferentially generate differentiated cells of their tissue of origin, suggesting a relevant role in the postnatal growth of organs, in the physiological turnover and in tissue repair.

Even if SC directly contribute to the regeneration of some injured tissues, it remains unclear whether SC participate in the turnover and repair of the kidney. The aim of this review is to illustrate the presently available evidence for the contribution of SC in kidney repair.

BM-Derived SC

Two main SC populations are present in the BM: the hematopoietic SC (HSC) and the mesenchymal SC (MSC), which reside within the stromal compartment of the BM [19]. HSC are undifferentiated cells capable of self-renewal and stepwise differentiation into fully specialized cells of the blood, e.g. erythrocytes, thrombocytes and leukocytes. Although much insight has been gained into the identity of these rare BM cells, their full identity is still debated, and there is not one single marker to truly identify this cell [20]. Recently, great attention has been directed to an endothelial committed type of progenitor cells derived from HSC lineage, defined as endothelial progenitor cells (EPC) and found in the BM and peripheral blood [21]. EPC share common stem/progenitor cells with HSC, and they coexpress SC markers such as CD34 and CD133 and endothelial markers such as vascular endothelial growth factor (VEGF) receptor 2 and vascular endothelial cadherin [22]. EPC have the ability to incorporate into injured vessels and to become mature endothelial cells during re-endothelialization and neovascularization processes [23]. Recent studies have suggested that EPC may promote local angiogenesis also by secreting angiogenic growth factors in a paracrine manner [23] or by horizontal transfer of mRNA mediated by microvesicles that induce a proangiogenic program in mature endothelial cells [24].

The MSC are undifferentiated adult SC of mesodermal origin that have the capacity to differentiate into cells of connective tissue lineages, including bone, fat, cartilage and muscle [13]. In addition, MSC play a role in providing the stromal support for HSC in the BM [25]. MSC represent a very small fraction, 0.001–0.01% of the total population of nucleated cells in the BM, but they can be isolated and expanded with high efficiency in culture as plastic adherent cells [26]. The characterization of MSC includes their multipotency, the expression of typical surface markers such as CD90, CD73, CD105, CD44 and CD29, and the absence of hemopoietic lineage markers such as CD34 and CD45. Beside their presence in the BM, MSC have been detected in perivascular tissue of several organs and in the fat [27]. Recent studies demonstrated that MSC are nonimmunogenic and display immunosuppressive properties, with the ability to inhibit maturation of dendritic cells and to suppress the function of naïve and memory T cells, B cells and NK cells [28]. These properties of MSC render these cells especially attractive for therapeutic application in several inflammatory and immune-mediated diseases, as well as in regenerative medicine [29–31].

Do SC Contribute to Repair in Acute Tubular Injury?

Contribution of Endogenous BM-Derived SC to Tubular Repair

The possibility that BM-derived SC might functionally contribute to the renal tubule regeneration is still a matter of debate. Several studies have demonstrated the presence of Y-chromosome-bearing cells in female kidneys transplanted into male recipients, suggesting that SC derived from the male BM migrate and differentiate into the transplanted organ [32–34]. However, only a small percentage of the total cells present in the kidney was of BM origin. Using whole-BM transplantation in the mouse, Poulson et al. [32] demonstrated that BM-derived cells could contribute to regeneration of the renal tubular epithelium. However, subsequent studies have challenged the relevance of differentiation of BM-derived SC into tubular epithelial cells after injury [35–37]. Lin et al. [38] showed that renal tubular resident cells provide a major contribution to renal repair after ischemia-reperfusion injury using transgenic mice expressing enhanced green fluorescent protein specifically and permanently in mature renal tubular epithelial cells. However, the studies confirmed an effective improvement of the renal function provided by the BM-derived SC, comparing irradiated animals and nonirradiated animals or irradiated animals with reconstituted BM [39]. The role of intrinsic epithelial cells in kidney repair after injury has recently been confirmed by Humphreys et al. [40], who provided evidence, using genetic phase mapping techniques, that surviving tubular cells are the predominant cellular components involved in the repopulation of ischemic injured tubuli.

The contradictory results in the localization of BM-derived SC may be ascribed to methodological hindrances in tracking BM-derived cells, particularly in injured tissues. Cell fusion may also account for discrepancy in the different studies. Indeed, Fang et al. [41] reported that 10–20% of BM-derived SC engrafted in the kidney during regeneration after folic acid injury were dependent on cell fusion with resident epithelial cells. Moreover, in a model of renal injury due to a toxic intermediate of tyrosine metabolism in a fumarylacetoacetate-hydrolase-deficient mouse, fumarylacetoacetate-hydrolase-positive transplanted BM-derived cells, which are resistant to this metabolite, produced a significant replacement of damaged proximal tubular epithelium by fusion with tubular cells reaching up to 50%, and not by transdifferentiation [42].

It remains to be determined whether the endogenous BM-derived SC that home to the injured kidney are HSC

or MSC. This may be particularly relevant to design therapy based on BM-derived SC mobilization. Results on BM-derived SC mobilization are discordant. Tögel et al. [43] reported that HSC mobilization has a potential detrimental effect on kidney regeneration. In contrast, experiments by Fang et al. [41] and Iwasaki et al. [44] demonstrated renoprotection in folic-acid- and in cisplatin-induced AKI by BM-derived SC mobilization with granulocyte colony-stimulating factor or with the combination of granulocyte and macrophage colony-stimulating factors.

Administration of Exogenous SC Favors Recovery of Experimentally Induced AKI

Several studies have demonstrated that the administration of in vitro expanded SC may protect and reverse AKI [39, 45–49]. Morigi et al. [45] demonstrated that the beneficial effect of BM-derived SC is not ascribed to the HSC but rather to the MSC. Based on these experiments, all subsequent studies were focused on the therapeutic potential of MSC. MSC are also capable of differentiating into various tissues of mesenchymal and nonmesenchymal origin and of migrating to sites of tissue injury and inflammation leading to tissue repair [30, 31].

The infusion of in vitro expanded MSC protects and improves the recovery from acute tubular injury induced by cisplatin and glycerol [45–47]. Moreover, MSC administration was shown to protect from ischemia-reperfusion injury [48, 49]. Interestingly, MSC improved the recovery also when administered after the injury had occurred [49]. Taken together these studies provide good evidence that, at least in the rodent models of AKI, MSC favored functional and morphological recovery.

Few studies have addressed the therapeutic potential of EPC in AKI. The rationale for the use of EPC is based on the presence of vascular injury in ischemic AKI and on experiments performed in SCID mice by administration of human umbilical vein endothelial cells that were shown to improve renal function. Moreover, chimeric cells expressing endothelial nitric oxide synthase, thus mimicking one of the functions of endothelial cells, were also partially protective, although less than mature endothelial cells [50]. Indeed, EPC induced a significant preservation of renal function in ischemic AKI [51].

Do MSC Contribute to the Recovery of AKI by a Mechanism of Protection or by Differentiation in the Kidney Tubule?

In cisplatin- and glycerol-induced AKI, MSC are localized within regenerating tubules [45–47]. Both mod-

els are characterized by extensive necrosis of proximal and distal tubules that may favor migration of MSC within regenerating tubules. The possibility of MSC transdifferentiation in various renal resident cells has been shown by Yokoo et al. [52] who injected MSC directly into the developing kidney followed by embryo and organ cultures. However, the low number of MSC detectable within tubules after injury together with the increase in proliferating cell nuclear antigen-positive tubular cells throughout the kidney suggest a trophic effect of MSC on resident tubular cells which survived the injury rather than a direct repopulation [48, 49]. Duffield et al. [39] observed a beneficial effect of MSC infusion in ischemia-reperfusion AKI. However, these authors found that culture conditions favoring in vitro differentiation in endothelial cells are required for the in vivo protecting effect in this model. In addition, they and others only found interstitial localization of SC without incorporation into tubules or endothelium [39, 48, 49]. The discrepancy in the results of MSC integration into tubules may be ascribed to the different degrees of severity of the model and protocols used. Indeed, Broekema et al. [53] demonstrated that the tubular engraftment of BM-derived cells depends on the severity of renal damage after ischemia-reperfusion injury and that once engrafted these cells acquire an epithelial phenotype.

Despite the low number of MSC that differentiated into epithelial cells, there is a general agreement that the beneficial effect of MSC infusion in AKI is due to the ability of these cells to determine an environment favoring proliferation of dedifferentiated epithelial cells surviving the injury or of resident SC [54].

Is the Recruitment of MSC within the Injured Kidney a Critical Factor?

The mechanisms of renal repair are still incompletely understood. It has been suggested that the local recruitment of MSC is required for their beneficial effect [54]. Fluorescence- or iron-labeled MSC were shown to localize within the injured renal cortex both in glomeruli [48–49] and peritubular capillaries [47] shortly after infusion. In particular, in the ischemia-reperfusion model, exogenous MSC were detected in the kidney, liver, lungs, BM and spleen 2 h after infusion. In the kidney, almost all MSC were located inside glomerular capillaries. By 24 h, occasional cells were still detected in the lung, whereas they were absent in the kidney [48].

Currently, little is known about the molecular mechanisms that underlie MSC recruitment. Recent studies suggest that triggering of the chemokine receptor CXCR4

by its ligand stromal derived factor may play an important role in the migration of transplanted MSC to sites of injury [55]. Although it is likely that several mechanisms, including chemokine-chemokine receptor interactions and possibly several adhesion receptor-ligand pairs, participate in MSC homing, we found that the interaction between CD44 and hyaluronans (hyaluronic acid) is critical for the localization of exogenous MSC to kidneys in glycerol-induced AKI. In this model, MSC administered intravenously are soon found in peritubular capillaries, in the interstitial space and occasionally within damaged renal tubules along with morphological and functional evidence of renal recovery [47]. The receptor for CD44 is upregulated in renal cortex after injury, and MSC migrate under a gradient of soluble hyaluronic acid suggesting a chemotactic mechanism. During injury, it is conceivable that protease-induced matrix degradation may release soluble hyaluronic acid fragments that may contribute to the recruitment of MSC. The reduced recruitment of CD44-negative MSC in the injured kidney was associated with a decreased protection from injury [47], suggesting that at least a transient accumulation of MSC is required for their beneficial effect. This experimental evidence is in agreement with the concept that MSC may exert their effect by a paracrine action on resident cells. According to this interpretation, the repopulation of tubules after injury cannot be ascribed to the transdifferentiation of the injected MSC but rather to a beneficial effect of mediators and growth factors that they release (fig. 1). MSC possess an anti-inflammatory, antiapoptotic and immunosuppressive potential that may be involved in the protection of tissue injury [28, 29]. Tögel et al. [56] showed a vasculotropic and paracrine action of infused MSC suggesting that the ability to home and the inhibition of apoptosis are important determinants for the renoprotective effect of MSC. The potential role of insulin-like growth factor 1 as a factor involved in the effect of MSC has recently been suggested by experiments based on the administration of insulin-like growth factor 1 gene-silenced MSC that showed limited protective effect [57]. Therefore, MSC may favor dedifferentiation and proliferation of the surviving tubular cells or stimulation of resident SC [54].

Recently, it has been suggested that homing is not an absolute need for the beneficial effect of MSC-based therapy provided that the systemic concentration of critical factors derived from MSC be sufficient to stimulate renal resident cells. Indeed, Bi et al. [58] demonstrated that humoral factors secreted by MSC, and not the local presence of these cells, are responsible for the renoprotective effect

Fig. 1. Acute tubular injury: role of endogenous and exogenous SC in repair. BM-derived SC may enter the circulation and reach the sites of tissue injury. Whether BM-derived HSC or MSC contribute to repopulation of tubules after injury by transdifferentiation/fusion or by a paracrine action remains controversial. MSC can be recovered from BM, expanded in vitro and administered for therapeutic purposes. Experiments using exogenous MSC suggest that MSC are recruited at the site of injury and act mainly by a paracrine effect on surviving tubular cells by stimulating dedifferentiation, proliferation, migration and eventually redifferentiation into mature epithelial cells. The beneficial effects of MSC on AKI may depend on the release of mediators such as VEGF, insulin-like growth factor, hepatocyte growth factor, prostaglandin E₂ and other soluble mediators that inhibit apoptosis and stimulate proliferation of tubular cells and reduce the recruitment of inflammatory cells. In addition, the administered MSC may modify the microenvironment by allowing expansion and differentiation of resident SC that may directly or indirectly contribute to repopulation of injured tubules.

of MSC-based therapy, suggesting an endocrine action. In other terms, local recruitment is seen only as a mechanism for increasing the intrarenal concentration of paracrine factors released by MSC.

Do Resident Progenitor Cells/SC Contribute to Renal Repair?

The paracrine/endocrine effect of exogenous MSC may induce dedifferentiation and proliferation of tubular cells which survived injury or alternatively stimulate an endogenous SC population.

Several studies indicate the presence of different renal resident precursor/SC populations in the adult kidney (table 1). However, the location and the characteristics of renal SC are controversial. Based on the retention of bromodeoxyuridine, Oliver et al. [59] identified slow cycling SC in the renal papilla of adult rat kidney suggesting the presence of an SC population capable of epithelial differentiation after ischemic injury. Based on these observations, the authors proposed that the renal papilla is a niche for the adult kidney SC in rats. Maeshima et al. [60] described the presence of bromodeoxyuridine-labeled

cells also in the renal tubules of adult rats, able to integrate into the kidney rudiments and to differentiate into epithelial structures. Kitamura et al. [61] characterized a clone of renal progenitor cells isolated from the S3 segment of the rat nephron. Recently, Gupta et al. [62] identified multipotent renal SC expressing mesenchymal markers, such as CD90, and embryonic SC markers, such as Oct4 and Pax2, in the tubuli of the rat kidney. Renal SC of different origin were shown to contribute to tubular regeneration in models of ischemia-reperfusion injury [61, 62]. An MSC population has also been identified in the glomeruli of mice [27]. These cells were shown to be multipotent and to express smooth muscle myosin, like the mesangial cells. Other SC populations have been isolated from the rodent kidney using the ability to extrude Hoechst dye (so-called side population). However, results on the characteristics of these cells, on their renal or hematopoietic origin and on their integration into the renal tissue are conflicting [63–65].

Iwatani et al. [63] described in the adult rat kidney the presence of a 'side' population; however, they excluded their differentiation into renal tissue, suggesting a hema-

Table 1. Different SC populations isolated from the kidney

Markers	Localization	Potential	Species	Reference
Bromodeoxyuridine	papilla	multipotent	rat	Oliver et al., 2004 [59]
	tubuli	unipotent	rat	Maeshima et al., 2004 [60]
Renal/embryonic markers (Pax2, Wnt4, Wnt1)	S3 segment	multipotent	rat	Kitamura et al., 2005 [61]
Mesenchymal markers (CD29, CD90, CD73, CD44)	glomeruli	multipotent	mouse	da Silva Meirelles et al., 2006 [27]
Side population	not done	none	rat	Iwatani et al., 2004 [63]
	not done	multipotent	mouse	Hishikawa et al., 2005 [64]
	tubuli	multipotent	mouse	Challen et al., 2006 [65]
Oct4	proximal tubuli	multipotent	rat/mouse	Gupta et al., 2006 [62]
CD133	interstitium and proximal tubuli	pluripotent	man	Bussolati et al., 2005 [18]
	Bowman's capsule	multipotent	man	Sagrinati et al., 2006 [69]

topoietic origin. On the contrary, Hishikawa et al. [64] reported the ability of cells of the 'side' population to differentiate in renal and several other cell lineages in vitro. However, no integration into the renal structures was observed when the side population cells were injected in rats with Thy-1 glomerulonephritis. Recently, Challen et al. [65] detected a 'side' population in the mouse embryonic and adult kidney, in particular in the tubular compartment, that was characterized as a heterogeneous population. 'Side' population cells from murine adult kidney showed multipotent differentiative ability and contributed to the repair of renal tissue in the Adriamycin nephropathy model, although no integration into the tissue was observed.

The first demonstration of the presence of resident progenitors/SC in the human adult kidney was obtained by our group using CD133 as an SC marker [18]. The CD133 is mainly known as a marker of HSC/endothelial progenitors [66], but recent reports indicate its expression in tissue SC such as those present in the prostate and brain [67, 68]. We found a rare population of CD133-positive cells in the interstitium in proximity of proximal tubules and glomeruli, or within tubules [18]. Once isolated, these cells lacked the expression of hematopoietic markers (CD34 and CD45), whereas they expressed some MSC markers, such as CD29, CD90, CD44 and CD73. Moreover, they expressed Pax2, an embryonic renal marker, suggesting their renal origin. These cells may undergo epithelial and endothelial differentiation both in vitro and in vivo [18]. When injected in vivo subcutaneously in Matrigel, CD133+ cells spontaneously differentiated in tubular structures expressing proximal and distal

tubular epithelial markers. In vivo, when injected subcutaneously in Matrigel, endothelial differentiated CD133+ cells formed vessels connected with the mouse vasculature. Moreover, when injected into mice with glycerol-induced acute renal injury, CD133+ renal progenitors homed to the kidney and integrated into proximal and distal tubules during the repair.

Recently, Sagrinati et al. [69] isolated and characterized a population of CD133+ CD24+ cells from Bowman's capsule of adult human kidneys. These cells exhibited a multipotent differentiation ability, being able to generate mature tubular epithelial cells, osteogenic cells, adipocytes and neuronal cells. When injected into mice with glycerol-induced acute renal injury, CD133+ CD24+ SC contributed to tubular regeneration.

Recent data acquired in malpighian tubules of adult *Drosophila* identified a population of renal and nephric SC able to differentiate and to generate all the different cell types of the malpighian tubules [70]. These SC were shown to control their own self-renewal or differentiation through the JAK/STAT signaling pathway in the absence of a fixed niche. Although several sources and types of renal SC have been identified in mammals, the data from *Drosophila* suggest that one type of SC may be enough to repair and regenerate the renal tissue after injury, and that a fixed niche may not be required for renal SC [71].

Whether resident SC contribute to the repair of injured kidney in physiopathological conditions either directly or by orchestrating the tubular regeneration, and whether MSC therapy may stimulate resident SC remain to be determined. However, preliminary experiments in

Fig. 2. Acute glomerular injury: role of EPC and MSC in repair. **a** Injection of BM-derived EPC in rats with Thy1.1 glomerulonephritis is followed by the incorporation of EPC in the endothelial lining of glomerular capillaries favoring revascularization and recovery of glomerular injury. **b** The administration of exogenous MSC accelerates glomerular healing in Thy1.1 glomerulonephritis by local production of VEGF and transforming growth factor β (TGF- β) and not by transdifferentiation into resident glomerular cell types. Glomerular healing depends on the stimulation of neoangiogenesis, matrix remodeling by production of metalloproteinases (MMP9, MMP2) and inhibition of inflammation. However, it has recently been demonstrated that human MSC may localize in renal glomeruli of athymic mice with glomerulonephritis and differentiate into mesangial cells.

our laboratory indicate that MSC/MSC-conditioned medium stimulate in vitro and in vivo morphogenesis of human renal progenitor cells and of mature tubular cells injected subcutaneously in SCID mice within Matrigel.

Do SC Contribute to the Repair of Glomerular Injury?

Relatively few studies have addressed the contribution of SC to the glomerular response to injury. It is now recognized that the progression of glomerular diseases is characterized by loss of microvasculature, reduced endothelial proliferative response, enhanced production of antiangiogenic factors and reduced expression of angiogenic factors [72]. In addition, there is evidence that stimulation of angiogenesis may slow the progression of glomerular injury [73, 74]. Therefore, depending on the type and intensity of the injurious stimuli, the glomerular response may encompass two possibilities: on one hand, capillary regeneration along with extensive remodeling of matrix may lead to repair; on the other, the lack of endothelial regeneration associated with mesangial expansion and uncontrolled matrix production may lead to glomerulosclerosis.

Contribution of Endogenous BM-Derived SC to Glomerular Repair

Most of the regeneration studies performed used the model of Thy-1 glomerulonephritis, which is an acute

model of glomerular injury, where neoangiogenesis plays a relevant role in the recovery of glomerular lesions.

Based on BM transplantation experiments, Ito et al. [75] demonstrated that the BM is a reservoir of repopulating mesangial cells during glomerular remodeling in anti-Thy-1 glomerulonephritis in rats. Rookmaaker et al. [76] also showed that BM-derived SC contribute to revascularization in anti-Thy-1 glomerulonephritis. In these experiments BM-derived cells are fully integrated in the glomerular structure as endothelial and mesangial cells [76] (fig. 2).

Moreover, BM-derived cells have also been shown to ameliorate the renal disease in a mouse model of Alport syndrome [77, 78]. In particular, the recruitment of BM-derived progenitor cells within the damaged glomerulus and their differentiation into podocytes and mesangial cells leads to a partial restoration of the expression of the type IV collagen α_3 -chain.

In all these studies of BM-derived SC recruitment to damaged glomeruli, the lineage of SC recruited has not been established.

Effect of Infusion of Exogenous BM-Derived SC in Experimental Glomerulonephritis

Experiments of BM-derived EPC injected in rats with Thy1.1 glomerulonephritis showed the incorporation of EPC in the endothelial lining and their contribution to revascularization and recovery of glomerular injury [79, 80] (fig. 2).

The effect of administration of exogenous MSC on glomerular healing of experimental glomerulonephritis has also been investigated. Injected MSC accelerate glomerular healing in Thy1.1 glomerulonephritis by local production of VEGF and transforming growth factor β and not by transdifferentiation into resident glomerular cell types [81]. In contrast, Wong et al. [82] recently demonstrated that human MSC localize in renal glomeruli of athymic mice with an antimesangial-antibody-induced glomerulonephritis and differentiate into mesangial cells in vivo after glomerular injury occurred (fig. 2). In subsequent experiments by Kunter et al. [83], MSC localized within glomeruli were found to exert an early beneficial effect but in the long term they may undergo adipogenic differentiation and may contribute to the development of sclerosis. MSC prevent progressive experimental renal failure but maldifferentiate into glomerular adipocytes. Therefore, in light of a possible therapeutic application of MSC, one should consider that once injected, MSC may also undergo undesired differentiation that in the long term may be detrimental. Taken together, these results seem to suggest that EPC are better candidates for cell therapy, at least in acute glomerular diseases.

Conclusion

In conclusion, preclinical studies suggest that the administration of exogenous SC may ameliorate renal injury and accelerate repair. Concerning acute tubular injury, the main focus is now on MSC-based therapy as HSC seem to be ineffective. However, experiments based on the administration of exogenous SC do not necessarily reflect the physiological role of endogenous BM-derived SC the role of which remains incompletely understood. When injected after injury, MSC are capable of selectively homing into the kidney and to accelerate mor-

phological and functional repair of the injured nephrons. Since the incorporation into repairing renal epithelium is a rare event, MSC most likely act by paracrine or even endocrine mechanisms related to the production of a broad array of mediators and growth factors with immunosuppressive, anti-inflammatory, antiapoptotic and proliferative effects. It would be therefore important to understand which signals regulate homing of SC to injured tissue and which secreted factors underlie the paracrine/endocrine mechanisms. In addition, different populations of progenitors/SC have been identified in the adult kidney. These cells may represent a remnant of embryonic SC in the adult tissue or populations of BM-derived SC homed within the kidney and modified by the local microenvironment. This may implicate a partial commitment or different degrees of maturation of the different SC populations. Resident SC may account for the growth of the organ during development and for the physiological cell turnover but it remains to be determined whether they participate in repair or in progression of renal injury. Preliminary evidence suggests that MSC may induce tubular morphogenesis both in resident SC and in tubular cells. Experiments aimed to investigate the potential regenerative effect of SC in chronic renal diseases are so far lacking. However, taken together the experimental studies so far available suggest the possibility to exploit the regenerative potential of adult SC for therapeutic purposes in AKI. This may be achieved either by administration of ex vivo expanded SC populations or by strategies aimed to expand and differentiate local progenitors/SC. At variance with pluripotent embryonic SC, adult SC have a good safety record in human studies so far performed. However, it is necessary to fill several gaps in our knowledge both on the mechanisms of action and in particular on the long-term behavior of in vivo administered SC, in view of their possible maldifferentiation or transformation.

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