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The Regenerative Potential of Stem Cells in Acute Renal Failure

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Adult stem cells have been characterized in several tissues as a subpopulation of cells able to maintain, generate, and replace terminally differentiated cells in response to physiological cell turnover or tissue injury. Little is known regarding the presence of stem cells in the adult kidney but it is documented that under certain conditions, such as the recovery from acute injury, the kidney can regenerate itself by increasing the proliferation of some resident cells. The origin of these cells is largely undefined; they are often considered to derive from resident renal stem or progenitor cells. Whether these immature cells are a subpopulation preserved from the early stage of nephrogenesis is still a matter of investigation and represents an attractive possibility. Moreover, the contribution of bone marrow-derived stem cells to renal cell turnover and regeneration has been suggested. In mice and humans, there is evidence that extrarenal cells of bone marrow origin take part in tubular epithelium regeneration. Injury to a target organ can be sensed by bone marrow stem cells that migrate to the site of damage, undergo differentiation, and promote structural and functional repair. Recent studies have demonstrated that hematopoietic stem cells were mobilized following ischemia/reperfusion and engrafted the kidney to differentiate into tubular epithelium in the areas of damage. The evidence that mesenchymal stem cells, by virtue of their renoprotective property, restore renal tubular structure and also ameliorate renal function during experimental acute renal failure provides opportunities for therapeutic intervention.

Key words: Stem cells; Acute renal failure; Tubular cells; Kidney repair

INTRODUCTION

Acute renal failure (ARF) is emerging as a public health problem worldwide. ARF complicates approximately 5% of all hospitalized patients, with a higher prevalence in critical care units (26,40,51,54). Despite major advances in dialysis and intensive care, the mortality rate among patients with severe ARF remains greater than 50%.

ARF is caused by nephrotoxic or ischemic insults to the kidney and is potentially reversible, being often just one element of multiple organ damage. Several pharmacological approaches have been attempted and resulted efficacious in experimental animals but have failed to manifest substantial protective effects in clinical practice (12,17).

Dysfunction and loss of tubular epithelial cells play central roles in the process underlying the failure of the kidney after ischemic or toxic challenge (31,53,54). Tubular alterations are related to intracellular ATP depletion, which leads to actin cytoskeleton dysregulation with consequent loss of the brush border, loss of focal cell contacts, and disengagement of the tubular cells from the underlying extracellular matrix. After detachment from the tubular basement membrane, sublethally injured cells and apoptotic or necrotic cells (32) can obstruct the tubular lumen, leading to increased intratubular pressure and decreased glomerular filtration rate (31, 53,54). Conversely, the epithelial lining of the tubule also has remarkable capacity to recover. In animal models, the rate of recovery strictly depends on the replacement of damaged and/or dead epithelium with a new functioning one. Growth factors, such as insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF), epidermal growth factor (EGF), and recently neutrophil gelatinase-associated lipocalin (NGAL) have been consistently used to potentiate tubular regeneration in experimental ARF (16,25,38). Protection may relate both to stimulatory actions on the regenerative potential of surviving tubular cells and to cell "rescue." One major limitation to such healing is the requirement for a critical number of surviving cells to restore structural integrity. An alternative strategy should consider the local supply of new cells to direct the replacement of damaged cells.

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Stem cells of adult organs have traditionally been viewed as multipotential precursor cells capable of maintaining, generating, and replacing mature cell types within their own specific tissue, as a consequence of physiological cell turnover or tissue injury (3). In the last years it has become very clear that adult bone marrow-derived stem cells have remarkable plasticity to the extent that they can differentiate into multiple lineages other than the tissue of origin. After mesenchymal or hematopoietic stem cell transplantation, donor cells have been shown to transdifferentiate into cardiomyocytes, skeletal muscle cells, hepatic epithelium, neuroectodermal cells, and vascular endothelium (10,27,30,44,50, 52,57). However, very recently, it was reported that cell fusion between transplanted donor bone marrow cells and recipient tissue has been claimed as an alternative novel mechanism to transdifferentiation, which can occur in vivo (59) and produce functional cells in liver (60) and brain (61). However, this is a controversial issue, because in other experimental systems—skeletal muscle and pancreatic islets of Langerhans—the cell fusion process has been ruled out as a way to explain bone marrow stem cell plasticity (21,29).

RENAL STEM/PROGENITOR CELLS IN THE ADULT KIDNEY

Although under physiological conditions the adult kidney displays a low cell turnover, after injury an increased cell proliferation is the driving event that directs towards tissue recovery. This behavior, proper of the kidney tissues during the repairing events, supported the hypothesis that resident cells can be involved in restoring structure and function by means of cell division and/or differentiation. The identity of these cells is still under investigation. Could these cells be true stem or progenitor cells that reside a specific niche in the kidney? Are they residual cells maintained since nephrogenesis? Do they originate from tubular epithelial cell dedifferentiation? An effort is being conducted by researchers to answer these questions and at our knowledge it is likely that one possibility does not exclude the other.

Tissue-based stem cells have been found to give origin to mature cells during a physiologic cell turnover or after tissue damage. Pluripotent kidney stem cells able to generate the various cell types present in the kidney and to self-renew have not been found yet. If such cells were to be present in the kidney, they would probably be residual cells maintained since nephrogenesis, sharing molecular markers of the embryonic renal stem cell. It has been demonstrated (19) that metanephric mesenchymal cells could generate all the different types of nephron epithelia (except collecting ducts), suggesting that these cells represent renal epithelia stem cells. Moreover, the metanephric mesenchyme contains cells that are pluripotent and able to generate not only epithelia but also other cell types such as myofibroblasts, smooth muscle cells, and cells expressing some endothelial markers (42). Further evidence that metanephric mesenchyme can develop nonrenal derivatives such as cartilage and bone, in addition to glomeruli and tubules, has been provided by Dekel et al. (9) in mice. When human metanephroi were transplanted into mice, they were able to engraft and differentiate into functional mature nephrons while accompanied by a profile of gene expression similar to normal human kidney development (9).

Defining the molecular characteristics of embryonic renal stem cells before and during the process of nephrogenesis could be crucial to direct research towards adult renal stem cell identification. A cell population that expresses a phenotype of metanephric mesenchyme epithelial precursor could be a good candidate for renal stem cell title.

Another strategy used by researchers for renal stem cell recognition is based on the property that stem cells cycle very slowly. Cells that divide infrequently could be localized by labeling their DNA [e.g., by using bromodeoxyuridine (BrdU)]. On the basis of this concept, Maeshima et al. demonstrated the existence of label-retaining cells in tubular cells of normal rat kidneys (34). During the regenerative process following ischemia, these cells express mesenchymal cell markers, vimentin, and e-cadherin, and undergo division, suggesting the existence of progenitor-like cells that participate in kidney regeneration. Based on the same method that uses BrdU incorporation, Oliver et al. found that renal papilla is a niche for kidney stem cells (43). The authors demonstrated the presence of BrdU-retaining cells in the papillary interstitium and in some tubules. During recovery from ischemia, BrdU-positive cells decreased in number, suggesting that they can be involved in kidney repair. In vitro, renal papillary cells are multipotent whereas when injected into the renal cortex they incorporate into parenchyma. Cells with the characteristic of renal progenitor cells have been isolated from the tubular fraction of normal renal cortex by targeting CD133, a marker known to be expressed by hematopoietic stem and progenitor cells, undifferentiated human intestine-derived epithelial cells, and embryonic kidney (6). These cells were able to differentiate in vitro towards epithelium and endothelium. In SCID mice with glycerol-induced acute tubular injury, intravenously injected human CD133+ renal progenitor cells were found localized in the proximal and distal tubuli.

Another possibility, which attributes to terminally differentiated resident tubular cells a role in kidney repair, has been documented. Tubular epithelial cells that survive to damage are able to proliferate, generate identical cells and/or dedifferentiate, and subsequently reen-

ter the cell cycle. Tubular cell dedifferentiation is a phenomenon that is documented and involves acquisition, by tubular cells, of an immature mesenchymal phenotype, vimentin positive. While dedifferentiating, these cells also express pax-2, a factor involved in kidney development (63).

Giving the variety of possibilities here described for kidney regeneration after injury, it could be speculated that one mechanism can be selectively involved into a specific situation of damage depending on type and/or the severity of the injury.

ADULT BONE MARROW-DERIVED STEM CELLS PARTICIPATE IN KIDNEY REMODELING

Several reports have shown that adult bone marrow-derived stem cells contribute to turnover and regeneration of several compartment of the kidney (47). Female mice recipients of male bone marrow graft showed colocalization of Y chromosomes and the tubular epithelial marker Lens culinaris lectin, in up to 8% of tubular epithelial cells, indicating that bone marrow cells can traffic into the kidney and participate to the normal tubular epithelial cell turnover (47). In men receiving a kidney transplant from female donors, Y chromosome-containing tubular epithelial cells were observed in kidney suffering damage as a consequence of acute tubular necrosis (47). Similarly, Gupta et al. have documented in patients with sex-mismatched kidney transplants that 1% of the tubular cells were Y chromosome positive in the kidneys after injury (14).

Hematopoietic Stem Cells

Bone marrow-derived hematopoietic stem cells (HSC) have a clearly defined therapeutic potential in liver, heart, and brain reconstitution (10,30,44). In a recent study, purified preparation of hematopoietic stem cells (Rh^{lo} Lin^- $Sca\text{-}1^{POS}c\text{-}kit^{POS}$ cells) isolated from Rosa 26 mice, transgenic for β-galactosidase (xGal), participated to renal tubular repair when transplanted into female nontransgenic mice with ischemic acute renal injury (33). Donor-derived cells, positive for xGal and Y chromosome, also expressed sodium/phosphate cotransporter type 2 and Fx1A, thus suggesting that HSC can differentiate into renal tubular epithelial cells (33). A further demonstration of translineage differentiation of HSC into renal epithelial cells derived from the evidence that Lin^- $Sca\text{-}1^{POS}$ HSC, homing bone marrow of irradiated mice, were mobilized by renal ischemia-reperfusion into peripheral blood, engrafted the kidney where they integrated and differentiated into tubular epithelium in the areas of damage (24). However, consistent with data of our group (39), hematopoietic stem cell infusion had no protective effect on renal function impairment of ischemic mice (24), although they limited further worsening of BUN induced by bone marrow ablation in these mice.

These studies have evoked new therapeutic strategies aimed at enhancing the circulation of HSC pool into the kidney for the treatment of acute tubular necrosis (22, 41,56). Mobilization of HSC with cyclophosphamide and granulocyte-colony stimulating factor (G-CSF) resulted in a significant increase in circulating peripheral blood stem and progenitor cells in mice with ischemic injury. Unexpected, it was found that mobilization protocol failed to exert any protective effects but rather was associated with increased severity of renal tubular injury and mortality, possibly due to a concomitant marked granulocytosis (56). At variance, in a model of cisplatin-induced ARF, treatment of mice with G-CSF mobilized Lin^- $CD34^+$ $ckit^+$, and Sca^+ cells, and significantly ameliorated renal function and reduced tubular necrosis (22) by accelerating tubular cell regeneration and preventing apoptosis (41).

Mesenchymal Stem Cells

Bone marrow stroma-derived mesenchymal stem cells (MSC) are progenitors of skeletal tissue components such as bone, cartilage, hematopoiesis-supporting stroma, and adipocytes (2,45,46,48). Recent experimental findings have shown the potential of MSC to differentiate along multiple cell lineages like neuronal, myogenic, and hepatocyte-like cells (23,27,50,57). As such, MSC are both an important paradigm of postnatal nonhematopoietic stem cells and an easy source for regenerative therapy.

From adult male mouse bone marrow we recently established a cell population with morphological and functional characteristics of multipotent mesenchymal progenitors that, once transplanted in female mice with ARF induced by cisplatin, attenuated severe epithelial cell injury and improved renal function (39). It has been documented that MSC, given 1 day after cisplatin, strongly protected from renal function impairment at days 4 and 5 as evaluated by blood urea nitrogen assessment. Mesenchymal stem cells repopulated the damaged tubule most presumably by recruitment at peritubular sites in which the Y chromosome MSC exhibited well-recognizable brush borders positive for the tubular binding sites Lens culinaris lectin. These data suggest a local recruitment of MSC at sites of injury and provide evidence that MSC actively participate in the reconstitution of the differentiated epithelial lining. High numbers of positive cells for Ki-67, a nuclear marker of cell proliferation, were detected within the tubuli at the time at which renal function was ameliorated in stem cell transplanted recipients, indicating that MSC engrafting the kidney could additionally act by accelerating, to a remarkable extent, tubular cell proliferation in response to

cisplatin-induced damage. The demonstration of a nuclear colocalization of Y chromosome and Ki-67 staining in tubuli indicates that at least some MSC may proliferate and directly reconstitute the tubular epithelium. Similar data were obtained in an experimental mouse model of glycerol-induced ARF where MSC engrafted the injured kidney and markedly accelerated the renal functional and morphological recovery (18).

Functional benefit of MSC could be due to their ability of producing growth and trophic factors (13,35,37, 62) that might play a role in tissue regeneration as also suggested by data in a mouse model of pancreatic regeneration (20). Relevant to this hypothesis is a recent article documenting that the renoprotective effects of MSC, in rat with ischemia-reperfusion injury, may be paracrine (55), as implied by the renal upregulation of anti-inflammatory IL-10 as well as organ protective growth factors βFGF, TGF-α, and antiapoptotic Bcl-2. The observation that the expression of proinflammatory cytokines such as IL-1β, TNF-α, and IFN-γ, as well as iNOS, were significantly reduced might also suggest a possible immunomodulatory effect of MSC on T-cell response likely involved in the pathogenesis of ARF.

STEM CELLS AND GENE THERAPY

Gene therapy represents an innovative tool for the treatment of human genetic diseases through the delivery of genetic material to target cells or organs to replace or counteract a faulty gene. Although gene therapy holds enormous promise, there are still major obstacles to its in vivo broad therapeutic application, mainly related to the difficulties in finding a delivery system capable of allowing high-level, long-lasting, and targeted expression with minimal toxicity. Ex vivo genetic engineering of cells followed by their reinfusion into the patient provides a unique window for efficient gene transduction with limited side effects, instead. One can envisage the possibility to utilize cells as vehicles for delivering a gene whose protein product could contribute to the regeneration of a damaged tissue. In this context, manipulation of stem cells, either hematopoietic or mesenchymal, has been proposed. The efficiency of different gene transfer vectors of nonviral and viral origin represents the first issue that was addressed. So far evidence on the use of nonviral vectors or physicochemical methods for stem cell transduction is scanty and shows relatively low efficiency. Refractoriness to adenoviral infection was reported as mainly due to a deficit of the native receptor for adenovirus on the surface of stem cells (58). Resistance against adenoviral vectors was overcome by using a genetically modified adenovirus carrying a mutation of the fiber of the viral capside, which resulted in increased transfection efficiency (58). Transduction, however, was transient and accompanied by inflammation induced by the proteins of the complex adenoviral genome.

Amphotropic retroviral vectors derived from Moloney murine leukemia have been widely used for both experimental and clinical gene therapy for their broad cellular tropism, their presumed lack of pathogenicity in humans, and their ability to permanently integrate their genetic material into the chromosome of the host cells (28). Permanent genomic integration enables long-term transgene expression in both the transduced cells and their progeny, although the multilineage transgene expression in vivo has been found to be fairly low (4,49). Division of the target cell is an absolute requirement for retrovirus to efficiently transfect and integrate into the cell genome. Ex vivo retroviral-mediated gene transfer protocols into CD34+ hematopoietic precursors have been found effective in correcting immunodeficiences caused by defects in the gene encoding the adenosine deaminase (ADA) enzyme or the common cytokine-receptor γ chain, necessary for the development of T and natural killer cells; the mutation of the latter results in the X-linked immunodeficiency (SCID-X1). Despite various attempts with transduced T cells or hematopoietic progenitors in patients with ADA deficiency, the therapeutic effect of gene therapy remains difficult to assess because the concomitant treatment with the enzyme could not be discontinued (5). Recently, the combination of an optimized gene transfer protocol in autologous bone marrow CD34+ cells with moderate conditioning resulted in multilineage, stable engraftment of transduced progenitors at substantial levels, restoration of immune functions, and correction of the metabolic defect in the absence of the enzyme administration (1). Full correction of disease phenotype was observed in SCID-X1 patients receiving autologous CD34+ retrovirally transduced to express the cytokine-receptor γ chain gene (7). The initial excitement for gene therapy for SCID-X1 patients turned to worry when three children developed T-cell leukemia, raising concern on the safety of retroviral vector-mediated gene therapy. Insertional mutagenesis occurred as a consequence of insertion of the retrovirus in the proximity of the LMO-2 proto-oncogene causing its activation in two patients (15); the insertion of the virus in the third patient is still undefined (36). A more recent study confirmed the initial positive results using different conditions of cell culture and a pseudotype vector; the lack of any side effect could be attributable to the short follow-up (11). Despite some positive results, an NIH advisory panel restricted gene therapy only to SCID-X1 patients for whom conventional treatment has failed (*Science*, March 2005). These results pose the question of the safe use of retroviral vectors in clinics. In this context a possibly less harmful approach could

be represented by data obtained in patients with osteogenesis imperfecta who carry mutations of the gene encoding type 1 collagen (8). Ex vivo transfection with a rAAV of mesenchymal stem cells from patients with osteogenesis imperfecta resulted in disruption of the mutant allele and expression of the wild-type type 1 collagen gene restoring collagen processing, stability, and structure in vitro. Whether this approach could be effective in vivo has to be demonstrated but the approach seems innovative.

The experience so far gained in transfection of stem cells would be of great help also for the treatment of nongenetic disorders, including acute renal failure. It can be hypothesized that stem cells, by virtue of their peculiar capacity to home to the damaged kidney, could be engineered to deliver specific factors to the site of injury, thus maximizing the regenerative process of the organ.

CONCLUSIONS

The use of stem cells or progenitor cells to treat or restore the function of injured organs is a new therapeutic concept. There is now a large body of evidence that offers a strong case for exploring the possibility that bone marrow-derived stem cells, by virtue of their renotropic properties and tubular regenerative potential, may have a role in the treatment of acute renal failure in humans. Further studies would be required to better direct progenitor cells from the circulation to areas of injury and to modulate their proliferation and differentiation, once cells have reached the target tissue. Moreover, stem cells may be suitable targets for ex vivo genetic manipulations. Engineered stem cells could replace defective genes for the cure of genetic defects after birth or even in utero, but could also represent a vehicle to deliver anti-inflammatory molecules or even drugs locally.

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