Stem Cells and the Kidney: A New Therapeutic Tool?

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In the past few years, a number of studies have shown that stem cells can be found in virtually every organ of the adult organism. The kidney is not an exception, and resident stem cells have been identified both in the papilla and along the tubules. Of interest, kidney-bound stem cells have been identified also in the bone marrow. When injected, both resident and bone marrow–derived stem cells are able to reach the injured renal tissue and, once there, to differentiate into renal cells. The evidence that, in humans, some of the acute and most of the chronic renal damages lead to ESRD suggests that in normal conditions, the reservoir of stem cells (considering both resident and bone marrow–derived stem cells) is insufficient to allow a major renal regeneration. Probably the number of stem cells that are ready to intervene in an adult kidney are sufficient to compensate for the normal cell turnover but largely inadequate to counteract a major injury. This is confirmed further by the finding that, even by transplanting a syngenic bone marrow in rats with ablation of 5/6 of the renal function, it is not possible to increase the life expectancy of the animals. Altogether, this evidence suggests that, to clarify the potentiality of a stem cell therapy for renal diseases, experiments that aim to clarify the ideal concentration of stem cells to be injected and to identify the best way of administration are needed.

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ignificant attention has been directed recently to study the potentiality of stem cells in the treatment of a number of acute and chronic diseases. Stem cells are undifferentiated cells that are characterized by a high degree of self-renewal and differentiation potential (1). Stem cells can be isolated from a variety of mammalian tissues and organs both during development and into adulthood. Among the characteristics of stem cells is the capability of self-maintenance, their indefinite proliferative potential, and the ability to generate many if not all of the differentiated cell types that are contained in an organ (2–4). In the presence of damage, these cells can replace the injured ones (5–7). Stem cells are responsible for the development and growth of different organs during embryogenesis and for tissue homeostasis and repair during adult life (8).

Although tissue plasticity during adulthood is manifest clearly in some organs, such as the small intestine, the liver, and the hematopoietic system, in some others, such as the central nervous system, the possibility of self-renewal has been recognized only recently (9). In the kidney, tubules and glomeruli show a totally different plasticity. It is widely known from the clinical practice that, in most cases, tubules are able to regenerate even after major damage (10), although postnatal glomerulogenesis has not been described in human. Probably for this reason, major acute or chronic glomerular damage invariably leads to ESRD.

The recent identification of renal progenitor cells both inside the kidney (11,12) and in the bone marrow (13–17) may pave the way toward the future regeneration of the damaged kidney. Appropriate functional experiments in animal models of renal damage now are needed to clarify the therapeutic potential of a stem cell approach in repairing a, so far, irreversibly damaged kidney.

Resident Renal Progenitor Cells

Resident progenitor cells have been identified in the papilla of the adult murine kidney (11). In the papilla, stem cells reside in niches and co-express mesenchymal and epithelial antigens; once injected under the renal capsule, they incorporate in renal parenchyma and tubules. More recently, renal progenitor cells have been found also in the tubular fractions of the cortex of adult human kidney (12). These cells differentiate in vitro in epithelial and endothelial cells, and, once injected intravenously in SCID mice with an induced acute tubular injury, they localize in proximal and distal tubules. The resident progenitor cells are potentially clinically useful because these cells, at difference with multipotent stem cells, should be available immediately to repair the kidney and therefore could be of great help in the treatment of acute renal injuries. However, it seems questionable that a single adult progenitor cell may be able to repair all of the various parts of the kidney. It seems possible that, in the near future, more renal progenitor cells will be identified inside the kidney, each one committed to repair a different component.

Bone Marrow–Derived Renal Progenitor Cells

A number of studies showed recently that bone marrow represents a reservoir of stem cells that are physiologically
involved in remodeling and repairing the kidney. Bone marrow can provide cells that integrate into the kidney and differentiate into new functional renal cells of a variety of types. There is evidence of engraftment and differentiation of stem cells during normal renal cellular turnover (13) and after acute and chronic damage (14–17). Irradiated female mice that received a transplant of male bone marrow formed renal tubular cells that contained the male donor Y chromosome, suggesting that bone marrow cells can migrate to the kidney and form tubular epithelium (13).

Several studies have reported the contribution of bone marrow stem cells in the repairing of damaged glomeruli. In particular, bone marrow cells were shown to differentiate into mesangial cells in murine recipients when the glomerulus was damaged by an antibody-mediated glomerulonephritis (16). Other studies documented how bone marrow contributes to the maintenance and repair of renal endothelium and interstitium (18,19). In the majority of the studies, the injected material was whole bone marrow, meaning a mixture of multiple types of stem cells, including hematopoietic stem cells, mesenchymal stem cells, multipotent adult progenitor cells, and side population cells.

Regarding the possibility that a specific stem cell type might be better than others for kidney repair, the literature is still controversial: In some studies, hematopoietic stem cells were shown to contribute to tubular epithelium repair (14), whereas in other models, only mesenchymal stem cells accelerated the structural recovery of the kidney after injury and conferred therapeutic benefit (16).

Can Renal Function Be Restored by Transplantation of Whole Bone Marrow?

Despite the large number of studies that aimed to identify renal stem cells, very few data are available concerning the possibility to restore renal function by means of stem cell therapy. To clarify whether an acute renal injury can benefit from a simultaneous injection of stem cells, we recently performed a study in which a classic 5/6 removal of renal function (20) was treated by a whole bone marrow transplant. This experiment was done in rats that maintained the native bone marrow.

As shown in Figure 1, 40 Milan normotensive strain rats were included in the study. After removal of one kidney and clamping of two of the three afferent arterioles of the contralateral kidney, only approximately one sixth of the total renal function was left. Ten rats, used as controls, received an intravenous (vena cava) injection of 100 μL of serum-free minimal essential medium (Sigma, St. Louis, MO), 10 rats received 25 million splenocytes that were obtained from syngenic donors (in 100 μL of minimal essential medium) as controls for cellular mass, 10 rats received 5 million whole bone marrow cells, and finally 10 rats received 25 million whole bone marrow cells. The rats were followed until death, and serum creatinine was measured on a weekly basis. As shown in Figure 2, the four groups of animals behaved in a similar way, and after an initial recovery of renal function in the first 2 to 3 wk after surgery, creatinine levels increased progressively. Death rate as a result of renal insufficiency also was similar in the various groups, and 3 mo after surgery, no animals were still alive. Renal mass rapidly recovered after surgery, but this was mostly due to tubular regeneration. New glomeruli could not be found in the regenerated area. Finally, the clamped area of the remnant kidney underwent necrosis and fibrosis, and no neovascularization could be appreciated inside this tissue.

Our results are in touch with previous reports suggesting that bone marrow engraftment in the presence of native bone marrow is very low (21), probably because of competition between the two components. The previous finding that, at
difference with glomeruli, renal tubular component is able to regenerate also was confirmed (10). New experiments now are needed to clarify whether less severe renal damage can be recovered using the same approach; whether small focal damage can be treated successfully with this kind of therapy; whether a direct injection of cells inside the renal parenchyma can exert a better result; and, finally, whether, by injecting selectively stem cells or renal progenitors rather than whole bone marrow, the final result can be improved.

Future Perspectives

Although some components of the kidney, such as the tubules, are able to regenerate spontaneously, some others, such as the glomeruli, cannot recover spontaneously from a major injury. This finding suggests that the reservoir of plastic cells that are able to regenerate the glomeruli probably is enough for supporting the normal cell turnover but insufficient to intervene in case of major tissue losses. The isolation and the expansion in vitro of the progenitors of the various kidney components along with the definition of the correct “dosage” and administration route should, at least in principle, allow in a near future identification of the correct stem cell therapy for both acute and chronic renal diseases.

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References


Figure 2. Plasma creatinine levels in the four groups of rats considered for the study during the 18 wk of follow-up. The number of rats that were alive at each creatinine measurement is indicated at the bottom of the figure.


