REVIEW

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Stem cells in nephrology: present status and future

Ewa Wątorek and Marian Klinger

Department of Nephrology and Transplantation Medicine, Wrocław Medical University, Poland

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Abstract

Stem cell biology is currently developing rapidly because of the potential therapeutic utility of stem cells. The ability to acquire any desired phenotype raises hope for regenerative therapies. Manipulation of these cells is a potentially valuable tool; however, the mechanisms of stem cell differentiation and plasticity are currently beyond our control. In the field of nephrology, the presence of adult kidney stem cells has been debated. Renal adult stem cells may be descendants of some early kidney progenitors, or may be derived from bone marrow. Evidence of a hematopoietic stem-cell contribution to renal repair encourages the possibility of bone marrow or stem cell transplantation as a means of treating autoimmune glomerulopathies. The transplantation of fetal kidney tissue containing renal progenitors, which then develop into functional nephrons, is a step towards renal regeneration. According to recent reports, the development of functional nephrons from human mesenchymal stem cells in rodent whole-embryo culture is possible. Establishing *in vitro* self organs from autologous stem cells would be a promising therapeutic solution in light of the shortage of allogenic organs and the unresolved problem of chronic allograft rejection.

Key words: stem cells, embryonic stem cells, hematopoietic stem cells, metanephric mesenchyme, regenerative medicine, stem cell diseases.

Abbreviations: ASC – adult stem cells, EBMT – European Group of Blood and Marrow Transplantation, ESC – embryonic stem cells, EULAR – European League Against Rheumatism, GFP – green fluorescent protein, HSC – hematopoietic stem cells, SCT – stem cell transplantation, SLE – systemic lupus erythematosus.

Corresponding author: Marian Klinger, M.D. Ph.D., Department of Nephrology and Transplantation Medicine, Wrocław Medical University, Romualda Traugutta 57/59, 50-417 Wrocław, Poland, tel.: +48 71 343-27-17, e-mail: klinef@am.centrum.pl

INTRODUCTION

Stem cells are units of development and regeneration. To carry out such a function, two properties are necessary: the ability to self-renew and unlimited differentiation potential. Stem cells are transiently present during embryogenesis in the pre-implantation stage of the zygote, and can be derived from the inner cell mass of the blastocyst 4–6 days after fertilization in humans [17]. Stem cells established from blastocysts are called embryonic stem cells (ESCs). These cells display a stable diploid karyotype after *in vitro* propagation. Under appropriate culture conditions, ESCs can be maintained in an undifferentiated state and expanded unlimitedly because of a high-level of expression of telomerase activity. Modulation of culture conditions results in the differentiation of ESCs into a wide variety of cell types. The concept of persistence of stem cells in the adult organism is based on the observation of the physiological regeneration of some adult tissues such as bone marrow and gut epithelium. Adult stem cells (ASCs) could be seen as a reservoir of cells predetermined to repopulate the tissue in which they reside. The commitment of ASCs to specific organs can be provided by an interplay between unique genetic regulation and the local environment, i.e. the specific niche. Organ or tissue specificity of ASCs seems, however, not to be a rule in view of ASCs' plasticity, i.e. the possibility to transdifferentiate into other types of tissue.

The potential of stem cells has opened a new research field: regenerative medicine. Stem cell therapy could be applied to reconstitute *in vivo* or *in vitro* damaged organs or to deliver genes to specific sites. Stem cell use has been attempted in animal models, as well as in humans, in the therapy of ischemic heart and limb disease, diabetes mellitus, and many other fields [4, 7, 28, 34]. In nephrology, regenerative stem cell therapy for end-stage renal disease could be an alternative to the only available and still insufficient renal replacement therapy. Recently, cell-based therapy utilizing adult renal cells has been attempted to restore lost renal function [16]. Kidney cells cloned from adult bovine fibrob-

lasts were seeded on collagen-coated polycarbonate membranes and transplanted subcutaneously into adult bovine host. Renal cell grafts underwent vascularization, differentiation into glomerulus-like structures, and produced fluid containing urea nitrogen, and creatinine. The expression of renal-specific proteins, such as aquaporins, synaptopodins, and Tamm-Horsfall protein, and the production of erythropoietin were observed. Stem cell-based gene therapy for glomerulonephritis has been successfully applied in animal models [42]. Stem cells from male mice donors transfected with an antagonist of the interleukin (IL)-1 receptor were transplanted into female mice with anti-glomerular basement membrane disease. Recruitment of the transfected cells identified by the Y chromosome into diseased glomeruli with subsequent preservation of renal function and histology in the female mice was observed. To apply stem cell-based gene therapy to clinical use, safe transduction vectors, precise organ targeting, and persistence of the therapeutic effect is needed.

Despite the progress, regenerative medicine faces such challenges as the identification of stem cell populations and the mechanisms of stem cell differentiation and transdifferentiation. The gene and protein expression patterns of stem cells, as well as the interplay between stem cells and their niche, are under investigation [39].

STEM CELLS IN THE KIDNEY

The search for adult kidney stem cells remains unresolved. The identification of ASCs in many organs [2, 13] together with evidence of renal repair following injury [10] suggests the presence of adult renal stem cells. Characterization of this cell population would be beneficial in inventing new and effective renal therapies. Approaches to the identification of renal stem cells are based either on tracking kidney development in order to identify a common renal progenitor cell, or on observing cells which contribute to kidney regeneration after renal injury in humans, or in animal experimental models. Developmental studies reveal that the generation of the kidney, which contains at least 26 cell types in the nephron, involves reciprocal inductive events between the ureteric bud growing from the Wolffian duct and the metanephric mesenchyme [37]. The ureteric bud induces the conversion of metanephric mesenchyme to nephron epithelial cells, while mesenchymal cells induce branching of the ureteric bud and formation of the structure of collecting tubules with the pelvic and ureteric epithelia. This signaling interplay involves the expression of more than 300 genes. The metanephric mesenchyme is the population of cells that contains renal epithelial stem cells [18]. The common precursor of the nephron epithelial cell was established using a lineage marker. The ancestor cell was tracked down by infecting induced metanephric mesenchymal cells with replication-defective retrovirus carrying a reporter gene. Selection of a progenitor committed only to the kidney development is difficult, because the mesodermal tissue preceding the metanephric mesenchyme also develops into somites and gonads. Induction of the metanephric mesenchyme results in restricting the cells to particular nephron epithelial lineages, and a fixed point of progenitor cell commitment to kidney development is not defined.

In the light of the broad differential potential of stem cells and the unique role of the niche in directing the path of stem-cell differentiation, it is reasonable to explore the mechanisms which induce the commitment of stem cells to kidney tissue. It was shown that transplanting a population of cells with a metanephric mesenchymal phenotype derived from human kidney fetal tissue into sheep fetuses gave rise to hematopoietic stem cells and to hepatocyte-like cells producing albumin [3]. Locating adult renal stem cells could be attempted in several ways, for example by identifying cells with the mesenchymal phenotype, by following cell divisions to define slowly cycling cells (a feature of stem cells), and by comparing genetic marker-gene expression patterns characteristic for mesenchymal cells. Another speculative method is based on the assumption that kidney stem cells should be sought in a hypoxic compartment of the adult kidney, such as the medulla, because nephrogenesis is completed in low-oxygen tension prior to establishing circulation [1].

The presence of adult renal stem cells is also supported by evidence of kidney tissue regeneration following injury. Data from humans and animal models indicate two possible sources of stem cells contributing to renal tissue regeneration, the first being a population of kidney stem cells persisting in the organ in a dormant state which are stimulated to differentiation as a result of an injury, and the second source being bone marrow. The probable bone marrow-derived populations are mesenchymal cells and hematopoietic stem cells (HSCs), whose nearly unlimited differential potential has been widely explored [26, 27, 34]. HSCs are found in the aorta-gonad-mesonephros region during embryogenesis [31]. The common origin of bone marrow cells and renal progenitor cells may suggest similarities in developmental potential.

The presence of resident kidney cells contributing to tubular regeneration after injury was demonstrated in an animal model of kidney ischemia [30]. Labeling with bromodeoxyuridine identified a population of slow-cycling cells in normal rat kidneys *in vivo*. These slow-cycling, label-retaining cells were present among renal epithelial tubular cells in normal rat kidneys. Following recovery from renal ischemia, the label-retaining cells proliferated actively, which was confirmed by the presence of proliferating cell nuclear antigen recognizing the early G1 and S phases of the cell cycle. At an early stage of tubular regeneration, label-retaining cells acquired epithelial phenotype, expressing E-cadherin. It was shown that a pool of resident kidney cells with characteristics of stem cells participates in the regeneration of tubular epithelium.

The second population of cells that can reconstitute damaged renal tissue is derived from bone marrow. In wild type rats, which were recipients of bone marrow from transgenic rats carrying green fluorescent protein (GFP), recruitment of bone marrow-derived cells marked with GFP to the glomeruli was observed after anti-Thy1-mediated mesangiolysis [22]. These cells made up 7–8% of the glomerular mesangial cells. In another experiment in mice receiving bone marrow from donors transgenic for GFP, the repopulation of glomeruli by bone marrow-derived cells was observed in a time-dependent manner, even without prior renal injury [21]. Participation of extrarenal cells in the recovery of acute renal failure was also observed in humans. In male patients with resolving acute tubular necrosis, who had received a kidney transplant from female donors, 1% of the tubular cells contained Y chromosome [14]. The origin of these recipient-derived cells was unclear.

Recently a side-population cells characterized by low stain with the DNA-binding dye Hoechst 33342 and regarded as posessing both functional and phenotypic properties of HSCs, has been identified in adult rat kidneys [23]. Although these bone marrow-derived cells were shown to home to the kidney after bone marrow transplantation, intravenous injection of the side-population cells into recipient animals did not result in repopulation of kidney cells, even after induction of kidney tissue injury. The side-population cells were shown to contribute to skeletal muscle, hepatocytes, and bone marrow [23].

Although bone marrow transplantation experiments could answer whether extrarenal progenitors contribute to renal regeneration, accurate quantification of the extent to which these cells participate in the reparatory process may not be possible. Furthermore, the total-body radiation required for bone marrow transplantation experiments may cause renal cell damage, with subsequent higher renal cell turnover and promotion of the proliferative capacity of bone marrow-derived renal progenitors rather than resident ones.

TISSUE RECONSTRUCTION IN NEPHROLOGY

Reconstruction of the whole organ from the cellular level demands, apart from the identification of kidney stem cells, an insight into the genetic regulation of renal progenitors, and belongs to the far future. Kidney tissue regeneration is far more complex than developing single-cell-type tissues such as neurons, cartilage, or muscle. Currently available renal replacement therapies are not free of limitations. Dialysis is lifesaving, but substitutes only a part of renal function, and kidney transplantation is restricted by the availability of kidney donors. Therefore, renal tissue regeneration as an alternative to replacement therapies is being investigated and has been approached in several ways [16]. One of the approaches involves transplantation of embryonic kidney tissue containing renal progenitor cells that develop into nephrons or whole kidney. Metanephros transplantation, primarily conducted to define immune response to fetal kidney tissue or identify the origin of renal vasculature [9, 38], was then employed as a means to enhance renal function. An animal model provides evidence that renal subcapsular metanephros transplantation results in nephron development, the formation of the collecting system, and vascularization of glomeruli [8]. When embryonic tissue is transplanted into the omentum, it undergoes growth and differentiation which is not restricted by the renal capsule and acquires the kidney shape. Transplants of early kidney precursors located in the omentum form cysts containing fluid with higher urea nitrogen and creatinine concentrations than the recipient serum, which is a proof of function. However, spontaneous incorporation of the collecting system of the transplant into the collecting system of the host was not observed.

There are few aspects of metanephros transplantation that promote their use in renal regenerative therapy. Embryonic tissue is less immunogenic than adult tissue because of the immaturity of the antigen-presenting cells and lower expression of MHC class I and II antigens. These features are time dependent and only transplants derived at early gestational age, containing mainly metanephric mesenchymal stem cells with the ureteric bud, undergo growth and differentiation [8, 12]. The decreased immunogenicity of fetal kidney tissue was demonstrated in an experimental model in which human peripheral blood mononuclear cells were injected into immunodeficient animal recipients of either adult human kidney fragments or fetal kidney tissue derived from various gestation periods [8]. In adult kidney fragments, massive infiltration and graft rejection were observed, whereas in fetal kidneys the degree of leukocyte infiltration depended on the time of fetal tissue harvesting before transplantation. Fetal tissue derived from a later gestation period was infiltrated and graft growth was inhibited, but early gestation grafts exhibited no human T cells and growth was not disturbed.

Transplanted metanephros is supplied with blood vessels of host origin, which may reduce the risk of vascular rejection after transplantation [25]. A recipient contribution to vasculogenesis was demonstrated by positive staining for mouse endothelial marker CD31, found on the vessels supplying human and porcine metanephros transplanted into immunodeficient mice [8, 35].

The shortage of allogenic human kidney donors would make the possibility of xenogenic metanephros transplantation an interesting alternative. Due to the immunological advantages of metanephros, transplantation of early embryonic renal tissue followed by nephron development was observed in various transplantation animal models: allotransplantation was feasible without immunosuppresion [36], whereas xenotransplantation in concordant (rat to mouse) [35] or highly disparate

(pig to rodent) models demanded immunosupression [8, 15]. The clinical applicability of metanephros transplantation requires resolution of the following problems: successful pig-to-primate transplantation should be demonstrated, the risks of abnormal development of embryonic tissue and pathogen transmission through the xenogenic barrier should be eliminated, a level of transplant function sufficient for long-term life sustainment should be established, the optimal time for ureterostomy post-transplantation should be defined, and finally immunosuppressive protocols need to be developed.

Recently, a successful use of human mesenchymal stem cells derived from adult bone marrow in the generation of metanephroi in rodent whole-embryo culture was presented [41]. Human mesenchymal stem cells were injected into *in vitro* cultured rodent embryos. After 48 h of culture, developed metanephroi were isolated and subjected to further organ culture. The contribution of human cells to the rodent kidneys was confirmed by positivity for the Lac Z gene used for human mesenchymal cells labeling in the cells of the developed organs. Lac Z-positive cells were shown to express podocyte and tubular epithelial cell-specific genes [41].

STEM CELL DISEASES IN NEPHROLOGY

Some human glomerular diseases have an autoimmune background [5]. In autoimmune diseases, autoreactivity seems to originate from defects in HSCs, which are precursors of immune cells. Data from animal models and human case reports indicate that autoimmunity can be either transferred or eliminated by bone marrow transplantation [19, 20, 33]. In an animal model of focal segmental glomerulosclerosis after HSC-enriched bone marrow transplantation, almost complete regression of proteinuria and reconstitution of the light microscopic appearance of glomeruli was observed [33]. Transmission of glomerulosclerosis from the diseased to normal animals was also demonstrated [33]. There is also evidence suggesting the involvement of HSCs in the pathogenesis of IgA nephropathy [19, 20]. Increased serum concentration of macromolecular IgA, probably contributing to renal pathology, is determined at the stem-cell level. Bone marrow transplantation from normal animal donors attenuates glomerular lesions in diseased animals, whereas bone marrow cell transplantation from IgA-nephropathy-prone mice to normal mice results in complement deposition in the glomeruli and in an increase in serum IgA level [19, 20].

Evidence of the potential therapeutic utility of stem cell transplantation (SCT) for systemic lupus erythematosus (SLE) can be drawn from animal lupus models and human case reports. A significant reduction in the level of anti-ssDNA anti-dsDNA autoantibodies and an improvement in kidney pathology following transplantation of T cell-depleted bone marrow into SLE-diseased from SLE-resistant mice was observed [29]. Renal involvement in SLE occurs in 30–50% of patients and is the most common severe manifestation, with a 10-year mortality rate of 6–20% and rate of end-stage renal failure of 9–25% [24]. Therefore, SCT, allogenic, syngenic, or autologous, is considered an optional therapy for severe, refractory autoimmune diseases which fail to respond to conventional immunosuppressive treatment. The European League Against Rheumatism (EULAR) and The European Group of Blood and Marrow Transplantation (EBMT) have reached a consensus on the disease indication for SCT [40]. This experimental procedure can be applied only in severe autoimmune diseases which have an increased risk of mortality, these including SLE, sclerodermia, autoimmune pulmonary hypertension, amyloidosis, multiple sclerosis, autoimmune thrombocytopenia, and hemolytic anemia. Autologous SCT is preferred to allogenic due to the lower mortality risk (3–5% vs. 15–35%) and the lack of graft-versus-host complications. Autologous SCT may carry a greater risk of autoimmunity recurrence. However, in favor of autologous SCT is the assumption that an aberrant immune reaction is acquired and that memory cell ablation will reconstitute a new, tolerant immune system. Recently, EBMT/EULAR carried out a retrospective registry survey to assess the efficacy of autologous SCT for sustained remission induction in refractory SLE [24]. Data were collected from 53 patients with SLE treated by autologous SCT in 23 centers. Nephritis was present in 62% of the patients. Stem cells in the majority of the patients were harvested from peripheral blood after mobilization with granulocyte cell-stimulating factor. In 41% of the patients, positive selection of $CD34^+$ cells was carried out. Of these patients, two had negative T cell selection. The rest of the group had no graft manipulation. One-year transplant-related mortality was 12% and was positively associated with longer pretransplant disease course, but not with the graft manipulation or disease activity before SCT. Remission was achieved in 66% of the patients, 32% of whom relapsed in longer follow-up. The study presents the efficacy of SCT in SLE remission induction; however, the procedure is not curative. It seems that SCT may change disease phenotype to a more benign, treatment-responsive form with a lower rate of severe renal or hematological involvement. The relapse rate was not reduced by *in vitro* graft manipulation carried out to decrease contamination with autoreactive T cells, but further, larger studies are needed. To improve the safety of the procedure, appropriate criteria for SCT based on the severity of organ involvement, prognostic markers of death, duration of the disease, and conditioning regimens need to be defined.

Another example of SCT application in the field of nephrology was reported for induction of regression of metastatic renal-cell carcinoma [6]. SCT in patients with renal carcinoma was aimed at evoking a graft-versus--tumor effect. The assumption that the new immunological environment created after SCT would be beneficial in fighting the disease was based on evidence of the sus-

ceptibility of renal-cell carcinoma to immunomodulation. Rare, spontaneous regression of metastatic disease as well as low (less than 20%) but complete response to IL-2 and interferon α were noted [11, 32]. In the study of Childs et al. [6] 19 patients with metastatic renal-cell carcinoma underwent non-myeloablative allogenic peripheral-blood stem-cell transplantation. In 10 patients regression was noted, 3 of whom had total regression and 7 partial regression with 50% reduction of tumor burden. Regression was noted after complete donor T cell chimerism had been established, which supports the assumption of the antitumor effect of SCT.

CONCLUSION

Attempts to harness stem cell biology may result in the development of new therapeutic strategies in many medical branches. In nephrology, the evidence of progenitors of major renal cell types invites hope for applying them in the reversion or prevention of renal damage. Circulating progenitors derived from bone marrow may constitute an easily accessible pool of cells either for autologous, rejection-free regenerative therapy or for allogenic transplantation to treat inherited autoimmune diseases such as lupus erythematosus or IgA nephropathy. Knowledge of the mechanisms of the homing of ASCs would allow for utilizing them to regenerate damaged tissue or to deliver certain gene products to specific tissues. Apart from the many unresolved problems, stem cell biology is advancing rapidly, hopefully towards new and effective therapeutic solutions.

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