Renal Stem Cell

Hongbao Ma *, ***, Shen Cherng **, Yan Yang ***

* Bioengineering Department, Zhengzhou University, Zhengzhou, Henan 450001, China, mahongbao@zzu.edu.cn, 01186-137-331-67674

** Department of Electrical Engineering, Chengshiu University, Niaosong, Taiwan 833, China, cherngs@csu.edu.tw; 011886-7731-0606 ext 3423

*** Brookdale University Hospital and Medical Center, Brooklyn, NY 11212, USA, youngjenny2008@yahoo.com

Abstract: The renal disease is a common problem in human society. End-stage renal disease is a big heath problem in the United States and in all places of the world. Embryonic stem cells, pluripotent derivatives of the inner cell mass of the blastocyst, are the most primitive cell type likely to find application in cell therapy. Their potential to generate any cell type of the embryo makes them to be the most attractive stem cell therapy. It is possible to introduce stem cells into a damaged adult kidney to aid in repair and regeneration. Transdifferentiation offers the possibility of avoiding complications from immunogenicity of introduced cells by obtaining the more easily accessible stem cells of another tissue type from the patient undergoing treatment, expanding them in vitro, and reintroducing them as a therapeutic agent. Adult stem cells may possess a considerable degree of plasticity in the differentiation. Immunoisolation of heterologous cells by encapsulation creates opportunities for their safe use as a component of implanted or ex vivo devices. [Journal of American Science. 2009;5(5):213-222]. (ISSN 1545-4570).

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1. Introduction

Normally to say, stem cells could grow to all kinds of cells. In animal tissues stem cells serve as an internal repair system to replace other cells as long as the life is still alive. When a stem cell divides, it could remain a stem cell or become another type of adult cell, such as a muscle, nerve, red blood or a sperm cell. Stem cell is the origin of an orgnism's life (Ma, 2005).

End-stage renal disease (ESRD) is a big heath problem in the United States and it costs more than US$30 billion each year on ESRD therapy in USA (Arnold, 2000; Mai et al., 2006; Ross et al., 2006). It is estimated that there are over 2 million patients in USA who suffer from ESRD. Chronic kidney disease is increasing at the rate of 6-8% per year in the Unite States. The acute renal failure (ARF) is even worse. The cause of death by ARF is generally the development of systemic inflammatory syndrome. It is important to know the kidney's role in reclamation of metabolic substrates and there is considerable drive to develop improved therapies for renal failure (Mehta et al., 2007). About 60,000 patients in the United States are waiting for a kidney transplant, and some patients have waited for several years before an appropriate donor can be found. The shortage of donor organs limits treatment for the ESRD patients and requires many patients to make dialysis to extend the life time. At present, dialysis and transplantation are the common treatment options. However, it is possible to use stem cells and regenerative medicine for kidney disease treatment (Hopkins et al. 2009). The alternate methods stem cell therapy is offering new hope for the renal disfunction patients (Berzoff et al., 2008; Sirmon, 1990).

The kidney dialysis and transplantation techniques have been proved successful, but are marred by inflammation and limited organ availability and graft survival due to immune rejection. Recently, hope has been placed in the development of stem cell therapies. Possible sources for these cells include differentiated embryonic stem (ES) cells and adult renal stem cells. Using the patient's own stem cells to repair kidney damage could circumvent the problems of immune rejection and organ availability.

Embryonic stem cells are the stem cell that can be grown in large numbers in the laboratory and retain the ability to grow into any type of cells including renal, nerve, heart muscle, bone and insulin-producing cells. Adult stem cells, such as skin, nerve and bone marrow stem cells, normally grow into a limited number of cell types (Snykers et al. 2008). The role of embryonic or adult stem cells, in particular bone marrow-derived stem cells, in regenerating the kidney after injury has been the subject of intensive investigation. Bone marrow-derived stem cells have been shown to give rise to small numbers of most renal cell types, including tubular cells, mesangial cells, podocytes, vascular cells and interstitial cells. Injections of bone marrow-derived cells do improve renal function in many animal models of renal disease. Many stages of nephrogenesis can be studied using cultured embryonic kidneys. ES cells

have unlimited developmental potential and can be manipulated at the molecular genetic level by a variety of methods. ES cell technology may obtain a versatile cell culture system in which molecular interventions can be used in vitro on the normal kidney development program in vivo can be studied (Steenhard et al. 2005).

Stem cells and progenitor cells are necessary for repair and regeneration of injured renal tissue. Many factors influence the stem cell growth in damaged kidney. For example, low levels of erythropoietin induce mobilization and differentiation of endothelial progenitor cells and erythropoietin ameliorates tissue injury. Full regeneration of renal tissue demands the existence of stem cells and an adequate local milieu, a so-called stem cell niche. Stem cell may eventually contribute to novel therapies of the kidney disease (Perin et al. 2008).

Recently researchers used a rat model of chronic renal failure in which one kidney is excised so as to increase the load of the remaining kidney, thus causing a chronic deterioration that resembles the clinical situation of renal failure (Alexandre et al. 2008). In Alexandre's project, **t**he rats were divided into 4 groups: Group 1 were sham operated and both kidneys left in place; Group 2 had a kidney removed but were not administered cells; Group 3 were administered $2x10^6$ lineage negative bone marrow cells on day 15 after one of the kidneys was removed; Group 4 were administered $2x10^6$ lineage negative bone marrow cells on days 15, 30, and 45 after one of the kidneys was removed. They found: (1) Expression of inflammatory cytokines was reduced on day 16 in the kidneys of rats receiving stem cells as compared to rats that were nephrectomized but did not receive cells. (2) On day 60 rats receiving stem cells had decreased proteinuria, glomerulosclerosis, anemia, renal infiltration of immune cells and protein expression of monocyte chemoattractant protein-1, as well as decreased interstitial area. (3) Injured rats had higher numbers of proliferating cells in the kidney, whereas rats receiving stem cells had less. (4) Protein expression of the cyclin-dependent kinase inhibitor p21 and of vascular endothelial growth factor increased after nephrectomy and decreased after stem cell treatment. (5) On day 120, renal function (inulin clearance) was improved in the rats which were administered bone marrow cells compared to controls. This study supports the possibility of using bone marrow cells for various aspects of kidney failure. Other studies have demonstrated that administered stem cells promote kidney repair by secretion of insulin growth factor-1 (Cornelissen et al. 2008).

Bone marrow stromal cells, also known as mesenchymal stem cells or fibroblastic colony-forming units, are multipotent non-hematopoietic stem cells adhering to culture plates (Abdallah and Kassem 2009). Mesenchymal stem cells of the bone marrow have the ability to renew and differentiate themselves into multiple lineages of conjunctive tissues, including bone, cartilage, adipose tissue, tendon, muscle, and bone marrow stroma. Those cells have been first described by Friedenstein et al., who found that mesenchymal stem cells adhere to culture plates, look like in vitro fibroblasts, and build up colonies (Friedenstein et al. 1987).

Bone marrow is the site of hematopoiesis and bone marrow transplant has been successfully used for decades as a means of treating various hematological malignancies in which the recipient hematopoietic compartment is replaced by donor-derived stem cells. Progenitor cells in bone marrow are capable to differentiate into other tissues, such as cardiac tissue. Clinical trials have been conducted demonstrating beneficial effects of bone marrow infusion in cardiac patients. It is believed that injured tissue, whether neural tissue after a stroke, or injured cardiac tissue, has the ability to selectively attract bone marrow stem cells, perhaps to induce regeneration. Bone marrow has therapeutic effect in conditions ranging from liver failure, to peripheral artery disease, and the possibility of using bone marrow stem cells in kidney failure has been relatively understudied (Ma et al. 2009).

Mesenchymal stem cells have been brought to the attention of many researchers, because these cells are of great interest for treating various human diseases. Many studies have isolated mesenchymal stem cells and controlled, in vitro, its differentiation into cartilaginous tissue and bone using specific growth factors, with the objective of using this technology for repairing injured tissues of mesenchymal origin (Xian and Foster 2006; Kurdi and Booz 2007).

The origins for renal parenchymal cells could be: (1) re-entry into cell cycle of differentiated cells; (2) direct transdifferentiation of one cell type into another; (3) differentiation from stem cells of the kidney.

2. Native Renal Stem Cells and Renal Regeneration

In embryo, most types of renal parenchymal cells are derived from metanephric mesenchymal cells. In animal models, embryonic metanephroi transplanted into the abdominal cavity of adult animals are colonized by host vasculature, undergo nephrogenesis and produce urine, even if the operation is carried out across species barriers, and with a surprising lack of rejection (Little 2006). Human and porcine embryonic kidney progenitor cells have been isolated and, when injected into mice, can lead to the formation of miniature kidneys producing urine (Dekel et al. 2003), or protect against acute renal failure (Lazzeri et al. 2007). However, there are ethical issues to deal with human ES

cells. It is important to identify the stem cells. In adult mammals, many methods have been used to identify potential multipotent precursor cells, such as label retention in slow cycling cells, identification of a side population, and expression of stem cell markers (e.g. CD133), etc. This has led to the identification of several candidate renal stem cells which are located amongst the tubular cell population (Dekel et al. 2006; Gupta et al. 2006), in the Bowman's capsule, papillary region or cortical interstitium (Bussolati et al. 2005; Sagrinati et al. 2006; Rad et al. 2008). Of note, other studies have not confirmed the presence of a large pool of precursor cells amongst the tubular population and instead argue that regeneration occurs through proliferation of differentiated tubular cells (Vogetseder et al. 2008; Witzgall 2008). Some of the candidate renal stem cells have been shown to enhance recovery after tubular injury, possibly by integration in the tubular epithelium (Rad et al. 2008).

3. Bone Marrow-Derived Stem Cells and Renal Regeneration

Bone marrow stem cells would be an ideal source of multipotent cells: they are an unlimited source of expandable autologous cells, plasticity and easy to harvest. The plasticity has been observed both for the haematopoietic stem cell and for the bone marrow mesenchymal stem cells. There are important discrepancies in the literature addressing the role of bone marrow cells in renal regeneration. The bone marrow transplantation is the most common technique to study bone marrow cell plasticity. The host bone marrow is replaced by donor bone marrow, and after bone marrow chimerism is established, donor cells are tracked down in the kidney. The donor bone marrow cells are distinguished from host cells by virtue of their chromosome content, the expression of a reporter molecule (β-galactosidase, luciferase, enhanced green fluorescent protein), or the performance of a function (re-establishment of a function in a knockout mouse model). The type of host cell that the bone marrow-derived cell has given rise to (tubular, mesangial, etc.) is ascertained most often using immunohistochemistry.

Discrepancies between studies are attributable to several factors: (1) observations in different species (mouse, rat, human); (2) use of different models of renal damage (ischaemia/reperfusion, toxic, immunological); (3) different protocols for bone marrow transplantation (irradiation doses, quantity of cells injected); (4) injection of different subgroups of bone marrow cells (whole bone marrow, haematopoietic stem cell, mesenchymal stem cell); (5) sensitivity and specificity of the detection method for bone marrow cell origin (in situ hybridization for the Y chromosome, detection of reporter molecules, functional assays), and (6) sensitivity and specificity of the detection method of the renal cell type (immunohistochemistry for specific cell types such as tubular cell, mesangial cells, etc.). Renal failure can be the result of an initial insult directed against the tubular epithelium, the glomerular cells or the vascular compartment. In the search for remedies for these varied renal diseases, studies have therefore addressed potential bone marrow origin for various renal cell types. It is useful to bear in mind these technical variations when analysing results reported in the literature (Roufosse and Cook 2008).

4. Tubular Epithelium

Only a small proportion of tubular cells are bone marrow-derived, and there is disagreement over whether mesenchymal stem cells, haematopoietic stem cells or both are contributing (Humphreys and Bonventre 2008). The predominant source of tubular regeneration is through the proliferation of differentiated tubular cells (Lin et al. 2005). A few authors have not found any bone marrow cells engrafted in tubules, and propose that positive observations of bone marrow-derived tubular cells are the result of artifact (Bussolati et al. 2009). Firstly, under certain circumstances, bone marrow engraftment in tubules can be dramatically increased. Held et al. made use of a transgenic fumarylacetoacetate (FAH)-/- mouse, in which discontinuation of the rescue drug NTBC leads to acute tubular necrosis (Held et al. 2006). After transplanting bone marrow from wild-type mice into FAH-/- mice, a few bone marrow-derived tubular cells are noted. In a subset of the FAH-/- mice, there is, in addition, loss of heterozygosity (LOH) in the liver for homogentistic acid hydrogenase, which induces a more severe, ongoing form of acute tubular necrosis. In FAH-/- animals with additional hepatic LOH, up to 50% of tubular cells are bone marrow-derived cells. Engraftment of these wild-type bone marrow-derived cells leads to morphological resolution of ATN and to disappearance of the aminoaciduria present in control mice. In this model, the bone marrow cells have a strong survival advantage over native tubular cells, due to their ability to metabolise toxic products. It is possible that this strong positive selective pressure is necessary for regeneration to occur through wild-type bone marrow cells. Interestingly, most of the bone marrow-derived tubular cells are derived from cell fusion between bone marrow cells and tubular cells. This is supported by a study by Li et al. in which fusion of bone marrow cells to tubular cells account for part of bone marrow-derived tubular cells after ischaemia/reperfusion (I/R) injury, but not all. In this model without selective pressure, the percentage of bone marrow-derived tubular cells is low (1.8%) (Li et al. 2007b). Secondly, although there is disagreement

concerning the underlying mechanism, injection of bone marrow cells, particularly mesenchymal stem cells, has repeatedly been shown to improve renal function in ATN, whether induced by toxins (cisplatin and glycerol) or I/R (Imai and Iwatani 2007). With the role of actual engraftment of bone marrow cells as tubular cells thought to be minimal or absent, mesenchymal stem cells may exert their beneficial effects through their antiapoptotic, mitogenic, immunomodulatory and angiogenic properties, or through the contribution of the bone marrow cells to endothelial cell replacement in the peritubular capillaries. It is important to know the nature of the mediators involved in these properties, and the mechanisms governing the homing of mesenchymal stem cells to the kidney (Imai and Iwatani 2007). Imberti et al. confirmed the importance of paracrine mechanisms using co-culture of mesenchymal stem cells with tubular cells in a Transwell® culture excluding contact between the two cell types, which led to less cisplatin-induced tubular cell death. mesenchymal stem cells have been shown to produce vascular endothelial growth factor, basic fibroblast growth factor, monocyte chemoattractant protein-1, hepatocyte growth factor, and insulin-like growth factor, as well as immunomodulators TGF-β and PGE_2 (Imai and Iwatani 2007; Imberti et al. 2007). In a recent study, administration of conditioned medium from cultured stromal cells provided the same renoprotective effects as injection of mesenchymal stem cells, suggesting that systemic administration of the beneficial mediators may be just as good as mesenchymal stem cell injection, and safer (Imberti et al. 2007). It is a concern that there have been a few observations of adipogenesis associated with fibrosis and osteogenesis after injection of mesenchymal stem cells (Imai and Iwatani 2007).

Mesenchymal stem cell homing to the kidney has been linked to interactions between molecules upregulated in the injured kidney (SDF-1, hyaluronic acid and PDGF) and ligands expressed on mesenchymal stem cells (respectively, CXCR4, CD44 and PDGF-R) (Imai and Iwatani 2007). Similar beneficial effects on renal function may be induced by mobilizing bone marrow cells from the patient's own bone marrow by administration of growth factors (GF) such as granulocyte colony-forming factor, granulocyte/monocyte colony-forming factor, monocyte colony-forming factor, and stem cell factor. Possible explanations for improved renal function include increased numbers of bone marrow-derived tubular cells, a decrease in neutrophilic infiltrate, or increased cell proliferation and decreased apoptosis in kidneys of GF-treated mice (Roufosse and Cook 2008).

The role the bone marrow-derived tubular cells play in improved renal function is probably insignificant, with intrinsic renal cells, either stem cells or differentiated, more likely to play the predominant role in regeneration. Administration of bone marrow cells or mobilization of bone marrow cells using GF may be used to protect against renal injury. There may be a therapeutic role for bone marrow-derived cells engineered to replace a defective gene, due to a local strong positive selective pressure. mesenchymal stem cells have emerged as the most promising candidate for stem cell therapy, and appear safe, such that phase I clinical trials of mesenchymal stem cell injection for the treatment of acute kidney injury are scheduled to begin shortly (Imai and Iwatani 2007).

5. Isolation of Kidney Stem Cells

It is difficult to find a definitive marker for kidney stem cells that makes it difficult to isolate and define kidney stem cells. However, kidney stem cells have been isolated from other organs using 4 different ways. For the first method, when the DNA of the cells is labeled with a marker such as bromodeoxyuridine, the cells retain the label for a long period of time. This label retention is used to identify and isolate stem cells. The second method references the side-population (SP) cells that extrude Hoechst dye through the activity of multidrug resistance proteins, which are part of the ATP-binding cassette transporter superfamily. The third method isolates kidney stem cells referencing specific cell surface markers that have been used to identify stem cells in other organs or the metanephric kidney. The markers used to isolate kidney stem cells include Oct-4, Nanog, CD24, CD133 and stem cell antigen-1 (Sca-1). The fourth method uses culture conditions that select stem cells in other organ systems (http://content.karger.com/produktedb/produkte.asp?typ=fulltext&file=000117311#SA4).

As Zheng et al described in 2008, any unique characteristic can be used to isolate a pure population of stem cell is still lacking. There is few specific biomarker found for epidermal stem cells alone, but epidermal stem cells and transient-amplifying cells share some biomarkers (Bickenbach, 2003) (Zheng, et al, 2008).

6. Culture of Renal Stem Cell

Shimony et al characterized a new model of renal, stromal and mesenchymal stem cell (MSC) matrix deprivation, based on slow rotation cell culture conditions (ROCK). This model induces anoikis using a low shear stress, laminar flow. The mechanism of cell death was determined via FACS (fluorescence-activated cell sorting) analysis for annexin V and propidium iodide uptake and via DNA laddering. Their results showed while only renal epithelial cells progressively died in STCK, the ROCK model could induce apoptosis in stromal and transformed cells; cell survival decreased in ROCK versus STCK to 40%, 52%, 62%

and 7% in human fibroblast, rat MSC, renal cell carcinoma (RCC) and human melanoma cell lines, respectively. Furthermore, while ROCK induced primarily apoptosis in renal epithelial cells, necrosis was more prevalent in transformed and cancer cells [necrosis/apoptosis ratio of 72.7% in CaKi-1 RCC cells versus 4.3% in MDCK (Madin-Darby canine kidney) cells. The ROCK-mediated shift to necrosis in RCC cells was further accentuated 3.4-fold by H(2)O(2)-mediated oxidative stress while in adherent HK-2 renal epithelial cells, oxidative stress enhanced apoptosis. ROCK conditions could also unveil a similar pattern in the LZ100 rat MSC line where in ROCK 44% less apoptosis was observed versus STCK and 45% less apoptosis versus monolayer conditions. Apoptosis in response to oxidative stress was also attenuated in the rat MSC line in ROCK, thereby highlighting rat MSC transformation. They concluded that the ROCK matrix-deficiency cell culture model may provide a valuable insight into the mechanism of renal and MSC cell death in response to matrix deprivation (Shimony et al., 2008)

(1) Morphology and proliferation: Mixed population of cells with approximately 70% attached cells and the other 30% in suspension; need to change cell culture media every day after 48 hours of initial cell culture or when the media starts changing color to slight yellow for pink. Fast growing cell culture. Change media with Celprogen's Human Kidney Stem Cell Complete Growth Media with the appropriate Human Stem Cell Extracellular matrix and tissue culture media for differentiation, expansion or maintaining stem cells in their un-differentiated stage. Temperature 37^0C in 5% CO_2 humidified incubator. Positive markers could be CD34, Nestin & CD133.

(2) Subculturing

A. Thaw the vial with gentle agitation in a 370C water bath or a dry 370C shaking incubator. For water bath thawing
B. Keep the O-ring out of the water, thawing time 2-3 minutes.
C. Remove the thawed vial and wipe with 70% ethanol. Then transfer to the tissue culture hood.
D. Transfer the vial contents to a 15 ml sterile centrifuge tube, and gently add 7 ml of pre-warmed Human Kidney Stem Cell Complete Media to the centrifuge tube. Use an additional 0.5 ml of Human Kidney Stem Cell complete media to rinse the vial and transfer the liquid to the centrifuge tube repeat this once more to ensure you have all the cells transferred to the 15 ml centrifuge tube. Add 1 ml of Human Kidney Stem Complete Media to bring the final volume to 10 ml in the 15 ml centrifuge tube.
E. Centrifuge the cells at 100 g for 5 minutes. Remove the supernatant and resuspend the cell pellet in 500 ul of Human Kidney Stem Cell Complete Growth Media.
F. Add the 500 ul of cells to T75 flask pre-coated with Human Kidney Stem Cell Extracellular matrix with 15 ml of Human Stem Cell Complete Growth Medium.
G. Incubate the cells in the T75 flask in a 37^0C in 5% CO_2 humidified incubator. Perform 100% Media Change every 24 to 48 hours.
H. Medium renewal every day, and recommended sub-culturing ratio: 1:3.

(3) Freezing Medium: Human Stem Cell Complete growth Medium supplemented with 90% Fetal Bovine Serum with 10% DMSO.

(4) Storage temperature: liquid nitrogen vapor phase (San Pedro, CA 90731, USA, http://www.celprogen.com; http://ftp.celprogen.com/Technical_Resources/36100-27%20Human%20Kidney%20Stem%20cell%20data%20sheet.pdf.

7. Application of Kidney Stem Cells

Stem cell has powerful potential application purpose in science, medicine and industry, but it is also potentially danger for its enexpected plasticity. The evidence for bone marrow-derived stem cell contributions to renal repair has been challenged. The research and application for adult renal stem cells are also debated. The use of embryonic tissue in research continues to provide valuable insights but will be the subject of intense societal scrutiny and debate before it reaches the stage of clinical application. Embryonic stem cells, with their ability to generate all of kind of cell in living body, are great chance for our human civilization but have ethical and political hurdles for human use (Brodie and Humes, 2005). Stem cell research has attracted great attention because it could be used for the regeneration of damaged organs that are untreatable by conventional medical techniques, and stem cells (such as endothelial stem cells and neural stem cells) have been discovered to be practical useful in clinical applications. The potential for stem cell gene therapy has increased and many therapeutic applications have already been done. Chronic renal failure is a candidate for stem cell gene therapy. In the application of renal stem cell in medical treatment, mesenchymal stem cells could be transplanted, and in contrast, hematopoietic stem cells may be used for gene delivery for diseases, which need foreign cytokines and

growth factors, such as glomerulonephritis. The stem cell gene therapy for chronic renal failure and the potential of the novel strategy and the major practical challenges of its clinical application are big targets for the stem cell researches (Yokoo et al., 2003). Ectopic expression of the human telomerase reverse transcriptase gene in human mesenchymal stem cells can reconstitute their telomerase activity and extend their replicative life-spans (Li, et al, 2007).

8. Discussion

Kidney is derived from the ureteric bud and metanephrogenic mesenchyme, and these two progenitor cells differentiate into more than 26 different cell types in adult kidney. The ureteric bud contains the precursor of the epithelial cells of the collecting duct and the renal mesenchyme contains precursors of all the epithelia of the rest of the nephron, endothelial cell precursors and stroma cells, but the relatedness among these cells is unclear. A single metanephric mesenchymal cell can generate all the epithelial cells of the nephron, indicating that the kidney contains epithelial stem cells. These stem cells also are present in the adult kidney. Embryonic renal epithelial stem cells can generate other cell types (Al-Awqati and Oliver, 2002). The key important target in kidney stem cell research and application is to get kidney stem cells from other types of the cells, and it is also important to find the better way to change kidney stem cells to other cell types. As the nature will, to live eternally is an extracting dream in all the human history. Stem cell is the original of life and all cells come from stem cells. Germline stem cell (GSC) is the cell in the earliest of the cell stage. It is possible to inject the GSC into adult human body to get the eternal life. This article is to try to describe the stem cell and to explore the possibility of the eternal life with the stem cell strategy The production of functional male gametes is dependent on the continuous activity of germline stem cells. The availability of a transplantation assay system to unequivocally identify male germline stem cells has allowed their in vitro culture, cryopreservation, and genetic modification. Moreover, the system has enabled the identification of conditions and factors involved in stem cell self-renewal, the foundation of spermatogenesis, and the production of spermatozoa. The increased knowledge about these cells is also of great potential practical value, for example, for the possible cryopreservation of stem cells from boys undergoing treatment for cancer to safeguard their germ line (Ma, et al, 2007).

It is possible to introduce stem cells into a damaged adult kidney to aid in repair and regeneration. Transdifferentiation offers the possibility of avoiding complications from immunogenicity of introduced cells by obtaining the more easily accessible stem cells of another tissue type from the patient undergoing treatment, expanding them in vitro, and reintroducing them as a therapeutic agent. Adult stem cells may possess a considerable degree of plasticity in the differentiation. However, the differentiation of stem cells is normally unresolved. Pluripotent cells can be derived from fibroblasts by ectopic expression of defined transcription factors. A fundamental unresolved question is whether terminally differentiated cells can be reprogrammed to pluripotency (Hanna et al., 2008).

Developing nephrons are derived from renal stem cells and transplantation of fetal kidneys may be thought of as a therapeutic stem cell application. There are two bioengineering programs with the aim of producing a device providing full renal replacement therapy in the short to medium term. Both employ biomaterial scaffold structures to overcome the as yet insurmountable difficulties inherent in marshalling cells into organized three-dimensional structures capable of coordinated filtration, resorption / meta- / catabolism / secretion, collection, and disposal of waste. Initial experiments involved adult rabbit renal cortex harvested and fractionated into glomeruli, distal, and proximal tubules, expanded separately in vitro, and seeded onto biodegradable polyglycolic acid sheets for subcutaneous implantation into syngenic hosts. The potential impact of advances in stem cell technology on all the prospective cell-based therapeutic approaches for the treatment of renal failure discussed above is enormous. The kidney has a dramatic capacity to regenerate after injury. Whether stem cells are the source of the epithelial progenitors replacing injured and dying tubular epithelium is an area of intense investigation. Many surviving renal epithelial cells after injury become dedifferentiated and take on mesenchymal characteristics. These cells proliferate to restore the integrity of the denuded basement membrane, and subsequently redifferentiate into a functional epithelium. An alternative possibility is that a minority of surviving intratubular cells possess stem cell properties and selectively proliferate after damage to neighboring cells. Some evidence exists to support this hypothesis but it has not yet been rigorously evaluated (Vigneau et al., 2007).

In recent years, it has been shown that functional stem cells exist in the adult bone marrow, and they can contribute to renal remodelling or reconstitution of injured renal glomeruli, especially mesangial cells, and hMSC found in renal glomeruli differentiated into mesangial cells in vivo after glomerular injury occurred (Wong et al., 2008). In mice with cisplatin-induced acute kidney injury, administration of bone marrow-derived mesenchymal stem cells (MSC) restores renal tubular structure and improves renal function (Imberti et al., 2007).

Correspondence to:
Hongbao Ma
Bioengineering Department
Zhengzhou University
Zhengzhou, Henan 450001, China
Email: mahongbao@zzu.edu.cn
Telephone: 01186-137-331-67674

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