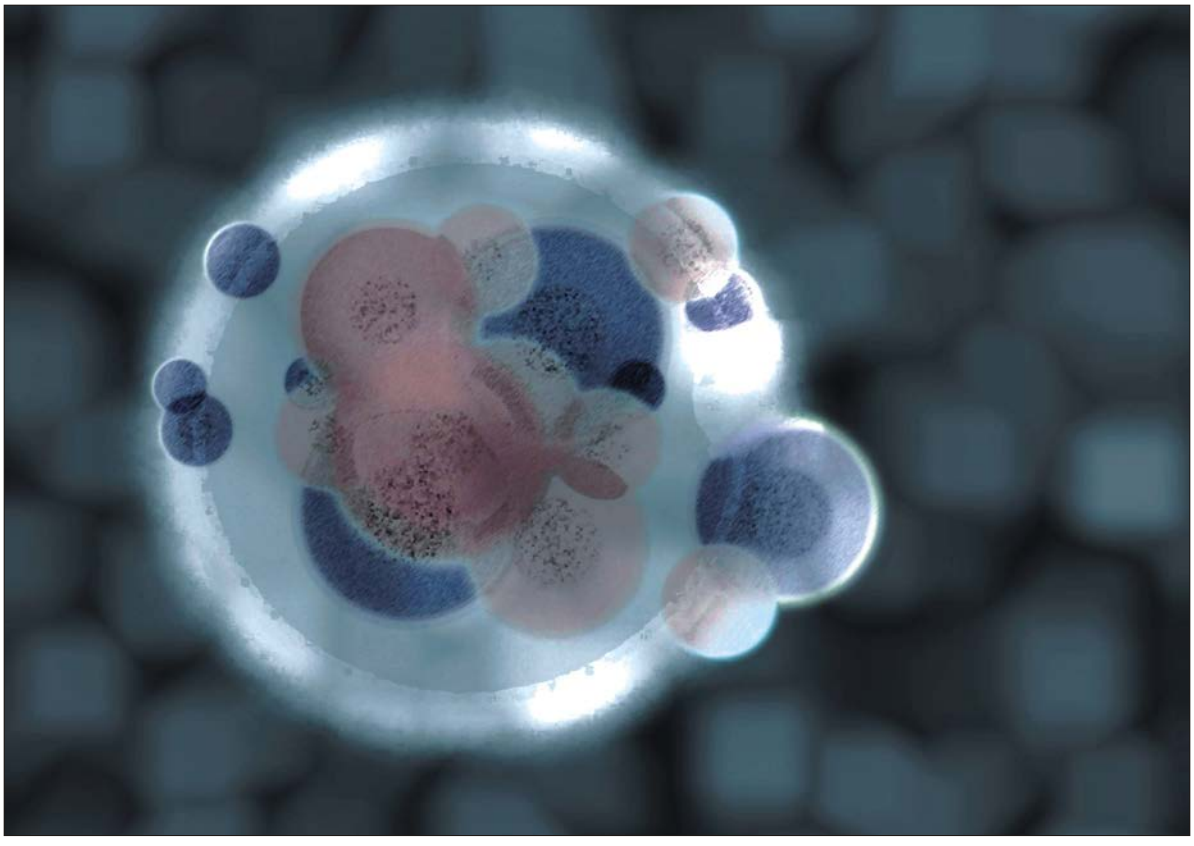

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Endogenous and Exogenous Approaches Towards Kidney Regeneration: A Review

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Abstract: This review focused on our current understanding of the renal adult stem cells and their participation in kidney repair and regeneration. Currently, cells (growing *in vitro*) are being used as a replacement therapy/regenerative medicine with the great potential to treat kidney failure or other degenerative diseases. Regenerative medicine is now considered of great hope not only to control but also to cure some of the diseases which is otherwise difficult to treat. Recent studies have indicated that adult stem cells, either in the kidney itself or derived from the bone marrow, could participate in this repair process and might therefore be utilized clinically to treat acute renal failure. After renal ischemic injury, there is a upregulation of stromal cell-derived factor-1 expresson found in the kidney, which can induce leukocytosis and kidney repair. Renal stem cells, both from the renal papilla or the CD24+CD133+ cell niche of the Bowman's capsule could differentiate into adult epithelial cells or tubular cells such as podocytes participate in this renal repair. Bone marrow-derived stem cells appeared to have a capacity for transdifferentiation and to be able to replace damaged renal tissue by replacing tubular epithelial cells, mesangial cells, endothelial cells and even podocytes. It is apparent from this review that there is a hidden potential within the kidney as well as in the bone marrow cells to stimulate endogenous or exogenous kidney regeneration. Further it can be speculated that harnessing the potential of these stem cells will go a long way in management and recovery of kidney failure through regenerative medicine approach.

Key words: Renal failures, renal stem cells, mesenchymal stem cells, CD133+ cells, mesangial cells and Nestin-GFP

INTRODUCTION

During mammalian embryonic development, embryo undergoes a series of cell divisions during subsequent stages, cells become specialized to form germ layers viz., ectoderm, mesoderm and endoderm. These specialized cells form an organ or tissues of their origin. Although, increasing number of cells become specialized, a certain pool of cells remain in undifferentiated/uncommitted stage until it receives signal to develop into specialized cell. These sets of uncommitted cells are termed as stem cells. Stem cell is a special kind of cell that has a unique capacity to renew itself and to differentiate to give rise to specialized cell types (Bag *et al*., 2010; Meenambigai and Sejian, 2011). Primarily stem cells are of two types-Embryonic Stem Cells (ES) and Adult stem cells. Embryonic stem cells are stem cells derived from the inner cell mass of an early stage embryo (blastocyst) and ES cells have the ability to give rise to any type of cell on receiving signal, indicating that ES are totipotent in nature (Flaquer *et al*., 2010). Whereas, Adult stem cells are derived from the adult organs (like bone marrow, brain, pancreas, kidney, skeletal muscles, skin etc.) or adult tissues (specific niche). Adult stem cells are characterized according to the ability or potency of their differentiation, like -corneal stem cells are unipotent, hematopoietic and bone marrow stem cells are either mutipotent or pleuripotent in nature, etc.

Currently, stem cells are being used as a Regenerative medicine for Cell replacement therapy because stem cells have the ability to differentiate (plasticity) into different types of specialized cells *in vitro* under specific environmental conditions/signals. Regenerative medicine and Cell replacement therapy is the most exciting cell

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based therapeutic in which scientists grow tissues and organs in the laboratory with a hope to safely implant them in the body of the patient. Importantly this process has the potential to solve the problems like (1) limited regenerative capacity/healing ability of certain organs (kidney etc), (2) shortage of organs for donation to meet the demand of the number of patients that require life saving organ transplantation. Also, the use of stem cells from the patient itself to treat degenerative disease reduces the possibility of donor rejection by the patient's immune system (Meenambigai *et al*., 2010; Stalin *et al*., 2010).

As stem cells have the ability to grow *in vitro* and to differentiate into different cell lineage pathway, they can be employed to treat degenerative diseases like Alzheimer's, Parkinson's, arthritis, kidney disease (chronic renal failure/end stage renal failure), myocardial infarction etc. Scientist primarily work with the adult stem cells as a regenerative medicine/cell based therapy to treat degenerative disease, and not with the ES cells because of the ethical issues associated with the use of ES cells (Srivastava and Sejian, 2010).

IMPORTANCE OF KIDNEY

Kidney is a multifunctional organ and under normal condition, it not only controls the conservation of fluid and the removal of bodily wastes but also takes part in the regulation of bone and calcium (including vitamin D3) metabolism (Abdel-Moneim and Said, 2007; Onyeanusi *et al*., 2009). Production of red blood cells by bone marrow is stimulated by the erythropoietin which is produced by the kidney when red blood cells are in short supply. And electrolyte concentrations (primarily sodium, potassium, calcium, phosphorous, chloride) are delicately adjusted for blood pressure regulation etc (Hulya Uz and Muberra, 2005; Bayazit *et al*., 2005). However, when the kidney function is impaired, kidney imbalance or dysfunction occurs, it leads to the inadequate filtration. Removal of waste products can result in excessive circulation of toxins that damage other tissues, such as mucosal layers of the gastrointestinal tract (uremic ulcers) including the tissues of the mouth, stomach, small and large intestines and may also affect the central nervous system, resulting in neurological signs, such as seizures (Al-Ankari, 2006; Al Kahtani, 2010).

The causes of kidney (renal) disease and failure are numerous and in some instances, not understood, but normally two types of kidney failures have been reported viz., Acute Renal Failure (ARF) and Chronic Renal Failure (CRF). The most common causes of ARF are: presence of toxic substances in the blood stream, infection and the conditions which impede, reduce or completely block blood flow to the kidney thus reducing the availability of oxygen and nutrient. Chronic Renal Failure (CRF) occurs as an insidious, irreversible progression of damage to essential kidney structure that results in its reduced function. Common causes of CRF include: -prolonged and unresolved ARF, prolonged and excessive stimulation of the immune system by any cause in the body resulting in the accumulation of "immune complexes" in the circulatory system. And these complexes when deposited into the kidney seriously diminish kidney capacity, function and structure. And when about 95% of kidney functions have been lost, the condition is known as End Stage Renal Disease (ESRD). In ESRD, the kidney can no longer excrete water ions and waste products. Renal failure is harmful to body because it just not cause kidney dysfunction/or progress to end stage renal failure but more because these renal abnormalities are associated with a manifold increase in risk of diabetic nephropathy and cardiovascular complications and premature cardiovascular death. For patients with CRF or end-stage renal disease, new therapies are required. Numerous studies have recently been conducted to determine the role of stem cells in the treatment of various acute and chronic diseases (Spangrude *et al*., 1988).

CONVENTIONAL TREATMENT FOR KIDNEY DYSFUNCTION /FAILURE

The existing treatments for kidney failure are hemodialysis and peritoneal dialysis. These treatments help replace the work kidney does but do not cure kidney failure and continuous use of dialysis have major medical, social and economic problems. Kidney may also be successfully transplanted from a donor individual to a recipient patient. However, the lack of availability of suitable transplantable matching organ has prevented kidney transplantation from becoming a practical solution to most cases of chronic renal failure (Yakoo *et al*., 2003). And also before transplanting the kidney to the patient there is a need for checking 3 factors-(a) blood type (blood group must be compatible with the donor's) (b) Human Leucocyte Antigens (HLAs) and (c) cross-matching antigens and even after the transplantation of kidney drugs called immuno-suppressants need to be taken to prevent rejection of kidney (transplanted kidney) by the body's immune system. Continuous intake of immuno-suppressants can weaken body's immune system and increase the risk of developing cancer, diabetes and high blood pressure bone disease or kidney damage.

The numbers of kidney transplants performed per year is limited by the availability of donor organs. One novel solution to this shortage is the vision to grow new kidneys in situ via xenotransplantation of renal anlagen. It has been reported that transplantations of developing kidneys might be advantageous relative to developed kidneys because (a) antigen presenting cells would be absent from the renal primordium, having not yet developed in the donor or migrated into the metanephros (b) donor antigens such as MHC may not be expressed on renal anlagen to the extent that they are expressed in developed kidney (c) the T-helper immune response to transplanted fetal tissue differs from the response of adult tissue and (d) the endothelial lining of its blood vessels which are exposed directly to components of the immune system of the host may originate from the host's circulation. Yokoo *et al*. (2006) reported that immune protection relates to the absence of donor dendritic cells in early rat anlagen, although immune suppression is required for the rejection to be prevented when crossing more disperate immunologic barriers such as pig to human (Hammerman, 2002).

Another possible therapy is the use of "Bio-artificial glomeruli and renal tubules "(an artificial device)". The kidney was the first organ whose partial function was replaced by an artificial device or bioengineering of devices to replace filtration or reabsorption. In the case of filtration micoporous synthetic biocompatible hollow fibers that were coated with MDCK cell extracellular matrix and then seeded autologous endothelial cells that were harvested from the patient's circulating blood that were shown to decrease the albumin loss and for mimicking tubular function resporptive capacity, a Renal Assist Device (RAD) in which renal parenchyma cells are harvested and seeded into the internal surface of hemodialysis hollow fibers were developed. Blood from the patient is passed along the outside of such fibers. The viability of the seeded cells is maintained via exogenous and substrates that provided by the passing blood and ultrafiltrate (Little, 2006). The challenges to this include the maintenance of potency reaching a size that is small enough for implantation and providing the normal function that normally are provided by the kidney. But it is noticed that the functional capacity of bioengineered kidney organ to provide filtering and reabsorptiive capacity like the endogenous kidney is doubtful. These limitations in treatment of acute and chronic renal failure have led to the search for enhanced therapeutic options. Promising results have been reported from application of different types of stem cells for treatment of kidney failure in animal models (Behr *et al*., 2007; Chen *et al*., 2008; Curtis *et al*., 2008). Major problems are associated with the above mentioned kidney treatments. So, to treat damaged kidney now a day's scientists are putting their more efforts in finding stem cells inside the kidney and also trying to differentiate the extra renal (bone marrow cells) stem cells into kidney cells (*in vivo* and *in vitro*). In this context it is desirable to take stock of renal and extra renal stem cells.

RENAL RESIDENT STEM CELLS

In most of the adult organs, under normal conditions, there is constant cellular death and regeneration. (e.g., in the skin, bone marrow, intestinal epithelia) i.e., these organs have a regular turnover of cells. But in many other organs viz, the heart, kidney, CNS etc the cellular turnover is infrequent. It is observed, that in mammalian kidney, partial nephrectomy stimulates hypertrophy of remaining tissue, but not complete regeneration of new nephrons. But it is interesting to note that kidney shows a remarkable regenerative and reparative potential after ischemic tubular necrosis. So the basic question arises, do organs with very limited turnover rate harbor stem cells within them or not? The kidney retains the potential to regenerate itself as long as the damage is not too severe and the kidney structure remains intact. Therefore, regenerative medicine for such kidney diseases should aim to activate or support this potential.

The discovery of stem cells in organs such as the central nervous system was unexpected and the number of reports/work done by the scientists proved the presence of organ resident stem cells that continued to grow after injury. It appears very likely that the kidney also contains renal specific stem cells which might also have a role in its limited repair process. This concept emerged through the understanding of kidney development. During nephron formation the cells that eventually make up the glomerular epithelium, proximal tubule, loop of Henle and distal convoluted tubule all originate as mesenchymal cells, which condense around the tip of the uretic bud and undergo transformation to epithelial cells. If these mesenchymal cells persisted in the adult renal tissue, they would provide a reservoir of cell progenitors that could be activated to migrate in the tubule and differentiate into epithelial cells in response to renal injury (Caplan, 1991; Cantley, 2005).

Maeshima *et al*. (2003) tried to find out renal progenitor like tubular cells in the kidney which may participate in the regeneration of the kidney after injury. They labeled the slow cycling cells (termed as Label Retaining Cells, LRC) of the normal rat kidney. They observed that after renal ischemia, LRC underwent cell division and most of them become positive for PCNA

(Proliferating Cell Nuclear Antigen) which specially recognizes the early G1 and S phases of the cell cycle, it indicates that cells proliferating during tubular regeneration are essentially derived from LRC. During early phase of tubular regeneration, descendants of LRC expressed mesenchymal marker, vimentin and eventually became positive for an epithelial marker E-Cadherin, after multiple cell divisions. This study indicates that LRC may be playing some role in kidney regeneration (Maeshima *et al*., 2003).

In another study, Oliver *et al.* (2004) detected cells having a low cycling rate, located in specialized regions (niche) of the kidney. They administered a pulse of the bromo deoxy uridine (BrdU) to rat and mouse pups after a long chase (more than 2 months), when adult kidneys were examined, the label retaining cells were very sparse except that in the renal papilla, where they were numerous. But during the repair phase of transient renal ischemia, these cells entered the cell cycle and BrdU signal quick disappeared from the papilla, despite the absence of apoptosis in this part of the kidney. So, they isolated renal papillary cells *in vitro* which showed the characteristics of adult stem cells and when injected into the renal capsule they incorporated into the kidney parenchyma. The experiments putatively proved the presence of stem cells in the kidney and proposed that the papilla is the reservoir for such cells (Oliver *et al*., 2004). The pictorial location of Brdu-retaining cells in adult mouse kidney can be referred to the figure described by Oliver *et al*. (2004) with outer cortex with no BrdU-positive cells and outer papilla with abundant BrdU-retaining cells.

During Kidney development, a unique plasticity exists between epithelial and mesenchymal cells (metamorphic mesenchymal to epithelial transition). Keeping the same developmental view in mind, Zeisberg *et al.* (2005) reported that BMP-7 can induce MET (Mesenchymal to Epithelial Transition) and which potentially facilitate the repair of tubular epithelial structure in injured kidney. They found that in the injured adult kidney, renal epithelial-mesenchymal transition which facilitates renal fibrosis and inhibition of EMT can prevent the progression of fibrosis, demonstrating that BMP is an important contributor to the progression of renal disease. They also found that BMP involved in the morphogenesis and differentiation of S-shaped tubule in the formation of the glomerulus, distal and proximal tubule elements associated with the mature nephron. Moreover, they also showed a gradual cessasion of nephrogenesis, associated with a reduction of ureteric bud and the loss of metahephric mesenchyme in BMP-7 deficient kidneys. Hence, it was concluded that the BMP-7 (also called as osteogenic protein-1) is a principal regulator of MET in kidney development and on treatment with BMP-7 might induce MET involving adult renal fibroblasts in the injured kidney, generating functional epithelial cells (Zeisberg *et al*., 2005).

Many problems were faced by the researchers for the identification of the tissue specific stem cells, especially with the kidney stem cells. Earlier it was found that, endothelial progenitor cells, hematopoietic progenitor cells, neural stem cells and embryonic intestinal epithelial cells express CD133+ surface marker (Uchida *et al*., 2000; Peichev *et al*., 2000; Corbeil *et al*., 2000). Moreover, Bussolati *et al.* (2005) explored the possibility that endogenous renal stem cells also express CD133+ surface marker. They isolated small number of CD133+ cells from the interstitium of adult human kidney, approximately 1% of total cell, in culture. They found that purified cells expressed the early nephron developmental marker PAX2, as well as several markers typical of bone Marrow Stromal Cells (MSCs) but were negative for hematopoietic cell markers such as CD34 or CD45. These cells when cultured with the CD133+ cells in the presence of HGF and fibroblast growth factor-4, the cells stopped expressing CD133+ and began to express epithelia makers such as cytokeratin, E-cadherin and Zona occludens-1. Cells also continued to express the mesenchymal markers vimentin indicating that the cells were not fully differentiated. But when they cultured the CD133+ cells in the presence of VEGF resulted in expression of endothelial markers including VE- Cadherin and Von Willebrand factor and they concluded from the *in vitro* results that CD 133+ renal cells might be pleuripotent, having the capacity to differentiate into either tubular cells or vascular cells if presented with the appropriate conditions. To explore this potential *in vivo*, the investigators intravenously injected fluorescently labeled CD133 cells into mice that had been given an intramuscular injection of glycerol to induce rhabdomyolysis and subsequent myoglobin-mediated acute renal failure. Then they examined mice kidney after 3 days and they reported that the transplanted cells were proliferating and had been incorporated into cortical proximal and distal tubular portions. Hence they concluded that, CD133+ cells derived from the renal interstitium might also have the capacity to differentiate toward an epithelial lineage *in vivo,* and can cure kidney (Bussolati *et al*., 2005). Patschan *et al.* (2007) explored that Nestin, a marker of multilineage stem and progenitor cells, is a member of intermediate filament family, which is expressed neuro-epithelial stem cells, several embryonic cell types, including mesonephric mesenchyme, endothelial cells of developing blood vessels and in the adult kidney also. Investigators used Nestin-green Fluorescent Protein (GFP) to characterize the Nestin

expression in normal and post-ischemic kidney. They found large clusters of Nestin-GFP expressing cells within the papilla, along the vasa rectae and less prominent in the glomeruli and juxta-glomerular endothelial and peri-vascular cells showed increased nestin expression. They did time lapse micro scopy before and after ischemia and concluded t hat there is a migration of Nestin-GFP-positive cells from medulla to cortex during the first 3 h and was detectable after 30 min of incubation. When they cultured as explants of kidney and aortas exhibited sprouting angiogenesis with cells co-expressing Nestin and endothelial marker, Tie-2. These migrating Nestin-positive cells (after ischemic injury) from medulla towards the renal cortex may be involved in the process of tissue regeneration of injured kidney (Patschan *et al*., 2007). Goodell *et al*. (1996) isolated hematopoietic specific stem cells on the basis of the cells ability to extrude Hoechst 33342 dye. Cells having this property, called Side Population (SP) cells and found in several organs including kidney. Zhou *et al*. (2001) and Asakura *et al*. (2002) found and isolated SP cells not only from hematopoietic but also from non-hematopoietic stem cells. As there was a major problem associated with the isolation of endogenous renal stem cells because of the lack of the cell surface marker for renal stem cells, Hishikawa *et al*. (2005) have shown that the renal interstitium contained SP cells. They created rodent with acute tubular injury induce by cisplatin injection and injected intravenously SP cells, infusion of these cells can counter act the rise in Blood Urea Nitrogen (BUN) and creatinine in rodents (Kinomura *et al*., 2008). When SP cells isolated from the acutely injured kidney expressed high levels of messenger RNA for several GFs (growth factors) implicated in renal development and/ or repair, including HGF, VEGF (vascular endothelial Growth factor) and leukemia inhibitory factor.

Earlier it was thought that the stem cells present in the organ like bone marrow is the major source for regeneration in post-ischemic kidney but Lin *et al*. (2003) proved that 89% epithelial cells originated from the host cells and the rest 11% originated from donor BMSCs. For proving this they created cre^{ksp}; Z/EG, a double reporter mouse strains (to measure the contribution of intrinsic renal cells to tubular regeneration). After Ischemia/Reperfusion Injury (IRI) EGFP-positive cells showed incorporation of BrdU and expression of vimentin which gives direct evidence that the cells generating tubules are derived from renal tubular epithelial cells. And they also created mice having renal IRI in which they transplanted BMC (BMCs from male donor into female recipients with IRI ,they measure that 11% of the BrdU positive tubular cells were donor derived and 89% were derived from the host. They also found that several genes that are expressed during embryonic development are all down regulated in the mature kidney are re-expressed during recovery from renal injury. For example, the transcription factor paired box gene 2 (Pa×2) which is transiently expressed in developing nephrons (nephrogenesis) is re-expressed in regenerating proximal tubules. The intermediate filament vimentin is expressed in the metanephric mesenchymal cells that are progenitors of the epithelia cells of the nephron and vimentin is normally not present in the well differentiated renal tubular epithelia cells but is re-expressed injured tubular cells. Hence, they concluded that kidneys also have self renewal capability (Lin *et al*., 2005).

Gupta *et al*. (2006) isolated stem cells from the rat kidney and termed as MRPC (Multipotent Renal Progenitor Cells) having spindle shaped morphology, self renewed for >200 population doubling without senescence, expresses vimentin, having normal karyotype and DNA analysis, Pax 2 and Oct - 4 but not cytokeratin, CD 90 (thy 1.1), MHC I or II. Other markers of differentiated cells and proved that MRPC exhibit plasticity because after induction or giving proper environment MRPC express endothelial, hepatocyte and neural markers. They also found expressions of Oct 4 in some tubular cells in the adult kidney and hence they concluded that it could be the candidate for renal stem cells. They also proved that the stem cells exist in the metanephric mesenchyme and can give rise to all of the cell types of the adult kidney, expect those that are derived from ureteric bud (Gupta *et al*., 2006).

In contrast to the activity of tubular stem cells during ischemic injury, Dekel *et al*. (2006a) reported the existence of non-tubular cells that express stem cell antigen -1 (sca-1) and are CD 45 negative and reside in the renal interstitial space in adult mouse kidney. And these non tubular cells are also negative for Beta-integrin, cytokeratin (surface marker that typically found on BM derived mesenchymal stem cells). They also found (microarray profiling) many genes that involved in signaling and self renewal pathways, such as TGF - Beta/ BMP (Bone Morphogenic Protein), WNT or fibroblast growth factors as well as those that are involved in the specification of mesodermal lineages (myocyte enhance factor 2 A, 441-associated factor) and filamin-Beta. Hence, they proved that non tubular stem cells are present in the kidney and they have ability to adopt a tubular phenotype and the potential for repairing injured kidney (Dekel *et al*., 2006a).

Sagrinati *et al*. (2006) characterized multi-potent progenitor cells from the Bowman's capsule of adult human kidneys, a subset of Parietal Epithelial Cells (PEC)

in the Bowman's capsule exhibit co expression of the stem cell markers (CD24) a surface marker that has been used to identify different types of human stem cells and is also expressed by uninduced metamorphic mesenchyme during renal embryogenesis) and CD133, a marker of adult tissue and also the presence of stem cell specific transcription factors such as Oct-4 and BMP -7 in the absence of lineage specific markers. Investigators found that under normal culture conditions, individual clones of CD 24+ CD 33+ PEC could be induced to generate natural, functional tubular cells with phenotypic features of proximal and/or distal tubules (Sagrinati *et al*., 2006).

Patschan *et al*. (2006) showed that the Endothelial Progenitor Cells (EPCs) participate in tissue repair under diverse physiological and pathological conditions. They subjected mice to unilateral renal artery clamping (UC) for 25 min, at 10 min, 3, 6, 24 h and 7 days after UC and they found pool of circulating and splenic CD34+/ flk -1+ cells within the monocytic population. When they performed immuno-histochemical analysis of the kidneys, they found six fold increases in the number of C-kit+/Tie-2+ cells localized in the medullo-papillary region in mice kidney by 7 day after ischemia. For further clarification they made chimeric mice having C- kit+/Tie-2+ cells population, in which they made Tie-2 green fluorescent protein and subjected these chimeric mice to Ischemic Pre Conditioning (IPC). Then they isolated cells (C- kit+/Tie-2+ cells) and transplanted to wild type mice with acute renal ischemia resulted in the improvement of renal function in recipients. Investigators concluded that (1) renal ischemia rapidly (within 3-6 h) mobilizes EPCs which transiently home so the spleen, acting as a temporary reservoir of mobilized EPCs, (2) the late phase of IPC is associated with the mobilization of the splenic pool and accumulation of EPCs in the renal medulapapillary region (Patschan *et al*., 2006). All the literature cited above suggest that there are kidney resident stem cells but the origin of renal stem cells is not restricted to a specific place within the kidney. Hence, it is necessary to harness hidden potential of the renal stem cells for developing novel therapeutic approaches towards kidney regeneration.

ROLE OF BONE MARROW STEM CELLS IN KIDNEY REPAIR AND REGENERATION

In addition to the ability of the kidney stem cells (endogenous renal stem cells) and other tubular cells in repair, studies in other organ systems have raised the possibility that adult stem cells from the bone marrow might participate in kidney repair (Ricardo and Deane, 2005). Cantley (2005) have described the schematic representation of possible role of Bone Marrow Stem Cells (BMSCs) in facilitating renal repair. He had put forth four mechanisms for BMCs in this process: (1) indicate that bone marrow stem cells can differentiate into small numbers of tubular epithelial cells, peritubular vascular endothelial cells, or both; (2) a second possibility is that BMSCs secrete factors that can either augment the capacity of resident renal stem cells to proliferate and enter the tubule during the repair process; (3) BMCs act to prevent tubular cell death and/or enhance proliferation by an endocrine effect on the tubular cell itself, or suppression of inflammatory responses and (4) BMSCs that enter the kidney and surround the injured tubules could act in a paracrine or direct fashion to mediate cell protection and proliferation. Although, adult stem cells exist in various tissue-specific guises and have been reported in organs such as bone marrow (Gronthos *et al*., 2003; Jiang *et al*., 2002; Gage, 2000), brain (Kruger *et al*., 2002), the peripheral nervous system (Beltrami *et al*., 2003), heart (Beltrami *et al*., 2003), skeletal muscle (Gage, 2000) and skin (Poulsom *et al*., 2001). Bone marrow-derived stem cells appeared to have a capacity for transdifferentiation and to be able to replace damaged renal tissue by replacing tubular epithelial cells (Rookmaaker *et al*., 2003), mesangial cells (Imasawa *et al*., 2001; Ito *et al*., 2001), endothelial cells (Sugimoto *et al*., 2006) and even podocytes (Prodromidi *et al*., 2006; Dalakas *et al*., 2005).

Sakai (1997) previously reported a patient with IgA nephropathy which is the most frequent form of glomerulonephritis, associated with chronic myeloblastic leukemia in which mesangial deposits disappeared after allogenic bone marrow transplantation. These findings provided the first evidence that abnormalities of bone marrow stem cells may be involved in the pathogenesis of some renal disease and gave rise to the hypothesis that some renal progenitor cells are resident in and could be mobilizd from bone marrow (Patschan *et al*., 2007). The bone marrow contains two major categories of cells, the Hematopoietic cells lineage and the Stromal cells (Goodell *et al*., 1996). Hematopoietic cells include the pleuripotent hematopoietic stem cells and their progeny from which all the cellular blood elements divide. These elements include the precursors of polymorph nuclear leukocytes, T cells, B cells, macrophages, megakaryocytic and erythrocytes and all these elements collectively termed "lineage-positive" Cells. Whereas MSCs (Mesenchymal Stem Cells) are not well characterized and they comprise a heterogeneous group of cells thought to be crucial for the maintenance of an environment, conducive for survival and maturation of HSCs (Hematopoietic stem cells). Individual cells from this stromal cells population can differentiate into other types such as adipose, muscle and bone (Cantley, 2005).

In the year 2007, Mc Taggart and co-workers reported that MSC are non-immunogenic and are immunosuppressive with the ability to inhibit maturation of dendritic cells and suppress the function of natïve and memory T cells, B cells and NK cells (McTaggart and Atkinson, 2007). In addition to their immunodulatory properties, MSC was originally tailored for the regenerative capacity of this cell type through its ability to differentiate into mesodermal cell types including adipocytes, chondrocytes, osteoblast, and stromal cells (Friedenstein *et al*., 1996; Pittenger *et al*., 1999; Prockop, 1997; Banas *et al*., 2007). When cultured MSCs were also observed to adopt characteristics of cardiomyocytes (Hishikawa and Fujita, 2006), hepatocytes (Lee *et al*., 2004; Xu *et al*., 2004).

MSC are capable of differentiating into various tissues of mesenchymal and non-mesenchymal origin and migrating to sites of tissues injury (McTaggart and Atkinson, 2007). Grimm *et al.* (2001) also reported evidence for host derived mesenchymal cells in renal transplants that were experiencing chronic rejection but they did not describe the generation of tubular cells in kidney (Grimm *et al*., 2001). But the other group Morigi *et al.* (2004) reported that the hematopoietic stem cells do not contributed to the renal repair like mesenchymal stem cells. Morigi *et al.* (2006) injected mesenchymal stem cells of male bone marrow origin into the cisplatin-treated female mice. They reported that Y-chromosome containing cells localized in the tubular epithelial lining, indicating that mesenchymal cells markedly accelerate tubular proliferation or regeneration, whereas hematopoietic stem cells failed to exert beneficial effects (Morigi *et al*., 2004).

In contrast to the above mentioned report, Duffield *et al.* (2005) studied kidney repair in chimeric mice expressing GFP or bacterial beta gal or harboring the male Y chromosome exclusively in bone-marrow derived cells. And when investigators injected bone-marrow mesenchymal stromal cells i.v (intraveneous) postischemic functional renal impairment was reduced, and there was no evidence of differentiation of these cells into tubular cells of the kidney. Thus, it indicates that bone marrow mesenchymal stromal cells do not make a significant contribution to the restoration of epithelial integrity after as ischemia insult (Duffield *et al*., 2005). Unfortunately, there is currently no clear consensus on how many individual cell types constitute MSCs, how MSCs should be isolated and purified or even which MSCs are actually stem cells capable of asymmetric division.

On the other hand, Bone marrow Hematopoietic Stem Cells (HSCs) have been shown to facilitate regeneration in multiple nonhematopoietic tissues by either generating epithelial cells or altering the inflammatory response (Chen *et al*., 2008). Hematopoietic stem cells have been shown to be capable of differentiating into hepatocytes, cardiac, myocytes, gastrointestinal epithelial cells and vascular endothelial cells during tissue repair. Fangming Lin *et al.* (2003) isolated HSC from male Rosa 26 mice that express B-galactosidase constitutively when transplanted into female non-transgenic mice after renal I/R injury. They found B-galaclosidate positive cells after 4 weeks in renal tubular. Hence they concluded that HSCs may contribute to the renal repair. This was the first report that showed that HSC can differentiat into renal cells after I/R injury (Duffield *et al*., 2005).

Okabe *et al.* (1997) transplanted crude bone marrow cells in C57BL/6, mice from Green Fluorescent Protein (GFP)-transgenic mice and then examined for the development of donor cells into glomerular residential cells. The number of green cells in the glomeruli increased markedly in a time dependent manner from 2 weeks until 24 weeks after transplantation and these cells possessed properties of mesangial cells, such as positive for desmin and potential to contract in response to angiotensin II, suggesting that bone marrow cells contain mesangial stem cells (Okabe *et al*., 1997). Related work was also done in 2001 by Imasawa and co-workers. In contrast to this work Ito *et al.* (2001) used a similar technique, GFP transgenic rat and reported that very few transplanted donor cells are able to differentiate into mesangial cells on normal conditions but the numbers increase during glomerular remolding. These data suggested that renal stem cells may be resident in the bone marrow but the signals for migration, homing and differentiation vary between species and even genetic background. For demonstrating this they did in situ hybridization to detect Y-chromosome and they found that circulating stem cells frequently engraft into the kidney and differentiate into renal parenchymal cells (Ito *et al*., 2001). Kale *et al.* (2003) reported improvement of renal function with hematopoietic stem cells transplantation in mice with renal IRI. Further, Poulsom *et al.* (2001) reported that tubular epithelial cells and interstitial cells as well as podocytes might be formed from bone marrow cells by detection of the Y chromosome in the female mice that have received, male whole bone marrow transplants.

Whereas Fangming lin and co-workers reported that no renal functional improvement was observed in mice that were transplanted with exogenous BMCs only 11% renal originate from the donor BMCs and 89% renal epithelia cells originate from host cells.In contrast to the above mentioned reopt, Dekel *et al.* (2006b) also investigated that the human adult CD 34 + progenitor cells

undergo renal differentiation once xenotronsplanted into ischemic and developing kidneys. They also concluded that hematopoietic stem cells improve the vascular function but not the kidney function so well.

CAN BM CELLS MOBILIZE TOWARDS THE KIDNEY AFTER INJURY

The studies above mentioned/described that bone marrow cells, itself can cause a modest increase in the number of circulating bone marrow derived cells. The mechanism of this mobilization of bone marrow derived cells is not fully understood. Number of groups have shown that cells residing in the bone marrow (BMSc) have an unexpected degree of plasticity. Volker and co-workers proved that the damaged kidney by ischemia causes the release of cytokines which act via the flowing blood and stimulate the bone marrow, which then mobilizes progenitor cells to the blood and directs them to adhere to and migrate into the damaged organ (Schachinger and Zeiher, 2005). Morgini *et al.* (2006) repored that in mice 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 (Morigi *et al.*, 2006). Zhang *et al.* (2004) showed that the HSC-mobilizating cytokine granulocyte colony stimulating fctor (G-CSF) is upregulated in the circulation and renal tubule following ischemia reperfusion injury.

In normal humans, circulating levels of G-CSF are generally below 40 pm mL^{-1}. However, under stress condition, such as infection, or following therapy with high dose cytotoxic agents, G-CSF levels increase dramatically and may exceed to 2,000 pg mL^{-1}. There are several reports by many scientists to see the effect of exogenous G-CSF on mouse ARF models. Togel *et al.* (2004) found favorable effect of G-CSF on ARF model when they compared treated model (mice) with the control mice with the same insult given to the kidney. They also deduced the adverse effect of G-CSF in ischemic renal injury because the use of G-CSF usually induces neutrophils and elicit inflammatory response that result in further injury in experimental model mice (Togel *et al.*, 2004). Nishida and Hamaoka (2006) described schematically the possible mechanism of action of endogenous or exogenous G-CSF to the kidney after acute toxic or ischemic insult.

Two groups, Iwasaki *et al.* (2005) and Fang *et al.* (2005) reported that treatment with G-CSF significantly increased BM-derived RTEC (renal tubular epithelial cells) and suggested that the contribution of boosted circulating HSCs by G-CSF to the regeneration of injured tubules. Furthermore, Iwasaki *et al.* (2005) also reported that G-CSF plus M-CSF (macrophage colony stimulating factor) accelerates the drop in BUN and creatinine in four days after cisplatin injection. They concluded that might be M-CSF enhanced the activity or effect of G-CSF. In contrast, the report given by Stokman *et al.* (2005) showed that 7 days after ischemic injury to the kidney only few BM derived RTECs were observed in both control and G-CSF treated female mice that received BM transplanted from male EGFP-transgenic mice. They concluded that incorporation of RTECs from BM origin was not increased with G-CSF treatment in their study and they also concluded that the effect of G-CSF for renal injury is not based on increased HSC or other BM stem cells involvement but rather on altered inflammatory kinetics. Because G-CSF treatment increases the number of neutrophils (which have reactive oxygen species), reduces the infilteration of granulocytes into the injured kidney and thus, is responsible for the worsening of the renal function (Stokman *et al.*, 2005). And also the other group Nishida and Hamaoka (2006) *et al.* reported that on treating the mice with cisplatin to induce ARF, which has a myelosuppressive effect, decrease the peripheral blood leukocyte count, and only few HSCs infilterated the kidney,even with G-CSF treatment, indicating that the effect of G-CSF is not due to increased HSF infilteration to the kidney (Nishida and Hamaoka, 2006).

In addition to the G-CSF other renotropic growth factors like HGF (hepatocyte growth factor), EGF (epidermal growth factor), and insulin like growth factor (IGF) also accelerates the renal regeneration in animal models after toxic or ischemic injury. Ernst *et al.* (2001) reported that these renotropic growth factors initiate biological effects on renal tubular cells by interaction with specific transmembrane receptor tyrosine kinases. But the exact mechanism how these renotropic GFs actually initiate the growth and differentiation of renal proximal tubular cells are still not understood and yet to be revealed (Ernst *et al.*, 2001). Related work was also done by many scientists to see the different growth factors that are involved in signaling pathway of tubular or renal regeneration after I/R, like Haug *et al.* (2000), Cao *et al.* (2005) and Ho *et al.* (1999) worked on the renotropic GFs and their interaction with specific receptor for the initiation of growth and differentiation of renal tubular cells after kidney injury. Flaquer *et al.* (2010) described pictorially the involvement of stem cells in renal regeneration.

Cell therapy, or stem cell mobilization, could revert chronic kidney damage. Bone marrow stem cells (BMSCs), whether haematopoietic (HSCs) or mesenchymal (MSCs),

could regenerate the kidney by different mechanisms but above all due to the local release of certain growth factors. Renal stem cells whether from the renal papilla or the CD24+CD133+ cell niche of the Bowman's capsule could differentiate into adult epithelial cells or tubular cells such as podocytes. They could also facilitate kidney regeneration by other mechanisms.

Report of G-CSF and other renotropic growth factor involvement in the bone marrow mobilization, another report by Togel *et al.* (2004) reported that after renal ischemic injury, there is a upregulation of stromal cell-derived factor-1 (SDF-1) expresson found in the kidney, which can induce leukocytosis. As this group found that SDF-1 attracts cells such as HSCs and endothelial progenitor cells, and these cells may have renotroprotective effects and they concluded that SDF-1 may be involved in the kidney repair (Togel *et al.*, 2005).

All these findings can lead to the conclusion that kidney harbors a resident progenitor population and the renal repair and regeneration can be taken up by these resident cells. Mobilized bone marrow cells may stimulate these cells by an immuno-modulatory effect and together with the secreted cytokines they actively participate in repair and regeneration.

CONCLUSION

Despite an excitation about the application of many of these novel regenerative approaches, many hurdles remain to be solved, with special reference to kidney. These include research obstacles, such as a paucity of identification of renal stem cell markers and their potential for tailor made differentiation. The unique architecture of the kidney creates an inherent/in house obstacle to the functional integration of a stem cell-derived nephron. Indeed, the functional capacity of a bioengineered organ to provide anything like the filtering and reabsorption capacity of the original kidney is questionable. It is worth speculating that the origin of renal stem cell is not restricted to a simple place within the kidney and may be supplied from the different places depending on the severity, location and duration of damage. Apart from the above-mentioned problems, the major obstacle is the degree of damage that is present in a patient with acute or chronic renal disease. It is unlikely that any organ-based repair process will overcome the extent of damage that is seen in a patient who has reached end-stage renal failure. This has major implications for the adoption of any autologous therapy. Even if an adult stem cell population does exist in the adult kidney, would it remain in an end-stage kidney? Indeed, the adoption of any organ-based cellular therapy is likely to succeed only if chronic renal disease can be diagnosed early and if such therapies are implemented well before end-stage renal failure is reached. In the end, it is unlikely that any such therapies will produce a physiologic outcome that is equivalent to that of a healthy kidney, but as patient numbers are on increase, a novel therapy that creates an improvement over dialysis and other kidney treatments will become not only a major achievement but also a necessity.

It is apparent from the above-cited literature that there is a hidden potential within the kidney as well as in the bone marrow cells to stimulate endogenous or exogenous kidney regeneration. Nonetheless, it is also important to understand the basic cellular mechanisms and the environment that can tigger the stem cell pool residing within the kidney itself or within bone marrow. We speculate that harnessing the potential of these stem cells will go a long way in management and recovery of kidney failure through regenerative medicine approach.

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