Bone Marrow Stem Cell

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Abstract: 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. Kidneys can regenerate, which varies among species. Some bony and cartilaginous fish continue to form new nephrons during adult life. Adult mammals cannot form new nephrons but, to a certain extent, tubules and glomeruli may recover structure and function after limited injury such as acute tubular necrosis. Severe or prolonged injury results in replacement of functional parenchyma by scar tissue, i.e. fibrosis, which correlates clinically with the development of renal failure. 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. 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.
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In the 20th century, an efficient treatment was given to patients with renal failure through the development of kidney dialysis and transplantation. These techniques have been proved successful, but are marred by inflammation and limited organ availability and graft survival due to immune rejection. More recently, hope has been placed in the development of stem cell-based therapies, in which the function of the failing organs is restored by injected multipotent cells. Possible sources for these cells include differentiated embryonic stem (ES) cells, adult renal stem cells, and circulating multipotent cells, such as bone marrow-derived stem cells. Using the patient's own stem cells to repair kidney damage could circumvent the problems of immune rejection and organ availability.

Kidneys can regenerate, which varies among species. Some bony and cartilaginous fish continue to form new nephrons during adult life. Adult mammals cannot form new nephrons but, to a certain extent, tubules and glomeruli may recover structure and function after limited injury such as acute tubular necrosis. Severe or prolonged injury results in replacement of functional parenchyma by scar tissue, i.e. fibrosis, which correlates clinically with the development of renal failure.

An effective treatment of renal disease is renal cell regeneration, or replacement of damaged renal cells, that discourage fibrosis. The origins for renal parenchymal cells could be: (1) the re-entry into cell cycle of differentiated cells; (2) direct transdifferentiation of one cell type into another, such as tubular cells into interstitial cells or vice versa; (3) differentiation from stem cells of the kidney or the bone marrow.

Embryonic stem cells are different from adult or tissue-specific stem cells. 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. It is difficult for the tissue-specific adult stem cells to grow in a great number, hard to isolate and are difficult to grow outside the body. Adult stem cells, such as skin 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, but there is no efficient technique available to readily knockdown or overexpress transgenes for rapid evaluation of resulting phenotypes. Embryonic stem cells have unlimited

developmental potential and can be manipulated at the molecular genetic level by a variety of methods. ES cell technology may achieve the objective of obtaining a versatile cell culture system in which molecular interventions can be used in vitro and consequences of these perturbations 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. Infiltrating or resident stem cells can contribute to the replacement of lost or damaged tissue. However, the regulation of circulating progenitor cells is not well understood. 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. It was reported that in the regenerating zone of the shark kidney, stem cells exist that can be induced by loss of renal tissue to form new glomeruli. Stem cell may eventually contribute to novel therapies of the kidney disease (Perin et al. 2008).

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, the 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, tendons, 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).

Bone marrow stem cells can differentiate into various renal cells including mesangial cells (Imasawa, et al., 2001), tubular epithelial cells (Gupta, et al, 2002) and podocytes (Poulsom, 2001). Moreover, bone marrow stem cell abnormalities have been shown to affect renal function, raising the possibility of the existence of a bone–kidney stem cell axis (Imasawa, et al., 1999; Terrier, et al., 2006). This possibility is further substantiated by the observation of Y chromosome-positive tubular epithelial cells in the transplanted kidney of a male patient who received a

kidney transplant from a female donor. In general, bone marrow-derived stem cells can migrate towards a site of injury and differentiate under the appropriate microenvironment (Zhang, et al, 2004). The circulating precursor cells can not only transdifferentiate, but can also fuse with the neighbouring cells to repair damaged tissue (Ying, et al., 2002). The interaction of CD44 and its ligand hyaluronic acid has been shown to influence the exogenous mesenchymal stem cells to localize in the kidneys with experimentally induced acute renal failure to enhance renal repair (Herrera, et al., 2007). The extent and involvement of the bone marrow-derived stem cells in renal repair is, however, an unsolved issue, and an intense area of research.

ES cells are pluripotent cells derived from the inner cell mass of blastocysts, and are in theory able to give rise to all the cell types of the body. ES cells can be directed into forming renal progenitor cells, and eventually differentiated renal cells. Ureteric bud epithelial cells and metanephric mesenchymal cells that comprise the metanephric kidney primordium are capable of producing nephrons and collecting ducts through reciprocal inductive interaction. Once these cells are induced from pluripotent ES cells, they have the potential to become powerful tools in regeneration of kidney tissues. However, there is **a** risk to use stem cells in clinical practice. In vivo, injection of ES cells can give rise to teratomas, which are tumors containing cells of all three lineages (ectoderm, endoderm and mesoderm). ES cell-derived teratomas in vivo, renal primordial structures, can be detected histochemically. Genes involved in metanephrogenesis express the potential of ES cells to produce renal primordial duct structures and provide the insight into the regeneration of kidney tissues (Yamamoto et al.). This same potential was reported when ES cells were injected into embryonic mouse kidneys in vitro, and gave rise to ES cell-derived tubules, in this case without forming teratomas (Steenhard et al. 2005). In vitro, transfection of murine ES cells with renal developmental gene Wnt4, as well as the addition of hepatocyte growth factor and activin-A, both promote the formation of renal tubule-like structures, with expression of tubular marker aquaporin-2. Cultured Wnt4-EBs have an ability to differentiate into renal tubular cells; and second, that Wnt4, HGF, and activin A may promote the differentiation of ES cells to renal tubular cells (Kobayashi et al. 2005). The Wnt4-transfected cells can be transplanted into mouse renal cortex, where they also express aquaporin-2 and formed tubular structures. According to Kim et al reported, murine ES cells primed in vitro with retinoic acid, activin-A and BMP-7 (Liu et al.), activin-A alone (Vigneau et al. 2007), or BMP-4, differentiate into cells expressing markers of the intermediate mesoderm, early kidney development and/or renal tubule-specific markers (Bruce et al. 2007). After injection of these primed murine ES cells into embryonic kidney cultures, ES cells are incorporated into developing renal tubules (without cell fusion) or into the nephrogenic zone. The primed cells are enriched for renal progenitor cells by FACS and are injected in vivo into the kidneys of newborn mice, where they are integrated as proximal tubular cells, without teratoma formation (Vigneau et al. 2007). Human ES cells differentiate in vitro into WT1- and renin-expressing cells following treatment with a combination of specific growth factors (Schuldiner et al. 2000). However, research of the role for ES cells in renal regeneration is still in its infancy (Roufosse and Cook 2008).

Bone marrow stem cells would be an ideal source of multipotent cells: they are easy to harvest and are in theory an unlimited source of expandable autologous cells. They display an unexpected plasticity which has been the subject of extensive research over the last few years. The plasticity has been observed both for the hematopoietic stem cell, which gives rise to all differentiated blood cell types, as well as for the bone marrow mesenchymal stem cells, which provide stromal support for haematopoietic stem cell in the bone marrow, and also give rise to various mesenchymal tissues, such as bone, cartilage and fat.

There are important discrepancies in the literature addressing the role of bone marrow cells in renal regeneration. The technique most commonly used to study bone marrow cell plasticity is bone marrow transplantation. 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 (male Y chromosome-positive cells in a female host), the expression of a reporter molecule (B -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.).

Turritopsis nutricula is capable of rejuvenating itself due to a process called transdifferentiation. Transdifferentiation occurs when a non-stem cell turns itself into another type of cell. But, it is not clear if stem cells are involved in this immortality or not. As my opinion, the transdifferentiation in *Turritopsis nutricula* has related mechanism to stem cell when the life cycle reverted. It is important to reveal the relationship of this *Turritopsis nutricula* transdifferentiation and stem cell (Ma and Yang, 2010).

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