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Human Stem Cell as Therapeutic Agent for Renal Disorders

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Abstract:

Kidney is a highly complex organ which maintains blood pressure, pH and red blood cell count by producing key hormones. Ischemia injury is a common cause of acute renal failure which affects up to 5% of the hospitalized patients. This results in the loss of kidneys function and the patient needs dialysis or a kidney transplant. The renal transplant is a successful treatment but the main disadvantage is the serious shortage of donor organs. Therefore, the use of stem cells for the treatment of kidney diseases represents a critical clinical target. There are four types of stem cells which are used for kidney regeneration: human embryonic stem cells (hESCs), renal adult stem

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cells, non renal adult stem cells and bone marrow derived stem cells (BMSC). The hESCs are derived from the early mammalian embryo and have the ability of undifferentiating and can differentiate to kidney cells but it has two major problems, the ethical problem and the immune rejection. Therefore, we use adult stem cells for the regeneration of human kidney. This review summarizes the current literature on the physiological role of some of the stem cells responsible for renal regeneration.

Key words: Kidney regeneration, Stem cells, Human embryonic stem cells, Bone marrow derived stem cells

Introduction

Kidneys are highly complex organs which filter the entire blood volume 30 times a day, reabsorbing more than 95% of what is filtered and produce only 1 to 2 L of urine (Bussolati et al. 2009). They also help in the adjustment of pH and fluid balance and also maintain red blood cell count, Blood Pressure and bone density by producing the key hormones (Little 2006). They are composed of more than 30 different types of cell, such as tubular epithelial cells, interstitial cells, glomerular cells and cells of the vasculature. The proliferation rate, turnover and regenerative potential of these cells and tissues are different from each other. Even the different compartments of the nephron (smallest functional unit of the kidney) exhibit different regenerative capacity. The proliferation rate of podocytes is virtually zero, and if they are lost due to necrosis, apoptosis or detachment, they are not replaced by proliferation of neighboring podocytes; on the other hand proximal tubular cells have a slow cell turnover under normal physiological conditions (Bussolati et al. 2009). Due to this complex structure of kidneys, bioengineers face a major challenge (Little 2006). Acute kidney injury (AKI) is a sudden and prolonged reduction of the renal glomerular filtration rate causing the retention of metabolites (Bussolati et al. 2009). Ischemia reperfusion injury

is the general cause of acute renal injury (Lin et al. 2003). In the United States, up to 200,000 people are affected from acute renal failure (ARF) annually and this is a common condition which affects up to 5% of the hospitalized patients (Brodie et al. 2005). The "ARF" results due to an ischemic or toxic insult to the kidney and is potentially reversible; still the mortality rate ranges from 30 to 80% (Morigi et al. 2004).

The chronic kidney disease (CKD), also known as chronic renal disease, is a progressive loss in renal function over a period of months or years having no symptoms at early stages. The loss of function usually takes months or years to occur. It may be so slow that symptoms do not occur until kidney function is less than one-tenth of normal and at this stage it is called end-stage renal disease (ESRD). The kidneys no longer function and the patient needs dialysis or a kidney transplant. It is a leading cause of mortality and morbidity in Western countries (Sagrinati et al. 2006). The kidney may be replaced by an artificial device and it was the first organ of human body whose partial function was replaced by an artificial device. (Humes et al. 1999) There is no significant impact on overall mortality by using modern dialysis techniques, such as continuous renal replacement therapy because hemodialysis outside of the body replaces only the filtration activity and does not restore metabolic, and endocrine functions of the kidney (Yokoo et al. 2006; Humes et al. 2002).

To improve survival after an ARF using pharmacologic therapy has been largely unsuccessful and an alternative strategy should be used to overcome these problems. Therefore, the use of stem cells for the treatment of kidney diseases represents a critical clinical target (Sagrinati et al. 2006). Tissue based stem cells are multipotential stem cells and are capable of regenerating tissue specific cells (Morigi et al. 2004). In stem cell technology tremendous advances have occurred over the past few years. Due to the development in induced pluripotent stem cell technology the reprogramming of adult

cells to differentiate into multiple cell types, including renal cells has become possible and holds great promise for treatment of chronic diseases such as kidney failure in the future (Nagy et al. 2010).

Kidney Regeneration Using Stem Cells

The term regenerative medicine refers to bioengineering with the objective to regenerate or repair a damaged organ or tissue type. It can also be defined as the use of cells for the treatment of disease by repairing it or regenerate the entire organ. Organ repair can be achieved in situ or ex vivo. The most important and attractive strategy for organ repair is to enhance the ability of the kidney to repair itself by means of a soluble reparative factor. The kidney has the ability to undergo significant remodeling as a result of acute damage. For example, blockage of the ureter can result in the destruction of the kidney medulla, but once the blockage is removed there is a rapid reconstruction and repair that will lead to the regeneration of the tubules of the medulla without forming new nephrons. The mammalian kidney seems to have a very little ability for true regeneration (Little 2006).

Tissue regeneration as a replacement for affected tissues has expanded after recent progress in the field of stem cell research. The kidney function may be replaced by dialysis and renal allotransplantation but these are not complete therapies and patients having ESRD and using dialysis for treatment may have major medical, social, and economic problems. Therefore the use of stem cell therapy for kidney is needed because of its complexity and the chances of damage at the time of diagnosis. There are four types of stem cells which are given below and used for the development of such treatments.

1. Embryonic stem cells (ESCs)
2. Nonrenal adult stem cells
3. Renal adult stem cells and

4. Bone marrow derived stem cells (BMSCs)

1. Embryonic Stem Cells

Embryonic stem cells (ESCs) are the stem cells derived from the embryo. After the derivation of hESCs the concept of stem cell based therapy has grown rapidly. The ESCs are obtained from the inner cell mass of a developing embryo having pluripotency and can be dividing indefinitely while retaining a pluripotent phenotype (Little 2006). They can be preserved in vitro without any noticeable loss of differentiation potential (Yousaf et al. 2012). The pluripotency of ESCs expose one possible approach for the replacement of damaged kidney tissue (Ward et al. 2011). Kidney development can occur by placing isolated embryonic kidneys into organ culture or by co-culturing isolated tissues using transwell filters to separate metanephric mesenchyme from the ureteric bud (Steenhard et al. 2005). The use of ES cells to repair or regrow organs has increased after the derivation of embryonic gonadal stem cells from human tissue, but ESCs also have some possible obstacles such as immune rejection, teratomas and other cancers (Ward et al. 2011).

2. Non renal Adult Stem Cells

Mesenchymal Stem Cells (MSCs) are the adult stem cells which are present in the bone marrow in low numbers and have the ability to differentiate into a wide range of mesenchymal tissue types, including cartilage, bone, muscle, stroma, fat, tendon and other connective tissues. The MSC recently refers to plastic adherent fibroblastic cells which show mesenchymal multipotency (Little et al. 2009). Recent studies reported evidence for improved renal function after infusion of MSC using the ischemia/reperfusion model of acute damage in the rat (Little 2006). After the infusion of MSC into an ischemia/reperfusion model of acute damage reduction in the production of proinflammatory cytokines and increase in the

anti-inflammatory cytokines (IL-10, TGF-α, Bcl2) and basic fibroblast growth factor occur (Togel et al. 2005).

3. Renal Adult Stem Cells

The presence of multipotent adult stem cells that have the ability to regenerate into skin, bone marrow, stomach, intestine, and cornea has been known for a long time. The existence of adult stem cells having the ability of regeneration to a much greater degree has now been reported in many organs. The potential of stem cells has been reported in the postnatal murine kidney and develops a cell line which was derived from S3 segment of the proximal tubules, which can be maintained without transformation for long term (Kitamura et al. 2005). To study the potential of CD133 cells as renal stem cells, they were isolated from the adult kidney. These cells express some MSCs, but its differentiation capacity is limited (Little 2006). Bromodeoxyuridine, BrdU-labeled cells where identified in the renal tubules, which were termed as renal progenitor-like tubular cells. These cells are responsible for the reentering of the cells into mitosis as a result of renal damage and change into fibroblasts (Maeshima et al. 2003). In vitro they have the ability to become proximal tubule and collecting duct cells when cultured in collagen gel (Little 2006). BrdU label–retaining cells were also identified within the papilla of the kidney (Oliver et al. 2004).

4. Bone Marrow Derived Stem Cells

Bone marrow derived stem cells (BMSCs) are the stem cells which are derived from bone marrow and have the ability to differentiate into hepatocytes, biliary epithelial cells, endothelial cells, skeletal muscle fibres, and neuronal cells (Poulsom et al. 2001). Bone marrow contains at least three stem cell lineages: hematopoietic stem cells (HSCs), mesenchymal stem/stromal cells (MSCs), and endothelial progenitor cells (Lmai et al. 2007). The HSCs have been shown to be capable of

differentiating into hepatocytes, cardiac myocytes, gastrointestinal epithelial cells, and vascular endothelial cells during tissue repair (Lin et al. 2003).

The BMSCs have a high ability to transdifferentiate and are able to replace damaged renal tissue with tubular epithelial cells, mesangial cells, endothelial cells, and even podocytes (Little 2006). In the early 2000s it was thought that BMSCs have the ability to contribute directly to kidney regeneration (Poulsom et al. 2001). Therefore kidney regeneration using bone marrow stem cells has attracted considerable attention, because they can contribute to the formation of kidney cells, including mesangial cells, tubular epithelial cells and podocytes. According to recent reports the injured tubular epithelial cells may be replaced using bone marrow in acute renal failure. Such a strategy applicable in chronic situations is still unclear (Yokoo et al. 2006). Differentiations of BMSCs into cells of non hematopoietic origin give rise to the thought that BMSCs population could be involved in tissue turnover and regeneration but the possibility of BMSCs to contribute in renal tubular regeneration is still a matter of debate (Bussolati et al. 2009). I/R injury recovery needs renal tubular regeneration (Lin et al. 2003). It has been reported that administration of BMSCs considerably improved renal function in the ischemia reperfusion model, but they do not differentiate into tubular or endothelial cells (Togel et al. 2005). The new facts are that humoral factors from BMSCs are necessary for recovery from acute kidney injury not BMSCs (Lmai et al. 2007). The Integration and differentiation of BMSCs into renal cell types was also observed after AKI. Transplantation of bone marrow into rats with Thy-1 GN has been shown to support the regeneration of renal capillaries. The capacity of stem cell to regenerate the glomerular from adverse extra cellular matrix production during Glomerulonephritis GN was demonstrated in a mouse model for Alport syndrome (Bussolati et al. 2009). In muscle and neuronal stem cells these pathways can be bi-

directional i.e. having the capability to form bone marrow. The adult stem cells have a remarkable plasticity i.e. muscle and nerve-derived stem cells can differentiated to bone marrow while the bone marrow stem cells themselves can differentiate into hepatocytes, endothelial cells, and muscle (Poulsom et al. 2001). The enhancement mobilization of endogenous BMSCs or infusions of BMSCs have been used as a treatment in preclinical models of renal disease such as ischemia-reperfusion injury, the model of mesangial proliferative glomerulonephritis, renovascular disease, and Alport syndrome (Nagy et al. 2010).

Conclusions

In this review article we summarized the recent researches on the physiological role of some of the stem cells which can be used for the treatment of the renal diseases and their possible potential in the regeneration of the injured part of the kidney. Before the total loss of kidney, its function can be restored by using different types of kidney cells. The stem cells which can be used for the treatment of the kidney are hESCs, non renal adult stem cells, renal adult stem cells and BMSCs. Such knowledge of the kidney stem cells may lead to the development of the new curative strategies that help in the restoring of kidney function.

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