Review Article

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Cell-based therapy for kidney disease

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The prevalence of renal disease continues to increase worldwide. When normal kidney is injured, the damaged renal tissue undergoes pathological and physiological events that lead to acute and chronic kidney diseases, which frequently progress to end stage renal failure. Current treatment of these renal pathologies includes dialysis, which is incapable of restoring full renal function. To address this issue, cell-based therapy has become a potential therapeutic option to treat renal pathologies. Recent development in cell therapy has demonstrated promising therapeutic outcomes, in terms of restoration of renal structure and function impaired by renal disease. This review focuses on the cell therapy approaches for the treatment of kidney diseases, including various cell sources used, as well recent advances made in preclinical and clinical studies.

Keywords: Acute kidney injury; Cell- and tissue-based therapy; Chronic kidney failure; Clinical trial; Evaluation studies

INTRODUCTION

Renal failure is a global health issue with 8%–16% of the adult population suffering from chronic kidney disease (CKD), which is defined as a reduced glomerular filtration rate and increased urinary albumin excretion [1]. Another type of renal failure, acute kidney injury (AKI), is defined as a sudden increase in serum creatinine concentration and decreased urine output [2,3] that often progresses to CKD. Current treatment of AKI and CKD includes life-long dialysis, which has demonstrated therapeutic effects on the improved renal functions. While dialysis replaces kidney filtration function by removing certain toxic substances from the blood, many other renal functions, such as erythropoietin (EPO) production and activation of Vitamin D, are not restored [4]. Lack of functional renal structures contributes to the inefficient recovery of kidney function and leads to high morbidity. Consequently, treatment of renal disease should promote efficient regeneration of functional renal-specific cells [5]; thus, cell-based approach that can replace or restore damaged renal cells may be an excellent alternative to the current treatment.

Recent development in the field of tissue engineering (TE) and regenerative medicine (RM) has provided various alternative cell-based approaches for the treatment of renal failure [6]. Such treatments include biotechnological approach using bioartificial renal systems, transplanting cells, and implantation of bioengineered kidney constructs. In early studies, fabrication of bioartificial renal constructs has been performed to improve clinical outcomes of patients with AKI and CKD. One type of such bioartificial kidney constructs was created by incorporating kidney cells to the conventional dialysis system [7,8]. By seeding renal tubular cells onto dialysis membranes, the reconstructed bioartificial renal construct was able to efficiently replace renal functions of an acute uremic dog model using an extracorporeal

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perfusion system [8]. The improved renal functions such as filtration, transport, metabolic of the damaged kidney were prominent compared with the system without incorporation of kidney cells. This study suggests that the extracorporeal perfusion system can be used *ex vivo* to "rescue" the patient until kidney transplantation [7,8]. Recent development of material and chemical engineering technologies has enabled a miniature of extracorporeal perfusion system [9] for implantation purpose, however several practical challenges, such appropriate size of pump and water volume for dialysis, need to be addressed prior to clinical translation.

Another type of cell-based therapies for renal treatments is through implantation of bioengineered kidney constructs. The basic strategy is to seed cultured cells into a three-dimensional (3D) scaffold system *in vitro* and implant the cell-seeded scaffold *in vivo* to augment and restore kidney functions. Using TE techniques, several studies have been reported using various scaffolding systems, including natural (e.g., collagen) [10-12] and synthetic biodegradable materials [13-15] combined with various cell types. The application of engineered 3D renal constructs in several animal models [13] showed integration with the host tissue system with renal functions. While 3D renal constructs have been considered as a promising cue for the treatment of renal pathologies, implementation of this technology is still in infancy due to difficulties in fabrication of large sized functional renal constructs with complex renal structures that could readily integrate into host kidney tissue for clinical translation [16].

Recent advances in stem cell biology and cell culture techniques have facilitated the development of cell therapy for clinical translation [17,18]. Compared with the two approaches described above, the cell therapy approach can be more practically applied to renal treatment due to the relatively simple cell manipulation process, easy access to the target site in a less-invasive manner, and effective integration of infused cells with the host tissues. As such, most studies have been performed using the cell therapy approach to treat renal failures [17,19,20]. This review focuses on the cell therapy approaches for the treatment of kidney diseases, including various cell sources used as well recent advances made in preclinical and clinical studies.

CELL SOURCES

1. Kidney tissue-derived cells

1) Primary Kidney cells

Kidney tissue consists of more than 20 specialized cell types that are structurally organized into anatomically and functionally distinct compartments [21]. Primary kidney cells can be harvested from normal and diseased kidney tissue and expanded in culture while maintaining the phenotype and function from which they are derived. Among different types of renal cells in the native kidney, proximal tubular cells (PTCs) play important roles in kidney functions [22,23]. Such roles of PTC include reabsorption of proteins and electrolytes, hydrolase activity, and EPO production. In normal kidney, the PTCs occupy the highest percentage of cell population (≈60% of total cell population) among the other types, which include distal tubular cells, descending Loop of Henle cells, collecting duct cells and podocytes [24]. Therefore, isolation and expansion of functional primary PTCs from kidney tissues can be considered as an attractive renal cell source for cell-based therapy. Primary PTC cultures have many advantages and are more representative of normal PTC physiology than immortalized cell lines; however, primary renal cells, including PTCs, lose expression of specific genes during culture and are limited to only 2–5 passages [25]. The optimal combination of high purity, consistently well-preserved proliferation, and differentiation is observed at passage 2–3 [26].

Our group established a cell culture method that enabled expansion of primary kidney cells from human kidney tissues [12]. Histological analyses show that the majority of the cultured cells retained a proximal tubular phenotype while distal tubular cells and podocytes were present in a lower percentage of the entire cell population. Additionally, when the expanded cells were cultured under a 3D environment, the cultured cells form tubule-like structures with functional properties. These results demonstrate that the established cell harvesting and culture method may potentially be developed as an effective cell-based therapy for patients with renal failure.

While numerous studies have been conducted on PTC culture and physiology, several protocols have been established on other kidney cell types. Presnell et al. [27] established a culture method for primary cell cultures isolated from all major compartments of the kidney. In particular, two subpopulations, the tubular cell-enriched subpopulation and the EPO-producing subpopulation, were reproducibly developed from both normal and diseased kidneys. Owing to recent advances in immunomagnetic cell isolation, Baer and Geiger [28] isolated additional subtypes of kidney-derived epithelial cells. Human renal epithelial cells were separated from the ascending limb and the distal tubule using glycoprotein-coated magnetic beads. The results demonstrate a successful *in vitro* system to study the thick ascending limb of Henle's loop and early distal tubule as well as a promising cell source for

treatment of renal failure.

2) Renal stem or progenitor cells

Existence and identification of renal stem or progenitor cells in the adult kidney tissues have been somewhat controversial [19]. Numerous peer-reviewed articles have identified progenitor cells in the Bowman's capsule [29], glomeruli [30], proximal tubules [31-34], and renal papilla [35]. Human renal cells were isolated from unused donor kidneys, expanded in culture, and maintained their renal phenotypes through numerous passages [12]. This result may support that differentiated renal epithelial cells isolated from the kidney tubule structures have proliferation capacity through dedifferentiation of the surviving epithelia during cell culture. Recent evidence demonstrates that kidney nephrons contain a rare cell population with proliferative capability [31,34,36-38]. Those stem or progenitor cells express several stem cell markers such as CD24, CD133, CD106, vimentin and Pax-2, and they possess high clonogenic potential, self-renewal ability, and differentiate into specific renal cell lineages, which suggest a potential therapeutic cell source for renal regeneration.

2. Pluripotent stem cell

1) Embryonic stem cell

Embryonic stem (ES) cells have been studied as a cell source for various cell-based therapies [39]. ES cells exhibit two remarkable properties: the ability to grow in an undifferentiated state (self-renewal) and the capacity to differentiate to several cell types of the mesodermal, endodermal, and ectodermal lineages (multidifferentiation). This makes ES cells an attractive cell source for TE and RM. Renal differentiation of ES cells has been reported by several investigators [40-43]. Interestingly, using a versatile *in vitro* culture system, Steenhard et al. [42] demonstrated that integration of ES cells into embryonic metanephric kidney produced kidney-like organs *in vitro*. This efficient integration and creation of new kidney tissue strongly supports the therapeutic feasibility of the use of ES cells; however, several limitations decreased the enthusiasm for active development. These include uncontrolled growth and developing into teratoma formation *in vivo* as well as legal and ethical problems associated with the use of embryonic tissue.

2) Induced pluripotent stem cell

Another cell source that possesses pluripotent capability is the induced pluripotent stem cell (iPS), which was first developed by Takahashi and Yamanaka [44] through reprogramming human fibroblasts by introducing four genes (*Oct3/4, Sox2, c-Myc,* and *Klf4*). Recent advances in the production of iPS cells from both mesangial and epithelial cells derived from urine [45] has encouraged the application of iPS cells to the treatment of kidney diseases. In addition, iPS cells have been generated from other renal sources such as PTCs and podocytes [46], which demonstrate the high universality of iPS cell technology. When compared with ES cells, the use of iPS cells has advantages for RM that includes the absence of ethical issues related to tissue sourcing and fewer immune rejection complications. Therefore, iPS cells may be a promising cell source for treatment of kidney diseases in a clinical setting once safety and other issues, including control of outgrowth and teratoma formation of undifferentiated iPS cells, are resolved. Several studies have demonstrated that iPS cells express abnormal genes and induce T-cell dependent immune response in syngeneic recipients [47]. This unexpected immune response by iPS cell infusion should be clarified before clinical application. Therefore, sophisticated renal differentiation protocols should be established by defining optimal cell culture conditions and additional factors such as a choice of a target cell type and reprogramming options [20].

3. Fetal and adult stem cells

Unlike pluripotent stem cells such as ES and iPS cells, fetal and adult stem or progenitor cells can be practically applied for cell-based therapies with fewer safety concerns and ethical issues. In the lineage-specified tissues or organs at fetal, neonatal, and adult stages, presence of stem or progenitor cells with self-renewal and multidifferentiation capability have been identified. As multipotent stem cells at the fetal stage, amniotic fluid-derived stem cells (AFSCs) have been considered an interesting source for RM [48]. AFSCs are theoretically easily harvested and retain high self-renewal potential and multiple differentiation capacity without development of teratoma formation compared with ES and iPS cells [48]. In particular, Perin et al. [49] isolated human AFSCs (hAFSCs) from male amniotic fluid obtained at 12–18 weeks gestation and showed that hAFSCs expanded *in vitro* could survive, proliferate, and integrate into the embryonic kidney and underwent organ development, demonstrating a potential source for renal regeneration. In another study, Siegel et al. [50] reported that mammalian target of rapamycin is an important factor in renal differentiation of hAFSCs.

Unlike hAFSCs derived from fetal origins, adult stem cells have been more practically and extensively used for

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regenerative purposes. Adult stem cells include hematopoietic stem cells from blood; neural stem cells from brain and spinal cord; liver stem cells from liver; muscle satellite and progenitor cells from skeletal muscle tissues; and mesenchymal stem cells (MSC) from bone marrow (BM) and fat tissues [51]. In particular, MSCs have been utilized as a promising source for therapeutic purposes and are easily isolated via minimally invasive BM extraction and liposuction. Having been generated throughout life, the plentiful supply of MSCs can be isolated and cultured *in vitro* and pose minimal ethical problems compared to many other cell sources. Owing to their multiple-differentiation potential and ability to migrate, repair, and restore injured organs [52], MSCs have been extensively used in the field of RM to attempt regeneration of a wide range of tissues and organs.

4. Cell therapy for kidney diseases (Table 1)

1) Mechanism of kidney regeneration

The idea of cell-based therapy to treat renal failure originated from the discovery of the natural regenerative ability of the damaged kidney [53]. After their early study, Cuppage and Tate [54] developed an acute renal injury model by treating rats with mercury chloride and examined the reparative phase of the injury to demonstrate the correlation of structural and functional parameters of recovery. Their studies showed that squamous cells attached to the basement membrane were able to regenerate the tubular epithelium in AKI and suggested that the basement membrane could be a site of origin of the regenerating cells and a key regulator of kidney regeneration. Importantly, these researchers discuss the requirement of an up-regulation of protein synthesis within the activated microenvironment for the efficacy of renal regeneration. Therefore, it can be considered that the success of cell-based therapy in the treatment of renal disease depends on the efficient integration of the transplanted cells to the activated renal microenvironment and subsequent growth to induce renal regeneration after injury.

2) Acute and chronic kidney failure: preclinical studies

Most preclinical studies use rodents to create AKI. As a cell source, BM-MSCs have been utilized extensively in a wide range of studies [55-62]. Early studies have shown that the predominant recovery mechanism of the AKI was mediated through the trans-differentiation of the infused

Table 1. Cell therapy to treat kidney diseases

Cell source	Type of disease	Animal model/cell origin/infusion route; [ref.]
BM-MSC	Acute	I/R on SD and F344 rat/rat MSC/intracarotid; [55], I/R on C57BL6 mouse/mouse MSC/intravenous; [56], cisplatin on SCID mouse/human MSC/intrarenal; [57], gentamycin on Wistar rat/rat MSC/intravenous; [58], cisplatin on C57BL6 mouse /IGF-1 preconditioned mouse MSC/intrarenal: [62], rhabdomyolisis and glycerol-induced on SCID mouse/human MSC/intravenous; [68]
	Chronic	Remnant kidney model on rat/rat MSC/intravenous: [59], kidney allograft model on Lewis rat received from F344 rats/SD rat allogeneic MSC/intravenous: [60], Alport syndrome on mouse/mouse MSC/intravenous; [64]
	Acute (clinical trials)	Kidney transplantation/autologous MSC/intravenous; [93-95]
ADSC	Acute	I/R on mouse/mouse ADSC/intraperitoneal; [78], I/R on SD rat/autologous ADSC/intravenous; [77], cisplatin on rat/human ADSC/intravenous; [79]
	Chronic	Atherosclerotic renal artery stenosis/pig ADSC/intrarenal; [80,81]
Renal stem or progenitor cells	Acute	Glycerol induced SCID mouse/$CD133^+$ renal cells/intravenous; [36], Rhabdomyolysis induced SCID mouse/$CD24^+$ $CD133^+$ $CD106^-$ human renal cells/intravenous; [31]
	Chronic	5/6 nephrectomy on SCID mouse/human $NCAM^+$ renal progenitor cells/intravenous; [82]
Primary renal cells	Chronic	Two step 5/6 nephrectomy on rat/rat renal cells/intrarenal; [86], I/R and gentamycin on nude rat/human renal cells/intrarenal; [85]
iPSC	Acute	I/R on rat/mouse iPS/intrarenal; [91], cisplatin on mouse/human iPSC/intravenous; [92]
AFSC	Acute	Glycerol induced SCID mouse/human AFSC/intravenous; [87], cisplatin on SCID mouse/human AFSC preconditioned with GDNF/intravenous; [88], renal autotransplantation on pig/autologous AFSC/renal artery injection; [90]
	Chronic	Alport syndrome on mouse/mouse AFSC/intra cardiac injection; [89]

BM-MSC, bone marrow-derived mesenchymal stem cells; I/R, ischemia/re-perfusion; SD, Sprague Dawley; SCID, severe combined immunodeficiency; IGF-1, Insulin growth factor-1; ADSC, adipose derived stem cells; NCAM, neural cell adhesion molecule; iPSC, induced pluripotent stem cells; AFSC, amniotic fluid-derived stem cells; GDNF, glial derived neurotrophic factor.

MSCs into renal specific cell types, particularly renal tubular cells [63], podocytes [64], mesanglial cells [65], and glomerular cells [66]. More recent studies support the concept that trophic factors secreted from the injected MSCs stimulate endogenous cells to proliferate and regenerate the infused renal tissues [61,67-69]. In terms of autocrine and paracrine effects of the secreted factors on the renal regeneration, immune-related response [70], antiapoptotic, mitogenic, and vaso-protective effect [62] were suggested. Several studies suggest that the effect of BM-MSCs in acute renal injury models is mediated by paracrine mechanisms. As evidenced by reports that BM-MSC-conditioned medium contains microvesicles and growth factors that reduce inflammation and accelerate renal repair through interactions with renal progenitors [66,71-73]. While numerous positive effects have been observed using BM-MSCs for renal regeneration, negative results were reported following infusion of BM-MSCs into the renal disease model that promoted interstitial fibrosis [74] and development of angiomyelproliferative effect [75]. Therefore, safety studies to evaluate complications are needed to ensure that successful clinical outcomes are obtained with the use of BM-MSCs.

Another source of MSCs, adipose-derived MSCs (ADMSCs), has been tested in the renal failure model. De Almeida et al. [76] demonstrated that infusion of ADMSCs into an acute renal injury model reduced renal fibrosis at six weeks. Chen et al. [77] also showed that an intrarenal injection of ADMSCs resulted in improved angiogenesis and preserved the renal structure integrity, which restored renal function at 14 days. Several other studies also demonstrated the effectiveness of ADSC on the improved renal functions using mouse [78], rat [79], and pig [80,81] models.

As described earlier, primary kidney progenitor cells are promising cell sources for the treatment of renal disease. Recent developments in stem cell biology have provided researchers with better isolation and culture techniques that have enabled identification of stem or progenitor cells from kidney tissues. Bussolati et al. [36] reported that $CD133^+$-cells could be isolated from the normal adult kidney tissue and cultured *in vitro*. When the $CD133^+$-cells were intravenously injected in severe combined immunodeficiency mice with glycerol-induced tubulonecrosis, the expanded kidney-derived $CD133^+$-cells were grafted into the injured kidney and integrated into kidney tubules. These researchers proposed that $CD133^+$-cells isolated from normal kidney represent a multipotent adult resident stem cell population that may contribute to the repair of tissue damaged by renal injury. Using a more specific set of surface markers, Angelotti et al. [31] also reported that $CD24^+$-$CD133^+$-CD106-renal progenitor cells are resistant to apoptosis and provide regenerative potential for tubular tissue damage in the rhabdomyolysis-induced AKI model of rats. Harari-Steinberg et al. [82] identified nephron progenitor cells (hNPCs) in human kidney tissue. Neural cell adhesion molecule (NCAM1)-positive cells showed clonogenic and renal progenitor properties. After transplantation into the chick embryo, NCAM-positive hNPCs formed a renal-like structure. After hNPCs were infused into the kidneys of rats with renal failure, it was observed that disease progression was inhibited and renal function was increased. Together, these results support the idea that kidney-derived stem or progenitor cells have the capacity to migrate and proliferate to restore structural and functional kidney tissue.

Recent studies by our group have demonstrated that primary renal cells isolated from human kidneys facilitate beneficial effects toward the recovery of renal functions. As previously described, we developed a cell isolation and culture system to obtain sufficient numbers of human primary renal cells for cell therapy [12]. We have established two rodent kidney injury models by varying the length of the renal ischemic time [83]. In particular, we demonstrated that the use of a longer renal ischemic time (75 and 90 minutes) could be used to evaluate novel therapies for acute renal disease, whereas a shorter renal ischemic time (60 minutes) could be appropriate to study therapies for chronic renal failure [83]. To investigate the therapeutic effects of primary kidney cells on the improvement of renal functions, cultured renal cells were harvested and infused into a CKD rat model [83], and renal functions were evaluated. In particular, several reports focused on a cell population of EPO-positive renal cells. EPO, a cytokine produced by fibroblast-like cells in the kidney [84,85], has recently been shown to act as a renoprotective factor with anti-inflammatory and antioxidant activity. Our group established a cell purification protocol to enrich the EPO-positive renal cell population [85]. The results showed that intra-renal delivery of an EPO-positive-enriched cell population facilitated beneficial effects in the treatment of renal injury, with respect to inflammation and oxidative stress, compared to unpurified cell cultures in a CKD model. The results demonstrated that EPO-positive cells from primary kidney cells can be considered as a potential cell population for treating degenerative kidney diseases. Another CKD model using two-step 5/6 nephrectomy in rats was used to demonstrate the beneficial effects of primary renal cells on the recovery of renal functions [86]. In this study, the authors demonstrated that the tubular cells-enriched population provided better therapeutic effects

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compared to unfractionated heterogeneous renal cells by attenuating canonical pathways of profibrotic extracellular matrix production.

The use of hAFSCs to treat renal disease shows promise toward restoration of normal kidney functions. Hauser et al. [87] have shown that intravenous infusion of hAFSCs resulted in more rapid recovery of renal function in an AKI model compared to infusion of BM-MSCs. The authors of the study suggest that a range of cytokine and growth factors produced by hAFSCs gives them the advantage in renal regeneration. In addition, the preconditioning effects of hAFSCs were evaluated for renal function recovery. Rota et al. [88] demonstrated that hAFSCs that were preconditioned with glial cell line-derived neurotrophic factor were observed to promote better functional recovery by contributing to renal regeneration in acute kidney models when compared to hAFSCs alone. Also, other kidney failure model such as Alport syndrome was used to examine the effect of AFSC on the improved renal function [89]. Moreover, a large porcine animal model was evaluated for efficiency of renal regeneration. Baulier et al. [90] reported that hAFSCs were capable of preventing fibrosis and preserved renal function in a porcine model of renal transplantation. As a pluripotent cell source, iPS cells have shown improvement of renal functions using an AKI rodent model [91,92].

3) Clinical studies

To date, few clinical trials have been performed to evaluate the safety and efficacy of cell injection for renal disease [17], particularly targeting amelioration of renal transplantation-related complications. In most cases, MSCs have been used due to their low immunomodulatory effects and high regenerative capability. Reinders et al. [93] performed a safety and feasibility study on kidney allograft patients. Autologous BM-MSCs were administrated into the patients, and clinical and immune reaction was monitored up to 24 weeks after MSC injections. Results of this trial showed that the autologous injection improved resolution of interstitial fibrosis/tubular atrophy (IF/TA), and the authors concluded that autologous treatment with BM-MSCs in kidney transplant recipients with subclinical rejection and IF/TA is clinically feasible and safe; furthermore, the findings are suggestive of systemic immunosuppression. Similarly, autologous MSCs were infused into a group of kidney recipients to evaluate acute rejection in the event of graft-versus-host-disease as compared to the non–cell-injected groups. Tan et al. [94] demonstrated that the use of autologous MSCs compared to no treatment facilitated lower incidence of acute rejection, decreased risk of infection, and better estimated renal function at 1 year. In another clinical trial composed of two kidney recipients, autologous MSCs were evaluated for feasibility of cell injection and therapeutic effects. Following kidney transplant, Perico et al. [95] demonstrated positive effects of infusion of autologous MSCs through the reduction of immune rejection through the enlargement of regulatory T cells (Treg) in the peripheral blood and control of $CD8^+$ T cell function.

In addition to the clinical outcomes in the treatment of acute rejection from kidney transplant patients through infusion of MSCs, as described above, a few clinical trials have begun to examine the effects of cell-based therapy on restoration of renal functions in the AKI and CKD. According to a recent clinical report [96], several companies will initiate Phase I/II clinical trials to treat acute kidney failure using autologous MSCs or other cell types.

CONCLUSION AND FUTURE PERSPECTIVES

Recent advances in cell-based therapy using various cell sources have demonstrated great promise towards restoring normal kidney functions in the AKI and CKD preclinical models. A few clinical trials using autologous MSCs have demonstrated the feasibility of cell infusion and improvement of renal functions. While the recent progress has resulted in successful therapeutic outcomes to treat renal diseases, several concerns need to be addressed: (1) development of appropriate preclinical models to reflect clinical symptoms; (2) establishment of sophisticated approaches to deal with immunological issues; (3) understanding the complicated mechanism of improved renal function, in terms of renal physiology and integration with host vascular and nervous system; and (4) additional clinical trials to evaluate the safety and efficacy of therapeutic cells in the AKI and CKD.

When AKI and CKD progress to end-stage renal disease (ESRD), the only definitive treatment is kidney transplantation. Due to shortage of implantable kidneys and other complications such as immune rejection, kidney transplantation remains a challenge. To address this issue, whole organ bioengineering that is based on the decellularization/recellularization techniques has been developed to bioengineer implantable kidney constructs to resolve the shortage of transplantable organs [97-99]. Despite the steady progress of this approach, continued collaborative efforts are required to achieve the production of a bioengineered kidney that is capable of restoring renal function in patients with ESRD.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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