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Stem cell technology for the treatment of acute and chronic renal failure

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Abstract

Acute and chronic renal failure are disorders with high rates of morbidity and mortality. Current treatment is based upon conventional dialysis to provide volume regulation and small solute clearance. There is growing recognition that renal failure is a complex disease state requiring a multifactorial therapy to address the short-comings of the conventional monofactorial approach. Kidney transplantation remains the most effective treatment, however, organ availability lags far behind demand. Many key kidney functions including gluconeogenesis, ammoniagenesis, metabolism of glutathione, catabolism of important peptide hormones, growth factors, and cytokines critical to multiorgan homeostasis and immunomodulation are provided by renal tubule cells. Therefore, cell-based therapies are promising multifactorial treatment approaches. In this review, current stem cell technologies including adult stem cells, embryonic stem cells and induced pluripotent stem cells will be discussed as cell sources for the treatment of acute and chronic renal failure.

Keywords

stem cell; adult stem cell; renal stem cell; embryonic stem cell; induced pluripotent stem cell; metanephroi; renal assist device; renal replacement; acute renal failure; review; acute renal failure; chronic renal failure; end stage renal disease; cell-based therapy; tissue engineering

I. Introduction

A. Kidney Disease

In 2007, expenditure on end-stage renal disease (ESRD) in the United States was $23.9 billion, accounting for 5.8% of the total Medicare budget [1]. This included an incidence of approximately 360 new patients with ESRD per million people, and an overall prevalence of almost 1,700 patients with ESRD per million Americans. Morbidity and mortality rates associated with maintenance dialysis remain high, and outcomes are considerably improved following transplantation, however, organ supply lags far behind demand. In 2007 the kidney

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transplant rate was only 58.1 per million people, a small portion of the patient population with ESRD.

Acute renal failure (ARF) affects up to 200,000 people in the United States annually, with a high mortality rate of around 50% [2–4]. ARF develops predominantly due to the injury and necrosis of renal proximal tubule cells (RPTCs) as a result of ischemic or toxic insult [5]. The cause of death subsequent to ARF is generally the development of systemic inflammatory response syndrome (SIRS), frequently secondary to bacterial infection or sepsis, resulting in cardiovascular collapse and ischemic damage to vital organs, culminating in multiple organ failure (MOF) [6].

There is considerable impetus to develop improved therapies with the capacity to replace a wider range of the kidney's functions, thereby reducing morbidity, mortality, and the overall economic impact associated with chronic and acute renal failure. These goals exceed the limitations of conventional medicine, normally a monofactorial approach, in the treatment of this complex disease state. Cell therapy is a promising approach, which harnesses the native abilities of the cell afforded by a billion years of evolution [7].

B. Stem cells

Briefly, stem cells (SC) are characterized by their capacity for self-renewal and ability to differentiate into specialized cell types. For an in-depth treatment of the biology of stem cells and their relationship to more general aspects of regenerative medicine, see reviews [8–11].

Embryonic stem (ES) cells, pluripotent derivatives of the inner cell mass of the blastocyst, have the potential to generate any given cell type which makes them an attractive stem cell source for cell therapy. However, the political and ethical questions that surround the use of human ES cells have added a further layer of complexity to research aimed at bringing their potential benefits into the clinical arena [12–15]. These factors have combined to intensify the focus on multipotent adult stem cells, and more recently induced pluripotent stem (iPS) cells as sources for cell-based therapeutics. ES and iPs approaches currently have substantive safety and regulatory issues not completely understood or evaluated.

In this review, we consider several potential cell-based therapies for the treatment of renal failure currently under development. The direct application route is exemplified by simple administration of stem cells to the diseased kidney, which relies on the inherent capabilities of stem cells to differentiate, organize, and integrate into existing tissues to restore function. Tissue engineering approaches are based on *in vitro* differentiation of stem cells on biomaterial scaffolds and applied *in vivo* to provide therapy.

C. Renal stem cells

Metanephric development is initiated as the ureteric bud (UB), an offshoot of the nephric duct, invades the metanephric mesenchyme (MM) and morphogenesis proceeds by reciprocal induction events between these two tissues [16]. Prior to induction by the UB, the MM consists of a few thousand morphologically indistinguishable mesenchymal cells which, together with the UB, give rise to the 26 or so cell types that make up the mature kidney [17]. Several studies now suggest that these diverse differentiated cell types are derived from multipotent, adult stem cells of the kidney. A variety of approaches have been taken to identify such renal stem cells, including retention of nuclear labels to identify slow cycling cells, interrogating specific physical locations, and identifying patterns of cell surface marker expression.

Single cells within the MM were initially shown to have the potential to generate all the epithelial elements of the nephron, with the exception of the collecting duct [18]. Subsequently, evidence of a broader differentiation potential for the progeny of individual MM cells was

reported, with the expression *in vitro* of markers suggestive of smooth muscle cell, myofibroblast, and endothelial fates [19]. Oliver et al. identified a population of slow-cycling cells residing in the papilla of the adult kidney that commence proliferating in response to ischemia injury and may migrate to the medulla [20]. Sangrinati et al. have characterized a multipotent progenitor cell population in adult human glomeruli that are CD24+ and CD133+ parietal epithelial cells (PECs). In a model of ARF, CD24+, CD133+ PECs significantly ameliorated kidney damage [21].

Though the existence of renal stem cells is still controversial, tools being added by current studies such as the identification of a combination of cell-surface markers specific to renal progenitor cells will assist in the isolation of putative adult renal stem cells. A well defined renal SC source would have an immediate impact on the development of cell therapies for kidney disease. See reviews on putative resident progenitor/stem cells of the kidney: [22–25].

II. Direct application of stem cells

A. Mode of action

The main strength of strategies involving the introduction of supplementary cells into a damaged adult kidney to aid in repair and regeneration is that they are rooted in the natural healing process. Numerous studies have shown that renal cell repair and regeneration following ARF follows a program of de-differentiation, migration and proliferation, and restoration of differentiated function [26–27]. Accelerating and augmenting this process through direct cellular supplementation is a promising approach to improve the treatment of acute kidney injury (AKI). The question of mechanism of action and engraftment, whether applied cells are permanently incorporated in healing renal tubules is contested for many SC based approaches, however, ease of direct administration and multiple positive reports of therapeutic efficacy to treat renal disease are cause for wide-spread interest. Rapid, new developments in the stem cell field in the areas of induced pluripotent stem cells and embryonic stem cells hold promise for future therapies.

B. Transdifferentiation of Mesenchymal Stem Cells (MSCs)

The transdifferentiation approach is based on obtaining easily accessible stem cells from another, non-diseased tissue from the patient undergoing treatment. These cells are expanded *in vitro* under carefully selected conditions, and then reintroduced in order to integrate into a target damaged tissue. This approach is supported by the fact that adult stem cells, long thought to be highly restricted in their differentiative potential, possess a considerable degree of plasticity [28–30].

Briefly, Jiang et al. first identified a rare subpopulation of BMSCs designated multipotent adult progenitor cells (MAPCs), which were able to demonstrate multilineage differentiation *in vitro* [31]. BMSCs are a multifaceted population made up of mesenchymal stem cells (MSCs), MAPCs, and side population cells [32]. Some studies have suggested that BMSCs ameliorate the effects of ischemic renal injury, as measured by blood urea levels in ischemic renal animals that received transplantation [33]. The mechanism of BMSC action was originally thought to be engraftment, however, there are several studies that have produced evidence to the contrary [34–35]. Variations in results utilizing BMSCs may be due to different starting populations of donor cells, as they are a heterogeneous cell source, and also may be due to the methods employed.

The current view is that therapeutic MSCs do not appreciably integrate long-term or differentiate into renal tubule cells [36–37]. However, when administered after injury, adult stem cells, particularly MSCs, have been shown to exert therapeutic action through complex paracrine and endocrine action including the secretion of growth factors, cytokines, mitogenic,

antiapoptotic, anti-inflammatory, vasculogenesis and angiogenesis factors [38–39]. Furthermore, microvesicles derived from MSCs may activate a proliferative program following AKI by shuttling a specific subset of cellular mRNA [40]. For a review of this mechanism, see the review by Camussi et al [41]. MSCs do not express blood group antigens, MHC class II antigens or co-stimulatory factors, and therefore are appropriate for allogeneic applications. Ongoing clinical trials are assessing the safety and efficacy of allogeneic MSC to treat Acute Kidney Injury [42], and open-heart surgery patients who are at high risk of post-operative AKI [43].

In preclinical studies, systemic administration of MSCs have also shown potential to treat diabetic nephropathy. Ezquer et al induced type 1 diabetes in C57BL/6 mice through the administration of streptozotocin, and found that a single intravenous dose of MSCs led to the recovery of renal and pancreatic function, with significantly lower blood glucose levels [44]. Similar results were reported in Sprague-Dawley rats which received an introcardiac infusion of MSCs and cyclosporin [45].

Another cell source for therapy utilizing transdifferentiation, endothelial progenitor cells (EPs), are a homogenous group that originates from HSC or their angioblastic subpopulation and MSCs characterized by the markers CD34, VEGF-R2 and CD133, which is lost upon differentiation. Use of EPs for the treatment of kidney disease remains insufficiently explored, see review by Goligorsky et al [46].

C. Embryonic Stem Cellls (ES)

Embryonic Stem cells hold great potential for renal regeneration given their pluripotency. However, due to ethical considerations, ES cell research has experienced limited progress. There have been a small number of studies in which mouse ES cells were differentiated into renal tubular cells [47–49]. Morizane et al used the murine ES cell, EB3 transfected with Oct 3/4 Blastocidin resistant gene, so that differentiated cells could be eliminated through the supplementation of culture media with Blastocidin. Embryoid bodies (EB) were formed using hanging drop method and transferred to gelatin coated dishes for differentiation. Expression of Oct 3/4 decreased with differentiation, and metanephric mesenchyme markers Six2, WT-1 and Pax2 increased over differentiation progression. Podocyte markers, WT-1 and Nephrin, and the tubular specific marker, KSP, were expressed in differentiated cells, suggesting that mature renal lineages of podocytes and tubular cells can be produced from ES cells [50].

The work of Steenhard et al, investigated whether ES cells could differentiate into kidney stuctures when placed in the embryonic kidney microenvironment. After injection of ES cells expressing β-galactosidase into embryonic kidneys, β-galactosidase-positive cell clusters were seen throughout the kidney. Furthermore, ES cells expressing β-galactosidase were shown to form tubules and glomerular epithelial toughs [47]. Despite these promising results, a vast amount of further research is required to determine the contribution of ES cells to renal regeneration therapies. Relaxed governmental regulation may allow for this nascent research to progress, however, there remain many basic biological questions to be answered before this modality can be considered for either renal augmentation or regeneration.

D. Induced Pluripotent Stem Cells (iPS)

Induced Pluripotent Stem cells (iPS) are reprogrammed mature cells developed to be a non-controversial, embryonic stem cell-like cell source. Takahashi and Yamanaka first demonstrated the induction of iPS cells from adult fibroblasts of a mouse by introducing Oct 3/4, Sox2, c-Myc, and Klf4 under culture conditions similar to those used with ES cells [51]. These transcription factors associated with multipotency were introduced using retroviral transfer. Pluripotency was confirmed by teratoma formation, and global gene expression

profiles confirmed that iPS cells are similar but not identical to ES cells. Human iPS cells were later induced using the same method [52]. Initial studies in iPS production were characterized by low induction efficiency (< 0.01%), however, methods to improve reprogramming, such as application of ascorbic acid during iPS generation, have increased induction efficiency 100-fold, as well as enhancing their progression to pluripotency [53].

There is some controversy over whether generated iPS cells are truly epigenetically and biologically indistinguishable from ES cells. Recently, Lanza et al have suggested that low replication rates and early senescence associated with iPS cells [54], which impede their efficacy in producing differentiated cells, may be attributed to the viruses used to create them. Fewer anomalies in iPS cells may be obtained by using virus-free reprogramming strategies, such as ones that use proteins or small-molecule drugs [55].

Morizane et al. have compared ES and iPS differentiation to renal lineage. Their data shows that both ES and iPS cells have a potency to differentiate into mature renal cells, however, iPS cells have a tendency to remain undifferentiated, with less sensitivity to renal differentiation cues in comparison to ES cells [50]. iPS cells have a great potential for renal regenerative therapies, however, differences in regenerative capacity in the kidney between ES and iPS cells have not yet been elucidated [56].

E. Metanephroi Transplantation

Metanephroi are constituted by renal stem cells, and therefore metanephroi transplantation may be thought of as a therapeutic stem cell application. The work in this field has been comprehensively reviewed by Hammerman (2003).

In rats and mice, metanephroi have been transplanted beneath the capsule of adult kidneys or into tunnels fashioned in the renal cortex of neonates have been shown to give rise to nephrons with vascularized glomeruli and mature tubules [57–58]. By intravascular administration of fluorescently labeled dextran shortly before sacrifice of metanephric-transplant recipients, Woolf et al. were able to demonstrate glomerular filtration by donor-derived nephrons. It was not, however, determined whether integration with the host's collecting duct system had been achieved. Transplantation of metanephroi into the omentum [59], has shown some promise in that implanted tissue grows to approximately one-third the diameter of native kidneys, and develop mature glomeruli and tubules, and are vascularized by arteries originating from the omentum.

Metanephroi transplantation, however, faces a number of safety concerns with xenotransplantation, and therefore clinical implementation would likely theoretically require metanephroi sourcing from aborted human fetuses, or require the development of new alternative sources. Stem cell technology may provide precursor cells in the future, which can be differentiated and organized into a functional kidney precursor *in vitro* for transplant, which could have a serious impact on the treatment of renal failure.

III. Tissue and Bioengineering Approaches

The tissue and bioengineering approaches are, in general, based on in vitro manipulation of the cells of interest and their association with biomaterials, which may be either biodegradable or permanent in nature, to produce a device for implantation or incorporation into an extracorporeal circuit. Strategies such as cell therapy with a single differentiated cell type to replace a specific metabolic or catabolic function are currently in practice, whereas the biotechnology tools required to fabricate a complete, functioning organ for transplantation are still in their infancy.

Cell-based therapies rely on the expansion of large cell populations that are uniform in activity and pathogen-free. Current tissue engineering methods typically depend on progenitor or transformed cell types, although the emphasis is likely to shift more and more to stem cells, with advantages to be gained in scalable production without the safety concerns attached to transformed cell lines.

A. Cellular Implants to Remove Toxins and Deliver Therapeutic Agents

Possible approaches to the treatment of renal failure involve using cell implants to remove toxins caused by the disease state or deliver therapeutic agents to the circulation. For example, Saito et al. used a collagen sponge-based implant seeded with megalin-expressing cells to degrade circulating β2M [60]. In order to incorporate implants clinically, methods to ameliorate host-implant immunology are required or the use of autologous cell sources. Encapsulation is a method commonly used to circumvent the problems associated with cell implants. Encapsulation within a semipermeable, non-degradable polymeric membrane offers the advantage of immunoisolating allogeneic or xenogeneic cells and allows a greater degree of control over their destination within the body, while still allowing their contact with the bodily fluid required to elicit the desired physiological response [61]. For example, sodium alginate beads have been used to deliver genetically modified bacteria expressing the urease enzyme in order to degrade toxic levels of urea [62].

Another method of encapsulation is to house cells within hollow fibers incorporated into an implantable device. For example, incorporation of erythropoietin (EPO) producing HepG2cells, known to display oxygen-regulated EPO production [63], within the hollow fibers of an intravascular implanted device [64] represents a promising alternative to the administration of recombinant human EPO [65].

B. Renal Assist Devices and Renal Replacement

Current methods toward full renal replacement have focused on the expansion of primary kidney cells in culture, and organization on biomaterial scaffolds for either subcutaneous implantation or for use in extracorporeal perfusion systems. Atala and coworkers have expanded renal cells in culture and seeding them onto collagen-coated cylindrical polycarbonate membranes, relying on the cells' innate morphological and organizational properties to reconstitute functional nephron units [66–68].

Renal tissue harvested and fractionated into glomeruli, distal, and proximal tubules, was expanded separately *in vitro*, and seeded onto biodegradable polyglycolic acid sheets for subcutaneous implantation into syngeneic hosts [66]. Retrieval and histological examination of the scaffolds revealed evidence of vascularization and identifiable nephronal elements: glomeruli, proximal tubules, distal tubules, loops of Henle, collecting tubules, and collecting ducts [66]. However, these elements did not appear to be continuous, or display higher-order organization. A device constituted of renal cells seeded on a cylindrical polycarbonate membrane connected at one end to a silastic catheter and terminated in a reservoir, was then assessed in mice [66]. The investigators reported vascularization and the formation of glomeruli and tubule-like structures [66]. A fluid collected from the reservoir was shown to have uric acid and creatinine, raising the possibility that the reconstituted nephronal units may possess some level of functional capacity.

Embryonic renal cells derived from the metanephros of a 56-day-old bovine embryo generated by nuclear transfer were used as a cell source for a similar renal cell device [67]. For nuclear transfer and therapeutic cloning techniques see reviews [69–70]. These devices were implanted subcutaneously into the flank of the same animal from which the cloned tissue was derived. Upon device recovery, the reservoir was found to contain small amounts of fluid, which had

elevated urea and creatinine, with properties similar to bovine urine [67]. Examination of the tissue revealed vascularization and the presence of glomeruli and tubule-like structures, with no evidence of immune rejection. In at least some cases, continuity was noted between glomeruli, their tubules, and the polycarbonate membrane [67].

The strategy adopted by Humes and colleagues has been to administer cell therapy from an extracorporeal circuit, allowing for immunoisolation of a cell device, eliminating immunorejection issues, and enabling the use of allogeneic cells. This strategy uses hemofiltration as a working substitute for glomerular filtration, with metabolic and secretory functions of proximal tubule cells replaced through the application of a renal tubule assist device (RAD). This approach has shown considerable promise following testing in animal models and in Phase I/II clinical trials on human patients with ARF.

In brief, this method has its foundation in the ability to isolate and expand renal cells from adult kidneys *in vitro* [71–72], which are then seeded on the inner surface of a standard hemofiltration, hollow fiber cartridge [73–75]. For RAD circuit schematic, see Figure 3 in Tiranathanagul et al [76]. Cell attachment to the hollow fiber polysulfone membrane is promoted by coating with extracellular matrix, such as collagen type IV [77]. The membrane acts as both a scaffold and immunological barrier for the cells. *In vitro* testing of the RAD demonstrated differentiated renal tubule cell function including active transport, renal cell specific metabolic activity, and endocrine secretion [77].

In *ex vivo* animal testing, RADs containing either porcine or human cells have been evaluated on uremic dogs following bilateral nephrectomy. Improvements in multiple physiological parameters were observed in RAD treated animals compared to acellular RAD controls [77–78]. Furthermore, in canine and porcine models of ARF with septic shock, RAD treatment was shown to modulate plasma cytokine levels, maintain better cardiovascular performance, and increase survival times [79–80].

A Phase I/II FDA clinical trial on 10 critically ill patients with ARF and MOF receiving continuous venovenous hemofiltration (CVVH), utilized RADs seeded with human kidney cells isolated from cadaveric kidneys not suitable for transplantation due to anatomic or fibrotic defects [81]. The results from this study demonstrated that RAD treatment can be safely delivered under study protocol guidelines in this critically ill patient population for up to 24 h and that the device retains viability, durability, and functionality throughout therapy [81].

In a Phase II randomized, controlled, open-label trial, involving 58 patients with AKI at 12 clinical sites, RAD treatment for up to 72 hours promoted a statistically significant survival advantage (33% mortality at day 28) over patients treated by conventional CVVH (61% mortality at day 28) [82]. A follow-up Phase IIb study to evaluate a commercial manufacturing process was not completed due to difficulties related to production and distribution of RAD devices.

A major obstacle in the widespread adoption renal cell therapy is the lack of a cryopreservable system to enable distribution, storage, and therapeutic use at point-of-care facilities [83]. Building from the success of the RAD, Humes and colleagues have developed the bioartificial renal epithelial cell system (BRECS), a device which functions as a combined bioreactor, cryostorage device, and cell therapy delivery system. Briefly, porous, niobium-coated carbon disks were used as cell scaffolds within the BRECS, and culture media was perfused through and around the porous disks. A recently developed technique of expanded propagation (EP) allowed for the amplification of kidney progenitor cells from primary isolates, to serve as a robust therapeutic cell source for seeding BRECS. Application of the defined EP method resulted in an increase of up to 8 orders of magnitude in cell yield over historic, standard propagation techniques [84]. *In vitro* measurements of glucose and oxygen consumption,

lactate generation, and glutathione degradation suggest the maintenance of more than 1×10^8 cells in each BRECS during 5 months in culture [85]. *Ex vivo* large animal studies suggest that utilizing the BRECS in conjunction with standard hemofiltration is a promising approach to treat both ARF and ESRD [85–87].

IV. Conclusions and Future Perspectives

Critical to the translation of stem cell therapies for the clinical treatment of kidney disease, there are several regulatory, technical, and economic hurdles that must be overcome concurrently. Cell sources for clinical therapy must be plentiful, or easily scalable, to be economically favorable, while meeting technical requirements of a precisely defined, uniform, pathogen-free, therapeutic cell population. Transformed cells as are easily generated, but may pose a safety issue with the potential for malignant transformation, and therefore utilization is prevented by regulatory concerns. Though autologous cell sources may circumvent immunorejection, a technical hurdle, autologous cell sourcing may not be as economically viable as non-autologous sources. These complex interrelationships are important considerations for the methodological choices made for cell sourcing, summarized in Table 1. As the understanding of adult SC, ES and iPS cell biology deepens and protocols are developed to more robustly and reproducibly differentiate these cells into specific cell fates *in vitro*, they will continue to provide answers to the cell sourcing question critical to the clinical implementation of cell therapy. Clinical applications will require the use of human cells [88], and therefore both bioethics as well as scientific advancement will play roles in which techniques for creating nonimmunogenic cell sources will prevail [89]. In the meantime, the approaches that address regulatory, technical and economic issues concurrently are most likely to advance the treatment of renal failure, and translate to clinical use.

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Table 1

Cell Therapy Approaches in Renal Failure

Cell therapy approach	Cell sourcing	Mode of Application	Need for immunosuppression?	Clinical Studies
MSC	autologous	injection portal vein, systemic administration	no	Phase I/II[42,43]
ES	allogeneic	to be determined	no	none to date
iPS	autologous	to be determined	no	none to date
Primary renal cells	allogeneic	encapsulated, extracorporeal circuit	no	Phase I/II [81,82]
Metanephroi	allogeneic/xenogeneic	implanted	yes	none to date