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Stem Cell and Regenerative Science Applications in the Development of Bioengineering of Renal Tissue

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ABSTRACT: A rising number of patients with acute and chronic renal failure worldwide have created urgency for clinicians and investigators to search out alternative therapies other than chronic renal dialysis and/or organ transplantation. This review focuses on the recent achievements in this area, and discusses the various approaches in the development of bioengineering of renal tissue including recent discoveries in the field of regenerative medicine research and stem cells. A variety of stem cells, ranging from embryonic, bone marrow, endogenous, and amniotic fluid, have been investigated and may prove useful as novel alternatives for organ regeneration both *in vitro* and *in vivo*. Tissue engineering, developmental biology, and therapeutic cloning techniques have significantly contributed to our understanding of some of the molecular mechanisms involved in renal regeneration and have demonstrated that renal tissue can be generated *de novo* with similar physiologic functions as native tissue. Ultimately all of these emerging technologies may provide viable therapeutic options for regenerative medicine applications focused on the bioengineering of renal tissue for the future. **(*Pediatr Res* 63: 467–471, 2008)**

Acute and chronic renal failure is a major health issue all over the world. The number of patients with end-stage renal disease (ESRD) is estimated at over 300,000 and rising every year, greatly expanding the need for chronic renal dialysis and/or transplantation, but also creating increasing demands on already limited resources. Therefore, there is a sense of urgency for investigators to search out alternative therapies that will someday prove useful in the treatment of patients with renal disease.

Acute renal failure usually results from temporary renal loss subsequent to a variety of acute insults such as surgery, trauma, hypothermia, or sepsis. When patients are younger or when the injury is less severe, renal tubules can regenerate and regain almost normal function within days; however, in more severe cases of injury or in older patients, the repair process can be prolonged or even fail completely, resulting in long-term dialysis and a marked increase in patient mortality. Despite a great effort in studying the pathogenesis and searching for new therapies, very little progress has been made in improving the outcomes for acute renal failure patients. Repair of renal tubules after injury is mediated by the surviving tubular cells that border the region of injury. After the insult occurs, these cells rapidly lose their brush border and dedifferentiate into a more mesenchymal phenotype. This process seems to be followed by migration of the dedifferentiated cells into the regions where cell necrosis, apoptosis or detachment have resulted in denudation of the tubular basement membrane. There they proliferate and eventually redifferentiate into an epithelial phenotype, completing the repair process. In general, it is thought that the local release of human growth factor, epidermal growth factor, and Insulin-like growth factor-1 coordinates this process of dedifferentiation, migration, proliferation, and eventual redifferentiation (1).[1]

In contrast to acute renal failure, chronic renal disease results from more unremitting causes, most commonly diabetes, but also hypertension, congenital malformations, autoimmune disorders, or chronic infection that can affect the individual for many years before organ failure is achieved. Obviously, therapies aimed at prevention for some of these causal factors can possibly prevent kidney failure or delay its onset significantly, but end stage disease in still many cases is still inevitable. ESRD usually occurs when kidney function is less than 10% of normal (http://www.nlm.nih.gov/medlineplus/ency/article/000500.htm).

Renal transplantation is a good treatment option for a majority of these patients with ESRD; however, a shortage of compatible organs remains a critical issue from most of these patients.

A variety of alternative technologies have been explored for the development of donor tissue for purposes of transplantation in the future: for instance, xenotransplantation with porcine kidneys. Genetic engineering has made it possible to manipulate these donor kidneys to express human genes so that hyperacute rejection is avoided. However, exposure to possible viral contaminants from porcine or other animal donors to human recipients is a major cause for concern and has significantly limited its widespread application. Various technologies to create kidneys or artificial nephrons from human cells are also emerging as possible future alternative therapies. Initial attempts to create artificial nephrons from renal cells seem encouraging, but so far, have had limited success. Stem cells have also demonstrated some promise. Human embryonic stem cells (ESCs) have the capacity to

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Abbreviations: AFS, amniotic fluid stem cells; **EB,** embryoid body; **ESC,** embryonic stem cells; **ESRD,** end stage renal disease; **MSC, MM,** metanephric mesenchyme; **UB,** ureteric bud

differentiate *in vitro*, *in vivo*, or *ex vivo* into various cell types of the body, including the kidney (2). Bone marrow stem cells have also shown similar plasticity. Transformation *in vitro* of primitive cell types into nephrons has been demonstrated in amphibians. Advances in biotechnology and genetic engineering have extraordinary potential for the future and will continue to be developed and examined for regenerative medicine purposes (3).

Both, basic science and clinical investigators alike will continue to advance our knowledge and understanding of renal disease in the new century. We hope that clinicians will have various new options to their disposal for the treatment of such patients so that eventually end stage disease or dialysis no longer exist or at minimum better therapies will emerge. New innovative developments are within sight and these are outlined and discussed in this brief review. The prevention and possible cure of progressive renal disease represents the challenge incurred by all involved in this area of study.

STEM CELLS AND KIDNEY REPAIR

The kidney is a complex organ with very important functions that are vital for the organism. These vital functions are made possible by specialized cell types that compose the glomeruli and tubules of the nephron but also within the surrounding extracellular matrix. Trying to identify an appropriate source of stem cells that will ultimately function to replace these specialized cells is very difficult. Stem cells are frequently classified as either embryonic or adult (mesenchymal in origin). It is clear from review of the literature that stem cells commonly used for purposes of bioengineering kidney cells or tissue can come from either exogenous or endogenous sources (4). However, it is unclear now whether stem cells have the ability to entirely recapitulate the very complex differentiation pathways involved in kidney regeneration and completely replace one or all of the very complex cell types involved in this process. Therefore, this remains a very active area of research among many investigators today.

As many as 3000 Americans die daily from diseases that in the future may be treatable with tissues derived from embryonic stem cells. Nonetheless, the recovery of human embryonic tissue for therapies carries with it highly controvertible and ethical dilemmas. ESC have the capacity to give rise to cell types derived from all the three germs layers (2,5). Kidney markers involved in the beginning of nephrogenesis are expressed during the early steps of embryoid body (EB) formation, while terminally differentiated renal cell types are present in late EB development. Kramer *et al.* (6) demonstrated that within the EB cells expressing markers characteristic of differentiated podocytes and epithelial cells of distal renal tubules could be detected. In addition, they showed that these cells are also capable of resembling complex glomerular like structures. When transplanted *in vivo*, ESC form teratomas that contain renal tubules and fetal glomeruli (2,7). This shows promise because ESCs elucidate the genetic, molecular and cellular mechanisms that induce renal differentiation but also show real potential in kidney structure differentiation. However, uncontrolled growth and tumorgenic properties of ESCs still raise concerns about their ultimate clinical applications in regenerative medicine, apart from the ethical issue surrounding their widespread use.

The potential role of mesenchymal stem cells (MSC) as a tool for cell-based therapies aimed at kidney regeneration is an emerging interest among various scientific groups. Organs and tissues have the capacity to maintain cellular homeostasis because of cell turnover and specific tissue proliferation rates. Organs such as the kidney, lung, liver, and heart possess these characteristics (8–11). MSC can be isolated from different tissues, ranging from bone marrow (12), fat (13), and within niches of the organs themselves. They express common cell markers (such as CD105, CD90) and can give rise to different cell types (14). These proprieties, along with others, have interested many groups to start utilizing MSC to see if they can rescue and perhaps regenerate damaged organs and tissues in animal models. They also avoid some of the controversial points seen with using embryonic stem cells. Although some encouraging results were obtained from liver, lung, skin, and hematopoietic systems, these results can vary with different animal models and protocols (15,16).

Some of the most interesting results have been obtained within *in vivo* systems using mice. Y-chromosome, bone marrow stem cells were transplanted into female murine hosts with ESRD. Transplanted bone marrow stem cells were found integrated into the damaged kidney (17,18), Morigi *et al.* (19,20) and Herrera *et al.* (21) demonstrated that MSC are capable of integrating into damaged tubules and believe that exogenous MSC from bone marrow have the ability to differentiate into renal epithelial cells. Yokoo *et al.* (22) injected MSC from bone marrow into kidneys during development and confirmed their integration into various compartments of the kidney suggesting real engraftment of these cells within nephron structures. The physiologic benefit of incorporation of these cells within damaged tubules of the kidney is still unclear however.

In contrast, there have been other groups, which have shown that MSC have a role in restoring function to damaged kidneys through some other mechanism other than incorporation and replication (23–25). Bonventre and coworker (26) in their investigations underscored the importance of MSC in renal repair, however they emphasized that the process of renal epithelial cell replication occurred too rapidly for MSC to truly transdifferentiate into tubular cells. In addition, the percentage of exogenous MSC found in the tubules was less than 0.1% of the total population of injected cells at 24–48 h postinjection. Thus, these cells could not have had a predominant role in repair of the nephron structure in such a short period of time. One important aspect that recently is under investigation is the possibility that the MSC may mediate their reparative effect on the inflammatory process following acute renal injury. Damaged endothelial cells attract leukocytes, vasomediators are released with injury, and epithelial cells of the tubule create proinflammatory and chemotactic cytokines (27). Togel *et al.* (28) have shown that injection of MSC is protective against ischemic renal injury as early as 24 h based on measurements of creatinine levels in these animals. The physiologic parameters in these animals were restored, but not

through integration and differentiation of the injected MSC because of the very short period of time with which a response was observed. The exact mechanism that regulates this inflammatory response is still being elucidated and is an area of active research today, but it has been postulated that MSC may protect renal cells through an intrarenal paracrine effect, which decreases inflammation, or through systemic immune modulation. It has been well described that MSC can modulate innate immunity by generating a large number of agents that modify the inflammatory reaction. Stagg and Galipeau (29). Even with all of these encouraging results, it will be necessary for future experiments to determine the exact role of MSC before and after engraftment for tubular or glomerular regeneration, and whether these stem cells can restore the important physiologic parameters of injured kidneys to confer a therapeutic benefit to the patient.

When analyzing the role of adult stem cells in kidney repair, it is also essential to take into consideration stem cells of endogenous origin. Different research groups have acquired supporting data identifying various endogenous cell populations involved in the repair process during organ damage. Lin (4) has shown that within kidney tubules there exists a subset of cells that have the capability to proliferate rapidly after injury. In addition, a stem cell population in the papilla of the kidney also exists regulated under a slow cell cycle during organ homeostasis that is induced toward rapid proliferation during injury (7). These progenitors were able to differentiate into a few varying cell types and, when injected under the capsule of the kidney, were capable of incorporating into renal tubules. Moreover, it was confirmed that EGFP-positive mature renal tubular epithelial cells when reactivated, were able to proliferate at high rates and participate in tubular regeneration (almost 90%) after an ischemic injury to the kidney (24). These results seem to implicate that endogenous renal repair due to homing of these progenitor cells within the organ may offer more overall benefit to the patient in the future than exogenous injection of MSC. There seems to be evidence to support that endogenous epithelial cells and perhaps other progenitors have a key role in the immediate response to damage and repair of renal tubular structures while perhaps exogenous, or other sources of MSCs, are mainly responsible for the restoration of kidney function acutely by involving secondary mechanisms that regulate or are regulated under an immune cascade. Perhaps both are necessary to achieve the desired effect.

Apart from embryonic and MSCs (those from bone marrow or kidney-specific progenitors), no other types of stem cells have been reported in literature for renal regeneration purposes until recently. Atala and coworkers in 2007 (30) published on a new pluripotent stem cell population isolated from amniotic fluid (AFS). A c-kit positive subpopulation of cells was described as capable of presenting embryonic characteristic. These cells are clonal and have a high self-renewal capacity but most importantly do not form teratomas when injected *in vivo*, which potentially makes them a very desirable source of pluripotential cells. They can differentiate into cell types derived from all the three germ layers and express both embryonic and mesenchymal markers. Our group has shown for the first time the use of amniotic, c-kit derived cells for kidney regeneration (31). Undifferentiated AFS were injected into the kidney of an embryonic mouse in an *ex vivo* culture and were demonstrated to integrate into the organ while developing and participating in all steps of nephrogenesis during development. We also performed preliminary *in vivo* experiments (data submitted) in which direct injection of AFS into damaged kidneys were able to survive and integrate into tubular structures and expressed mature kidney markers after 3 wk. Creatinine levels in these animals, which increased significantly after injury, were restored shortly after injection of AFS as previously demonstrated for bone marrow derived MSC (32). It is therefore suggested from these results that AFS participate in similar immunologic mechanisms postulated for MSC, as discussed previously, during early phases of injury and perhaps toward the eventual structural repair of the damaged nephron during later phases of organ repair. AFS represents a very suitable source of stem cells for kidney regeneration. AFS seem to have a great differentiation potential, without risk of teratoma formation, and also avoid the ethical concerns surrounding embryonic stem cell use; taking into account that amniocentesis is a very safe technique, which presents minimal risk to either the mother and/or developing fetus. The presence of this preliminary data are affirming, nevertheless, further investigations are still required to confirm the ability of these cells to participate in kidney regeneration that would make it beneficial for future therapeutic options.

SOMATIC CELL NUCLEAR TRANSFER AND TISSUE ENGINEERING

Together with very promising stem cell-based studies of kidney regeneration, investigators are also pursuing two other promising methods to restore kidney function for future regenerative medicine applications. These include somatic nuclear transfer and tissue engineering. Somatic cell nuclear transfer involves the removal of an oocyte nucleus and its replacement with a nucleus, and its associated complement of DNA, derived from a somatic cell obtained from a patient or donor. The oocyte is stimulated to undergo multiple divisions using chemicals or electrical pulse until it reaches the blastocyst stage where it can be either transplanted *in utero* for reproductive cloning, or used to harvest embryonic stem cells for expansion in culture for therapeutic cloning. The first mammal cloned was Dolly (33). Then, in the subsequent years important advanced studies were performed to try to understand this mechanism and other animals were subsequently cloned such as cattle (34), goats (35,36), mice (37), and pigs (38–41), using similar techniques. However, the obvious controversy surrounding reproductive cloning (42,43) has limited its expansion and therefore investigators have recently focused their research and attention toward therapeutic cloning because of the possibility of deriving embryonic stem cells that can differentiate into various cell lines and provide an alternative source for transplantable cells. Lanza *et al.* used therapeutic cloning to produce genetically identical renal tissue in a bovine model (44). The nucleus of a skin fibroblast was microinjected into an enucleated oocyte that was trans-

planted *in utero* for 12 wk and then the cloned renal cells were seeded onto a biodegradable scaffold and transplanted *in vivo*. The authors confirmed that the kidney-like organ that resulted was capable of secreting urinary fluid confirming that the implant contained regenerated cells capable of filtration, reabsorbtion, and secretion. These results were the first demonstration that renal tissue could be created by applying techniques of tissue engineering and therapeutic cloning. It is clear that somatic nuclear transfer technology has many implications for the future, and yet this technology will require more improvement to instill the necessary confidence for its application toward real clinical situations.

Tissue engineering, that combines natural or biodegradable polymers with cells and growth factors, has also contributed to the field of kidney regeneration in recent years. The perfect implantable device needs to mimic the main physiologic function of the native kidney and it needs to operate incessantly to remove solutes. Current dialysis techniques are quite efficient but they do not have great adaptability. The optimum situation would be to design a perfect membrane that has the same filtration capability as the nephron. Humes *et al.* (45) demonstrated the creation of a membrane that has both pore selectivity and at the same time hydraulic permeability as the native kidney. The creation of the perfect bioartificial hemofilter will overcome the problem of loss of filtration due to thrombotic occlusion and protein deposition and will exclude the use of anticoagulants in current extracorporeal units that very often results in bleeding for the patient (46).

Experiments have also been conducted where renal cells were cultured *in vitro* and then seeded onto a polyglycolic acid polymer scaffold and subsequently implanted into athymic mice (46). Over time the formation of nephron-like structures within the polymer were observed. These preliminary results implementing techniques of harvesting and expansion of renal cells *in vitro* combined with the use of synthetic scaffolds allowed investigators the ability to produce three-dimensional functioning renal structures that could be used as *ex vivo* or *in vivo* filtering units. It is important to keep studying this technology and try to ameliorate these devices combining different disciplines ranging from cellular biology, nanotechnology, molecular biology, and tissue engineering.

EMBRYONIC ORGAN MODELS AND DEVELOPMENTAL BIOLOGY

Researchers have already demonstrated that bioengineering of the kidney is possible from embryologic precursors of the urinary tract under specific culture conditions and using techniques of developmental biology (47). Embryonic kidneys in an *ex vivo* model have been studied to understand the development of the organ itself (48–54). The *in vitro* culture of ureteric bud [UB, an embryonic tissue that together with the metanephric mesenchyme (MM) give rise to the entire adult nephron] has been demonstrated before (55). This UB can be used as a bioactive scaffold that can help the differentiation of embryonic kidney structures that eventually function as filtration units when cultured, with MM. In addition, it has been shown that if growth factors are added to the system *in vitro*, three generations of UB branching can be cultured which subsequently can induce the growth and differentiation of the MM into a primordial kidney structure ready for transplantation (56). Developmental biologists have been successful at recombining primordial embryologic structures such as the UB and MM to create a scaled down kidney complete with its parenchyma and collecting system, also termed the metanephroi. It is possible to transplant these embryonic metanephroi (the primordial kidney) into an *in vivo* model and demonstrate that these primordial kidneys are able to survive, develop and also secrete concentrated filtrate (57–61). These primordial structures also required less immunosuppression compared with normal kidney transplantation. The major problem related to this technique, however, is the very small amount of final product obtained which is a direct result of the embryonic size of the metanephroi that one starts out with. One of the obvious challenges for this promising technology in the future will be the ability to maintain these structures during growth and development indefinitely that would result in an organ of adequate size appropriate for larger animal models and perhaps patients someday.

In conclusion, we can affirm that there are different cell and organ-based approaches using stem cells that are being investigated for the purposes of kidney regeneration. The normal development of the kidney requires the integration of cells, extracellular matrix, and important growth factors that are fundamental for all this process to occur correctly. Thus, it is important to mention that in trying to engineer appropriate renal tissue or cells, all these components need to be merged appropriately to ultimately rescue the kidney from end stage disease or provide viable therapeutic options for regenerative medicine applications focused on the bioengineering of renal tissue for the future.

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