Human Kidney Cell Reprogramming: Applications for Disease Modeling and Personalized Medicine

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ABSTRACT

The ability to reprogram fully differentiated cells into a pluripotent embryonic state, termed induced pluripotent stem cells (iPSCs), has been met with great excitement. iPSC technology has advanced the fundamental study of disease modeling with the potential for cell-replacement therapy, especially in the neuronal and cardiac fields. However, renal medicine as of yet has not benefited from similar advancements. This review summarizes the unique characteristics of iPSCs and their potential applications for modeling kidney disease. Pioneering such endeavors could yield constructs that recapitulate disease phenotypes, open avenues for more targeted drug development, and potentially serve as replenishable sources for replacement of kidney cells in the setting of human disease.


Through experimentation involving nuclear fusion came the realization that differentiated somatic cells have potential to show a plasticity that is not unidirectional.1–3 Subsequent studies suggested the transfer of a single somatic cell nucleus into an enucleated unfertilized egg possessed the ability to not only form all three germ layers but also produce viable offspring.4–6 Decades later, the direct reprogramming of fibroblasts into a pluripotent state, so-called induced pluripotent stem cells (iPSCs),7,8 has renewed interest in what constitutes the reprogramming process. An explosion of subsequent studies confirms that a large variety of somatic cells can be efficiently reprogrammed into iPSCs9–13 and subsequently redifferentiated into other cell types that recapitulate disease phenotypes.14–16 Such information offers proof-of-principle for the use of iPSCs as useful in vitro modeling systems that could ultimately lead to novel drug development and testing. Additionally, as iPSCs are produced from individual patients, the derivation of patient-specific stem cell lines could provide a limitless source of clinically useful immune and genetically matched cells.

Since the pioneering discovery by Takahashi and Yamanaka,7,8 iPSCs have now been successfully generated from a wide array of human tissues.14,16–20 Despite such advances, cell reprogramming with respect to the kidney remains in its infancy. Only recently has it been possible to derive iPSCs from kidney mesangial cells21 or epithelial cells sourced from urine.22 Furthermore, the directed differentiation of mesangial cell-derived iPSCs to podocyte-like cells (iPSC-podocyte)23 and the generation of iPSCs from kidney disease patients has only recently been reported.24

Here we review our current knowledge regarding the use of pluripotent stem cells targeted at kidney disorders. Specifically, it will address certain shortcomings of traditional model systems, current knowledge regarding the differentiation of pluripotent stem cells into the kidney mesodermal lineage, and the advantages of reprogramming for in vitro disease modeling and therapeutic interventions. Finally, the efficiency and safety of iPSC technology that governs the prospective applications and clinical promise for kidney regeneration will also be discussed.

KIDNEY REGENERATION AND CELL REPLACEMENT

The kidney is a highly complex organ with many different cell types, including tubular epithelial, glomerular, and interstitial cells. Additional complexity exists within distinct compartments of the nephron, which possess divergent regenerative capabilities after kidney insult. For example, the tubular epithelium has the highest potential for self-renewal,25,26 whereas replacing glomerular cells, in particular podocytes, remains challenging.27,28 Glomerular podocytes display a complex cytoarchitecture and appear to enter cell quiescence after birth, a characteristic that makes podocyte replacement after injury difficult.29–31

Podocyte damage results from many...
factors, including genetic, immunologic, toxicologic, and mechanical insults, and as such podocyte depletion remains a hallmark of a broad spectrum of clinical syndromes termed podocytotopathies.\textsuperscript{32–34} In addition to the primary insult to podocytes, secondary damage of neighboring podocytes may result in a vicious cycle of progressive damage.\textsuperscript{35}

Despite the minimal regenerative potential of glomerular podocytes, the kidney has an inherent ability for endogenous remodeling of tissue architecture and cellular replacement after injury.\textsuperscript{36} The kidney's repair response, consisting of cellular replacement of the injured tubular epithelium, does not involve specialized kidney progenitors.\textsuperscript{37} Epithelial cell replacement most likely arises from surviving cells capable of intrinsic proliferation and expansion. Moreover, endogenous tubular epithelial cellular replacement and tissue remodeling may be accelerated by administering bone marrow–derived mesenchymal stem cells that home to the sites of damage and modulate the inflammatory responses to facilitate tissue repair.\textsuperscript{38–43} Furthermore, CD133\textsuperscript{+} and CD24\textsuperscript{+} renal progenitors committed toward a podocyte or tubular lineage reside at the urinary pole of the Bowman capsule and provide a source of replacement cells during normal homeostasis and after injury.\textsuperscript{44–47}

Understanding the process of endogenous kidney regeneration is important for the development of new therapeutic strategies aimed at cellular replacement and reversal and/or attenuation of fibrosis. As such, the reprogramming of adult cells to generate iPSCs\textsuperscript{47,48} with high proliferative ability and broad differentiation capacity represents a major advance for both preclinical and clinical applications.

**PLURIPOTENT STEM CELLS TARGETED AT THE KIDNEY**

**Embryonic Stem Cells**

Embryonic stem cells (ESCs) are pluripotent and thus could offer important alternative avenues for regenerative therapies through differentiation into distinct kidney cell types. Pioneering studies in *Xenopus laevis* show presumptive ectoderm (animal cap) can be induced to produce all three components—tubules, glomus, and ducts—of the pronephros when cultured with known mesoderm-inducing factors, such as activin A and retinoic acid.\textsuperscript{49–51} In light of such success, subsequent studies using the same mesoderm-inducing factors have been applied to the mammalian metanephric kidney.\textsuperscript{52–55} It was apparent not only that the same mesoderm-inducing factors could direct the differentiation of embryonic bodies into various renal progenitors in vitro\textsuperscript{52–55} but also that such cells when injected *ex vivo* into developing mouse kidneys could integrate into tubules with at least 50\% efficiency (reviewed in Table 1).\textsuperscript{53,56} Nonetheless, whether the ESC-derived progeny contributes to function of the nephron is not yet evident.

Because of the vast pluripotent potential of undifferentiated human ESCs (hESCs), teratoma formation results after their injection *in vivo*.\textsuperscript{54} Thus, the therapeutic applications resulting from this technology have been slow to develop. In an attempt to circumvent deleterious consequences of pluripotency, a study by Vigneau and colleagues differentiated ESCs into renal progenitors and subsequently enriched for such populations. Injection of these enriched kidney progenitors into newborn kidneys reduced the risk of teratoma formation.\textsuperscript{55} Since these discoveries, more recent work has identified the role of other lineage-specifying factors, such as bone morphogenetic protein (BMP)-2, BMP-4, and BMP-7\textsuperscript{57} and other small molecules\textsuperscript{58} in the establishment of intermediate mesoderm, from which most nephron-specific cell types are derived. Furthermore, the exploration of specific culture conditions and cell markers demonstrates that it is possible to enrich for cells resembling a kidney progenitor state (Table 1).\textsuperscript{59}

Extending previous *in vitro* work,\textsuperscript{60} a recent report by Xinaris and colleagues provides novel advancement toward the therapeutic application of embryonic tissue in the potential treatment of renal diseases.\textsuperscript{61} In this report, renal aggregates (organoids) constructed from single cell suspensions of fully dissociated embryonic day (E) 11.5 mouse kidneys grown in culture were subsequently transplanted into immune-deficient rats. Remarkably, the implanted organoids were capable of generating vascularized nephrons consisting of functional glomerular and tubular tissue (Table 1).\textsuperscript{61} Although the transplanted tissue survived for only 3–4 weeks, the ability to grow and mature developing fetal kidney tissue *in situ* offers advantages, including the ability to better understand the gene regulatory networks required for both early and late kidney lineage specification and ascertaining of the local microenvironment necessary for renal stem cell differentiation and nephrogenic maintenance. With the organoids already committed down a lineage of kidney development, such an application relieves the need for an in-depth knowledge of the gene regulatory networks necessary for direct reprogramming, a feature that is a prerequisite for any directed differentiation of pluripotent cells into kidney lineages. Despite these advances, ethical constraints surrounding hESCs have limited their widespread use in disease modeling and other applications, forcing the investigation into alternative solutions.

**iPSCs**

The landmark discovery by Takahashi and Yamanaka in mice\textsuperscript{7} and humans,\textsuperscript{8} involving the expression of four transcription factors (Sox2, Oct4, c-Myc, and Klf4) that direct the reprogramming of fibroblasts into a pluripotent state, has revolutionized the field of stem cell biology (Figure 1). Since the discovery of iPSCs, extensive investigation has focused on the derivation of new cocktails of factors that give rise to such pluripotent cells more efficiently. Such cocktails involve both integrating and nonintegrating methods, combined with growth factors and chromatin-modifying elements.\textsuperscript{62} Although iPSCs and hESCs show similarities in terms of transcription, epigenetics, self-renewal, and pluripotent
potential, they are not identical.63 Growing evidence demonstrates that genetic, epigenetic, and transcriptional differences exist among these pluripotent cells.64–66 One obvious difference is the presence of epigenetic memory, whereby the reprogrammed cell retains a profile reminiscent of its somatic cell of origin.67,68 Large-scale comparisons between iPSCs and hESCs further show that the former fails to efficiently silence the expression pattern of the somatic cells from which they were derived, potentially affecting the models reliability for disease modeling and drug discovery.63 The extent of this memory has been reported to diminish, however, with extended passaging.67

Functional consequences for this memory also persist, whereby an inability to silence the original expression pattern equates to a tendency for iPSCs to preferentially differentiate back to the parental cell type.69 Thus, the potential exists for the residual epigenetic memory to be exploited in cases where limited knowledge regarding the gene regulatory networks involved in the production of renal progenitor cells is present—like that for the nephron. However, the difficulty in collecting viable kidney tissue hinders the ability to exploit such features. Innovative approaches, such as the isolation of various kidney cells from urine for cell reprogramming,22 have overcome such obstacles, making the ability to derive numerous patient specific iPSCs more feasible.

A recent report representing the largest of its kind to investigate factors that

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RA, retinoic acid; FGF, fibroblast growth factor; BMP7, bone morphogenetic protein 7; bNGF, β nerve growth factor; HGF, hepatocyte growth factor; bFGF, basic fibroblast growth factor; EGF, epidermal growth factor; BMP2, bone morphogenetic protein 2; BMP4, bone morphogenetic protein 4; WT-1, Wilms tumor 1; EB, embryonic body; VEGF, vascular endothelial growth factor.
may affect the ability of pluripotent cells in modeling potential diseases shows that genomic sites previously thought to be stable, in effect, imprinted loci and X-chromosome inactivation, actually differ from the reprogrammed somatic cells. Because of the scope of the study, the authors were able to attribute many of the abnormal DNA methylation sites to the reprogramming process itself or specific culture conditions. Such genomic instabilities thus warrant a degree of caution, particularly in cases where the disease is sensitive to imprinting or X chromosome inactivation status.

**IPSCs for Disease Modeling and More Targeted Drug Therapy**

**Disease Modeling**

Given the numerous proof-of-principle studies showing the ability of iPSCs to recapitulate the molecular basis and pathogenesis of multiple diseases, it is increasingly apparent that direct reprogramming might allow for the effective generation of pluripotent cells that carry the disease-associated genotype.

The surrogate application of iPSCs as representative of kidney diseases is increasingly becoming reality given (1) recent advances involving the production of iPSC from both mesangial and epithelial cells derived from urine using the four traditional reprogramming factors (Sox2, Oct4, Klf4, and c-Myc), (2) the identification that certain kidney diseases do not hinder the reprogramming process, (3) the generation of iPSCs from renal proximal tubular cells with only two factors (Sox2 and Oct4), and (4) the recent reports of reprogramming of iPSCs into iPSC-podocytes (Figure 1).

Primary human podocytes show rapid dedifferentiation in vitro, and because of their limited capacity to proliferate, represented by irreversible growth arrest, long-term propagation remains difficult. In contrast, iPSC-podocytes maintain differentiated features for at least 3 months.

The production of iPSC-podocytes, and potentially epithelial cells, allows an alternative culture method that facilitates both quantitative and qualitative interrogation of kidney cell function in disease. Despite these advances, numerous challenges hinder the development of in vitro iPSC-kidney disease models. These include the immense complexity owing to the involvement of myriad interwoven kidney cell types, the pathologic heterogeneity among various forms of kidney diseases, and a lack of knowledge regarding the developmental gene networks involved in directing the efficient production of specific kidney cells. Despite such complexity, it is essential to focus efforts on whether iPSC-kidney cell lines recapitulate disease processes across a range of renal disorders (Figure 2A).

Aside from avoiding the ethical dilemmas associated with use of hESCs, iPSCs provide particular advantages for modeling disorders where the cause of disease is unknown. Patient-specific iPSCs allow for the study of disease-specific pathogenesis in vitro and in the long term could conceivably provide alternatives for cellular replacement therapies (Figure 2D). Using lentiviral transduction, iPSCs have been generated from kidney transplant recipients with a history of ESRD due to autosomal dominant polycystic kidney disease, systemic lupus erythematosus, and Wilms tumor. Importantly, the autosomal dominant polycystic kidney disease–derived iPSCs obtained from skin keratinocytes were confirmed to maintain the PKD1 gene mutations, although any additional somatic mutations in the tubular epithelium that are important for cyst development may not exist.

It would be necessary for disease-specific iPSCs to retain the disease-related mutation to recapitulate their pathogenic phenotypes. Furthermore, to allow for reliable measurements and effective extrapolation of data to be useful in disease modeling, the choice of controls to compare the diseased line is essential. Such approaches could involve using identical genetic backgrounds to avoid confounding the interpretation of results. Alternatively, correction for the genetic trait in the diseased iPSC line by overexpression of the affected protein or pharmacologic intervention could act as a sufficient control, as could knockdown of the product under investigation by RNA interference in control cells.

Finally, for the purposes of disease modeling, an assay of gene expression should be used at various time points after differentiation. A study conducted by Nguyen and colleagues reported that iPSC-derived neurons obtained from a patient with Parkinson disease showed varying gene expression profiles dependent on the stage of differentiation. Thus, iPSC-derived patterns of gene expression may be similar to that of the developing human counterpart.
The ability for cells derived from iPSCs to recapitulate the disease phenotype could be influenced by such processes.

**Therapeutics and Targeted Drug Therapy**

The incidence of AKI and CKD is rising and reaching epidemic proportions. In patients with CKD, the progressive decline in renal function is multifactorial and attributable to a variety of mechanisms, including failure to resolve the inciting proinflammatory injury leading to the onset of self-perpetuating damage and ultimately the development of fibrosis and tissue attenuation. With such complexity, the need for disease models that recapitulate human kidney disorders is paramount. Mouse models that are genetically manipulated, bred, and maintained have been vital to advancing medical research and the study of disease pathogenesis. However, given the species-specific differences in physiology, genomics, and metabolic demands that exist between mice and humans, application of discoveries in rodents cannot be easily translated, especially with respect to therapeutics, where direct translation is vital.

Equally critical for understanding fundamental mechanisms of disease is the role of cultured cells providing controlled environments for the elucidation of disease mechanisms. Improvements in microimmunodissection techniques have made purification and isolation of specific kidney cells possible. Disadvantages exist, however, in primary cell culture, whereby certain cells, such as podocytes, exhibit rapid growth arrest and dedifferentiation, losing their ability to replicate and maintain certain characteristics as effective models. Advances in immortalization of cells have overcome the detrimental growth arrest characteristics, facilitating their use in *in vitro* dissection of physiologic and disease-specific mechanisms. Despite this, immortalization of cell lines requires genetic manipulation that invariably leads to deleterious downstream consequences and a failure to conserve the native characteristics of the original cell type. For example, proximal convoluted tubules lose their brush-border microvilli upon repeated passaging.

There are many advantages of developing pluripotent cells as a therapeutic strategy for patients with a variety of kidney disorders. Compared with other human kidney cell lines, iPSCs derived from mesangial cells have long-term proliferative ability and potentially a broad range of differentiation capacities, including podocytes. Furthermore, noninvasive procedures can be used, such as the collection of urine to obtain the necessary cells for reprogramming. However, it remains uncertain whether iPSC-derived kidney cells can be differentiated from target cells of other germ lineages, for example, skin fibroblasts that originate in the ectoderm. Nonetheless, iPSC technology provides a valuable tool to interrogate human disease and offers an unprecedented opportunity to develop self-renewing models that will facilitate mechanistic studies of disease.

The screening of genetic mutations in disease-derived iPSCs and the development of functional assays in cells can also serve as a fundamental step for future studies to correct the genetic defects in selected tubular epithelium or in podocytes that maintain a proliferative capacity. For example, several genes encoding for podocyte nuclear and cytoplasmic proteins, slit diaphragm, and cell membranes have been identified as driving podocyte phenotype and functional abnormalities in subsets of patients with FSGS and nephrotic syndrome. The generation of iPSC-derived kidney cell lines from these patients that maintain...
their genotype and phenotype will be a valuable tool for better understanding how mutations cause disease, for screening new drug compounds, for developing disease-modifying assays, and potentially for developing autologous cell replacement therapies. These cell lines may provide information to optimize an affected individual’s personalized medical care and open up new sources for stem cell banking. Moreover, in the long term, the autologous transplantation of patient-derived iPSC-kidney cells, with correction of the underlying genetic defect, may provide an innovative approach for kidney cellular replacement.

Finally, the discovery of unexpected adverse reactions and toxicities to new medicines before and during phase I–III clinical trials remains a challenge. With pharmaceutical companies facing increased pressure to speed drug discovery and reduce costs, the development of patient-derived iPSC kidney cells may enhance both productivity of drug development and patient safety. Therefore, the generation of iPSC cells from patients with genetic and nongenetic kidney disease will open new avenues for toxicology testing using high-throughput platforms earlier in the drug discovery process, with high translational power back to the individual (Figure 2B). The ability to easily obtain large numbers of patient-specific tissue could allow for the assessment of why factors cause certain individuals to benefit from a given drug, while others have toxic adverse effects. Personalized drug treatment could then be facilitated by the stratification of populations based on certain factors, such as genetic determinants that result in patients being nonresponders versus responders (Figure 2C).

**FUTURE CHALLENGES AND CONSIDERATIONS**

Although promising in the field of disease modeling and therapeutic discovery, current iPSC technology may not be of any direct therapeutic benefit due to the oncogenic potential of some of the reprogramming factors (c-Myc and Klf4).

Ideally, the use of small molecules that induce reprogramming is favored. However, it should be noted that chemicals used could also induce toxicity, including carcinogenicity.

Given that the injection of undifferentiated iPSCs in vivo inadvertently results in teratoma formation, additional refinements need to occur for their effective use therapeutically. Investigations into the production of somatic stem cells with a more limited potential for differentiation could circumvent this. The generation of induced neural stem cells by lineage reprogramming (explained below) is a useful example because such somatic stem cells have the ability to differentiate into a number of neuronal cell types; such a feature is important in their application therapeutically. Additionally, such cells also provide an unlimited source of neurons and other neural cell types for studying.

With respect to the kidney, however, the possibility of a mammalian nephron progenitor stem cell, such as the cap mesenchyme, which gives rise to all epithelium of the kidney, being able to survive, differentiate, and contribute to repair after nephrogenesis is distant. Nevertheless, the identification of nephron stem/progenitors in the adult zebrafish provides optimism for a multipotent self-renewing progenitor in the adult kidney. In addition to iPSC reprogramming, other avenues for kidney cell reprogramming are being investigated, such as those involving lineage reprogramming. Although providing benefits over direct reprogramming of iPSCs, one disadvantage of lineage reprogramming is the requirement for information about target gene regulatory networks in order to transform one cell type into another. The use of six genes in the direct reprogramming of adult proximal tubule cells to nephron progenitors, reminiscent of the embryonic kidney, has recently been reported. This extends the future regenerative potential of stem cells in renal medicine. Direct reprogramming is arguably best suited to the kidney because it relies on information of the optimal culture conditions, which, in the case for certain cell types (such as podocytes), is already available. Another potential advantage of direct reprogramming is differentiation into desired cell types that can potentially be facilitated by the exploitation of the residual epigenetic memory favoring spontaneous differentiation to the parental cell type (discussed above). Future endeavors should aim to determine whether kidney-derived iPSCs show a tendency to redifferentiate back into the parental cell type. Understanding what genes are necessary for this spontaneous redifferentiation may provide further information on the regulatory networks sufficient for nephron and progenitor cell production. Although limited, methods aimed at efficiently inducing mouse ESCs into renal progenitors and fully differentiated cell types have already been developed (Table 1). Hijacking the knowledge of such technology to generate mesodermal and renal lineage cells from iPSCs could be possible.

Finally, it is yet to be explored whether dedifferentiation and redifferentiation processes induce changes in the resulting somatic cell that are different from the parental cell type, such as changes involved in proliferation and senescence that give iPSC a more immature phenotype. Differentiation of iPSCs into cardiomyocytes provides evidence of this, where these differences could potentially confound any results obtained in the disease modeling and drug discovery potentials.

**CONCLUDING REMARKS**

Although knowledge that differentiated cells can be reprogrammed into a pluripotent state, or indeed another lineage, has been known for decades, the recent interest in this phenomenon can be attributed to the latest developments in
somatic cell reprogramming over the past several years. Effective disease models and drug screens are the current focus, but more ambitious applications with respect to regenerative medicine will follow. In contrast to many other fields, the kidney is yet to substantially gain from such technology. The accumulation of recent reports describing the manipulation of iPSCs for applications in kidney disease modeling act to address certain shortcomings that hinder their widespread use, such as the derivation of iPSCs from epithelial cells isolated from the urine. With so much left to learn, future challenges will involve mapping the redifferentiation of iPSCs into the many cell types of the kidney and investigate potentials into gaining new insights into disease processes and therapeutic interventions.

DISCLOSURES
None.

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