Induced Pluripotent Stem Cells from Human Kidney

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Kidney disease is a growing health issue for modern society,1–3 and there are a number of causes, including prematurity, genetic abnormalities, inflammation, hypertension, and diabetes. Current treatments for ESRD include dialysis and transplantation, but both are expensive, rely on continuous intervention, and are imperfect in their application.4–6 Transplantation also suffers from lack of available organs, resulting in mismatches between the donor organ and the patient, which invariably leads to some degree of tissue rejection. As of January 2011, approximately 88,000 patients were registered on the kidney transplant waiting list at the United Network for Organ Sharing in the United States, with an average wait time of 3 to 5 years.7

With the discovery of embryonic stem cells more than 25 years ago and, more recently, the production of induced pluripotent stem cells (iPSCs), stem cell therapy now holds the promise of novel treatments and raises considerable hope for offsetting the worldwide shortage of organs for transplantation.8 However, the ability to produce functional tissues or organs derived from stem cells is in its infancy,9–11 leaving a bottleneck in the transition from bench to bedside.

Renal progenitor cells have been identified in zebrafish12 but not found in mice requiring tubular repair.13 although parietal epithelium may serve as a progenitor niche for glomerular podocytes, and a stem cell from fetal kidney with limited potential for differentiation has been described recently.16 Although both embryonic and adult stem cells have the potential to differentiate into every cell type of the body, in the vast majority of studies, the efficiency is low and differentiation is sporadic. Therefore, with notable exceptions,17 the road to clinical application of native stem cell–based therapy for kidney has been uncertain.

Consequently, the recent potential for inducing iPSCs from mature cells in tissue has been eye-opening for the field of regenerative medicine.8,18 The ability to generate patient-specific, tissue-specific, or matched iPSCs is well under study. Induced pluripotent cell technology offers advantages over donor-derived tissue-specific stem cells or embryonic stem cells because patient-derived stem cells may also attenuate the need for immunosuppressive drugs.

Producing patient-specific iPSCs from a targeted organ should also enhance the differentiation efficiency of the stem cells. Studies indicate that tissue-specific iPSCs retain the epigenetic pattern of the original parent cell.19 This suggests, for example, that kidney-derived iPSCs may differentiate back into mature kidney cells more efficiently than from unrelated tissue iPSCs or even embryonic stem cells. For genetic-based defects, gene therapy coupled with iPSC production or deriving iPSCs from a matched related donor may also be possible. Furthermore, taking advantage of the fact that iPSCs retain their epigenetic memory means that complete reprogramming back to a pluripotent state may not be necessary.

Partial reprogramming will also likely generate an intermediate phenotype that has regenerative properties specific to the original organ without the problem of abnormal tissue formation as is sometimes seen with blood-derived stem cells.20 iPSC technology may also help to establish kidney-specific in vitro assays to study kidney disease and screen for potential drugs.21 All this suggests that for treatment of kidney disease, kidney cell–derived iPSCs may have a bright future.

It is of great interest, therefore, that in this issue of JASN, Song et al.22 and Zhou et al.23 demonstrate that human kidney cells are agreeable to reprogramming, thus leading the way to developing tissue-specific iPSC therapy for kidney disease.

In the first study, Song et al.22 demonstrate that iPSCs can be made from a normal human mesangial cell line. In their report, they fully reprogrammed the cells, demonstrating that such iPSCs can form all three embryonic germ layers and express the stem cell genes Oct3/4, TRA-1-60, and TRA-1-81 while downregulating genes characteristic of mesangial cells. Although genetic-based diseases should equally affect the genome of kidney cell and fibroblasts, it is possible that epigenetic changes to the DNA are tissue specific for the disease.19 Having iPSC derived from the glomerular cells of a patient with Alport syndrome, for example, may help determine whether iPSCs can recapitulate the developmental defects of the original kidney to shed light on the cause and progression of the disease. Furthermore, having a kidney-derived iPSC line should allow for direct comparison with fibroblast-derived iPSC lines for kidney differentiation potential. If studies demonstrate the superiority of kidney-derived iPSC for the treatment of kidney disease, then a clinically relevant source of kidney cells will be required.
Accessibility to patient cells is key to the successful development of clinically relevant cell-based therapies. Invasive techniques such as surgery and biopsy may inhibit patient interest and reduce adoption of new stem cell technologies. Being able to establish iPSC lines from all patients must also be considered when determining the clinical usefulness of reprogrammable technology. Unlike blood or skin, which is relatively easy to obtain, the kidney is not accessible, and innovative solutions must be found.

In the second study in this issue of JASN, Zhou et al. found that kidney cells collected from the urine are also a suitable source for reprogramming studies. For most cell types, including fibroblasts, the efficiency of iPSC production is low, so having a sufficient number of starting cells is vital. The issue is also complicated by the fact that most primary cells are difficult to expand in culture and reach senescence quickly. Although iPSCs have been made from adult cells, it is more efficient when fetal or neonatal cells are used. Nevertheless, Zhou et al. demonstrate that cells from the urine are easy to collect and expand, resulting in the establishment of iPSC lines from a single collection. Efficiencies ranged from a low of 0.01% for cells from a 65-year-old to 4% from a younger patient. They also show that iPSC lines can be produced from frozen and thawed samples. The authors have found solutions to many of the problems encountered during iPSC production.

Together, these two articles demonstrate the feasibility of using kidney cells as a source of iPSCs, and efficient production of adult iPSCs from urine means that cells can be collected at anytime, eliminating the need for cell banks. The advantage of these cells for the diagnosis and treatment of kidney disease is great but the ease of collection and the high frequency of reprogramming also means there are may be benefits to urine cells for iPSC production beyond kidney disease.

DISCLOSURES
None.

REFERENCES

See related articles, “Generation of Induced Pluripotent Stem Cells from Human Kidney Mesangial Cells,” on pages 1213–1220 and “Generation of Induced Pluripotent Stem Cells from Urine,” on pages 1221–1228.