Induced Pluripotent Stem Cells from Human Kidney

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Kidney disease is a growing health issue for modern society, 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. 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.

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. However, the ability to produce functional tissues or organs derived from stem cells is in its infancy, leaving a bottleneck in the transition from bench to bedside.

Renal progenitor cells have been identified in zebrafish but not found in mice requiring tubular repair, 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. 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, the road to clinical application of native stem cell–based therapy for kidney disease 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. 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. 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.

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. iPSC technology may also help to establish kidney-specific in vitro assays to study kidney disease and screen for potential drugs. 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. and Zhou et al. 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. 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. 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.23 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.23 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.
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COULD PATIENTS’ OWN KIDNEY CELLS CURE KIDNEY DISEASE?

Reprogrammed kidney cells could make transplants and dialysis things of the past

Highlights
• Patients’ own kidney cells can be reprogrammed and used as therapy against kidney disease
• Cells can easily be collected from the urine
• 88,000 patients are waiting for a kidney transplant in the United States, and they wait for an average of 3 to 5 years

Washington, DC (July 27, 2011) — Approximately 60 million people across the globe have chronic kidney disease, and many will need dialysis or a transplant. Breakthrough research published in the Journal of the American Society Nephrology (JASN) indicates that patients’ own kidney cells can be gathered and reprogrammed. Reprogramming patients’ kidney cells could mean that in the future, fewer patients with kidney disease would require complicated, expensive procedures that affect their quality of life.

In the first study, Sharon Ricardo, PhD (Monash University, in Clayton, Australia) and her colleagues took cells from an individual’s kidney and coaxed them to become progenitor cells, allowing the immature cells to form any type in the kidney. Specifically, they inserted several key reprogramming genes into the renal cells that made them capable of forming other cells.

In a second study, Miguel Esteban, MD, PhD (Chinese Academy of Sciences, in Guangzhou, China) and his colleagues found that kidney cells collected from a patient’s urine can also be reprogrammed in this way. Using cells from urine allows a technology easy to implement in a clinic setting. Even better, the urine cells could be frozen and later thawed before they were manipulated.

If researchers can expand the reprogrammed cells—called induced pluripotent stem cells (iPSCs)—and return them to the patient, these iPSCs may restore the health and vitality of the kidneys. In addition to providing a potentially curative therapy for patients, the breakthroughs might also help investigators to study the causes of kidney disease and to screen new drugs that could be used to treat them.
In an accompanying editorial, Ian Rogers, PhD (Mount Sinai Hospital, in Toronto, Ontario, Canada) noted that “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 any time.”

Just as exciting, the ease of collection and high frequency of reprogramming described in these articles may help improve future therapies in many other areas of medicine.

Dr. Ricardo’s co-authors include Bi Song, Jonathan Niclis, Maliha Alikhan, Samy Sakkal, Aude Sylvain, Andrew Laslett, Claude Bernard (Monash University, in Clayton, Australia); and Peter Kerr, (Monash Medical Centre, Australia, in Clayton, Australia).

Dr. Esteban’s co-authors include Ting Zhou, Christina Benda, Yinghua Huang, Xingyan Li, Yanhua Li, Xiangpeng Guo, Guokun Cao, Shen Chen, Duanqing Pei (Chinese Academy of Sciences, in Guangzhou, China); Sarah Duzinger (University of Natural Resources and Life Sciences); Lili Hao, Jiayan Wu (Chinese Academy of Sciences, Beijing, China); Yau-Chi Chan, Kwong-Man Ng, Jenny Cy Ho, Hung-Fat Tse (University of Hong Kong, Pokfulam, in Hong Kong, HKSAR, China); Matthias Wieser (University of Natural Resources and Life Sciences and Austrian Center for Industrial Biotechnology (ACIB), in Vienna, Austria); Heinz Redl (Austrian Cluster for Tissue Regeneration, Vienna, Austria); and Johannes Grillari, Regina Grillari-Voglauer (University of Natural Resources and Life Sciences and Evercyte GmbH, in Vienna, Austria).

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The articles, entitled “Generation of Induced Pluripotent Stem Cells from Human Kidney Mesangial Cells” and “Generation of Induced Pluripotent Stem Cells from Urine,” as well as the editorial “Induced Pluripotent Stem Cells from Human Kidney,” are online at http://jasn.asnjournals.org/ doi 10.1681/ASN.2010101022, doi 10.1681/ASN.2011010106 and 10.1681/ASN.2011050501

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