Stem Cells Created from Adult Kidney Cells May Help Combat Disease

By Tracy Hampton

Researchers have genetically reprogrammed adult human kidney cells to become induced pluripotent stem (iPS) cells—a feat that may help in the study of kidney diseases and the development of novel therapies to treat them.

The findings could help millions of people with kidney disease, many of whom experience progression to end-stage renal disease, which has only two treatment options: long-term dialysis or kidney transplantation. Effective alternatives are urgently needed for these patients, given the poor quality of life associated with dialysis and the increasing organ transplant waiting lists.

The study “Generation of induced pluripotent stem cells from human kidney mesangial cells” appears in the July issue of the Journal of the American Society of Nephrology.

“This research is the stepping stone for the development of iPS cells from patients with kidney disease, particularly genetic kidney disease, which has an extraordinary potential for new drug discovery and personalized medicine,” said senior author Sharon Ricardo, PhD, of Monash University in Clayton, Victoria, Australia. “It will enable researchers to understand kidney disease in a way they have never been able to before.”

Reprogramming kidney cells

Researchers have recently succeeded in reprogramming certain somatic cells to produce iPS cells. For example, pluripotent cells can be derived from mouse and human fibroblasts by the induced expression of four transcription factors (OCT4, SOX2, KLF4, and c-Myc), and iPS cell lines are available in 1985. The CDC’s recent Morbidity and Mortality Weekly Report offers recommendations to help prevent such a serious event from occurring in the future (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6010a1.htm?s_cid=mm6010a1_w).

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Recommendations Target Prevention of HIV Transmission to Transplant Recipients

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In 2009, a kidney transplant recipient in New York City received a kidney that was far from ideal—it carried HIV.

The Centers for Disease Control and Prevention (CDC) recently released the details of a public health investigation into the case, which revealed the first confirmed case of HIV transmission through organ transplantation from a living donor reported since 1989 and the first such transmission documented in the United States since laboratory screening for HIV infection became available in 1985. The CDC’s recent Morbidity and Mortality Weekly Report offers recommendations to help prevent such a serious event from occurring in the future (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6010a1.htm?s_cid=mm6010a1_w).

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Prevention of HIV

As officials work to prevent transplantation of organs infected with HIV, they question whether it should be legal to transplant organs from donors who test positive for the virus to others who test positive.

Unlike in the late 1980s, now many individuals infected with HIV are living long lives and are developing conditions such as kidney disease. Also in contrast to the beginning of the AIDS epidemic, today’s infected individuals are considered healthy enough to receive transplants.

Because transplant wait lists are so long, some experts are calling for a repeal of the National Organ Transplant Act, which was passed more than two decades ago and bans transplants from HIV-positive donors to HIV-positive recipients. Others are concerned about the ethical implications of making such a change, though they are motivated by the potential to increase the supply of organs.

Pennsylvania School of Medicine’s Scott Halpern, MD, PhD. “However, this extremely rare event provides both an opportunity for clinicians and transplant programs to revisit their practices and a useful reminder for clinicians and the public alike that no form of organ transplantation can ever be risk-free.” Halpern has published numerous articles on ethical issues related to transplantation.

Public investigation

The public health investigation was initiated after the test results for both the recipient and the donor were positive for HIV approximately one year after the transplant. During the investigation, the donor and recipient, as well as the recipient’s transplant coordinator, nephrologist, and HIV physician, and the donor’s primary care physician and transplant nephrologist, were interviewed. Medical records were also reviewed. The donor reported unprotected sex with only one male partner during the year before the transplant, including the time between his initial evaluation and organ recovery.

HIV nucleic acid testing on donor leukocytes collected 57 days before the transplant yielded negative results; however, DNA sequences for three HIV genes (envelope gp41, polymerase, and reverse transcriptase) for both chronic and acute infections from donor leukocytes were nearly identical, suggesting that the two viruses are highly related.

When to screen

In this particular case, the donor was screened by enzyme immunoassay 10 weeks before organ procurement but was not re-screened closer to the date of transplant surgery. According to the CDC, because individuals may acquire infections after such an interval, repeat testing is needed before organs are recovered from living donors.

Transplant centers should screen living donors for HIV as close to the time of organ recovery and transplantation as possible, but no longer than seven days before organ donation, using sensitive tests (such as serology and nucleic acid testing) for both chronic and acute infections from HIV-positive donors. The guideline also highlights new measures to prevent unexpected transmissions of infectious diseases from donors to recipients.

Halpern participated in an expert panel that oversaw the development of a new guideline, soon to be issued by the Centers for Disease Control and Prevention (CDC), that includes recommendations on research into the risks and benefits of the use of organs from HIV-positive donors. The guideline also highlights new measures to prevent unexpected transmissions of infectious diseases from donors to recipients.

The draft Public Health Service Guideline for Reducing Transmission of HIV, HBV, and HCV through Solid Organ Transplantation currently is in Health and Human Services clearance,” said Matthew Kuehnert, MD, the director of the CDC’s Office of Blood, Organ and Other Tissue Safety. It is being published to replace the 1994 guideline and is being issued to improve transplant patient safety and to provide providers with options for recommendations to organ procurement organizations and transplant centers. Kuhehnert said.

Pennsylvania School of Medicine’s Scott Halpern, MD, PhD, “I see no clear reason for drawing this dichotomy when similar restrictions are not placed on the donors from whom patients with hepatitis C may receive organs.”

Halpern has published numerous articles on ethical issues related to transplantation.
Infections. Nucleic acid testing can detect HIV infection before antibodies develop and are detectable by serology.

The window between the time of HIV infection and the time of development of detectable HIV-specific antibodies ranges from three to eight weeks, whereas with nucleic acid testing, the window is estimated to be eight to 10 days. Currently, the combination of HIV nucleic acid testing and serology is used to screen all donors who give blood or tissue; however, nucleic acid testing is not consistently used for screening organ donors.

The CDC recommends that all living donors be informed about modes of transmission and risk factors for HIV infection and counseled to avoid behaviors that would place them at risk for acquiring HIV infection before organ recovery. Individuals with a history of previous high-risk behaviors—such as high-risk sexual activity or use of injection drugs—that are identified during evaluation should receive individualized counseling and should be advised about specific strategies for avoiding risky behaviors. In addition, all transplant candidates should be informed during the evaluation process that despite donor screening, they have a very small risk of acquiring HIV or other infections as a result of transplantation.

"From a public health perspective, the goal is to enact policies that reduce the probability of disease transmission through organ transplantation without further restricting an already scarce organ supply," Halpern said. "The current CDC recommendations seem likely to toe that line appropriately, but follow-up will be needed to ensure that the new recommendations do not have unintended consequences such as unnecessarily delaying transplantations."

In 2009, the Living Donor Committee of the Organ Procurement and Transplantation Network (OPTN) and the United Network for Organ Sharing (UNOS) developed a voluntary guidance document for transplant programs regarding the medical evaluation of potential living donors. The document recommends that HIV testing be performed, but it does not identify the type of testing or the timing of the test.

"There is as yet no absolute testing requirement for living donors," said Connie Davis, MD, who is chair of the committee. "However, UNOS, in cooperation with transplant practitioner societies, is preparing recommendations for the medical evaluation and consent for living donors based upon current scientific knowledge and they should be ready in the next few months. This is part of the OPTN’s new mandate to establish national policy for living donation in addition to that already accomplished for deceased donation.

"Optimizing safety will be a focus of the development of this document. We recognize the unique needs and circumstances involved in living donation and must act to maintain the health and safety of donors and recipients alike," Davis said.