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Researcher eliminates viral vector in stem cell reprogramming

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Shinya Yamanaka MD, PhD, of Kyoto University and the Gladstone Institute of Cardiovascular Disease (GICD) has taken another step forward in improving the possibilities for the practical application of induced pluripotent stem (iPS) cell technology.

Previously, Dr. Yamanaka had shown that adult cells can be reprogrammed to become embryonic stem cell–like using a cancer-causing oncogene as one of the four genes required to reprogram the cells, and a virus to transfer the genes into the cells. In the last year, Dr. Yamanaka and other labs showed that the oncogene, c-Myc, is not needed. However the use of viruses that integrate into the genome prohibit use of iPS cells for regenerative medicine because of safety concerns: its integration into the cell's genome might activate or inactivate critical host genes.

Now Dr. Yamanaka's laboratory in Kyoto has eliminated the need for the virus. In a report published this week in *Science*, they showed that the critical genes can be effectively introduced without using a virus. The ability to reprogram adult cells into iPS cells without viral integration into the genome also lays to rest concerns that the reprogramming event might be dependent upon viral integration into specific genomic loci that could mediate the genetic switch.

"The iPS field and stem cell research in general is progressing rapidly," said GICD Director Deepak Srivastava, MD. "But, as Shinya has shown, each step forward reveals a new set of challenges."

Dr. Yamanka's team began this series of experiments by replacing the retrovirus with an adenoviral vector. While transfections with the genes on separate vectors didn't work, they did work when the genes were arranged in a specific order on a single vector. The same arrangement worked when the genes were incorporated into a plasmid.

To determine if the plasmid-mediated reprogrammed cells were pluripotent, the scientists transplanted the cells under the skin of immunocompromised mice. The resulting tumors contained a wide variety of cell types from all three germ layers. iPS cells injected into embryos resulted in chimeric mice with the injected cells contributing to almost all cell types.

Still, other problems remain to be solved. The efficiency of the gene transfer with the plasmid was lower than with the retrovirus. Nevertheless, this significant step moves us closer to realizing the promise of stem cells in the understanding and eventual cure of diseases.

Source: Gladstone Institutes