

Memories of the Way They Used to Be

Human iPS Cells Retain Some Gene Expression of Donor Cells

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A team of researchers from the University of California, San Diego School of Medicine and the Salk Institute for Biological Studies in La Jolla have developed a safe strategy for reprogramming cells to a pluripotent state without use of viral vectors or genomic insertions. Their studies reveal that these induced pluripotent stem cells (iPSCs) are very similar to human embryonic stem cells, yet maintain a "transcriptional signature." In essence, these cells retain some memory of the donor cells they once were.

The study, led by UCSD Stem Cell Program researcher Alysson R. Muotri, PhD, assistant professor in the Departments of Pediatrics at UCSD and Rady Children's Hospital and UCSD's Department of Cellular and Molecular Medicine, will be published online in *PLoS ONE* on September 17.

"Working with neural stem cells, we discovered that a single factor can be used to re-program a human cell into a pluripotent state, one with the ability to differentiate into any type of cell in the body" said Muotri. Traditionally, a combination of four factors was used to create iPSCs, in a technology using viral vectors - viruses with the potential to affect the transcriptional profile of cells, sometimes inducing cell death or tumors.

In addition, while both mouse and human iPSCs have been shown to be similar to embryonic stem cells in terms of cell behavior, gene expression and their potential to differentiate into different types of cells, researchers had not achieved a comprehensive analysis to compare iPSCs and embryonic stem cells.

"One reason is that previous methodologies used to derive iPSCs weren't 'footprint free,'" Muotri explained. "Viruses could integrate into the genome of the cell, possibly affecting or disrupting genes."

"In order to take full advantage of reprogramming, it is essential to develop methods to induce pluripotency in the absence of permanent changes in the genome," added Fred H. Gage, PhD, a professor in the Laboratory for Genetics at the Salk Institute and the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases.

By creating iPSCs from human neural stem cells without the use of viruses, the scientists learned something new. While the genetic transcriptional profile of the new iPSCs was closer to that of embryonic stem cells than to human neural stem cells, the iPSCs still carried a transcriptional "signature" of the original neural cell.

"While most of the original genetic memory was erased when the cells were reprogrammed, some were retained," said Muotri. He added that, in the past, it wasn't known if this was caused by the use of viral vectors. "By using a footprint-free methodology, we have shown a safe way to generate human iPSCs for clinical purposes and basic research. We've also raised an interesting question about what, if any, effect the 'memory retention' of these cells might have."

Additional contributors to the study include Gene W. Yeo, UCSD's Department of Cellular and Molecular Medicine and the UCSD Stem Cell Program; Osamu Kainohana and Martin Marsala, UCSD Department of Anesthesiology; and Maria C. N. Marchetto and Fred H. Gage, the Salk Institute for Biological Studies, La Jolla, CA.

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