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Genetic Abnormalities Discovered Associated With The Creation Of Stem Cells

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Scientists at the Samuel Lunenfeld Research Institute of Mount Sinai Hospital, Canada, and at the University of Helsinki, Finland, have identified genetic abnormalities associated with reprogramming adult cells to induced pluripotent stem (iPS) cells. The findings give researchers new insights into the reprogramming process, and will help make future applications of stem cell creation and subsequent use safer. The study will be published in *Nature*.

The team showed that the reprogramming process for generating iPS cells (i.e., cells that can then be 'coaxed' to become a variety of cell types for use in regenerative medicine) is associated with inherent DNA damage. This damage is detected in the form of genetic rearrangements and 'copy number variations,' which are alterations of DNA in which a region of the genome is either deleted or amplified on certain chromosomes. The variability may either be inherited, or caused by de *novo* mutation.

"Our analysis shows that these genetic changes are a result of the reprogramming process itself, which raises the concern that the resultant cell lines are mutant or defective," said Dr. Nagy, a Senior Investigator at the Lunenfeld. "These mutations could alter the properties of the stem cells, affecting their applications in studying degenerative conditions and screening for drugs to treat diseases. In the longer term, this discovery has important implications in the use of these cells for replacement therapies in regenerative medicine."

"Our study also highlights the need for rigorous characterization of generated iPS lines, especially since several groups are currently trying to enhance reprogramming efficiency," said Dr. Samer Hussein, a McEwen post-doctoral scientist who initiated these studies with Dr. Otonkoski, before completing them with Dr. Nagy. "For example, increasing the efficiency of reprogramming may actually reduce the quality of the cells in the long run, if genomic integrity is not accurately assessed."

The researchers used a molecular technique called single nucleotide polymorphism (SNP) analysis to study stem cell lines, and specifically to compare the number of copy number variations in both early and intermediate-stage human iPS cells with their respective parental, originating cells.

Drs. Nagy and Otonkoski and their teams found that iPS cells had more genetic abnormalities than their originating cells and embryonic stem cells. Interestingly, however, the simple process of growing the freshly generated iPS cells for a few weeks selected against the highly mutant cell lines, and thus most of the genetic abnormalities were eventually 'weeded out.'

However, some of the mutations are beneficial for the cells and they may survive during continued growth," said Dr. Otonkoski, Director and Senior Scientist at the Biomedicum Stem Cell Center.

Stem cells have been widely touted as a source of great hope for use in regenerative medicine, as well as in the development of new drugs to prevent and treat illnesses including Parkinson's disease, spinal cord injury and macular degeneration. But techniques for generating these uniquely malleable cells have also opened a Pandora's Box of concerns and ethical quandaries. Health Canada, the U.S. Food and Drug Administration and the European Union consider stem cells to be drugs under federal legislation, and as such, subject to the same regulations.

"Our results suggest that whole genome analysis should be included as part of quality control of iPS cell lines to ensure that these cells are genetically normal after the reprogramming process, and then use them for disease studies and/or clinical applications," said Dr. Nagy.

"Rapid development of the technologies in genome-wide analyses will make this more feasible in

the future," said Dr. Otonkoski. "In addition, there is a need to further explore if other methods might mitigate the amount of DNA damage generated during the generation of stem cells," both investigators agreed.

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"Copy number variation and selection during reprogramming to pluripotency"
Hussein SM, Batada N, Vuoristo S, Ching RW, Autio R, Närvä E, Ng S, Sourour M, Hämäläinen R, Olsson C, Lundin K, Mikkola M, Trokovic R, Peitz M, Brüstle O, Bazett-Jones DP, Alitalo K, Lahesmaa R, Nagy A and Otonkoski T
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