Research carries cautionary warning for future stem cell applications

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Hebrew University stem cell researchers (from left): Uri Ben-David, professor Nissim Benvenisty and Dr. Yoav Mayshar. Credit: The Hebrew University of Jerusalem

Research work carried out at the Hebrew University of Jerusalem arouses a cautionary warning in the growing field of the development of stem cells as a means for future treatment of patients through replacement of diseased or damaged tissues by using the patient's own stem cells. The research indicates a possible danger of cancerous tissue development in the use of such cells.

Embryonic stem cells, which are undifferentiated cells, have the potential to develop into all cell types of the adult body, and thousands of researchers all over the world are working to develop the techniques which will make possible their eventual application.

Research in the field has been carried out initially using embryonic stem

cells taken from human embryos. However, a breakthrough occurred when, a number of years ago, Japanese scientists succeeded in creating embryonic-like stem cells from mature human cells through an induced "reprogramming" process. This made it possible to obtain stem cells from a patient which can be used in his or her own treatment, thus avoiding the possibility of cell rejection. These cells are called induced pluripotent stem (iPS) cells.

In order for stem cells to be used in the clinic, however, they must be raised in cultures for an extended period. During this period, it has been observed that embryonic stems cells underwent chromosomal changes, which included changes that characterize cancerous tumor growth.

Research that has been carried out in the laboratory headed by Nissm Benvenisty, the Herbert Cohn Professor of Cancer Research at the Silberman Institute of Life Sciences at the Hebrew University of Jerusalem, has now shown that the iPS cells also undergo abnormal chromosomal changes in culture.

Prof. Benvenisty, together with his post-doctoral fellow Yoav Mayshar and his doctoral student Uri Ben-David, developed a new analytical method for determining the genetic structure of the chromosomes in the iPS cells through determining the cellular patterns of gene expression.

Each cell generally bears two copies of each chromosome in the genome. The Hebrew University researchers discovered that, in time, three copies of chromosomes (trisomy) began to appear in the culture, and that the cells with the extra chromosome were able to rapidly overpower the other, normal cells in the culture. Such trisomies are present in abnormal tissue development, including cancerous growths.

The researchers examined over 100 cell lines which were published by 18 different laboratories around the world, in addition to the iPS cultures

raised in their own laboratory, and in this way were able to solidly verify a great number of chromosomal changes in cell lines that until now were considered normal.

In an article published in *Cell Stem Cell* journal, the Hebrew University researchers have reported their discovery. They noted that the chromosomal changes were not incidental, but rather appeared systematically on chromosome 12 and involved up-regulation of specific genes which reside on that chromosome. This discovery is liable to hinder progress on the development of the use of human iPS cells in future therapy because of the tumorigenic danger involved.

"Our findings show that human iPS cells are not stable in culture, as was previously thought, and require reassessment of the chromosomal structure of these cells," said Prof. Benvenisty. "Also, our work shows for the first time the gene expression changes that accompany these chromosomal aberrations found in the culture, paving the way for our beginning to understand the mechanism by which these changes occur.

"The chromosomal changes in these iPS cells require everyone to exercise great care in continuing to work with them, since these changes apparently will influence the differentiation potential and the tumorigenic risk of these cells."

According to Prof. Benvenisty, "The method we have developed for identifying chromosomal changes through gene expression is likely to serve also in other work involving analysis of different kinds of cells, including cancer cells. It is relatively simple to use and enables one to observe the changes without having to directly analyze the DNA of the cells." The discovery is patented by Yissum, the Technology Transfer Company of the Hebrew University of Jerusalem, which is currently searching for commercial partners for further research and development.

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Provided by Hebrew University of Jerusalem

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