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UCLA STEM CELL RESEARCHERS USE HIGH RESOLUTION TECHNOLOGY TO EXAMINE THE GENOME OF HUMAN EMBRYONIC STEM CELLS

Technique Should Aid Scientists in Determining Quality of Stem Cell Lines Used to Treat Human Diseases

Stem cell researchers from UCLA used a high resolution technique to examine the genome, or total DNA content, of a pair of human embryonic stem cell lines and found that while both lines could form neurons, the lines had differences in the numbers of certain genes that could control such things as individual traits and disease susceptibility.

The technique used to study the genome, which contains all the genes on 46 chromosomes, is called array CGH. The use of higher resolution techniques, such as array CGH and, soon, whole genome sequencing, will enhance the ability of researchers to examine stem cell lines to determine which are best – least likely to result in diseases and other problems – to use in creating therapies for use in humans.

Array CGH provided a much better look at the gene content on the chromosomes of human embryonic stem cells, with a resolution about 100 times better than standard clinical methods. Clinical specialists commonly generate a karyotype to examine the chromosomes of cancer cells or for amniocentesis in prenatal diagnosis, which has a much lower resolution than Array CGH, said Michael Teitell, a researcher with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and the senior author of the study. Small defects that could result in big problems later on could be missed using karyotyping for stem cells.

“Basically, this study shows that the genetic makeup of individual human embryonic stem cell lines is unique in the numbers of copies of certain genes that may control traits and things like disease susceptibility,” said Teitell, who also is an associate professor of pathology and laboratory medicine and a researcher at UCLA’s Jonsson Comprehensive Cancer Center. “So, in choosing stem cell lines to use for therapeutic applications, you want to know about these differences so you don’t pick a line likely to cause problems for a patient receiving these cells.”

The study appears in the March 27, 2008 express edition of the journal *Stem Cells*.

Differences between individual DNA sequences provide the basis for human genetic variability. Forms of variation include single DNA base pair alterations,

duplications or deletions of genes or sets of genes, and translocations, a chromosomal rearrangement in which a segment of genetic material from one chromosome becomes heritably linked to another chromosome. These changes can be benign, but they can also promote diseases such as certain cancers, or confer increased risk to other diseases, such as HIV infection or certain types of kidney ailments.

In this study, Teitell and his team sought to determine copy number variants (CNVs), or differences in the numbers of certain genes, in two embryonic stem cell lines. The CNVs provide a unique genetic fingerprint for each line, which can also indicate relatedness between any two stem cell lines. Teitell used embryonic stem cell lines that made different types of neurons and studied them with array CGH for comparison. His team found CNV differences between the two lines in at least seven different chromosome locations below the level of detection using standard karyotype studies. Such differences could impact the therapeutic utility of the lines and could have implications in disease development. More studies will be required to determine the effect of specific CNVs in controlling stem cell function and disease susceptibility, he said.

“In studying embryonic stem cell lines in the future, if we find differences in regions of the genome that we know are associated with certain undesirable traits or diseases, we would choose against using such stem cells, provided safer alternative lines are available,” Teitell said.

Large genome-wide association studies are underway in a variety of diseases to determine what genetic abnormalities might be at play. When the genetic fingerprint or predisposing genes for a certain disease is discovered, it could be used as key information in screening embryonic stem cell lines.

The Institute for Stem Cell Biology and Medicine was launched in 2005 with a UCLA commitment of \$20 million over five years. A \$20 million gift from the Eli and Edythe Broad Foundation in 2007 resulted in the renaming of the Institute. With more than 150 members, the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research is committed to a multi-disciplinary, integrated collaboration of scientific, academic and medical disciplines for the purpose of understanding human adult and embryonic stem cells. The institute supports innovation, excellence and the highest ethical standards focused on stem cell research with the intent of facilitating basic scientific inquiry directed towards future clinical applications to treat disease. The center is a collaboration of the David Geffen School of Medicine, UCLA’s Jonsson Cancer Center, the Henry Samueli School of Engineering and Applied Science and the UCLA College of Letters and Science. To learn more about the center, visit our web site at <http://www.stemcell.ucla.edu/>.