High-res technology shows significant differences in stem cell lines

April 3 2008

UCLA stem cell researchers using a high-resolution technique to examine the genome of a pair of human embryonic stem cell lines have found that while both lines could form neurons, they differed in the numbers of certain genes that could control such things as individual traits and disease susceptibility. The study appears in the April issue of the peer-reviewed journal *Stem Cells.*

The researchers used a technique known as array CGH (comparative genomic hybridization) to study the total DNA content of the lines, all the genes on 46 chromosomes. The use of higher-resolution techniques like array CGH and, soon, whole-genome sequencing will enhance the ability of researchers to examine stem cell lines to determine which are best — or least likely to result in diseases and other problems — for creating therapies for use in humans.

Array CGH provided a much better look at the gene content on the chromosomes, with a resolution about 100 times better than standard clinical methods. Clinical specialists commonly generate a karyotype — a technique involving the staining and photographing of a cell sample — to examine the chromosomes of cancer cells or for amniocentesis in prenatal diagnosis; karyotyping 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 at UCLA 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."

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 — chromosomal rearrangements 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 the 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 — differences that could not have been detected 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.

Source: UCLA