Stem cell study advances regenerative medicine research

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Researchers from A*STAR Singapore took lead roles in a study that identified a portion of the genome mutated during long-term culture of human embryonic stem cells (hESCs). The study was a worldwide collaboration, led by Drs Peter Andrews of the University of Sheffield (UK), Paul Robson of the Genome Institute of Singapore (GIS), Steve Oh of Singapore's Bioprocessing Technology Institute (BTI), and Barbara Knowles and others in the international stem cell community.

Involving 125 ethnically diverse hESC lines originating from 38 laboratories globally, and now identified to represent multiple ethnic groups from different parts of the globe, the study is the largest to be conducted on the genetic stability of cultured hESCs. The findings are published today in the journal *Nature Biotechnology*.

Research into the variability of hESCs is very important as these cells may lead to future cell therapy and regenerative medicine. During long-term culture, however, these cells can acquire genetic changes (mutations), some of which could compromise the cells' utility for regenerative medicine. It is believed that mutations that arise and endure over long-term culture provide a selective advantage for the cells, such as a greater propensity for self renewal.

The study re-emphasized that many chromosome changes occur repeatedly, resulting in increased copies in specific areas of the genome. Interestingly, through molecular karyotyping performed in Dr Robson's laboratory at the GIS, about 20% of the karyotypically normal cell lines

exhibited subkaryotypic amplifications of a specific region in chromosome 20. This is also one of the karyotypically defined areas of change. The minimal region common to these cells contains three ES-cell expressed genes, and one of them, BCL2L1, is a strong candidate for driving hESC culture adaptation. The data generated in this study will be useful for understanding the frequency and types of genetic changes affecting cultured hESCs, an important issue in evaluating the cells for potential therapeutic applications.

Dr Paul Robson, Senior Group Leader of the Developmental Cellomics Laboratory, GIS, said: “Not only does this work provide important information for evaluating human embryonic stem cell genetic integrity, it also highlights the general utility of these cells in understanding human biology and disease. This same region has recently been identified to repeatedly occur in numerous human cancer cell types, this likely indicative of similar selection pressures at play in stem cells and cancer cells. Interestingly, we found the propensity for mutation at this location is associated with a relatively recent chromosomal rearrangement that occurred in the last common ancestor of the human, chimp, and gorilla thus pointing to the value of having a comparative perspective for understanding human biology.”

Dr Barbara Knowles, Principle Investigator at IMB added: “This is a prodigious piece of community work comparing the genome of cell lines from around the world that were sampled after they had been grown in cell culture for a short period of time to samples from the same cell lines taken after they had been in culture for a longer period of time. Scientists at GIS used these globally obtained samples to pinpoint an area of the genome that contains a gene(s) that affects the cell’s ability to control its own growth.”

Dr Steve Oh, Principal Scientist at BTI said: “This study took over three years to complete and is a great testimony of the international stem cell

community working persistently together as a force for good. A special thanks goes to Prof Peter Andrews for his leadership! The fact that of the 125 cell lines tested, over 65% of them exhibited normal karyotypes in long term culture bodes well for the use of human embryonic stem cells for cell therapy in the future."

More information: "Screening a large, ethnically diverse population of human embryonic stem cells identifies a chromosome 20 minimal amplicon that confers a growth advantage", *Nature Biotechnology*, dx.doi.org/10.1038/10.1038/nbt.2051

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