MedicalXpress

Scientists discover ancient viral invasion that shaped human genome

June 7 2010

Scientists at the Genome Institute of Singapore (GIS) and their colleagues from the National University of Singapore, Nanyang Technological University, Duke-NUS Graduate Medical School and Princeton University have recently discovered that viruses that 'invaded' the human genome millions of years ago have changed the way genes get turned on and off in human embryonic stem (ES) cells.

The study provides definitive proof of a theory that was first proposed in the 1950s by Nobel Laureate in physiology and medicine, Barbara McClintock, who hypothesized that transposable elements, mobile pieces of the genetic material (DNA), such as viral sequences, could be "control elements" that affect gene regulation once inserted in the genome.

This finding is an important contribution to the advancement of stem cell research and to its potential for regenerative medicine. Led by GIS Senior Group Leader Dr Guillaume Bourque, the study was published in Nature Genetics on June 6, 2010.

Through the use of new sequencing technologies, the scientists studied the genomic locations of three regulatory proteins (OCT4, NANOG and CTCF) in human and mouse embryonic stem (ES) cells. Interestingly, while the scientists found a lot of similarities, they also found many differences in the methods and the types of genes that are being regulated in humans. In particular, it was discovered that specific types of viruses that inserted themselves in the human genomes millions of years ago have dramatically changed the gene regulatory network in

human stem cells.

"This study is a computational and experimental tour de force. It provides undeniable evidence that some transposable elements, which are too often dismissed as merely junk DNA, are key components of a regulatory code underlying human development," said Dr Cedric Feschotte, Associate Professor of the University of Texas Arlington.

The comparisons between the human and mouse model system in the study of gene regulatory networks help to advance the understanding of how stem cells differentiate into various cell types of the body. "This understanding is crucial in the improved development of regenerative medicine for diseases such as Parkinson's disease and leukaemia," said Dr Bourque. "Despite the advantages of using mouse ES cells in the study of gene regulatory networks, further research must focus more directly on human stem cells. This is due to the inherent challenges of converting the results of studies done from one species to that of the next. More research will need to be done in both human and non-human primate stem cells for findings on stem cells to be used in clinical application."

Prof Raymond L. White, PhD, Rudi Schmid Distinguished Professor of Neurology, University of California said, "The paper reports very exciting new findings that establish a new and fundamentally distinct mechanism for the regulation of gene expression. By comparing the genomes of mouse with human, the scientists were able to show that the binding sites for gene regulatory factors are very often not in the same place between the two species. This by itself would be very surprising, but the investigators go further and demonstrate that many of the sites are imbedded within a class of DNA sequences called "transposable" elements because of their ability to move to new places in the genome. There are a number of such elements believed to be the evolutionary remnants of viral genomes, but it was very surprising to learn that they

were carrying binding sites for regulatory elements to new locations. These changes in regulation would be expected to create major changes in the organisms which carry them. Indeed, many think that regulatory changes are at the heart of speciation and may have played a large role in the evolution of humans from their predecessors. This is likely to be a landmark paper in the field."

Dr Eddy Rubin, Director of the U.S. Department of Energy Joint Genome Institute and Director of the Genomics Division at Lawrence Berkeley National Laboratory in Berkeley added, "This study using a comparative genomics strategy discovered important human specific properties of the regulatory network in human ES cells. This information is significant and should contribute to helping move the regenerative medicine field forward."

Provided by Agency for Science, Technology and Research (A*STAR)