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Human embryonic stem cells remain embryonic because of epigenetic factors

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A human embryonic stem cell is reined in – prevented from giving up its unique characteristics of self-renewal and pluripotency – by the presence of a protein modification that stifles any genes that would prematurely instruct the cell to develop into heart or other specialized tissue. But, thanks to the simultaneous presence of different protein modifications, stem cells are primed and poised, ready to develop into specialized body tissue, Singapore scientists reported in last month's issue of the journal *Cell Stem Cell*.

The molecules central to this balancing act, H3K4me3 and H3K27me3, are among the so-called epigenetic modifications that influence the activity patterns of genes in both human embryonic stem (ES) cells and mature human adult cells.

Determining how ES cell genes are modified by these epigenetic markers may explain these cells' unique characteristics, said the scientists, who are based at the Genome Institute of Singapore (GIS) and the Bioprocessing Technology Institute (BTI), both under the Agency for Science, Technology and Research (A*STAR), as well as at the National University of Singapore (NUS).

The scientists also discovered that genes modified only by one of the epigenetic markers, H3K4me3, contain the DNA recipes for proteins that enable an ES cell to proliferate, or duplicate itself. In the Cell Stem Cell paper, the scientists wrote, "The prevalence of these genes may be related to the self-renewal property of ES cells."

The scientists also found that the genes that do not carry either of the two epigenetic modifications are completely silenced in ES cells. These genes, which are crucial to sensory processes, immunity, and drug metabolism, are active in highly specialized, mature adult cells.

Although epigenetic markers attach themselves to the tightly wound bundle of protein material called histones that package and compress the DNA in the nucleus of each human cell, they do not change the cell's DNA code. Therefore, epigenetic markers are not permanent.

If they were permanent, ES cells would never be able to differentiate into heart, kidney, brain, bone, skin and the other specialize cells crucial to normal human functioning.

"This discovery will advance our understanding of stem cell epigenetics and chromatin structures, provide potential mechanisms on maintaining the hallmark properties of ES cells, and help researchers with the rich source of information to better understand some of the unique features – such as self-renewal and pluripotency – of human embryonic stem cells," said Ng Huck Hui, Ph.D., senior group leader at GIS and a member of the Singapore team that conducted this research.

Such findings, Dr. Ng added, "will ultimately lead to the development of new therapies and clinical treatments."

His GIS colleague, Wei Chia-Lin, Ph.D., who headed the Singapore research team, said, "This study demonstrates the power of a whole genome and robust sequencing technology, when applied in the epigenetic analysis of ES cells, can reveal features of the genomes that were not previously appreciated. The new knowledge and target candidate genes resulted from such unbiased study are ultimately important for researchers to understand the fundamental nature of stem cell proliferation and differentiation."

Drs. Wei and Ng and the other researchers used cutting-edge technologies developed at GIS, to sequence, or decipher, the DNA of human ES cells. With the sequence data in hand, the scientists were able to categorize the genes into three groups, each modified by different combinations of the two epigenetic markers.

The researchers discovered that the majority of the regions in the genome harbor active histone marks that act as sign posts and allow cells to quickly find genes “to turn on” or activate them.

Identifying the locations of these genomic signposts will also be crucial for discovering human genes that are important for different functions in ES cells.

Of the two epigenetic markers, H3K4me3 was found to be the most prevalent – the scientists reported and noted that it occurs near the DNA areas that are promoters of two-thirds of human genes. Of the 17,469 nonredundant unique human genes that the scientists sequenced, 68% contained H3K4me3, and only 10% contained overlapping H3K27me3.

More information about epigenetic modifications:

In living cells, DNA is packaged along with histone proteins, which are chief protein components that act as spools around which DNA winds. The histone proteins are decorated with different marks, which can affect the various activities of the modified DNA such as transcription, gene silencing, imprinting and replication. Such marks key roles in the process of cellular differentiation, allowing cells to maintain different characteristics despite containing the same genomic material. While different cells can have identical genetic DNA sequences, their characteristics and differentiation patterns are influenced by the different marks on the histone proteins. Therefore, histone marks represent an epigenetic marker or code that can be used by the cells to

expand their plasticity and complexity.

Source: Agency for Science, Technology and Research, Singapore