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Study reveals dynamic changes in gene regulation in human stem cells

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A team led by scientists at The Scripps Research Institute and the University of California (UC) San Diego has discovered a new type of dynamic change in human stem cells.

Last year, this team reported recurrent changes in the genomes of human pluripotent stem cells as they are expanded in culture. The current report, which appears in the May 4, 2012 issue of the journal *Cell Stem Cell*, shows that these cells can also change their epigenomes, the patterns of DNA modifications that regulate the activity of specific genes—sometimes radically. These changes may influence the cells' abilities to serve as models of human disease and development.

"Our results show that human pluripotent stem cells change during expansion and differentiation in ways that are not easily detected, but that have important implications in using these cells for basic and clinical research," said team leader Louise Laurent, assistant professor in the UC San Diego School of Medicine.

Human pluripotent stem cells can give rise to virtually every type of cell in the body. Because of this remarkable quality, they hold huge potential for cell replacement therapies and drug development.

Many avenues of stem cell research focus on determining how genes are turned on and off during the course of normal development or at the onset of a disease transformation. It is widely accepted that gene activation and silencing play important roles in transforming all-purpose stem cells into the specific adult cell types that make up the specialized tissues of organs such as the heart and brain.

In the new study, Laurent and her collaborator, Professor Jeanne Loring of Scripps Research, and their colleagues focused on understanding gene silencing via DNA methylation, a process whereby bits of DNA are chemically marked with tags that prevent the genes from being expressed, effectively switching them off. Errors in gene silencing via DNA methylation are known contributors to serious developmental defects and cancer.

Specifically, the team assessed the state of both DNA methylation and gene expression in the most comprehensive set of human stem cell samples to date, comprised of more than 200 human pluripotent stem cell samples from more than 100 cell lines, along with 80 adult cell samples representing 17 distinct tissue types. The researchers used a new global DNA methylation array, developed in collaboration with Illumina, Inc, which detects the methylation state of 450,000 sites in the human genome. The results showed surprising changes in patterns of DNA methylation in the stem cells. Because of the unprecedented breadth of the study, the researchers were able to determine the frequency of different types of changes.

One of the anomalies highlighted by the study centers on X chromosomes. Since female cells contain two X chromosomes and males only one, one of the X chromosomes in females is normally silenced by DNA methylation through a process called X-chromosome inactivation (XCI). The new study demonstrated that a majority of female human pluripotent stem cells cultured in the lab lost their X chromosome inactivation over time, resulting in cells with two active X chromosomes.

This phenomenon could affect stem cell-based models of diseases caused by mutations of the X chromosome, such as Lesch-Nyhan disease, the researchers note. These cell-based models require that only the diseased copy of an X-linked gene be expressed, with the normal copy of the gene in females silenced via XCI. As the originally inactive X chromosome becomes active, the normal copy of the gene is expressed, changing the phenotype of the cells from diseased to normal.

"If an X chromosome that was assumed to be inactive is actually active, scientists may find that their cells perplexingly change from mutant to normal over time in culture," Loring said.

Another epigenomic aberration noted in pluripotent cells was in imprinted genes. Human cells contain two copies of most genes: one inherited from the mother and one from the father. In most cases, both the maternal and paternal copies of a gene are expressed equally. This is not the case, however, for imprinted genes, some of which are only expressed from the paternal chromosomes and others expressed only from the maternal chromosomes. This parent-of-origin specific gene expression involves silencing of one of the copies of the gene. Abnormalities in this selective silencing of genes can lead to serious developmental diseases.

The study found that, while the patterns of DNA methylation required to maintain imprinted gene silencing were stable in all of the somatic tissues, surprisingly, frequent aberrations in the patterns of DNA methylation existed in imprinted genes in the stem cells. Some of these aberrations arose very early in the establishment of the cell lines, while others crept in with the passage of time.

Interestingly, the team was able to link at least some of these aberrations to the conditions under which the stem cells were cultured in the lab. This suggests that researchers who use stem cells to study diseases linked to genomic imprinting will need to use conditions that best maintain imprinted gene silencing.

The researchers found another surprise—this one having to do with the basic process by which stem cells become specialized adult cells. Scientists have assumed that most genes are active at the earliest stages of human development, and that unnecessary ones are switched off as the cells developed specialized functions.

"For example, during the process of differentiation from a stem cell into a neuron, you might expect to observe silencing of all the genes that are important for the kidney, the pancreas, and the liver," said Kristopher Nazor, a Scripps Research Kellogg School of Science and Technology graduate student who is lead author of the study. "But we found something quite different."

When the team compared stem cells with adult cells taken from tissue samples, rather than seeing mostly active genes in the stem cells and selectively silenced genes in the adult ones, they saw the opposite: in the stem cells, the researchers found that genes linked to the development of specialized tissue cells were silent and methylated, while in the adult cells regions of DNA involved in cell type specification were active and unmethylated. The scientists could reproduce some aspects of the developmental changes in culture: when stem cells were differentiated into neural cells in the culture dish, the patterns of DNA methylation became similar to those seen in human brain tissue.

This implies that, contrary to conventional wisdom, the genes responsible for transforming stem cells into tissue cells were initially silent, and were switched on during the process of differentiation.

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