Scientists reveal how induced pluripotent stem cells differ from embryonic stem cells

November 5 2009

The same genes that are chemically altered during normal cell differentiation, as well as when normal cells become cancer cells, are also changed in stem cells that scientists derive from adult cells, according to new research from Johns Hopkins and Harvard.

Although genetically identical to the mature body cells from which they are derived, induced pluripotent stem cells (iPSCs) are notably special in their ability to self-renew and differentiate into all kinds of cells. And now scientists have detected a remarkable if subtle molecular disparity between the two: They have distinct "epigenetic" signatures; that is, they differ in what gets copied when the cell divides, even though these differences aren't part of the DNA sequence.

"Relatively little study has been done on the epigenetic nature of stem cells," says Andrew Feinberg, M.D., M.P.H., a professor of medicine at the Johns Hopkins University School of Medicine. "To date, the bulk of what is known about stem cells is focused on how you create them and grow them and so forth, but not on the essence of them, and what is fundamentally different about these cells."

To compare and contrast mature connective tissue cells called fibroblasts with the pluripotent stem cells into which they were reprogrammed, the investigators focused on a chemical change known as methylation. This chemical change which, associated with silencing genes, is classified as epigenetic because, although not part of the DNA sequence, is copied when a cell divides. They identified and then measured so-called

differentially methylated regions (DMRs) of genes whose expression was changed in the process of being reprogrammed from a parent cell to a stem cell.

Building on previous research that looked at where differently methylated sites were located in cancer cells, as well as on research that had shown these same sites matching up with many of the methylated areas that had been implicated in the differentiation of normal brain, liver and spleen tissues, the team discovered that the reprogramming of a cell to become a stem cell apparently involves many of the very same DMRs and genes.

"The surprise," says Feinberg, "is that there is such a degree of overlap between the differently methylated regions and genes that are involved in turning a fibroblast into a stem cell and turning a normal cell into a cancer cell."

The study, done jointly with George Q. Daley, M.D., Ph.D., and colleagues from Harvard University, was published Nov. 1 in the advanced online edition of *Nature Genetics*. The researchers suggest in the study that certain sites throughout the genome appear to be generally involved in distinguishing DNA methylation among different cell types and cancers, and these same sites are involved in reprogramming fibroblasts back into stem cells.

The scientists used the CHARM method (comprehensive high-throughput arrays for relative methylation) to survey where, across the genomes of nine human iPS cell lines, genes had been silenced, or turned off, and then compared these DNA methylation sites with those of the fibroblasts the iPS cells were derived from.

"This type of research gets to the fabric of the fundamental differences between stem cells and their parental cells," says Akiko Doi, a doctoral

candidate in the graduate program in Cellular and Molecular Medicine at Johns Hopkins. "Clearly, that fabric involves these DMRs, which are essential to our understanding the nature of these potentially therapeutic iPS cells."

As scientists learn more about the epigenetics of reprogrammed cells, they may find new ways of creating them or using them. "If we discover that certain genes or regions are altered in iPS cells," says Feinberg, "then we might be able to target these and come up with new ways of approaching stem cell therapy.

"We can try to correlate these differences with the ways these iPS cells behave, and answer questions such as which ones are more stable and which ones form tumors. If we can use the epigenetic information to characterize these cells, this could inform how we might use them therapeutically."

Adds Daley, director of the Stem Cell Transplantation Program at HHMI/Children's Hospital in Boston, "Our data also point to differences between iPS cells and embryonic stem (ES) cells, which everyone has felt were similar if not identical. Such differences may prove important in the behavior of iPS cells in studies on tissue formation and may complicate therapies based on iPS cells. We need to develop ways of generating iPS cells that are a closer match to ES cells in their methylation patterns. Only then will we be confident that iPS cells are a safe replacement for ES cells in research and therapy."

Source: Johns Hopkins Medical Institutions

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