Pluripotent and differentiated human cells reside in decidedly different epigenomic landscapes

May 6 2010

Human embryonic stem cells (hESCs) possess remarkable properties of self-renewal and pluripotency, the ability to become almost any kind of cell within the body. And yet they share the same genome or set of genes with lineage-committed cells, cells fated to be or do one thing.

Scientists have long suspected that the distinct properties of different cells were attributable to their particular epigenomes - the collection of attendant molecules, compounds and chemicals that direct and influence the behaviors and functions of genes. The question has been: how much do the epigenomes of hESCs and lineage-committed cells differ? The answer was not clear.

In a paper published in the May 7 issue of *Cell Stem Cell*, Bing Ren, PhD, a professor of cellular and molecular medicine at the University of California, San Diego and a member of the Ludwig Institute for Cancer Research, reports with colleagues that the epigenomic landscapes of hESCs and lineage-committed cells are, in fact, drastically different.

"You can think of it this way," said Ren. "Neurons and skin cells share the identical set of genetic material - DNA - yet their structure and function are very different. The difference can be attributed to differences in their epigenome. This is analogous to computer hardware and software. You can load the same computer with distinct operating systems, such as Linux or Windows, or with different programs and the

computer will run very different types of operations.

"Similarly, the unique epigenome in each cell directs the cell to interpret its genetic information differently in response to common environmental factors. Understanding the differences of epigenomic landscapes in different cell types, especially between pluripotent and lineage-committed cells, is essential for us to study human development and mechanisms of human diseases."

To compare these epigenomic landscapes, Ren and colleagues looked at chromatin-modification profiles and DNA methylomes in hESCs and primary fibroblasts, the latter a type of cell commonly found in animal connective tissues. Chromatin is a complex combination of DNA and proteins that makes up chromosomes. The basic component of the chromatin is a complex of proteins called histones. Histone proteins can be chemically modified depending upon the contexts of the underlying gene sequences and can influence gene activities locally.

The scientists found that nearly one-third of the genome differs in chromatin structure. Most of the changes arise from dramatic redistributions of repressive chromatin modifications that involve the addition of methyl-groups to particular lysine residues on the histone protein.

"A fundamental question is how the identical genome sequence gives rise to a diversity of cell types with different gene expression profiles and cellular functions," said David Hawkins of the Ludwig Institute and co-first author of the study. "We've found evidence that lineage-committed cells are characterized by significantly expanded domains of repressive chromatin that selectively affect genes involved in pluripotency and development. In other words, these epigenetic mechanisms play a critical role in deciding a cell's fate and function, and in maintaining it."

The findings are likely to push forward the emerging science of epigenetics, which seeks to identify the processes that impact gene regulation and help determine human development and disease. Ren is director of The San Diego Epigenome Center at the Ludwig Institute. San Diego is one of four centers in the United States participating in the National Institutes of Health's Roadmap Epigenomics Program, a five-year, $190 million effort.

Provided by University of California - San Diego