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Mapping the embryonic epigenome

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A large, multi-institutional research team involved in the NIH Epigenome Roadmap Project has published a sweeping analysis in the current issue of the journal *Cell* of how genes are turned on and off to direct early human development. Led by Bing Ren of the Ludwig Institute for Cancer Research, Joseph Ecker of The Salk Institute for Biological Studies and James Thomson of the Morgridge Institute for Research, the scientists also describe novel genetic phenomena likely to play a pivotal role not only in the genesis of the embryo, but that of cancer as well. Their publicly available data, the result of more than four years of experimentation and analysis, will contribute significantly to virtually every subfield of the biomedical sciences.

After an egg has been fertilized, it divides repeatedly to give rise to every cell in the human body—from the patrolling immune cell to the pulsing neuron. Each functionally distinct generation of cells subsequently differentiates itself from its predecessors in the developing embryo by expressing only a selection of its full complement of genes, while actively suppressing others. "By applying large-scale genomics technologies," explains Bing Ren, PhD, Ludwig Institute member and a professor in the Department of Cellular and Molecular Medicine at the UC San Diego School of Medicine, "we could explore how genes across the genome are turned on and off as embryonic cells and their descendant lineages choose their fates, determining which parts of the body they would generate."

One way cells regulate their genes is by DNA methylation, in which a molecule known as a methyl group is tacked onto cytosine—one of the

four DNA bases that write the genetic code. Another is through scores of unique chemical modifications to proteins known as histones, which form the scaffolding around which DNA winds in the nucleus of the cell. One such silencing modification, called H3K27me3, involves the highly specific addition of three methyl groups to a type of histone named H3. "People have generally not thought of these two 'epigenetic' modifications as being very different in terms of their function," says Ren.

The current study puts an end to that notion. The researchers found in their analysis of those modifications across the genome—referred to, collectively, as the epigenome—that master genes that govern the regulation of early embryonic development tend largely to be switched off by H3K27me3 histone methylation. Meanwhile, those that orchestrate the later stages of cellular differentiation, when cells become increasingly committed to specific functions, are primarily silenced by DNA methylation.

"You can sort of glean the logic of animal development in this difference," says Ren. "Histone methylation is relatively easy to reverse. But reversing DNA methylation is a complex process, one that requires more resources and is much more likely to result in potentially deleterious mutations. So it makes sense that histone methylation is largely used to silence master genes that may be needed at multiple points during development, while DNA methylation is mostly used to switch off genes at later stages, when cells have already been tailored to specific functions, and those genes are less likely to be needed again."

The researchers also found that the human genome is peppered with more than 1,200 large regions that are consistently devoid of DNA methylation throughout development. It turns out that many of the genes considered master regulators of development are located in these regions, which the researchers call DNA methylation valleys (DMVs).

Further, the team found that the DMVs are abnormally methylated in colon cancer cells. While it has long been known that aberrant DNA methylation plays an important role in various cancers, these results suggest that changes to the cell's DNA methylation machinery itself may be a major step in the evolution of tumors.

Further, the researchers catalogued the regulation of DNA sequences known as enhancers, which, when activated, boost the expression of genes. They identified more than 103,000 possible enhancers and charted their activation and silencing in six cell types. Researchers will in all likelihood continue to sift through the data generated by this study for years to come, putting the epigenetic phenomena into biological context to investigate a variety of cellular functions and diseases.

"These data are going to be very useful to the scientific community in understanding the logic of early human development," says Ren. "But I think our main contribution is the creation of a major information resource for biomedical research. Many complex diseases have their roots in early human development."

Laboratories led by Michael Zhang, at the University of Texas, Dallas, and Wei Wang, at the University of California, La Jolla, contributed extensively to the computational analysis of data generated by the epigenetic mapping.

Provided by Ludwig Institute for Cancer Research

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