WHAT'S HOT IN... BIOLOGY , November/December 2008

Newfound Lands Added to the Genomic Atlas

by Jeremy Cherfas

PDF

What do you get when you cross genome-wide mapping with stem-cell analysis? A very highly cited paper—and the opening of whole new continents for the cartographers of the genome to explore. At # 5, from Bradley Bernstein and Eric Lander and their colleagues at the Broad Institute of Harvard and MIT, is a paper that uses a new DNA-sequencing technique to shed light on cell regulation.

The paper explores the fundamental differences between genetic and epigenetic changes. Genetic changes, to the DNA itself, are obviously crucial to the ways in which cells operate, and are passed from generation to generation. Epigenetic changes affect the way that the DNA is acted on, and they too can be passed from generation to generation. Most of these epigenetic changes involve changes in interactions between histones and other proteins and specific areas of the DNA. The DNA-protein complex is known as chromatin, and as the DNA wraps around the proteins it forms structures called nucleosomes that influence the transcription of the DNA. Other chemical groups attached to the chromatin, often methyl groups on specific residues, can change the structure of the nucleosome, and researchers believed that these "marks" were linked to the on-off switches that determine whether genes are expressed.

One important type of epigenetic change takes place as cells differentiate, first from embryonic stem cells, which can become any type of cell, to pluripotent stems cells,

Biology Top Ten Papers

Rank	Papers	Cites Mar-Apr 08	Rank Jan-Feb 08
1	E. Bettelli, *et al.*, "Reciprocal developmental pathways for the generation of pathogenic effector T_H17 and regulatory T cells," *Nature*, 441(7090): 235-8, 11 May 2006. [Harvard Med. Sch., Boston, MA] *040YP	52	1
2	K. Takahashi, *et al.*, "Induction of pluripotent stem cells from adult human fibroblasts by defined factors," *Cell*, 131(5): 861-72, 30 November 2007. [Kyoto U., Japan; CREST, Kawaguchi, Japan; Gladstone Inst. Cardio. Dis., San Francisco, CA] *243MG	41	†
3	M. Wernig, *et al.*, "*In vitro* reprogramming of fibroblasts into a pluripotent ES-cell-like state," *Nature*, 448(7151): 318-24, 19 July 2007. [5 U.S. institutions] *191GC	40	7
4	The ENCODE Project Consortium (E. Birney, *et al.*), "Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project," *Nature*, 447(7146): 799-816, 14 June 2007. [80 institutions worldwide] *178FV	39	2

which can become any one of a restricted range of cell types, to the final differentiated cell, which (unless tinkered with) can only divide into the same type of cell. Another type is known as epigenetic imprinting; the expression of the gene depends on other genes that were present in one of the parents. These changes are definitely linked to changes in the chromatin state of the DNA, but exactly how has hitherto been a mystery.

Current methods for studying chromatin use an antibody to one of the proteins to seek out nucleosomes that include that protein. Chromatin-enriched immunoprecipitation (ChIP) DNA can then be sequenced using a DNA micro-array. This technique—known as ChIP-chip—is fine for an individual nucleosome of interest, but it does not scale well, making it less useful for a genome-wide view of chromatin. Instead, the Harvard group adopted a new DNA sequencing technique that promises to be much cheaper and quicker than anything to date. (A paper in *Cell* [A. Barski, *et al.*,, 129(4): 823-7, 2007], by a team led by Keji Zhao of the National Heart, Lung, and Blood Institute in Bethesda, Maryland, describing an almost identical approach, narrowly missed the Top Ten this time around but seems certain to return.)

The sequencing method, developed by Illumina/Solex, attaches single copies of small random fragments of DNA to spots on a glass surface. These are then amplified in situ, resulting in a tuft of identical fragments of DNA at each spot. Fluorescent tags then allow researchers to visualize each letter in the sequence in turn and finally massive computing power assembles the millions of tiny fragments into a coherent overall sequence. The Harvard/MIT group put this new technique, which they call ChIP-seq, to work on ChIP DNA from three types of cell, representing different levels of differentiation: embryonic stem cells, neural progenitor cells, and embryonic fibroblasts. For each, they prepared ChIP samples of histones with specific marks and for RNA polymerase II, which is involved in transcribing active parts of the DNA. The end result was 18 chromatin-state maps.

5	P.R. Mangan, *et al.*, "Transforming growth factor-ß induces development of the T_H17 lineage," *Nature*, 441 (7090): 231-4, 11 May 2006. [U. Alabama, Birmingham; NIDCD, NIH, Bethesda, MD] *040YP	38	4
6	A. Barski, *et al.*, "High-resolution profiling of histone methylations in the human genome," *Cell*, 129(4): 823-37, 18 May 2007. [NHLBI, NIH, Bethesda, MD; U. Calif., Los Angeles] *172FA	38	†
7	D.F. Easton, *et al.*, "Genome-wide association study identifies novel breast cancer susceptibility loci," *Nature*, 447 (7148): 1087-93, 28 June 2007. [87 institutions worldwide] *183HT	37	†
8	K. Okita, T. Ichisaka, S. Yamanaka, "Generation of germline-competent induced pluripotent stem cells," *Nature*, 448(7151): 313-7, 19 July 2007. [Kyoto U., Japan; Japan Sci. Tech. Agency, Kawaguchi] *191GC	35	5
9	Intl. HapMap Consortium (K.A. Frazer, *et al.*), "A second generation human haplotype map of over 3.1 million SNPs," *Nature*, 449(7164): 851-61, 18 October 2007. [72 institutions worldwide] *221LY	31	†
10	Hara, *et al.*, "Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice," *Nature*, 441 (7095): 885-9, 15 June 2006. [10 Japanese institutions] *052SL	30	†

SOURCE: Thomson Reuter's Hot Papers Database. Read the Legend.

The *Nature* paper goes into considerable detail about the many ways in which the distribution of the different kinds of histone marker seem to be associated with different kinds of cell. For example, in embryonic stem cells, gene promoters, especially for "housekeeping" genes, are associated almost exclusively with one kind of marked histone. In more differentiated neural progenitor cells and fibroblasts those same markers remain associated with the housekeeping genes, but a few of the housekeeping genes are now associated with a different histone marker. In essence, and oversimplifying drastically, some histone markers are associated with active genes in undifferentiated cells, other markers are associated with those same genes, inactivated, in differentiated cells, and some genes appear to be associated with two different kinds of histone markers. The researchers suggest that these "bivalent markings" indicate genes that are "poised for repression" as the cell continues to differentiate. But there is certainly no simple on-off switch.

The paper discusses many other fundamental aspects of the epigenetic landscape: different promoters

activating the same gene; specific histone markers associated with the further differentiation of neural progenitor and fibroblast cells; markers present in some adult tissues and not others. These, and others, are important contributions. But the real value of the work surely lies in the new ways it offers of looking at the genome. The authors end with a shopping list of grand projects. Most will feature on these pages in due course.

Dr. Jeremy Cherfas is Science Writer at Bioversity International in Rome, Italy.

Keywords: Eric Lander, Bradley Bernstein, cell differentiation, genome maps, chromatin, histone markers, Broad Institute, gene promoters, pluripotent stem cells, embryonic stem cells.

PDF

back to top

What's Hot In... : What's Hot In Biology Menu : Newfound Lands Added to the Genomic Atlas

Scientific Home | About Scientific | Site Search | Site Map