EPIGENETICS

Mapping the methylome without chips

DOI:

10.1038/nrg2147

URLs

A new resource provides a map of histone methylation across the human genome at the resolution of a single nucleosome. Methylation was mapped using a new technique that replaces the chip step of ChIP–chip analysis with direct sequencing.

In ChIP–chip analysis, DNA bound to a particular protein of interest is precipitated by antibody binding and then identified by hybridization to microarrays. It has been used with antibodies to various modified histones to build up an extensive picture of genome-wide histone modifications in yeast. However, this has proved to be technically harder in human cells and only a few modifications have been looked at on this scale, with

limited resolution and coverage. For increased efficiency and accuracy, Barski *et al.* therefore cut out the need for the microarray stage by using highly parallel direct sequencing of ChIP DNA samples with a Solexa 1G genome analyzer, a technique they call ChIP–Seq.

The authors digested chromatin from human T cells with micrococcal nuclease to produce single-nucleosome fragments. These fragments were then precipitated with antibodies to 20 different histone lysine and arginine methylations, as well as RNA polymerase II, the insulator protein CTCF and the H2A.Z histone variant. From this they were able to build a map of the distribution of these modifications across the entire genome, and they then compared this with data on gene expression in T cells, as well as data on chromosomal breakpoints and banding patterns.

Many of their findings confirmed previous data, such as associations of H3K4 and H3K36 methylation with active genes, and H3K27 and H3K9 methylation with repressed ones. However, there were important differences between different types of methylation at the same amino acid: levels of monomethylation of H3K27 and H3K9 were actually higher at active genes, whereas trimethylation of these residues followed the expected pattern.

The authors also found that CTCF binding at insulators demarcated regions with different methylation patterns, and that the visible chromosome bands can be explained by differential methylation. The light-staining regions have high levels of H3K4 methylation, whereas the dark-staining ones are characterized by H3K9 trimethylation.

These results are a powerful resource for analysing the effect of chromatin structure on a range of genomic characteristics. Indeed, the authors themselves demonstrate that the patterns they observe can be used in a predictive fashion to identify novel transcription units. One challenge will be to account for the effects of all possible combinations of modifications on a single histone — a recent paper by Garcia *et al.* used mass spectrometry to identify more than 150 differently modified forms of one histone, H3.2, in human cells.

Patrick Goymer

ORIGINAL RESEARCH PAPERS Barski, A. *et al.* High-resolution profiling of histone methylations in the human genome. *Cell* **129**, 823–837 (2007) | Garcia, B. A. *et al.* Pervasive combinatorial modification of histone H3 in human cells. *Nature Methods* **21** May 2007 (doi:10.1038/nmeth1052)

FURTHER READING Esteller, M. Cancer epigenomics: DNA methylomes and histone-modification maps. *Nature Rev. Genet.* **8**, 286–298 (2007)

WEBSITE
<http://dir.nhlbi.nih.gov/papers/lmi/epigenomes/hgtcell.html>