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Between genotype and phenotype

Genome-wide profiling of cytosine methylation for three human chromosomes in a variety of normal tissues provides a reference resource to begin to decode the epigenetic regulation of gene expression in normal development and to understand gene silencing in cancer.

DNA methylation has been proposed to perform various functions that comprise a layer of gene regulation. Hypermethylation is sparse in promoter-associated CpG islands but abundant in parentally imprinted loci, silenced pseudogenes and repeats. It also accumulates on genes silenced in some cancers. Now, a comprehensive account of genome-wide methylation patterns has been generated by Florian Eckhardt and colleagues (page 1378) on a scale that can only be described as epigenomic.

Surprisingly, this study did not find any significant age- or sex-specific methylation patterns across pools of DNA, each derived from several people. However, the authors demonstrated tissue-specific methylation in evolutionarily conserved regions. They confirmed that CpG islands associated with promoters are rarely methylated and that 5′ regions without CpG islands are prone to methylation. The association of tissue-specific regions of methylation with gene expression is a more complex story. In only one-third of such sites was hypermethylation negatively associated with transcript levels; in the remainder, no correlation was seen. Tissue-specific methylation might therefore control the use of distant *cis*-acting elements (such as enhancers or insulators rather than promoters), or these modifications might perform a role less directly related to gene expression.

Does cytosine methylation perform a small set of consistent functions across the genome, or does it make a partial contribution in many individual, context-specific processes? The picture of epigenetic regulation of gene expression derived from bisulfite sequencing is complex and somewhat confusing, reminding us that DNA methylation is only one of several layers of covalent modification. Modified histones and other proteins bound to chromatin perform additional and partially overlapping roles in determining the cell-specific activity of each gene.

The epigenome sequence is the basis for much genomic speculation. Since the pattern of DNA methylation is available at single–base pair resolution, it should be possible to predict the effect of some SNPs and to study the epigenetic consequences in regions affected by structural genomic variation. During development, methylation contributes to imprinting, and presumably tissue-specific methylation either influences or reports the stability of cellular identity. What, then, is the level of granularity and developmental meaning of mosaic DNA methylation? When does this happen in development, and does it change qualitatively or quantitatively with age?

Epigenetic regulation is critical for loss of genetic control in two cancer-specific processes. Peter Laird and colleagues (*Nat. Genet.* **38**, 787–793; 2006) definitively showed that coordinate CpG island methylation of a range of genes across the genome is a hallmark of a subset of colon cancers. It is thought that a common process underlies this phenomenon, which has been termed the CpG methylator phenotype (CIMP). Second, cancer-specific gene silencing can be coordinated not only by a common process but also in common across a contiguous genomic region. In a surprising paper earlier this year, Susan Clark and colleagues (*Nat. Genet.* **38**, 540–549; 2006) reported that coordinate silencing of the transcription of adjacent genes across a whole chromosome band was associated with both histone methylation and DNA methylation in colon cancer cells and tumors. Now, on page 1386 of this issue, Nicolas Stransky and colleagues show that such regional gene silencing is indeed a general phenomenon in cancer, a source of correlated cancer-specific transcriptional changes that is second in frequency only to structural rearrangements. They further demonstrate for one such region that histone methylation, rather than DNA methylation, correlates with the loss of gene activity.

Thus, although the role of DNA methylation in normal epigenetic regulation remains something of an enigma, the epigenome sequences are a most welcome baseline against which to investigate gene regulation both in development and in disease. ■