

# Epigenetic modifications and human disease

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Epigenetics is one of the most rapidly expanding fields in biology. The recent characterization of a human DNA methylome at single nucleotide resolution, the discovery of the CpG island shores, the finding of new histone variants and modifications, and the unveiling of genome-wide nucleosome positioning maps highlight the accelerating speed of discovery over the past two years. Increasing interest in epigenetics has been accompanied by technological breakthroughs that now make it possible to undertake large-scale epigenomic studies. These allow the mapping of epigenetic marks, such as DNA methylation, histone modifications and nucleosome positioning, which are critical for regulating gene and noncoding RNA expression. In turn, we are learning how aberrant placement of these epigenetic marks and mutations in the epigenetic machinery is involved in disease. Thus, a comprehensive understanding of epigenetic mechanisms, their interactions and alterations in health and disease, has become a priority in biomedical research.

Even before DNA was identified as the molecule of inheritance, scientists knew that not every gene in an organism can be active in each cell at all times. Even so, all cells in an organism share the same genetic information. Conrad Waddington coined the term 'epigenetic landscape'<sup>1,2</sup> for the molecular mechanisms that convert this genetic information into observable traits or phenotypes. In many instances, epigenetic gene expression patterns and associated phenotypes persist through mitosis or even meiosis, although no change in the primary DNA sequence has occurred. Consequently, epigenetics is generally understood to be the study of mechanisms that control gene expression in a potentially heritable way.

Recent breakthroughs in the understanding of the mechanisms underlying epigenetic phenomena and their prevalence as contributors to the development of human disease have led to a greatly enhanced interest in epigenetic research.

On a molecular level, covalent modifications of cytosine bases and histones, and changes in the positioning of nucleosomes are commonly regarded as the driving epigenetic mechanisms. They are fundamental to the regulation of many cellular processes, including gene and microRNA expression, DNA-protein interactions, suppression of transposable element mobility, cellular differentiation, embryogenesis, X-chromosome inactivation and genomic imprinting.

In multicellular organisms, the ability of epigenetic marks to persist during development and potentially be transmitted to offspring may be necessary for generating the large range of different phenotypes that arise from the same genotype<sup>1,3-5</sup>. For instance, cloned animals

generated from the same donor DNA are not identical to, and develop diseases with different penetrance from, their donor<sup>1,3</sup>. Human clones that arise spontaneously—monozygotic twins—are identical at the DNA sequence level, but have different DNA methylation<sup>4,5</sup> and histone modification profiles<sup>4</sup> that might affect the penetrance of several diseases, such as cancer<sup>4</sup> or autoimmune disorders<sup>6</sup>. But this phenomenon is also observed at a single cell level: how can stem cells develop into any type of cell and how does a liver cell always give rise to two new liver cells after cell division? Again, epigenetics seems to be part of the answer as it has been described as one of the key factors in cellular differentiation<sup>7,8</sup> (see the review by Meissner<sup>9</sup> in this issue).

The importance of epigenetics in maintaining normal development and biology is reflected by the observation that many diseases develop when the wrong type of epigenetic marks are introduced or are added at the wrong time or at the wrong place<sup>10</sup>. For instance, a clear causality role for DNA methylation in cancer is suggested by hypermethylation of some genes (e.g., *p16<sup>INK4a</sup>*, *p14<sup>ARF</sup>* and *MGMT*) as an early event in tumorigenesis, as well as by tumor type-specific methylation landscape<sup>11</sup>. Here we summarize recent progress in the field of epigenetic research and its role in disease, preparing ourselves for the surprises that epigenetics might hold in the future.

## Epigenetic modifications and their machineries

For didactic purposes, epigenetic modifications can be grouped into three main categories: DNA methylation, histone modifications and nucleosome positioning. It is important to keep in mind the interplay between epigenetic factors—as the observed outcome is always the sum of their interactions—and the many positive and negative feedback mechanisms.

**DNA methylation.** The most widely studied epigenetic modification in humans is cytosine methylation. DNA methylation occurs almost exclusively in the context of CpG dinucleotides. The CpG dinucleotides tend to cluster in regions called CpG islands<sup>1</sup>, defined as regions of

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Published online 13 October 2010; doi:10.1038/nbt.1685