

EPIGENETICS: A PRIMER

There are many ways that epigenetic effects regulate the activation or repression of genes. Here are a few molecular tricks cells use to read off the right genetic program. **By Stefan Kubicek**

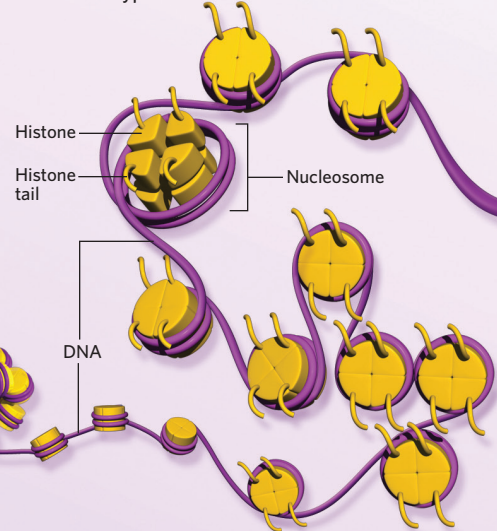
What makes the ~200 cell types in our body remember their identity? What prevents them from becoming cancer cells? Why do we inherit some traits from our father, others from our mother? How do our experiences and environment influence our thinking? Why do plants bloom in spring but not in winter? These important and quite different questions are all addressed by the field of epigenetics, which studies heritable changes in a phenotype arising in the absence of alterations in the DNA sequence. The idea of transgenerational inheritance of acquired characteristics goes back to Lamarck in the early 19th century, but still only correlative evidence exists in humans. In contrast, many cellular epigenetic phenomena are now well understood on the molecular level. In humans, they include the parent-of-origin specific expression of genes (imprinting) and the shutting-down of almost all genes on one of the two X chromosomes in females (X-chromosome inactivation).

All these epigenetic phenomena are characterized by chemical modifications to DNA itself (DNA methylation) or to histones, the proteins around which DNA is wound. These modifications change during development as stem cells give rise to liver cells and neurons, but also in response to environmental signals—in plants, for example, during the cold of winter or in humans when immune cells are activated after an infection. One of the biggest controversies in the field is whether histone modifications are inherited through cell division (called the “histone code hypothesis”) or whether they only form transient indicators of transcriptional states (“signaling model”).

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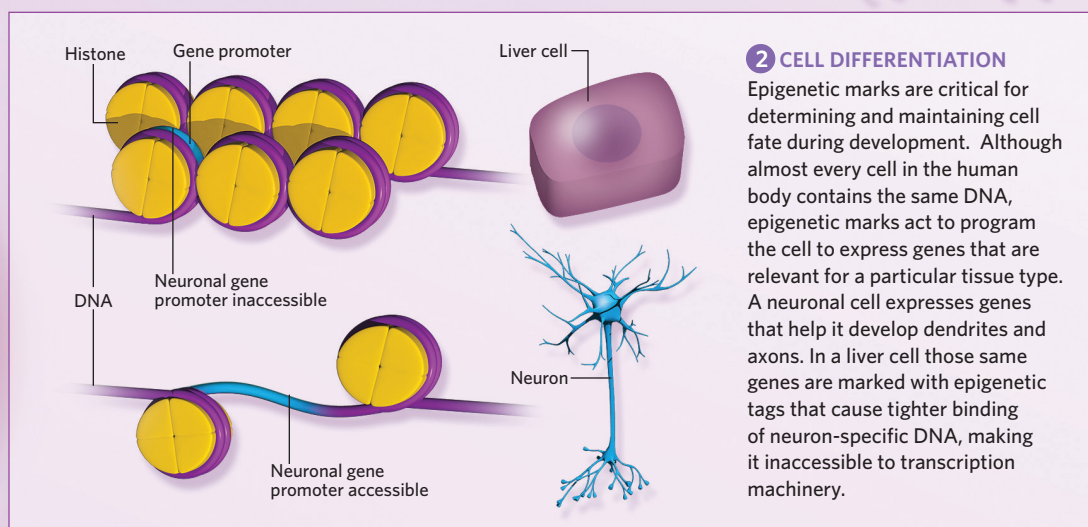
1 OVERVIEW

Epigenetic events regulate the activities of genes without changing the DNA sequence. Different genes are expressed depending on the methyl-marks attached to DNA itself and by changes in the structure and/or composition of chromatin. The main components of chromatin are histones (in bundles of eight units) around which 146 base-pairs of DNA are wound like a thread around a spool, forming a structure called the nucleosome. There are various epigenetic mechanisms that can affect the nucleosome: chemical modification (via molecular additions to histone tails or DNA), a change its positioning on DNA (via chromatin remodeling proteins), or a variation in histone subtypes.



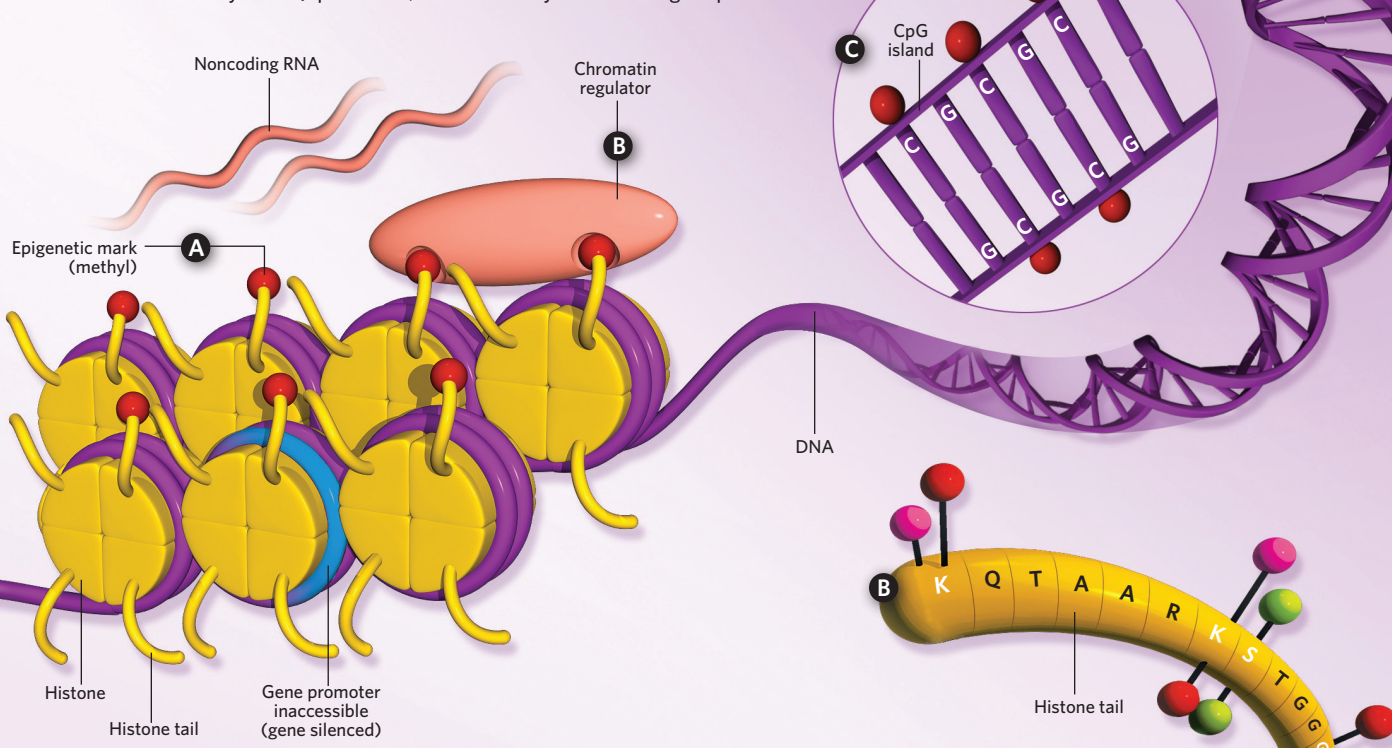
2 CELL DIFFERENTIATION

Epigenetic marks are critical for determining and maintaining cell fate during development. Although almost every cell in the human body contains the same DNA, epigenetic marks act to program the cell to express genes that are relevant for a particular tissue type. A neuronal cell expresses genes that help it develop dendrites and axons. In a liver cell those same genes are marked with epigenetic tags that cause tighter binding of neuron-specific DNA, making it inaccessible to transcription machinery.



3 INACTIVATING MARKS

There are many epigenetic modifications that change whether or how much of a gene is transcribed into RNA. Epigenetic marks that inactivate genes include methylation at certain positions on histone tails **A**. These chemical modifications are made by a number of histone-modifying enzymes and then recognized by other chromatin regulators **B**. Evidence is beginning to emerge that different classes of noncoding RNAs (ncRNA) regulate these enzymes. Many of the histone modifications that inactivate genes can be reversed by other epigenetic changes (see below). However, direct methylation of DNA causes a permanent and heritable change in gene expression **C**. Methylation of the DNA often occurs at clusters or “islands” of cytosine (CpG islands) that commonly occur within gene promoters.



4 ACTIVATING MARKS

The heritability of DNA methylation, which often occurs in the early stages of development, allows cells to keep irrelevant genes silenced in successive generations of liver or skin cells. However some genes—such as the plant genes that govern winter dormancy and springtime flowering—require silenced genes to be reactivated. Several modifications, including the acetylation, phosphorylation, as well as methylation of certain positions on a histone tail **A**, can cause DNA to unwind, releasing the genes that are otherwise inaccessible. These modifications occur mostly at specific positions on the accessible tails of the histones, and subsequently recruit additional activating proteins **B**. Histone-remodeling complexes, which slide histones in one direction or another, can also make genes accessible to transcription **C**.

