Faddish Stuff: Epigenetics and the Inheritance of Acquired Characteristics

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A RECENT BOOK (1) that skewers scientific fads and fashions introduces "epigenetics" with the following words:

> "Epigenetic changes are short-term heritable alterations in gene expression that are not due to mutations . . . . Like variations in a letter's font . . .we are still at sea as to how it all works . . . short term bar codes on our cells so that they remember where they've been and where they should be going . . . if they get lost we call it cancer, etc. . since epigenetic changes can be induced by diet, etc . . ."

This gallimaufry obscures, rather than illuminates, our understanding of a basic biological process. I'll explain, starting with a statement of the problem in a simple form.

States of gene expression tend to be maintained as cells—be they bacterial or mammalian—divide. That is, absent changes in the environment, the genes that are "on" (i.e., are being transcribed) in one cell tend to be on in the daughter cells as well. Why is this true?

In recent years, attention has been drawn to two "bar codes" (see the above quote) in eukaryotes: enzymatic modifications to histones (the protein components of nucleosomes, around which DNA is wrapped) and enzymatic modification of DNA residues by the addition of methyl groups. Let us put aside the latter for the moment, as many respectable organisms (flies and worms, for example) do not encode DNA methylating enzymes, and so, that process cannot provide a general answer. But, all eukaryotic (by definition) DNA is wrapped in nucleosomes, and all eukaryotes express, in various arrays, enzymes that modify nucleosomes. Moreover, there are correlations between these modifications and gene activity. For example, actively transcribed genes are "associated with" nucleosomes that are more highly acetylated than most.

Somehow, the following ideas caught fire, even entering the standard textbooks: nucleosome modifications not only determine states of gene expression, but those modifications can be copied to maintain states of gene expression. The modifications were called "epigenetic", implying that they convey self-perpetuating information as cells divide.

The problem with this characterization is that overwhelmingly, experiments have shown it to be false: histone modifications are *not* maintained as cells divide.

"A Chip of the Old Block," J. L. Marks, London (1832), Epigenetics in London, 1831: a mid-wife holds up a newborn baby with a wooden leg; just like the happy father! Image courtesy of the National Library of Medicine.

These modifications turn over rather rapidly, and the nucleosomes themselves are too labile to carry information across cell divisions (2–6). Moreover, there is no plausible molecular mechanism by which a gene that is on could be maintained on by such modifications (7).

Why then do daughter cells tend to mimic their mothers in their states of gene expression? There is no mystery: genes are "activated" (caused to be transcribed) by regulatory proteins, called transcription factors, which bind to DNA and work on nearby genes (7, 8).

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Exogenously added genes encoding regulatory proteins can cause somatic cells to change their identities, even forming pluripotent stem cells (9, 10), and the modern study of development entails, to a very large extent, the action of these proteins (11, 12).

Regulatory proteins in mother cells are, as a matter of course, distributed to daughter cells, where they bind DNA and turn on the same genes they activated in the mother cell (8, 13). Indeed, for a mother cell to give rise to two different daughters requires, in general, sequestration of one or more regulatory proteins (14), or the two daughter cells must receive from the environment different signals to which the regulatory proteins respond. In bacteria and in eukaryotes, the continuing presence of the activator is required to keep the gene on.

Why are active genes often associated with acetylated nucleosomes? One reason is that as genes are transcribed, their nucleosomes are removed and then replaced to make way for the transcribing enzyme (called RNA polymerase). The way this nucleosome-replacement machinery works, it turns out, is to replace one set of nucleosomes with others that are more highly acetylated (15). Thus, nucleosome acetylation accompanies but does not cause transcription (16). Jacob and Monod taught us to distinguish regulation of a gene (i.e., whether or not it is transcribed) from the many and complex reactions involved in transcription *per se*. It's a lesson too often ignored.

There is a form of gene regulation that *is* properly called epigenetic (17): an environmental signal can cause a gene to become transcribed (by a DNA-binding activator), and transcription of that gene can be maintained in the absence of the original signal. The effect can be perpetuated over many cell generations and can extend to fully differentiated cells (8, 18, 19). The mechanism, observed in bacteria and eukaryotes, involves a positive-feedback mechanism, rather simple to evolve and to understand. But, let's leave that aside for now. Here is a different kind of epigenetic effect: individual *Caenorhabditis elegans* (worms) exposed to a virus can foster offspring over several generations that are resistant to the virus. Do histones and their modifications transmit this vaccine-like effect? No; it turns out that small, protective RNAs are transmitted from one generation to the next in the sperm (20).

Histone modifications are mislabeled; they are not self-perpetuating and hence, should not be called epigenetic. It's not just a matter of semantics, it's a question of how things actually work. FJ

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