Rachel Cox

Faculty

Rachel Cox has taught Biology at Riverdale for four years and directs the Research Program. She graduated from Reed College, where her senior thesis investigated the ichthyotoxic effects of an indigenous plant used to stun fish. She received her Ph.D. from Boston University School of Medicine, where her research focused on non-mammalian comparative enzymology. Cox worked for many years at the Marine Biological Laboratory in Woods Hole, where she began her studies of a cancer-like disease in molluscs. This research led her to Columbia University where she was at work in a cancer genetics lab when she found her way to Riverdale. Then the fun really started.

She would welcome comments from readers.

Beyond the Genes

BIOLOGISTS ARE EXPERIENCING DISQUIET IN THE LAB and in the field. Researchers, professors, teachers, and students, including those of us at Riverdale, have noticed and started asking questions. There is a transformation in the works, and it has to do with our way of thinking about inheritance. Since inheritance is the information stream that fuels evolution, we now find ourselves in the uncomfortable position of having to rethink the theory upon which our science is based.

Evolutionary theory provides an essential framework for the many subdisciplines that compose the foundation of life science. Across these disciplines, however, persistent questions have arisen that cannot be addressed under the influence of our current framework.

Long demonstrated but never thoroughly explained by embryologists, a well-orchestrated cellular process selectively turns portions of the genome on and off at crucial moments. A two-day-old mouse embryo carries the gene for insulin, but insulin is not made. Only after the pancreas is formed, and the mouse requires energy, does the previously silent insulin gene get a message to turn on. Developmental processes like this require context. A fertilized egg cannot produce an embryo once it has been cracked open, even though all the genes are there. The genes by themselves are not sufficient.

What tells a gene to turn on at the appropriate developmental moment? The answer to this question lies in the science of epigenetics. "Epi" from Greek "above" or "over" makes "epigenetics" the study of processes occurring on top of the DNA. Our understanding of epigenetics has vastly

improved our understanding of the bridge that links the genetic code to physical traits.

It turns out that a few surprisingly simple chemical modifications to the DNA act as directors of gene expression. This means that physical traits can be altered with no concurrent change to the genetic code. Essentially, the fastening of a few carbons and hydrogens—we call them "epigenetic tags"—to the DNA and its associated proteins controls expression of a gene. The exact proportion of our traits that is controlled by epigenetic tags is not yet known. But we do know that these simple chemical changes are frequent, interrelated, mutually enforcing, and reversible—and this explains how gene expression is altered during development and over a lifetime.

Molecular biologists, mavens of the laboratory, who have pushed the field at a blistering pace since the discovery of the genetic code, are churning out data that elucidates epigenetic mechanisms. Surprisingly, epigenetic tags are easily swayed by environmental cues. In a notable experiment that is surely bound for the textbooks, a mouse fed a diet deficient in particular carbon and hydrogen formations ("methyl" groups) experienced an epigenetic shutdown in key metabolic genes and became obese as a result. What's more, this mouse gave birth to obese mice (Waterland and Jirtle, 2003).

This is where epigenetics becomes revolutionary. Our traditional explanation of heredity is based on a simple paradigm ushered in with the discovery of the structure of DNA. We call this the "central dogma" of molecular genetics. It dictates that DNA determines traits by irreversibly directing protein synthesis via RNA. Variation in a given trait arises by the generation of random mutations in the genetic code. The environment "selects" well-adapted traits and "rejects" maladapted traits. Enshrined in this paradigm is the notion that *the environment cannot change our genome.* Here's the problem: we've now learned that the environment *can* change the epigenome. Changing the epigenome is as important as changing the genome, because the genes that you have are not nearly as important in determining your traits as the genes that you express.

The concept that the environment may shape our physical traits harks back to the ideas of Jean-Baptiste Lamarck, an early nineteenth-century naturalist who contributed to the development of evolutionary theory. His idea, that traits acquired during lifetime could be inherited, was eventually rejected. Today, biologists are uneasy about the return of a previously rejected theory. Epigenetics does not require "the return of Lamarck," at least not until we can consistently demonstrate that epigenetic tags are

inherited through multiple generations. If we continue to show that offspring inherit traits that were acquired during the lifetime of parents, then we face a return to Lamarckian ideas. This is what fuels current disquiet in the biological sciences.

The plant kingdom offers up indisputable evidence in support of these controversial ideas of inheritance. Plant biologists, long the quiet leaders in genetic engineering, can point to several molecular mechanisms by which the environment shapes the heritable genome. Just as plants served Gregor Mendel so well as model organisms, so too they make ideal candidates for epigenetic studies. Plants can't run away, so their adaptive mechanisms are finely tuned and easily measured. In dandelions, repeated stress due to drought causes consistent modifications to the DNA that lead to a shutdown of certain genes in future populations (Hauser et al., 2011). Various mechanisms are thus induced epigenetically—such as increased root-to-shoot ratios—and this contributes to increased fitness of the population in the face of drought.

In the case of dandelions, the Lamarckian "inheritance of acquired characteristics" is occurring in an *asexually* reproducing population. This gets to the heart of our debate. A gamete, an egg or sperm, contains half the genomic imprint. During sexual reproduction, two gametes from different individuals undergo fertilization to generate a wholly unique being. Biologists have long believed that a surveillance mechanism erases all epigenetic markers during fertilization or early in embryogenesis. This is said to create a clean slate for the expression of the newly inherited genome. Mounting evidence from studies of sexually reproducing species suggests, however, that epigenetic markers, laid down on the DNA during one generation, are somehow escaping erasure. This appears to be the explanation for the fat baby mice, for example. Arising from the current data, novel models and fiercely debated theories seek to explain how, during DNA replication, the epigenetic markers find ways to get themselves loyally copied or memorized along with the code. Apparently, the central dogma of molecular genetics is too simple.

Thus, random mutations are not the only source of inheritable changes to the genome. This is tough to swallow. Nevertheless, this new perspective may shed light on the persistent questions that traditional genetics never adequately answered. For instance, can it really be that transformation from a primordial, unicellular organism to a highly adapted multicellular conscious being occurred entirely as the result of chance events? Does it not make sense that the process could have been enhanced and streamlined through the environmental sculpting of future genomes?

On a different scale, very much within our grasp: do epigenetic changes to the genome constitute a viable source of adaptive traits? Can we identify genetic changes arising in one generation as a result of stress? This is an issue that my students and I are directly trying to assess in our Bronx River study. The environmental impact sustained by this urban watershed over the last century resulted in the virtual loss of herring and oyster populations. One of the river's remaining species, the surprisingly resilient Atlantic ribbed mussel, is the subject of our study. We are analyzing molecular mechanisms that facilitated the success of this species, and we hope to determine whether their adaptations arose epigenetically.

Finally—a most pressing issue—can Earth's diversity of life be perpetuated in the face of a warming climate and changing habitats? Humankind relies on healthy eco-systems, yet we struggle still to get a handle on how small changes, such as the loss of a particular species or habitat, may impact global processes like climate change and disease transmission. We need a clear picture of the evolutionary unit of change. Can we count on—or, to take it even further—can we engineer the epigenetic changes that we deem necessary for preservation of diversity?

Ultimately, population biologists working in the field will be the ones who will have to find ways to test the idea that the environment directs evolution. This will not be easy, as it will require adding new variables and redesigning theoretical frameworks in order to account for nonrandom evolutionary forces. This is not an enviable position: everything is easier in a test tube or a greenhouse. The weight of new evidence supporting non-randomly-generated genetic variation certainly requires a transformation in our thinking. Perhaps through this process we will gain a better vision of the more confounding features of life whose explanations continue to elude us.

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