Lamarck and the Missing Lnc

Epigenetic changes accrued over an organism’s lifetime may leave a permanent heritable mark on the genome, through the help of long noncoding RNAs.

By Kevin V. Morris | October 1, 2012

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Rudyard Kipling’s *Just So Stories* tell tales not so much of evolution, but of the magic and wonder of the animal world. He describes the wizard who gave the camel a hump for its laziness, and the alligator who snapped and stretched the nose of a naïve young elephant to its current lengthy proportion. Those delightful fables, published some 70 years after Jean-Baptiste Lamarck’s death, provide entertaining explanations for such evolved traits, and were clearly inspired by Lamarck’s description of adaptive change, not Charles Darwin’s. In his 1809 publication *Philosophie Zoologique*, Lamarck wrote of the giraffe, from whose habit of reaching for the green leaves of tall trees “it has resulted . . . that the animal’s forelegs have become longer than its hind legs, and that its neck is lengthened to such a degree that the giraffe, without rearing up on its hind legs . . . attains a height of six meters.”

Although biologists have generally considered Lamarck’s ideas to contain as much truth as Kipling’s fables, the burgeoning field of epigenetics has made some of us reconsider our ridicule. While no biologist believes that organisms can willfully change their physiology in response to their environment and pass those changes on to their offspring, some evidence suggests that the environment can make lasting changes to the genome via epigenetic mechanisms—changes that may be passed on to future generations.

**Epigenetics: genome gatekeeper**

Epigenetic changes can range from chemical modifications of histone proteins—such as acetylation and methylation—to modifications made to the DNA itself. Such changes usually cause chromatin compaction, which limits the ability of the RNA polymerase II transcription complex to access DNA, ultimately resulting in reduced messenger RNA (mRNA) and protein output. Many view epigenetics as an annotation or editing of the genome that defines which genes will be silenced in order to streamline protein production or squelch unnecessary redundancy. That annotation, they say, does not and cannot permanently change the original manuscript (i.e., DNA), but merely access to the manuscript.

Infographic: The Epigenetic Lnc  
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Just as epigenetics was gaining acceptance within the general scientific community, scientists began reporting observations of a newly identified phenomenon called transgenerational epigenetic inheritance, or the passage of epigenetic changes from a parent to its offspring. Recent experimental work in mice, worms, and pigs has found evidence that some degree of transgenerational epigenetic inheritance may take place.¹²³₄

A fascinating 2008 study that looked at people born during the Dutch Hunger Winter in 1944–1945 hints at the possibility that transgenerational epigenetic inheritance also occurs in humans.¹ Adults who were conceived during the famine had distinct epigenetic marks that their siblings born before or after the famine did not. These marks reduced the production of insulin-like growth factor 2 (IGF2) and affected the growth of the famine-gestated children. Notably, these marks were retained for several decades in
the afflicted individuals. While these observations suggest the possibility of transgenerational epigenetic inheritance, the modifications could also have occurred in utero as a result of famine conditions rather than being inherited in the germline. Therefore, whether such a distinct phenomenon occurs in humans remains to be definitively determined.

However, in model experimental systems, there is strong evidence for transgenerational epigenetic inheritance. In one study carried out in mice, an environmental stress that resulted in aggressive behavior in males caused the same behavior in their offspring. Notably, the offspring had changes in the DNA methylation patterns of particular genes. Collectively, these and other transgenerational studies all point to the notion that selective pressure can be applied from the environment and passed on to daughter cells and offspring.

**Controlling epigenetics**

While epigenetic modifications to the genome are well studied, far less is known about how particular epigenetic marks are directed to their target loci. Clearly, something is guiding the modifications, which appear to be differentially distributed based on particular stresses induced on the cell or organism. Recent studies suggest that epigenetic changes, and possibly transgenerational epigenetic inheritance, could be explained by a somewhat unexpected molecular player: long noncoding RNA.

Long noncoding RNAs (lncRNAs) are transcripts generally expressed from regions of “junk” DNA that are not thought to code for proteins. Estimates of lncRNA abundance range from 70 to 98 percent of transcripts present in the cell, and some are several thousand bases long. Unlike short noncoding RNAs, such as short interfering RNA, which silence genes by cutting mRNAs in the cytoplasm, lncRNAs appear to bind to transcripts in the nucleus as they emerge from the replication fork of the DNA, and recruit enzyme complexes to induce epigenetic changes at these loci.

Some of these lncRNAs bind transcripts from the protein-coding gene during the normal transcription process. The associated chromatin remodeling proteins then modify the local chromatin and DNA, suppressing gene expression. One such modification is methylation of the DNA, which presumably occurs when the lncRNAs direct enzymes such as the DNA methyltransferase DNMT3a to targeted spots on the genome. Alternatively, lncRNAs can direct modifications of nearby histones, usually in the form of methylation of the histone tail.

DNA methylation itself can be passed down from a cell to its daughter cells. In addition, it has been known for some time that such modifications can also lead to permanent changes in the genetic code. Methylation of a cytosine (C), for example, can cause that nucleic acid to change to a thymine (T)
through deamination, or the removal of an amine group. Nearly 80 percent of methylation sites in the human genome occur on a cytosine that is followed by a guanine, in a CpG sequence. Deamination occurs when the methylated C undergoes a hydrolysis reaction resulting in the production of ammonia, followed by the conversion of the cytosine to a thymine at that spot in the DNA sequence. While this C-to-T conversion is considered random, the spontaneous deamination of methylated CpGs has been found to be about 2-fold faster than C-to-T conversions in nonmethylated CpG sequences, suggesting a bias toward CpG regions in the deamination process.

Although these ideas have yet to be substantiated by complete experimental evidence, one can envision this as a model for how the system might work—a mechanism by which epigenetic changes, guided by IncRNAs, could make permanent and heritable changes to the genome. Indeed, such a IncRNA-based DNA editing system could be driving some aspects of genetic variation and could explain the common appearance of single nucleotide polymorphisms within a species. If this is true, one has to wonder what role IncRNA-directed DNA methylation has been playing in the evolution of the genome.

**Driving diversity**

DIRECTING EVOLUTION: Epigenetic modification most often occurs on cytosines (C) that are followed by a guanine (G) (top). These methylated cytosines are more likely to undergo a chemical reaction that converts the C into a thymine (T), permanently changing the genetic sequence. When that altered sequence is replicated during cell division, the newly generated matching strand will copy this altered sequence (bottom), giving the next generation a slightly altered genomic manuscript. This new manuscript could alter the structure of the encoded protein, or change the mRNA homology sequence for IncRNA binding, rendering the IncRNA unable to bind and suppress that gene,
thus allowing the altered sequence to be transcribed again.

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Intriguingly, a greater frequency of targeted C-to-T changes could also result in an overall loss of complementarity between the sequence and the lncRNA that targets it. As a result, rather than initiating suppression of the target gene, the change could result in renewed transcription in subsequent generations. At the same time, this process could permit the target transcript to fold into a different conformation, thereby allowing other subsets of lncRNA interactions to occur at slightly different loci.

Alternatively, changes to the lncRNAs themselves might lead to a loss of lncRNA-protein associations, resulting in different cellular machinery being localized to the particular target loci. Thus, the over-activity of one lncRNA could doom that lncRNA to a loss of function, but simultaneously result in the evolution of a new regulatory lncRNA network with potentially different downstream effects.

Furthermore, a site frequently targeted by lncRNAs would likely contain a larger proportion of T:A bonding between the DNA strands, due to deamination events. Such permanent and heritable changes in the genetic code could change the shape of the encoded protein, its function, or its ability to be transcribed altogether.

One can begin to envision how environmental variation, by instigating epigenetic changes, could increase organismal complexity, thus giving populations a greater chance at surviving new and perhaps permanent environmental threats. In other words, epigenetics, rather than random genetic point mutations, could provide the missing link between environmental pressure and the resulting genetic variability that generates robustness of a species.

Most certainly, if such a pathway were to exist in human cells, one would expect it to be elusive purely due to the sheer complexity of the process—involving lncRNAs, epigenetic changes, DNA methylation, and deamination. Thus, it is not out of the realm of possibility that such a mechanism exists, but has yet to be elucidated by science.

The inner molecular workings of the cell are vastly complex, and the emerging realization that lncRNAs are active modulators of gene transcription and epigenetic states only complicates the picture. Clearly, as more data emerges in this exciting area of research, additional layers of regulation will need to be added to the central dogma of molecular biology. Although an organism cannot pass down specific information about its own experiences—the giraffe will not be able to help its offspring reach taller trees just by stretching its own neck—it may give succeeding generations a fighting chance in a difficult environment by offering them a slightly altered arsenal of genetic tools.

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References


