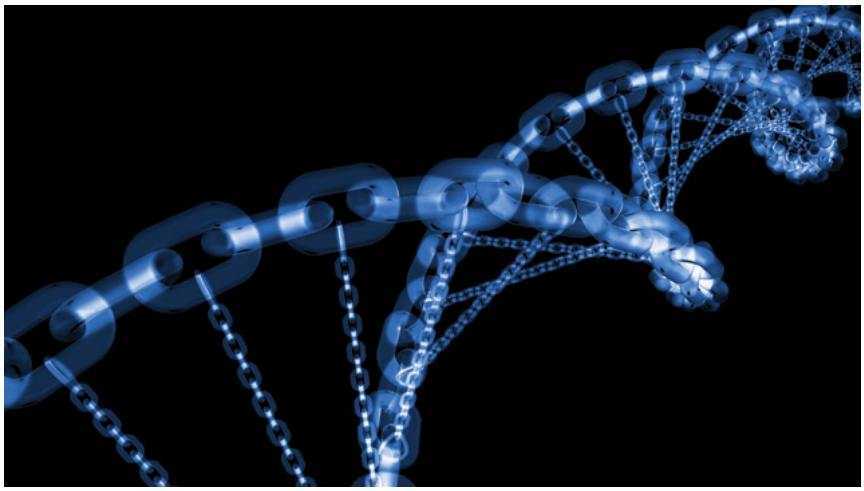
Lamarck and the Missing Lnc

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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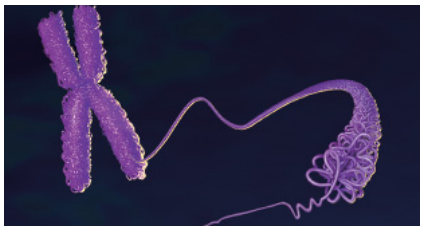
Rudyard Kipling's *Just So Stories* tell tales not so much of evolution, but of the magic and wonder of the animal world. He describes the wizard who gave the camel a hump for its laziness, and the alligator who snapped and stretched the nose of a naïve young elephant to its current lengthy proportion. 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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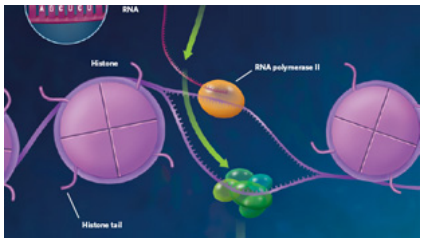
Just as epigenetics was gaining acceptance within the general scientific community, scientists began reporting observations of a newly identified phenomenon called transgenerational epigenetic inheritance, or the passage of epigenetic changes from a parent to its offspring. Recent experimental work in mice, worms, and pigs has found evidence that some degree of transgenerational epigenetic inheritance may take place.[1. B.T. Heijmans et al., "Persistent epigenetic differences associated with prenatal exposure to famine in humans," *PNAS*, 105:17046–49, 2008.][2. T.B. Franklin et al., "Epigenetic transmission of the impact of early stress across generations," *Biol Psychiatry*, 68:408–15, 2010.][3. O. Rechavi et al., "Transgenerational inheritance of an acquired small RNA-based antiviral response in C. elegans," *Cell*, 147:1248–56, 2011.][4. M. Braunschweig et al., "Investigations on transgenerational epigenetic response down the male line in F2 pigs," *PLoS ONE*, 7: e30583, 2012.]

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.[2,3,4] In one study carried out in mice, an environmental stress that resulted in aggressive behavior in males caused the same behavior in their offspring.[5. T.B. Franklin, I.M. Mansuy, "Epigenetic inheritance in mammals: evidence for the impact of adverse environmental effects," *Neurobiol Dis*, 39:61–65, 2010.] 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.



Infographic: A Mechanism for Targeted Change
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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.[6. T.R. Mercer et al., "Long non-coding RNAs: insights into functions," *Nat Rev Genet*, 10: 155–59, 2009.] 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.[7. K.V. Morris, "Long antisense non-coding RNAs function to direct epigenetic complexes that regulate transcription in human cells," *Epigenetics*, 4:296–301, 2009.]

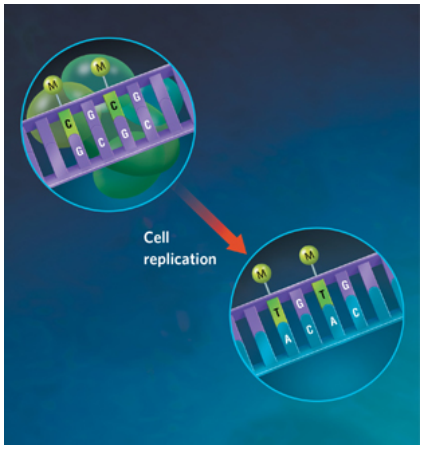
Some of these lncRNAs bind transcripts from the protein-coding gene during the normal transcription process.[8. K.V. Morris et al., "Bidirectional transcription directs both transcriptional gene activation and suppression in human cells," *PLoS Genet*, 4: e1000258, 2008.][9. W. Yu et al., "Epigenetic silencing of tumour suppressor gene p15 by its antisense RNA," *Nature*, 451:202–06, 2008.][10. P.G. Hawkins, K.V. Morris, "Transcriptional regulation of Oct4 by a long non-coding RNA antisense to Oct4-pseudogene 5," *Transcr*, 1:165–75, 2010.] 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.[11. M.S. Weinberg et al., "The antisense strand of small interfering RNAs directs histone methylation and transcriptional gene silencing in human cells," *RNA*, 12:256–62, 2006.] 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,[12. J.C. Shen et al., "The rate of hydrolytic deamination of 5-methylcytosine in double-stranded DNA," *Nucleic Acids Res*, 22:972–76, 1994.] 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 lncRNAs, could make permanent and heritable changes to the genome. Indeed, such a lncRNA-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 lncRNA-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 lncRNA binding, rendering the lncRNA 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.

Kevin V. Morris is an associate professor at The Scripps Research Institute in La Jolla, California, and the University of New South Wales in Sydney, Australia.

Categories

Features

Tags

noncoding RNA, lncRNA, Lamarck, genetics & genomics, evolution, epigenetics, DNA methylation and Darwin

Comments

jvkohl
posts: 53

October 1, 2012

In an article published earlier this year, I detailed how an environmental drive evolved from that of nutrient chemical ingestion in unicellular organisms to that of socialization in insects. Using the honeybee model organism as an example, the article also makes it clear that food odors and pheromones cause changes in hormones, which also have developmental affects on behavior in nutrient-dependent, reproductively fit individuals across species of vertebrates.

It is the epigenetic effects of nutrient chemicals and pheromones on intracellular signaling, on stochastic gene expression, and on genetically predisposed behavior that enable transgenerational epigenetic inheritance in species from microbes to man. There are now hints in the literature that transgenerational epigenetic effects on behavior are receiving the consideration that is due. But the idea that there are transgenerational epigenetic effects on behavior has already been substantiated by complete experimental evidence from every species that requires nutrient chemicals for individual survival and pheromones to control reproduction.

I wrote: "The concept that is extended is the epigenetic tweaking of immense gene networks in â€˜superorganismsâ€™ (Lockett, Kucharski, & Maleszka, 2012) that â€˜solve problems through the exchange and the selective cancellation and modification of signals (Bear, 2004, p. 330)â€™. Those immense gene networks enable epigenetic effects of nutrient chemicals and pheromones on stochastic gene expression that lead to species-specific changes in behavior via transgenerational epigenetic inheritance. Don' they? (That was a rhetorical question.) Can random mutations cause adaptive evolution? (That was a foolish question.)

Kohl, J.V. (2012) Human pheromones and food odors: epigenetic influences on the socioaffective nature of evolved behaviors. Socioaffective Neuroscience & Psychology, 2: 17338. DOI:10.3402/snp.v2i0.17338.

Report

corrigible
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October 2, 2012

While there are, no doubt, epigenetic repercussions from nuances of differences in food and pheromon variations upon species over time, there also are other epigenetic consequences of other ecological parameters. Selective pressures come in many varieties -- not merely in olfactory influences.
To survive over numerous generations, during local environmental changes, niche changes, a species must not merely hang on. It must, as a species, change morphologically. Else it would persist in applying antiquated solutions to no-longer-extant challenges.
Until the current century, there were -- in regard to biological theorizations -- many lay thinkers and many astute biology-specialized thinkers who presumed that changes in a species over time are a result of fortuitous (or not-so-fortuitous) mutational happenstances. More and more, however, we realize that the odds against any new mutation's being beneficial, rather than carcinogenic or mal-adaptive are diminuitive to so great an extent that the presumption that fortuitous mutational accidents will come along by pure chance and produce a few individuals who have superior adaptive DNA-scripted morphologies to pass on to future generations.
The more we learn about mutations generally, and breakdowns in "corrective" processes, the more clear it becomes that such "MAINTENANCE" work does NOT bring about supra-generational adaptations to environmental change.
What is NECESSARY for supra-generational adaptation is mechanisms of adaptation that are "solution-appropriate" -- that is, RESPONSIVE adaptation of an epigenetic kind.
A random, drunken sailor kind of random mutation would take far too long to luck up to the extent necessary. Some mechanisms MUST bring about appropriate changes in morphology for APPROPRIATE SOLUTIONAL supra-generational changes to occur. Were it not for such necessarily appropriate changes, there would be such INAPPROPRIATE changes in a species over time as would cause mal-adaptive changes to be "tested," which would merely result in population loss and, ultimately, population

extinction.
To demonstrate one single route of epigenetic signalling pathway alternatives is not to establish it is the sole such set of alternatives.
It is inconceivable in any rigorous analysis of supra-generational changes in a species over thousands of generations, that just one set of epigenetic influences upon morphologies being posed for selection to act upon, would explain all variations of all morphological adaptations.
And to rule in one pathway is not to rule out the likelihood of others.

Report

jvkohl
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October 2, 2012

"To demonstrate one single route of epigenetic signalling pathway alternatives is not to establish it is the sole such set of alternatives."

In the context of adaptive evolution via ecological, social, neurogenic, and socio-cognitive niche construction, I demonstrated the only known route: gene, cell, tissue, organ, organ system, and concluded that "Olfaction and odor receptors provide a clear evolutionary trail that can be followed from unicellular organisms to insects to humans."

What other pathway would you like to rule in? Suggesting there may be one is not like detailing the fact that there is not, and exemplifying that fact via the common molecular biology in species from microbes to man.

Did you have trouble understanding what I detailed in my published work, or have you simply commented without reading it?

Report

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October 2, 2012

Please provide a link and I'll buy a copy of your study.

Report

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October 2, 2012

http://www.socioaffectiveneuro...
It's open source - no fee. TTFN

Report

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posts: 74

October 2, 2012

Google the full name. The system assumes a link is spam. It's a free article.

Report

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October 2, 2012

Kohl, J.V. (2012) Human pheromones and food odors: epigenetic influences on the socioaffective nature of evolved behaviors. Socioaffective Neuroscience & Psychology, 2: 17338. Open access: http://dx.doi.org/10.3402/snp....

Report

Carl Badgley
posts: 1457

October 2, 2012

thanks.

Report

October 2, 2012

There was a paper some years back about environmental stress causing

EllenHunt
posts: 74

genes to be expressed, relieving suppression. This was proposed as a mechanism for apparent evolutionary leaps of phenotype. Now, where is that article?

Report

jvkohl
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October 2, 2012

If you find the paper, please let us know.

The environmental stressors are primarily linked to nutrient chemical acquisition that is required for maintenance of an ecological niche by conspecifics that establish themselves in an ecotypically evolved social niche. Nutrient chemical stressors, when there is a lack of food, and social stressors, which are linked to control of nutrient-dependent reproduction, drive adaptive evolution because the chemical ecology of the environment must be balanced between how many conspecifics or heterospecifics can be supported in a given ecological niche.

That's life in or outside the microbiology department and the variable always is nutrient chemical-dependent and pheromone-controlled epigenetic effects on intracellular signaling and stochastic gene expression, which leads to de novo odor receptor gene expression and the transgenerational epigenetic inheritance of receptor-mediated behavior that helped ancestral species survive.

Some people think that stochastic means random. In the context of adaptive evolution, however, stochastic gene expression for de novo odor receptor proteins is driven by the epigenetic effects of nutrient chemicals (e.g., food odors) and social odors (e.g., pheromones). It's a simple concept that's been bastardized by those who would rather have a random event, like a mutation, cause adaptive evolution via some unknown but somehow beneficial intracellular/intermolecular change, but even endocrine disruptors alter the same evolved pathway as nutrient chemicals and pheromones in vertebrates.

Besides, most of us know that mutations are not adaptive. But if you look at the data and comments from the ENCODE project research groups, you find that most of the 442 researchers seem to want to continue to hang on to the idea that randomness might still be useful to explain something about adaptive evolution that is obviously nutrient chemical-dependent and pheromone dependent. I never expected geneticists to hold on so tightly to what can only be called the "Just-So" stories of evolutionary theorists, which is why I am interested in where this article takes us.

Report

Carl Badgley
posts: 1457

October 2, 2012

has anyone begun epigenetic studies on human environment and health?

Report

Vincent Maldia
posts: 1457

October 3, 2012

Someone is bound to use research like these to jump to conclusions that "darwin's theory of evolution has been discredited". AFAIK the epigenetic effects are quite small compared to the effect of the usual genes and this in no way disproves evolution

Report

Ed M.
posts: 2

October 6, 2012

This is going to leave a *La Marck* on the strict Darwinists.

When scientists mock one another's ideas they should remember how many once proud theories have fallen into the ether.

And how many others have been proven correct after decades of scorn.

Get my continental drift?

Report

ufsapog
posts: 1

October 7, 2012

You might be interested to look at the book Escape of the Ufsapog which is free at www.ufsapog.com which puts forward in the later chapters a speculative suggestion as to how change in the genome might have occurred.

Report

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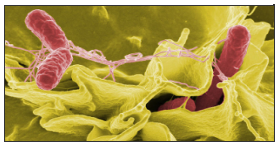

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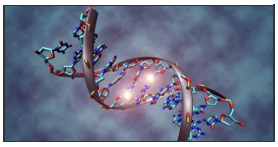

Pioneer DNA Researcher Dies

By Jef Akst

Leonard Lerman, who helped elucidate the process from gene to protein, passed away last month at age 87.