Q&A

Go BACK

QUESTION

Submitted by

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In HHMI's 2005 Holiday Lectures on Science, “Evolution: Constant Change and Common Threads,” a recurring theme is that all metazoans possess the same toolkit of genes and that the origin of new forms came from mutations in the parts of the genome regulating this universal toolkit. I can see how the universality of this toolkit could be evidence for modified descent from a common metazoan ancestor by means of mutation, especially if one can isolate distinct DNA segments separate from this toolkit corresponding uniquely to each hypothesized distinctly arising form. But I do not see how this toolkit could be seen as evidence for randomness. After all, how does it just happen that some primitive metazoan from 600 or more million years ago inherits a toolkit of genes that has embedded in it the potential to form all future metazoan anatomies by precisely mutating the DNA space surrounding it?

Science
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ANSWER

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A common theme of both the 2005 Holiday Lectures and a new discipline called evolutionary developmental biology (or “evo devo” for short) is indeed the universality of the “toolkit” genes that pattern animals from flies to humans. Most toolkit genes pattern animals by telling other genes when and where to be expressed, allowing cells to become different cell types and create the complex patterns and arrangements of cells that we recognize as tissues and organs. For example, these toolkit genes tell cells whether they will be eye tissue, nerve cells, or limbs or where they are along one of the major axes of the body (such as the anterior-posterior, or head-to-tail, axis). These genes act in different combinations with each other, making many different cell types possible.

Morphological evolution occurs in large part when these toolkit genes 1) change their expression patterns or 2) lose and acquire target genes (the genes they regulate), or as Sean Carroll put it in the lecture, “when very old genes learn new tricks.” Changing which toolkit genes are expressed in a given cell gives it a new fate. Changing which target genes respond to which

toolkit genes can create new cell types expressing different combinations of genes than before. There are numerous examples where one or the other case has been demonstrated, but that was not your question. You seem to understand how this process might work, so I won't go into detail.

So, how is a universal toolkit evidence for randomness? It is not. The notion that evolution is a random process is a common but fundamental misconception. Evolution requires two things: 1) heritable genetic variation and 2) differential reproductive success that depends, at least in part, on this genetic variation. The first requirement, genetic variation, comes from a well-studied process called mutation, which has some predictable probabilities based on the underlying chemistry and physics but is essentially random with respect to which biological variants are created. This is probably where people mistakenly get the idea that evolution is entirely random. The second requirement for evolution is anything but random; indeed, it is termed “selection” because some genetic variants are favored, or selected for, over others. It is this second component that allows species to adapt to new conditions by changing their genetic makeup, often by building on existing machinery and adding complexity.

From the perspective of selection, there are three types of mutations. First, many mutations actually do not do much at all. The language of DNA is “degenerate,” so there are many ways of producing the same effect. These mutations are retained or lost by chance. Second, many mutations are bad for the organism and are continually being removed from the gene pool by selection as new ones are created by mutation; we know many of these as genetic diseases in humans. Third, some mutations confer an advantage over the “normal” version of the gene and may gradually replace it and become the new “normal.”

A special type of mutation called a “gene duplication” creates two copies of a gene where there used to be one. As each copy acquires additional mutations, their sequences diverge, and they can evolve slightly different functions. One can spot duplicate gene pairs by examining their sequences. If the sequences are very similar, they probably shared an ancestor gene fairly recently. If they are somewhat similar, sophisticated statistical techniques are used to determine whether they are more similar than expected by chance. Since there are so many possible sequences, a fairly small amount of similarity can conclusively demonstrate the common ancestry of a gene, although it could be in the distant past. Of course, duplicated genes can be duplicated again and again such that some gene families have hundreds of members. However, each member of a gene family is descended from a single gene at some point in the distant past. As different duplications happen in different lineages of organisms, there is sometimes not a one-to-one relationship between the genes of one organism and another, and reconstructing the precise relationships can be quite difficult, even if it is quite certain that they are all family members.

Any gene can duplicate, but if a toolkit gene is duplicated, the toolkit grows in size and complexity. It turns out that most toolkit genes are members of large gene families that have shared signature sequences and conserved molecular functions. For example, many toolkit genes perform their functions by binding to the regulatory sequences of other genes and telling the cell's machinery when that gene should be expressed. (These toolkit genes are called transcription factors.) However, the basic molecular process of controlling gene expression has to be done by all living organisms. Even one-celled yeasts have genes that are turned on only when they encounter specific environments, such as different nutrient sources. As you may have guessed by now, many transcription factor toolkit genes are part of large gene families that include members from plants and yeast and other fungi that are performing the same molecular function of gene regulation. Thus, many toolkit genes are not only shared by animals but have distant cousins scattered across the spectrum of life.

While there are many families of toolkit genes and a fascinating story to go with each, one of the most interesting is the family of homeodomain transcription factors. Distant but undisputed members of the family regulate

mating and other processes in yeast and have roles in regulating plant form. This family has grown to 100 members in flies and 160 in humans, but the *Hox* subfamily is of special interest. *Hox* genes are expressed along the anterior-posterior axis in the order in which they appear on the chromosome and cause cells to adopt the fate appropriate to their position along the axis. Mutations or misexpression of these genes causes dramatic changes in body plan, such as causing a fly to sprout legs where its antenna belong or causing vertebrae to change from one type to another.

One of the early surprises of evo devo was that *Hox* genes were present in nearly all animals and were doing the same thing—regulating gene expression and cell fate along the anterior-posterior axis. I say “nearly all animals” because most animals are bilaterians, meaning they are bilaterally symmetrical and have a common ancestor before the Cambrian explosion. These animals includes worms, flies, mollusks, fish, mice, humans, and most of the ones you are thinking of but not sponges, cnidarians (e.g., jellyfish, corals, and sea anemones), or a few other less common animals. Considering the relatedness and functions of *Hox* genes in bilaterian animals, it appears that the common ancestor contained a diverse array of at least seven *Hox* genes expressed along the anterior-posterior axis as in the descendant species.

How do we know they were not all just put there and given their functions all at once? As already mentioned, the *Hox* genes are just a subfamily of the larger family of homeodomain genes that regulate gene expression in animals, fungi, and plants, but *Hox* genes themselves have a subfamily tree. *Hox* genes expressed toward the anterior are more closely related to each other, and *Hox* genes expressed toward the posterior are more closely related to each other. The fact that some *Hox* genes are more closely related to each other than to other *Hox* genes betrays their sequential creation by gene duplication. More convincing still, sea anemones (a type of cnidarian) have *Hox* genes corresponding to only three out of the seven *Hox* genes shared by the last common ancestor of all bilaterians. While sea anemones do not have a true anterior-posterior axis, they have a similar oral-aboral axis where the *Hox* genes play their patterning role. Thus, it appears that the *Hox* complex was put together gradually, starting with a single homeodomain transcription factor regulating cell fate. This gene was duplicated at least twice to create the three *Hox* genes present in the common ancestor of cnidarians and bilaterians. After cnidarians and bilaterians diverged, additional duplications in the *Hox* complex occurred in the bilaterian lineage to bring the total to at least seven. The Cambrian explosion followed, with the bilaterians making use of these and many other toolkit genes to adopt much of the dazzling array of diversity seen in the animal kingdom. Additional duplications occurred in many other lineages, including just before the origin of the vertebrates, when the whole *Hox* cluster was duplicated at least twice.

How do we know all the mutations were not directed precisely? As mentioned above, there are statistical patterns and probabilities associated with the underlying chemistry and physics of mutation, but it is essentially random with respect to biological function when studied in the lab. Moreover, we have a record of past mutations written in the DNA of the *Hox* genes (and all other genes). In addition to those mutations that have slightly changed the functions of the genes, there have been several mutations that did not change the functions but are nonetheless recorded in the DNA. If mutations were precisely directed toward a particular target sequence or goal, these changes would be unnecessary and would not have been made by any rational engineer trying to build a particular animal. The sequences of the *Hox* genes fit much better with the normal evolutionary model, where mutations occur randomly in the DNA sequence, with some mutations being favored and retained by selection, others kept by chance, and others rejected by selection.

The 2005 Holiday Lectures are available online:

http://www.hhmi.org/biointeractive/evolution/index.html

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