Epigenetics, evolution and the survival of the non-unfit

Carlos Guerrero-Bosagna

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The transition that occurred in vertebrates moving from water to land was a major step in the evolution of terrestrial animals. This is an evolutionary step that has always fascinated scientists and the general public. The land-to-water vertebrate transition happened around the Devonian period and involved structural changes such as the transition from fin to limb, a reduction of the gill arch, loss of the mid-fin and a reduction in the number of scales, among others. I will use this interesting example to depict how the same evolutionary process can be seen through two different lenses. One view, which is the most widespread way of seeing evolution, is the ‘survival of the fittest’. The other is intentionally stated in the title as the double negative ‘survival of the non-unfit’. Only semantic differences? Not in my view.

Evolution through the lens of the ‘survival of the fittest’ can be defined as benefit-driven evolution, and assumes that the majority of the traits we observe in organisms exist because they confer, or have conferred, advantage to some individuals over others. Moreover, these advantageous traits are assumed to be fully encoded within the genome, so that natural selection upon the phenotype will also act upon the genome that generated that phenotype.

Let’s now see the water-to-land transition from the other perspective. Let’s imagine that the novel structures didn’t originate to produce adaptation. Let’s imagine that they appeared previously as a non-detrimental characteristic, which allowed some individuals to explore outside the aquatic world and finally establish themselves on land. This is the same evolutionary process seen now through the lens of the ‘survival of the non-unfit’, or in other words, neutral evolution. From this perspective, most of what has survived in evolution has not necessarily conferred advantage to individuals, it has simply survived due to not being detrimental. Thus, the survivors would not only be the fittest, but would also include those that did not have detrimental traits (e.g. those that survived negative selection), in other words, those non-unfit. How realistic is such a proposition? This we will see in the next sections.
The neutral theory of evolution

The neutral theory of molecular evolution was introduced by Motoo Kimura, formally in 1968, after having described the concept of genetic drift in previous years. In Kimura's own words: "the neutral theory claims that the overwhelming majority of evolutionary changes at the molecular level are caused by random fixation of selectively neutral mutants under continued inputs of mutations" and "rejests the notion that the majority of [DNA or protein] polymorphisms are adaptive and actively maintained in the species by some form of balancing selection". In other words, according to Kimura, most of what has survived in evolution does not, and has not, conferred fitness advantages to individuals.

But what about experimental biology? Is Kimura’s prediction sustained by available data? In 2007, a study by Eyre-Walker and Keightley quantified the influence of genomic variability on fitness across species and concluded that advantageous mutations are indeed rare. Estimates by Ponting and Lunter in 2006 indicate that in addition to 2.5–5% of the human genome that would have evolved by purifying selection, essentially all of the remaining sequences would have evolved neutrally, with positive selection (i.e. associated with adaptation and increased fitness) being rare. Recent experimental evidence indicates a similar trend. A 2014 study of the radiation of African cichlid fish concluded that neutral evolution was key in producing the genetic variability related to the variety of phenotypes observed. Adaptive processes, in turn, would only have helped in partially sorting this variation.

Another example of interest relates to whole-genome amplification events leading to the formation of new bacteria or organelles. The evolution of mutation rates, genome size and chromosome structure in these scenarios has been shown to be remarkably fast, and with unexpected degrees of interdependency. Non-adaptive processes have been shown to be behind the expansion of non-coding regions in organelle genomes, as well as involved in whole-genome amplifications that lead to lineage duplication in bacteria. Thus, as Kimura predicted in 1968, it seems that neutral mechanisms (non-adaptive processes) have had a preponderant role in evolution, for which there is substantial evidence across species. This raises the question of whether too much effort and many resources have been devoted to studying adaptive evolution, which would correspond to rare evolutionary processes, to the detriment of the majority of changes that would occur in nature, which would be of a neutral basis.

Biased vs stochastic changes in the genome

One of the main assumptions of seeing evolution as the ‘survival of the fittest’ is that mutations emerge stochastically in the genome. Once they emerge, according to this view, these mutations may or may not confer a beneficial outcome to individuals within a population. However, the mutations that will finally prosper will be those that associate with a phenotype that confers a reproductive advantage. Here, we can distinguish two processes, (i) that of how genetic variation originates and (ii) that of how it becomes evolutionarily maintained.

If we focus only on how genetic variation originates, many studies have shown that mutations are indeed not stochastic in their origins, rather they might be biased according to features within the genome or reproduction. For example, GC-bias describes biased conversion due to a distortion produced during the segregation of gametes, in which G and C bases become over-represented with regards to As and Ts. This process takes place during recombination, during
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which AT/GC heterozygotes end up producing more gametes carrying G/C than A/T. GC-bias may occur in any region of the genome (functional or not) and is known to have influenced GC content in mammalian genomes. Biased conversions can also occur exclusively out of the chemical nature of nucleotides. For example, it is well known that transitions (A→G; C→T) always outnumber transversions (A→C; A→T; C→G; G→T). This results in codon changes with increased mutability of some amino acids (e.g. threonine and tryptophan). In addition, so-called epigenetic factors such as DNA methylation are also known to bias mutation rates, as described below.

What is epigenetics?

Epigenetics is a term described by Conrad Waddington, a British geneticist, who wanted to explain the meaning of epigenesis in a genetic context. Epigenesis is a term that has been around since Aristotelian times, and describes novel biological properties (emergent properties) that arise within a developing embryo, and in connection with the surrounding environment. In the 18th century, the concept of epigenesis was seen to be in opposition to 'Preformation', which stated that all the components needed for the embryo to become an adult individual were already present inside the gametes. Epigenesis, in contrast to Preformation, proposes that much of what happens during development is due to emergent properties and the role of the surrounding environment, which in a broad sense includes physical factors such as temperature, or chemical factors such as hormones or inorganic chemicals.

Waddington posed the question “how do genes interact with their products and the environment to bring phenotypes into being?” By combining the term 'epigenesis' and 'genetics' he came up with a term that is now becoming highly important in all fields of biological sciences: epigenetics.

One of the main concepts of epigenetics is to see the genome as a reactive chemical entity rather than as a code directing the development of organisms towards an adult phenotype. DNA is a molecular structure, and as such, chemically interacts with an array of other molecules; these can be complex molecules such as proteins (histones), small fragments of RNA or simply methyl groups that attach to the DNA structure. If the interaction of these molecules with the DNA can be maintained even after cell divisions, then they can be defined as epigenetic modifications. A remarkable feature of epigenetic modifications is that on the one hand they can regulate gene expression, while on the other hand they can be influenced by environmental factors.

From epigenetic to genetic changes

DNA methylation is the enzymatic addition of a methyl group (-CH3) to some nucleotides. Within the mammalian genome, the nucleotides most affected by this chemical modification are Cs neighbouring Gs, so-called CpG sites. The presence of methylation in regions of the genome can regulate gene expression by interacting with transcription factors that promote or repress gene expression.

But, where do these methyl groups come from? Ultimately, they come from our diet, from sources such as folic acid, betaine and vitamin B12. Thus, the maintenance of the patterns of DNA methylation during our lifetime will depend in part upon the dietary availability of these (and other) compounds.

One interesting aspect of DNA methylation is that it can be regarded as a ‘half mutation’, because it is one hydrolytic deamination reaction short of a full conversion to T. Due to this, the mutation rate of methylated CG dinucleotides (CpGs) to TGs is increased by ~12 times in comparison to the situation in which the CpG is not methylated. This conversion, which is more frequent than any other point mutation, is thought to contribute to the deficit of CpGs observed in vertebrate genomes. Indeed, experiments in bacteria (Escherichia coli) have shown that CpGs are hotspots of mutations only when methylated.

Another connection between epigenetics and genomic variability comes from genomic regions known as ‘transposable repeat elements’ or transposons for short. The activity of transposons is generally repressed by DNA methylation. However, if transposons become active, duplications and insertions can be produced in the genome. Interestingly, recent evidence has shown that transposition of repeat elements played a crucial role in the genomic diversification related to the radiation of African cichlid fish.

Impact of epigenetic changes on genome variability and evolution

In summary, the biochemical machinery of a cell contains the necessary pathways that allow environmental agents to induce mutations. Moreover, these pathways include the participation of epigenetic modifications. However, can induced mutations mediated by epigenetic mechanisms be evolutionarily maintained, or relevant?

For epigenetically induced genetic modifications to be maintained across generations, one aspect is needed: that they are transgenerationally transmitted through the gametes. Recent evidence has shown that when rodents are exposed to environmental toxins inside the womb, not only are epigenetic changes in the gametes transmitted, but these can also induce genetic variability as a consequence.
Now, even if these epigenetically induced mutations are maintained, are they evolutionarily relevant? To answer this question, it is important to go back to the concepts described at the beginning of this article. According to neutral evolution, if these epigenetically induced mutations are not detrimental for the species or individuals, they will be evolutionarily maintained. If that is the case, it should not be unthinkable that the action of environmental agents, mediated by epigenetic mechanisms, may be and may have been an important component in the generation of genomic variability. Then the question becomes 'how much of the genomic variability observed in nature mediated by epigenetic mechanisms has emerged after being induced by environmental conditions?' Answering this question will be an exciting scientific exercise in the coming years, and might provide grounds to change our general perception of evolution from the 'survival of the fittest' to the 'survival of the non-unfit'.

Further reading