A half-century after the molecular clock: new dimensions of molecular evolution

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The EMBO workshop on 'Evolution in the Time of Genomics' took place in May 2012 in the magnificent sixteenth century Palazzo Franchetti near Ponte dell'Accademia in Venice. The meeting focused on phenomena that are not part of the traditional narrative of molecular evolution and which might signal a paradigm shift in the field.

The molecular clock and beyond

In 1962, Emile Zuckerkandl and Linus Pauling introduced the idea of the molecular clock. In so doing, they laid the foundations of molecular evolution [1]. The EMBO workshop on 'Evolution in the Time of Genomics' celebrated this anniversary and was organized by Giorgio Bernardi (Stazione Zoologica Anton Dohrn Napoli, Italy), with the assistance of Werner Arber, Takashi Gojobori (National Institute of Genetics, Japan), Daniel Hartl (Harvard U., USA) and Bill Martin (Institute for Molecular Evolution, Heinrich-Heine U., Germany). It was supported by the Istituto Veneto di Scienze, Lettere ed Arti and the Università Roma Tre, and opened with a lively televised address from Zuckerkandl, who took us back more than 50 years to his days at Caltech, during which the first protein sequence comparisons were performed. At that time, Zuckerkandl and Pauling had no idea that they were founding a new scientific discipline, they simply marvelled at their astonishing realization that protein sequences seem to change at a close to uniform rate over long time intervals.

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Perhaps surprisingly, little was said about the molecular clock at the meeting. Instead, the most striking aspect of the meeting involved the advance of phenomena that are not part of the traditional narrative of molecular evolution and are coming to the fore: pervasive exaptation,

the wide spread of the Lamarckian mode of evolution, diverse mechanisms of evolvability and epigenetics. Taken together, these phenomena challenge the foundations of traditional evolutionary biology and could signify a paradigm shift.

Evolution as genome engineering

In a sweeping presentation, effectively an extended abstract of a book [2], James Shapiro (U. Chicago, USA) offered a new vision of the entire evolutionary process. Shapiro posits that evolution is not so much the outcome of random, stochastic mutation that provides material for natural selection—the neodarwinian picture of evolution—but that it is actually a far more complex process of natural 'genome engineering'. Genome engineering is construed as the active, dynamic process of the accumulation of various kinds of change in the genome, driven in part by direct environmental cues, under the Lamarckian modality of heredity and evolution [3]. Perhaps the most clear-cut case of directed Lamarckian evolution is the clustered regularly interspaced short palindromic repeats-CRISPR-associated proteins (CRISPR-Cas) adaptive immunity system. This system modifies archaeal and bacterial genomes by incorporating fragments of viral DNA into specific loci and then uses the transcripts of these phage-specific sequences to abrogate the replication of the respective virus [4]. In many other processes, such as horizontal gene transfer in archaea and bacteria, and transposable element exaptation in eukaryotes, adherence to the Lamarckian principle—which is best described by the engineering metaphor—is less obvious,

and yet it is clear that environmental factors substantially affect genomic changes [3]. Shapiro boldly submitted that genome engineering, rather than the (neo)darwinian process of natural selection that drives randomly occurring mutations to elimination or fixation, is the dominant mode of evolution. Fundamentally similar ideas were presented by Werner Arber (U. Basel, Switzerland) who introduced the idea of 'second-order selection', that is, selection on the properties of genes that affect the evolution of other genes [5]. Whether or not the genome engineering concept is taking the paradigm shift a step too far, some of the presentations at the Venice meeting provided strong evidence in favour of active, partly directed genome evolution.

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Venice is certainly the ideal location to discuss exaptation, given that Stephen Jay Gould and Richard Lewontin introduced this term through their famous comparison with the spandrels of the Basilica di San Marco [6]. Exaptation is the recruitment of biological molecules or structures for a function distinct from their original role including, under a broader interpretation, the recruitment of non-functional elements such as transposable elements. At the meeting, Michele Caselle (U. Torino, Italy) took

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the well-documented story of transposable element exaptation for transcription regulation to a new level. He presented a genome-wide analysis of the binding sites for oestrogen receptor alpha, a global transcriptional regulator. The results show a striking correspondence between binding sites for transcription factors—some of which are known cofactors of oestrogen receptor alpha—and distinct families of transposable element, primarily mammalian interspersed repeat elements. The conclusions are far-reaching: Caselle suggested that a ‘transposon code’ underlies the evolution of the network of gene expression regulation in mammals, and that the expansion of specific classes of transposable elements enabled the combinatorial regulation of transcription, the key regulatory principle in vertebrates. This startling hypothesis is clearly within the genomic engineering paradigm. How robust and how general these findings are remains to be seen.

Tinkering rather than engineering?

Jerzy Jurka (Genetic Information Research Institute, Mountain View, CA, USA) presented a new theory of the evolution of transposable elements. Jurka submits that transposable element bursts are not adaptive, but are brought about by a drift in small populations, which result from the subdivision of larger populations [7]. According to Jurka’s concept, differential expansion of transposable element families in such small populations could be a significant contributor to speciation in animals—comparative genomic analysis seems to show that distinct families of transposable elements are consistently linked to speciation events. This theory is fully in line with the concept of non-adaptive evolution of genomic complexity [8], but is not in tune with Shapiro’s ‘genome engineering’ view. There is no doubt that transposable elements that propagate through a neutral process are often exapted for a variety of biological functions. However, this process is more akin to tinkering *sensu* Jacob [9] than to *bona fide* engineering. Neither are the transposable elements

typical spandrels, which are supposed to be necessary constructive elements—such as the pendentives of San Marco—that are subsequently put to double-use. The transposable elements propagate in a selfish mode ‘because they can’, and are then on occasion recruited ‘because they are there’. Stochasticity dominates this process, which is not what an engineer usually wants.

Evolvability as an evolvable trait

The extensive propagation of transposable elements provides organisms, especially complex ones in which the genome is rife with transposable elements, with an enhanced potential for evolutionary change that is often called evolvability. Whether or not evolvability itself can evolve under selection, or put another way, whether there are special mechanisms of evolvability, is a fundamental and hotly debated question in evolutionary biology [10,11]. The prevailing wisdom for a long time has been—and apparently still is—that evolvability is not selectable, and is simply maintained at a sufficient level by inevitable errors at all levels of biological information processing. Evolutionary biologists are often suspicious of the evolution of evolvability, generally because ‘evolution has no forecast’. Nevertheless, evidence in support of this controversial idea is mounting.

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At the meeting, Daniel Jarosz (Whitehead Institute, USA) presented striking evidence of evolvability enhancement through phenotypic, prion-mediated inheritance. The common, best-studied yeast prion Sup35 seems to be a genuine evolvability device [12]. When this protein, which is a ribosomal release factor, assumes the prion (amyloid) conformation, the rate of translational read-through increases, leading to markedly increased variability of molecular phenotypes. This effect is driven directly by environmental stress, which increases the rate of Sup35 misfolding into the prion conformation. The accurate segregation of prion fibrils

between daughter cells is mediated by the molecular chaperone HSP104 [13], making this heritable enhanced evolvability state a *bona fide* Lamarckian inheritance phenomenon. Other, less thoroughly characterized prions—for example the transcription repressor MOT3+—have similar evolvability-enhancing properties [14]. It has been shown that a path exists from the phenotypic, prion protein-mediated inheritance to genetic inheritance, when yeast strains with diverse backgrounds are crossed and a significant frequency of genetic fixation of prion-mediated beneficial traits has been observed [12]. Thus, prions effectively violate the central dogma of molecular biology, as information is transmitted from proteins changing under direct influence of the environment to stable changes in the genome. The recent screening of numerous yeast strains described by Jarosz indicates that, contrary to the previous beliefs, prions are common in the wild [12]. Taken together, these results leave no reasonable doubt that at least some prions are indeed dedicated evolvability devices that function on the principle of Lamarckian inheritance.

Prions could be the most remarkable, unexpected example of an evolvability mechanism, but there are certainly others that are no less important. Thus, gene transfer agents—a form of defective prophage discovered in a variety of bacteria and archaea—seem to represent a specialized device for horizontal gene transfer and hence a catalyst of evolution [15]. Additionally, stress-induced mutagenesis—an elaborately controlled group of mechanisms that operates in all organisms—definitely attests to the reality of evolvability as an adaptation [16].

In parallel with these striking experimental findings, several mathematical models have been developed that derive the evolution of evolvability from a theoretical population genetic perspective [17,18]. It seems that the pertinent question at this time is not ‘is evolvability evolvable?’, but rather ‘what are the patterns and trends in the evolution of evolvability mechanisms?’

New balance of chance and necessity

It is impossible to deny that our ideas on evolution are shifting from the simple and rigid ‘random mutation-selective fixation’ scheme epitomized in the Modern Synthesis, to a much more complex, nuanced picture. Under the new view, the interplay between

Fig 1 | The new balance of chance and necessity in evolution. (A) Stochastic and deterministic components in genetic variation and fixation of mutations. (B) The interplay between the Lamarckian and darwinian modalities of evolution.

stochasticity and adaptive mechanisms is extensive and essential, both in the generation of variation and in the fixation of the changes (Fig 1A; [19]). The background of random mutations that inevitably occur, during the replication of the genetic material, certainly remains the foundation of the evolutionary process. However, it has become clear that this random background is extensively manipulated, regulated and channelled by various evolvability mechanisms. The ultimate manifestation of these mechanisms is direct, Lamarckian adaptation

through environmentally driven changes in the genome, as in the case of the CRISPR-Cas system. Conversely, the fixation of mutations includes a significant random component—genetic drift, the intensity of which depends on population dynamics—that, counterintuitively, can lead to the emergence of complex features that superficially seem to be adaptive [8].

It has become clear that the evolutionary regimens might differ depending on the conditions: the Lamarckian modality (directed mutations) is key under stress, whereas the darwinian modality (random mutations) dominates under lower environmental pressure [3]. Moreover, as the striking results with prions indicate, epigenetics can directly bridge these two evolutionary regimens (Fig 1B).

The new picture of evolution that is emerging at the time of genomics is incomparably more complex, and rich, than the somewhat simplistic scheme of the Modern Synthesis. What is perhaps most exciting is that the experimental and theoretical study of the phenomena, which will undoubtedly be central to the forthcoming new synthesis, such as the evolution of evolvability and epigenomics, is only in its infancy. Certainly, much more remains to be discovered in these areas than has been discovered already. There could hardly be a better tribute to the founders of molecular evolution than this new and rapidly evolving vision.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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