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Molecular Darwinism: The Contingency of Spontaneous Genetic Variation

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Abstract

The availability of spontaneously occurring genetic variants is an important driving force of biological evolution. Largely thanks to experimental investigations by microbial geneticists, we know today that several different molecular mechanisms contribute to the overall genetic variations. These mechanisms can be assigned to three natural strategies to generate genetic variants: 1) local sequence changes, 2) intragenomic reshuffling of DNA segments, and 3) acquisition of a segment of foreign DNA. In these processes, specific gene products are involved in cooperation with different nongenetic elements. Some genetic variations occur fully at random along the DNA filaments, others rather with a statistical reproducibility, although at many possible sites. We have to be aware that evolution in natural ecosystems is of higher complexity than under most laboratory conditions, not at least in view of symbiotic associations and the occurrence of horizontal gene transfer. The encountered contingency of genetic variation can possibly best ensure a long-term persistence of life under steadily changing living conditions.

Key words: evolution genes, molecular mechanisms of variation, natural strategies of variation, variation generator, modulator of rates of variation, systemic aspects of evolution.

According to the Neo-Darwinian theory, biological evolution is driven by the occasional spontaneous generation of genetic variants in populations of organisms. The directions that biological evolution takes depend on natural selection and on the available genetic variants. Natural selection results from the success of individual organisms in their interaction with the encountered inanimate and animate environments. Reproductive and geographic isolations modulate the evolutionary progress.

Stable genetic variations that cause phenotypic changes and that are also inherited into the progeny correspond to alterations of the nucleotide sequence of DNA, that is, of the genome, although by far not all sequence changes result in altered phenotypes. A DNA sequence change occurring within an open reading frame can affect the activity of a gene product. The availability of a gene product can become altered by a mutation affecting a control signal for the expression of the particular gene.

Recent advances in molecular genetics and genomics enable us to investigate the molecular mechanisms of spontaneous genetic variation. Single mutagenesis events can best be studied with small genomes, such as those of bacteria and of viruses. In addition, computational sequence

comparisons of DNA from evolutionarily more or less-related organisms can reveal what kind of mechanisms must have been involved to generate observed differences in the compared DNA sequences.

A striking result of these experimental studies is the parallel involvement of several specific molecular mechanisms that contribute at different rates to the spontaneous generation of genetic variants. The so far identified mechanisms can be assigned to three qualitatively distinct, so-called natural strategies of genetic variation (Arber 2003, 2007). These strategies and selected examples of specific mechanisms will be briefly described in the following sections.

Relatively often, a novel mutation is explained by a local DNA sequence change, affecting one or a few adjacent nucleotides. Some of such changes are explained by limited chemical or structural stabilities of nucleotides, whereas other changes are assigned to activities displayed by the enzyme complex mediating DNA replication. Depending on the particular mechanisms at work, local sequence changes can result in the substitution of a nucleotide by another one, in the deletion of one or a few adjacent nucleotides, in the insertion of one or a few additional

nucleotides, or in the scrambling of a few adjacent nucleotides. For an individual genome, the rate of local sequence changes is expected to depend on the genome size. However, living organisms possess enzymatic repair capacities that can prevent with some efficiency the stable establishment of local sequence changes in their genome. This ensures a relatively high degree of stability of the genome. The evolutionary quality of local sequence changes resides in the occasional improvement of a biological function. Local sequence changes can more or less randomly occur anywhere in a genome and thus affect any gene function. Note that specific gene products as well as nongenetic elements, such as intrinsic properties of matter, are involved in the generation of local DNA sequence changes.

A second natural strategy of genetic variation resides in the intragenomic reshuffling of DNA segments. In general, these recombinational events are mediated by specific enzymes. Examples are general, homologous recombination, transposition of mobile genetic elements, and site-specific recombination. In the latter case, relatively short specific nucleotide sequences can serve as crossing over sites, or such sites may correspond to a consensus sequence. Occasionally, so-called secondary sites of crossing over may also serve in a rearrangement, although with considerably lower frequencies than between specific crossing over sites. Such conjectural DNA rearrangements are of high evolutionary relevance. For some of the enzyme systems mediating DNA rearrangements, an additional gene product acts on still other DNA sites as factor for inversion stimulation, so that a given DNA segment becomes inverted at its residential site. Depending on the functional characteristics of the involved enzyme systems, enzyme-mediated DNA rearrangements can principally involve specific or consensus sequences at different genomic locations, whereas in other systems, other genome areas may occasionally also become involved, in some cases with a statistical reproducibility. Similar observations were made for the target selection of transposing mobile genetic elements. Some such elements may highly favor insertion into specific nucleotide sequences; others, in contrast, may guide the insertion into particular genomic regions whereby used sites of insertion do not reveal any sequence homology. Generally speaking, DNA reshuffling can affect parental functions either positively or negatively or it can open new possibilities for future evolution, such as upon the duplication of a DNA segment. Some rearrangements may end up in a deletion, others in a novel fusion product. A gene fusion occurring between two different open reading frames may occasionally bring about a novel biological activity. A so-called operon fusion may associate a given open reading frame with an alternative expression control signal. Events of intragenomic DNA rearrangements can be seen as an aimless reassortment of available parts of genetic information. Chances for functional improvements or for resulting in a novel functional

capacity might be minute but still of relevance for the evolutionary progress. Such rare beneficial events may explain parts of the sudden emergence of novel functional capacities.

Various mechanistically different processes in eukaryotic organisms are known to contribute to the duplication and further amplification of genomic segments, of chromosomes and of entire genomes. Polyploidy that must have resulted from irregularities in cell division has been studied by microscopic observations long before nucleotide sequence analysis and comparison became available. Chromosomal amplification and its functional and evolutionary impacts have since these early investigations become textbook knowledge. Polyploidy is also of practical importance because it can improve the vigor of the organism in question, in particular of agricultural crops.

A third natural strategy for the spontaneous generation of genetic variants can also contribute to the emergence of novel genetic functions: the strategy of DNA acquisition by horizontal transfer of genetic information from a donor organism to a recipient organism. In the world of bacteria, horizontal gene transfer can involve any part of a genome by any of the three ways that have been intensively studied by microbial geneticists. In transformation, donor DNA that has been released from a donor bacterium into its environment can enter a recipient bacterial cell where it can become an added part of the cellular genome. In conjugation, donor DNA is transferred into a recipient upon close cellular contact between the donor and the recipient cells. Alternatively, bacterial viruses can also serve as natural gene vectors in horizontal gene transfer; this is called virus-mediated transduction. Several natural barriers limit horizontal gene transfer among bacteria to low rates. Surface compatibilities are required for the early steps of DNA acquisition. In addition, many bacteria possess restriction-modification systems enabling them to distinguish between the cell's own DNA and foreign DNA entering the cell. In the latter case, the foreign DNA gets cleaved into fragments. Although such DNA fragments fast get completely degraded by still other enzymes, some of the fragments of invading DNA may become part of the recipient genome. A last barrier consists then in the question of the impact that may become exerted on the functional harmony of the resulting hybrid. In other words, natural selection will finally decide on the longer term maintenance of the hybrid formed upon DNA acquisition. In the positive cases, for example, upon the acquisition of genetic information for resistance to antibiotic drugs, a single step of DNA acquisition can considerably extend the cellular capacities. The bacteria in question do not need to develop their own genetic potentials in a long-term multi-step evolutionary process. Rather, with the strategy of DNA acquisition, recipient cells can profit from earlier evolutionary progress made by other organisms. In the DNA acquisition strategy, contingency is clearly seen in the randomness

of encounter of donor DNA with a recipient cell, in the chance of integration of the invading genetic information into the genome, and in the functional characteristics of the resulting hybrid.

In short, molecular genetic investigations revealed that a number of different gene products, as well as several nongenetic elements, are at the basis of the spontaneous generation of genetic variants. Some of the involved gene products obviously also serve for the normal cellular life, whereas other gene products, such as recombinases, transposases and restriction and modification enzymes, are inessential for the life of individual cells and carry out only evolutionary functions at the level of populations. We therefore call their genetic determinants evolution genes. Some of their gene products act as variation generators, others as modulators of the rates of spontaneous genetic variation. As we have seen, nongenetic elements contributing to the generation of genetic variants include intrinsic physicochemical properties of biomolecules as well as random encounter. Still other nongenetic elements contributing to spontaneous mutagenesis are internal and environmental mutagens.

A philosophical conceptual aspect of the actual scientific knowledge on genetic variation is the rather unexpected conclusion of a duality of the genome. Besides a majority of genes serving to each individual organism to fulfill its own life, the genome also carries genes enabling populations of organisms to undergo biological evolution. This can be seen as the basis for the expansion of forms of life, that is, for biodiversity.

Although the scientific knowledge presented here in a condensed form resides to a large extent on experimental investigations with microorganisms, increasing evidence, coming for example from computational DNA sequence comparisons, indicates that principally the same natural strategies of genetic variation, local sequence changes, intragenomic DNA rearrangements, and DNA acquisition, are also in action in higher multicellular organisms. Here, genetic variation can also become relevant at the somatic level, for example, in the generation of antigenic diversity or at the basis of cancer development. Generally speaking, one can postulate that all kinds of organisms living today on our planet earth dispose of a set of evolution genes that had

become fine-tuned in the course of long periods of past evolution for their evolutionary functions. This provides to the organisms their evolutionary fitness. In a well-balanced interplay between products of evolution genes and various nongenetic intrinsic factors, the natural reality takes actively care of biological evolution, whereby a relatively comfortable genetic stability is provided to the individuals, on the one hand, and where the natural potency to undergo biological evolution ensures a slow but steady replenishment of biodiversity, on the other hand.

Various aspects of contingency have already been discussed for the spontaneous generation of genetic variants, in which each of the involved specific mechanisms reveals its characteristic local and temporal contingencies. We are aware that the situation in natural ecosystems is considerably more complex than under defined laboratory conditions for experimental explorations. Symbiotic associations between different kinds of organisms and in particular endosymbiosis but also pathogenicity effects can bring about various functional interdependencies of cohabitation partners. These mutual relationships can undergo considerable variations as a function of time and in response to environmental impacts. Established scientific knowledge on the dynamic of evolutionary developments in natural ecosystems is still relatively poor. Although difficult to be approached, the underlying systemic aspects deserve increased attention. Nevertheless, we can conclude here that contingency is widely present in the natural generation of genetic variants and that it thus influences to a large extent the course of biological evolution of the living world. The complex systemic nature of natural ecosystems with inbuilt contingencies can be supposed to best ensure a long-term persistence of many forms of life under steadily, although slowly changing environmental conditions.

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