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Molecular Darwinism and its Relevance for Translational Genetic Research

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Evolutionary biology and genetics have their roots around 1860 in fundamental publications by Charles Darwin and by Gregor Mendel, respectively. At that time, both of these fields of the life sciences had their experimental basis in the observation of inherited phenotypical traits of higher organisms, plants and animals. It is only around 1940 that microbial genetics made its start. Within a few years, bacterial transformation revealed that the nucleic acid DNA is the carrier of genetic information [1], and bacterial conjugation showed that genetic information of a donor bacterium became linearly transferred into a recipient bacterium upon close contact between the two cells [2]. This latter observation soon turned out to be consistent with the filamentous, double-helical molecular structure of DNA described in 1953 [3]. At that time, it became clear that genetic information is encoded by the linear arrangement of building blocks of DNA, i.e. nucleotides in a single strand of DNA or base pairs in the double-stranded helical DNA molecules. Already before this fundamental insight, bacteriophage-mediated transduction was discovered [4], in which a bacterial virus acts as a vector for bacterial genes which thereby can become horizontally transferred from a donor bacterium into a recipient bacterium. It is on the basis of these discoveries of research in microbial genetics and in structural biology that molecular genetics started and developed rapidly in the second half of the 20th century. It became thereby known that classical genes consist of linear sequences of nucleotides that encode in their reading frame a gene product that is mostly a protein and sometimes an RNA molecule. The average gene length is about 1000 nucleotides. Much shorter nucleotide sequences serve as expression control signals with which other gene products can positively or negatively interact. In view of this advanced knowledge it became clear that spontaneously appearing altered phenotypical traits of individuals must have their cause in an alteration in the nucleotide sequence of the genome. While classical genetics had defined a mutation as an altered phenotype that gets transmitted to the progeny, molecular genetics now defines the mutation by an altered nucleotide sequence. An experimentally based critical evaluation of this situation shows that by far not all spontaneously occurring nucleotide sequence alterations

result in altered phenotypes. Indeed, many nucleotide alterations in the genome remain without immediate influence on life processes. Some of these silent, neutral mutations may at some later times become of functional relevance together with still other mutational alterations of the genome. Among the spontaneously occurring nucleotide sequence alterations affecting a biological function, a majority is functionally unfavorable and provides a selective disadvantage. In contrast, favorable, 'useful' mutations providing a selective advantage are relatively rare. This situation can serve as an argument that spontaneous mutagenesis is, in general, not directed towards a particular, identified goal. Rather spontaneously occurring genetic variations must be largely contingent.

According to the theory of biological evolution spontaneously occurring genetic variation drives biological evolution. Without genetic variation there would be no evolution. The directions that evolution takes depend on the impact of natural selection and on the, at any time, available genetic variants. Natural selection is seen as the impact exerted by both physicochemical and biological, environmental constraints on the organisms living in ecosystems. A third pillar of biological evolution besides genetic variation and natural selection is reproductive and geographic isolation. This isolation modulates the evolutionary process.

Thanks to research strategies of molecular genetics, it has become possible to experimentally investigate molecular mechanisms of spontaneous genetic variation. Without going into experimental details, we will summarize here the available results of studies that were mostly carried out with microorganisms and then also validated for higher organisms. Relatively unexpectedly these studies revealed that a multitude of specific molecular mechanisms contribute to the overall genetic variation. These mechanisms can be assigned to three natural strategies of genetic variation, namely local sequence changes, intragenomic rearrangements of segments of the DNA filaments, and DNA acquisition by horizontal transfer of a DNA segment from another kind of living organism [5,6]. These natural strategies of genetic variation contribute with different qualities to the steady but slow progress of biological evolution.

Local nucleotide sequence changes can, for example, occur for various known reasons during DNA replication. This can result in a nucleotide substitution, in the deletion or the additional insertion of one or a few nucleotides or in a scrambling of a few adjacent nucleotides. These processes can occasionally lead to a stepwise improvement of an available biological function. The genetic variant in question may then profit from its selective advantage and eventually overgrow its parental population.

Intragenomic DNA rearrangements are often guided by genetically encoded recombination enzymes, such as for general recombination between largely homologous DNA segments, for transposition of mobile genetic elements, and for site-specific DNA reshuffling. By pure chance, a segment-wise DNA rearrangement may lead to an improvement or to novel combinations of available functional capacities. The fusion of two different functional domains of open reading frames, as well as the fusion of an open reading frame with an alternative expression control signal, may have their origin in such occasionally occurring DNA rearrangements. This might perhaps lead to a sudden emergence of novel properties, a phenomenon that had so far not found a satisfactory explanation.

Emergence of a novel property might also have its cause in the acquisition of a foreign DNA segment by horizontal gene transfer. A number of viruses are known to act occasionally as natural gene vectors, both in microorganisms as already discussed and in higher organisms. Horizontal gene transfer can serve in nature for the acquisition of a foreign functional domain, a single gene or a small group of genes. This strategy of sharing in successful developments made by others is quite effective and can provide to an organism a novel functional capacity in a single step of evolutionary progress. This process is facilitated by the universality of the genetic code [7].

The scientific insights into the mechanisms and natural strategies of genetic variation can validly contribute to our worldview and they have thus cultural, philosophical values. Particular genes that we now call evolution genes contribute as variation generators and/or as modulators of the rates of genetic variation to the evolutionary progress of populations. They do this together with non-genetic elements such as a limited chemical stability and structural flexibilities of biologically active molecules. Still other non-genetic elements involved in genetic variation are environmental mutagens and random encounter. We can conclude that the natural reality takes actively care of biological evolution. This represents an expansion of the Darwinian theory to the level of molecular processes that we call here molecular Darwinism.

We assume that the evolution genes exerting their activities in today's available living beings had become fine-tuned in their functions by second-order selection [8] in the course of their long past history. Biological evolution is governed by two natural antagonistic principles: on the one hand the promotion of genetic variation which is the driving force of biological evolution, and on the other hand a limitation of the rates of genetic variation. This provides a relatively comfortable genetic stability to most individual organisms, and it contributes to the longer-term preservation of species. Biological evo-

lution is the source of biodiversity. The natural potency to evolve guarantees for the future a steadily developing, rich biodiversity. This evolutionary progress could be considered as a permanent creation.

Since evolution genes belong to the genome of each living organism, the genomes show a conceptual duality: on the one hand, many genes work for the benefit of the individuals, for the fulfillment of their lives. The underlying genetic determinants are housekeeping genes, accessory genes of use under particular life conditions, and genes contributing in higher, multicellular organisms to the embryonic development of each individual. On the other hand, evolution genes contribute with their products to the occasional genetic variation in randomly involved individuals. This evolutionary driving force serves for an expansion of life and, as we have already discussed, for biodiversity.

We must be aware that life in natural environments is much more complex than under most experimental laboratory conditions. Nevertheless, the laws of nature discussed here guiding biological evolution are very likely to be of general validity. Most living species possess an evolutionary fitness by being equipped with evolution genes for each described strategy to generate genetic variants. We are more and more aware that symbiosis between different kinds of organisms plays important general roles in ecosystems. Plants, animals and human beings are full of microorganisms without being sick. Rather, these cohabitating organisms provide mutual help (symbiosis) to the partners in the communities. Their evolutionary potency also helps the populations to occasionally adapt to changes occurring in the composition of the ecosystems. This can include the possibility of horizontal gene transfer that might be favored under conditions of cohabitation.

Research strategies based on genetic engineering have been developed since the 1970s and they now serve both in fundamental and in applied research. In genetic engineering segments of DNA can be separated, purified and differently spliced together. Recombinant DNA often contains DNA segments from more than one genome. Genetic engineering can also produce local nucleotide sequence alterations by site-directed mutagenesis. All of these research methods are very similar to natural events of genetic variation that we have outlined above. As a matter of fact, both natural genetic variation and genetic variation directed by genetic engineering follow the same rules based on natural laws of biological evolution. This mainly involves relatively small steps of genetic alterations. In addition, any resulting genetic variants and hybrids become subsequently submitted to the laws of natural selection based on the requirement for a functional harmony and on the ability to deal with the encountered environmental conditions.

It follows from these considerations that longer-term evolutionary risks of genetically engineered organisms must be similar to comparable risks occurring in the natural processes of biological evolution. Similar risks are also expected for classical plant and animal breeding strategies. From long-time experience we know that such risks are quite small both for breeding techniques and for natural biological evolution. Thus, we can expect similarly low long-term evolutionary risks for genetic engineering. This holds as long as experimental procedures do not involve specifically designed, entirely novel DNA sequences which may, so far, have not been present in the biosphere. These reflections are of relevance for any project of translational genetic research. In addition, such research projects, particularly those involving human beings and higher animals, should pay full respect to ethical considerations on a case-by-case basis of specific projects.

As far as genetically modified food crops are concerned, a road map for agro-biotech applications has recently been proposed which would deserve to be followed for a functional improvement of nutritional values and for a more stable health of our most important food plants [9,10]. This could considerably improve the nutritional conditions and the food security for the world population. It has been reminded, however, that such a beneficial development in the next few decades should not be taken as a signal for a continued population growth. Rather, in view of improved health conditions and significant reduction of malnutrition and hunger, the human society should be reminded to attain a stable equilibrium of the population density by a responsible parenthood. Such an equilibrium could ensure a long-term sustainability of our cultural evolution, respecting the high diversity of forms of life and of the habitats for all living organisms on our planet Earth.

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