THE USE OF INDUCED MUTAGENESIS IN GENETIC RESEARCH REVIEW – PART TWO

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Abstract. *The review article shows the chronology of the development of the theoretical directions of genetics on the basis of quantum and gene theories that arose simultaneously and received further rapprochement due to common laws. The role of research by I.A. Rapo-port in microgenetics, concerning the study of fine levels of the structural and functional organization of the genetic material of organisms. At the junction of the integrated sciences, wide horizons open up for penetrating into the depths of the phenomena of the material world, which led I.A. Rapoport to the discovery of chemical mutagens and the phenomenon of chemical mutagenesis. The rapid development of nanobiotechnology currently confirms the validity of I.A. Rapoport in the aspect of interdisciplinary synthesis of sciences and provides an opportunity to study nanostructures and manipulate them, which is of interest for medicine, biotechnology and other branches of scientific knowledge. Modern scientists predict a closer interaction of quantum mechanics and genetics, since it is in the field of joint action of these two sciences, operating with discrete units, that a number of urgent problems of nanotechnology are expected to be solved. Methodology of chemical mutagenesis I.A. Rapoporta makes his revolutionary contribution to the development of the ideas of genetic atomism, biotechnology and materials science, expanding the scale of the source material for them.*

Keywords: *mutagenesis, genetic variability, selection, microgenetics, quantum physics, nanobiotechnology, materials science.*

Introduction. The use of the method of experimental mutagenesis in plant breeding has made a great contribution to the theory of genetics, to the development of genetic breeding methods, the development of microbiology and raw agricultural products, as well as health problems [21-23]. Currently, studies in the field of artificial induction of mutations show the effectiveness of their use in solving problems of protecting the external environment from pollution [9]. In this regard, the task of managing the processes of variability comes to one of the first places in theoretical research and practical selection, and the construction of genotypes becomes a fundamental problem of these processes [6].

Induced mutagenesis in the development of theoretical genetics

If an idea doesn't seem crazy at first,
then it is hopeless (A. Einstein)

The year 1900 in natural science was marked by the birth of two great theories: quantum and genetic, which established two fundamental features of the material world - discreteness and discontinuity. The discoveries of the electron, the portioning of electromagnetic energy, the discovery of X-ray quanta, the phenomena of radioactivity, as well as the phenomena of heredity paved the way for the dominance of atomistic views in the theory of the structure of matter. A great contribution to the development of the ideas of genetic atomism was made by the experimental and theoretical studies of I.A. Rapoport. These studies have shown that the same patterns operate in genetic systems as in microphysics: atomism, high ordering of discrete units, their divisibility into other orders of discontinuity, abrupt transitions from one state to another [5].

These conclusions were preceded by I.A. Rapoport, as well as practical and theoretical achievements of other scientists. G. Möller, for example, was the first to show that the finest hereditary structures of chromosomes can change abruptly under the influence of X-rays - thus, there are transformations of some genes into others. The discovery of the possibility of accelerating the mutational process in all its various forms has given researchers a powerful method that makes it possible to put concretely some of the most difficult questions of modern genetics [6, 22].

A.S. Serebrovsky and N.P. Dubinin successfully used this method in solving theoretical problems of genetics, and by the end of the 30s of the 20th century, the creation of a general theory of the occurrence of mutations, the so-called “target theory”, was completed [1, 3, 16].

In the 40s of the last century, an intensive study of the mutagenic action of organic compounds began. The discovery of I.A. Rapoport and S. Auerbach in 1947, the mutagenic activity of ethyleneimine and diethyl sulfate further contributed to the wide scope of work on the induction of mutants in plants. Studies on chemical mutagenesis, which were initially carried out on Drosophila, were, however, of broader importance in the development of the problems of mutagenesis, since they served as the basis for the widespread use of chemical agents in studies of mutagenesis in various living organisms [17, 22].

I.A. Rapoport in the field of hereditary and phenotypic variability is largely due to the fact that he was able to integrate the fundamental sciences for these purposes: genetics, physics and chemistry. At the junction of integrated sciences, wide horizons open up for penetration into the depth of phenomena, which led I.A. Rapoport to his main discoveries [21]. Rapoport's discovery of chemical mutagens and the phenomenon of chemical mutagenesis are among the greatest discoveries of the XX century, for which he was nominated for the Nobel Prize. I.A. Rapoport discovered about 300 strong chemical mutagens that cause hereditary variability, and weaker - several times more, with which he also worked a lot. Iosif Abramovich called the most effective chemical substances supermutagens [19-21]. I.A. Rapoport found that the specificity of the spectrum of action of chemical mutagens is caused by the ensemble of physicochemical properties inherent in each substance, as well as by the richness of combinations in the mutagen molecule of radicals directly involved in the formation of valence bonds with the attacked gene [8].

It was found that the selectivity of the action of a chemical mutagen is associated with the characteristics of the metabolism of the biological system: the sensitivity of individual stages of the life cycle to the agent, the presence or absence of enzymes that inactivate the functional group of the mutagen, the permeability of cell membranes, etc. Mutations taken into account at the level of the organism are the result of a complex of phenomena at different levels of organization of genetic systems - from molecular to organismal and population. The specificity of the organism in mutagenesis as a whole manifests itself as a reflection of the action of the mechanisms of organismic homeostasis, based on the functioning of the genetic and physiological protective-restorative systems of the organism [21, 22]. The specificity of the manifestation of mutations depends not only on the type of the influencing factor (mutagen) and the genetic characteristics of the target, but also on the modifying effect of external conditions when the mutagen affects the body [17], as well as on the growing conditions of M-1.

The specificity of the action of supermutagens at the cellular and molecular levels is associated with their chemical affinity for certain structures of the genetic material of the cell, precursors of DNA and protein synthesis (triplets, nucleotides, amino acids) and certain regions - chromosome loci due to the fact that the dipole moments of the molecules of chemical mutagenic substances correspond to the dipole moments moments of certain molecular structures of the cell [10-12, 19, 20]. In the formation of ideas about specificity, it is important that when using the most efficient alkylating mutagens I.A. Rapoport in moderate doses, they are able to enter into alkylation (methylation) reactions with DNA bases. In this case, the euchromatin-heterochromatin ratio can change towards an increase in the amount of heterochromatin (epigenetic processes), which, apparently, is one of the reasons for the emergence of highly adaptive properties [18, 21].

Non-hereditary variability has also been deeply studied by I.A. Rapoport. He discovered a large number of chemical compounds that cause modifications (morphoses), in particular, phenocopies that mimic mutations. Among the modifiers, the most interesting is a highly effective physiologically active substance, an antioxidant, para-aminobenzoic acid (PABA) [20]. By activating the enzyme DNA polymerase, PABA causes repair - restoration of chromosomes damaged by ionizing radiation or high doses of chemical mutagens [2]. PABA has been widely used in agriculture since the 1980s on cereals, vegetables and forage crops, in domestic and farm animals, in which immunity, survival, weight and fertility are increased. PABA is also used in forestry, cell culture, tissue culture. It is used in gerontology and in the treatment of eye diseases. Such a broad positive effect of PABA on various taxonomic objects is mainly based on the activation of a wide range of vital enzymes, which are often depressed under the influence of unfavorable conditions, and on the restoration of damaged chromosomes. In this regard, PABA is especially effective in those cases when the external conditions are unfavorable [20].

At the annual All-Union meetings on chemical mutagenesis, held by I.A. Rapoport at the ICP USSR AS from 1966 to 1990, in his traditional reports on theoretical issues of genetics, he substantiated the need to study more subtle levels of the structural and functional organization of genetic material. In this regard, he predicted the convergence of genetics with quantum physics in the very near future. At the time, these statements caused confusion among most of the audience, since the idea itself seemed paradoxical. Many years later, the executive editor of the book "Iosif Abramovich Rapoport - scientist, warrior, citizen", professor V.G. Mitrofanov, wrote in the preface to it: "... the originality and novelty of his ideas were not always and not immediately appreciated by contemporaries properly, because ideas outside the dominant paradigm of most people, as you know, are not perceived" [7]. In this context, we have cited A. Einstein's statement as an epigraph to this article.

Here are some more fragments from the works of S. Zakhidov, O.G. Stroeva and other authors for the purpose of a synopsis of the topic raised.

The fundamental provisions of this line of research were published in the book by I.A. Rapoport "Microgenetics" (1965), the circulation of which in the same year was completely destroyed by order of the authorities. Only thanks to the efforts of his followers and like-minded people and, mainly, his wife and associate I.A. Rapoport, professor O.G. Stroeva, the book "Microgenetics" received a second life in 2010 and the possibility of its "entry into scientific use, pushed back by 45 years" [10].

"Microgenetics" is the first experience of an interdisciplinary approach to understanding the phenomenon of life. "Microgenetics", and then all subsequent theoretical works of I.A. Rapoport gave the keys for obtaining deep knowledge about the structure and function of hereditary information, including from the standpoint of thermodynamic science [4].

Microgenetics is a new direction in genetics concerning the structure, properties and functioning of the apparatus of heredity, which are considered in the light of certain physicochemical constants and laws of thermodynamics at the level of autocatalysis monomers (nucleotides, triplets and amino acids) using chemical mutagens as test bodies. "Microgenetics is related to classical genetics (macrogenetics - in Rapoport's terminology) as quantum physics - to classical physics" [10, 13].

"Rapoport postulated: quantum mechanics and genetics have a strong theoretical relationship. Both study complex discrete sets, ... subordinate to one "ideal scheme", to the same laws, and wholly belonging to the system of natural atomisms, in which the classical hierarchy (ideal nesting) prevails. Discreteness endowed both fermionic and gene systems with stationarity. In the genetic system, as in the quantum system, there is uncertainty. For example, it is difficult to predict in which gene a mutation will occur" [5, 10].

In the microgenetic material of almost all living forms, one and the same extremely strict standard for the composition of the ensemble of amino acids and nucleotides is observed. This limited set of structural members remains almost unchanged throughout the long history of the development of living things. Zero entropy, which is maintained only in triplets and nucleotides within genes, far surpasses all molecules in order of order. Therefore, free nucleotides and triplets without the participation of a template cannot create a gene structure, although once this happened or occasionally occurs in a spontaneous order. In general, genetic matter is capable of changing state without losing its privileged structure and stationarity. This is the thermodynamic peculiarity of the microgenetic apparatus [4, 10].

According to experts in the field of nanotechnology, DNA and protein molecules can become the basis for the creation of hybrid, mixed nanomaterials with new unique properties. It is also proposed to use double-stranded DNA molecules as important elements for microcircuits and to replace inorganic semiconductors with them [4]. The rapid development of nanobiotechnology today confirms the validity of I.A. Rapoport in the aspect of interdisciplinary synthesis of sciences and provides an opportunity to study nanostructures and manipulate them.

The nanoscale is unique because the fundamental properties of the elements of the nanoworld depend on their size to an extent that they do not depend on any other scale. At the molecular level, new physical and chemical properties emerge, determined by the behavior of atoms, molecules and nanocomplexes. Biological nanoobjects with linear dimensions of 1-100 nm include protein molecules, DNA, RNA, cytoskeletal polysaccharides, membrane channels, an intracellular signaling system, etc. DNA autoreplication can be considered a nano-phenomenon [14].

Russian scientists from the Institute of Bioorganic Chemistry of the Russian Academy of Sciences were the first to develop a technology for the automatic assembly of nanoparticles using molecules of some proteins isolated from rod-shaped bacteria. Nanoparticles collected in this way are of interest for medicine and biotechnology. Drug molecules and radioactive particles can be attached to these nanoparticles for the diagnosis and treatment of cancer. A radioactive isotope, fluorescent particle, drugs, toxins can be embedded in a nanoparticle [15]. The positive therapeutic effect of using protein nanoparticles with antimicrobial properties is largely due to the fact that they easily overcome the blood-brain barrier and fight infection already “in the field”. This cannot be achieved with conventional antibiotics [14]. Fundamental results on the creation of nanostructures based on nucleic acid molecules containing molecules of "guests" were recently obtained by the laboratory of Yu.M. Evdokimov at the Institute of Molecular Biology. V.A. Engelhardt RAS. The authors believe that such nanostructures hold great promise for practical application in various fields of science and technology, from optics and electronics to medicine and ecology. It is in nanotechnology that the interests and methods of physics and chemistry, biology and materials science are closely intertwined ... because the peculiarity of nanoscience and nanotechnology is their interdisciplinarity [5].

Thus, "the new time will certainly push quantum mechanics and genetics to an even greater convergence, since it is in the field of joint action of these two sciences, operating with discrete units, that a number of urgent problems of nanotechnology, a new representative of high technologies, are expected to be solved. And in this regard, Rapoport's methodology of chemical mutagenesis could make its revolutionary contribution by expanding the scale of the source material" [5].

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