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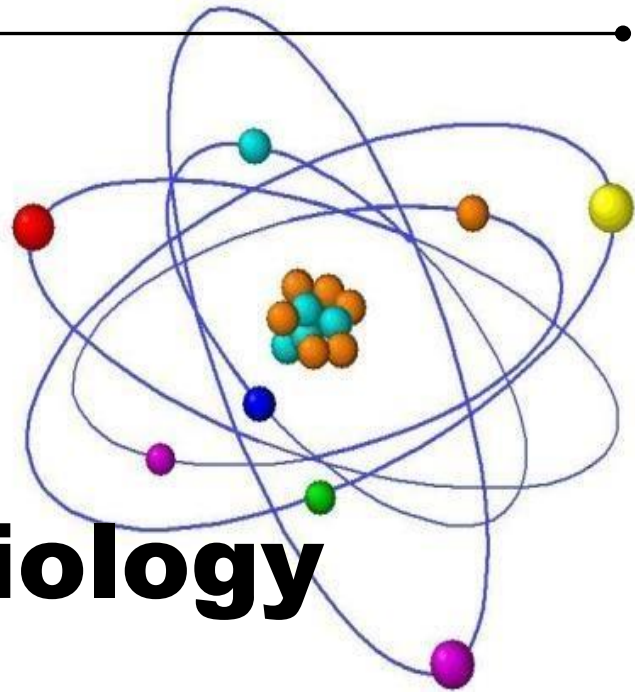


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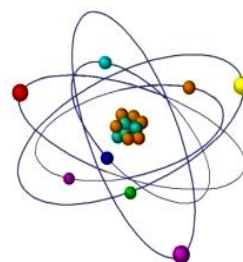
THE EVOLUTION OF RADIORESISTANCE

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ABSTRACT: *The relationship between the information capacity of the eukaryotic genome and the potential for epigenetic variability is shown. The progressive evolution of the genome is due to the need to increase the information capacity of the genome and improve genetic reliability systems to ensure a stable operation of the growing genetic apparatus of prokaryotic organisms.*

Key words: radioresistance, evolution, genetic reliability

The first direct experimental evidence of the genetic determination of radioresistance (GDR) was the production of mutations in *E. coli* that lead to a change in radioresistance. A mutant form B/r was isolated from a UV-irradiated suspension of cells which significantly exceeded the initial strain in terms of radioresistance (RR). For eukaryotes, several dozens of genes that affect RR are currently known, and many of them have been mapped. At the same time, it was shown that they are located randomly in the genome without forming clusters, i.e., they are characterized by chromosomal non-localization. In addition, the GDR system has a number of other properties: polygenicity, recessiveness (predominantly), and non-specificity. Undoubtedly, progressive evolution could not take place without the improvement of systems that ensure the stability of the genome in general and against radiation exposure in particular. In this regard we were primarily interested in the phylogenetic aspect of RR, therefore, it is extremely important to conduct research on the comparative RR of biological objects that are at different stages of phylogenetic development and differ in structural and functional organization. Such studies have a rather rich history, and their results have been expressed in a number of attempts to create the concept of Radiotaxon.

The range of RR variation determined, for example, by LD_{50} , is quite wide - from several Gy (mammals) to several thousands of Gy (bacteria, viruses, lichens), i.e. within four orders. In 1961 Terzi M.[1] for the first time tried to establish the relationship between RR and the structural organization of the genome of 32 species of organisms using the efficiency of genome inactivation as an indicator of RR:

$$E = 3,7 \times 10^{11} \frac{D}{N}$$

where: E —inactivation efficiency; D —radiation dose, P ; N —molecular weight of the genome, daltons.

As a result of the analysis - 4 groups of organisms were identified that differ significantly in E : 1) ($E_{sr} = 0.64$) single-stranded RNA and DNA viruses; 2) ($E_{sr} = 0.62 \times 10^{-1}$) double-stranded viruses; 3)

($E_{sr} = 1.23 \cdot 10^{-2}$) bacteria (with the exception of *Haemophilus influenzae* which fell into the second group) and haploid yeast; 4) ($E_{sr} = 0.69 \times 10^{-3}$) mammalian cells, as well as di- and polyploid yeasts. According to TerziM. the difference in the effectiveness of the inactivation of the selected groups of organisms could be due to the differences in the structural organization of their genetic systems.

This direction was further developed in the work of Kaplan G. and Moses L. (who drew attention to a significant correlation between RR and the content of nucleic acids, and especially in the works of Sparrow A. and coauthors [2]). Studying the dependence of RR (determined by D_0) on the volume of the interphase nucleus, Sparrow A. divided a sample of 79 organisms into eight groups which he called radiotaxa, within which the correlation between D_0 and the volume of the interphase nucleus was 0.85-0.99. However, the organisms that differ fundamentally in the structural organization of the genome fell into the same radiotaxon. For example, some viruses, bacteria, and yeasts fell into radiotaxon 4, while other bacteria, yeasts, and mammalian cells fell into radiotaxon 5. On the contrary, the forms similar in the genetic organization often appeared in different radiotaxa. Thus, different strains of the bacterium *E. coli* got simultaneously into four radiotaxa - from the 4th to the 7th inclusively. Based on the obtained results Sparrow A. was forced to conclude that radiation taxonomy has nothing to do with the biological classification of species and does not reflect their phylogenetic relationships.

Of course, with all the evidence of the connection of RR with the taxonomic position of the organism, it was difficult for the researchers to agree with such a categorical conclusion of Sparrow A., and the research continued in the direction of searching for a more adequate assessment of the radioresistance of organisms.

Shalnov M.I. [3] identified six radiotaxa (according to the correlation of D_0 with the genome size), each of which had its own regression curve with the corresponding coefficient K_i that has the dimension of the radiation chemical yield. Shalnov M.I. also drew attention to the fact that along with the complication of the genome structure in the process of progressive phylogenetic development the radiation-chemical yield of reactions leading to reproductive cell death decreases, i.e., increasing the reliability of the genetic systems. An increase in RR upon the transition from taxon to taxon due to the improvement of DNA repair mechanisms could be characterized by a dimensionless factor f_i and G_i at the radiation-chemical yields corresponding to each radiotaxon determined by the structural and functional organization of the genome. In accordance with this, the coefficients K_i of six regression lines, obtained as a result of the product of the factors f_i and G_i form, according to Shalnov M.I. steps of adaptive variability of the genome in the direction of the increasing of radioresistance. Proposed by Shalnov M.I. approach allowed him to assess the contribution made to the overall resistance of the genome by changes in its structural and functional organization and improvement of enzymatic repair processes. So, according to Shalnov M.I., in the course of phylogenesis, the RR of the genome increased by 100 times due to changes in the structural and functional organization and as a result of the improvement of enzymatic repair systems, also by 100 times (and that - by 10^4 times).

Developing the ideas of Shalnov M.I. and Korogodin V.I. [4] introduced the concept of "genome reliability" and analyzed the distribution of organisms by radiotaxa from the point of view of genome reliability. As a measure of genome reliability, Korogodin V.I. proposed to use a value equal to the amount of the radiation energy the absorption of which in DNA is necessary and sufficient for the appearance of one elementary damage. As an estimate of the reliability of the genome the product D_0C was used, where D_0 is the radiation dose at which, on average, one lethal damage occurs in each cell, and C is the amount of DNA in the genome. If D_0 is expressed in Gy (Gray) and C is expressed in nucleotides, then the reliability of the genome (K) is:

$$K = 3,31 \times 10^{-6} D_0 C \text{ (eB)}$$

The introduction of this ratio allowed Korogodin V.I. to answer the question about the relationship between the reliability of the genome and its size. If K remained constant during the entire time of the phylogenetic processes, then for an increase in the size of the genome (and this is an inevitable process that ensures progressive evolution) which varies within 8 orders of magnitude (from 1.3×10^3 base pairs in the tobacco necrosis satellite virus to $2,3 \times 10^{11}$ bp in *Tradescantia Virginiana*) living organisms would have to “pay” with a proportional increase in the radiosensitivity (RS). However, the data of radiobiological experiments indicate that the differences in the RS of biological objects are much smaller than might be expected and are less than five orders of magnitude.

Korogodin V. I. singled out not six, but four radiotaxa combining the 4th and 5th into one and discarding the 6th due to the unrepresentative information. The distribution of biological objects according to radiotaxa corresponded well to their distribution according to the levels of structural organization of genetic systems. The set of organisms with the same level of structural organization of the genome Korogodin V.I. suggested calling it a karyotaxon. According to Korogodin V.I., the reliability of the genome of the organisms of the first three karyotaxons is mainly due to physicochemical factors - the transition from the single-stranded structure of nucleic acids (karyotaxon 1) to the double-stranded structure (karyotaxon 2) and then to the DNA-protein complex of the haploid genome (karyotaxon 3). A sharp increase in the reliability of the genome of organisms of the 4th karyotaxon is due to the appearance of the mechanism of "diploid-specific" repair. However, according to Sarapultsev B.I. and Geraskin S.A. [5] data on the reliability of eukaryotic polychromosomal genomes do not require additional hypotheses about the existence in eukaryotes of any special ways to increase the reliability of the elementary genome for their interpretation. In particular, the number of repaired double breaks per chromosome of a eukaryotic cell does not exceed the number successfully repaired by prokaryotic genomes. The mentioned authors believe that the phylogenetic development of the elementary genome reliability systems is probably fully completed within the framework of the prokaryotic genome and the high reliability of the eukaryotic cell genome is mainly due to the transition to the polychromosomal organization of genetic information storage and the effect of polyploid protection.

The hierarchy of radiotaxa directly reflects the main stages of the structural reorganization of the genome in the course of a progressive phylogenetic process from “bare” single- and double-stranded virus-type nucleic acid molecules to pro- and eukaryotic genomic molecules organized into a nucleoid and a true nucleus. The latter circumstance unequivocally testifies to the general biological significance of radiotaxonomy and allows to raise the question of the biological meaning of the phenomenon of radiation resistance of organisms.

Thus, radiotaxonomic studies while remaining within the framework of radiobiological studies were quite successful and led to the establishment of a relationship between either the taxonomic position and radioresistance (RR) or between the physical size of the interphase nucleus and RR (karyotaxa). For some time it seemed that these investigations and the corresponding results were of significance only for radiobiology. However, a certain paradoxical nature of these results, namely the low RR of eukaryotic organisms compared to the RR of prokaryotic organisms, forced radiobiologists to search the solutions to this problem using molecular genetic and phylogenetic methods and approaches.

Radiobiologists are faced with the second most important radiobiological paradox the resolution of which can have not only general radiobiological but also general biological significance.

In connection with the need to resolve this paradox, it is difficult to overestimate the research of Shalnov M.I. who established that in parallel with the phylogenetically determined structural and functional complication of the genome, there was a decrease in the radiation-chemical yield of damage

to nucleic acid molecules leading to the inactivation of the irradiated object. Without going into the essence of the mechanisms that ensure a decrease in the yield of damage (recombination, enzymatic repair, a “coat” of histone proteins), it should be stated that the reliability of genetic systems increases in the process of progressive phylogenetic development of biological systems.

The idea of the adaptive significance of a high level of reliability of the genome of eukaryotic organisms in relation to the action of the ionizing radiation factor had to be abandoned because since the birth of life the radiation factor has varied within a maximum of three orders of magnitude and could not cause a difference in the RR of some representatives of prokaryotic and eukaryotic organisms by four orders of magnitude. Nor could RR be the result of developed nonspecific resistance, since there is also an inverse relationship between the phylogenetic "advancement" of species and their resistance to other extreme factors. This pattern is explained by the fact that the progressive direction of the development of life on Earth which has so far been the predominant direction has led mainly to the emergence of adaptations that help isolate biological objects from the action of extreme environmental factors (including biotic factors) or the development of means to avoid dangerous environmental factors. In other words, the development of the adaptations did not follow the path of acquiring “oak” resistance, but along the path of acquiring highly organized behavioral responses (in plants, in particular, the division of ontogenesis into actively functioning and passively experiencing unfavorable phases).

Thus, it remains to be assumed that the reliability of the genome which is generally calculated as the product of D_0 and the volume of the genome (see above) expressed as the number of nucleotides characterizes, first of all, its ability to function reliably under normal conditions, and not radioresistance. The factor of the spontaneous degradation of nucleic acid molecules (a consequence of the thermodynamic instability of the DNA molecule, the influence of reactive oxygen species, as well as a consequence of the erroneous processes of DNA repair and replication) in itself is significant enough to act as a phylogenetic adaptation factor. Indeed, the reliability of the genome of most eukaryotic organisms is far superior to that of prokaryotic organisms. Such superiority is ensured by a whole hierarchical system of means for ensuring the reliability of the genome.

How could a whole hierarchical system have arisen in the process of progressive phylogenesis that ensures the reliability of the genome (which in its turn just ensured the possibility of progressive development)? And in general, what is a progressive phylogenetic process? And why do organisms coexist in the biosphere at present which differs so much from each other in the complexity of their genetic apparatus and, accordingly, in the reliability of its functioning?

Here, there is a reversal (transformation) of the 2nd radiobiological paradox. So, if at first, it seemed incomprehensible the existence of eukaryotic organisms with their relatively low radioresistance, now the existence of prokaryotic organisms with their relatively low level of genome reliability and low information capacity becomes unclear.

In most cases, prokaryotic organisms have a high RR which to a much greater extent than in eukaryotic organisms correlates with the high resistance to other external extreme factors of a physical and (or) chemical nature. The minimum ability of prokaryotic organisms to maintain the constancy of the internal (intracellular) environment is due to the comparative primitiveness of their genetic apparatus which in its turn causes high resistance to the destructive action of environmental factors. A kind of “payment” for the high and nonspecific (universal) resistance of prokaryotic organisms is their inability to maintain their genetic individuality as evidenced by the high level of their genetic variability.

Prokaryotic organisms used one of two possible ways to ensure adaptability to the environment - the way to increase the stability of the genome by reducing its physical size and, consequently, the

level of organization (complexity). In contrast, eukaryotic organisms in the process of progressive phylogenetic development used another opportunity - autonomization (or avoidance) from environmental factors through the acquisition of a complexly organized genetic apparatus (with the participation of proteins that did not have high thermal stability) which provides complex behavior in a variety of environments. Since complex behavior requires a large amount of memory a necessary condition for the functioning of eukaryotic genomes is their high reliability which is achieved due to the duplication of genetic information and its mosaic location on nonhomologous chromosomes as well as due to the existence of recombination and repair systems. The last two of the listed mechanisms are “inherited” from prokaryotic organisms and constitute the repair “foundation” of the entire system that ensures the reliability of the functioning of the genome (storage, processing, and transmission of genetic information) and on this basis the phenome.

Finally, the high information capacity of the eukaryotic genome provides a wide opportunity for epigenetic variability (differentiation) of cells which by specializing, probably formed the basis for the emergence of multicellular organisms and subsequently multi-tissue organisms. The direction of the phylogenetic process of genome change is determined not only and not so much by adaptive variability and selection of forms with nonspecific RR but by a tendency to increase the information capacity of the genome and the reliability associated with this process of improving genetic systems to ensure stable (accurate) operation of the growing genetic apparatus.

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