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Michael Golubovsky

MOBILE GENETICS AND FORMS OF HERITABLE CHANGES IN EUKARYOTES

The real insight in the eukaryotic genome means knowledge of the structure of genetic elements, the character of dynamic links between them and some holistic features of the system. The structure of the eukaryotic genome can be naturally subdivided on two classes of elements: an obligatory and facultative ones. Accordingly, we need to discriminate between two different forms of heritable changes — mutations and variations. Mutations correspond to all changes with genes. Variations are various kinds of changes in the populations of genomic facultative elements. Variations may be directed and connected with multiple site specific alterations. The spontaneous mutation process in nature is mediated by the system of facultative elements. Their activation in nature induces sudden mutation outbursts, appearance of new genetic constructions and site specific rearrangements. Facultative elements are the first to react on environmental challenge. Variations can be presented as an operational memory of the genome. Between obligatory and facultative elements there is constant flow. The behavior of transposons in the eukaryotic genome may be model for the adequate description of epigenic inheritance. There is logic and real necessity to use the epigene concept for describing of elementary units of epigenetic inheritance.

In this paper I try to present a general approach to the description of heritable alterations in eukaryotes. This task seems important. «Mobile» genetics in many aspects contradicts classical genetics on which the current theory of evolution is based.

An adequate description needs to take into account the complexity of the structure of the cell hereditary system. Inheritance can be considered as the cell's property to provide transmission in a series of generations all the specific structural and functional traits and specific character of ontogenesis. We will use word genome in a broad sense as an equivalent of the whole cell genetic system which determines individual heritable differences. Such a meaning corresponds to the final words of the classical paper about genetic regulation that «the genome contains not only a series of blue-prints, but a coordinate programme of protein synthesis and the means of controlling its execution» [1].

Mutations in the framework of traditional genetics implicit any changes of molecular structure of genes, their position and number. But do the mutations in this sense embrace all possible hereditary alterations? The answer is no.

Mobile genome: obligatory and fecultative elements. The birth of mobile genetics is dated in the earlier 1950s with a series of publications by Barbara McClintock and the A. Lwoff, F. Jacob and E. Wollman from Pasteur Institute. McClintock concluded that the mutant condition may depend on the action of controlling mobile elements able to be inserted in various loci. They may be present or absent in the genome. The difficulty to connect controlling elements with definite DNA structures increased the mystery of McClintock's conclusions.

However, the principal support of her ideas came from studies of other facultative elements: episomes and lambda phages in all their incarnations. The lysogeny model was published by A. Lwoff in 1953. As this event were into history we can conclude that its impact on the progression of genetics together with subsequent analysis of episomes by

E. Jacob and E. Wollman appeared to be as essential as the discovery of the DNA double helix in the same year. The virus with all its genetic machinery might be a genomic facultative element. In the integrated state viruses are indistinguishable from a chromosome element with the potential to supply the host cell with new properties. Thus the genome does not have an absolute barrier from invasion by foreign genetic elements.

In the context of this paper I can't resist the temptation to cite the prophetic conclusion made at the beginning of 1960s: «All intermediate categories may be formed between the viruses (extrinsic, infectious, plasmids) and the normal genetic determinants of a cell (intrinsic, noninfectious, and integrated). Between heredity and infection, between cellular pathology and cellular physiology, between nuclear and cytoplasmic heredity, the episomes, as studied in bacteria, provide the link» [2]. The authors, E. Jacob and E. Wollman, regarded these considerations as main contribution of bacterial genetics. In fact, episome studies appeared to be crucial for the development of the new mobile genetics with discovery a whole kingdom of facultative elements.

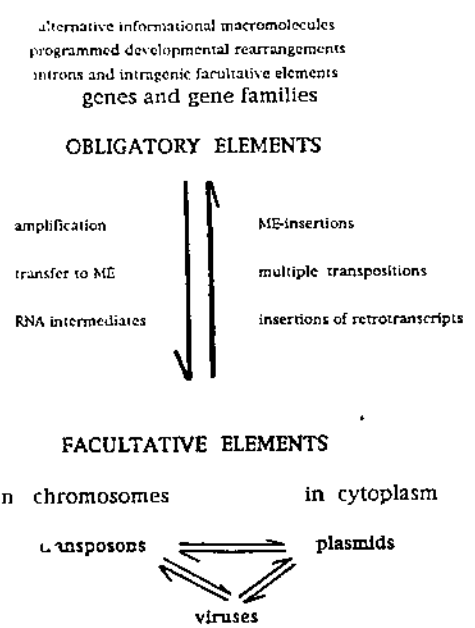

Fig. 1. Main potential ways of interconversions between obligatory and facultative elements of the genome. Arrows indicate directions of transitions. It is shown that aspects of facultativness concerns also behavior of obligate genes. Exogenous retroviruses can be mutationally transformed to plasmids and transposons and vice versa. Other facultative elements are shown on the fig. 2

The eukaryotes in their essence are multigenomic symbiotic constructions. But apart from self-reproducing organelles the structural elements of the genome may be naturally subdivided on two subsystems or parts: the OBLIGATORY ELEMENTS and the FACULTATIVE ones or OE and FE [3].

The chromosomal genetic loci are only the skeleton of the genome. The subsystem of FE includes the hierarchy of intra and extrachromosomal elements varying from highly repeated and satellite DNA, to transposons, pseudogenes and retrotranscripts, amplicons, plasmids, additional chromosomes and various endosymbionts. The FE may be defined operationally by two criteria: [1] they can be present or absent, and when present their number and topography vary in different cells, tissues, individuals; [2] their intrinsic properties promote to deviations in the character of basic informational processes: replication, transcription, translation and segregation. For instance, highly repeated sequencies are characterized by frequent under or overreplication, they usually are not transcribed; plasmids and B-chromosome do not segregate regularly, etc.

Absence of linkage of DNA content in the haploid genome with taxonomic status and frequent cases of its drastic differences in closely related species was called as «C-paradox». The word paradox was given due to the evident violation of some basic implicit postulates of classical genetics: (a) all genetic material of chromosomes consists of genes, all DNA has an informational function; (b) the list of genes with their al-

leles correspond to genotypes. However, a lot of structural aspects of eukaryotic genome appeared to be paradoxal (Fig. 1): mosaic structure of genes, programmed ontogenetic rearrangements, ability of many segments to exist both in chromosomal and plasmid states, the abundance of transposons in their different incarnations and the ubiquitous presence of cytobionts.

Nearly 50 families of mobile elements (ME) are described in Drosophila. They comprise up to 12 % of the haploid DNA content. The mammalian genome contains up to 50 000 dispersed copies of retroposon LINE near by 6500 base long. Short Alu mobile element family has about 300 000 dispersed copies. In fact, each individual has his own pattern of number and topography of mobile elements.

Intracellular symbionts (viruses, bacteria, protozoa) need also to be viewed as FE of the genome. They may confer on the host cell important new properties especially in physiology and mode of reproduction. The behavior of rhabdovirus sigma in Drosophila is one of the best studied examples [4]. The single-stranded RNA virus is non-contagious. But it is stabely transmitted maternally through egg cytoplasm and makes flies sensitive to CO_2. Each oogonia of stabilized sensitive females contains 10—40 virus particles and mature oocytes contain about 10^6 ones. This physiological trait is inherited cytoplasmically and its expression depends on the concentration of the intracellular viral population. Males of stabilized line transmit sensitivity only sporadically. Some Drosophila stocks are immune to virus infection and some sigma mutants can overcome this immunity. The striking analogy of Drosophila hereditary sensitivity to CO_2 with the behavior of a phage-bacteria system was noticed long before the rhabdovirus sigma was actually isolated [2]. The general approach needs to use the term «horizontal transfer» to all relatively stable presence in the genome various facultative cytobionts. Thus it is became clear that in nature such transfers are regular events.

It should be stressed that aspects of facultativeness concern also obligatory genes (Fig. 1, upper lines). Introns in some sense may be viewed as facultative intragene elements. As they are spliced they have the capacity to «absorb» different kinds of inserts without any apparent consequences on normal gene function. Many genes can undergo an alternative splicing depending on developmental stage and tissues. Facultative translation is also described.

Interconversions in the subsystems of OE and FE. The prophetic scheme titled as «possible variations of episomes» [2] predicted continuous gradation in the behaviour and properties of FE. In fact, the be stabilized as duplicated gene copies. These events may be viewed as interconversions in subsystems of the OE and FE. There is constant flux between the obligate and facultative subsystems.

Mutations and variations. The two structural subsystems of the genome exhibit different characteristics of heritable alterations. Mutation, in the classical sense, connected mainly with alterations of OE, i. e. changes in the structure, position and number of genes. (In a more general sense mutations implicit any changes in linear structure of genetic elements). But FE exist in the genome as populations of informational macromolecules. The character of their alterations and their response to the action of external factors is quite different in comparison with OE. To describe the various heritable alterations in the subsystem of FE, I have suggested [8] the term VARIATION firstly used by F. Jacob and E. Wollman for episome behaviour [2]. Recently P. Foster after studies on an adaptive mutation problem offered to use the term «variant» «to distinguish potentially transient changes in the cell's informational macromolecules from mutations, which are heritable sequence changes in the DNA» [9].

Thus there are **mutations** and **mutants** and there are **variations** and **variants.** Spontaneous mutations according classical theory occur in the progeny of some individuals, by chance, rarely with frequency near 10^{-6}

for a gene/generation. Mutations can be induced by action of strong environmental factors (radiation, chemical mutagens et al).

Heritable changes of FE occur on the level of intracell population of informational macromolecules. Let's take the well studied phenomenon of hybrid dysgenesis in Drosophila. In the case of P-M dysgenesis in F1 hybrids from paternal P-stock having active P transposons with the females of M-stock devoid of P-active copies and cytoplasmic repressor of transposition, an outburst of mobility of P-elements occurs. This results in an outburst of insertion mutations and chromosomal rearrangements,

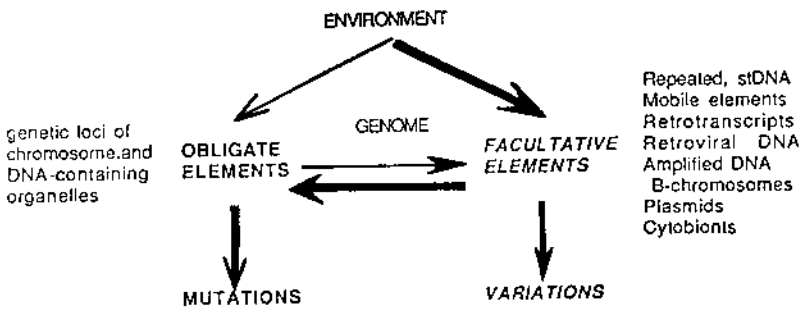

Fig. 2. Mutations and variations and character of their occurrence under action of environment. Arrows indicate the direction of the links, while their width corresponds to the intencity of their force

damages of germinal cells and sterility. There are multiple transposition events in the separate sensitive cells. The general frequency of chromosomal rearrangements in the F1 progeny of dysgenic crosses may reach fantastic frequencies — more 10 %. The chromosomal breaks are ordered and site-specific. They occur at the sites of the original localisations of P-elements. The multisite inversions were observed with the same frequency as simple ones [10].

Thus in the case of variations, on the contrary to mutations, genolype changes (a) occur simultaneously in many individuals, (b) the alterations are ordered, multisite and site-specific, (c) the positions of genome rearrangements are predeterminated by the original topography of FE, (d) the activation of FE may be induced by trivial «non-mutagenic» factors as temperature, interline crosses.

There is an additional important item. The genotype alteration can occur due to simple changes in the cell topography or relative amounts of two classes OE/FE. Heritable transmission of fly CO_2 sensitivity in stabilized lines can be cut off by the temperature shock: keeping egg-laying females for about 6 days at 30 °C. Such treatment blocks the reproduction of cytoplasmic sigma virus particles. The all adults flies of CO_2 sensitive stock became virus-free after one-time treatment and they become heritably tolerant to CO_2 [4]. This example shows that on the level of FE situations may occur which were prohibited by the tenets of classical genetics, the so called inheritance of traits acquired during ontogenesis [11].

The character of interactions in the triad ENVIRONMENT-FE-OE is illustrated by the scheme (Fig. 2). In nature spontaneous heritable changes mainly occur through the response of the FE subsystem which is sensitive both weak and strong environmental influences [12]. Changes in FE represent an operational memory in the structure of the genome. Mutations as changes of OE occur mainly indirectly, by a two step mechanism mediated by the activation of the subsystem of FE. The comparative molecular anatomy of mobile elements both in prokaryotes and eukaryotes demonstrated various paths of interconversions of ME from simplest to complex ones: insertion sequences — transposons — plasmids — retroviruses and vice versa [5].

Let's consider recent evidence on transition of typical chromosomal mobile element *gypsy* to retroviral infectious condition. The element may be transmitted to *gypsy*-free permissive fly stock and incorporated into its germ line when larvae are fed on extracts of infected flies [6]. Such retrovirus-like elements were discovered in yeasts, plants and animals. Retroviruses appear to be universal vector in the ecosystems. The similar or same retrotranscripts were found in non-related species indicated on regular cases of horizontal transmission. The same is justice for transposons-like P in Drosophila Ac and SpM in maize, which use DNA to DNA transposition mechanism [7].

There is no severe barrier between OE and FE parts of genome. The obligatory genes and chromosomal segments may be transformed to the category of FE due to three main processes: amplification, integration into the ME and through production of cytoplasmic RNA intermediates. Conversely, the transition from FE to OE occurs mainly due to insertions, transposon-induced rearrangements and reverse transcription (Fig. 1).

Insertion mutations (transition from FE to OE) may constitute, as in the case of Drosophila, near 70 % of spontaneous visible mutations. Nearly 10—15 % of the chromosomal DNA of mammals consists of pseudogenes and retrotranscripts — transitions from OE to FE [8]. Selection by cytostatic agents in eukaryotes is frequently connected with an amplification of chromosomal segments (amplicons) carrying resistant genes. The amplicons may be located in tandem chromosomal blocks or be transformed into plasmids. In both cases their number and topography vary in different cells and cell lines. Sometimes part of the duplicated genes may insertion mutations as result of activation of ME represent the best example. The behaviour of FE in turn is usually under control of genes.

Mutation process mediated by mobile elements in nature. I want to confirm the above mentioned conclusions by some inferences from my long-term studies on the spontaneous mutation process in natural populations of *D. melanogaster*. I selected here only three examples.

1. *The puzzling phenomenon of mutation outburst.* The concept of mutation rate fluctuation in the life of species was firstly developed by Hugo de Vries in 1901. He also predicted an existence of unstable genetic factors. Both ideas were neglected for decades. However, de Vries appeared to be right in principle. The fluctuations of both general mutability and sudden mutation outburst of definite loci are well documented [13—15]. In 1973—1979 we observed the global outburst of sex-linked gene *singed* bristle. It was the first time when the series of unstable insertion alleles was extracted from nature [14, 15]. Their mutation rate both in germinal and somatic cells reached in some cases more 20 %! Multiple allelic transitions occurred in pre-meiotic cells giving cluster of changed gamets in the progeny of a single mating [14, 15]. The *sn* gene appeared to be preferential target for the now famous P-transposons and for some retrovirus-like ME [16]. Thus we demonstrated that the mutations outbursts in nature are due to an activation of FE.

However, the puzzle of phenomenon became unsolved. According to regular observations [13—15] the *sn* mutations were quite rare in Drosophila populations during decades before 1973. Then unstable alleles of this gene suddenly appeared in many geographically distant populations. The outburst ended in 1980. Then other gene sharply increased its mutability rate [17]. What may be the origin of such periodical genomic epidemies or «mutation fashions»?

The answer may consists of fact that all living species in the ecosystem are continuously interacting with different viruses. Viruses are not only powerful infectious and selective agents. They act also as peculiar mutagenic factor inducing unstable mutations and multisite chromosomal damages due to an activation of intrinsic genomic FE [18—20].

Different viral agents cause insertion mutations at different sites. The regular reshuffling of the set of viruses and their genotypes (the latter is well known for the influenza virus in humans) occur in the ecosystems during the process of parasite-host interaction. So the periodical mutation outbursts and the genomic epidemics may be the indirect result of periodical ecosystem fluctuations. We need systematic studies on the consequences of viral epidemics on the rate of variations and mutations in human populations [13, 18].

2. *Appearance of new genetic constructions.* In the Far East population two adjacent genes *singed* and *club wing* (*clw*) appeared to be linked by the *copia*-like ME. Both genes became simultaneously expressed and mutated. The mutation behaviour of this quite unstable double-gene transposon system was ordered with predicted intralocus and outlocus transpositions [22]. This first demonstration of ME-mediated fusion of separate genes in one system may be viewed as an example of the phenomenon of «natural genetic engineering» [23].

3. *Site-specific insertions and ME-mediated deletions.* During systematic study of the genetic load of natural populations we found that lethal alleles of tumor-supressor gene *lethal* (2) *giant larvae* or simply *lgl* (2—0,0) are ubiquitous in *D. melanogaster* populations (14). One out 20—50 fruit flies in nature was heterozygous on this oncogenic recessive lethal. The +/*lgl* animals had selective advantages in stress conditions in comparison with lethal free +/+ flies (14). High *lgl* mutability appeared to be connected with site specific insertional mutagenesis. The *lgl* locus became «promiscuous» for the specific insertions in the case of the presence in the same chromosome of the MR factor [24]. The same B104 transposon was found inserted in the case of alleles extracted from the distant populations of Russian and USA [25].

These three examples showed that in nature through subsystem of FE may occur fast directed and massive heritable changes.

Epigenetic inheritance and mobile elements. The hereditary memory implies three main aspects: coding, storage are transfer of an information. There exist both structural and dynamic modes of coding, storage and transfer of heritable information. As for as of the structure of genome the coding is based on definite order of DNA sequences and informational transfer on the phenomenon of convariant reduplication. The dynamic modes of inheritance are mediated by protein products of regulater genes. The heritable alterations can occur without any changes in DNA text. J. Mono and F. Jacob on the basis of the operon concept firstly presented a theoretical models with two operons connected into circuits. Such cyclic system can switch from one stable state to the other and maintain it in a series of generations. Thus, «transition of state in such systems should very closely mimic true transmissible alteration of the genetic material itself» [26]. Namely such transitions were found by B. McClintock in the case of the SpM mobile controlling element.

The dynamic aspects of the genome organisation and functioning were called in the middle of 1950s as epigenetic. The spectrum of phenomena epigenetic inheritance is quite wide from transformation of serotypes in Paramecium up to chromosomal and genomic imprinting. But terminology in this field is not yet stabilized. What is the elementary epigenic system and elementary epigenetic event? For adequate description of epigenetic inheritance it seems quite instrumental to use the concept of an EPIGENE coined by R. Tchuraev [27] and term EPIMUTATION suggested by R. Holliday [28].

Epigene represents autoregulatory hereditary unit, genetic system with cyclic links or feedback, having two or more functional states and capable to maintain each state in a series of generations. The simplest one-component epigene is shown in Fig. 3. The feedback may be positive as in the case of first described autoregulated *cI* gene which different states rule by the lambda phage behaviour. Autoregulation may be negative as in the case of Tn3 in *E. coli* [5].

The transposons P in Drosophila, Ac and SpM in maize are constructed as epigenes with positive autoregulation [29—31]. Autoregulation by circuit may be based on different mechanisms or levels. In the case of sex determining gene *Sxl* in Drosophila autoregulation occur on the level of alternative splicing [32]. In the case of P-transposon autoregulation involves both alternative splicing and transcription. [29]. Ac

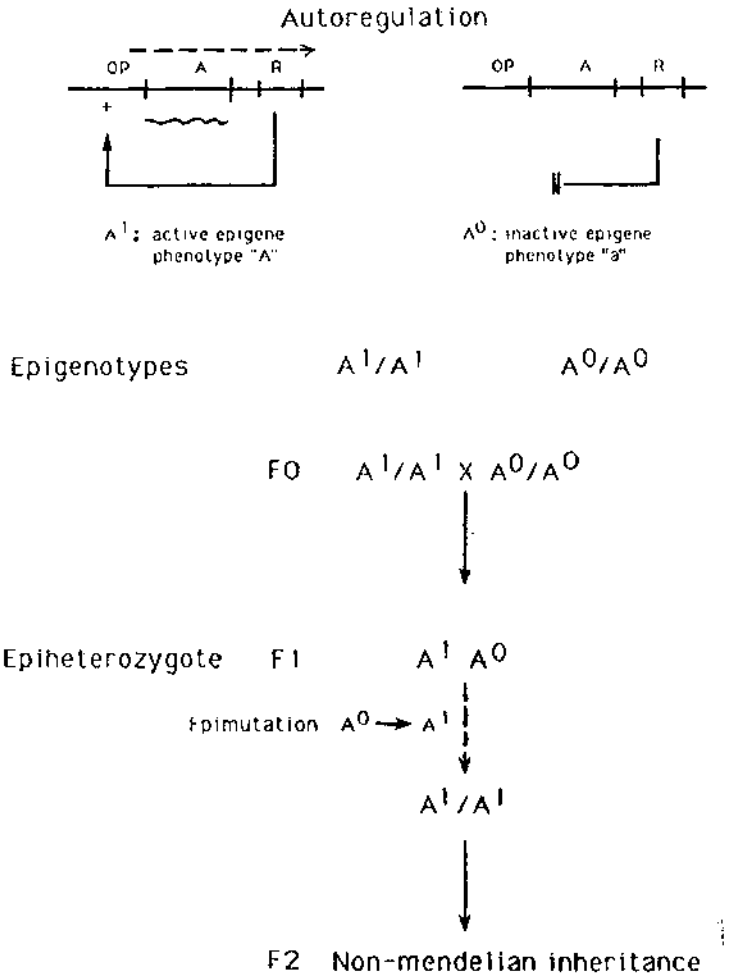

Fig. 3. An epigene and principal scheme of possible heritable changes in the case of epigenic crosses. In the scheme the positive regulation is shown on the level of transcription. *R* — gene regulator; *A* — structural gene; *OP* — regulator zone

and SpM transposons in maize discovered by B. McClintock are regulated by methylations of up and down promotor sites [30, 31, 33].

The scheme (Fig. 3) shows that in the case of positive autoregulation in cell epiheterozygotes A^1/A^0 where A^1-active state of an epigene and A^0 inactive one may occur the switching on the epigene from A^0 to A^1 state. This switching described as **epimutation** is well documented for an Ac and SpM transposons in maize [30, 31, 33]. Epimutation may occur both in somatic and germinal cells. In last case the non-mendelian inheritance results in. Even situation is possible with complete absence of F2 segregation (Fig. 3).

The transposon SpM in the maize apart from active and complete inactive states may exist in third so called «programmed» state with varying level of inactivity, increased possibility to be trans-activated in epiheterozygotes. The transposon encoded positive autoregulatory gene product can both reactivate an inactive element and promote its developmental heritable reprogramming [30, 31]. The authors which had con-

ducted detailed genetic and molecular analysis of SpM element came to conclusion that to the concept of epimutation «it may be necessary and *epivariation*» [31]. I cite this conclusion as an important sign of logic and terminological convergence with the approach developed in the paper.

Analysis of SpM behaviour demonstrated that the epigenetic changes in the present generation can influence the expression pattern of the transposon in the next generation. Similar phenomenon described in maize in 1960s and titled as paramutation seemed quite peculiar. In the framework of mobile genetics it may be regular. From the point of theory of inheritance it means violation of one of the basic mendelian principle about absence of influence of heterozygous condition on the allelic structure and function in the next generation. Other important point consist of a possibility of an existence in the genome a series of independent epigenes. Thus if we have only 10 epigenes with two states for each one we receive 2^{10} or 1024 different states! Thus cell can select needed strategy of response on environmental challenge. The cell response is teleonomic [12, 26].

Conclusion. The real insight in the eukaryotic genome means knowledge of the structure of genetic elements, the character of dynamic links between them and some holistic features of the system. The structure of the eukaryotic genome can be naturally subdivided on two classes of elements: an obligatory and facultative ones.

Accordingly, we need to discriminate between two different forms of heritable changes-mutations and variations. Mutations correspond to all changes with genes. Variations are various kinds of changes in the populations of genomic facultative elements. Variations may be directed and connected with multiple site-specific alterations. The spontaneous mutation process in nature is mediated by the system of facultative elements. Their activation in nature induces sudden mutation outbursts, appearance of new genetic constructions and site-specific rearrangements. Facultative elements are the first to react on environmental challenge. Variations can be presented as an operational memory of the genome. Between obligatory and facultative elements there is constant flow. The behaviour of transposons in the eukaryotic genome may be model for the adequate description of epigenetic inheritance. There is logic and real necessity to use the epigene concept for describing of elementary units of epigenetic inheritance.

The shift of postulates from classical genetics to current one may be expressed as following.

Classical genetics

1. All newly occurring hereditary changes are mutations with definite localisation.
2. Mutations occur in the progeny of some individuals, rarely, by chance.
3. The rate of mutation process is constant, genes are relatively stable.
4. Epigenetic changes have relation only to development, they are found mainly in some protozoa and in the case of cell-somatic hybrids.
5. Inheritance of acquired traits is impossible in the framework of chromosomal theory.
6. Species genomes are genetically closed systems.

Current mobile genetics

1. Mutations are only part of the wide spectrum of heritable alterations; there are variations and epigenetic changes (epimutations).
2. Variations and epimutations may be ordered, directed, programmed and adaptive.
3. In natural populations regularly occur explosions of mutability both global and local ones due to an activation of inherent mobile elements.

4. Epigenetic alterations of genome elements are regular events; most transposons are organised as epigenes.

5. Inheritance of ontogenetically induced traits is quite possible in the framework of variations and epimutations.

6. There is constant intracell and interspecies flow of genetic elements.

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This article is dedicated to the memory of André Lwoff (1902—1994).

М. Голубовський

МОБІЛЬНА ГЕНЕТИКА І ФОРМИ СПАДКОВОЇ МІНЛИВОСТІ ЕУКАРІОТ

Р е з ю м е

Реальне розуміння еукаріотичного геному означає знання структури генетичних елементів, характеру динамічного зв'язку між ними і філософії цілосності системи. Структура еукаріотичного геному може бути підрозділеною на два компоненти: облігатний і факультативний. Відповідно до цього ми повинні розрізняти дві форми спадкової мінливості — мутаційну і варіаційну. Мутації лов'язані з усіма змінами в генах. Варіації є різними видами змін у популяціях факультативних елементів геному. Варіації можуть бути визначеними і лов'язаними з багатьма сайт-специфічними змінами. Спонтанний мутаційний процес у природі обумовлений системою факультативних елементів. Їх активація у природі індукує раптові мутаційні «вибухи», появу нових генетичних конструкцій і сайт-специфічних перебудов. Факультативні елементи першими реагують на зміни навколишнього середовища. Варіації можуть бути представлені керуючою ам'яттю геному. Між облігатними і факультативними елементами спостерігається постійна взаємодія. Поведінку транспозонів в еукаріотичному геномі можна взяти за модель для адекватного опису епігенетичної спадковості. Використання концепції епігена є логічною і реальною необхідністю для характеристики елементарних одиниць епігенетичної спадковості.

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