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HYPOTHESIS

Biological Evolution Based on Nonrandom Variability Regulated by the Organism

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Abstract—A hypothetical mechanism for rapid and nonrandom emergence of evolutionary adaptations is proposed. It is supposed that some transcription factors and transcription regulators that are able to cross membranes can leave the cells of their origin and move within the organism using a specialized transport system when individual development occurs under conditions extreme for the given species. This system, in particular, connects soma with germline. The supply of germline cells with unusual transcription regulators changes the balance of their nuclear regulatory RNAs, thus initiating RNA-dependent epigenetic modifications of the germline genome and therefore changes in phenotypes of the progeny. It is highly probable that some of these phenotypes are adaptive and lay the basis for the origin of the next biological species. The proposed mechanism can serve as a basis for a new theory of the origin of species.

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Present-day evolutionary biology is in crisis. There are several reasons for this. Neo-Darwinism does not withstand the trial by molecular biology [1]. It is also impossible to explain evolution by means of Lamarck's inheritance of acquired characters due to direct conflict with the indisputable central dogma of molecular biology. Because of this, there are unceasing attempts, still unsuccessful, to search for a way to escape the dead end that has emerged [2, 3].

Hence, it is reasonable to suggest a way out of the collision. It is based on an assumption concerning the existence of a novel, previously unrecognized system in organisms that is responsible for creation of adaptations and involves special interactions between cells and molecules that have been known for a long time. This system is designated as the creatron (from Latin creates and transcribere + on). Even the simplest mechanical clock with its single function has six main units. The creatron – a special system for adaptation of an organism to its environment, or in a wider sense as a machine for biological evolution – also has a complex structure. Here only the main details of its structure and function are considered.

Abbreviations: CNS, central nervous system; TF, transcription factors.

OUTLINE OF THE CREATRON SYSTEM

Evolution progresses via attempts to create during the sequence of ontogeneses the innovations in the form of various adaptations to a changing environment. It is supposed that organisms have a specialized structure necessary for carrying out this function most important for species survival, namely a function for creating biological adaptations. It should be formed during ontogeny.

The fundamental process of early individual development is a cascade of multiple translocations of cell sheets and individual cells, drastically and differently changing the shape of embryos in various species and simultaneously making especially fascinating the search for universal principles of their development [4-10].

Here the idea is put forward that the numerous rearrangements and migrations of cell sheets and individual cells, especially at early development in animals, occur not only for the sake of exposure of the cell targets to sources of inducers of next differentiations upon creation of anlages and development on their basis of organs and the whole embryo, but besides for an completely different purpose not considered before. This goal is formation of such both regulatory and transport construction that connects with each other all organs and systems to assure the potential ability to generate evolutionary adap-

tations. In essence, I speak about a "machine for evolution" – a creatron. It should be emphasized that despite disclosing a new system in organisms, no additional entities are required; all constituents discussed here have already been described as structural essentials of an organism, and the outline of the proposed system become clear after an attempt simply to bring together the disembodied known facts. The transport part of a creatron in higher animals includes neurons with their capability of axonal transport [11-14] and a special system of so-called tunneling nanotubes (see in section "Intercellular Connections"). Plants and fungi have their own variant of this system, but here the examination is focused on the creatron of higher animals. The key structures of the creatron are so-called "morphons" (they are considered below in "The Set of Morphons" section). The main useful load moved along the transport system of a creatron, when the latter is activated and engaged in creation of adaptations, are transcription regulators and transcription factors (TF) that are able to penetrate through membranes, as is known for various homeoproteins. TF can be transferred along the abovementioned traffic system from individual somatic organs into gonads, to the germline. This trafficking system is structurally of the relay race type, with an intermediate system of retransmitters located in higher animals at the central nervous system. TF enter the transport system in the amounts able to cause transformations in gametogenic cells via generation in them of regulatory RNAs responsible for RNA-dependent epigenetic modifications of the germline genome. This happens only when the organism's homeostatic systems are placed under extreme conditions such as long-term and unusual for the given biological species working load, i.e. practically an analog of Lamarckian "exercise". Possible examples are chronic, i.e. over a series of generations, mechanical effect on a certain group of muscles, ligaments, and bones, or unusual temperature, extreme water salinity, continuous presence of any parasite or symbiont factors, etc. The morphon system is responsible for control of topographically nonrandom transportation through an organism of signal TF, finally delivered into gonads and even into their different parts.

THE SET OF "MORPHONS", OR "HOMUNCULUS"

In connection with morphons, let me address the problem of Penfield's homunculus. The homunculus concept includes neural projections (sometimes they are called somatotopic) of body parts in the brain in the form of a "manikin" represented there by corresponding groups of neurons [15, 16]. It has undergone alterations due to improving brain cartography, and it was even criticized due to the revealed disconnection of some somatotopic projections differing from the initial Penfield's schemes [17], but the general principle of individual representation in the brain of body parts involved in a particular function appeared to be absolutely correct and has been confirmed many times [18-25]. Corresponding body part projections have been found in the brains of different biological species [26-29]. As applied to animals, the term "homunculus" is rather irrelevant. Keeping in mind the fact of individual, isolated somatotopic representation of organs (or their separate parts) in the brain, such parts of the central nervous system (CNS) could be designated as somatotopes or morphons. Since there are morphon-associated projections into gamete-forming tissue and, in addition, their own creatron variants exist in plants, the term morphon seems more appropriate. Morphons of nose, paw, tail, etc. can be found in the brain, though concrete relative morphon position in the CNS differs from that of the real body organs. Thus, it was found that representations of the human face skin regions corresponding to forehead, nose, and chin are projected into the somatosensory cortex sites located between representations of thumb and lower lip [30]. In the central sulcus of the human brain, the face representation is inverted [31, 32]. The lips are represented in the somatosensory cortex by a disproportionately large area [33], while the chin and lower jaw of the macaque are projected into regions adjacent to its hand representation [32]. Certainly, such a capricious topography does not prevent morphons from carrying out both their traditional physiological functions (reactions to local irritation, etc.) and their function of adaptation as participants of the creatronic system of the whole organism. It is important to emphasize that projections from periphery depart not only to the cortex but to other brain regions such as the thalamus [34]; therefore, there are also corresponding morphons in them. Since neuronal projections not only join body periphery with brain, but also connect different brain regions to each other [35], then the creatron system sending TF to a certain brain regions via axonal transport is able in principle to forge adaptations within the brain exactly like, according to the hypothesis, it does this for all other body parts.

INTERCELLULAR CONNECTIONS

Plants, like fungi, are complex supracellular ensembles pierced by intercellular channels. Plasmodesmata covered by membranes and joining the cytoplasms of adjacent cells, as well as phloem and xylem, jointly ensure trafficking signal and trophic substances over the whole plant organism [36, 37]. It appears that something similar exists in animals. The process of formation of special intercellular channels endowed with contractile proteins, so-called tunneling nanotubes, has been found in animal cell culture [38]; cells use these nanotubes for transportation of proteins and other factors [38-41]. Previously unknown forms of intercellular connections are still being

revealed in addition to gap junctions, desmosomes, nanochannels, and cytonemes [42]. As for nanotubes, they are membrane-covered true pipelines along which the cytoplasm content is transferred between cells [43, 44], probably for regulatory and trophic purposes. Their diameters are 50-200 nm, which allows transfer of endosomes, mitochondria, and virions, and their length reaches several cell diameters [45]. Structures resembling tunneling nanotubes are also found *in vivo* in mouse blastocysts and cornea [46, 47]. Nanotubes form a syncytium of animal cells, essentially similar to the symplast in plants. These highly dynamic and transitory structures emerge and disappear after existing for from minutes to several hours. The mechanism of formation of intercellular tunneling nanotubes could not arise in nature for animal cell culturing, but their role is still unknown [45]. The ability of viruses to induce formation of intercellular channels (cytonemes and tunneling nanotubes) has been found [43, 48, 49]. It seems justified to suppose that parasites simply enjoy the feature of a multicellular organism retained not for the benefit of infectious diseases, but for its own needs. In this context, it is reasonable to assume that the abovementioned regulated intercellular transport system could be formed, when necessary, dynamically, not by an order from viruses, but in response to the requirement of the creatron system of the organism. The tunnel system of animal nanotubes along with axonal transport could be an important creatron component allowing factors delivery from soma to germline in the course of transgenerational creation of adaptations. In plants intercellular transfer of homeodomain transcription factors and regulatory small RNA via plasmodesmata has been already found and is a highly regulated process dependent on tissue, stage of development, and nature of transported macromolecules [50-52].

"EXERCISE"

TF in relatively high concentration enter the intercellular medium from cells of an organ undergoing any kind of intensified chronic loading in response to "exercise" understood in a broad sense, though not under conditions of relative quiescence. The possible signal functions of TF, provided with the ability of penetrating through membranes due to homeodomain properties, have already been mentioned though in another context [53]. During chronic "exercise", as it can be supposed, TF, via a system of channels (via nanotubes and the nerve transport system), penetrating through membranes and synaptic barriers, leave the original somatic organ, and enter the corresponding morphon in the brain. There corresponding neurons retransmit the signal to gonads (during this retransmitting, neurons might synthesize their own TF that eventually enter gonads). In this case, these factors are only markers of the fact of receiving an appropriate signal from a somatic organ: neuronal TF, sent to the gonad, can differ in sequence from the protein of the somatic organ. Gonads have their own variants of morphons: different gonadal sectors receive signals from projections of different virtual organs of the brain "homunculus", and each such virtual organ communicates just with the like item in gonads. Such similarity is organized in order to allow signal molecules to get into strictly appropriate regions of gamete-forming tissue. It is also supposed that, in accordance with their belonging to the corresponding virtual organ, gamete-forming cells, being identical in genomic sequence, are differently specialized by their chromatin configuration and activity. Therefore, for example, epigenetically different gametocytes are located in gonadal segments corresponding to the virtual nose and virtual ear projections. Owing to this, different chromosome segments are exposed and available for transcription in different regions of the gonad.

Let us designate the whole transcribed part of chromatin of any given *individual* cell as a "tergid" (from territory, genome, and individual). The individual transcriptome of a cell is that what is allowed to transcribe by properties of the given tergid. Tergids of cells in different sectors of gamete-forming tissue in gonads are correspondingly different and will differently react to signal molecules delivered to them via the abovementioned transport system. For tergid organization controlled by different chromatin packing, long spacers are required. Mainly intergenic protein-noncoding DNA and introns are charged with this function. As a result, in different tergids different structural genes with their introns as well as nonidentical noncoding (but transcribed) chromatin sequences will be available for transcription. All transcribed but non-protein coding genome sequences, including introns, are coding for RNAs (let us call them balance RNAs), whose balance of content could be disturbed by TF supplied from the outside (under extreme conditions of development). The tergid individuality allows gamete-forming cells to most specifically apprehend the signals entering the corresponding gonadal morphon. The balance RNAs, transcribed from differently configured tergids, form nonrandom targets for the creatron system signals. Finally, balance RNAs serve as a pool, whose shifts result in accumulation in the nucleus of regulatory RNAs that are then directly involved in RNA-dependent epigenetic (sometimes also in genetic) modifications of specific tergids of the sex genome. Most genome sequences are transcribed and produce a great number of various, non-protein coding RNA molecules, but in extremely low amounts (one or two molecules per allele), and in this case transcription from one or both strands takes place [54]. Besides, antisense RNA is also transcribed from a part of the genome and the sense/antisense pairs often exhibit coordinated regulation. An artificial disturbance of the antisense RNA level can change expression of sense RNA [55]. If antisense RNA interacts

with promoter-associated RNA, it is able to create specific epigenetic modifications such as transcription inhibition and gene methylation [56, 57]. It was shown that low-copy promoter-associated RNA can be recognized by the antisense strand of siRNA, thus suppressing the corresponding gene [58]. Processes of emergence of RNA-dependent epigenetic modifications were documented in different variants [59]. And just such transcriptome properties could allow "foreign" TF, entering the cell, to shift easily the RNA balance towards the side, unusual for the norm, which is used by the creatron in the brain and gonadal morphons for necessary operations. Thus, in the CNS morphons that obtained unusual TF from the somatic periphery, TF are produced in response that are in store for a long distance (including crossing synapses via homeoproteins) and can enter the gonadal morphons; the whole set of gonadal morphons is the gonadal homunculus, though it not resembling the host human organism in external features. The term "morphunculus" is more applicable to species other than human. The creatron is thereby able to cause nonrandom epigenetic alteration of appropriate gametes by shifting the balance of regulatory noncoding RNAs in a certain region of gamete-forming tissue (in a particular gonadal morphon). In this case, the gonadal morphon gametes are unalike concerning the epigenetic label. In gametes produced by one gonadal part, that did obtain foreign TF, the label will appear, whereas it will be absent from other gamete groups. Therefore, only some of the progeny will acquire the epigenetically altered phenotype, just that which got gametes from the modified "organ" of the gonadal morphunculus. The phenotype alterations in the progeny will be topographically nonrandom: only a definite and quite real organ will be gradually changing in the progeny, just that on which the creatron is "working". Such a process, occurring within a comparatively small number of generations (probably 20 will be enough in many cases), makes possible creation of various adaptations for survival in an unusual environment. Of course, all unsuccessful variants will be excluded by negative selection, i.e. by simple elimination. No "creative" role of selection, which has been discussed for decades, is required for creation of adaptations and emergence of new biological species. The abovementioned process does not require disturbance of the central dogma, and features acquired by parents are not at all inherited by progeny as such. Instead, topographically nonrandom epigenetic alterations (some of which can be useful) are inherited not by rare descendants, but rather in mass. The frequency of useful alterations in progeny sharply increases because changes in their epigenome are produced in a topographically aimed manner. Later epigenetic alterations have an increased chance to become genetically fixed due to emergence of point mutations and larger genetic transformations, also epigenetically initiated and probably RNA-dependent.

CONCLUSION

The high probability of nonrandom adaptations is achieved because the sex genome modifying molecules are sent by soma to topographically nonrandom sex genome regions. This is carried out by a special system of guidance control, the key feature of which in animals is possession of the morphon system. Probably in plants there is a similar system of projections which joins their somatic and generative organs by transport links. Not all modifications initiated by a creatron are successful, and due to this neutral and even harmful variants are created and then eliminated by negative, i.e. purifying, selection. Adaptivity is created by activity of living organisms that would die out, while awaiting the random favorable mutations in the face of ecological cataclysms. The variability formed under control of the creatron under extreme habitat conditions of a series of generations appears topographically nonrandom (for modified genome regions) and therewith frequent. The combination of these factors strongly increases the probability of appearance of relatively useful genome modifications. Owing to this, the creatron mechanism makes it possible to achieve necessary aims in adaptation to the environment in a short time.

It is important to emphasize that a new feature acquired by chronic "exercise" of parents (powerful muscle, increased thermal resistance, etc.) are not reproduced as such in children. Characters acquired during life are not adopted immediately and forever. This would be Lamarckism in pure form. First, in response to creatron signals from soma there emerge RNA-dependent epigenetic modifications in the parents' sex genome, which are preserved (completely or in part) in the sex genome and soma of their children. Therefore, soma of descendants of the first generation have some phenotypic alterations, and their creatron system is already forced to deal with the epigenetically altered (compared to parental) transcriptome; owing to this the same "exercise" now initiates the appearance in their gametes of similar, but somewhat different epigenetic modifications. In descendants of the following generation, "exercise" causes more significant deviations in phenotypes because the creatron continues searching for optimal conditions for "equilibration" of all of the organism's systems reacting to the extreme environment. Under conditions of long (during a series of generations) continuation of the same effect of extreme environment, requiring constant "exercise", transformations of the sex genome and phenotype continue in next descendants. Therefore, the process of polymorphism enhancement in the sequence of generations will temporarily increase and then, after achievement of necessary balance with the environment, will slow down and cease. Variants generated by the creatron are nonrandom and topographically pertained to the organism's structures and functions (both in the sex genome and in phenotype) involved in the corresponding "exercise". All unfavorable

variants are eliminated by negative selection, while relatively adequate adaptations help the organisms to survive. In principle, already this is enough for organisms with epigenetically modified phenotype to exist successfully over a long series of generations under conditions poorly suitable for their recent ancestors. Replacing epigenetic mark by topographically nonrandom mutation provides a more reliable form of genome memory. But it is reasonable to use this means not immediately, but only after verification of any innovation over several generations for its adequacy to the environment. The criterion of such verification can be the presence of similar epigenetic marks in both sex partners. This would be indicative of successful survival of partners and, hence, of timeliness of genetic fixation of the acquired epigenetic changes. Epigenetic homozygotes will inevitably appear in their progeny. For example, epigenetic homozygotes and heterozygotes can differ by factors influencing local RNA-dependent events, including site-specific recombination in meiosis, etc. Thus, prohibition for corresponding meiotic recombination can be epigenetically inhibited in these homozygotes, and owing to this it will be possible during the sex process at definite epigenetically modified sites just in homozygotes. Possibly, just the necessity of creation of homozygotes in epigenetic modifications is one of the main reasons for subdivision of the overwhelming majority of biological species into two sexes. This long-standing enigma still remained unsolved in evolutionism: division into sexes halves the species productivity, but nature preferred just this way.

The role of positive (Darwinian) selection, instead of the main driving force of evolution, becomes a secondary factor, because organisms are themselves involved in adaptation and themselves create advantages in survival, and as a result in selective reproduction of the fittest. The requirement of a "creative" role of natural selection as a force that allegedly creates species appears superfluous on the background of the work of the creatron. Note that the creatron is also useful for evolution by its ability to compensate for unfavorable random mutations by creation of compensating mutations, or counter-mutations. Moreover, the creatron is able to help the organism to adapt to new information that enters the organism during horizontal gene transfer. Although evolution gives examples of many adaptive innovations, there are also quite doubtful compromises in it. They are also created by this machine for evolution. The result of adapting, i.e. evolutionarily homeostatic efforts of the creatron, is far from being covered just with roses of success.

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