THE CONCEPT OF BIOCHEMICAL ORGANIZATION AND PROBLEMS OF BIOCHEMICAL EVOLUTION

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Abstract — Biological organization is defined as the unity of structure, function and regulation of biological systems. For multilevel hierarchical biological systems, biological organization is represented by the hierarchy of functioning controllable structures. The hierarchy of structural levels predetermines the functional hierarchy and the hierarchy of regulatory mechanisms. Biochemical organization includes the levels of the matter organization starting with the cell and lower. Subcellular and supramolecular structures are considered as distinct levels in the organization of biosystems. This concept is used for analyzing problems of the origin of life and biochemical evolution. The traditional view according to which the evolution of biological systems of lower levels preceded the formation of systems of higher levels is criticized. It is suggested that the formation of the cell and biological systems of lower levels occurred in a coordinated manner. Nussinov—Mekler's hypothesis that regolith grains coated with a lipid shell were cell predecessors and Rudenko's concept of the evolution of elementary open catalytic systems (EOCS) are modernized. The evolution of EOCS occupying various compartments of regolith grains resulted in their integration into a system of higher rank where EOCS played the role of standard blocks (the supramolecular structure level). Further evolution occurred by rearrangement of the standard blocks.

1. INTRODUCTION

Two fundamental principles are the methodological basis of biological sciences. One of these principles is the historical principle realized in the evolution theories of Lamarck, Darwin, and their followers and in Oparin's theory of life origin. The other principle is the structural—functional one according to which biological systems are considered as

Evolutionary Biochemistry and Related Areas of Physicochemical Biology
Edited by B.Poglazov et al., Bach Institute of Biochemistry and ANKO, Moscow, 1995

multilevel hierarchical systems. An unification of these principles is one of the main problems of modern theoretical biology [1—4].

The explosive growth of information in physicochemical biology have permitted us to formulate the concept of biochemical organization [5—7] which is based on the perception of unity of the structural—functional—regulatory relationships in biochemical systems. A problem of origin and evolution of biochemical organization have remained without consideration. However, contemporary state of investigations of the origin of life permits us to connect the concept of biochemical organization with the Oparin's theory. Such a combination of structural—functional and historical approaches enables, on the one hand, the concept of biochemical organization to be presented in more unitized form and, on the other hand, the theory of the origin of life to be modernized.

2. BIOLOGICAL ORGANIZATION

The concept of organization in biology is usually identified with that of regularity, and the latter — with the concept of structure. The limitations of such an approach are evident. Biological systems are functionally active structures and are characterized by a definite arrangement of their components and interactions between them, which impart a biological function to the structure. Therefore it is reasonable to consider the organization of living matter as a unity of structure and function [8].

However, this approach is also insufficient. It is necessary to bear in mind that biological systems are multilevel hierarchical systems [9—11]. On the one hand, the principle of hierarchy asserts that a biological system with any degree of complexity is always included as an element in a system of a higher rank. On the other hand, it is a set of elements or subsystems of a lower rank. Organization of multilevel hierarchic biological systems is impossible without appropriate interactions of structural levels. Such interactions are achieved by effective regulatory mechanisms [12]. Therefore we should view the biological organization as the unity of structure, function and regulation [5—7].

It seems that the recruitment of regulation as the third and equally important component of biological organization is not obligatory, since function is usually considered to embrace regulation. But regulation cannot be limited to the functional aspect only, since the structural aspect of regulation also plays an important role: many regulatory mechanisms include deep structural changes; each level accommodates special structures with associated regulatory functions. Moreover, in one

respect, namely, from the point of view of temporal organization, regulation should be at the first place, since it determines "the proper time" for various biological processes. In other words, function is related to "What?", structure — to "Where?", and regulation — to "When?".

2.1. Structural Hierarchy of Biological Systems

Though the hierarchical nature of biological systems is generally recognized, the question what structural levels of the organization of living matter should be distinguished remains in dispute [10, 11, 13, 14]. The hierarchical levels widely accepted by biologists are based on a structural approach: low–molecular–weight compounds — biomacromolecules — cells — tissues — organs — organ systems — organisms — populations — biogeocenosis — biosphere (in order of complexing) [10]. Though this approach is rather attractive, it is unclear why only certain biological structures are included in this list as independent levels. In particular, the lack of the intermediate structural levels between the biomacromolecules and the cells seems surprising.

Biological systems of various levels differ from each other first of all by their size. Therefore the "metric approach" can be applied to distinguish between structural levels. Zhirmunsky and Kuzmin [14] believe that the ratio between critical values of neighboring levels should be e^e. They have proposed nine different size ranges in the human organism. The eighth range corresponds to the biomacromolecule level and the fifth — to the cellular level. Thus, two ranges separate the cell from biomacromolecules, and these correspond to the structural levels. In our opinion, the sixth range corresponds to subcellular structures and the seventh to supramolecular structures. Levels higher than the cell are not discussed here.

Though the "metric approach" is simple, it is contradictory. In order to analyze the structural levels, one should use a systemic approach. Whithin the framework of this approach each level is made up of definite elements (blocks) of the lower level. So, the hierarchy of structural levels in living organisms can be depicted as concentric spheres, each including the lower levels (Fig. 1).

Being the biological system, each structural level possesses systemic properties, i.e., the properties that cannot be derived from the properties of its blocks (elements). In other words, the transition from any level to the higher one means not only the emergence of a more complex system, but also the appearance of a new, more complicated function and a new regulatory mechanism occupying a higher hierarchical position relative to regulatory mechanisms realized at lower levels. Thus,

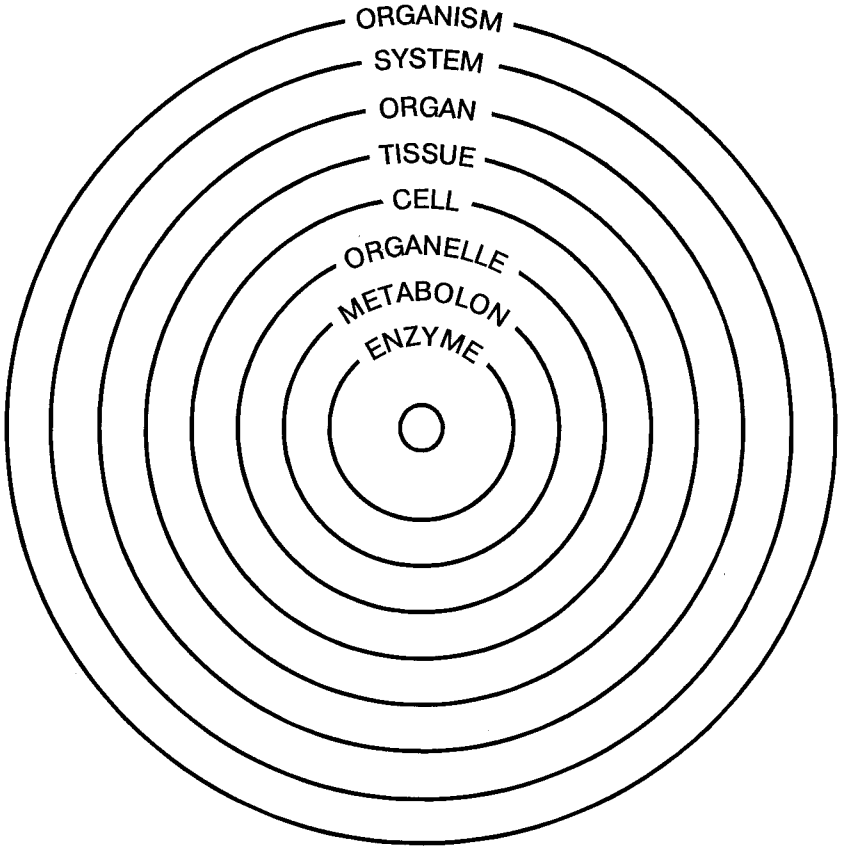

Fig. 1. Scheme for hierarchy of structural levels in biological systems. The central part of the scheme corresponds to low–molecular–weight compounds. The enzyme is indicated as structural level corresponding to biomacromolecules, metabolon — as a level corresponding to supramolecular complexes.

the hierarchy of structural levels predetermines the existence of the functional hierarchy and the hierarchy of regulatory mechanisms.

2.2. Functional Hierarchy

The hierarchy of biological structures is more widely discussed than the hierarchy of biological functions. As a result, the "function" has not been strictly defined. Ugolev [15] writes that sometimes a function is

defined as a set of the activities performed by a structure (e.g., secretion of hydrochloric acid, pepsin, mucus, etc. by the stomach). Sometimes the function is defined as the purpose of the structure (e.g., for stomach — digestion and food deposition), and sometimes as the biological effect (for stomach — denaturation and initial stages of protein digestion).

However, if we propose that there is a hierarchy of functions, which are predetermined by the structural hierarchy, the obscurity observed by Ugolev can be clarified. In fact, the stomach is an organ of the digestion system, but it consists of blocks of a lower level. Secretion of pepsin and hydrochloric acid are not functions of the stomach itself but of the blocks (in this case the corresponding secretory cells). On the other hand, digestion and food deposition are functions of the digestion system as a whole, and not of the stomach alone. The role (function) of the stomach within this system is restricted to initial stages of digestion.

Thus, the function of a biological system at any level is the role it plays within the system of the next hierachically higher level. In this case we cannot separate the function from the function–induced effect as proposed by Ugolev [15], since the role of any biological system is to generate a definite biological effect.

Let us illustrate the functional hierarchy with another example. The function of the circulatory system is to provide all parts of the organism with necessary nutrients and to remove "waste products". The heart is the pump in the system. The muscle tissue in the heart (myocardium) performs the mechanical work. The function of myocardial cells is contraction of muscle fibers. Mitochondria inside these cells supply the necessary energy.

It should be emphasized here that the transition to a higher level is accompanied by the appearance of a new function (the function of a higher level). The myocardium cannot function as the pump by itself, since this work requires the whole organ having resevouirs, valves, etc. The heart cannot fulfill its function without arteria, blood vessels, capillars, i.e., if it is not built into the system of blood circulation.

2.3. Regulation of Biological Systems

The third component of biological organization, regulation, is also hierarchical in nature. As previously stated by us [16—18], the hierarchy of regulatory mechanisms should correspond to the hierarchy of structural levels. The regulatory mechanisms implemented at low levels of organization are subordinate to the regulatory mechanisms that act at higher structural levels.

At each level there are two types of regulation: autoregulation, which maintains "key" parameters at a constant level, and "tracing" the

signals coming from upper levels [19—21]. The tracing mechanism involves recognition of these signals and their transmission to the subsystems. An example is the binding of "first messengers" (hormones, neuromediators, etc.) by cell surface receptors, which results in the generation of "second messengers" (cyclic AMP, inositol triphosphate, diacylglycerol, Ca^{2+} and so on).

Autoregulatory mechanisms include the feedback signals coming from lower levels which act on the center of control of the system, as well as the signals between the subsystems. A unified and organized system cannot exist without mechanisms of autoregulation. As to tracing mechanisms, they provide functioning of the given system as a whole within the system of the higher level. Regulatory factors governing the system as a whole are external with respect to the system (hormones relative to the cell, allosteric effectors relative to the enzyme, etc.).

The division of regulatory mechanisms into those of autoregulation and tracing is only relative and depends on the level of the system being considering. For instance, if we examine the level corresponding to an enzyme, the allosteric regulation is a tracing mechanism for the enzyme (control from above). If we consider the cell level, the same allosteric mechanism falls into the group of autoregulatory mechanisms providing homeostasis.

An important peculiarity of the structural organization of biological objects as controllable systems is the spatial separation of the working centers and control centers. The working centers perform the basic function of the given level, while the control centers are in charge of the mechanisms of tracing, i.e., control over the functioning of the structural level as a whole. Let us consider the structural level corresponding to biomacromolecules such as enzymes. The working center of an enzyme is its active site, where chemical transformation of the substrate occurs, while the control center is the allosteric site, where binding of the metabolite—regulator (allosteric effector) takes place. The action of an allosteric effector on the functioning of the active site is mediated by changes in the conformation of the protein molecule [22]. The allosteric regulation of the enzyme activity can be classified as the tracing mechanism, which assures optimal functioning of the enzyme within a system of a higher level of complexity, the metabolic system.

3. BIOCHEMICAL ORGANIZATION

3.1. Biochemical Systems

Initially biochemistry was thought to be the science dealing with chemical compounds and chemical processes in biological systems. However, since biochemical processes occur predominantly in cells, biochemistry is aimed mainly at studying intracellular levels: low–molecular–weight compounds, biomacromolecules, metabolic systems, and subcellular structures. At the same time, these biological systems were subjects of investigation of other biological sciences such as bioorganic chemistry, molecular biology, cytology, and some aspects of biophysics. At present, all of the above sciences are interwoven so tightly that one can call it a new science, viz., physicochemical biology [23]. Nevertheless, we can consider biochemistry as the science dealing with all the structures and all the processes at the cell level and lower.

Thus, biological systems such as cells, subcellular structures, supramolecular structures, biomacromolecules, and low–molecular–weight biologically active compounds are termed biochemical systems. Cells and biomacromolecules (as well as low–molecular–weight compounds) are considered to be special levels of the biological organization. There is no agreement as yet about the subcellular and supramolecular structures. In the previous section, we postulated the existence of two levels by the "metric" approach. Nevertheless, according to our concept of biological organization as a unity of structure, function and regulation, each level should differ not only in structural characteristics but also in special function and special regulation mechanisms. Let us prove from this point of view the existence of these new two levels.

3.2. Subcellular Structures as Independent Levels in the Organization of Matter

The existence of definite subcellular structures (cell organelles, cytoskeleton, plasma membrane) and their defined functions is undoubted. However, to consider these structures as independent levels, one should prove that subcellular structures have their own mechanisms of regulation which control these structures as a unified system.

The idea that cell organelles are controllable systems was first formulated by Konev and his colleagues [24]. In this work cell organelles (mitochondria, chloroplasts, etc.) are considered as systems with cooperative properties. This viewpoint is confirmed by data on the existence of discrete functional states of the cell organelles and abrupt

change in these functions of the organelles when there is a structural transition.

Recently new data have been obtained which show that a mitochondrion is a controllable system. Halestrap [25] showed that the mechanism of action of some hormones (glucagon, vasopressin, and adrenaline) on mitochondria is mediated through Ca^{2+} and involves an increase in volume of the mitochondrial matrix. In this regard, model experiments performed by Krasinskaya et al. [26] may be of interest. They have shown that matrix volume change, induced by lowering the tonicity of the incubation medium, causes a structural rearrangement of the membrane polyenzyme ensembles and, as a result, a transition of mitochondrion from one functional state to another.

Thus, the data given imply that mitochondria are regulated as a unified system and, consequently, can be considered as the independent level in the organization of matter.

3.3. Supramolecular Structures as an Independent Level

Supramolecular structures are organized functional complexes of biomacromolecules [27]. The ribosomes are perhaps the most investigated among these structures [28]. In this section we shall consider one of the least investigated types of supramolecular biostructures called metabolons. Metabolons are complexes of the enzymes involved in a common metabolic pathway. Srere [29] has summarized some experimental data in favor of the existence of such complexes for 16 metabolic systems including biosynthesis of DNA, RNA, protein, glycogen, purines and pyrimidines, urea cycle, electron transport, oxidation of fatty acids, degradation of cyclic AMP, glycolysis, tricarboxylic acid cycle. It is noteworthy that the assembly of multienzyme ensembles combining the enzymes of a common metabolic pathway occurs on cell structures such as cytoskeleton, biomembranes, and the structural proteins of muscle tissue. This observation was taken into account by Srere [30] when he proposed the term "metabolon" which means "a supramolecular complex of sequential metabolic enzymes and cellular structural elements". One example of a cellular structural element included to metabolon is the integral protein of the erythrocyte membrane (the band 3 protein), which is a component of the glycolytic metabolon in erythrocytes [31—33]. Another example is succinate dehydrogenase, being the integral protein of the inner mitochondrial membrane, which is a member of the tricarboxylic acid cycle metabolon [34, 35]. Thus, metabolons uniting the enzymes (i.e., the structures of the biomacromolecule level) are included into the system of the higher level — subcellular structures.

Since metabolons are very labile, their exact structure remains poorly understood. Only hypothetical models of the glycolytic metabolon and the tricarboxylic acid cycle metabolon [18, 27, 33—35] are currently available.

We propose that the transition from individual biomacromolecules to structurally ordered ensembles should be accompanied by the appearance of a new function and a new hierarchically higher regulatory mechanism. Clearly, the function of a metabolon is to perform the metabolic process. We believe that this new function emerges only with structural organization of the enzymes.

Upon assembly of a metabolon a microcompartment encompassing the active sites of all the enzymes in the complex is formed [36]. Conversion of metabolic intermediates occurs on the "conveyer belt" of active sites, thus preventing the intermediates from straying and their undesirable involvement in other metabolic pathways. So, metabolic system acquires a new property, namely, microcompartmentation of metabolic pathway. Examples of such microcompartmentation have been widely described in the literature [37—42].

The assembly of enzymes of a metabolic pathway into a unified structure makes it possible to control the metabolic system as a whole. Above we have noted two general principles in the regulation of biological systems: first, spatial isolation of working and control centers and, secondly, existence of external factors acting as control factors. These principles are true for a metabolon as well. A metabolon, as a controllable system, should have spatially separated working and control centers. The microcompartment, where chemical conversion of substrates occurs, is a working center. The anchor protein of the support is a control center [16—18]. We proposed that the overall control of the metabolon is achieved by second messengers acting on the anchor protein. In other words, factors external to the complex are the real control factors which assures optimal functioning of the metabolon.

3.4. Biochemical Organization

As describe above, the unity of structure, function and regulation is a common theme in biological organization. We have noted that the lower levels of organization (low–molecular–weight compounds, biomacromolecules, supramolecular structures, subcellular structures, and the cell) can be considered as biochemical levels. In line with this notion, it is reasonable to consider biochemical organization as a combination of principles of the structural organization, function and regulation at the biochemical levels.

The concept of biochemical organization can serve as the methodological basis in designing investigations of biological chemistry and other frontier fields, and to compile curricula in biological chemistry. It also allows the arrangement of experimental data from studies structure—function—regulatory relationships in biochemical systems. Related concept was developed by Testa and Kier [43] for the analysis of structure—activity relationships in pharmacology.

4. BIOCHEMICAL EVOLUTION

4.1. Evolutionary Problems in the Context of the Concept of Biochemical Organization

In terms of the concept of biochemical organization, a theory of the biochemical evolution should answer two principal questions. First, it is necessary to understand how the evolution of structures is correlated with the evolution of functions and control mechanisms. The second problem is the interrelation between the origin and evolution of different levels. As applied to biochemical systems, the problem is formulated as follows. In what sequence did such levels as biomacromolecules, supramolecular complexes, subcellular structures, and cells emerge and evolve?

It is most widely believed that structural levels were formed in succession "from bottom to top" in the course of biochemical evolution: initially low–molecular–weight organic compounds emerged, then biopolymers formed, further supramolecular structures (micelles, coacervates, microspheres, etc.) arose, and, finally, protocells appeared. It is precisely this scheme which is stated in most of reviews on the problem of origin of life [44—49]. Besides, Bernal [50] supposed that one more stage, namely, the stage of separate organelle formation had to exist.

At present the validity of the first stage is doubtless. Numerous experiments demonstrated the possibility of the formation of biologically significant low–molecular–weight organic compounds under the conditions mimicking those presumably occurred on the abiotic Earth (for reviews, see [44—46, 49, 51—53]). On the other hand, numerous attempts to simulate a prebiotic synthesis of polymers similar to biological ones have failed (for reviews, see [49, 52, 54]). The main difficulties were the low rate of polymerization and formation of links atypical for biopolymers. This led Mekler [54] to believe that only oligopeptides (up to ten monomers) and oligonucleotides (up to twenty monomers) could be formed in prebiotic water.

Besides, the mechanism of transition from biopolymers to cellular structures remains unclear. There are two approaches to this problem. According to Bernal [50], the mechanisms of template synthesis of proteins and nucleic acids emerged before the appearance of phase–separated systems (PSSs). Oparin and his followers had the alternative view. According to them [44, 49, 55—58], the emergence of PSSs was a necessary precondition for the evolution of biologically significant mechanisms. The latter is proved by the following fact. Living organisms are able to counteract an increase in entropy due to spatial separation which permits the organisms to interact with the environment selectively. Hence, the transition from the chemical evolution to the biological forms of organization of matter is associated with the appearance of PSSs.

This conclusion completely agrees with the concept of biochemical organization. In Sub–section 3.3 we have noted that an organized metabolic system acquires microcompartmentation. In recent years the problem of the importance of spatial separation (i.e., compartmentation) of biological processes has been actively discussed [37—40, 59—61]. According to Friedrich [40], "compartmentation is one of the fundamental principles in the organization of living matter: the very existence of cell is a manifestation of biological compartmentation". Much attention is given to microcompartmentation, i.e., localization of processes in a small volume as compared to the volume required for statistical description. We believe that it is microcompartmentation which permits a system to be led out of the sphere of the obedience to statistical laws, thus avoiding entropy increasing and equilibrium [27, 59, 62].

Coacervates [44], proteinoid microspheres [45], marigranules and marisomes [63, 64], and other structures based on insoluble polymer complexes [49] are suggested to be examples of PSSs. Some of these systems were formed from artificial polymers, and the possibility of their abiogenic synthesis has not been proved. The others were formed from polymers with links atypical for biopolymers, and it is unclear how these polymers can transform to the usual biopolymers. Besides, all the systems do not provide microcompartmentation.

According to Oparin, the emergence of PSSs was also necessary for the appearance of another characteristic feature of life, namely, "purposeful" structure of the parts and the whole. He rejected the idea that "the intrinsically organized protein and nucleic acid molecules, purposefully adjusted in their structure to the functions they fulfil in living systems, could emerge in the aqueous solution" [55]. Oparin considered that "the functional fitness of the parts of the organism, especially of the biologically significant molecules, could emerge only

in the course of evolution as a result of natural selection; but this had to be a selection not of the separate parts, but of the whole integral system".

An analogous opinion was given by Keosian [65], who considered to be impossible that "biochemical compounds, biochemical reactions and mechanisms ... appeared in probiotic water with the functions they would have in a living thing before there were living things".

In terms of the concept of biochemical organization the function of a biological system of a certain level should be realized as the role of this system in the system of the higher level (see Sub–section 2.2). Therefore, the evolution of a function is impossible, while the corresponding structure evolves separately.

Similar considerations can be applied to the evolution of control mechanisms. The concept of biochemical organization suggests two kinds of control: autoregulation and "tracing" signals from the higher levels (see Sub–section 2.3). It is clear that mechanisms of "tracing" cannot appear while the system evolves in isolation. It should be emphasized that it is mechanisms of "tracing" which provide the appropriate functioning of the given system in a system of a higher level. Thus, these mechanisms are a significant system–forming factor. Therefore, it is hard to imagine the appearance of a new level without regulatory links with lower levels.

4.2. The Origin of the Protocell

Thus, according to the concept of biochemical organization, the appearance of the levels from biomacromolecules to cells by the scheme "from bottom to top" is invalid. On the other hand, the supposition that the formation of biochemical systems occurred "from top to bottom" is even more absurd, because higher systems consist of systems of lower levels. Therefore, we consider as the most acceptable the notion about the simultaneous and coordinated formation and development of the structures of biochemical levels.

This supposition can seem absurd as well, if we do not take into account the following consideration. As Cairns–Smith noted [66], a cooperative system (e.g., an arch) can be gradually constructed, if it is built on some support. According to Cairns–Smith, living systems "used to lean on something low tech". He supposed that first organisms might be crystals of clay.

Wächtershäuser [67] advanced a hypothesis that metabolism had originated at mineral surfaces prior to the origin of the first cells. Clegg and Wheatley [68] adopted this position and supposed that these

non–biological surfaces had been subsequently replaced by membranes and nuclear and cytoplasmic matrix proteins.

Kuhn and Waser [69] suggested a model in which early mechanisms of translation could evolve in pores of different sizes in rocks. Baltscheffsky and Jurka [70] discussed the possibility of the simultaneous, stepwise emergence of interacting oligopeptides, oligonucleotides, and protomembranes. These authors, however, did not propose concrete mechanisms of the interaction and evolution.

In some respects, the notion about simultaneous evolution of the structures of biochemical levels is present in Oparin's theory as well. Indeed, Oparin [55] suggested that "at first, there could appear only the protein–like and nucleic acid–like polymers, whose intramolecular structure had no biological purposiveness. Only when these polymers were combined in multimolecular PSSs, their interactions brought to a mutual adjustment of their molecular structure and biological functions as a result of natural selection of the whole open systems". Thus, in Oparin's theory protein–like and nucleic acid–like polymers play the role of a support providing the evolution of structures and functions of each biochemical level. But, as it has been discussed above, this model of support is unlikely.

Deamer and Oró [71] supposed that the structures formed by amphiphilic non–polymeric molecules (like liposomes) were a more adequate model of protocells than biopolymeric structures, because liposomes demonstrated barrier functions (see also [52, 72]). Day [73] came to the same conclusion, but he considered, however, that polynucleotides had been formed outside lipid vesicles. Cavalier–Smith [74] suggested a model of "obcell" consisting of genes and ribosomes attached to the outer surface of a lipid vesicle containing a light–driven proton pump and proton–driven pyrophosphate synthase, but the origin of these protein and nucleoprotein structures was not discussed.

Woese [75] supposed that life emerged not in the ocean but in salt water droplets in the early Earth's atmosphere. He casually noted that these droplets could have been coated with membranes, but he did not discuss the origin of the membranes. Oberbeck et al. [76] modified Woese's hypothesis and concluded that in the atmosphere only the polymerization step could occur.

Russel et al. [77] proposed that life emerged from iron sulphide bubbles formed by a contact of sulphidic spring water and iron–bearing ocean water. These "sulphide membranes" inserted abiogenic organic molecules and evolved to cells. Analogous model of sulphide vesicle was proposed by Erokhin [78]. These vesicles could be formed from liposomes with iron–rich inner contents as a result of diffusion of H_2S.

In our opinion, the hypothesis suggested by Nussinov and Vekhov and elaborated by Mekler is the most interesting.

Nussinov and Vekhov [79] supposed that up to the appearance of liquid water the Earth surface had been covered by clay–like dust grains called regolith grains by the authors by analogy with Moon's ground. Unlike Moon's regolith Earth's one had to possess considerable porosity. They were lighter than water and could float. Nussinov and Vekhov supposed that regolith grains could serve as platforms for the origin of life.

Mekler [54] advanced a hypothesis that floating regolith grains sorbed lipids located on the water surface and covered with a lipid shell. A similar supposition was further made by Nussinov and co–workers as well [80, 81]. The regolith grains covered by a lipid layer sorbed and concentrated various organic (mainly hydrophobic) compounds, including oligopeptides and oligonucleotides synthesized in small quantities in the ocean.

Mekler called such particles "reinforced liposomes". This term was accepted in some following works [78, 82, 83]. Now we prefer to use a new term *regosomes*.

Further, biopolymers could be formed by dehydration condensation in the hydrophobic environment of the liposomes. Complexes of metal ions with oligopeptides served as pre–enzymes. The functional activity of the pre–enzymes increased simultaneously with the molecular mass as far as regosomes evolved.

Mekler explains the appearance of the connection between the phenotype and the genotype on the basis of the principle of cross stereocomplementarity postulated by him [54]: the complementarity of amino acids to their anticodons is suggested[1]. In accordance with this principle oligopeptides and oligonucleotides interacted with each other being outside liposomes, and liposomes presumably sorbed finished blocks of the future genome of the protocell.

Nussinov–Mekler's hypothesis combines the earlier ideas of many researchers. Similar to Oparin's theory, it assumes that PSSs were formed in an early stage of evolution. Like Deamer and Oró [71], Mekler considers the lipid shell to be a necessary component of protocells. Besides, Nussinov and Mekler supported the idea of the important role of mineral surfaces in the origin of life which was

[1] The principle of cross stereocomplementarity and some other postulates of Mekler's general theory have not gained wide recognition yet. Recent data [84, 85] have testified, however, to their validity. In any case, Mekler's hypothesis on the origin of life has independent significance.

suggested by Bernal [50] and developed by many investigators [66, 67, 69, 78, 86, 87]. In addition, like Woese [75] and Cairns–Smith [66], they also supposed the presence of a mineral support at the beginning of the evolution.

Thus, the regosome model has some advantages. On the one hand, lipid shell provides the barrier function and hydrophobic environment for synthetic processes. In regolith pores hydrophobicity of different degrees could be achieved. On the other hand, regolith support not only could stabilize the lipid shell but could provide a great surface, realize the catalytic activity and concentrating K^+ ions [2, 82].

The main advantage of regosomes is that they provide microcompartmentation in contrast to other models. This feature approximates them to contemporary cells and help us to understand how protocells can counteract an increase in entropy.

4.3. From Protocell to Cell

Thus, according to regosome model, precursors of protocells had appeared before biomacromolecules, supramolecular complexes, and cellular organelles were formed. Nevertheless, there were precursors of structures of all the above–mentioned levels in the regosome. Indeed, oligopeptides and oligonucleotides are precursors of biomacromolecules, and complexes of oligopeptides and oligopeptides with oligonucleotides are precursors of supramolecular structures. As to cellular organelles, regolith pores may be considered as their precursors. Thus, the biochemical levels from biomacromolecules to the cell could evolve simultaneously (Fig. 2).

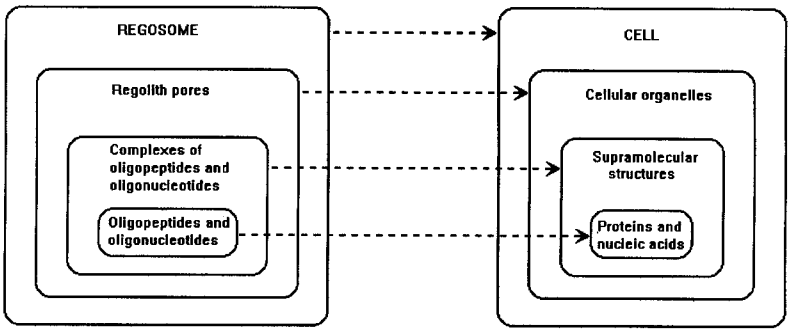

Fig. 2. Scheme illustrating simultaneous evolution of the biochemical levels.

The regosomes were open systems. The sun activity and geophysical processes provided them with an energy flow ensuring nonequilibrium state and conditions for self–organization [88]. The methods of nonlinear thermodynamics of open nonequilibrium systems have been used to model the early stages of evolution [3, 88—91], but such models are macroscopic and do not take into account microcompartmentation.

Rudenko suggested a theory of evolutionary catalysis [92—96] (see also [27, 97]). According to the theory, "elementary open catalytic systems" (EOCSs) are an object of chemical evolution. EOCS is an integral aggregate of a catalyst, reacting substances and products. According to Rudenko, such systems are capable of autoevolution and autocomplication. The foundation of such autoevolution is a basic exoergic reaction accomplished by the catalyst. Irreversible alterations of EOCS are possible under the action of accidental factors; if this alteration is coupled with the basic reaction, it can have an endoergic character and be accompanied by complication of the system. Thus, EOCS undergoes evolutionary alterations which result in changes in many parameters of the system including the catalytic activity. Rudenko infers the principal law of EOCS evolution. According to this law, the evolutionary alterations which are accompanied by the maximal increasing of the absolute catalytic activity of the system proceed with the maximal rate and probability.

Using the theory of evolutionary catalysis we can consider catalytic systems arising inside the regosome as EOCSs. Unlike Rudenko we consider that EOCSs were included into the high level system from the very beginning. This supposition does not contradict the theory of evolutionary catalysis, but supplements it. Besides, we suppose that the absolute catalytic activity is not the only criterion of selection in the course of EOCS evolution. The parameter characterizing the efficiency of the system, namely, the coefficient of utilization of energy of the basic reaction for useful work in the evolving catalytic system, is not of lesser importance. While Rudenko considers that the probability of positive or negative results at a single evolutionary alteration is equal to 1/2, in our opinion this probability depends on the absolute catalytic activity and the efficiency. Since positive alterations are usually endoergic, they become more probable as the efficiency increases. The efficiency is connected with the degree of system organization. Hence, as the structural organization of the system is complicated, its catalytic activity increases.

Rudenko did not discuss concrete mechanisms of coupling basic reaction with positive alterations of EOCS. One of possible mechanisms has been suggested by Erokhin [78]. The photocatalytic reduction of

H_2S by Fe^{2+}/Fe^{3+} has been considered as a basic reaction. A hydrated electron being one of the products of the reaction has a high energy and is capable of starting a succession of organic syntheses. Peptides and coenzymes, i.e., substances capable of catalyzing basic reaction and other reactions of the succession, could be among the products of these syntheses. Thus, self–development of a system of sequential metabolic reactions, rather than a separate EOCS, should be discussed, and Erokhin's scenario may be called as a *self–development of metabolic system.*

The initial set of EOCSs and their distribution within the regosome were accidental. However, the interactions between different EOCSs had to play a decisive role in the course of autoevolution, as it was described in Erokhin's scenario. As a result of the natural selection it is precisely EOCSs which could be integrated into a united protocell metabolic network had to remain. Such processes having played an important role in the cell formation may be called as an *integrative selection.*

In the course of the evolution of regosomes the development of biopolymer structures occurred owing to utilization of energy of basic exoergic processes. Protein and glycoprotein systems making the protocell framework (plasma membrane and cell wall, cytoskeleton, vacuolar system) were gradually formed. They replaced and ousted the inorganic framework. In the end the evolution has led to systems constructed of biomacromolecules united into complex supramolecular structures and forming plasma membrane, organelles, etc.

The formation of reproduction mechanisms occurred simultaneously. While protocells retained the inorganic framework they could not be reproduced by division. Nevertheless, the mechanisms of translation and transcription could be evolved just at this stage. The replacement of the inorganic framework with the biopolymer one permits the realization of the mechanism of division. From this moment we may speak about appearance of real cells.

5. SUPRAMOLECULAR BIOSTRUCTURES AS STANDARD FUNCTIONAL BLOCKS

According to Rudenko [92, 93] EOCS can be altered towards complication of the mechanism by dividing the process into elementary stages. In this case the evolution of EOCS leads to the formation of a multienzyme system. Another approach is reported by Karasev and Stefanov, who considered EOCSs as precursors of individual enzymes [27, 97, 98].

The most significant argument in favor of the first approach is that the basic reaction should be exoergic. At the same time, many reactions

catalyzed by individual enzymes are endoergic. The functioning (and, hence, autoevolution) of such enzymes is possible only within a multienzyme system (or under artificial conditions). Another argument in favor of the assumption that EOCS is the precursor of the multienzyme system is data on physical interactions of enzymes within metabolic systems. The fact that two or more consecutive enzymes are capable of forming a complex [29, 40, 99, 100] means that these enzymes have recognition sites on their surfaces. This testifies in favor of their co–evolution. On the basis of the numerous data on enzyme—enzyme interactions together with other experimental data the conclusion has been drawn that the enzymes of a common metabolic system can form ordered multienzyme ensembles, namely, metabolons (see Sub–section 3.3). We suppose that it is metabolons which are the final result of EOCSs evolution.

Analyzing principles of construction and evolution of complex specialized systems, Ugolev [15] has put forward a concept of standard functional blocks. The essence of the concept is that different functions fulfilled by cells of different animal tissues are composed of elementary functions realized by certain combinations of a limited number of functional blocks. It should be noted that such blocks have to possess a basic control mechanism besides an elementary function [5]. Evolution is associated with appearance of new combinations of standard blocks. According to Ugolev, functional blocks are molecules or supramolecular complexes, i.e., structures of different levels of organization. Nevertheless, Ugolev has given emphasis to supramolecular complexes, and it is not by accident. In our opinion, it is the structures of this level that should be considered as standard blocks.

As has been noted above, one of the most characteristic features of living matter is compartmentation. This feature appears in going from the level of individual macromolecules to supramolecular structures [5, 6, 27, 36]. Another indispensable feature of living systems is vector character of accomplished processes [101]. When analyzing different biological levels from this view point, it may be seen that the above–mentioned features appear at the level of supramolecular structures. Indeed, an individual enzyme (biomacromolecular level) catalyzes direct and reverse reactions with the same efficiency: the reaction direction depends solely on the ratio of the concentrations of substrates and products of the reaction. The situation changes, however, in going to supramolecular structures.

Owing to the structural and functional coupling of proteins accomplishing exoergic and endoergic (or equilibrium) processes, the resulting process performed by a supramolecular structure is of a vector

character. Ribosome [28], multienzyme complexes, e.g., pyruvate dehydrogenase complex [40, 102], and myosin ATPase [103] may serve as examples. Besides, many supramolecular structures are associated with membranes, which further promote the vector character of processes owing to division of compartments [103]. Active transport systems [104], coupling of translocator with an enzyme adsorbed on the membrane surface, e.g., adenine nucleotide translocator with creatine kinase [105], coupling of electron transfer with ATP synthesis [101, 106] are examples of the vector character of processes performed by supramolecular structures.

Thus, the transition from biomacromolecules to supramolecular biostructures leads to the emerging of compartmentation and the appearance of the vector character of processes. This allows us to conclude that it is supramolecular biostructures that form the first really biological level. The notion about supramolecular structures as standard functional blocks whose combination and rearrangement lead to the formation of functioning structures of the higher level will enhance the understanding of evolution both of biological structures and biological functions.

ACKNOWLEDGMENTS

We are grateful to Dr. A.S.Erokhin and Dr. M.D.Nussinov for useful discussion.

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