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CONFERENCE MATERIALS

The Origin of Elementary Units of Multicellularity and Development of a Spatial Organization of Cell Layers

G. A. Savost'yanov

Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, pr. Morisa Toreza 44, St. Petersburg, 194223 Russia

e-mail: gensav@iephb.ru

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Abstract—The concept of the elementary unit of multicellularity, the histion, which also serves as a morphofunctional unit of cell layers, is introduced. Histions are cell groups formed as a result of division of labor between cells. Cell layers are regarded as regular cell networks (lattices) formed through polymerization of histions. The theory constructed based on this concept allows the composition and structure of a multitude of histions to be calculated; their development to be quantified; and families of topological and geometrical models for the histoarchitecture of cell layers to be constructed, visualized with computer programs, and experimentally verified. In addition, this model can predict previously unknown topological variants of the histoarchitecture of epithelial tissues, as well as their presence in normal development and pathology.

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Sequencing of genome do not provide understanding of the patterns and mechanisms of morphogenesis, i.e., the transition from linearly encoded genetic information to development of three-dimensional structures of the body. This resumes interest in the old question raised as early as Goethe and Haeckel on the development of theoretical morphology, which, similar to crystallography, would be able to calculate a multitude of possible structural variants of the body and its parts, describe the transformation patterns of shapes, and predict the directions of their further development (Beklemishev, 1925; Thompson, 1942; Lyubishchev, 1982; Webster and Goodwin, 1984; Thom 2002). In other words, the three pillars of current molecular biology (biophysics, biochemistry, and informatics) should be supplemented with theoretical morphology, based on topological and geometrical rules for the spatial organization of biological objects.

The successful development of such morphology is exemplified by the so-called structural biology. It is based on developed theory, has state-of-the-art tools for computer simulation and visualization, and is able to calculate and predict different variants of the three-dimensional structure of macromolecules (Schutt and Lindberg, 2000).

Theoretical advances are also taking place in other fields of morphology (Russ, 1999; Isaeva et al., 2004; Mestetskii, 2009; Chub, 2010). However, we should admit that this field in biology and medicine still remains purely descriptive and is unable to figure out and predict possible variants for the structures of organisms and their parts. This is completely applicable to the spatial organization of biological tissues, in particular, the cell layers, the development of which is one of the first stages in morphogenesis.

Thus, what do we know about their structure? We know only what a tissue looks like from the surface or in sections. In other words, the current concepts about the structure of cell layers are planar, whereas the three-dimensional organization remains unknown. What particular things do we not know? Indeed, we do not know the three-dimensional cell shape and, in particular, the number of cell sides contact with the nearest neighbors, but the most important thing still unknown is the pattern of cell interactions within a layer. The set of such interactions allows the tissue to be regarded as an integral system in a form of a network. Correspondingly, since cells with the same number of sides can form networks of various compositions and structures, their study is a separate problem. The importance of this problem is explained by the fact that the functional properties of a tissue are determined not only by the cells per se, but also by the structure of the overall network. However, it is still implicitly considered that the cells in tissues are packaged in a random manner; correspondingly, the need for special studies into the structure of the cell network and, especially, their topology, is insufficiently understood. This is an important gap in our knowledge, which hinders studies into the patterns of tissue morphogenesis during normal development and interferes with our understanding of the essence of tissue transformations in pathology.

ASSESSMENT OF THE AVAILABLE APPROACHES TO STUDYING TISSUE STRUCTURE

The current situation is explainable by the absence of any approach to studying cell networks. First and foremost, this is connected with insufficient development of a formalized theory describing the topology and geometry of biological tissues and, in particular, the structure of cellular mosaics in layers (Lewis, 1946; Dormer, 1980; Smolyaninov, 1980; Maresin, 1990). This theory is based on excessively strict axiomatics (in particular, Thompson's rule, according to which only three cell sides meet at the intersection of mosaics; Smolyaninov, 1980). Therefore, this theory in its present form allows for only one variant of correct models of tissue structures for monolayer and multilayer cell arrays, where the cells do not differ in the differentiation types and have the shape of a hexagon and a tetrakaidekahedron, respectively. Correspondingly, the theory reflects only a small part of the real tissue structures and especially does not at all take into account the variation in tissue structure in pathology. The weakness of this theory has led to the fact that it currently has no influence on the studies of the spatial organization of cell layers.

In this situation, the only available approach is empirical. However, the main method in histology is examination of thin (actually two-dimensional) sections, which gives no information about the cell packaging type within the 3D space of the layer. The known method for reconstructing a three-dimensional structure based on serial sections still remains a complex and laborious procedure even using the state-or-the-art techniques, such as confocal microscopy, optical tomography, and computer technologies (Budantsev and Aivazyan, 2005; Fiala, 2005; Barthel, 2006). Moreover, the resolution of such a method is insufficient for discovering patterns in cell network topologies. Note also that the methods of morphometry and stereology (Avtandilov, 1990), available to histologists, are currently focused mainly on different geometric characteristics of cells (sizes, areas, volumes, etc.) rather than on the topology of cell layers.

Thus, with all the advances in the techniques of preparation, microscopy, and analysis of images, the current histology still deals with the intracellular mechanisms underlying life activity. So far, the final result in morphological study is actually a planar description of what is seen in a microscope rather than determination of the composition and structure of the cell network. (Can anyone imagine the description of a rock chip or section without determining the structure of its crystal lattice?) The need for a special study of the cell network structure in epithelial tissues in development and pathology has not been understood sufficiently. The set of informative traits for characterizing the topology of cell networks has not been defined, and approaches to studying their structure are still absent.

THE ESSENCE OF THE NEW APPROACH TO STUDYING THE STRUCTURE OF CELL LAYERS

To overcome the difficulties mentioned, a new approach to studying the spatial organization of tissues and clarification of the structure of their cell networks has been developed. This approach is based on the concept referred to as structural histology (Savost'yanov, 2005). The following two ideas form the background for this approach: (1) the concept of elementary units of multicellularity, histions, as morphofunctional units of tissues, and (2) the concept of tissues as regular cell networks developed by polymerization of histions.

The concept of histions. It is known that, cells until recently were regarded as elementary tissue units. However, the majority of tissues are formed of several cell types rather than only a single type (mucosal, ciliary, villous, etc.), which are present in different quantitative ratios and are connected with different functional interactions. Since the elementary morphofunctional tissue unit should represent both the cell composition and the pattern of intercellular interactions characteristic of this particular tissue, it becomes clear that it is impossible to reflect all these aspects by a single cell. Therefore, a novel understanding of the elementary tissue units is necessitated.

In this connection, the concept of elementary units of multicellularity, that is, the minimal cell groups called histions, has been developed recently (Savost'yanov, 2005). These units appear during development from individual cells as a result of division of labor between them. A formalized description of such division allows the composition and structure of a multitude of histions to be figured out. It has been shown that the development of histions obeys a periodic law and their classification is similar to a periodic table (Savost'yanov, 2010a, 2010b). The parameters of this table have a biological meaning and are applicable for a quantitative description and measurement of a progressive development of elementary units of multicellularity. Thus, histions may be considered as specific "molecules" of multicellularity. They represent a separate but still overlooked level of biological organization located between the levels of cells and tissues.

The concepts of tissues as polymerized histions. According to the above described situation, it is assumed that the tissues are constructed of histions rather than cells. The tissue histion is the elementary morphofunctional tissue unit comprising all the cell types constituting the tissue in the proportion typical of this tissue and interconnected with the same intercellular interaction as in this tissue. Unlike the differon, which unites the related cells based on their genealogy, the histion contains cells with possibly dif-

ferent origins but united by their functional interactions. Such an understanding of elementary tissue units suggests that tissue is a regular cell network appearing through polymerization of histions. This definition does not pretend to be complete, since its goal is to put to the forefront the interconnection of tissue cells in space, to underline the importance of histions and cell networks, and to attract attention to these concepts as novel histological realities.

The concept of a histion structure of the cell layers made it possible to propose a new more adequate axiomatics for them and, thereby, to further develop the existing theory. The main points in this theory are that the limitation on the junction of only three cell sides at the crossing points of mosaics is removed (Savost'yanov, 2005, 2008a), and that mosaics can be composed of different cell types. The new theory considerably expands the family of cell layer models, as well as the rules of their polymerization, and for the first time opens the possibility to calculate them. In particular, the knowledge about the composition and structure of histions and the rules for their polymerization provide for finding the set of possible variants of the cell network structure and for constructing the families of their topological and geometric models. Examples illustrating these possibilities are listed below.

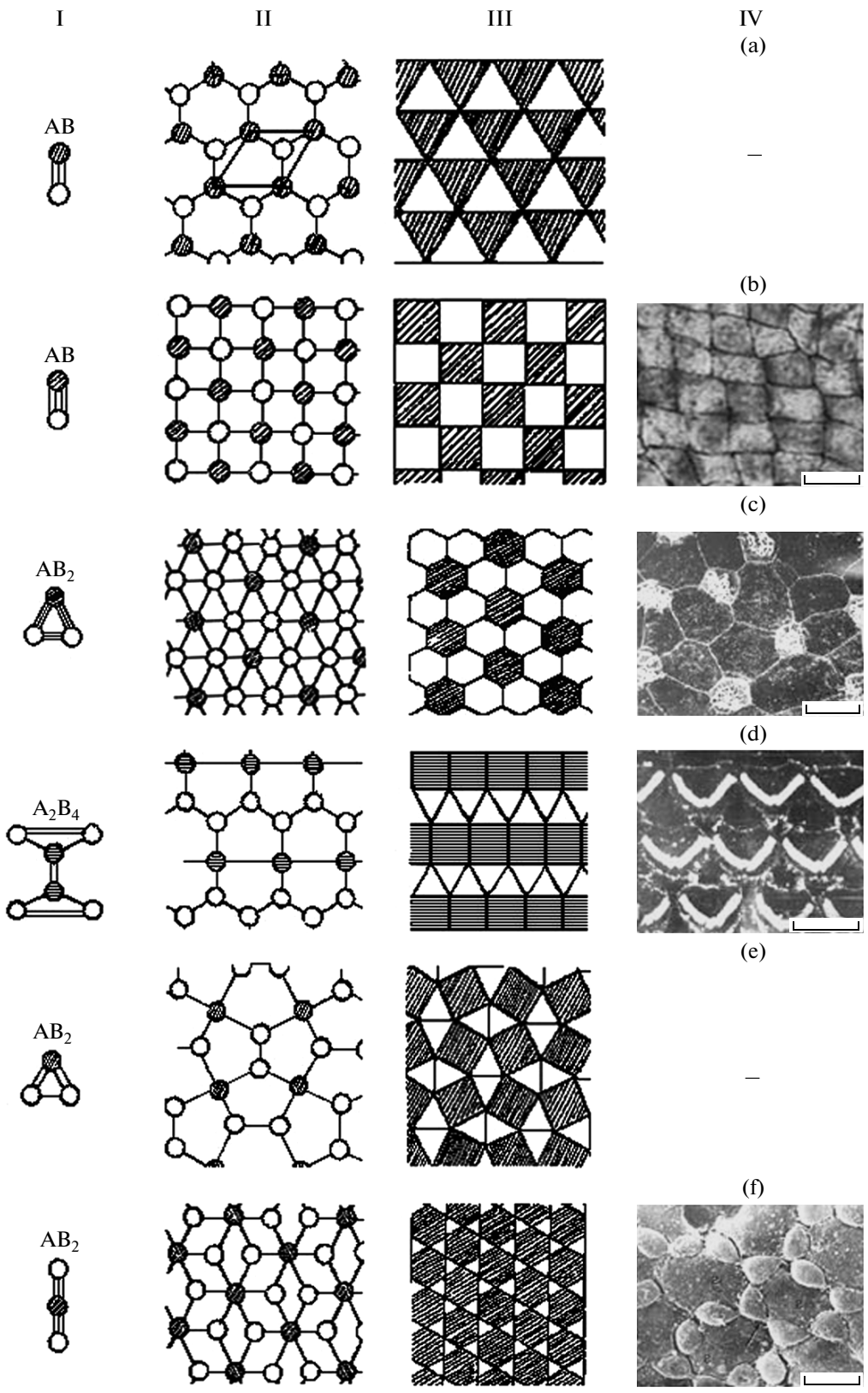
THE FAMILY OF TWO-DIMENSIONAL MODELS FOR CELL NETWORKS

This family contains 11 topological variants of histoarchitectonics (Fig. 1) rather than one as has been considered thus far. Their models can be represented in two forms. In the first variant, the network is represented as a lattice where cells are shown as circles and the links between them are shown as lines. In the second variant, the networks are shown as mosaics with the cells as densely packaged polygons. In mathematics, these lattices are known as Shubnikov–Laves networks and mosaics are known as Archimedes parquet (Grunbaum and Shepard, 1986). We interpreted them as mathematical models for the structure of cell layers. Note that the lattices reflect only the structural scheme of a network, i.e., its topology, while mosaics also take into account the specific geometric features of the cell shape. The diversity of these models may also be increased by varying their cell composition (in a formal manner, mosaic coloring). In addition, they can exist in various allotropic modifications.

These models not only give a global description of a network, i.e., a spatial organization of cell layers, but also a local characterization of the microenvironment of each cell, or the structure of its intraepithelial niche. For example, each cell A (hatched) in the model with a composition AB_2 of hexagons (Fig. 1c) is surrounded by six cells B (light), whereas each cell B is surrounded by three of the same cells alternating with cells A. Such a description characterizes the orientational order of the cell layer. This order makes it possible to describe the intraepithelial cell niches for the remaining models as well. In addition, the model structures have other characteristic features that constitute a new informative complex, including cell composition, numerical ratios of the cells, their contiguity, and the number of cell sides joining at the crossing points.

All these models are formal. This means that the same variant of histoarchitecture may be implemented in different tissues (for example, the cuboidal epithelium is present in various tissues with different functions). An important feature of these models and the cell network they represent is that they are of a coordination nature. Therefore, direct observation of histions is impossible (which is the reason why they have not been discovered and described thus far). However, the fact that histions have a regular structure with periodically repeated mutual arrangement of the cells of different types is a macroscopic manifestation of the histion structure of the lattices and mosaics. In other words, characteristic of the cell networks is their translational symmetry. Another manifestation of the histion structure of the cell networks is in that cells of different types in these networks can be present only in stoichiometric ratios rather than random ones, for example, AB, AB_2, AB_3, AB_2C_3, etc., where A, B, and C are cells of different types. It is possible to distin-

Fig. 1. The family of two-dimensional models and their correspondence to real tissues (Savost'yanov, 2005, with some modifications): (I) monomeric histions and their cell compositions; (II) the cell lattices characterizing the topology of cell layers; (III) geometric models of layers in the form of cell mosaics; (IV) cell mosaics of real tissues, (a), (e) the variants of tissue structure that have not been thus far observed; (b) the mosaic with composition AB displaying a chessboard pattern of ciliary (light) and glandular (dark) cells in the oviduct epithelium of a sexually mature Japanese quail, light microscopy (LM); scale bar, 10 μm (for (a)–(f), and 20 μm (h); Honda et al., 1986); (c) mosaic with a composition AB_2 of ciliary and villous cells in the ectoderm of the common frog embryo, scanning electron microscopy (SEM; Landstrom, 1977); (d) mosaic with the composition $A_2B_2C_2$ from the receptor (carrying stereocilia) and supporting (trigonal) cells of the spiral organ, SEM (Engstrom and Borg, 1983, with some modifications); (f) mosaic with the composition AB_2 of hexagonal and trigonal cells (Sertoli cells and spermatogonia, respectively) in the sperm duct of rat testis from the side of the basal membrane after its removal with collagenase, SEM (Nagano and Suzuki, 1983); (g) mosaic with the composition AB_8 from the ommatidia, hair cells, and pigment cells detected in the drosophila embryo eye at one of the developmental stages, confocal microscopy (CM); scale bar, 25 μm (Fehon et al., 1991); (h) mosaic with the composition A_2B_2 from the square and octagonal cells in the gecko retina, LM (Loew et al., 1996); (i) mosaic with the composition AB_3C_2 from hexa-, tetra-, and trihedral cells in the avian embryonic cochlea, LM (Goodyear and Richardson, 1997); (j) mosaic with the composition A_2B_4 from triangles and dodecagons in the parenchymatous tissue of celery stem with defects seen as tetrahedral inclusions, LM; scale bar, 100 μm (Esau, 1980); and (k) mosaic with the composition AB_2C_3 from the ommatidia (considered as a single element) and interommatidium (pigment) cells in the Drosophila retina (Miller and Cagan, 1998).


I
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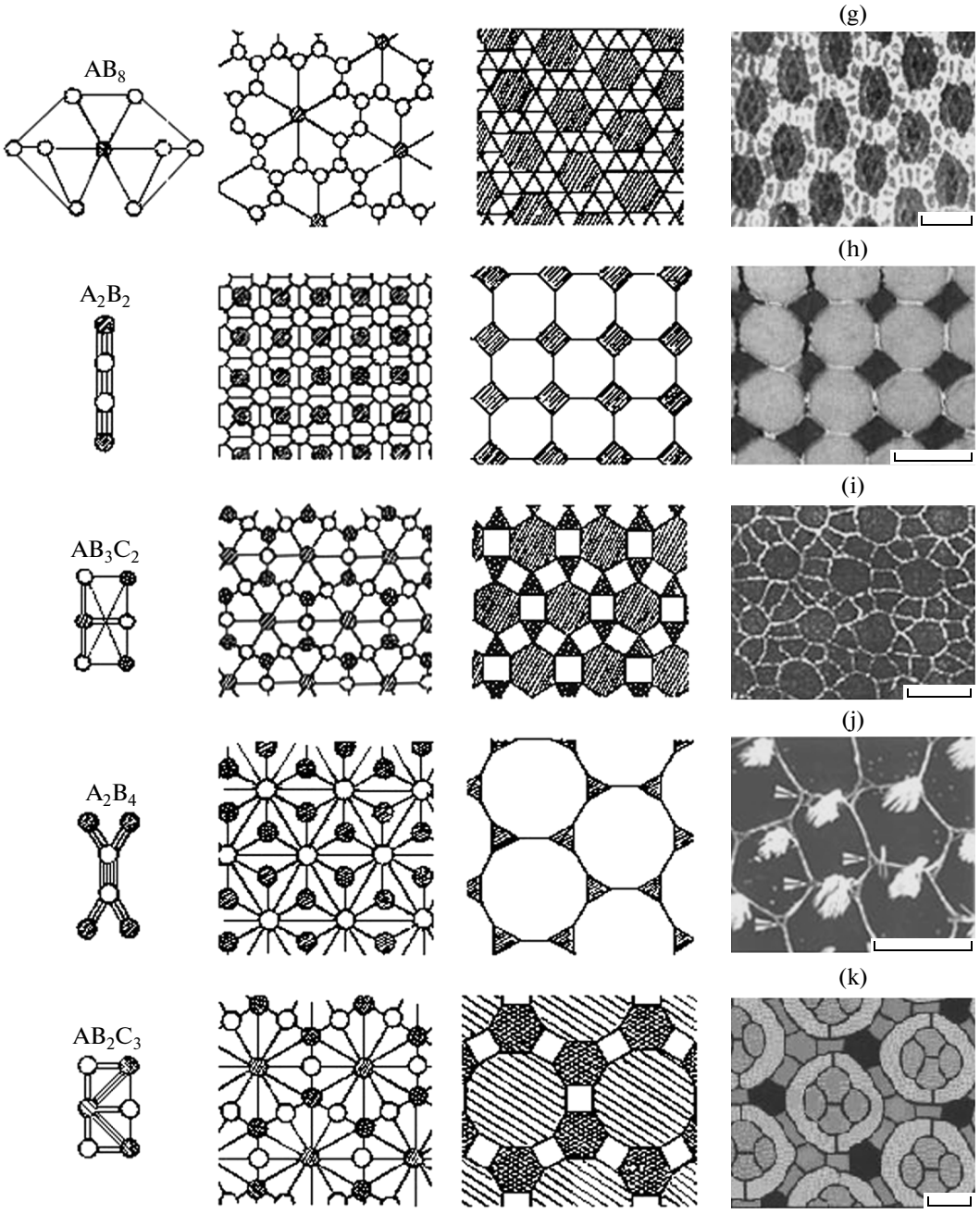

Fig. 1. (Contd).

guish the elementary units of lattices and determine the composition and structure of histions accurate to a cell and link based on the composition and symmetry parameters (as is done in crystallography). Note that the networks are isomorphic to their monomeric histions in the sense that they reflect the same composition and interconnections between cells.

The constructed models form the background for a new approach to studying the spatial organization of real epithelia, since these models predict possible variants of histoarchitectures and focus the study on their search. It is important to emphasize here that characteristic of all the constructed models is their anisotropy; therefore, their single sections fail to provide reliable representation of their composition and structure: depending on the direction of sections, different models can appear similar or vice versa. Correspondingly, the structure of cell mosaics in real tissues should be studied using tangential sections rather than commonly used basal–apical sections or on the surface of whole mount preparations with the help of confocal or electron scanning microscopy.

The performed search for the mosaics predicted using the published data and our own (Savost'yanov, 2005, 2008a) has shown so far that nine of the 11 variants of spatial organization suggested by the theory are actually present in tissues of various animals. This result for the first time allowed two still unobserved variants of the topology of monolayer epithelia to be described (Figs. 1a, 1e) and the possibility of their future discovery to be forecasted. In addition, this result allowed us to conclude that the variants of spatial organization predicted by the models actually constitute the developmental repertoire of real cell layers in phylogenesis and ontogenesis.

The constructed two-dimensional models form the basis for the transition from plane to space and construction of three-dimensional models for multirowed and multilayered epithelia. Note also that there is another interesting family of models for cell mosaics with an aperiodic structure. These models were proposed by Penrose (Nelson, 1986). However, the question on the possibility of their implementation in biological tissues is still open.

THE PRINCIPLE FOR CONSTRUCTING FAMILIES OF THREE-DIMENSIONAL MODELS FOR STRUCTURAL ORGANIZATION OF MULTIROWED AND MULTILAYERED CELL LAYERS

One of the major specific features of these tissues is that different variants of cell mosaics and lattices rather than the same one (as in monolayer epithelia) will be implemented at their basal, medial, and apical levels. Correspondingly, the approach to constructing three-dimensional models for multirowed and multilayered epithelia is based on the possibility of transformations and transmutations of two-dimensional cell mosaics. Additional changes in the axiomatics with a complete rejection of the Thompson rule were necessary to make these transformations feasible within the formalized theory (Savost'yanov, 2005).

A special trick was developed to implement transformation of mosaics, namely, selection of an initial two-dimensional mosaic from the above-mentioned family and introduction of new cells into it. The cells may be introduced to both junction points of cell faces and the boundaries between cells to all of them or only some cells in various combinations. Interpreting the stages of such transformations as sections of the cell layer at different levels, it is possible to construct three-dimensional models for spatial organization of the layers and represent them also in two variants: as lattices of rods (cells) and the connecting segments (links) and as three-dimensional mosaics of contacting polyhedrons. The first variant reflects only the layer morphology, and the second, also the geometry of its cells.

To make such construction easier and create animated versions of the models, a specialized program, Histoarch, was elaborated (Savost'yanova et al., 2007). This program visualizes the cell shape and interactions, illustratively representing both the character of the cell microenvironment and the structure of intraepithelial cell niches and the structure of cell networks of the overall cell layer. In addition, Histoarch makes it possible to obtain the model sections and study their appearances on the sections made in any directions.

This method was used to construct the families of three-dimensional models of different compositions and structures. Characteristic of all these models are the translational symmetry and stoichiometry of composition as well as anisotropy and allotropic modifications. For the first time, the models predict possible variants of the three-dimensional structure of epithelia and pose the question of search for these variants. Such a search reduces to comparison of physical or optical tissue sections with the model sections and selection of those model sections that match with reality. The corresponding model will reflect the three-dimensional structure of the epithelium and the topology of its cell network.

EXAMPLES OF APPLICATION OF THE MODELS AND A NEW APPROACH TO RECONSTRUCTING THE THREE-DIMENSIONAL STRUCTURE OF REAL TISSUES

The reconstruction of the spatial organization of the sensory epithelium in the avian auditory organ (Savost'yanov, 2005) is an example of application of the approach in question. For this purpose, the initial mosaic of hexagons was transformed by adding new cells to the points of cell sides crossing and their subsequent propagation until complete displacement of the initial cells. The model with a composition AB_2 was constructed based on this transformation. Two forms of this model as a three-dimensional lattice and a mosaic are shown in Fig. 2. The lattice in the form of a stack reflects the topology of the network for the entire cell layer. The three-dimensional mosaic of polyhedrons reflects the cell shape, the number of their faces, and the types of contiguity at different model levels. The microenvironment of cells A (i.e., the structure of their intraepithelial niches) consists of six cells B, while the niche of cells B is composed of three cells A alternating with three cells B.

An important specific feature of this model (and all the other three-dimensional models) is that its topology (i.e., the contiguity of the cells) at different levels is not the same. This suggests the important conclusion that the layer models in the direction perpendicular to the basal membrane have a slice structure, where the slice is an interval of the layer with an unchanged topology included between two different mosaics. The concept of slices is important for histology, since they are elementary standard "building blocks." The real layers can consist of one or several

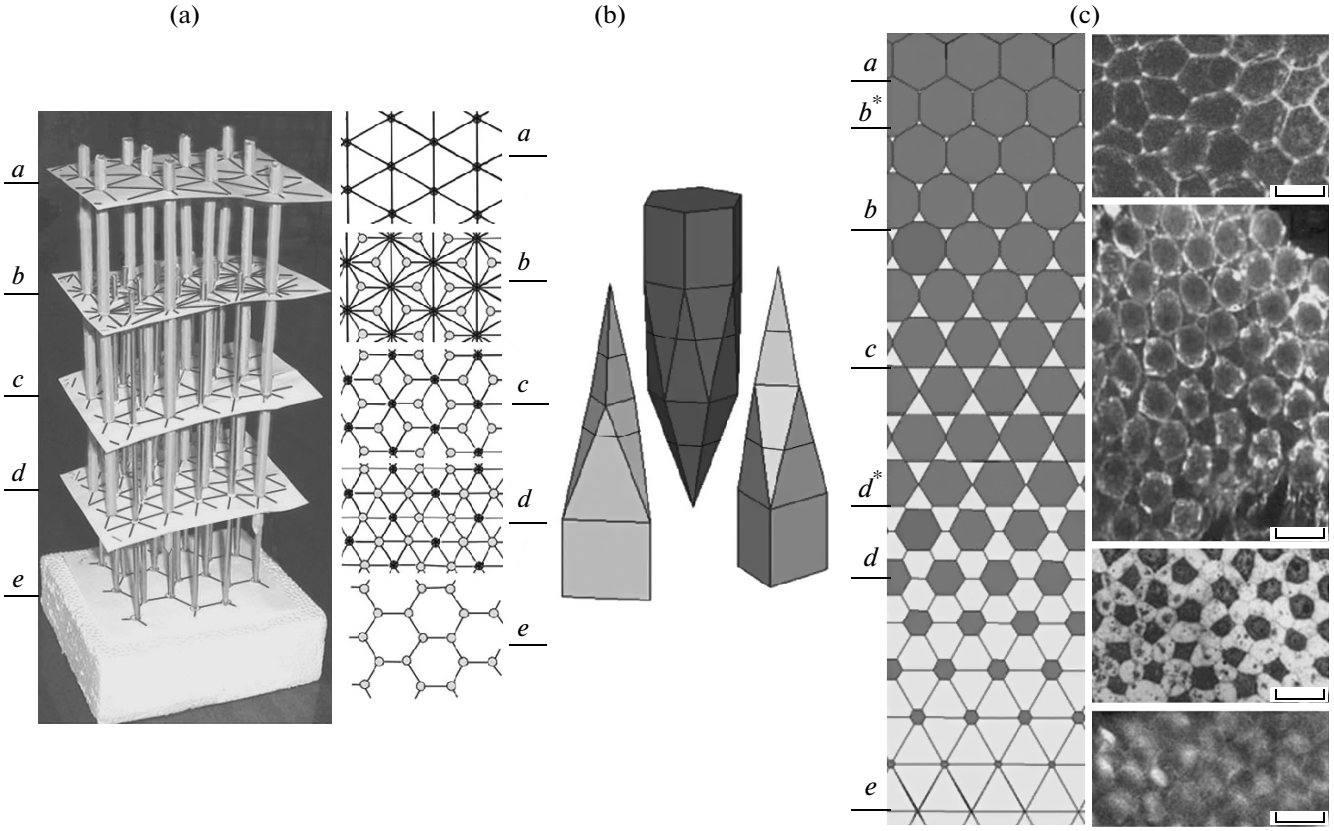

Fig. 2. Two variants of the three-dimensional model with the composition AB_2 and its correspondence to the sensory epithelium of the pigeon auditory organ: (a) the lattice reflecting the overall layer topology and the local topologies at its individual levels; (b) model in the form of polyhedrons reflecting the shape and number of faces of sensory and supporting cells (exposed on the apical and basal surfaces, respectively); left, the mosaics corresponding to the tangential sections of the model at different levels and demonstrating the cell shape and contiguity, regularity of their location, and the number of joining cell faces at the corresponding levels of the layer; (c) real cell mosaics with the composition AB_2 visible in the optical and physical tangential sections made at different levels of the auditory epithelium in the pigeon cochlea; (*b**) the subapical mosaic consists of large hexagonal profiles of sensory cells encompassed with light small apices of supporting cells; the mosaic corresponds to level *a* of the model, CM; (*b*, *c*, and *d**); cell mosaics of deeper levels corresponding to mosaics *b* and *c* of the model, CM; *d* semithin tangential section of the cochlear sensory epithelium at a medium level of the layer; the mosaic of the hexagonal profile of the sensory (dark) and supporting (light) cells of approximately equal areas; their characteristic mutual arrangement corresponds to mosaic *d* of the model; semithin section, LM; objective, ×40; eyepiece, ×10; and *e* fragments of the mosaic of supporting cells with their profile approaching a triangle; the mosaic corresponds to level *e* of the model, CM. Scale: 10 μm.

slices, and their combinations give rise to many variants of histoarchitecture. In particular, the constructed model with a composition AB_2 consists of five slices included between the mosaics of levels *a*–*e*. Each slice has its own topology and is characterized by its own histion. For example, the histion of the slice included between levels *c* and *d* contains both cell types and has composition AB_2. It can be regarded as a representative histion of this model.

Using Histoarch, we obtained the model sections as a set of two-dimensional mosaics. These sections were compared with tangential sections of real tissue (Fig. 2). Here, the hair and supporting cells were associated with cells A and B of the model, respectively. Since the sections of models matched the patterns seen in the tissue sections in all the above-listed sets of characteristics, it was concluded that the model in question reflects accurately the topology of the spatial organization of the real tissue and, schematically, even the geometry of its cells.

In an analogous manner, other surface and sensory epithelia of different compositions and structures have been reconstructed (Savost'yanov, 2005). Finally, it has been demonstrated that the models constructed within the new theory actually reflect the spatial organization of real tissues; i.e., they reflect the structure of their cell network, predict their variants, and enhance their study. In general, the obtained results demonstrate the adequacy of these models and, correspondingly, the adequacy of the formalized theory used to construct these models.

NOVEL PROPERTIES OF CELL LAYERS

Characteristic of all the constructed two- and three-dimensional models as well as the already examined real tissues is the regularity in their structure, i.e., translational symmetry and stoichiometry of composition as a manifestation of their histion structure. In addition, a novel principle in their structure is characteristic of the multirowed and multilayered tissues and their three-dimensional models, consisting in the fact that they are formed of standard histoarchitectural blocks, slices. Note that the same slices in various combinations can be present in different tissues.

Another important property of cell layers is that a comparatively small number of possible cell shapes (tens) gives a considerably larger number of their combinations, and correspondingly, of the cell networks formed of them. This means that the cells of the same shape can give networks of various structures, i.e., the allotropic modifications analogous to polymorphism in solid state physics are characteristic of the cell networks. These networks actually represent the diversity of "phase" states of the cell layer. Therefore, the studies not only of the cell shape, but also of the cell network structures (i.e., their phase analysis), are an important new problem in developmental histology and biology and they can also be useful in studying carcinogenesis.

When speaking about cell layers as regular cell networks, note another important aspect of their structure. This is the fact that unlike ideal models, comparable to monocrystals, most of the real cell layers are rather comparable to polycrystals and consist of many relatively small regions ("grains") with their own regular patterns. These regions are oriented in different directions, and this decreases the overall regularity of the cell layer. In addition, various alterations in the regular patterns and cell periodicity are observed within the regular regions themselves. In other words, the cell networks of real tissues typically contain various local defects of cell packaging. Such defects appear due to cell proliferation, death, and migration as well as shifts in part of the layer relative to another part, formation of cavities within the layer, and many other reasons. All these defects can be classified according to their dimensionality, as is done in solid state physics. Then it is possible to distinguish point (zero-dimensional), linear (one-dimensional), surface (two-dimensional), and space (three-dimensional) defects. One more important characteristic of defects is their concentrations. At a low concentration, defects can only slightly modify the layer properties. At a considerable concentration, they can lead to formation of new sublattices and give rise to tissues with a novel structure and properties.

It is important to emphasize that defects may represent not only the structural irregularity of the cell layer. Causing a local change in the cell specialization and integration (i.e., altering the division of labor between cells), these defects can become active functional centers conferring additional abilities on tissues. This suggests posing the question on a separate consideration of structure- and defect-dependent tissue properties (Savost'yanov, 2005). The study and description of these issues are an important independent research field and are beyond the focus of this paper. Here, we just specify the problem seeking to attract attention to it.

DEVELOPMENT OF CELL NETWORKS IN NORM AND PATHOLOGY

The proposed foundations for the theory of the histion-based structure of cell layers open the possibility to compute all the possible structure variants for cell networks and construct the family of their models (i.e., to find the "space of logical possibilities"). Similar to the system of crystal lattices in geometric crystallography, these models will be able to forecast the variants of tissue architecture that could appear in the development of different organisms. Then, such development can be defined as the choice determined by the environment and implementation of these variants. This particular understanding of development is characteristic of nomogenesis (Berg, 1977) and "idealistic morphology" (Neff, cited according to Blyakher, 1962). This opinion has also been expressed by many other authors (Lyubishchev, 1982; Grodnitskii, 2002). Since the set of possible variants of histoarchitectures is limited, the same variants can take place in the development of most distinct organisms. This viewpoint on development serves as a natural explanation for histological parallelisms (Thompson, 1942; Zavarzin, 1986).

Estimation of the sequence of implementation of histoarchitectural variants in phylogenesis suggests that its general trend is an increase in the dimensionality of cell networks from points (cells) to filaments, monolayers, and multilayered tissues (Borisov et al., 1986). In ontogeny, this is supplemented with accumulation of local defects in the structure of a layer ("noise masking" of its regularity) and abrupt transformations with a total change in the layer topology and conversion of one variant of spatial organization into a completely different one (similar to the phase transitions of graphite to diamond, white to red phosphorus, and so on). Examples of layer transformations were described earlier (Savost'yanov, 2005).

In addition, the completeness of implementation of multislice models may change in multirowed and multilayered epithelia. For example, the layer structure becomes more complicated from a monolayer to multirowed and multilayered patterns in the normal development due to an increase in the number of slices, while the opposite processes take place in the case when the layer is damaged. We have recently analyzed some stages in these processes (Magnitskaya et al., 2009). Certainly, both the cells and the activity of their genes also change in all such cases; however,

they change only in connection with the changes in the network structure (i.e., with the changes in the division of labor implemented in the network).

The developed concepts suggest that the main events in carcinogenesis take place at the level of cell networks and their histions (Savost'yanov, 2008b) rather than at the intracellular level, as is currently considered. Taking this fact into account could promote a better understanding of the essence of malignant transformation.

SIGNIFICANCE OF THE NEW CONCEPTS OF TISSUES AS CELL NETWORKS

The concepts of histions and cell networks contribute to further development of the current formalized theory of the structure of cell layers and confer a predictive ability on it. Due to refinement of the axiomatics, the theory has become able to calculate the families of two- and three-dimensional models that reflect both the topology of cell networks in a tissue and the geometry of the constituent cells. These families form the space of logical possibilities of the cell layer structures and serve as the background for a novel direction in morphology, namely three-dimensional structural histology as part of the modern network biology (Kapra, 2002). The object of such histology is a new reality—the histion and its polymer in the form of a regular cell network—rather than the cells per se.

Application of computer methods to constructing and visualizing models provides for implementing a new approach to the studies of spatial organization of real cell layers. This approach has demonstrated its high efficiency. For the first time, it has become feasible to analyze the structure of cell networks in epithelia by reconstructing their three-dimensional structure; moreover, this procedure requires a minimal number of tissue sections. The models also provide a set of the new informative characteristics necessary for this purpose. The family of models not only enhances the reconstruction, but also predicts yet unobserved variants of spatial organization in tissues, inducing a directed search for such variants.

Thus, the shift of focus from cells to cell interactions means a change in the current paradigm: the goal of a histological study should be determination of the composition and structure of the cell network of a tissue and its histion rather than the description of what is visible under a microscope on a slide. Since it is the histion (not the cell) that is an elementary morphofunctional tissue unit, the problem of tissue classification is reducible to the classification of their histions and the tissue changes in development reduce to changes in the structure of histions.

The morphological results can also form the basis for resolving the question of the functional meaning of various histions and networks. In particular, interpreting them as implementation of different variants of cell specialization and integration (division of labor between cells), it is possible to give a physiological interpretation for the interplay between the cells, to study their molecular biological mechanisms, and to correlate them with gene activity. Since malignant transformation can also be connected with rearrangements of histions and cell networks, their study should be included in the topical problems in experimental oncology.

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