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REVIEW

Cellular Search Migrations in Normal Development and Carcinogenesis

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Abstract—This review describes the large group of morphogenetic processes designated as search migrations. Search migrations typically include two stages: i) search, when a group of cells or of the cytoplasmic processes migrate over the cell-free spaces, and ii) choice, the stage when migrating cells reach specific loci where they stop and undergo specific differentiations induced by local factors such as cell–cell contacts and humoral agents. Migrating cells that do not meet their targets usually undergo apoptosis. Numerous examples of search migrations range from gastrulation to formation of axon–muscle connections. Critical stages of carcinogenesis such as acquisition of cell ability for invasion may be regarded as the genetic aberration of normal search migration: cancer cells perform an endless search but cannot make final choice.

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CONCEPT OF SEARCH REACTIONS

We now know numerous cellular reactions accompanied by very different cell reorganizations and responsible for various components and stages of ontogenesis. Therefore, it is natural to try to classify these reactions, that is, to find groups of their common features. In this review, we have made an effort to identify and to characterize one group of reactions, namely so-called search migrations. These migrations can be considered as a subtype of a large class of so-called search reactions. Examples and mechanisms of normal search reactions, as well as genetic aberrations of these reactions in carcinogenesis, will be considered. Exploratory (search) processes form a very important category of evolvability described by Gerhart and Kirschner [1, 2].

These authors define two stages of these reactions: the first stage of search, when the cells or cell components perform the random search; in the second stage, they make the choice of their fate. Search reactions are profoundly different from deterministic reactions, during which all stages of interactions of structures are both specific and unequivocal. Assembly of viral particles or of complex protein particles from subunits can be regarded as examples of these deterministic processes. Most molecular interactions are strictly deterministic reactions; in contrast, many (if not all) more complex cellular processes responsible for individual development are at initial stages probabilistic or exploratory reactions, and only at final stages do these reactions become deterministic. This concept has much in common with concept developed by I. M. Gelfand and coauthors and based on studies of quite another group of biological processes, neurophysiological mechanisms of rhythmic animal movement [3-6]. According to this concept, elements of a complex system are not controlled individually, and complex functional units are made from separate cells as a result of search interactions between these cells.

SEARCH MIGRATIONS DURING NORMAL DEVELOPMENT

Search migrations represent a most important variant of search reactions. Characteristics of these migrations are: displacement of whole cells or of their components, which after a series of "wanderings" make final choice — stop at the contact with their "targets". The typical example of search migration during normal embryonal development is formation and fate of neural

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crest [7]. Cells of neural crest migrate from neural tube of embryo and are moving individually through extracellular space until they stop at certain regions and choose to "settle" there. During the migration, cells of neural crest, moving in various directions, are morphologically similar. On the other hand, at places of setting the cells differentiate into various cellular elements — from chondrocytes and melanocytes to neurons; this differentiation is determined by the place the migrating cells reached. These differentiations might be induced by some local factors yet not identified. Whole cells as well as their parts are involved in search migrations. As a rule a cell before migration creates a special (temporary or constant) "tool" for search, that is pseudopodia of different shape and size: flat lamellipodia, cylindrical filopodia, etc. Combinations and modifications of pseudopodia lead to formation of more complex extensions, e.g. axons and dendrites of neurons. These pseudopodia can participate in migration of the whole cell or perform the independent search: pseudopodia elongate or become shorter while the body of the cell remains immobile. In other cases, contraction of pseudopodia displaces the whole cell body. The last mechanism leads to gastrulation – formation of bilayer embryo in sea urchin [8-10]. During this process the cells at one pole of monolayered blastula extent long processes moving through the internal cavity of the embryo until they attach themselves to the internal surface of the ectoderm. Attached processes later contact, pulling inside the whole ventral blastula; thus the cellular layer invaginates and forms entoderma. In some other systems (e.g., in avian embryos) gastrulation is due to migration of the whole individual cells.

Axons formed by the neurons of spinal cord migrate into the body cavity and at later stages after random wanderings attach themselves to muscle cells [11-14]. The number of migrating axons is usually much larger than the number of axons forming at last synapses at muscles.

Growth of axons from different regions of brain as well as formation of their connections with corresponding "targets" are also continued at following stages of development of the nervous system. Both extension and retraction of processes in neurons might be also of basal importance for many adaptive reactions (e.g., conditioned reflexes) in the adult nervous system.

Growth of blood vessels (angiogenesis) can also be considered as search reactions of a special type; during these reactions ends of ramifying capillaries are finding and later choose a territory of blood supply. Numerous other examples of search reactions in development remain unstudied.

CULTURAL ANALOGS OF SEARCH MIGRATION

Search migrations are organized by complex combinations of numerous molecular mechanisms. Many aspects of the molecular processes have been elucidated due to investigation of cultural analogs of these migrations. It was shown that polymerization of fibrillar actin from actin globular monomers is the basis of extension of lamellipodia and cell migration. The polymerization goes on at the anterior pole of moving cells and leads to extension of lamellipodia [15]. A complex of special cofactor proteins is involved in the polymerization [16]. Other special proteins such as cofilin take part in depolymerization of recently formed actin filaments after retrograde movement. Depolymerized globular actin is transferred back to the sites of polymerization by diffusion [17]. Uninterrupted protrusion and retraction of lamellipodia of the active cellular edge are results of this dynamic polymerization–depolymerization.

Formation of adhesion contacts with extracellular matrix (so-called focal contacts) is another important process, going on at the internal surface of lamellipodia [18-21]. These contacts are made from a large complex of special proteins. The transmembrane proteins, integrins, on their external pole bind proteins of extracellular matrix (fibronectins, collagens, and others). On their internal pole, molecules of integrins bind a series of proteins specific for contacts (paxillin, vinculin, and many others). These intermediate proteins bind the ends of actin filaments. Focal contacts are dynamic structures — they grow, mature, and regress.

Mechanisms of regulation of maturation of focal contacts by tension remained unexplored [19-21].

Both intensity of polymerization of actin microfilaments and contractility of actin–myosin fibrils are regulated by a special system of small GTPases (Cdc42, Rac, RhoA, and RhoC), determining intensity of lamellipodia formation as well as tension of a matrix-attached cell [22, 23].

Another part of the cytoskeleton, that is the system of microtubules, plays a very important role in determining direction of active edge formation or, more strictly speaking, division of active and inactive edges. Depolymerization of microtubules by specific agents such as colchicine and others inhibits completely directionality of movement, making all edges of the cell weakly active [24]. Mechanism of this orienting action of microtubules is not clear; perhaps some small GTPases of the Rho group are specifically localized at the ends of microtubules at the cell periphery. Location of the active edge, that is cell orientation, is under the influence of a series of external factors, mainly by contacts with extracellular matrix and with other cells, as well as by gradients of some chemotactic agents in liquid culture medium. These external factors probably act by activating corresponding cellular receptors, which later transmit inside the cell signals, changing locally the state of actin and microtubules, as well as small GTPases of the Rho system. So random search of direction is regulated by exogenous inducers, and then the direction of movement is stabilized by the microtubules.

The same mechanisms are probably involved in migrations of cells and their processes during search reactions *in vivo* and in culture.

Cells of another tissue type, epitheliocytes, form in contrast to fibroblasts compact layers or islands where directed movements are only possible along the free edges. Lamellipodia are formed on these edges; formation of lamellipodia is blocked by intercellular contacts. The molecular mechanism of this block is not yet clear. During movement the active edge of epithelial layer is displaced toward free substrate; however, mutual positions of the cells are relatively little changed, that is, intensity of search for optimal directions of cell migration is very small. Interestingly, there exists a special mechanism greatly increasing the degree of freedom for search reactions in epithelial layer. This is so-called epithelio–mesenchymal transformation [EMT] [25-30]. EMT is a most adequate cultural analog of the above-mentioned dissociation of cells in neural crest. The compact cellular layer dissociates during EMT into separate cells moving individually and independently from each other. This process in culture begins several hours after the action of various agents. The most typical agent inducing EMT is HGF/SF (hepatocyte growth factor/scatter factor), secreted by some types of fibroblasts in culture and *in vivo* [29, 30].

HGF/SF binds specific receptors c-met, present on membranes of epitheliocytes sensitive toward HGF/SF [31]. Receptor binding activates a signaling pathway involving (as expected) modifications of some Rho proteins and microtubules. Reconstruction of cells in EMT is accompanied by profound changes of the whole actin–myosin cytoskeleton; EMT is also accompanied by degradation and disappearance of E-cadherin intercellular contacts typical for epithelia. An interesting and important variant of search migration is observed in experiments with HGF/SF treatment of cultures of epitheliocytes in three-dimensional collagen gel; in control cultures epithelium formed compact cysts [32, 33]; after addition of HGF/SF the cysts do not dissociate into individual cells but forms multicellular extensions; these extensions in turn form tubes, which repeatedly branch and fill large spaces. Detailed analysis of dynamics of these tubes revealed polarized cells of elongated shape with an active edge at their poles; these cells are fibroblast-like but their posterior ends are firmly bound with other cells of the tube. Apparently these anterior cell "leaders" are moving along three-dimensional matrix and bind it by leading edges, pulling other cells attached to their posterior poles. These structures are extremely similar to growing epithelial tubes during formation of glands, lungs, kidneys, and many other organs in embryogenesis; it is also very similar to growing blood vessels. It was shown that after treatment with corresponding ligand (vascular growth factor) endotheliocytes are also growing in three-dimensional gels as tubes very similar to blood capillaries [34]. So, three-dimensional culture is a very close analog of both tubulogenesis and angiogenesis.

APOPTOSIS AS A MOST IMPORTANT COMPONENT OF EXPLORATORY REACTIONS

Apoptosis, programmed cell death, is now investigated in great detail [35, 36]. This process plays an important role in many physiological and pathological reorganizations of tissues and organs. The role of apoptosis is essential at the final stages of search reactions. Cells during the final stage of search migration choose between organization of structurally and functionally integrated units of tissue and organ or remaining out of these units. As mentioned above, during embryogenesis only a minority of axons of motor neurons migrating in the body cavity forms synapses with precursors of muscle; all other migrating axons are supernumerary [11-14]. These axons and corresponding cells undergo apoptosis.

Similarly cells (fibroblasts and epitheliocytes) suspended in fluid or semisolid medium and unable to attach to a firm culture substrate do not proliferate and enter apoptosis. This apoptosis can play an important physiological role, eliminating cells unable to find necessary territory or target. In other words, apoptosis is a component of the second stage of search, that is, of choice of final structure.

We now know a lot about different molecular mechanisms of apoptosis as well as about apoptosis-inducing factors, e.g., about ligands like TNF, activating corresponding receptors and stimulating multistage signal pathways leading to cell death. Unfortunately, little is known about other factors inducing apoptosis, such as absence of functional and structural connections between neuronal axons and targets or between the cell and extracellular matrix. It is very important to understand, for example, how formation of a neuromuscular synapse induces signal, going retrogradely for a large distance to the body of the neuron, and preventing apoptosis of this cell. Apoptosis is necessary for correct morphogenesis in many systems. We suggest that there are common features between apoptosis of "nonfunctioning" cells and well-known atrophy of nonworking organs (e.g., of muscles). This dependency of viability of cells on their function has not yet been studied.

It is possible that apoptosis arises as a process at the very beginning of evolution of Metazoa, e.g., during development of gastrulation in animals. As mentioned above, gastrulation might result from specific search reactions.

Ability to undergo apoptosis might be closely related in evolution to formation of the p53 system [37]. This system plays a central role during induction of both inhibition of cell proliferation and many types of apoptosis.

SEARCH MIGRATIONS ENHANCE FREEDOM OF CHOICE AND OF ADAPTATION

As shown above, exploratory character of cellular interactions creates possibilities for wide variations of formation of precursors of tissues and organs as well as for adaptation of the process and function of precursor. For example, the changes in the number of targets during neuron-target connections (see above) may modulate in the corresponding neurons functions or structures. In particular, experiments with removal of a limb bud severely altered the nervous structures destined to innervate this bud; when an additional limb was grafted, neurons began growing into this limb and formed groups of corresponding cells innervating the additional limb and connecting it with the central nervous system [38, 39]. One can think that interactions of this type take place also during formation of other organs.

New tissue precursor or new function can be created by modification of already existing exploratory reactions. This principle of evolvability of search reactions gives wide possibilities for evolution of new systems and new functions [2]. In other words, preexisting search reactions can be utilized in evolution for creation of novel systems.

CARCINOGENESIS AS AN ABERRANT FORM OF SEARCH REACTIONS

Morphologic transformation of epitheliocytes during carcinogenesis can be regarded as an aberrant form of EMT. Carcinogenesis is a multistage process of genetic cellular alterations [37]. Genetically altered cells arise at each of stages of this evolution; these alterations lead to changes in both structure and behavior of cells. As a result, the cells deviate more and more from their normal prototypes. Of special interest among the stages of carcinogenesis is acquisition of malignancy, that is, of the ability of cells to leave normal tissue structure and to distribute themselves in other tissues locally (invasion) or in other organs (metastasis). Morphologic transformation in culture is an analog of acquisition of malignancy inducible, for example, by transfection of different oncogenes. In particular, well-studied transformation of epitheliocytes is expressed as exit of genetically altered cells from the epithelial layer; they lose specialized intercellular contacts and move individually, similarly to fibroblasts [25]. Thus morphologic transformation leads during carcinogenesis in epitheliocytes to changes phenotypically similar to EMT, but arising in the absence of a corresponding ligand such as HGF/SF [40, 41]. One can think that this morphological transformation in vitro corresponds to the exit from epithelial structure and to invasion of surrounding tissue *in vivo*. This change is very similar to search migration from nervous crest. In other words, development of invasion one can regard as a pathological variant of search migration. This development is a result of genetic alterations of mechanisms of normal search reaction. Absence of choice in search reaction is a radical difference of this pathologic reaction from its normal prototype. Tumor cells are constantly wandering in surrounding tissue, but do not make final choice. In some tumors cells are wandering not separately, but as tissue groups, for example, as epithelial tubes, similar in many aspects to the tubes formed during normal tubulogenesis. These dislocations in tumors might be spontaneous and random. Thus, in all these cases one can speak about the tumor as about an aberrant search reaction with altered choice stage, that is, a reaction which retains the first stage as wandering and search, but is deficient as to its second stage – choice. The nature of the series of molecular changes leading to morphologic transformation is not yet clear. It is to note, however, that in many human tumors mutation in protein C-Met (receptor for ligand HGF/SF), inducing EMT, are found [31]. It may be suggested that this mutation leads to spontaneous activation of a series of changes, resulting finally in EMT.

Dissemination of floating cells as a special variant of aberrant search reactions. We discussed cells and their groups separated from tissue structure during search migrations and crawling upon the extracellular matrix with help of pseudopodial reactions. Recently we succeeded in identification and characterization of a novel pathway of cell dissemination from tissue structure [42, 43]. This phenomenon was found during observations on epitheliocytes stably transfected by a plasmid with activated gene RhoA. Protein encoded by this gene activates by a series of intermediate stages of contractility of actin–myosin cytoskeleton and promotes formation of bundles of actin–myosin microfilaments. These cells form like their normal precursors a compact cellular monolayer. A distinctive feature of these monolayers formed by firmly linked and compressed cells is orientation of mitoses altered as compared to non-transfected layer. The axis of the mitotic spindle is almost exclusively oriented "horizontally", that is in parallel to the plane of both substrate and monolayer. In contrast, direction of the axis of spindle became "vertical", that is perpendicular to the plane of substrate in most cases in monolayers of cells overexpressing RhoA. We do not know what is determining this change of orientation of the mitotic spindle. Some data show that overexpression of RhoA altered interaction of actin–myosin cortex of a mitotic cell with ends of spindle microtubules [44]. A consequence of vertical orientation is that one of two daughter cells ("upper" cell) is located at the upper surface of monolayer where it is easily separated into the liquid medium above the monolayer. These separated, compressed, and spherical cells are able to float in the medium for a long time. Finally, many such cells are attached on the free bottom of the culture flask where they are spreading and form new colonies.

This mechanism of "floating migration" might be a prototype of formation by tumor cells of metastases at far distances from the primary lesion. It would be interesting to find out whether this "floating migration" of cancer cells has normal prototypes. For instance, migration of stem cells from bone marrow in the blood can be this prototype. These cells go through endothelium of bone marrow and float in the bloodstream, settling finally in other parts of bone marrow. This question is to be studied in more detail.

These examples demonstrate the role of investigations of pathologic migration in analysis of normal physiological processes, and *vice versa*.

Inactivation of p53 and loss of ability for apoptosis as an important aspect of search migration of tumor cells. As mentioned above, normal cells wandering in the first stage of the search reaction and not finding their target undergo apoptosis. Tumor cells genetically loose ability to bind the target and remain wandering. It is clear that both for survival of these cells and for their proliferation they must loose the ability to undergo apoptosis; the loss of this ability is a very frequent change in carcinogenesis. One of numerous examples is loss of substrate dependence: tumor cells, devoid of substrate and suspended in the fluid or semi-fluid medium, do not perish by way of apoptosis, but in contrast to normal counterparts continue to proliferate. Loss of ability for apoptosis is one of the key factors altering formation of tissue structures in tumor tissue.

In many cases, loss of ability to undergo apoptosis is a consequence of mutations changing expression of p53 [45-47]. As mentioned above, this p53 system plays the main role both in inhibition of proliferation and in induction of apoptosis of normal cells. Its inactivation during carcinogenesis was shown in many human neoplasia.

However, loss of p53 is in no case a single mechanism of non-sensitivity of tumor cells toward apoptosis, For example, as shown by Bharadwaj and coauthors, sensitivity to apoptosis after detachment of human breast cancer cells from the substrate is restored when expression of tropomyosin-1 is stimulated in these cells [48]. Tropomyosin-1 is one of the main proteins regulating the actin–myosin system. It is not clear what the specific link between actin–myosin system and apoptosis is.

QUESTIONS FOR FUTURE WORK

In this paper we try to describe a concept according to which many (if not most) cellular processes during normal development of Metazoa are realized in two stages: search and choice. The first stage of search is not strictly deterministic but "investigative"; in many cases, these are exploratory migrations of cells or of their components, first of all of different cellular extensions. At the second stage of these reactions, the search is changed to choice: cells find their final position and undergo differentiation into functionally active elements and multicellular structures. Molecular mechanisms of stages of search and choice should differ significantly. Search involves induction of cellular movements and is most probably related to reorganizations of cytoskeleton, primarily of the actin–myosin system. These reorganizations probably have common features during reactions that look very different at first glance, for example, during gastrulation and wound healing. During the stage of search cells possibly accumulate reactive oxygen species and secrete a series of cytokines. Changes at the stage of choice possibly are opposite to changes during the first stage. Here migration stops, antioxidants accumulate and (first of all) different signal pathways are activated, which lead to expression of different genes and to synthesis of different specialized proteins, that is to various differentiations. In other words, one may suggest that at the stage of search changes are similar, and at the stage of choice they are different. According to this concept, the cell of malignant tumor is at first approximation a cell in permanent and fruitless search, which is unable to make final choice. In these cells there is a constitutively acting mechanism, which induces cell migration, accumulation of reactive oxygen species, secretion of cytokines and other alterations, specific for the first stage of normal search reactions. This picture is, of course, characteristic only for extremely advanced stages of carcinogenesis and for maximally malignant tumors. During earlier stages of carcinogenesis, ability of cells to choose remains, but probability of choice is diminished, and choice-inducing factors are altered as compared to norm. Therefore, a fraction of migrating and proliferating cells is retained even in benign tumors that have a sizable fraction of differentiated cells.

All the concepts formulated above need experimental proof.

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REFERENCES

1. Gerhart, J., and Kirschner, M. (1997) *Cells, Embryos and Evolution. Toward a Cellular and Developmental Understanding of Phenotypic Variation and Evolutionary Adaptability*, Blackwell Science, Oxford.
2. Kirschner, M., and Gerhart, J. (1998) *Proc. Natl. Acad. Sci. USA*, **95**, 8420-8427.
3. Gelfand, I. M., and Tsetlin, M. L. (1966) in *Models of Structure-Functional Organization of a Number of Biological Systems* [in Russian], Nauka, Moscow, pp. 9-26.
4. Gelfand, I. M., Gurfinkel, V. S., Fomin, S. V., and Tsetlin, M. L. (1966) *Models of Structure-Functional Organization of*

a Number of Biological Systems [in Russian], Nauka, Moscow.
5. Berkinblit, M. B., Gelfand, I. M., and Feldman, A. G. (1986) *Biofizika*, **31**, 128-138.
6. Gelfand, I. M., and Latash, M. (1998) *Motor Control*, **2**, 306-313.
7. Le Dourin, N. M., Dupin, E., and Ziller, C. (1994) *Curr. Opin. Genet. Devel.*, **4**, 685-695.
8. Gustafson, T. (1975) in *The Sea Urchin Embryo* (Cziak, G., ed.) Springer-Verlag, Berlin, pp. 231-266.
9. Gustafson, T., and Wolpert, L. (1961) *Exp. Cell Res.*, **22**, 509-520.
10. Gustafson, T., and Wolpert, L. (1963) *Int. Rev. Cytol.*, **15**, 139-170.
11. Purves, D. (1988) *Body and Brain: A Trophic Theory of Neural Connections*, Harvard University Press, Cambridge.
12. Oppenheim, P. W. (1989) *Trends Neurosci.*, **12**, 252-255.
13. Hamburger, V. (1992) *J. Neurobiol.*, **23**, 1116-1127.
14. Balice-Gordon, R. J., and Lichtman, J. W. (1994) *Nature*, **372**, 519-524.
15. Bershadsky, A. D., and Vasiliev, J. M. (1988) *Cytoskeleton*, Plenum Press, New York.
16. Borisy, G., and Pollard, T. (2003) *Cell*, **112**, 453-465.
17. Zicha, D., Dobble, J. M., Holt, M. R., Monypenny, J., Soong, D. Y. H., Gray, C., and Dunn, G. A. (2003) *Science*, **300**, 142-145.
18. Bershadsky, A., Chausovsky, A., Becker, E., Lyubimova, A., and Geiger, B. (1996) *Curr. Biol.*, **5**, 1279-1289.
19. Chrzanowska-Wodnicka, M., and Burridge, K. (1996) *J. Cell Biol.*, **133**, 1403-1415.
20. Dugina, V., Fontao, L., Chaponnier, C., Vasiliev, J. M., and Gabbiani, G. (2001) *J. Cell Sci.*, **114**, 3285-3296.
21. Pletyushkina, O., Belkin, A. M., Ivanova, O. J., Oliver, T., Vasiliev, J. M., and Jacobson, K. (1998) *Cell. Adhes. Comm.*, **5**, 121-135.
22. Ridley, A. J., Schwartz, M. A., Burridge, K., Firtel, R. A., Ginsberg, M. H., Borisy, G., Parsons, J. T., and Horwitz, A. R. (2003) *Science*, **302**, 1704-1709.
23. Ridley, A. J., and Hall, A. (2004) *Cell*, **16** (2 Suppl.), S23-S25.
24. Vasiliev, J. M., Gelfand, I. M., Domnina, L. V., Ivanova, O. Y., Komm, S. G., and Olshevskaja, L. V. (1970) *J. Embryol. Exp. Morphol.*, **24**, 625-640.
25. Thiery, J. P., and Sleeman, J. P. (2006) *Nature Rev. Mol. Cell Biol.*, **7**, 131-142.
26. Hay, E. D. (1995) *Acta Anat.*, **154**, 8-20.
27. Boyer, D., Roche, S., Denoyelle, M., and Thiery, J. P. (1997) *EMBO J.*, **16**, 5904-5913.
28. Savagner, P., Yamada, K. M., and Thiery, J. P. (1997) *J. Cell Biol.*, **137**, 1403-1419.
29. Stoker, M. (1989) *J. Cell Physiol.*, **139**, 565-569.
30. Birchmeier, C., and Gherardi, E. (1998) *Trends Cell Biol.*, **8**, 404-409.
31. Ridley, A. J., Comoglio, P. M., and Hall, A. (1995) *Mol. Cell. Biol.*, **15**, 110-112.
32. Montesano, R., Schaller, G., and Orci, I. (1991) *Cell*, **66**, 697-711.
33. Montesano, R., Matsumoto, K., Nakamura, T., and Orci, L. (1991) *Cell*, **67**, 901-908.
34. Stokes, C. L., and Laufenburger, D. A. (1991) *J. Theor. Biol.*, **152**, 377-403.
35. Skulachev, V. P. (2002) *Ann. N. Y. Acad. Sci.*, **959**, 214-237.
36. Skulachev, V. P. (2005) *Vestnik RAN*, **75**, 831-843.
37. Kopnin, B. P. (2000) *Biochemistry (Moscow)*, **65**, 2-27.
38. Welker, E., and van der Loos, H. (1986) *Neuroscience*, **6**, 3355-3373.
39. Kossut, M. (1992) *Progr. Neurobiol.*, **39**, 389-422.
40. Schenenberger, C. A., Zak, A., Kendall, D. A., and Matlin, K. S. (1991) *J. Cell Biol.*, **112**, 873-879.
41. Gloushankova, N. A., Lyubimova, A. V., Tint, I. S., Feder, H. H., Vasiliev, J. M., and Gelfand, I. M. (1994) *Proc. Natl. Acad. Sci. USA*, **91**, 8597-8601.
42. Vasiliev, J. M., Omelchenko, T., Gelfand, I. M., Feder, H. H., and Bonder, E. M. (2004) *Proc. Natl. Acad. Sci. USA*, **101**, 12526-12530.
43. Vasiliev, J. M. (2005) *Vopr. Onkol.*, **51**, 9-14.
44. Rosenblatt, J., Cramer, L. P., Baum, B., and McGee, K. M. (2004) *Cell*, **117**, 361-372.
45. Lin, A. W., Barradas, M., Stone, J. C., van Aelst, L., Serrano, M., and Lowe, S. W. (1998) *Genes Devel.*, **12**, 3008-3019.
46. Pearson, M., Carbone, R., Sebastiani, C., Cloce, M., Fagioli, M., Salto, S., Higashimoto, Y., Apella, E., Minucci, S., Panolofi, P. P., and Pelicci, P. G. (2000) *Nature*, **406**, 207-210.
47. Agapova, L. S., Ivanov, A. V., Sablina, A. A., Kopnin, P. B., Sokova, O. I., Chumakov, P. M., and Kopnin, B. P. (1998) *Oncogene*, **18**, 3135-3142.
48. Bharadwaj, S., Thanawala, R., Bon, G., Falcioni, R., and Prasad, G. L. (2005) *Oncogene*, **24**, 8291-8303.