

Review

Intercellular adhesion disorders in tumorigenesis

Olga A. Bocharova¹, Regina V. Karpova¹, Evgeny V. Bocharov¹, Valerian G. Kucheryanu²,
Vyacheslav S. Kosorukov¹, Ivan S. Stilidi¹

¹ Blokhin National Medical Research Center for Oncology, Moscow, Russia

² Institute of General Pathology and Pathophysiology, Moscow, Russia

Received 29 December 2023, Revised 28 April 2024, Accepted 1 July 2024

© 2023, Russian Open Medical Journal

Abstract: The review discusses the problem of adhesion impairment in the course of tumorigenesis and aging. We hypothesize that impairment of homophilic intercellular adhesion in the target tissue results in developing conditions, which are favorable for malignancy, invasion, and metastases. Like a phoenix vanishing during the initiation of a primary tumor by breaking contacts between identical cells, adhesion molecules reappear with a new quality (the *phoenix rising* mechanism), thereby causing invasive and metastatic behavior of tumor cells. Due to this, primary tumor cells acquire motility and the ability to form metastases, which are the cause of most cancer deaths.

At the same time, the provision of adhesive bonds between cancer cells and immune effector cells can also be controlled by one of the main neurotransmitters, dopamine (DA). The discovery of peripheral DA in lymphocytes gave grounds to the assumption that DA is involved in the infiltration of tumor leukocytes. DA receptors are found on cells of the adaptive (specific) immune response: T and B lymphocytes. Direct communication between brain DA and peripheral DA is crucial in modulating immune function. Peripheral DA mediates differentiation, binding to tumor cells, and cytotoxicity of CD8+ T cells. The review also confirms the need for the development of adhesion pharmaceutical agents.

The disruption of intercellular adhesion in the target tissue and the general deficiency of immune surveillance can be controlled by central mechanisms involving brain DA, which is capable of regulating the active phase of immune responses against the tumor by means of adhesive interactions in the immune system, interfering with the process and thereby interrupting the development of a malignant neoplasm initiated by a local mutation in the tissue. The concept reveals the stress mechanism of cancer etiology and creates prospects for new methods of diagnostics, prevention and treatment of tumors, which can become another step towards solving the problem of malignant neoplasms.

Keywords: tumorigenesis, intercellular adhesion, leukocyte $\beta 2$ integrins, invasion, dopamine.

Cite as Bocharova OA, Karpova RV, Bocharov EV, Kucheryanu VG, Kosorukov VS, Stilidi IS. Intercellular adhesion disorders in tumorigenesis. *Russian Open Medical Journal* 2024; 13: e0301.

Correspondence to Olga A. Bocharova. Address: Laboratory for Immunopharmacology, Blokhin National Research Center for Oncology, 24 Kashirskoe Shosse, Moscow 115478, Russia. E-mail: imufarm@rumbler.ru.

*"You have to pull the main thread
to unwind the whole tangle of contradictions"*

Dan Brown

Introduction

Cancer biology research has accumulated a rich and complex body of knowledge about the molecular, cellular, and biochemical features of various human cancers. Tumorigenesis is a multistage process, and these stages reflect highly heterogeneous and chaotic changes in the genomic landscape that lead to the gradual transformation of normal human cells into highly malignant derivatives [1, 2].

Loss of proliferation control, insensitivity to growth inhibitory signals, evasion of programmed cell death (apoptosis), sustained angiogenesis, reprogramming of cellular metabolism, evasion of immune surveillance, invasion, and metastasis are the dramatic

changes in cell physiology that collectively command malignant growth and represent a successful subversion of anticancer defense mechanisms [3]. However, questions remain. Which regulatory circuits must be disrupted for normal cells to become malignant? How do tumor cells link the myriad events in the host to their own destruction?

Anticancer and immunotherapeutic approaches target one or a combination of specific molecules associated with cancer, such as growth factors, receptor/adaptor molecules, cytokines/chemokines, and others. Molecular targets are derived from mutated genetic elements (e.g., DNA damage, epigenetic hypo- and hypermethylation modifications, and expression products). However, each of these targets alone is not of key importance and independent significance for cellular transformation and modulation, as well as none of the above will prevent tumor development [4-9].

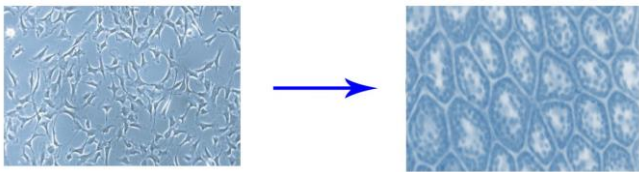


Figure 1. Mesenchyme and epithelial layer.

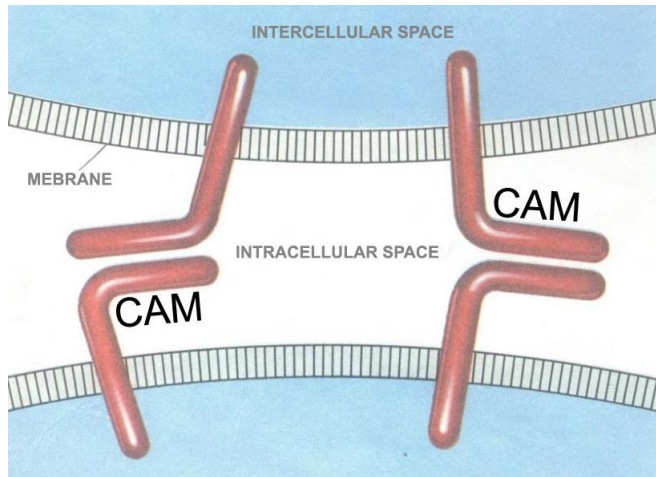


Figure 2. CAM (cell adhesion molecules) [16].

Scientists recognize that future directions in anticancer approaches that will benefit society and be more effective should focus on the homeostatic mechanisms of the body along the neuroimmune-endocrine axis. The International Agency for Research on Cancer (IARC) has proposed further development of effective preventive strategies, given the potential for activation of nonspecific homeostatic and adaptive responses of the body. Preventive measures become important at the stages of tumorigenesis, relapse and metastasis of the tumor. In addition, it can also be useful for controlling chronic stress, increasing the effectiveness, reducing the toxicity of chemoradiotherapy, and improving the quality of life during the rehabilitation of cancer patients [10-12].

In order to unravel the tangle of contradictions, it would be great to find the decisive thread. The main focus of our review is on the disruption of adhesion regulation as a decisive factor in the tumor process.

Cell-cell junctions in epithelial tissues

In normal epithelial tissues, tightly packed and nonmotile cells function as an element of an integrated system. In contrast, tumor cells with a poorly organized mesenchymal phenotype acquire such properties as loss of differentiation, reduced intercellular adhesion, increased motility, invasive capacity, and increased resistance to apoptosis [13-15].

Differentiation and transformation of embryonic tissues into mature tissues requires the synthesis of tissue-specific proteins: e.g., liver cells need some proteins known as liver cell adhesion molecules (L-CAM), nerve cells need others known as neural cell adhesion molecules (NCAM), etc. Such proteins and cell adhesion molecules can be encoded by different genes. But the genes of these two types must act in a coordinated manner [16].

During embryonic development, the mesenchyme is transformed into the epithelial layer. The mesenchyme is a group of motile cells that are not connected to each other in any way and are not organized in space. The epithelium is a layer of highly organized cells, the basal cells of which are usually connected to the extracellular matrix by substrate adhesion molecules (SAM) (Figure 1). Epithelial cells are connected with each other by specialized contact structures, cell junction molecules (CJM). Cell adhesion molecules (CAM) play a major role in the initial stages of epithelial formation (Figure 2). Then, following CAM-to-CAM binding, specialized cell-cell junctions (e.g., tight, gap junctions, etc.) are formed. Figure 3 shows a scheme of CJM. It seems that the action of CAM genes leads to the assembly of preexisting CJM into contact structures. The sites where the membranes of both cells are parallel to each other and are 150-200 Å apart (no visible structures) are called simple junctions (nonspecialized areas of cell-cell junction) (Figure 4). Their main players are the adhesion molecules cadherins [16-18].

Loss of contact: additional cells

Contactin (from the cadherin family) plays an important role in histospecific intercellular interactions, as well as normal morphogenesis and tissue development. Inactivating mutations in the gene encoding contactin trigger susceptibility to hereditary cancer [19-22].

The strength of cell adhesion (Figure 5) in the liver (a) and lungs (b) of inbred mice (mutual adhesion) in the early postnatal period of completion of tissue differentiation, along with the frequency of spontaneous tumors in late ontogenesis, are associated with a hyperbolic dependence [23, 24].

It was revealed that tissue-specific contactins, when exposed during the critical period of early postnatal ontogenesis, enhance cell-cell junctions and prevent the development of genetically determined tumors, thereby reducing the frequency of their occurrence in predisposed tissue (Figure 6, Table 1) [25, 26].

Using an electron microscope, we obtained the following picture. Elevated hydrostatic pressure causes divergence of the contact surfaces of hepatocytes, primarily in the areas of simple junction. Highly adhesive areas were detected in C57Bl mice three times more than in CBA mice (Figures 7 and 8). Under these conditions, no divergence of specialized contact structures (tight and gap junctions, desmosomes, etc.) was observed. It is likely that due to different levels of contactin, the degree of heterogeneity in simple junction can largely determine the observed differences in the strength of mutual adhesion between hepatocytes in CBA (male) and C57BL mice [27].

A previously unknown phenomenon of an increase in the homophilic forces of mutual cell-cell adhesion at a decisive stage of early ontogenesis was established, which leads to the completion of the tissue homeostasis formation and a decrease in the incidence of tumors in tissues predisposed to cancer [26, 28].

Cancer is a consequence of mutation in the contactin (cadherin) gene

Reduction of cell adhesion in the target tissue can be changed due to mutations under the influence of various environmental stressors, as well as chronic stress. In genetically predisposed tissues, hemophilic intercellular adhesion is primarily impaired [29; 30]. This can be caused by the loss or suppression of one allele in

the contactin gene (most likely, of the cadherin superfamily) known as zero hemizygosity state. It is important that zero hemizygosity of the contactin gene exists with a hereditary predisposition of this tissue to malignant growth.

This condition may transform into zero homozygosity (100%), since just one mutation of the existing contactin allele is sufficient, which usually occurs during ontogenesis under the impact of the environment multifactorial stress effects (Figure 9).

The contactin gene is represented by two alleles in the cells of tumor-resistant tissue (the cells are homozygous for this gene) at the final stages of differentiation and transition to active functioning (Figure 10). In this case, it is virtually impossible to reduce the situation to zero homozygosity, since the probability of two consecutive mutations in the same tissue, cell and gene is extremely (approaching 0) [19, 26].

Adhesion as a “a phoenix in the fire of malignant growth”

In epithelial tissues, contactin (E-cadherin) is a key mediator of stable cell-cell adhesion. Mutational inactivation of the contactin

gene yields impairment of proliferation, differentiation, epithelial homophilic cell-cell adhesion, and cellular structure, thereby disrupting one of the central mechanisms of antitumor protection [24, 26, 31-36].

A reduction in s-ICAM expression becomes evident much later after tumor formation: it causes further fragility of cell-cell junctions. First of all, tumor cells deficient in ICAM-1 can avoid elimination via reduced expression of the corresponding ligands from leukocyte $\beta 2$ integrins: lymphocyte function-associated antigen 1 (LFA-1, integrin $\alpha \text{L}\beta 2$, CD11a/CD18) and monocyte adhesion complex (Mac-1, integrin $\alpha \text{M}\beta 2$, CD11b/CD18) [37-39]. LFA-1 and Mac-1 are the main modulators of adhesion between natural killer (NK) cells or cytotoxic T lymphocytes (CTL) and cancer cells; on the other hand, they are involved in the release of cytotoxic granules that kill the tumor cells. Reduced ICAM-1 expression on tumor cells and disrupted contact between ICAM-1 and leukocyte $\beta 2$ integrins contribute to the lack of adhesion/localization of CTL and natural killer NK cells, which may prevent tumor cell death [40-45].

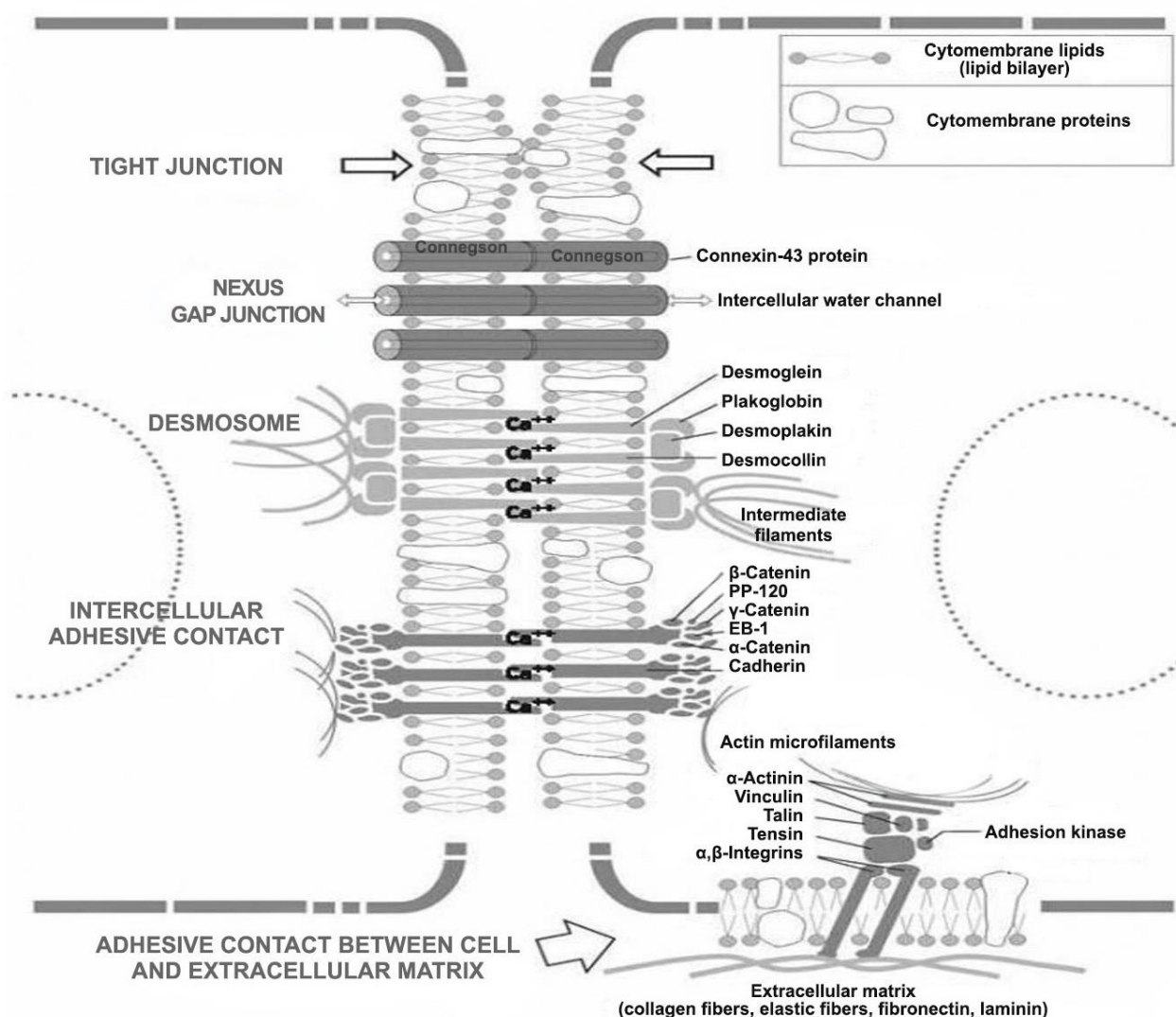


Figure 3. Scheme of specialized contact structures, CJs (cell junction molecules).

Secondly, changes in ICAM expression also appear to play a noteworthy role in invasion and metastasis. ICAM deficiency on a tumor cell is accompanied by shifts in the spectrum of integrin α or β subunits. Cells that are capable of escaping the primary tumor (known as *pioneers*) and colonizing new regions in the body switch the expression of integrins from those present in normal epithelium to others, such as very late activation antigens (VLA) from the $\beta 1$ integrin family. Diversity of $\beta 1$ integrins can be found in many cancers such as melanoma, breast carcinoma, prostate cancer, pancreatic cancer, lung cancer [46-51]. $\beta 1$ Integrin switching involves changes in their expression profile and functionality during cell detachment, thereby overcoming apoptosis and ensuring tumor cell survival and metastasis [46, 47]. Thus, increased dysregulation of adhesion leads to increased tumor evasion from immune surveillance and proliferation control [52-55]. As a result, disruption of homophilic cell-cell adhesion in tissues genetically predisposed to tumors leads to common conditions for malignancy, invasion and metastasis.

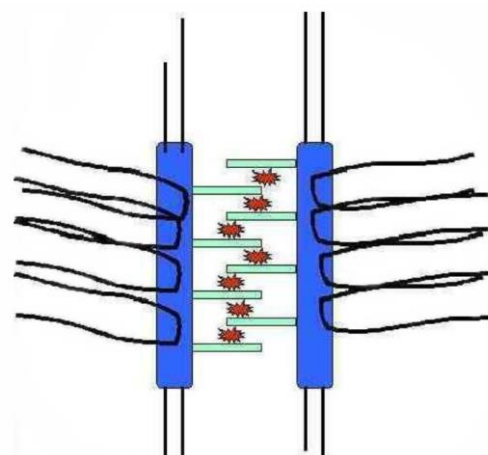
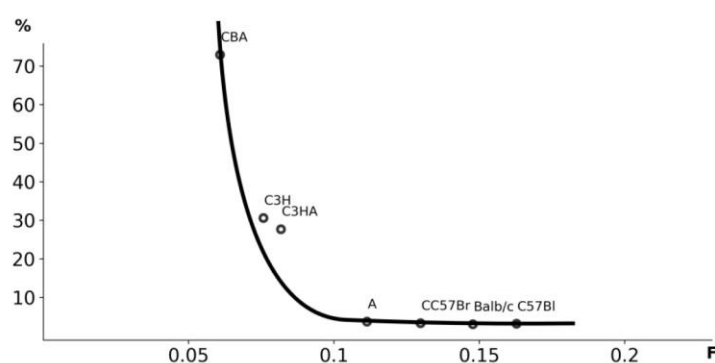
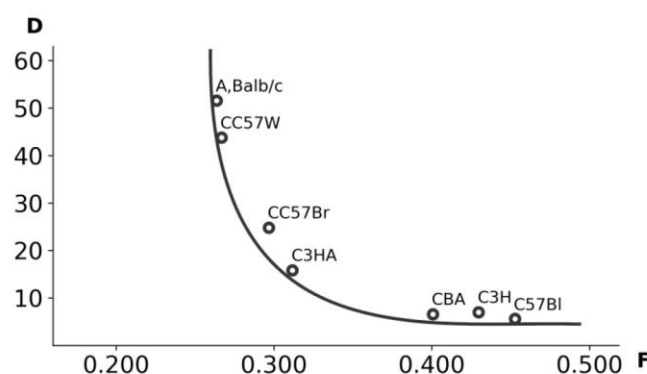


Figure 4. Simple cell junction (nonspecialized areas of cell-cell junction).
<https://present5.com/tema-2-citologiya-mezhkletochnye-kontakty-organelly-yadro-delenie/>



a)



b)

Figure 5. Strength of cell adhesion in the liver at the age of 1 month (a) and in the lungs at the age of 1-5 months (b) in inbred mice, and the predisposition of these organs to the occurrence of spontaneous tumors.

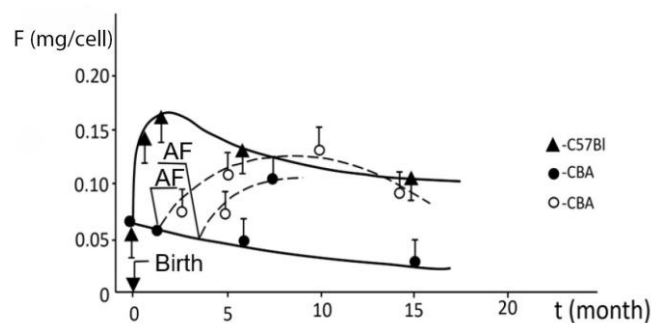


Figure 6. Effect of the contactin adhesion factor (AF) *in vivo* on the strength of mutual adhesion of hepatocytes (F) in male CBA mice during ontogenesis. The x-axis is F (mg/cell), the y-axis is the age of mice (months) [26].

Indeed, like a phoenix vanishing during the initiation of a primary tumor by breaking contacts between identical cells, adhesion molecules reappear with a new quality (this phenomenon is known as the *phoenix rising mechanism*), thereby causing invasive and metastatic behavior of tumor cells. This allows the primary tumor cells to acquire motility and form metastases, which are the cause of most cancer deaths.

One of the main notions of the proposed concept is that the key role in the loss of control over cell proliferation, invasion, metastasis, and evasion of immune surveillance is played by the disruption of homophilic cell-cell adhesion ([Figure 11](#)). The argument presented below substantiates the importance of disruptions in cell-cell adhesion in carcinogenesis.

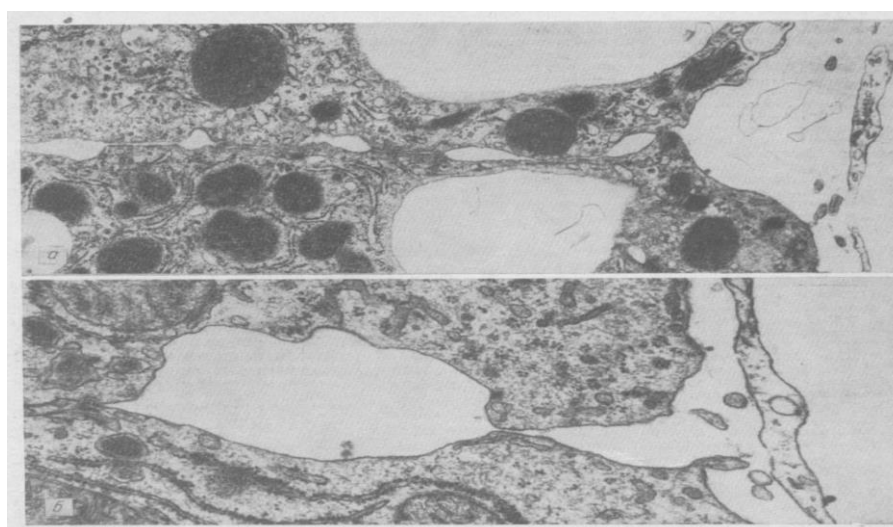


Figure 7. Destruction of nonspecialized areas (simple junctions) of hepatocyte contacts in C57Bl mice under the effect of elevated hydrostatic pressure as seen via an electron microscope. There are three times more areas of high adhesiveness than in CBA mice (a). With an increase in the hydrostatic load, the membrane divergence in C57Bl mice is longer, but the areas of high adhesiveness remain (b). a: Exposure to a pressure of 30 mm Hg for 15 s ($\times 19800$); b: Exposure to a pressure of 20 mm Hg for 60 s ($\times 35000$).

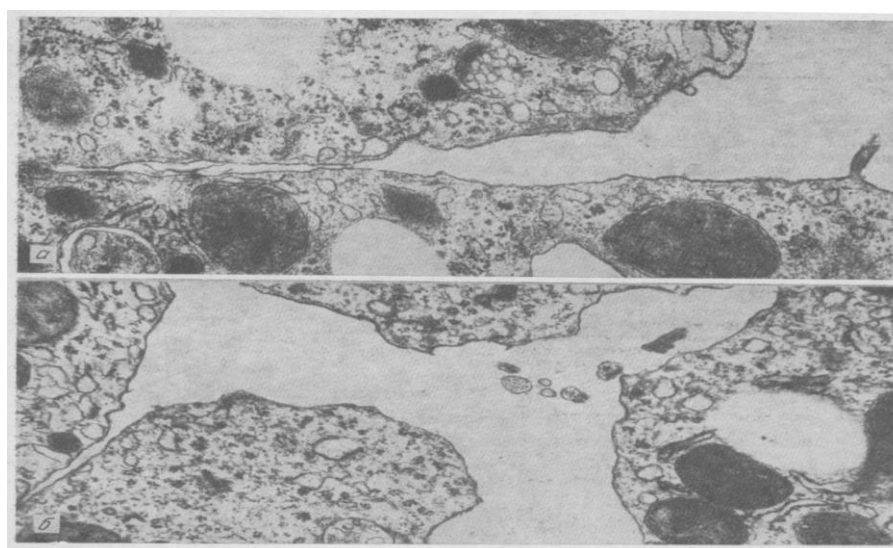


Figure 8. Destruction of nonspecialized areas (simple junctions) of hepatocyte contacts in CBA mice under the effect of elevated hydrostatic pressure as seen via an electron microscope. With an increase in the hydrostatic load, complete membrane divergence was observed in the simple junction region in CBA mice (b). a: Exposure to a pressure of 30 mm Hg for 15 s ($\times 43200$); b: Exposure to a pressure of 20 mm Hg for 60 s ($\times 33000$) [26].

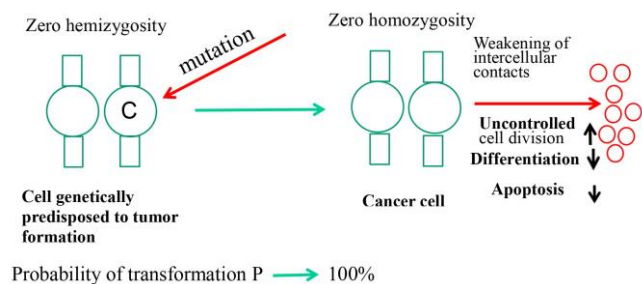


Figure 9. Hereditary predisposition of tissues to malignant growth.

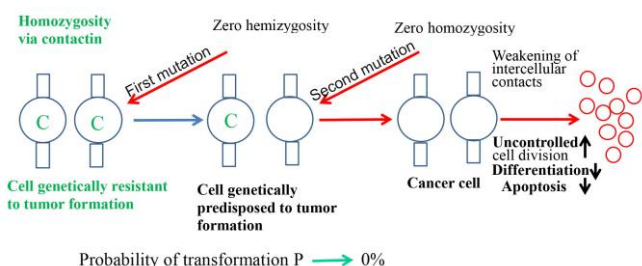


Figure 10. Normal tumor-resistant tissue.

1. The validity of the concept can be demonstrated by the evolutionary relationship of cadherin molecules that mediate homophilic cell-cell junctions, CJM that form specialized intercellular junctions, ICAM that regulate the recruitment of leukocyte integrin $\beta 2$ from the bloodstream to the target tissue, $\beta 1$ integrins that mediate invasive migration of cancer cells, proteins of the major histocompatibility complex (MHC) class I that present antigens to immune cells, IgG antibodies that redirect CTL or NK cells to the tumor, and growth factor receptors. They are gene products that evolved as a result of duplication of the original precursor, comparable to the duplication of the cadherin molecule gene.

Scientific data confirmed the importance of CAM for the evolution of multicellular organisms and the emergence of the adaptive immune system of vertebrates. Adhesion molecules provide tight contact between cells via maintaining the architectonics of tissues and organs, and also the homeostasis of the body. They can probably protect the body from the process of decay in tumor pathology (Figure 12) [16].

2. Identifying another factor that could destroy all stages of malignancy is a complex task. Almost all connections, mechanisms, and factors necessary for the development of cancer can be integrated into a single signaling system. The determining factor in this system may be adhesion disorders at the initial stage, leading to further adhesion disorders.

3. The hypothesis can explain why tumors develop mainly in a separate organ due to the suppression of the tissue-specific adhesion factor contactin and why there are differences in the degree of metastasis due to the $\beta 1$ integrin profile.

4. Reduced cell-cell junction due to impaired expression of tissue-specific cadherin (contactin) and ICAM, as well as an increase in the cell mass of the organ are specific properties of malignancy. In contrast, the development of inflammation, is associated, among other things, with a loss of cell mass and an

increase in the expression of ICAM-1, ICAM-2, LFA-1, and Mac-1 in response to inflammatory mediators [56, 57]. The latter entails the activation of CD8+ lymphocytes, NK cells, etc. In rare cases of spontaneous regression of a malignant tumor, increased expression of ICAM-1 was found on the membranes of its cells with multiple infiltration of the tumor by T cells (Figure 13).

5. Sir Frank Macfarlane Burnet hypothesized that tumor cell neoantigens cause an immune response to cancer and subsequently formulated the immune surveillance theory. However, the theory does not explain the decrease in antitumor immunity. For instance, tumors do not arise more frequently in organs protected by the blood-brain barrier (eye structures, nervous tissue, gonads, thyroid gland) than in peripheral organs. Multiple polyclonal tumors should arise in the case of deficiency of cell-mediated immunity, but they usually are distributed in individual organs. Immunodeficient nude mice and mice of other strains have the same tumor frequency of occurrence. It is more effective to inoculate smaller volumes of tumor cells than larger ones. Some long-term immunosuppression conditions (e.g., leprosy, sarcoidosis, and uremia) do not lead to an increase in tumor incidence [58, 59].

Adhesion molecules for diagnostics and prediction of therapeutic efficacy

The efficacy of anticancer therapy can be determined by the surface expression of ICAM-1 (CD54). Determination of the expression level of leukocyte $\beta 2$ integrins will allow to assess both the stage of malignancy and the efficacy of anticancer therapy (Table 2).

The prospect for determining the repertoire of $\beta 1$ integrins regulating the invasive migration of cancer cells seems promising. Besides that, the source of metastases can be determined by assessing combinations of $\beta 1$ integrins when the primary location of the tumor is uncertain (Table 3). The search for $\beta 1$ integrin inhibitory agents (specific and nonspecific) that reduce $\beta 1$ integrin signaling may be important for the regression of metastases.

Thus, adhesion molecules that mediate intercellular interactions in the target tissue, as well as with immune effector cells and the extracellular matrix, can be studied to understand tumor progression. Also, they can act as prognostic factors for the disease and important therapeutic targets for medicinal drug action.

Potential of adhesive preparations

Adhesive drugs constitute a promising strategy for developing new approaches to treating malignant tumors and innovative methods aimed at preventing or suppressing the development of malignant processes. Transfection of ICAM-1 into human colorectal cancer cell lines increased the adhesiveness and cytotoxicity of peripheral blood mononuclear cells towards cancer cells in vitro [60]. Intratumoral injection of ICAM-2 adenoviral vector significantly inhibited tumor growth, peritoneal metastasis and survival of mice with gastric carcinoma. Histopathological data showed that many NK cells infiltrated the lesions after injection of ICAM-2 adenoviral vector [61]. Apparently, transfection of the ICAM-1,2 gene via adenoviral vector can be an effective therapy for metastasis. These are examples of specific effects of adhesive agents.

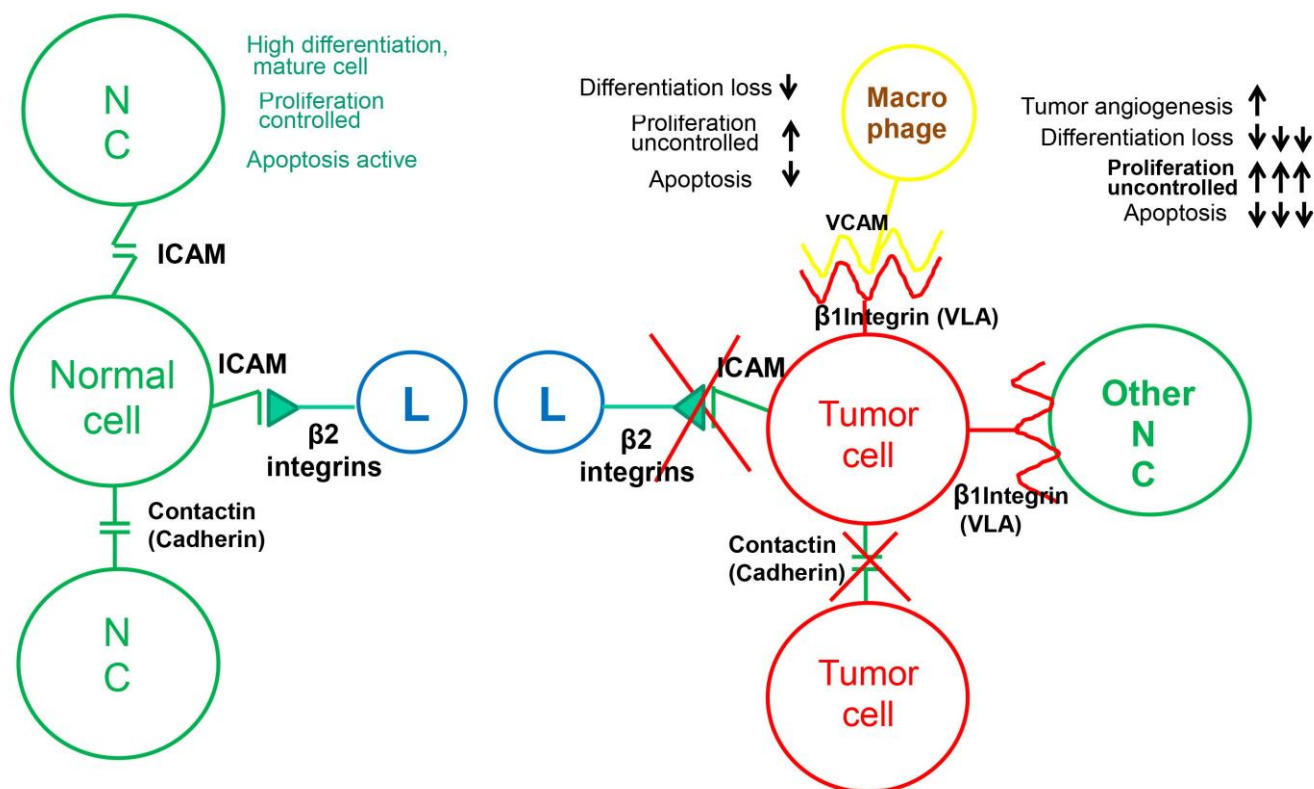


Figure 11. Expression of adhesion molecules in cancer: the *phoenix rising* mechanism in tumors.

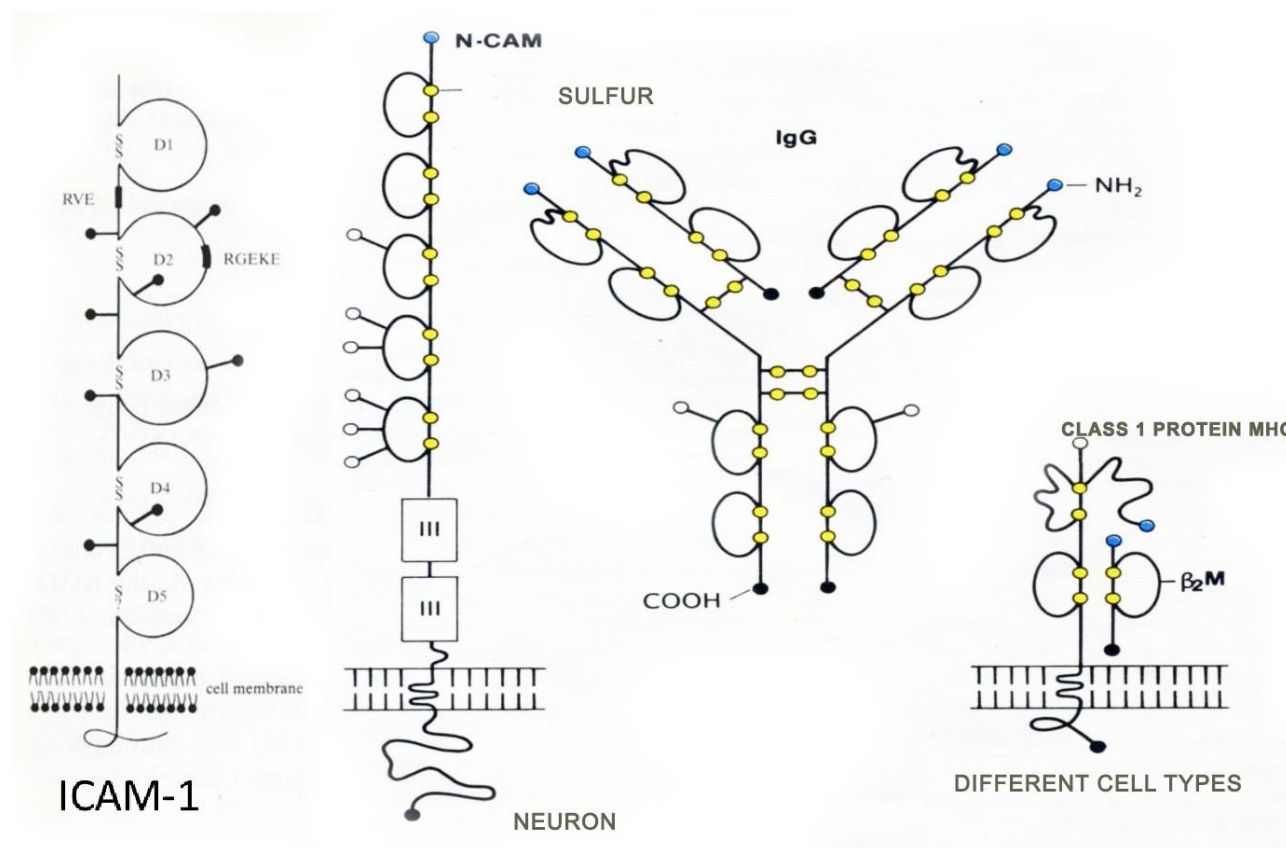


Figure 12. Evolutionary relationship of adhesion molecules.

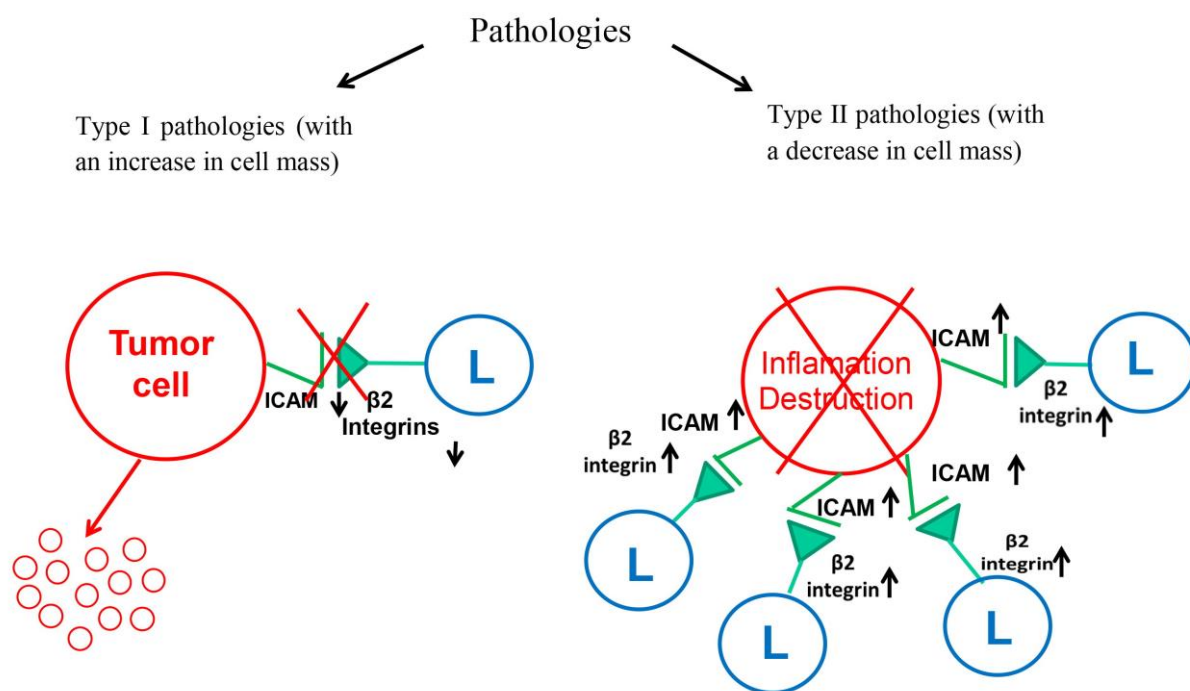


Figure13. Various types of pathologies and expression of adhesion molecules.

First-in-class synthetic agents that are agonists of the leukocyte $\beta 2$ integrins have already been developed abroad and are in phase I clinical trials as antitumor drugs. Among them, we should mention 7HP349 (Hills Pharma, USA) and ADH-503 or Leukadherin-1 choline (Gossamer Bio, USA).

7HP349, a small molecule agonist of LFA-1, promoted preferential localization of CD8⁺ CTL in melanoma cells by upregulating LFA-1-mediated binding to ICAM-1 on cancer cells. 7HP349 improved the antitumor response by synergistically interacting with neutrophils in inducing cancer regression [62]. GB1275, a Mac-1 agonist, improved antitumor immunity, which led to an increase in both the number of tumor-infiltrating CTL and their cytolytic activity in pancreatic ductal adenocarcinoma, as well as breast, prostate, and microsatellite stable colorectal cancer [63].

The results of the search for nonspecific drugs with adhesive action among plant substances are remarkable. For example, the plant polyphenol resveratrol suppressed the expression of $\beta 1$ integrin in the human colon carcinoma cell line HCT116, while SW480 simultaneously increased the expression of the histospecific adhesion factor, E-cadherin. Moreover, resveratrol impeded cell proliferation, colony formation, viability, and increased apoptosis in a concentration-dependent manner [64].

Our previous studies have shown that *Rhodiola rosea* extract components (a multitargeted natural compound with the ability to modulate various signaling pathways) exhibits adhesive properties in male CBA mice (a model of spontaneous hepatocarcinogenesis) by improving the cell-cell mutual adhesion of epithelial homophilic cells in the early postnatal period (on days 5-10 after the birth). This leads to a reduction in the frequency of spontaneous tumors in late ontogenesis. At the same time, an increase in the functional activity of T cells was noted [65].

The adhesive and antitumor efficacy of the multiphytoadaptogen complex (MPhA) was assessed in a large-

scale experiment involving almost 1,000 male CBA mice. MPhA is a standardized herbal formula. It contains components of 40 plant extracts officially recognized by pharmaceutical companies (*Panax ginseng*, *Glycyrrhiza glabra*, *Eleutherococcus senticosus*, *Helichrysum arenarium*, *Aralia mandshurica*, *Hypericum perforatum*, *Rhodiola rosea*, *Potentilla erecta*, *Oplopanax elatus*, *Schizandra chinensis*, etc.).

MPhA was used in prophylactic (during the first month of life of mice) and therapeutic (from 6 months on of life of mice, when the first tumors begin to appear, and until the natural death of the animals) modes. An increase in the number of blood cells expressing LFA-1 and Mac-1 was shown both with prophylactic and therapeutic use of MPhA. LFA-1 and Mac-1 play an important role in attracting activated CTL from peripheral blood to tumor tissue. As a result, the interaction between LFA-1 and ICAM-1 and the strong adhesion of leukocytes to target cells can be restored, facilitating the elimination of cancer cells [39, 66, 67].

Reduced levels of serum interleukin 10 (IL-10) and interleukin 6 (IL-6), as compared to control animals, were revealed [66]. IL-10 is known to inhibit T cell proliferation, antigen presentation, as well as T cell and NK cell cytotoxicity [68]. IL-6 is a pleiotropic cytokine involved in tumorigenesis by regulating multiple cancer signaling pathways, including proliferation, angiogenesis, invasiveness and metastasis [69]. Increased expression of LFA-1 and Mac-1, as well as inhibition of the corresponding interleukins by MPhA, may be useful for the elimination of cancer cells.

Immunoreactivity of experimental animals was reflected in the infiltration of spontaneous hepatocarcinomas by CD8⁺ CTL expressing the CD11a subunit of LFA-1 and the CD11b subunit of Mac-1 (Figure 14) [70, 71]. This may imply productive binding of LFA-1 and Mac-1 to their ICAM-1 ligand on target cells, promoting the infiltration of tumor tissue by CTL and the initiation of effector functions leading to tumor destruction [72, 73].

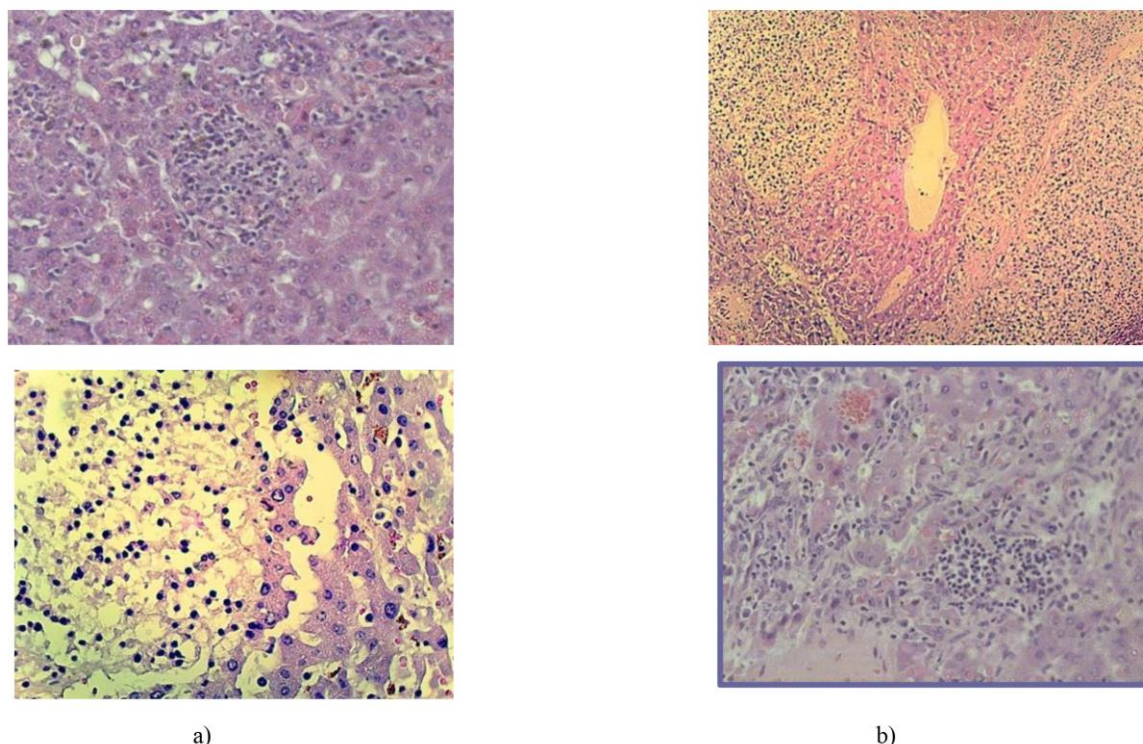


Figure 14. Infiltration of hepatocarcinoma lymphocytes in 22-month-old CBA mice exposed to MPhA. a: In prophylactic mode; b: In therapeutic mode.

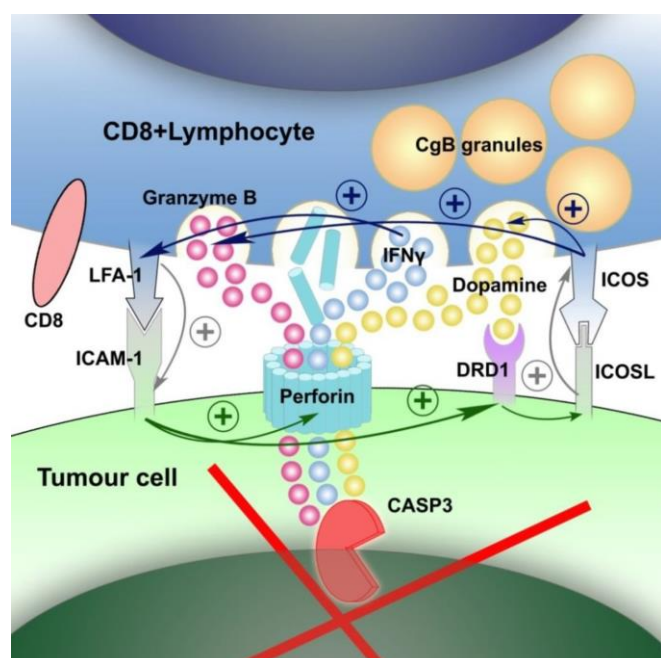


Figure 15. Model of contact interactions between a cytotoxic lymphocyte and a tumor cell (adopted from [59]).

The interaction between cancer cells and CTL can also be controlled by one of the major neurotransmitters, dopamine (DA). DA receptors have been found on immune effector cells, including T lymphocytes [74, 75]. Direct communication between brain DA and peripheral DA is crucial in the modulation of immune function.

Peripheral DA promotes differentiation and effector functions of CTL. It mediates the recruitment of these cells to the tumor microenvironment and junction with target cells, acting towards them as a toxin that suppresses cell proliferation ([Figure 15](#)) [59, 76].

The use of MPhA in preventive and therapeutic modes contributed to the preservation of a high number of dopaminergic neurons in the brain in late ontogenesis of male CBA mice. This correlated with a decline in the incidence of tumors (by 30%), their number, and size without affecting body weight, as well as with an increase in life expectancy (by 15-25%) and quality of life in animals with normalization of the stress hormone corticosterone elevated level. The lifespans of mice in the control, prophylactic, and therapeutic groups were 22, 25, and 27 months, respectively, which correlated with the human age of 62, 70, and 75 years, respectively, when converting the age of mice to the age of humans ([Figure 16](#)) [77-81].

Summarizing the obtained results, it is possible to assume the contribution of peripheral and central adhesion mechanisms in the immune system to the control of malignant tumor formation. It should be noted that the mechanisms of tumor growth acceleration by chronic stress can be detailed due to the modulation of peripheral and central DA levels, which are directly associated with each other.

Since we registered MPhA as a parapharmaceutical agent and confirmed its harmlessness in practice, we had the opportunity to study its use in a dental clinic in patients with oral leukoplakia (OLK), which can be considered a precancerous disease. It is known that OLK transforms into squamous cell carcinoma of the oral mucosa in 75% of cases [82-84].

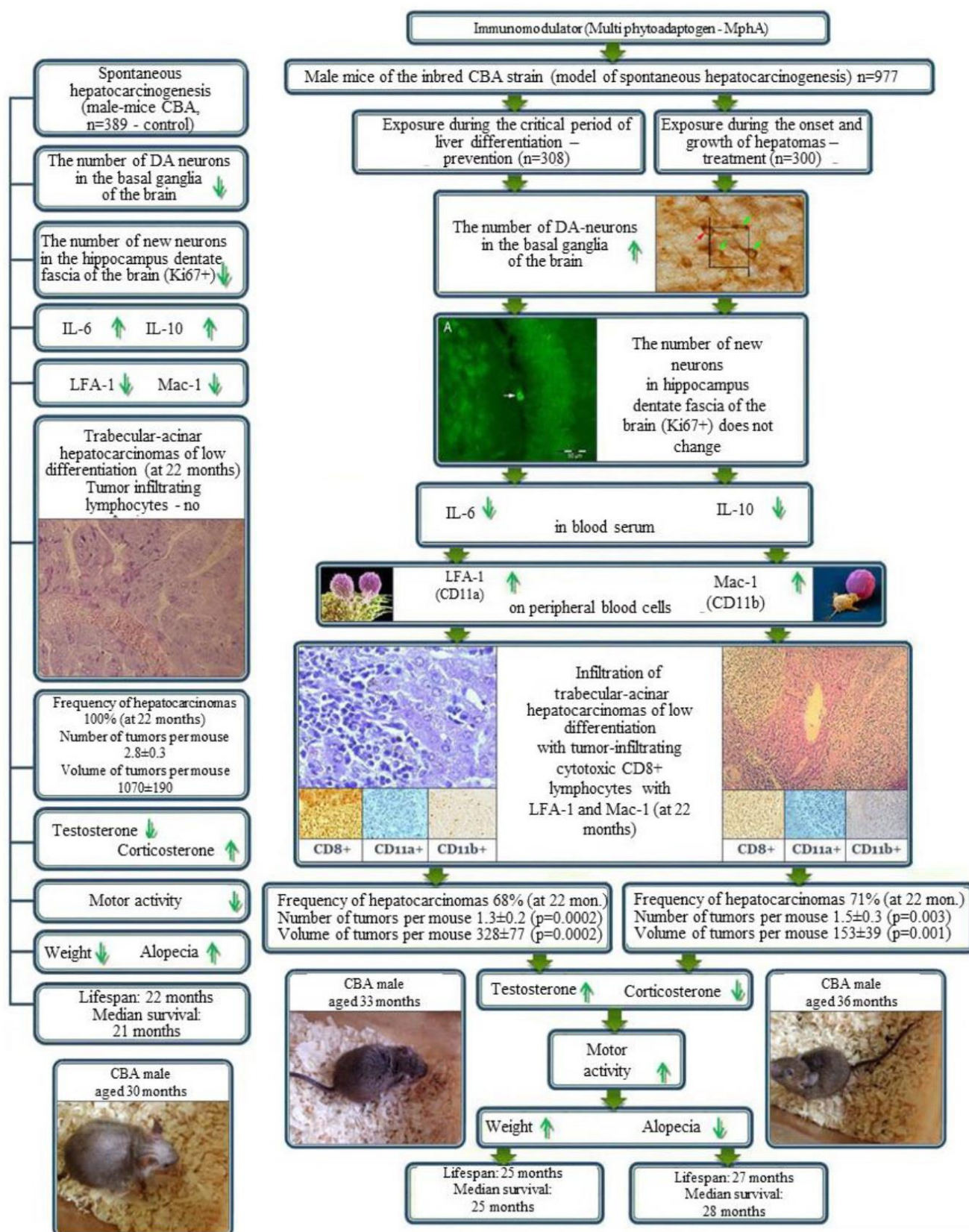


Figure 16. Flow chart of a large-scale experiment on the effect of multiphytoadaptogen in prophylactic and therapeutic modes on spontaneous hepatocarcinogenesis in inbred male CBA mice with high levels of cancer [81].

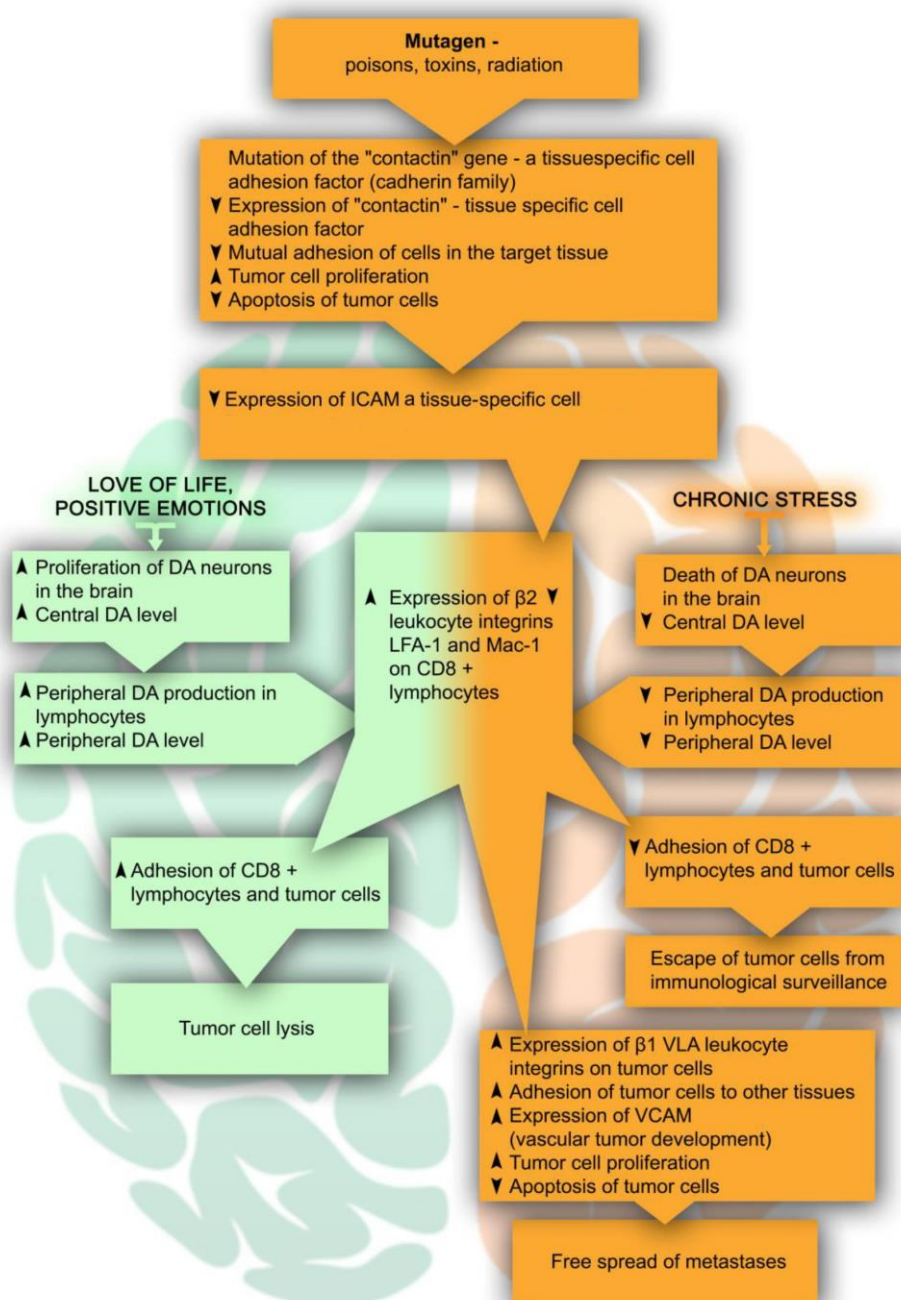


Figure 17. Flow chart of the adhesion concept in cancer biology: local and central mechanisms (adopted from [59]).

When MPhA was administered to patients with OLK, we observed an increase in ICAM-1 expression on the surface of oral mucosal epithelial cells. Also, expression of keratin 17 involved in keratinocyte proliferation was reduced, and expression of the Fas/APO-1 receptor, which activates apoptosis, was augmented. In 57% of patients, these changes correlated with a decrease in the size and density of OLK lesions. Clinical recovery was observed in 17% of cases. Compared with traditional vitamin A preparations, MPhA exhibited twice the clinical efficacy. Hence, the use of a nonspecific adhesive agent (MPhA) has shown potential for primary cancer prevention [85-90].

Increased expression of the CD11b of Mac-1 on peripheral blood cells was accompanied by a reduction in the level of tumor markers, CA19-9 and CEA, in patients with advanced gastric cancer under the effect of MPhA. As a result, the life expectancy of patients with concomitant use of MPhA was almost 2.5 times longer than that of patients in the control groups. Besides that, a decline in the elevated level of cortisol in the blood serum, an improvement in the antioxidant status, as well as normalization of cellular immunity parameters, were observed. When MPhA was added to standard treatment regimens for patients with gastric cancer, it was possible to almost double the number of polychemotherapy courses and reduce their toxic effects. A substantial decrease in sarcopenia symptoms was noted [91-93].

Table 1. Effect of contactin on liver tumor formation in male CBA mice after its tenfold administration

Cumulative diameter of all tumors in 1 mouse (cm)	Counts and percentages of mice	
	Experiment (contactin)	Control (Hank's salt solution)
D≥0.5	31 (62%)	38 (84.5%)
D<0.5	3 (6%)	6 (15.5%)
0 (no tumors)	16 (32%)	0

Table 2. The integrin family: leukocyte integrins

	LFA-1	MAC-1	P150,95
Structure	Heterodimer αX β2		
Common β chain	YES		
Individual α chain			
CD nomenclature	α β CD11a/CD18	α β CD11b/CD18	α β CD11c/CD18
Distribution	leukocytes		
Ligands	ICAM-1 ICAM-2	C3bi Fibrinogen factor X	C3bi
Main function	Adhesion of immunocompetent cells		

Table 3. The integrin family: very late activation antigens, VLA β1 integrins (heterodimers αX β1)

VLA-1	VLA-2	VLA-3	VLA-4	VLA-5	VLA-6	VLA-7
β	α β	α β	α β	α β	α β	-
/CD29	CDw49b/CD29	/CD29	CDw49d/CD29	/CD29	CDw49d/CD29	-
Different cell types (VLA-4: mainly on hematopoietic cells)						
Morphogenesis and wound healing						

Thus, in experiments and in the clinic, nonspecific adhesive MPhA has been used to obtain therapeutic antitumor effects, as well as the possibility of primary, secondary and tertiary prevention of malignant neoplasms. Therefore, our research has fully proven the effectiveness of MPhA for preventive oncology.

There is no model for studying the effect of pharmaceutical agent on cadherin mutations. Hence, the antimutagenic effect of MPhA was shown on the standard *Saccharomyces cerevisiae* model to complete the identification of MPhA activity within the adhesion concept. The frequency of spontaneous mutations of canavanine resistance (CANR) decreased 6.4 -fold, while mutations in the ADE4-ADE8 loci were reduced by over 100 times. This is a red-white test system. Red colonies are normal. Mutant cells grow white. Addition of MPhA to the culture medium significantly reduced the number of mutant (white) colonies. MPhA reduced the frequency of direct mutations induced by UV irradiation and nitric acid in yeast cells by 3.7 times and 33 times, respectively [94].

An antimutagenic effect of MPhA on chromosomal aberrations of lymphocytes in patients with age-related benign prostatic hyperplasia was also established. Patients received MPhA in courses for several months. As a result, an almost threefold decrease in the age-related frequency of chromosomal aberrations was revealed [95, 96]. High antimutagenic effects in vitro and in humans confirmed that MPhA is an effective antimutagen, including, possibly, its efficacy against mutations of tissue-specific adhesion factors from the cadherin family.

Given modern trends in the development of anticancer and anti-aging approaches, the study of nontoxic geroprotective medicinal drugs with adhesive properties opens up their potential

for further development of effective methods for the prevention and treatment of oncological and age-related diseases.

In March 2022, the World Health Organization (WHO) established the Global Centre for Traditional Medicine as a knowledge base with the mission of catalyzing “modern science with ancient wisdom for the health and well-being of the world’s people.” It is worth noting that the legal herbal medicine market in the world is \$136 billion. In August 2023, the first ever WHO conference on alternative medicine was held on 17 and 18 August 2023 in Gandhinagar, Gujarat, India. Ayurveda and naturopathy, including herbal medicine, were discussed. In this context, our results are relevant and timely.

In April 2023, as part of the *New Promising Antitumor Drugs* conference held at Blokhin National Medical Research Center for Oncology, the Integrative Oncology Drugs section was the first ever of the kind to be held within the framework of official medical science in Russia. We dedicated this section to the 100th anniversary of Academician Anatoly A. Vorobyov, who played a decisive role in supporting and developing our scientific field. The Section Chairs were Olga A. Bocharova, Professor, DSc (Biology); Natalia V. Pyatigorskaya, Corresponding Member of the Russian Academy of Sciences, Professor, Doctor of Pharmacy; and Fatima S. Datieva, DSc (Medicine). The Conference Chairs were Ivan S. Stilidi, Academician, Professor, DSc (Medicine) and Vyacheslav S. Kosorukov, PhD (Biology).

Cancer as rapid aging of cells. Dopamine as a geroprotector, antitumor agent, and antidepressant

Disruption of intercellular communication in the corresponding target tissue is an important modifying factor of tumorigenesis that leads to loss of cell differentiation. They lose maturity and the ability to perform certain adult functions of ‘adult’ cells. Malignancy can be considered as a manifestation of the individual cells aging according to the theoretical foundations of the concept under discussion [14, 58, 59]. The problem of cancer can thus be attributed to the mysteries of birth, aging, and death. Its solution requires boundless perseverance.

However, it is still possible to try to rely on the protective functions of the body, which prevent aging and prolong life. Activation of endogenous anti-stress and geroprotective mechanisms can be effective in preventing tumor development.

Brain DA is considered a central marker of aging in the body. Sufficient DA levels support motor activity, cognitive capabilities of the brain, and the tone of internal organs and blood vessels. Long-term viability of DA neurons also safeguards longevity [58, 59, 97-100]. That is why neuroprotectors are so important!

The neuroprotective and adhesive efficacy of MPhA was assessed in male CBA mice and C57Bl mice with induced parkinsonism syndrome (age-related disorder model). When using MPhA, an increase in motor activity and a decrease in rigidity of animals were observed. MPhA maintained the level of brain DA and its metabolites, prevented the death of brain dopaminergic neurons by suppressing the level of caspase-3, reduced the content of serotonin, and impeded the formation of lipid peroxidation products, such as malondialdehyde (MDA) [101].

When examined in a neurology clinic, patients with Parkinson’s disease (PD) received two courses of treatment during three months using MPhA against the background of standard therapy, which included drugs containing levodopa.

Complex standard therapy with MPPhA in patients with PD eliminated disorders of daily routine and physical activity (tremor, rigidity and bradykinesia). Normalization of immune, antioxidant and hormonal statuses was shown as well. The achieved noticeable improvement of life quality in patients with PD allow reducing the dosage of levodopa-containing medicines, which have serious side effects. MPPhA acted in a nontoxic, targeted manner in the body and proved its efficacy in reducing mortality as well as maintaining the level of viable DA-producing neurons [102, 103]. Hence, this only confirms the view that DA neurons are involved in the 'conspiracy' that limits life [58, 59, 76].

Conclusion

High levels of brain DA support intellectual, motivational, and motor activity, enhancing adhesive defense mechanisms in the immune system of the body against defective cells that can negatively affect life expectancy. With age and with chronic stress, loss of DA neurons in the brain occurs, which entails the suppression of peripheral DA with all ensuing consequences. With loss of brain DA, the proposed paradigm regarding the key role of impaired regulation of adhesion in target tissue and immunoreactivity processes in neoplasia reveals, among other things, the stress mechanism of cancer etiology. Therefore, an important conclusion of our reasoning may be a previously unknown answer to the question of the mechanism leading to the development of malignant neoplasms as a result of chronic stress.

Loss of contact with native cells as a result of the histospecific factor mutation in the tissue leads to the formation of additional tissue cells that quickly age, losing their mature functions and connections with immune effector cells. They form a malignant tumor ready to attach to new nutrient substrates, invading the body and leading to its death. However, central dopaminergic mechanisms are capable of restoring contacts between immune effector cells and tumor cells, which can lead to effective elimination of antisocial cells, thereby preventing a lethal outcome (Figure 17).

Finally, an important conclusion is that the activation of the central and peripheral mechanisms in the body in terms of the adhesion concept the described approaches implementation creates an unambiguous and specific prospect for increasing the effectiveness of diagnostic, prophylactic and therapeutic methods, which can become another step towards solving the problems of malignant neoplasms.

The entire philosophy linking adhesion molecules with molecules of the immune and dopaminergic systems would be impossible within the framework of highly specialized studies. Only by considering the problem from broad evolutionary, genetic, embryological, immunological and other scopes, and simultaneously conducting certain studies, we can unite into a coherent whole what at first glance seems unrelated. Experimental oncology using all the means of a broad and deep scientific horizon strives to solve the problem of malignant neoplasms, which is extremely difficult and requires endless perseverance.

Funding

This study has received no external funding.

Conflict of interest

The authors declare no conflicts of interest.

References

1. Zack TI, Schumacher SE, Carter SL, Cherniack AD, Saksena G, Tabak B, et al. Pan-cancer pattern of somatic copy number alteration. *Nat Genet* 2013; 45(10): 1134-1140. <https://doi.org/10.1038/ng.2760>.
2. Weinberg RA. Coming full circle-from endless complexity to simplicity and back again. *Cell* 2014; 157(1): 267-271. <https://doi.org/10.1016/j.cell.2014.03.004>.
3. Hanahan D. Hallmarks of cancer: New dimensions. *Cancer Discov* 2022; 12(1): 31-46. <https://doi.org/10.1158/2159-8290.CD-21-1059>.
4. Jacobs JJ, Snackey C, Geldof AA, Characiejus D, Van Moorselaar RJ, Den Otter W. Inefficiency of therapeutic cancer vaccines and proposed improvements. *Casus of prostate cancer. Anticancer Res* 2014; 34(6): 2689-2700. <https://pubmed.ncbi.nlm.nih.gov/24922629>.
5. Zavala VA, Kalgiris AM. New clinical advances in immunotherapy for the treatment of solid tumours. *Immunology* 2015; 145(2): 182-201. <https://doi.org/10.1111/imm.12459>.
6. Nakamura H, Fang J, Maeda H. Development for next generation drugs based on the EPR effect: challenges and pitfalls. *Expert Opin Drug Deliv* 2015; 12(1): 53-64. <https://doi.org/10.1517/17425247.2014.955011>.
7. Khatami M. Is cancer a severe delayed hypersensitivity reaction and histamine a blueprint? *Clin Transl Med* 2016; 5(1): 35. <https://doi.org/10.1186/s40169-016-0108-3>.
8. Lambert AW, Weinberg RA. Emerging biological principles of metastasis. *Cell* 2017; 168(4): 670-691. <https://doi.org/10.1016/j.cell.2016.11.037>.
9. Bonetto C, Trotta F, Felicetti P, Alarcyn GS, Santuccio C, Bachtar NS, et al. Vasculitis as an adverse event following immunization-systematic literature review. *Vaccine* 2016; 34(51): 6641-6651. <https://doi.org/10.1016/j.vaccine.2015.09.026>.
10. Khatami M. Unresolved inflammation and cancer: loss of natural immune surveillance as the correct "target" for therapy! Seeing the "Elephant" in the light of logic. *Cell Biochem Biophys* 2012; 62(3): 501-509. <https://doi.org/10.1007/s12013-011-9319-9>.
11. Khatami M. Immune surveillance in health and diseases of aging: Definitions of acute and chronic inflammation [Yin and Yang]. In: *Inflammation, aging and cancer*. Springer, Cham, 2017: 37-89. https://doi.org/10.1007/978-3-319-66475-0_2.
12. Maeda H, Khatami M. Analyses of repeated failures in cancer therapy for solid tumors: poor tumor-selective drug delivery, low therapeutic efficacy and unsustainable costs. *Clin Transl Med* 2018; 7(1): 11. <https://doi.org/10.1186/s40169-018-0185-6>.
13. Hanahan D., Weinberg RA. The Hallmarks of Cancer. *Cell* 2000; 100(1): 57-70. [https://doi.org/10.1016/S0092-8674\(00\)81683-9](https://doi.org/10.1016/S0092-8674(00)81683-9).
14. Bocharova OA. Adhesive cell interactions in the biology of cancer. *Vestn Ross Akad Med Nauk* 2002; (1): 22-25. Russian. <https://pubmed.ncbi.nlm.nih.gov/11882965>.
15. Wong SHM, Fang CM, Chuah LH, Leong CO, Ngai SC. E-cadherin: Its dysregulation in carcinogenesis and clinical implications. *Crit Rev Oncol Hematol* 2018; 121: 11-22. <https://doi.org/10.1016/j.critrevonc.2017.11.010>.
16. Edelman GM. Topobiology. *Sci Am* 1989; 260(5): 76-82, 84-86, 88. <https://doi.org/10.1038/scientificamerican0589-76>.
17. Stoeckli ET. Neural circuit formation in the cerebellum is controlled by cell molecules of the Contactin family. *Cell Adh Migr* 2010; 4(4): 523-526. <https://doi.org/10.4161/cam.4.4.12733>.
18. Garcia MA, Nelson WJ, Chavez N. Cell-cell junctions organize structural and signaling networks. *Cold Spring Harb Perspect Biol* 2018; 10(4): a029181. <https://doi.org/10.1101/cshperspect.a029181>.
19. Modyanova EA, Bocharova OA, Malenkov G. Prophylactic effect of contactine-chalones on spontaneous carcinogenesis in inbred mice. *Eksperimentalnaya Onkologiya* 1983; 5(3): 39-42. Russian. <https://www.elibrary.ru/item.asp?id=21749042>.

20. Halbleib JM, Nelson WJ. Cadherins in development: Cell adhesion, sorting, and tissue morphogenesis. *Genes Dev* 2006; 20(23): 3199-3214. <https://doi.org/10.1101/gad.1486806>.
21. Jeanes A, Gottardi CJ, Yap AS. Cadherins and cancer: How does cadherin dysfunction promote tumor progression? *Oncogene* 2008; 27(55): 6920-6929. <https://doi.org/10.1038/onc.2008.343>.
22. Mendonsa A, Na T-Y, Gumbiner BM. E-cadherin in contact inhibition and cancer. *Oncogene* 2018; 37(35): 4769-4780. <https://doi.org/10.1038/s41388-018-0304-2>.
23. Bocharova O.A., Modyanova E.A. Changes of cellular contacts between hepatocytes in the inbred mouse lines with the high (CBA) and low (C57BL) frequency of spontaneous hepatomas. *Ontogenez* 1982; 13(4): 427-430. Russian. <https://elibrary.ru/item.asp?id=21463190>.
24. Bocharova OA, Modyanova EA. Changes in hepatocyte contacts involved in orthoaminoazotoluene – induced hepatic carcinogenesis. *Voprosy onkologii* 1982; 28(9): 58-62. Russian. <https://elibrary.ru/item.asp?id=21463137>.
25. Bocharova OA, Modyanova EA, Malenkov AG. The role of cell contacts in tissue resistance to tumor formation. *Tsitologiya* 1982; 24(9): 1105. Russian. <https://elibrary.ru/item.asp?id=21463080>.
26. Bocharova OA, Karpova RV, Bocharov EV, Revishchin AV, Aksenov AA, Kazeev IV, et al. Inbred CBA Mice as a Model of Spontaneous Carcinogenesis for the Study of Oncoprotectors and Geroprotectors. Moscow: Academy Print, 2023; 208 p. Russian. <https://doi.org/10.18720/SPBPU/2/z23-10>.
27. Modyanova EA, Bocharova OA, Ushakov VF. Mechanical properties of intercellular junctions of hepatocytes in inbred mice and predisposition to spontaneous hepatoma. *Bull Exp Biol Med* 1980; 89(4): 459-462. Russian. <https://elibrary.ru/item.asp?id=21463136>.
28. Malenkov AG, Bocharova OA, Modyanova EA. The Phenomenon of Increase in Adhesive Forces During Intercellular Interaction in Epithelial Tissues in Early Postnatal Period. Patent No. 330 registered in the State Register of Discoveries of the USSR. State Committee for Inventions and Discoveries under the State Committee for Science and Technology of the USSR. Department of Discoveries. Discoveries in the USSR, 1987 Collection of Brief Descriptions of Discoveries Included in the State Register of Discoveries of the USSR. VNIPI, Moscow, 1988, VPTB, Department 57. Biology; 30-31.
29. Knudson AG. Mutation and cancer: Statistical study of retinoblastoma. *Proc Natl Acad Sci* 1971; 68(4): 820-823. <https://doi.org/10.1073/pnas.68.4.820>.
30. Thiery JP. Epithelial-mesenchymal transitions in tumour progression. *Nat Rev Cancer* 2002; 2(6): 442-454. <https://doi.org/10.1038/nrc822>.
31. Ilyas M. Adhesion molecule expression in breast cancer: the phoenix in tumour metastasis? *J Pathol* 2000; 190(1): 3-5. [https://doi.org/10.1002/\(sici\)1096-9896\(200001\)190:1%3C3::aid-path490%3E3.0.co;2-5](https://doi.org/10.1002/(sici)1096-9896(200001)190:1%3C3::aid-path490%3E3.0.co;2-5).
32. Yun SJ, Kim WJ. Role of the epithelial-mesenchymal transition in bladder cancer: From prognosis to therapeutic target. *Korean J Urol* 2013; 54(10): 645-650. <https://doi.org/10.4111/kju.2013.54.10.645>.
33. Petrova YI, Schecterson L, Gumbiner BM. Roles for E-cadherin cell surface regulation in cancer. *Mol Biol Cell* 2016; 27(21): 3233-3244. <https://doi.org/10.1091/mbc.e16-01-0058>.
34. Wong SHM, Fang CM, Chuah LH, Leong CO, Ngai SC. E-cadherin: Its dysregulation in carcinogenesis and clinical implications. *Crit Rev Oncol Hematol* 2018; 121: 11-22. <https://doi.org/10.1016/j.critrevonc.2017.11.010>.
35. Ebnet K, Kummer D, Steinbacher T, Singh A, Nakayama M, Matis M. Regulation of cell polarity by cell adhesion receptors. *Semin Cell Dev Biol* 2018; 81: 2-12. <https://doi.org/10.1016/j.semcdb.2017.07.032>.
36. Grupp K, Melling N, Bogoevska V, Reeh M, Uzunoglu FG, El Gammal AT, et al. Expression of ICAM-1, E-cadherin, periostin and midkine in metastases of pancreatic ductal adenocarcinomas. *Exp Mol Pathol* 2018; 104(2): 109-113. <https://doi.org/10.1016/j.yexmp.2018.01.005>.
37. Scholer A, Hugues S, Boissonnas A, Fetler L, Amigorena S. Intercellular adhesion molecule-1-dependent stable interactions between T cells and dendritic cells determine CD8+ T cell memory. *Immunity* 2008; 28(2): 258-270. <https://doi.org/10.1016/j.immuni.2007.12.016>.
38. Zhou Q, Xu J, Xu Y, Sun S, Chen J. Role of ICAM1 in tumor immunity and prognosis of triple-negative breast cancer. *Front Immunol* 2023; 14: 1176647. <https://doi.org/10.3389/fimmu.2023.1176647>.
39. Bocharova OA, Karpova RV, Bocharov EV, Vershinskaya AA, Baryshnikova MA, Kazeev IV, et al. LFA-1 and MAC-1 leukocyte integrins are targets for enhancing antitumor immunity. *Russian Journal of Biotherapy* 2020; 19(1): 53-58. Russian. <https://doi.org/10.17650/1726-9784-2019-19-1-53-58>.
40. Gérard A, Cope AP, Kemper C, Alon R, Köchl R. LFA-1 in T cell priming, differentiation, and effector functions. *Trends Immunol* 2021; 42(8): 706-722. <https://doi.org/10.1016/j.it.2021.06.004>.
41. Huse M. Mechanical forces in the immune system. *Nat Rev Immunol* 2017; 17(11): 679-690. <https://doi.org/10.1038/nri.2017.74>.
42. Jo JH, Kwon MS, Choi HO, Oh HM, Kim HJ, Jun CD. Recycling and LFA-1 dependent trafficking of ICAM-1 to the immunological synapse. *J Cell Biochem* 2010; 111(5): 1125-1137. <https://doi.org/10.1002/jcb.22798>.
43. Li N, Yang H, Wang M, Lü S, Zhang Y, Long M. Ligand-specific binding forces of LFA-1 and Mac-1 in neutrophil adhesion and crawling. *Mol Biol Cell* 2018; 29(4): 408-418. <https://doi.org/10.1091/mbc.E16-12-0827>.
44. Verma NK, Kelleher D. Not just an adhesion molecule: LFA-1 contact tunes the T lymphocyte program. *J Immunol* 2017; 199(4): 1213-1221. <https://doi.org/10.4049/jimmunol.1700495>.
45. Guo J, Xu Z, Gunderson RC, Michie S. LFA-1/ICAM-1 adhesion pathway mediates the homeostatic migration of lymphocytes from peripheral tissues into lymph nodes through lymphatic vessels. *Biomolecules* 2023; 13(8): 1194. <https://doi.org/10.3390/biom13081194>.
46. Heidemann J, Maaser C, Lügering A, Spahn TW, Zimmer KP, Herbst H, et al. Expression of vascular cell adhesion molecule-1 (CD 106) in normal and neoplastic human esophageal squamous epithelium. *Int J Oncol* 2006; 28(1): 77-85. <https://pubmed.ncbi.nlm.nih.gov/16327982>.
47. Aksorn N, Chanvorachote P. Integrin as a molecular target for anti-cancer approaches in lung cancer. *Anticancer Res* 2019; 39(2): 541-548. <https://doi.org/10.21873/anticancer.13146>.
48. García-Martín AB, Zwicky P, Gruber T, Matti C, Moalli F, Stein JV, et al. VLA-4 mediated adhesion of melanoma cells on the bloodbrain barrier is the critical cue for melanoma cell intercalation and barrier disruption. *J Cereb Blood Flow Metab* 2019; 39(10): 1995-2010. <https://doi.org/10.1177/0271678X18775887>.
49. Sun L, Guo S, Xie Y, Yao Y. The characteristics and the multiple functions of integrin $\beta 1$ in human cancers. *J Transl Med* 2023; 21(1): 787. <https://doi.org/10.1186/s12967-023-04696-1>.
50. Kong DH, Kim YK, Kim MR, Jang JH, Lee S. Emerging roles of vascular cell adhesion molecule-1 (VCAM-1) in immunological disorders and cancer. *Int J Mol Sci* 2018; 19(4): 1057. <https://doi.org/10.3390/ijms19041057>.
51. Huang R, Rofstad EK. Integrins as therapeutic targets in the organ-specific metastasis of human malignant melanoma. *J Exp Clin Cancer Res* 2018; 37(1): 92. <https://doi.org/10.1186/s13046-018-0763-x>.
52. Mierke CT. Cancer cells regulate biomechanical properties of human microvascular endothelial cells. *J Biol Chem* 2011; 286(46): 40025-40037. <https://doi.org/10.1074/jbc.M111.256172>.
53. Kourtidis A, Lu R, Pence LJ, Anastasiadis PZ. A central role for cadherin signaling in cancer. *Exp Cell Res* 2017; 358(1): 78-85. <https://doi.org/10.1016/j.yexcr.2017.04.006>.
54. Stachowicz K. Physicochemical principles of adhesion mechanisms in the brain. *Int J Mol Sci* 2023; 24(6): 5070. <https://doi.org/10.3390/ijms24065070>.
55. Hou CH, Yang RS, Tsao YT, Hou CH, Yang RS, Tsao YT. Connective tissue growth factor stimulates osteosarcoma cell migration and induces osteosarcoma metastasis by upregulating VCAM-1 expression.

- Biochem Pharmacol* 2018; 155: 71-81. <https://doi.org/10.1016/j.bcp.2018.06.015>.
56. Watts GM, Beurskens FJ, Martin-Padura I, Ballantyne CM, Klickstein LB, Brenner MB et al. Manifestations of inflammatory arthritis are critically dependent on LFA-1. *J Immunol* 2005; 174(6): 3668-3675. <https://doi.org/10.4049/jimmunol.174.6.3668>.
 57. Gulubova MV, Manolova IM, Vlaykova TI, Prodanova M, Jovchev JP. Adhesion molecules in chronic ulcerative colitis. *Int J Colorectal Dis* 2007; 22(6): 581-589. <https://doi.org/10.1007/s00384-006-0236-0>.
 58. Bocharova OA, Matveev VB, Bocharov EV, Karpova RV, Kucheryanu VG. Adhesion concept in cancer biology: local and central mechanisms (Part 1). *Russian Journal of Biotherapy* 2021; 20(3): 17-24. Russian. <https://doi.org/10.17650/1726-9784-2021-20-3-17-24>.
 59. Bocharova OA, Matveev VB, Bocharov EV, Karpova RV, Kucheryanu VG. Adhesion concept in cancer biology: Local and central mechanisms (Part 2). *Russian Journal of Biotherapy* 2021; 20(4): 42-50. Russian. <https://doi.org/10.17650/1726-9784-2021-20-4-42-50>.
 60. Tachimori A, Yamada N, Sakate Y, Yashiro M, Maeda K, Ohira M, et al. Up regulation of ICAM-1 gene expression inhibits tumour growth and liver metastasis in colorectal carcinoma. *Eur J Cancer* 2005; 41(12): 1802-1810. <https://doi.org/10.1016/j.ejca.2005.04.036>.
 61. Tanaka H, Yashiro M, Sunami T, Ohira M, Hirakawa-Y S Chung K, et al. Lipid-mediated gene transfection of intercellular adhesion molecule-1 suppresses the peritoneal metastasis of gastric carcinoma. *Int J Mol Med* 2002; 10(5): 613-617. <https://pubmed.ncbi.nlm.nih.gov/12373302>.
 62. Hickman A, Koetsier J, Kurtanich T, Nielsen MC, Winn G, Wang Y, et al. LFA-1 activation enriches tumor-specific T cells in a cold tumor model and synergizes with CTLA-4 blockade. *J Clin Invest* 2022; 132(13): e154152. <https://doi.org/10.1172/jci154152>.
 63. De Nardo DG, Galkin A, Dupont J, Bendell J. GB1275, a first-in-class CD11b modulator: Rationale for immunotherapeutic combinations in solid tumors. *J Immunother Cancer* 2021; 9(8): e003005. <https://doi.org/10.1136/jitc-2021-003005>.
 64. Brockmueller A, Shayan P, Shakibaei M. Evidence that β 1-Integrin is required for the anti-viability and anti-proliferative effect of resveratrol in CRC cells. *Int J Mol Sci* 2022; 23(9): 4714. <https://doi.org/10.3390/ijms23094714>.
 65. Bocharova OA, Serebriakova RV, Bodrova NB. Preventive effect of *Rhodiola rosea* in spontaneous liver carcinogenesis in a mice model of high-tumor strain. *Vestn Ross Akad Med Nauk* 1994; (5): 41-43. <https://pubmed.ncbi.nlm.nih.gov/7519925>.
 66. Bocharova OA, Bocharov EV, Karpova RV, Il'enko VA, Kazeev IV, Baryshnikov AYU. Integrins LFA-1 and Mac-1 and cytokines IL-6 and IL-10 in mice with high levels of cancer under the effect of a phytoadaptogen. *Bull Exp Biol Med* 2014; 157(2): 258-260. <https://doi.org/10.1007/s10517-014-2539-4>.
 67. Bocharov EV, Bocharova OA, Karpova RV, Kucheryanu VG, Kazeev IV, Inozemceva ES, et al. Immunoadhesive regulation using multiphytoadaptogene for spontaneous hepatocarcinomas prevention. *Russian Journal of Biotherapy* 2018; 17(2): 78-87. Russian. <https://doi.org/10.17650/1726-9784-2018-17-2-78-87>.
 68. Itakura E, Huang RR, Wen DR, Paul E, Wünsch PH, Cochran AJ. IL-10 expression by primary tumour cells correlates with melanoma progression from radial to vertical growth phase and development of metastatic competence. *Mod Pathol* 2011; 24(6): 801-809. <https://doi.org/10.1038/modpathol.2011.5>.
 69. Kumari N, Dwarakanath BS, Das A, Bhatt AN. Role of interleukin-6 in cancer progression and therapeutic resistance. *Tumour Biol* 2016; 37(9): 11553-11572. <https://doi.org/10.1007/s13277-016-5098-7>.
 70. Bocharov EV, Bocharova OA, Solov'ev YN, Karpova RV, Kucheryanu VG. Morphological studies of hepatocellular carcinomas in male CBA mice with high liability to cancer under the effect of phytoadaptogen. *Bull Exp Biol Med* 2016; 161(5): 727-730. <https://doi.org/10.1007/s10517-016-3495-y>.
 71. Karpova RV, Bocharov EV, Bocharova OA, Kazeev IV, Kucheryanu VG, Soloviev YuN. The influence of multiphytoadaptogen on leukocyte infiltration in mice hepatocarcinomas. *Russian Journal of Biotherapy* 2019; 18(2): 60-65. Russian. <https://doi.org/10.17650/1726-9784-2019-18-2-60-65>.
 72. Walling BL, Kim M. LFA-1 in T cell migration and differentiation. *Front Immunol* 2018; 9: 952. <https://doi.org/10.3389/fimmu.2018.00952>.
 73. Bocharova OA, Karpova RV, Bocharov EV, Solov'yov YN. Effects of phytoadaptogen on hepatoma development in cancer-prone CBA mice. *Bull Exp Biol Med* 2015; 159(5): 655-657. <https://doi.org/10.1007/s10517-015-3040-4>.
 74. Bergquist J, Silberring J. Identification of catecholamines in the immune system by electrospray ionization mass spectroscopy. *Rapid Commun Mass Spectrom* 1998; 12(11): 683-688. [https://doi.org/10.1002/\(sici\)1097-0231\(19980615\)12:11%3C683::aid-rcm218%3E3.0.co;2-n](https://doi.org/10.1002/(sici)1097-0231(19980615)12:11%3C683::aid-rcm218%3E3.0.co;2-n).
 75. Channer B, Matt SM, Nickloff-Bybel EA, Pappa V, Agarwal Y, Wickman J, et al. Dopamine, immunity and disease. *Pharmacol Rev* 2023; 75(1): 62-158. <https://doi.org/10.1124/pharmrev.122.000618>.
 76. Schiller M. Ben-Shaanan TL, Rolls A. Neuronal regulation of immunity: Why, how and where? *Nat Rev Immunol* 2021; 21(1): 20-36. <https://doi.org/10.1038/s41577-020-0387-1>.
 77. Bocharov EV, Karpova RV, Bocharova OA, Kucheryanu VG, Shprakh ZS. Effect of phytoadaptogen administration during early ontogeny on lifespan and somatic status of CBA mice with high incidence of tumors. *Bull Exp Biol Med* 2017; 163(6): 789-792. <https://doi.org/10.1007/s10517-017-3904-x>.
 78. Bocharova OA, Karpova RV, Bocharov EV, Aksyonov AA, Kucheryanu VG, Revishchin AV, et al. CBA strain mice as a model of spontaneous carcinogenesis. *Russian Journal of Biotherapy* 2022; 21(3): 23-33. Russian. <https://doi.org/10.17650/1726-9784-2022-21-3-23-33>.
 79. Bocharova O.A., Revishchin A.V., Bocharov E.V., Karpova R.V., Pavlova G.V., Kucheryanu V.G. Central neuronal and peripheral adhesive mechanisms in the immune system in the development of experimental tumors. In: IX Russian Conference "Neuroimmunopathology" with international participation, dedicated to the 100th anniversary of the birth of Academician of the Russian Academy of Medical Sciences G.N. Kryzhanovskiy. 10-11.11.2022. Pathogenesis 2022; 20(3): 71-72. <https://doi.org/10.25557/2310-0435.2022.03.71-72>.
 80. Bocharova OA, Ionov NS, Kazeev IV, Shevchenko VE, Bocharov EV, Karpova RV, et al. Computer-aided evaluation of polyvalent medications' pharmacological potential. Multiphytoadaptogen as a case study. *Mol Inf* 2023; 42(1): e2200176. <https://doi.org/10.1002/minf.202200176>.
 81. Bocharova OA, Karpova RV, Bocharov EV, Aksyonov AA, Chekalina TL, Chulkova SV, et al. Adhesive phytoadaptogens and geroprotectors in preventive oncology. *Cardiometry* 2023; 26: 55-68. <https://doi.org/10.18137/cardiometry.2023.26.5568>.
 82. Paches AI. Tumors of the head and neck. Moscow: Medicine, 2000; 459 p. Russian.
 83. Bocharova OA, Baryshnikov AYU. Phytoadaptogens in Oncology. Moscow: ZooMedVet, 2004; 138 p. Russian.
 84. Bocharova OA, Baryshnikov AYU, Davydov MI. Phytoadaptogens in Oncology and Gerontology. Moscow: Medical News Agency, 2008; 218 p. Russian.
 85. Bocharova OA, Chekalina TL, Pozharitskaya MM. Mechanisms of leukoplakia pathogenesis and the possibility of its correction with a complex phytoadaptogen. In: Experimental Oncology at the Turn of the Century. Baryshnikov AYU, Davydov MI, eds. Moscow: Blokhin National Medical Research Center for Oncology, 2003; 349-361. Russian.
 86. Chekalina TL, Pozharitskaia MM, Bocharova OA. Improving the effectiveness of combined therapy of patients with leukoplakia of the

- buccal mucosa using Phytomix-40 combined plant preparation. *Stomatology* 2004; 83(5):24-30. Russian.
87. Bocharova OA, Pozharitskaya MM, Chekalina TL, Lyzhenkova MA, Karpova RV, Mezentsseva MV, et al. Leukoplakia of oral mucosa: Pathogenesis and possible correction with phytoadaptogen. *Bull Exp Biol Med* 2004; 138(6): 578-583. <https://doi.org/10.1007/s10517-005-0132-6>.
 88. Bocharova OA, Pojaritskaya MM, Chekalina TL, Mezentsseva MV, Karpova RV, Semernina VV, et al. The role of adhesion disorders in the pathogenesis of leukoplakia and the possibility of their correction with a nonspecific immunomodulator. *Immunologiya* 2004; 25(1): 36-43. Russian.
 89. Pozharitskaya MM, Bocharova OA, Chekalina TL, Voronin VF. Current Aspects of the Pathogenesis and Treatment of the Oral Mucosa Leukoplakia. Guidelines for physicians. Moscow: GOU VUNMC, 2004; 46 p. Russian.
 90. Chekalina TL, Gladko VV, Pozharitskaya MM, Bocharova OA. Leukoplakia of the Oral Mucosa. Methodological guide for physicians. Moscow: Institute for Advanced Medical Training, 2010; 30 p. Russian.
 91. Chulkova SV, Bocharova OA, Klimenkov AA, Karpova RV, Benevsky AI, Gorozhanskaya EG. Phytadaptogen efficiency in complex treatment of advanced gastric cancer. *Russian Journal of Biotherapy* 2006; 5(2): 85-92. Russian.
 92. Bocharova OA, Davydov MI, Klimenkov AA, Baryshnikov AY, Karpova RV, Chulkova SV, et al. Prospects of using phytoadaptogen in the treatment of diffuse stomach cancer. *Bull Exp Biol Med* 2009; 148(1): 82-85. <https://doi.org/10.1007/s10517-009-0652-6>.
 93. Chulkova SV, Klimenkov AA, Bocharova OA, Peterson SB, Benevsky AI, Karpova RV, et al. Possibilities of Complex Treatment of Advanced Gastric Cancer Using Fitomix-40. Methodological guide for physicians. Moscow: SKTB-TOMASS, 2011; 52 p. Russian.
 94. Kurenaya ON, Karpova RV, Bocharova OA, Kazeev IV, Bocharov EV. Antimutagenesis of multiphytoadaptogen in yeast *Saccharomyces*. *Russ J Genet* 2013; 49(12): 1190-1194. <https://doi.org/10.1134/S1022795413120053>.
 95. Bochkov NP, Bocharova OA, Aksenov AA, Gorozhanskaya EG, Matveev VB, Karpova RV, et al. Frequency of chromosome aberrations in lymphocytes of patients with benign prostatic hyperplasia. *Medical Genetics* 2005; 5(1): 15-19. Russian.
 96. Bocharova OA, Matveev VB, Karpova RV, Aksyonov AA, Gorozhanskaya EG, Chebotaryov FN, et al. Phytoadaptogen correction of clinical and immunobiological parameters in patients with benign prostatic hyperplasia. *Bull Exp Biol Med* 2006; 141(5): 616-619. <https://doi.org/10.1007/s10517-006-0235-8>.
 97. Alperina EL, Bocharov EV, Bocharova OA, Vasilenko AM, Vetlugina TP, Votintseva MV, et al. Current issues in neuroimmunopathology: A guide. Kryzhanovskiy GN, Magaeva SV, Morozov SG, Eds. Moscow: Genius-Media, 2012; 423 p. Russian.
 98. Pornour M, Ahangari G, Hejazi SH, Ahmadkhaniha HR, Akbari ME. Dopamine receptor gene (DRD1-DRD5) expression changes as stress factors associated with breast cancer. *Asian Pac J Cancer Prev* 2014; 15(23): 10339-10343. <https://doi.org/10.7314/apjcp.2014.15.23.10339>.
 99. Krizanova O, Babula P, Pacak K. Stress, catecholaminergic system and cancer. *Stress* 2016; 19(4): 419-428. <https://doi.org/10.1080/10253890.2016.1203415>.
 100. Bernabé DG. Catecholamines mediate psychologic stress-induced cancer progression. *Cancer Res* 2021; 81(20): 5144-5146. <https://doi.org/10.1158/0008-5472.CAN-21-3077>.
 101. Bocharov EV, Kucheryanu VG, Kryzhanovskii GN, Bocharova OA, Kudrin VS, Belorustseva SA. Effect of complex phytoadaptogen on MPTP-induced Parkinson's syndrome in mice. *Bull Exp Biol Med* 2006; 141(5): 560-563. <https://doi.org/10.1007/s10517-006-0220-2>.
 102. Bocharov EV, Kucheryanu VG, Kryzhanovskiy GN, Bocharova OA, Ivanova-Smolenskaya IA, Poleschuk VV. Phytomix-40 in treatment of Parkinson's disease: Lymphocyte populations and cytokine production. *Eur J Neurol* 2006; 13(52): 415-418.
 103. Bocharov EV, Ivanova-Smolenskaya IA, Poleshchuk VV, Kucheryanu VG, Il'enko VA, Bocharova OA. Therapeutic efficacy of the neuroprotective plant adaptogen in neurodegenerative disease (Parkinson's disease as an example). *Bull Exp Biol Med* 2010; 149(6): 682-684. <https://doi.org/10.1007/s10517-010-1023-z>.

Authors:

- Olga A. Bocharova** – DSc, Professor, Head of the Laboratory for Immunopharmacology, Blokhin National Medical Research Center for Oncology, Moscow, Russia. <https://orcid.org/0000-0002-6365-2888>.
- Regina V. Karpova** – DSc, Senior Researcher, Laboratory of Immunopharmacology, Blokhin National Medical Research Center for Oncology, Moscow, Russia. <https://orcid.org/0000-0003-4893-1472>.
- Evgeny V. Bocharov** – PhD, Senior Researcher, Laboratory of Immunopharmacology, Blokhin National Medical Research Center for Oncology, Moscow, Russia. <https://orcid.org/0000-0003-2342-9881>.
- Valerian G. Kucheryanu** – MD, DSc (Medicine), Principal Researcher, Laboratory of General Pathology of the Nervous System, Institute of General Pathology and Pathophysiology, Moscow, Russia. <https://orcid.org/0000-0002-5071-3581>.
- Vyacheslav S. Kosorukov** – PhD, Director of the Research Institute for Experimental Diagnostics and Therapy of Tumors, Blokhin National Medical Research Center for Oncology, Moscow, Russia. <https://orcid.org/0000-0002-8462-2178>.
- Ivan S. Stilidi** – MD, DSc, Professor; Academician, Russian Academy of Sciences; Director, Blokhin National Medical Research Center for Oncology, Moscow, Russia. <https://orcid.org/0000-0002-0493-1166>.

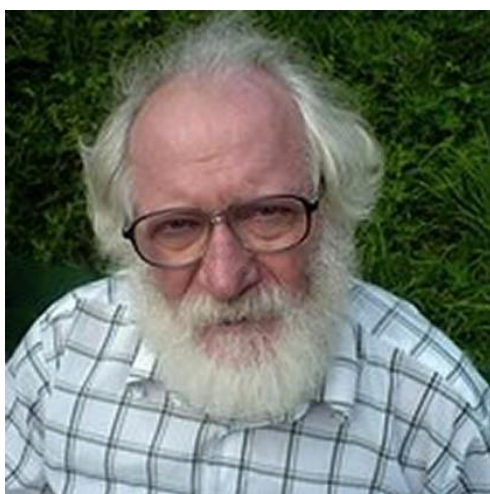
Supplement 1. Photos of scientists with the greatest contribution to the formation of the theory.

"A scientific hypothesis always goes beyond the facts that served as the basis for its construction"
V.I. Vernadsky



Andrey G. Malenkov, professor, biophysicist

He introduced me to the problem of intercellular adhesive interactions in tissues at the very beginning, in my sophomore year. He planted the seed! We carried out fundamental research on adhesion, which was included in my PhD thesis. These data have become part of a larger scientific study, for which we received a Diploma for the Discovery, *The Phenomenon of Increase in Adhesive Forces During Intercellular Interaction in Epithelial Tissues in Early Postnatal Period*. That was 35 years ago.



Vladimir M. Bukhman (1940-2021), professor, immunologist and toxicologist

I have met him back in 1978, right after graduating from the Academy, and it so happened that he revised the concept of adhesion from the very beginning. With his erudition, Professor Vladimir Mikhailovich Bukhman, contributed greatly to the clarification of the growing understanding of adhesion via uniting a large number of phenomena into a single entity.



Rakhim M. Khaïtov (1944-2022), academician of the Russian Academy of Sciences, professor, immunologist

Director of the Research Institute of Immunology. From the height of being a great scientific and practical leader in immunology, he supported my seemingly conceited theoretical statements. Due to the warm support from Professor Rahim M. Khaïtov, in 2002, we were the first in the world to publish the opinion that "cancer is the rapid aging of tissue cells." With gratitude to Fate and the Almighty, I recall our meetings and discussions of the adhesion theory in cancer biology.



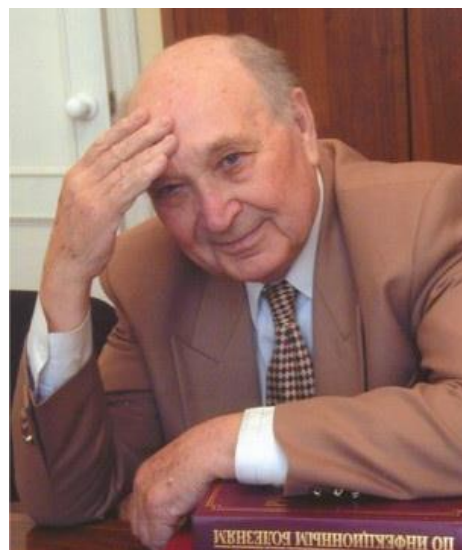
Georgy N. Kryzhanovsky (1922-2013), academician of the Russian Academy of Medical Sciences, professor, pathophysiologist

Director of the Research Institute of General Pathology and Pathophysiology. Academician-Secretary of the Medical and Biological Department of the Russian Academy of Medical Sciences. Founder and first President of the International Society for Pathophysiology. Without him, without his support of the central dopamine paradigm, our theory would not have received actual development as the third cornerstone, along with the mechanisms of adhesion at the level of target tissues and immunity.



Nikolay P. Bochkov (1931-2011), academician of the Russian Academy of Medical Sciences, professor, geneticist

Director of the Research Institute of Medical Genetics now bearing his name. Vice President of the Russian Academy of Medical Sciences. Evidence of high antimutagenicity of the adhesive neuroprotector in our experiment performed on *Saccharomyces* cells in collaboration with the Institute of General Genetics, as well as in another experiment on lymphocytes of patients with benign prostatic hyperplasia performed jointly with the Institute of Medical Genetics under the supervision and with the input of Professor Nikolay P. Bochkov, fully clarified the possibility of correcting mutagenesis during adhesion dysregulation in the target tissue, which in many ways reinforced our hypothesis scientifically.



Anatoly A. Vorobyov (1923-2006) Academician of the Russian Academy of Medical Sciences, immunologist, epidemiologist, microbiologist, Major General of the Medical Service

In 2023, we celebrated his 100th anniversary, dedicating scientific and popular science articles to him, as well as scientific reports at conferences. The scientific outlook of Professor Anatoly A. Vorobyov, the colossal scale of a talented scientist, doctor and teacher, as well as his philosophical views on science, were the support for novel ideas problem-solving tasks.

We will always remember these scientists who are extraordinary and bright personalities! They teach us to this day!



Gerald Maurice Edelman (1929-2014), American immunologist and neurophysiologist who shared the 1972 Nobel Prize in Physiology or Medicine work with Rodney Robert Porter for "discoveries concerning the chemical structure of antibodies"

Of course, he charmed me in absentia with his broad outlook and freedom of thought in publications on topobiology and the links between tissue adhesion molecules and immunity.