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ALTERATION OF TOTAL AND MITOCHONDRIAL ATPASE ACTIVITY IN THE BREAST AND LIVER IN BREAST CANCER-INDUCED RATS

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A preliminary evaluation of ATPase was performed in an experimental model of breast cancer. Total and mitochondrial ATPase activities were studied in the breast and liver of rats with DMBA-induced breast cancer. It has been shown that during the development of breast cancer in these tissues there is a significant increase in ATPase activity. At the same time, an increase in ATPase activity is seen in the liver of rats. In the case of treatment cancer rats with *Hypericum alpestre*, there are almost no changes in ATPase activity in rats' liver homogenate and mitochondria compared to untreated cancer animals. In the case of combined treatment with chemical inhibitors and *H. alpestre*, ATPase activity is significantly reduced with the use of L-NAME, the values obtained are lower even compared to healthy animals. However, with the use of nor-NOHA, a further increase in ATPase activity is observed. The obtained results will allow evaluation of the effectiveness of the therapeutic model by changing the energy balance, and selecting furthermore effective doses, to clarify the mechanisms of influence of these combination models.

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Introduction. In multicellular organisms, metabolic pathways are interconnected and subject to a single regulation. So any pathogenic condition, especially cancer development, leads to a chain change in the entire metabolic network (link). From this point of view, it is very important to have a comprehensive knowledge of the changes in metabolic processes during the development and treatment of any disease.

Cancer treatment is an ongoing struggle around the world, and research into its treatment and prevention is constantly evolving. From this point of view, any research aimed at clarifying the development of cancer and possible treatment mechanisms is very relevant.

Cancer cell metabolism alters and leads to glucose uptake and enhanced aerobic glycolysis. Such changes lead to increased production of ATP and lactic acid *n*

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the cytosol, even in the presence of oxygen and fully functioning mitochondria (link). Similar changes also occur in proliferating or developing cells [1].

One main reason for cancer development is that the immune system loses its ability to effectively eradicate aberrant cells. Tumor cells must generate sufficient ATP and biosynthetic precursors to maintain cell proliferation requirements. O. Warburg showed that tumor cells uptake high amounts of glucose producing large volumes of lactate even in the presence of oxygen, this process is known as "The Warburg effect or aerobic glycolysis". As a consequence of such amounts of lactate, there is acidification of the extracellular pH in the tumor microenvironment, ranging between 6.0 and 6.5 [2]. High levels of lactate harm the tumor-infiltrating immune cells. Clinical evidence indicates that lactate restricts immune cell infiltration in renal cell carcinoma (RCC) and damages the metabolism and cytolytic functions of T cells in the TME [3]. Thus, lactate and ATP should be thought of as important oncometabolite in the metabolic reprogramming of cancer.

Enhanced glycolysis compensates for insufficient production of mitochondrial ATP [4]. It can lead to the production of a sufficient amount of ATP and maintain the bioenergetic homeostasis of a rapidly growing cancer cell. Thus, the ATP reserve in the cancer cell replenishes. ATP can be hydrolyzed at a higher intensity, increasing ATPase activity. As a result, the energy released will meet the energy requirements of fast-growing cells.

Although there is no evidence for the role of ATP *in vivo* hydrolysis in the development of cancer for an osteosarcoma cell model, in which anoxia-like conditions were created, clones in which IF1 is dormant have been shown to hydrolyze ATP. Measurements of glucose consumption and lactic acid production in these cells, as well as in liver carcinoma cells, have shown that high levels of glycolytic metabolism are seen in both cases under hypoxia. ANT2 (the second isoform of adenine nucleotide translocase) is thought to facilitate the uptake of glycolytic ATP by mitochondria and its subsequent hydrolysis by the F1 component of ATP synthase. This suggests that ATP hydrolysis plays an important role in tumor cell proliferation, or that other studies suggest that ATP synthesis plays a crucial role in tumor growth. The literature data suggest that in the case of breast cancer, there is an increase in ATPase activity both in the cytoplasm and in intracellular structures, such as vacuoles and mitochondria. Thus, in the case of breast cancer, an increase in the activity of NKP (the ion transporter sodium/potassium (Na^+/K^+)-ATPase pump) was registered [5]. In breast cancer cells, the significantly increased ATPase activity was registered [6]. It has been shown that the V-ATPase is located at the cell surface in highly metastatic breast cancer cells and its activity at the plasma membrane is significantly greater in highly metastatic cells [7]. Thus, it has been shown that in breast cancer cells the activity of different ATPases is significantly increased. So, it is very relevant to clarify the issue of energy exchange in cancer cells and study the patterns of ATP synthesis and hydrolysis *n* case of breast cancer and after treatment cancer rats with *Hypericum alpestre*.

Breast cancer is widespread and has a high mortality rate in women in developed countries [8]. Because modern medicine does not have an effective treatment for breast cancer, it is necessary to find synthetic and natural potent factors or their combinations that will effectively fight malignant neoplasms, and any

research in this area is of great interest. The flora of Armenia is very diverse, but it has not been sufficiently studied in terms of the discovery of new biologically active extracts and compounds that may have promising anti-cancer therapeutic value. The combined effect of plant extracts and synthetic analogs of amino acids targeting arginase and the NOS family may be of great interest. The obtained data may reveal the combined anti-tumor therapeutic potential of Armenian herbal extracts, and their anti-tumor therapeutic potential joint with some synthetic amino acids in a model of breast cancer.

Our study aimed to investigate the total and mitochondrial ATPase activity in healthy and DMBA-induced breast cancer rat breast and liver during the development of the disease, as well as during the combined treatment with herb *H. alpestre* and chemical inhibitors. Nor-NOHA (Nω-hydroxy-nor-L-arginine, arginase inhibitor, tumor growth dose-dependent inhibitor [9]) and L-NAME (NG-nitro-L-arginine methyl ester, nitric oxide Ca^{2+} dependent non-selective inhibitor [10]) were used as chemical inhibitors.

Materials and Methods.

Animals and Tumor Induction. The object of the study was 8-week-old female 90–120 *g* wistar rats. By using the protocol, laboratory rats were randomized into 5 different groups (eight rats in each group) (Tab. 1).

Table 1

Experimental design and treatment
(the effect of inhibitors on healthy rats is presented in our previous work)

Groups	Experimental design	Number of rats in each group	25 *mg*/*mL* oil per rat, 7,12-DMBA	Treatment by *H. alpestre* 2.4 *mg*/*kg*/day in 0.25 *mL* saline	Treatment by nor-NOHA (3 *mg*/*kg*/day) and L-NAME (30 *mg*/*kg*/day) in 0.25 *mL* saline
1	Control	8	–	–	–
2	DMBA (Breast cancer)	10	on the 60th day, a single dose	–	–
3	Normal control + Saline	8	-	–	–
4	DMBA + *H. alpestre*	8	on the 60th day, a single dose	administered for 8 weeks (after tumors development in the 8th week, every 4th day)	–
5	DMBA + nor-NOHA + + *H. alpestre*	8	on the 60th day, a single dose	administered for 8 weeks (after tumors development in the 8th week, every 4th day)	
6	DMBA + L-NAME+ + *H. alpestre*	8	on the 60th day, a single dose	administered for 8 weeks (after tumors development in the 8th week, every 4th day)	

Mammary gland tumors were induced by a single dose of 25 *mg* of DMBA diluted in soy oil (1 *mL*) given injected subcutaneously, 2nd and 3rd pair of breasts. All rats in cancer groups received the chemical carcinogen at the age of 60–65 days. Each group was housed in a cage (3500 cm^2) and a well-ventilated room at 25°C. Animals have been left for one week for acclimatization. Rats were kept at constant environmental and nutritional conditions with room humidity (50–55%) at 12 *h* light/12 *h* dark cycle and were fed a standard pellet diet and with water ad libitum (Faculty of Biology, YSU). All surgical and experimental procedures were approved by the National Center of Bioethics (Armenia) and were by procedures outlined in the "guide for care and use of laboratory animals" (80–23). The possible effective anticancer concentration and treatment model (duration and frequency) of plant extract was chosen based on literature data. Experiments were concluded 200 days after DMBA administration. At the end of the 200 days (at the 28th week, after 7, 12 DMBA administration), rats in all groups were killed under anesthesia.

Tumour Inhibition Study. The experimental design and treatment scheme has shown in Tab. 1. The concentrations of plant extract were chosen based on literature data. The experimental rats were regularly monitored for food and water consumption, the apparent signs of toxicity, weight loss, or mortality and the number and size of the tumor. All the animals were sacrificed after 190 days (28 weeks after administration by DMBA). The organs were separated and stored in a freezer (–84°C).

Treatment of Cancer Rats. Treatment of breast cancer rats with *H. alpestre*, as well as with chemical inhibitors (nor-NOHA and L-NAME) was performed by injecting herbal extracts 2.4 *mg*/*kg*/day into experimental animals intra-abdominally, after 5 weeks of DMBA injection, when the first tumor has hatched. The injection was given over the next 8 weeks, every 4 days (12 injections) according to The Laboratory Rat [11].

The Extraction of H. alpestre. The dry matter of *H. alpestre* was extracted by crushing using methanol (98%) in a solvent volume/plant mass ratio of 10 : 1. The working solution of the plant extract was prepared by dissolving the dry extract in pure dimethyl sulfoxide (DMSO) [12].

Homogenate Obtaining from Rat Liver and Breast Tumour. Homogenates of breast tumors and livers of rats were obtained by homogenizer HG-15A ("DAIHAN Scientific Co. Ltd.", Korea) in 0.05 *M* Tris-HCl buffer (pH 8.5).

Determining the Protein Amount. The amount of protein was determined by the Lowry method [13].

Isolation of Mitochondrial Fraction. The mitochondrial fraction from tissue homogenate was isolated by differential centrifugation [14] at 0.25 *M* sucrose at 0°C. The resulting precipitate is the mitochondrial fraction. It was homogenized with a glass homogenizer in a 0.05 *mol* Tris-HCl (pH 8.5) buffer to break down the mitochondrial membranes.

Determination of Atpase Activity. The ATPase activity was determined by the amount of inorganic phosphorus released [15]. The specific ATPase activity was determined according to the amount of protein.

Data Processing and Reagents. Each experiment was repeated at least three times. Statistical data processing was performed by Statistica 10.0 (StatSoft) software. Standard errors were shown in Tab. Standard errors were calculated using

the corresponding function of Microsoft Excel 2013. Changes were evaluated by calculation of Student's validity criteria (p); differences between experimental data of different series (healthy and cancer rats) were valid if $p<0.05$.

The reagents of analytical grade were used in the study.

Results and Discussion. In the first phase of the study, we determined the ATPase activity in the breast of cancer rats. The results were compared with data for breast cancer rats treated with *H. alpestre*. Under influence of herbs, in the body of cancer rats, regenerative processes take place during the treatment, and their histological features are closer to those of healthy animals.

The results on ATPase activity related to breast homogenate and its mitochondria are presented in Tab. 2. The data show that the total ATPase activity in the breast homogenate of cancer rats is more than 3 times higher than in treated animals ($p<0.05$). In the case of DCCD-sensitive ATPase activity, the data obtained for cancer rats is 1.5 times higher than the value obtained for treated rats ($p<0.05$). Such a pattern is observed also in the mitochondria of rats with breast cancer: cancer rats treated with the *H. alpestre* show a decrease in total mitochondrial and DCCD-sensitive ATPase activity compared with animals with breast cancer ($p<0.05$).

Table 2

The ATPase activity in the breast of rats with cancer and treated with H. alpestre (mcg P/mg protein, n=3, p<0.05)

?	Homogenate		Mitochondria	
	Total ATPase activity	DCCD-sensitive ATPase activity	Total ATPase activity	DCCD-sensitive ATPase activity
Cancer rats	8.26 ± 0.70	1.48 ± 0.10	650 ± 50	150 ± 15
Treated rats with *H. alpestre*	2.56 ± 0.20	0.94 ± 0.08	43.75 ± 4.10	24.7 ± 2.2

Alteration of ATPase Activity in the Liver of Rats with Breast Cancer. Data on ATPase activity in the liver homogenates and mitochondria of rats with breast cancer are presented in Tab. 3. According to the obtained data, the ATPase activity in the liver homogenate of rats with breast cancer is 20% higher than in the case of healthy animals, and the DCCD-sensitive ATPase activity is approximately 5% higher ($p<0.05$).

Mitochondrial ATPase activity in the liver of rats with breast cancer is 15% higher than in healthy animals ($p<0.05$), and the DCCD-sensitive ATPase activity is almost doubled.

In addition, DCCD-sensitive ATPase activity in liver homogenate of healthy rats was 70% lower than total ATPase activity in healthy rats, and in the case of breast cancer rats that difference is 74.14% ($p<0.05$).

In the liver homogenate and mitochondria of rats treated with *H. alpestre*, a further increase in ATPase activity was observed compared to breast cancer rats. In the liver homogenate of treated animals, ATPase activity increased by 2.5% compared to cancer rats ($p<0.05$), and in the case of DCCD-sensitive ATPase activity, the difference was 35% ($p<0.05$). In comparison with healthy animals, these differences are more pronounced: the total ATPase activity in liver homogenate of

cancer rats was higher by 21.6%, and the DCCD-sensitive ATPase activity – by 38.5% ($p<0.05$).

Table 3

The ATPase activity in the liver of rats with breast cancer (μg P/mg protein, n=3, p<0.05)

		Homogenate		Mitochondria	
		Total ATPase activity	DCCD-sensitive ATPase activity	Total ATPase activity	DCCD-sensitive ATPase activity
Healthy rats		3.51±0.21	1.07 ± 0.09	180.62 ± 15.03	87.83 ± 6.22
Rats with breast cancer		4.37 ± 0.32	1.13 ± 0.11	212.54 ± 20.04	173.41 ± 15.09
Treated rats	*H. alpestre*	4.48 ± 0.42	1.74 ± 0.12	242.51 ± 19.22	153.51 ± 12.52
	H. alpestre + L-NAME	2.57 ± 0.17	0.65 ± 0.05	116.04 ± 10.14	68.02 ± 5.81
	H.alpestre + +L-NOHA	10.76 ± 0.82	2.28±0.12	384.63 ± 35.21	88.76 ± 7.90

The total ATPase activity in the liver mitochondria of treated animals is approximately 12% higher than that of cancer animals. This pattern is not observed only for DCCD-sensitive ATPase activity of the mitochondria of treated animals; a decrease in the ATPase activity of 11.5% is observed in comparison with cancer rats. At the same time, the DCCD-sensitive ATPase activity of mitochondria of treated animals is increased by 43% in comparison with healthy rats ($p<0.05$). Thus, the values of ATPase activity in the liver homogenate and mitochondria of rats treated with *H. alpestre* are close to those obtained for animals with breast cancer.

Interesting data have been obtained in the case of combination therapy with the chemical inhibitors and *H. alpestre*. Recently, herbal products in anti-cancer therapy have increased significantly and simultaneously with conventional chemotherapeutic treatment. Natural products contain a multitude of constituents that can act on a variety of targets in the body to induce pharmacodynamic responses. Acting together these compounds may culminate in an additive or synergistic therapeutic effect. Herbal extracts or isolated compounds, in combination with chemotherapeutic drugs, could represent a novel and exciting anti-cancer therapeutic approach.

In combination treatment of *H. alpestre* with L-NAME, there is a sharp decrease in ATPase activity, and significantly lower ATPase activity is observed even in comparison with healthy animals. In contrast, in the case of combination therapy with *H. alpestre* + nor-NOHA, the ATPase activity in both the liver homogenate and the mitochondria of the treated rats increases sharply, significantly exceeding the values obtained for healthy animals as well as for breast cancer.

The development of cancer in the body is accompanied by the reconstruction of the functioning of all organ systems, first of all, by their disruption. In addition, the development of any type of cancer in the body can increase the risk of cancer in other organ systems. Therefore, it is important to clarify the biochemical status of other organ systems in the development of cancer. Anti-cancer chemotherapeutic drugs are currently used to treat cancer, which has a non-selective cytostatic effect and causes side effects in all tissue cells of the body. Among these tissues, liver cells

are the most affected. The liver is the largest gland in the body's digestive system and plays a very important role in metabolism regulation. Liver cells neutralize toxins that enter the liver through the bloodstream. In addition, the liver is considered a secondary target organ for the spread of breast cancer. Therefore, it is very important to assess the risk of developing various cancers of the liver during the treatment of cancer, as well as the ability to prevent those injuries.

During the development of cancer in the affected tissue of rats, i.e. in the breast, there is a significant change in the ATPase activity, due to changes in the energy requirements of cells. Thus, the level of ATPase activity is significantly higher in breast cancer cells than in the *H. alpestre*-treated rats. Moreover, this tendency is observed both in cell homogenates and in mitochondria. Such an increase in ATPase activity probably provides the cancer cells with the energy they need to grow and vital activity.

At the same time, ATP hydrolysis is a potential source of phosphate in the cell, which may be involved in regulating the activity of enzymes in various metabolic pathways such as protein kinases. In this way, the activity of some enzymes can be increased, other enzymes can be inhibited, thus the hydrolysis of ATP can alter the work of different metabolic pathways. Therefore, an increase in ATPase activity is a potential indicator of the development of cancer, which directly affects the metabolism and cell signaling pathways.

The significant differences in ATPase activity are seen in other tissues of the cancer animal, particularly in the liver, which is not yet affected. Changes in the liver tissue of rats with breast cancer are not overcome by treatment with *H. alpestre*, so ATPase activity is maintained at almost the same level as in cancer animals. Concomitant use of *H. alpestre* with chemical inhibitors for therapeutic use significantly reduces ATPase activity in the case of using L-NAME, which may be considered a possible approach to prevent liver disease during the development of breast cancer. As for *H. alpestre*, the data obtained suggest that *H. alpestre* alone in the dose used is not appropriate to prevent liver disease during the development of breast cancer. In contrast, in the case of combination therapy with *H. alpestre* + nor-NOHA, the ATPase activity in both the liver homogenate and the mitochondria of the treated rats increases sharply. In the case of both inhibitors, our preliminary studies have shown that there is a reduction in the number and sizes of cancers (results are not given). Thus, the data obtained from us show that the recovery process in the case of the use of different inhibitors is carried out by completely different mechanisms.

Conclusion. In conclusion we can say that a preliminary evaluation of ATPase was performed in an experimental model of breast cancer. The obtained results will allow evaluation of the effectiveness of the therapeutic model by changing the energy balance, and selecting furthermore effective doses, to clarify the mechanisms of influence of these combination models.

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ԿՐԾՔԱԳԵՂՁԻ ԵՎ ԼՅԱՐԴԻ ԸՆԴՀԱՆՈՒՐ ԵՎ ՄԻՏՈՔՈՆԴՐԻՈՒՄԱՅԻՆ ԱԵՖ-ԱԶԱՅԻՆ ԱԿՏԻՎՈՒԹՅԱՆ ՓՈՓՈԽՈՒԹՅՈՒՆԸ ԿՐԾՔԱԳԵՂՁԻ ՔԱՂՑԿԵՂՈՎ ՀԻՎԱՆԴ ԱՌՆԵՏՆԵՐԻ ՄՈՏ

Կատարվել է ԱԵՖ-ազի նախնական գնահատում կրծքագեղձի քաղցկեղի փորձարարական մոդելում: Ընդհանուր և միտոքոնդրիումային ԱԵՖ-ազային ակտիվությունն ուսումնասիրվել է ԴՄԲԱ-յով հարուցված կրծքագեղձի քաղցկեղով հիվանդ առնետների կրծքագեղձում և լյարդում: Ցույց է տրվել, որ այս հյուսվածքներում կրծքագեղձի քաղցկեղի զարգացման ընթացքում նկատվում է ԱԵՖ-ազային ակտիվության զգալի աճ: Միևնույն ժամանակ, ԱԵՖ-ազային ակտիվության աճ է նկատվում առնետների լյարդում: Քաղցկեղով հիվանդ առնետներին *Hypericum alpestre*-ով բուժելիս առնետների լյարդի հոմոգենատում և միտոքոնդրիումներում ԱԵՖ-ազային ակտիվության մեջ գրեթե փոփոխություններ չեն դիտվում՝ համեմատած քաղցկեղային կենդանիների հետ: Քիմիական ինհիբիտորներով and *H. alpestre*-ով համակցված բուժման ժամանակ ԱԵՖ-ազային ակտիվությունը զգալիորեն նվազում է L-NAME-ի կիրառման դեպքում, ընդ որում ստացված արժեքներն ավելի ցածր են անգամ առողջ կենդանիների համեմատ: nor-NOHA-յի կիրառման դեպքում նկատվում է ԱԱԵՖ-ազային ակտիվության հետագա աճ: Ստացված արդյունքները թույլ կտան գնահատել թերապևտիկ մոդելի արդյունավետությունը՝ փոխելով էներգետիկ հաշվեկշիռը և ընտրելով ավելի արդյունավետ չափաբաժիններ՝ պարզաբանելու այդ համակցված մոդելների ազդեցության մեխանիզմները:

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ИЗМЕНЕНИЕ ОБЩЕЙ И МИТОХОНДРИАЛЬНОЙ АТФАЗНОЙ АКТИВНОСТИ В МОЛОЧНОЙ ЖЕЛЕЗЕ И ПЕЧЕНИ КРЫС, БОЛЬНЫХ РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ

Предварительную оценку АТФазы проводили на экспериментальной модели рака молочной железы. Изучали общую и митохондриальную АТФазную активность в молочной железе и печени крыс с ДМБА-индуцированным раком молочной железы. Показано, что при развитии рака молочной железы в этих тканях происходит значительное повышение активности АТФазы. В то же время в печени крыс наблюдается повышение активности АТФазы. При лечении крыс, больных раком молочной железы, лекарственным растением *Hypericum alpestre* изменения активности АТФазы

в гомогенате печени и митохондриях крыс практически отсутствуют по сравнению с нелеченными больными животными. При комбинированном лечении химическими ингибиторами и *H. alpestre* активность АТФазы значительно снижается при использовании L-NAME – полученные значения ниже даже по сравнению со здоровыми животными. Однако при использовании nor-NOHA наблюдается дальнейшее повышение активности АТФазы. Полученные результаты позволяют оценить эффективность терапевтической модели по изменению энергетического баланса, а также подобрать эффективные дозы и уточнить механизмы воздействия этих комбинированных моделей.