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OXAMATE, AN INHIBITOR OF LACTATE DEHYDROGENASE, CAN STIMULATE M2 POLARIZATION OF PERITONEAL MACROPHAGES IN MICE WITH LEWIS LUNG CARCINOMA

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***Background*: Inhibition of aerobic glycolysis of cancer cells is considered a promising therapeutic strategy for the treatment of neoplasms. Some inhibitors of energy metabolism can affect not only tumor cells but also the functional polarization of tumor-associated macrophages, which may either enhance the antitumor effect of such agents or impair their antitumor efficacy. *Aim*: To investigate the effect of oxamate, a lactate dehydrogenase (LDH) inhibitor, on the polarization of peritoneal macrophages (PMP) in both intact mice and mice with transplanted Lewis lung carcinoma (LLC). *Materials and Methods*: The low-metastatic LLC variant, LLC/R9, was transplanted to female C57Bl/6 mice. Sodium oxamate was used as the test agent at concentrations of 0.02, 0.2, and 2 mg/ml. Macrophage polarization in tumor-bearing mice was estimated on day 23 after tumor transplantation by assessing nitric oxide (NO) production and arginase activity as functional indices of PMPs polarization. *Results*: Oxamate can affect the functional polarization of PMPs in both intact mice and animals with transplanted LLC/R9. Oxamate in all studied concentrations changed the markers of PMPs polarization in intact mice (decreasing NO levels and activating arginase activity) that indicated the stimulation of M2 polarization. In tumor-bearing animals, stimulation of M2 polarization is observed at low concentrations of oxamate (0.02 mg/ml), but its high concentrations (2.0 mg/ml) causes M1 polarization, which is characterized by three-fold increase in the level of NO and a decrease in the level of arginase activity. *Conclusion:* Oxamate, an inhibitor of LDH, can stimulate M2 polarization of peritoneal macrophages of mice bearing LLC in a dose-dependent manner.**

***Key Words*: inhibitor of lactate dehydrogenase, oxamate, macrophages, M2-polarization, Lewis lung carcinoma.**

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Almost all invasive tumors, regardless of their origin, are characterized by a specific modification of energy metabolism, which is manifested in the dominance of aerobic glycolysis over oxidative phosphorylation (Warburg effect) [1]. This metabolic shift provides benefits in the survival of tumor cells because they can produce energy and maintain high levels of anabolic processes in the cell, even in the case of short-term or prolonged hypoxia. Moreover, aerobic glycolysis can guarantee a high rate of synthesis of glycolysis intermediates, which are required as a building material for actively proliferating cells.

This specificity of the energy metabolism of tumor cells represents a variety of ideal targets for therapeutic intervention aimed at the destruction of tumor cells without significant manifestations of systemic toxicity. This approach began to be developed about 10 years ago, and bioactive molecules that can inhibit aerobic glycolysis are now being combined into a new class of potential antitumor agents or drugs — the class of energy metabolism inhibitors.

A key trigger for aerobic glycolysis is pyruvate, competition for which between glycolysis and oxidative phosphorylation allows tumor cells to activate either energy or plastic processes. The switches in this trigger are lactate dehydrogenase (LDH) and pyruvate dehydrogenase (PDH).

LDH is considered the most promising therapeutic target for antitumor therapy [2], as its inhibition can almost completely block glycolysis, providing a powerful cytostatic effect, and a cytotoxic effect in hypoxia setting [3–5]

However, malignant tumors consist not only of heterogeneous populations of tumor cells but also of the vascular system, numerous residents and incorporated normal cells of the body (immune cells, fibroblasts), components of the extracellular matrix, which together form a microenvironment of tumor cells that can significantly affect tumor development.

Most immunocompetent cells in almost all solid malignancies are tumor-associated macrophages (TAMs) [6, 7]. Numerous experimental and clinical studies have shown that TAMs exhibit protumoral effects, promoting survival, proliferation, migration, and metastasis of tumor cells, stimulating tumor angiogenesis [8, 9]. These studies have shown a correlation between poor survival of cancer patients and high TAM density (which can be as high as 50% of tumor weight).

Macrophages are known to be a heterogeneous population of immune cells that perform different functions in homeostatic and immune responses. The high plasticity and adaptability of these cells complicate the classification of their phenotype, but in most cases, there is pro-inflammatory (M1) and anti-inflammatory (M2) polarization [10, 11]. This functional dichotomy of macrophages is also manifested at the metabolic level. In particular, the glycolytic pathway of energy metabolism

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Abbreviations used: LDH – lactate dehydrogenase; LLC – Lewis lung carcinoma; LLC/R9 – low-metastatic variant of Lewis lung carcinoma; NO – nitric oxide; PMP – peritoneal macrophage; PDH – pyruvate dehydrogenase; TAMs – tumor-associated macrophages.

dominates in M1 polarized macrophages, while M2 macrophages mainly use oxidative phosphorylation [12–14].

Based on this metabolic plasticity of macrophages, it can be assumed that inhibitors of energy metabolism can affect not only tumor cells but also the functional polarization of TAMs, which may either enhance the antitumor effect of such agents or impair their antitumor efficacy. Therefore, the study of inhibitors of energy metabolism of tumor cells as antitumor agents should include analysis of their effect on the metabolic and, as a consequence, functional polarization of macrophages. Despite the well-known close relationship between the metabolic and functional dichotomy of macrophages, there have been few publications regarding the effect of inhibitors of tumor energy metabolism on macrophage polarization [15, 16].

We aimed to study the effect of an LDH inhibitor on the polarization of peritoneal macrophages (PMP) in both intact mice and mice with transplanted Lewis lung carcinoma (LLC).

MATERIALS AND METHODS

Experimental animals and experimental tumors. Two-month-old female C57Bl/6 mice, weighing 20–22 g, bred in the vivarium of the R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the NASU were used in the study. All animal studies were performed in accordance with the requirements of the Regional Committee for the Ethics of Work with Experimental Animals and in compliance with the rules of work with laboratory animals.

A low-metastatic LLC variant, LLC/R9, obtained from the original LLC strain via 9 consecutive cisplatin courses *in vivo* was used as a tumor model.

For transplantation to experimental animals, LLC/R9 cells were cultured *in vitro* under standard conditions in RPMI-1640 medium (Sigma, USA) with the addition of 10% fetal calf serum (Biowest, USA) and 40 μg/ml gentamicin at 37 °C in humidified conditions, 5% CO_2. Transplantation of tumor cells was routinely performed by intramuscular inoculation of $1 \cdot 10^6$ cells in 0.1 ml of Hanks' solution.

Determination of primary tumor volume, number, and volume of metastatic lesions in mice was performed on day 23 of tumor growth after euthanasia of under light ether anesthesia.

The volume of the primary tumor was calculated by the formula:

$$V = 0.52 \cdot d^3$$

where d is the diameter of the tumor, which was measured using a caliper.

The number of metastases in the lungs and their diameter was assessed by conventional methods using a binocular magnifying glass and a millimeter ruler.

The volume of lung metastases was calculated by the formula:

$$V = \Sigma \left(n_i \cdot \frac{3.14 \cdot d_i^3}{6}\right); \; d_i = 0.5; \; 1.0; \; 1.5; \ldots;$$

where n_i **is** the number of metastases with diameter d_i.

Peritoneal macrophages. PMPs were obtained from peritoneal lavage from at least 4 mice. 3 ml of cold saline with heparin (final concentration 5–10 U/ml) were injected into the abdominal cavity of euthanized animals, after which the cell suspension was removed with a sterile Pasteur pipette under sterile conditions and the abdominal cavity was washed three more times with equal volumes of cold saline (the total volume of the obtained cell suspension was 10 ml). The resulting cell suspension was washed from heparin by centrifugation (10 min at 1500 rpm), and precipitated cells were resuspended in a cold complete culture medium. The concentration of cells was adjusted to $1 \cdot 10^6$/ml. To obtain an adherent fraction of peritoneal cells, 200 μl of cell suspension was placed into a 96-well culture plate and incubated for 1 h at 37 °C in 5% CO_2. After incubation, the non-adherent cells were removed by washing the wells 3 times with warm saline. The obtained adherent fraction of peritoneal lavage contained mainly cells with morphological features of macrophages.

Test agent. A competitive inhibitor of LDH, sodium oxamate (Sigma, USA) was used as the test agent. The test preparation was dissolved in RPMI-1640 medium (Sigma, USA) and added to PMPs obtained as described above at concentrations of 0.02, 0.2, and 2 mg/ml. Following 1.5 h, incubation at 37 °C, the plate was washed three times with warm saline, 200 μl of culture medium was added and incubation continued for 24 h at 37 °C.

Nitric oxide (NO) production. PMPs were exposed to the test agent for 24 h, and NO production was determined by the content of NO_2^- by the Griess reaction [17]. In brief, Griess reagent was added to 100 μl of the culture medium, the mixture was incubated for 10 min at room temperature. The results were recorded spectrophotometrically on a MicroELISA plate reader (StatFax 2100, USA) at a wavelength of 545 nm. The NO level was determined from a calibration $NaNO_2$ curve. Each variant of the experiment was assessed at least triply. The NO level was presented in mmol NO_2.

Arginase activity was measured in cell lysates by the rate of urea formation, as described [18, 19]. The cell lysate was obtained by a two-cycle freeze/thaw. Then 100 μl of lysate were mixed with 100 μl of 25 mm Tris-HCl and 10 μl of 10 mmol $MnCl_2$, the enzyme was activated by heating for 10 min at 56 °C. The resulting mixture was mixed with 100 μl of L-arginine (0.5 mol, pH 9.7; Sigma-Aldrich, USA), the hydrolysis of which was performed at 37 °C for 60 min. The reaction was stopped by adding 800 μl of a mixture $H_2SO_4/H_3PO_4/H_2O$ (1:3:7). Colorimetric determination of urea was performed by adding 9% α-isonitrosopropiophenone dissolved in 96° alcohol (Sigma-Aldrich, USA) followed by incubation at 95 °C for 30 min and then at 4 °C for 30 min. The urea concentration was determined spectrophotometrically at $\lambda = 545$ nm. Optical density values were converted to micrograms using a standard curve constructed from urea solutions of known concentration.

Arginase activity was presented in equivalent units of urea concentration.

Statistical analysis was conducted using descriptive statistics, parametric Student's *t*-test, and nonparametric Mann — Whitney test using MS Excel and Microcal Origin (v. 8.5).

RESULTS AND DISCUSSION

The biological characteristics of the LLC/R9 variant obtained via an experimental progression of LLC towards the formation of resistance to cisplatin *in vivo* are well described in [20, 21]. LLC/R9 variant had 3–4-fold lower metastatic potential, and a significantly higher growth rate of the primary tumor *in vivo* compared to LLC due to its high angiogenic potential, in particular, significantly higher level of VEGF secretion by LLC/R9 cells and their ability to stimulate endothelial cell proliferation *in vitro* [22].

Our choice of LLC/R9 as an experimental model to study the functional polarization of PMPs is determined by the fact that LLC/R9 cells are characterized by high production of humoral factors, which cause significant pressure on all systems and normal tissues (including macrophage system), changing their functional and metabolic properties. Thus, we have shown that the growth of LLC/R9 in mice leads to the formation of the paraneoplastic syndrome in the early stages of tumor development [23].

At the time of isolation of PMPs (23rd day of tumor growth) in LLC/R9-bearing mice, the volume of the primary tumor was 764.2 ± 75.1 mm^3, and the number and volume of lung metastases were 7.0 ± 1.3 and 5.2 ± 1.1 mm^3, respectively.

We have analyzed whether oxamate can affect the functional polarization of PMPs in intact mice and animals with transplanted LLC/R9. Table 1 presents the data on the effect of oxamate on the level of NO production and arginase activity of PMPs of intact animals. Incubation of PMPs with oxamate at concentrations of 0.02 mg/ml and 0.2 mg/ml caused a statistically significant reduction in NO levels by more than 78% ($p < 0.02$), while at a concentration of 2.0 mg/ml there is a pronounced tendency to an increase of NO level, but it remains lower by 44.5% ($p < 0.02$) compared to the corresponding control value.

The effect of oxamate on arginase activity is the opposite. An extremely low level of arginase activity of PMPs in the absence of oxamate is replaced by significant multiple increases in the activity ($p < 0.001$) when oxamate is added to the incubation medium at all concentrations studied. Comparison of arginase activity and NO levels in the absence of oxamate indicates the predominance of M1 polarized PMPs. Oxamate in all studied concentrations decreased NO levels and activated arginase activity that indicates the stimulation of M2 polarization.

The effect of oxamate on the arginase activity of PMPs in mice with LLC/R9 (Table 2) was non-monotonic. The maximum arginase activity was recorded at an oxamate concentration of 0.02 mg/ml, exceeding control value by 235% ($p < 0.002$) and demonstrating the growth 343% ($p < 0.0001$) and 169% ($p < 0.01$) in comparison to arginase activity at oxamate concentrations of 0.2 mg/ml and 2.0 mg/ml respectively.

Table 1. The effect of oxamate on NO production and arginase activity of PMPs of intact mice

Oxamate concentrations, mg/ml	NO, mmol NO_2^-	Arginase activity in urine equivalent (μg/ml)
0 (control)	14.6 ± 2.2	1.7 ± 1.4
0.02	3.1 ± 1.0*	52.0 ± 5.1*
0.2	2.7 ± 0.7*	37.3 ± 11.5*
2.0	8.1 ± 2.1*	33.3 ± 9.6*

Note: *significant difference compared to the corresponding control values

Table 2. The effect of oxamate on NO production and arginase activity of PMPs of mice with LLC/R9

Oxamate concentration, mg/ml	NO, mmol NO_2^-	Arginase activity in urine equivalent (μg/ml)
0 (control)	31.1 ± 8.0	98.4 ± 35.4
0.02	30.4 ± 10.5	329.2 ± 25.7*
0.2	37.1 ± 8.6	74.6 ± 9.2
2.0	103.6 ± 25.6*	122.5 ± 47.6

Note: *significant difference compared to the corresponding indices of all other groups

Thus, it is shown that in animals with tumors oxamate can stimulate M2 polarization of PMPs. However, in contrast to the effect of oxamate on the PMPs of intact mice, in the case of tumor-bearing animals, stimulation of M2 polarization is observed at low concentrations of this agent (namely 0.02 mg/ml). High oxamate concentration (2.0 mg/ml) causes M1 polarization, which is manifested in a three-fold increase in the level of NO and a decrease in the level of arginase activity.

The concentration-dependent effect of oxamate on the functional polarization of PMPs in animals with tumors can largely determine its dose-dependent antitumor activity in *in vivo* studies. At low doses of oxamate, the cytotoxic/cytostatic effect of oxamate on tumor cells can be neutralized by induction of M2 polarization of TAMs and, as a consequence, stimulation of tumor angiogenesis and growth of at least the primary tumor. At high doses, we can expect an increase in the direct cytotoxic effect of oxamate on tumor cells due to the activation of M1 polarization of TAMs.

This conclusion is confirmed by the results of some studies of the antitumor activity of oxamate in *in vivo* experiments. In the *in vivo* experiments [24] the antitumor efficacy of oxamate against nasopharyngeal carcinoma in an extremely high total dose (16 g/kg body weight of mice) has been shown. At significantly lower total doses, oxamate either did not affect the growth of the primary tumor or caused some tendency to its stimulation [25, 26].

Thus, research indicates that the development of new anticancer drugs based on modifiers/inhibitors of energy metabolism requires a detailed study of the nature of their effects (at least) on the macrophage system, which can largely determine the range of their effective therapeutic doses.

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ОКСАМАТ, ІНГІБІТОР ЛАКТАТДЕГІДРОГЕНАЗИ, МОЖЕ СТИМУЛЮВАТИ М2-ПОЛЯРИЗАЦІЮ ПЕРИТОНЕАЛЬНИХ МАКРОФАГІВ МИШЕЙ З КАРЦИНОМОЮ ЛЕГЕНІ ЛЬЮЇС

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Стан питання: Інгібування аеробного гліколізу пухлинних клітин розглядають як перспективну терапевтичну стратегію в лікуванні раку. Деякі інгібітори енергетичного обміну можуть впливати не тільки на пухлинні клітини, але й на функціональну поляризацію асоційованих з пухлиною макрофагів, що може як посилювати, так і послаблювати протипухлинний ефект таких агентів. ***Мета***: Дослідити вплив інгібітора лактатдегідрогенази (ЛДГ) оксамату на поляризацію перитонеальних макрофагів у інтактних мишей та у мишей з перещепленою карциномою легені Льюїс. ***Матеріали та методи***: Самкам мишей C57Bl/6 перещеплювали варіант карциноми легені Льюїс із зниженою метастатичною активністю — LLC/R9. Оксамат натрію, як тестуючий агент, випробовували в концентраціях 0,02, 0,2 та 2 мг/мл. Поляризацію макрофагів інтактних мишей та мишей з пухлиною (на 23-тю добу після перещеплення) оцінювали за функціональними індексами поляризації: за продукцією оксиду азоту та за аргіназною активністю. ***Результати***: Оксамат може впливати на функціональну поляризацію перитонеальних макрофагів як у інтактних мишей, так і у мишей з перещепленою LLC/R9. В усіх досліджених концентраціях оксамат змінював маркери поляризації макрофагів у інтактних мишей, що вказувало на стимулювання М2-поляризації. У мишей з пухлиною стимулювання М2-поляризації відзначали за низьких концентрацій оксамату (0,02 мг/мл), тоді як високі концентрації (2 мг/мл) спричинювали М1-поляризацію, яка характеризувалася трьохкратним збільшенням рівня NO та підвищенням рівня аргіназної активності. ***Висновки***: Інгібітор ЛДГ оксамат може дозозалежно стимулювати М2-поляризацію макрофагів у мишей перещепленою карциномою легені Льюїс.

Ключові слова: інгібітор лактатдегідрогенази, оксамат, макрофаги, М2-поляризація, карцинома легені Льюїс.