Biol. Stud. 2024; 18(3): 37–46 • doi: https://doi.org/10.30970/sbi.1803.787
www.http://publications.lnu.edu.ua/journals/index.php/biology

UDC: 577.35 + 576.38 + 547.789.1 + 615.277.3

CHANGES IN BIOENERGETIC CHARACTERISTICS OF THE MURINE LYMPHOMA CELLS UNDER THE ACTION OF A THIAZOLE DERIVATIVE IN COMPLEX WITH POLYMERIC NANOPARTICLES

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Shalai, Ya., Ilkiv, M., Salamovska, A., Mazur, H., Manko, B., Ostapiuk, Yu., Mitina, N., Zaichenko, O., & Babsky, A. (2024). Changes in bioenergetic characteristics of the murine lymphoma cells under the action of a thiazole derivative in complex with polymeric nanoparticles. *Studia Biologica*, 18(3), 37–46. doi:10.30970/sbi.1803.787

Background. Mitochondria can influence cancer cells both indirectly via reactive oxygen species mediation and directly through mitochondrial biogenesis. Energy production in mitochondria is crucial as it facilitates the synthesis of essential molecules needed for cellular biosynthesis, growth, and proliferation. The development of new anticancer drugs that target the energy metabolism of tumor cells shows promise in cancer treatment. Our study aimed to investigate how the thiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1), the polymeric nanoparticles based on the polyethylene glycol (PEG-PN, Th5), and their complex with BF1 (Th6) affect respiration and mitochondrial membrane potential in murine NK/Ly tumor cells.

Materials and Methods. The study was performed on white wild-type male mice with grafted NK/Ly lymphoma. The test substances were added to the cell suspension at a final concentration of 10 μM and incubated for 15 min at 37 °C. Oxygen uptake rates in NK/Ly cells were measured using a polarographic method with Clark electrode. Changes in mitochondrial membrane potential were assessed using the tetramethylrhodamine methyl ester fluorescence dye. The fluorescence intensity was evaluated using the ImageJ computer program.

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Results. After incubating NK/Ly cells with BF1 (10 μM), Th5, or the BF1 + PEG-PN complex (Th6) for 15 min, no changes were observed in glucose-fueled basal respiration. However, the Th6 complex significantly activated FCCP-stimulated respiratory processes in NK/Ly lymphoma cells. Fluorescent microscopy data indicated that BF1 or Th5 alone did not affect mitochondrial membrane potential values. However, the Th6 complex significantly decreased mitochondrial membrane potential, suggesting a reduction in NK/Ly cell viability.

Conclusions The investigated complex of thiazole derivative BF1 with PEG-based polymeric nanoparticles may realize its cytotoxic effect by depolarization of mitochondrial membrane in NK/Ly lymphoma cells.

Keywords: thiazole derivative, polymeric nanocarrier, cell respiration, mitochondrial membrane potential, lymphoma

INTRODUCTION

Cancer remains a leading cause of mortality worldwide, with millions of new cases diagnosed each year. Based on data published by the International Agency for Research on Cancer (IARC) there were an estimated 20 mln new cancer cases and 9.7 mln deaths in 2022 (Bray *et al.*, 2024). The relentless proliferation of tumor cells requires substantial alterations in their metabolic pathways to meet the high energy demands and biosynthetic needs for rapid growth and survival. One of the critical adaptations observed in cancer cells is the shift from oxidative phosphorylation to glycolysis for energy production, even in the presence of ample oxygen. This phenomenon is known as the Warburg effect (Chen *et al.*, 2016). This metabolic reprogramming supports the anabolic requirements of rapidly dividing cells and confers resistance to many conventional chemotherapeutic agents (Cunha *et al*., 2023).

Despite the reliance on glycolysis, mitochondrial function remains pivotal in cancer cell survival and proliferation. Mitochondria are not only the cell's powerhouses, that provide ATP through oxidative phosphorylation, or play a substantial role in shaping Ca^{2+} signals in many cell types, but also key regulators of apoptotic pathways and sources of reactive oxygen species (ROS). Elevated ROS levels can induce oxidative damage, promoting genetic instability and tumor progression; however, excessive ROS can also lead to cell death, presenting a potential therapeutic target (Liu & Shi, 2020). Anticancer drugs often exploit this vulnerability by inducing mitochondrial dysfunction and increasing ROS production, thereby overwhelming the antioxidant defenses of cancer cells and triggering apoptosis (Kapur *et al.*, 2022). Changes in mitochondrial membrane potential are a hallmark of mitochondrial dysfunction, and depolarization of the mitochondrial membrane can lead to the release of pro-apoptotic factors, culminating in cell death (Środa-Pomianek *et al.*, 2018).

Given the centrality of mitochondrial dynamics in cancer biology, studying the effects of anticancer agents on cellular respiration, mitochondrial potential, and ROS generation is crucial for the development of effective therapies. Thiazole derivatives, in particular, have shown significant promise as antiproliferative agents. The 2-aminothiazole fragment is a notable pharmacophore in drug discovery, with various derivatives demonstrating efficacy against multiple cancer targets (Wan *et al.*, 2021).

Previous research has highlighted the potential of thiazole derivatives in modulating redox balance and inducing apoptosis in cancer cells. For instance, the synthesized

2-aminothiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) was found to be cytotoxic to several tumor cell lines; it significantly increased the level of ROS in murine lymphoma cells by affecting their redox state without significantly altering mitochondrial membrane potential or oxidative phosphorylation (Hreniukh *et al.*, 2020). However, the poor solubility of such compounds often limits their therapeutic application, necessitating the development of more soluble formulations, such as complexes with polyethylene glycol-containing polymer nanoparticles (PEG-PN), to enhance their bioavailability and efficacy (Torchilin, 2014).

This study aimed to investigate the effects of BF1 and its complexes with PEG-containing polymer carriers on cellular respiration and mitochondrial membrane potential in murine NK/Ly tumor cells. We hope to advance the development of next-generation anticancer therapies that leverage mitochondrial dynamics and oxidative stress.

MATERIALS AND METHODS

The study was performed on white wild-type male mice (20–30 g) with grafted NK/Ly lymphoma. Animals were kept in standard vivarium conditions at constant temperature on mixed ration. Manipulations with animals were carried out in accordance with the General Ethical Principles of Experimentation on Animals approved by the First National Congress on Bioethics (Kyiv, Ukraine, 2001) and European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, France, 1985) as well as approved by the Ethics Committee of Ivan Franko National University of Lviv, Ukraine at the beginning of the research (Protocol No 17-02-2023 of 09.02.2023) and after the completion of the study (Protocol No 17-04-2024 of 01.04.2024).

Ascite lymphoma cells were passaged by intraperitoneal inoculation of $10–15 \cdot 10^6$ cells to mice. Ascites were drained from the abdominal cavity of anesthetized mice with a sterile syringe 7–10 days after the inoculation.

Determination of the mitochondrial membrane potential $\Delta\psi$ of NK/Ly lymphoma cells under the action of the studied compounds were recorded by fluorescence microscopy. The method is based on recording differences in cell fluorescence after treatment with a specific dye (Ilkiv *et al.*, 2023). An Olympus IX73 inverted microscope and a DP-74 digital camera were used to capture fluorescent images. We used the fluorescent dye tetramethylrhodamine methyl ester (TMRM) to record the relative values of mitochondrial membrane potential under the following technical characteristics: the wavelength of the excitation filter 540–585 nm, the beam splitter 595 nm, and the barrier filter 600 nm.

The medium for cell incubation contained the following composition (in mM): NaCl – 140.0; KCl – 4.7; $CaCl_2$ – 1.3; $MgCl_2$ – 1.0; HEPES – 10.0; glucose – 10; pH 7.4 (solution 1). Lymphoma ascites were washed and then diluted by a factor of 10. The test substances were added to the cell suspension at a final concentration of 10 µM. Dilution agent dimethylsulfoxide (DMSO) was added to a separate sample at a final concentration of 5%. Cells with the studied compounds were incubated for 15 min at 37 °C. After incubation, the cells were rewashed, and TMRM was added at a final concentration of 100 nM and incubated again for 15 min (37 °C). A few microliters of the cell suspension were taken from each sample using a pipette and placed on a glass slide. The drop was covered with a cover slip and placed under a microscope (microscope objective ×12.6). In the field of view, we selected 4–5 different variants of cell images, first in visible light and then switched to the fluorescent light spectrum. The fluorescence intensity, which reflected changes in the mitochondrial membrane potential $\Delta\psi$ was recorded and evaluated using the ImageJ computer program.

The respiration rate of lymphoma cells was recorded using the polarographic method and a 6-cell respirometer RC650 (Strathkelvin Instruments, Scotland). This method is based on recording oxygen uptake using a Clark electrode in a 1.5 mL glass chamber at 37 °C (Horbay *et al.*, 2011). A suspension of lymphoma cells ($2 \cdot 10^6$ intact cells/mL) was washed once from the ascitic fluid with extracellular saline (solution 1). The lymphoma cells were treated with the studied compounds at a concentration of 10 µM and incubated for 15 min. In the control group, an equivalent volume of extracellular saline was added.

After incubation, glucose was added to the cells, and oxygen consumption rate was measured. Next, the respiration rate was stimulated by adding the protonophore carbonyl cyanide-ptrifluoromethoxyphenylhydrazone (FCCP) every two minutes to increase its concentration by 0.25 µM (1st and 2nd doses) and 0.5 µM (3rd to 5th doses). Thus, the final cumulative concentration of FCCP was 2 µM.

All results were analyzed using Microsoft Office Excel. All data are presented as mean (M) ± standard error (m). Statistical analyses were performed using ANOVA test. P value of < 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

One of the main characteristics of tumor cells is their unlimited proliferation. To ensure this process, cancer cells must adjust their energy metabolism (Chen *et al.*, 2016). Tumor cells predominantly choose glycolysis for energy production, even if sufficient amount of oxygen is available (Warburg effect). However, recent studies indicate that mitochondrial metabolism is important for cancerogenesis (Fadaka *et al.*, 2017). Mitochondria can affect cancer cells through indirect action, mediated by ROS, or directly through mitochondrial biogenesis, because energy production also ensures the synthesis of many molecules necessary for cellular biosynthesis, growth and proliferation (Liu & Shi, 2020). Previous studies have proven that the thiazole derivative BF1 does not affect respiratory and oxidative phosphorylation parameters in isolated mitochondria of lymphoma cells (Hreniukh *et al.*, 2020). However, this effect could be associated with the poor solubility of compounds in water and C_2H_5OH, forcing the use of a powerful chemical solvent DMSO. This may potentially limit the therapeutic efficacy of BF1. As studied earlier, BF1 in a complex with PEG-PN significantly increased ROS content in NK/Ly lymphoma cells. Therefore, it was important to study the impact complex formation of BF1 with PEG-containing polymer carriers for processes of cellular respiration in tumor cells, which is associated with the formation of ROS.

Fig. 1*A* shows the rate of respiration of intact NK/Ly cells during glucose oxidation under the action of unconjugated thiazole derivative BF1, PEG-PN (Th5), and their complex (Th6). The rate of control (untreated) cells respiration was 0.031 nmol O_2/(s·mln cells). Thiazole derivative BF1, Th5 and Th6 complex did not change basic oxygen consumption in mouse lymphoma cells (**Fig. 1*A***).

In the next set of experiment FCCP protonophore was gradually added to cell suspension every two minutes (final maximum concentration was 2 µM). FCCP protonophore easily penetrates the cell plasma membrane and causes the uncoupling of the mitochondrial processes. No effect of the studied substances (BF1, Th5 and Th6) on cellular respiration was observed (**Fig. 1*B***) with the concentration of FCCP 0.25, 0.5 and 0.75 µM. However, the Th5 and Th6 complexes significantly activated FCCP-stimulated respiratory processes in NK/Ly lymphoma cells. The rate of FCCP-stimulated respiration (concentrations of 1.5 µM and 2 µM) increased by 62.5% and 81.2% under the action of Th6, respectively (**Fig. 1*B***).

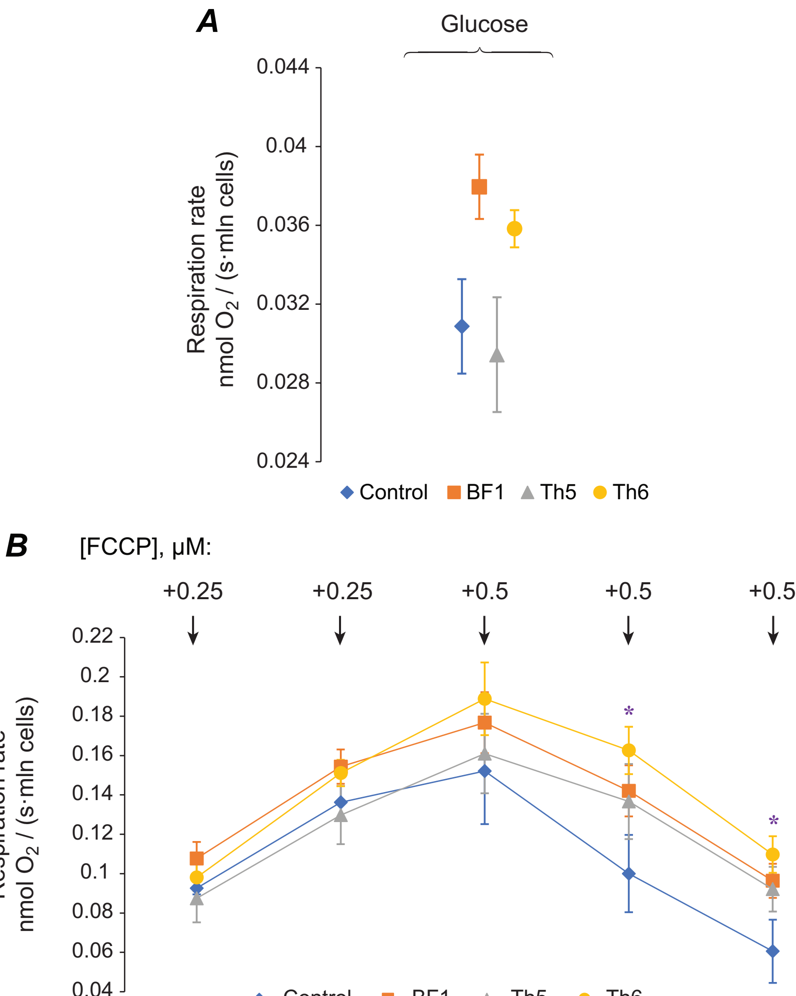

Fig. 1. Mitochondrial respiration rate in intact mouse NK/Ly cells. The oxidation substrate is glucose (10 mM). ***A*** – the basic level of respiration without FCCP. ***B*** – respiration stimulated by FCCP in increasing concentrations during exposure to thiazole derivative BF1, PEG-containing polymer carrier Th5 and complex BF1+Th5 – Th6. M ± m, n = 5. * – P ≤0.05 (vs control). The final cumulative FCCP concentration was 2 μM

Membrane potential is an important indicator of mitochondrial activity, which can be evaluated, in particular, through fluorescence microscopy using the potential-sensitive dye Tetramethylrhodamine (TMRM). The uncoupler of oxidative phosphorylation FCCP in high concentration (20 μM) was used for complete depolarization of mitochondria of nonpermeabilized NK/Ly cells and to confirm that fluorescence TMRM itself depends on the potential of the mitochondrial membrane. Because the studied compounds were dissolved in DMSO, the effect of this solvent was also checked on the mitochondrial membrane potential. FCCP reduced fluorescence intensity by 63% ($P < 0.01$), confirming uncoupling of mitochondrial membrane potential. At the same time, DMSO did not significantly change the membrane potential of mitochondria.

Fig. 2 shows fluorescent images of NK/Ly lymphoma cells under the influence of the investigated compounds. Fluorescence was less intense upon exposure to BF1 (**Fig. 2*B***) compared to the control (**Fig. 2*A***) reflecting a decrease in membrane potential. It is noticeable that the fluorescence of lymphoma cells under the action of Th6 (**Fig. 2*E***) was lower than the fluorescence under the action of BF1 or the control. The fluorescence of lymphoma cells under the action of PEG-PN Th5 (**Fig. 2*D***) was almost equal to the control data.

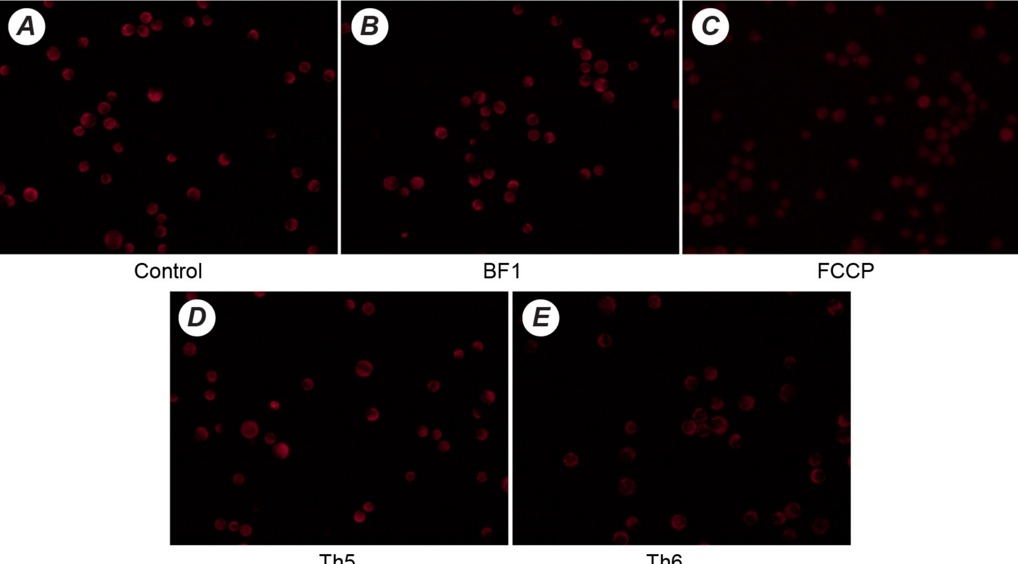

Fig. 2. Fluorescence of lymphoma cells with TMRM dye upon exposure to thiazole derivative BF1 in complex with PEG-containing polymer carrier: ***A*** – control; ***B*** – unconjugated thiazole derivative BF1; ***C*** – PEG-PN Th5; ***D*** – Th6 complex; ***E*** – protonophore FCCP

It was established that BF1 at a concentration of 10 μM slightly reduced the potential of the mitochondrial membrane of NK/Ly cells, but these changes were not statistically significant (**Fig. 3**, $P = 0.15$). PEG-PN (Th5) did not affect the mitochondrial membrane potential of a lymphoma cell. However, Th6 complex slightly but significantly reduced the membrane potential of mitochondria of lymphoma cells by 12% ($P < 0.05$), relative to the control (**Fig. 3**).

Mitochondrial energy processes and respiration are now recognized as critical elements influencing how cancer cells either react to or elude signals that trigger cell death (Winter *et al.*, 2022). Exploring the functional link between these processes could shed light on a longstanding and topical question: can we enhance apoptotic stress in cancer treatment by targeting respiration or downstream signaling pathways?

It is known that the hypoxic microenvironment in most types of cancer limits the ability of mitochondrial oxidative phosphorylation to generate ATP and increases anaerobic glycolytic intensity to compensate the energy deficit (Warburg effect) (Horbay *et al.*, 2011). However, mitochondrial processes play an important role in tumor initiation and progression and may contribute to cancer development through activation of glucose metabolism, production of ROS and internal disorders of apoptotic functions

(Fogg *et al.*, 2011). On the other hand, mitochondrial dysfunctions, such as violation of breathing processes, change in mitochondrial membrane potential, or a decreased synthesis of ATP can cause damage to tumor cells and lead to their death.

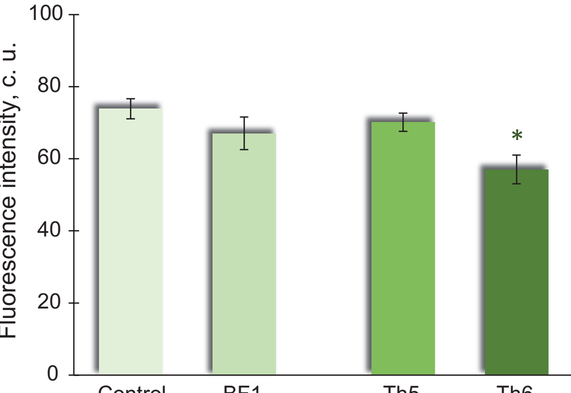

Fig 3. Changes in the membrane potential of lymphoma cell mitochondria under the action of thiazole derivative BF1, PEG-containing polymer carrier (Th5) and their complex (Th6). M±m, n=5. * - $P < 0.05$ (vs control)

In this study, it was found that BF1 complexed with PEG-PN Th5, but not unconjugated BF1, significantly increases the rate of FCCP-stimulated respiration in intact lymphoma cells. This effect can be explained by the improved solubility of BF1 in complex with PEG-PN. It is known that the activation of respiration can be associated with a large-scale production of ROS by mitochondria and the disruption of internal apoptotic processes (Fogg *et al.*, 2011). Intensive generation of ROS under the influence of BF1 and its complexes with PEG-PN may be associated with damage to the integrity of the mitochondrial membrane and activation of respiratory processes.

The increase in the rate of FCCP-stimulated cellular respiration in our studies can be explained by the need to synthesize more ATP or uncoupled processes in the mitochondrial membrane of NK/Ly cells. In particular, damage to the integrity of the mitochondrial membrane can cause membrane uncoupling. Violation of the integrity of the mitochondrial membrane under the ROS influence may lead to the dispersal of membrane potential, release of cytochrome *c*, activation of proapoptotic caspases and, ultimately, to cell apoptosis (Środa-Pomianek *et al.*, 2018).

We have established that the studied complex of BF1 with PEG-PN, but not the unconjugated thiazole derivative, significantly reduces the mitochondrial membrane potential of NK/Ly lymphoma cells by 12% compared to the control. These data correlate with our previous study on an increased content of ROS in lymphoma cells (Ilkiv *et al.*, 2022). An increased content of ROS causes depolarization of mitochondrial membranes and the induction of compensatory reactions of the respiratory chain in the form of activation of cellular respiratory processes under the influence of BF1 complexes with PEG-PN, however, not free BF1.

Therefore, BF1+PEG-PN complex, but not free BF1, significantly reduces the membrane potential of mitochondria of lymphoma cells, which causes compensatory intensification of oxygen consumption.

CONCLUSION

The effect of the thiazole derivative BF1 and its complex with a nanosized polyethylene glycol-based carrier on FCCP-stimulated respiration and the membrane potential

of NK/Li lymphoma cells was investigated. It was found that only the BF1 complex with a nanocarrier (but not BF1 itself) causes a higher level of cell respiration activated by 1.5 and 2 μM FCCP. At the same time, the value of the mitochondrial membrane potential decreased, which may indicate that improving the transport of the thiazole derivative to cancer cells causes increased toxicity, damage to energy-generating processes in mitochondria, and in the future can be used to increase the effectiveness of lymphoma treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: this article does not contain any studies with human subjects performed by any of the authors.

Animal Studies: all international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [Ya.Sh.; M.I.]; methodology, [M.I.; Ya.Sh.]; validation, [Ya.Sh]; formal analysis, [Ya.Sh; A.S.].; investigation, [M.I.; Ya.Sh.; H.M.; B.M.]; resources, [N.M; O.Z.; Yu.O.]; data curation, [A.B.]; writing – original draft preparation, [M.I., Ya.Sh., A.S.]; writing – review and editing, [M.I.; Ya.Sh., A.B.]; visualization, [Ya.Sh, M.I.]; supervision, [A.B.]; project administration, [A.B.]; funding acquisition, [-].

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ЗМІНИ БІОЕНЕРГЕТИЧНИХ ХАРАКТЕРИСТИК КЛІТИН МИШАЧОЇ ЛІМФОМИ ЗА ДІЇ ПОХІДНОГО ТІАЗОЛУ В КОМПЛЕКСІ З ПОЛІМЕРНИМИ НАНОЧАСТИНКАМИ

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Актуальність. Мітохондрії можуть впливати на метаболізм ракових клітин як опосередковано через продукування активних форм Оксигену, так і безпосередньо через мітохондріальний біогенез. Виробництво енергії в мітохондріях має вирішальне значення, оскільки воно сприяє синтезу основних молекул, необхідних для клітинного біосинтезу, росту та проліферації. Розробка нових протипухлинних препаратів, спрямованих на енергетичний метаболізм пухлинних клітин, є перспективною для лікування раку. Наше дослідження мало на меті дослідити, як похідне тіазолу N-(5-бензил-1,3-тіазол-2-іл)-3,5-диметил-1-бензофуран-2-карбоксамід (БФ1) та його комплекс із полімерною наночастинкою на основі поліетиленгліколю (ПЕГ, наночастинка Th5) і комплекс Th5 з БФ1 (Th6) впливають на дихання та потенціал мітохондріальної мембрани в мишачих пухлинних клітинах лімфоми Немет–Келнера (NK/Ly).

Матеріали і методи. Дослідження проводили на білих мишах-самцях дикого типу з прищепленою лімфомою NK/Ly. Досліджувані речовини додавали до суспензії клітин у кінцевій концентрації 10 мкМ та інкубували протягом 15 хв за 37 °C. Швидкість поглинання кисню клітинами NK/Ly вимірювали за допомогою електрода Кларка полярографічним методом. Зміни потенціалу мітохондріальної мембрани визначали за допомогою флуоресцентного барвника тетраметилродаміну. Інтенсивність флуоресценції аналізували за допомогою комп'ютерної програми ImageJ.

Результати. Після інкубації клітин NK/Ly з БФ1 (10 мкМ), з Th5 або з комплексом БФ1 + Th5 (Th6) протягом 15 хв не спостерігали достовірних змін у базальному диханні, за наявності глюкози. Проте інкубування клітин лімфоми з комплексами Th5 і Th6 достовірно сприяли вищому рівню FCCP-стимульованого дихання в клітинах лімфоми за високих концентрацій протонофора (1,5 та 2 мкМ). За результатами флуоресцентної мікроскопії було встановлено, що некон'юговані БФ1 чи полімерні наночастинки на основі поліетиленгліколю (Th5) не впливали на значення потенціалу мітохондріальної мембрани. Натомість комплекс Th6 достовірно знижував потенціал мітохондріальної мембрани, що свідчить про послаблення життєздатності клітин лімфоми.

Висновки. Комплекси похідного тіазолу БФ1 з полімерним носієм на основі ПЕГ можуть реалізовувати свою цитотоксичну дію через деполяризацію мембрани мітохондрій і, відповідно, зниження мембранного потенціалу мітохондрій клітин лімфоми.

Ключові слова: похідне тіазолу, полімерний наноносій, клітинне дихання, мітохондріальний мембранний потенціал, лімфома

Received / Одержано	Revision / Доопрацьовано	Accepted / Прийнято	Published / Опубліковано
13 May, 2024	18 July, 2024	30 August, 2024	25 September, 2024