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Resistance and chemosensitivity restoration in human cytomegalovirus-infected tumor cells to doxorubicin through combined treatment with aqueous fullerene dC₆₀

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Abstract

Introduction. Human cytomegalovirus infection can induce tumor cell resistance to chemotherapeutic agents through modulation of apoptotic pathways. In the search for alternative approaches to overcome virus-associated drug resistance, the application of nanomaterials (aqueous fullerene dC₆₀) represents a promising strategy. The potential to overcome human cytomegalovirus mediated chemoresistance opens new avenues for developing combined therapeutic approaches in oncology.

Aim – to evaluate the impact of human cytomegalovirus infection on the resistance of hepatocellular carcinoma and promyelocytic leukemia cells to doxorubicin, as well as the potential of aqueous fullerene dC₆₀ to restore chemosensitivity in monocytic leukemia cells.

Materials and methods. Hepatocellular carcinoma cells (Huh 7.5), promyelocytic leukemia cells (HL-60), monocytic leukemia cells (THP-1), and HCMV AD169 were used. The experimental procedures included standard cell culture techniques, virological methods, immunocytochemistry, Western blotting, Real-Time Polymerase Chain Reaction, Quantitative Reverse Transcription Polymerase Chain Reaction and MTT assay.

Results. Human cytomegalovirus infection reduced doxorubicin cytotoxicity by 30% in both hepatocellular carcinoma and promyelocytic leukemia cells. In monocytic leukemia cells, combined treatment with doxorubicin and dC₆₀ restored chemosensitivity to human cytomegalovirus infected cells, achieving 93% tumor cell death at half the standard doxorubicin concentration.

Conclusion. Human cytomegalovirus infection induces doxorubicin resistance in both hematopoietic (promyelocytic leukemia, monocytic leukemia) and solid (hepatocellular carcinoma) tumor models. Importantly, combined treatment doxorubicin with aqueous fullerene dC₆₀ not only overcomes virus-mediated drug resistance in monocytic leukemia cells but also enhances cytotoxicity at reduced doxorubicin concentrations, offering prospects for developing less toxic combined therapeutic regimens.

Keywords: human cytomegalovirus; aqueous fullerene C₆₀ (dC₆₀); Huh 7.5; THP-1; HL-60; hepatocellular carcinoma; leukemia

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

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Устойчивость и восстановление чувствительности опухолевых клеток, инфицированных цитомегаловирусом человека, к доксорубину при сочетанном применении с дисперсным фуллереном dC₆₀

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Резюме

Введение. Цитомегаловирусная инфекция способна индуцировать развитие резистентности опухолевых клеток к химиотерапевтическим препаратам посредством модуляции апоптотических путей. В поиске альтернативных препаратов, направленных на преодоление вирус-ассоциированной резистентности, перспективным направлением является применение наноматериалов (дисперсной формы фуллерена dC₆₀). Возможность преодоления вирус-ассоциированной лекарственной устойчивости открывает новые возможности для разработки комбинированных терапевтических стратегий в лечении опухолей.

Цель – оценить влияние цитомегаловирусной инфекции на резистентность клеток гепатокарциномы и промиелоцитарного лейкоза к доксорубину, а также потенциал дисперсного фуллерена dC₆₀ в восстановлении чувствительности к химиотерапии доксорубином клеток моноцитарной лейкемии.

Материалы и методы. Исследовали клетки: гепатокарциномы (Huh 7.5), промиелоцитарного лейкоза (HL-60), моноцитарной лейкемии (THP-1); цитомегаловирус (штамм AD169). Экспериментальная часть включала общепринятые культуральные и вирусологические методы, иммуноцитохимию, иммуноблоттинг, полимеразную цепную реакцию в режиме реального времени, полимеразную цепную реакцию с обратной транскрипцией, МТТ-тест.

Результаты. Цитомегаловирусная инфекция в клетках гепатокарциномы и промиелоцитарного лейкоза снижала цитотоксическое действие доксорубина на 30%. В клетках моноцитарной лейкемии сочетанное применение доксорубина с дисперсным фуллереном dC₆₀ приводило к восстановлению чувствительности инфицированных клеток к химиотерапии. При этом 93% гибель опухолевых клеток достигалась с применением доксорубина в 2 раза меньшей концентрации.

Заключение. Цитомегаловирусная инфекция формирует резистентность к доксорубину на гемопоэтических (клетки промиелоцитарного лейкоза и моноцитарной лейкемии) и солидных (клетки гепатокарциномы) опухолевых моделях. Примечательно, что сочетанное действие доксорубина с дисперсным фуллереном dC₆₀ не только позволяет преодолевать вирус-опосредованную лекарственную устойчивость в клетках моноцитарной лейкемии, но и позволяет достичь выраженного цитотоксического эффекта при сниженных концентрациях доксорубина, что открывает перспективы для разработки комбинированных терапевтических схем со сниженной токсичностью.

Ключевые слова: цитомегаловирус человека; дисперсный фуллерен dC₆₀; Huh 7.5; THP-1; HL-60; гепатокарцинома; лейкоз; лейкемия

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Introduction

In the recent decades, there has been an accumulation of data that indicates the important role of infectious agents in the development of oncological diseases [1]. Cytomegalovirus (CMV) is not a classical oncogenic virus, despite experimental data indicating its ability

to transform fibroblasts [2], hepatocytes and HepG2 cells [3]. However, numerous studies confirm the oncomodulatory effect of CMV [4], with viral DNA and/or proteins being detected in 90–100% of patients with various types of tumors [5], making the study of its role in the pathogenesis of malignant neoplasms relevant.

CMV is a polyhistotropic virus that persists in the body after the primary infection, periodically reactivating. Blood cells serve as the primary reservoir for latent infection. We have shown that CMV infection of the THP-1 monocytic leukemia cell line induces resistance to doxorubicin [6]. Notably, antiviral therapy with ganciclovir does not restore sensitivity to chemotherapy [7], indicating the need to explore new approaches to overcome virus-mediated resistance.

Doxorubicin (DOX) is one of the most effective antitumor drugs, widely used in the therapy of various malignant neoplasms. However, the clinical use of DOX is limited by its pronounced cardio- and nephrotoxicity. An urgent problem in many studies is overcoming the resistance of tumor cells to chemotherapy while simultaneously reducing the toxic effects of DOX. It has been shown that resveratrol enhances the cytotoxic activity of DOX against human breast cancer cells when applied simultaneously or 24 hours prior to DOX application [8] and increases the cytotoxic effect of DOX in colorectal carcinoma cells [9]. Other strategies include the use of combinations such as AICAR and DOX in nanoparticle formulations to overcome toxicity issues in targeted therapy while maintaining potent anticancer effects in lung carcinoma, colon carcinoma, cervical adenocarcinoma, acute T-cell leukemia and pancreatic carcinoma cells [10], as well as the application of TPGS1000 and curcumin-based micelles to overcome resistance in lung cancer cells [11]. Moreover, the oligonucleotide DT01 has shown potential in enhancing the effect of DOX in hepatocellular carcinoma [12].

Dispersed fullerene dC_{60} is a promising agent in biology and medicine; publications on its chemical and biological properties indicate low toxicity, antioxidant and anti-inflammatory activity, as well as wound-healing properties [13, 14]. According to the literature, nanostructures of fullerene C_{60} with hydrophilic properties demonstrate pronounced antiviral activity against a wide range of pathogens, including HIV, Ebola virus, various strains of influenza virus (H1N1, H3N2, H5N1), adenoviruses and RSV [15–17], herpes simplex virus type 1 and CMV [18].

Therefore, **the aim** of this study was to investigate the effect of CMV infection on the development of resistance to doxorubicin (DOX) in hepatocellular carcinoma and promyelocytic leukemia cell lines, and to assess the ability of nanodispersed fullerene dC_{60} to overcome chemoresistance in CMV-infected monocyte leukemia cells when used in combination with DOX.

Materials and methods

Cells. The study utilized the following: human embryonic lung fibroblast cell line (HELFL), Huh 7.5 hepatocarcinoma cells, HL-60 promyelocytic leukemia cells, and THP-1 monocytic leukemia cells, obtained from the cell culture bank of the N.F. Gamaleya Federal Research Center for Epidemiology and Microbiology of the Ministry of Health of the Russian Federation. To maintain the cell cultures of HELFL and Huh 7.5, DMEM medium was used, while the HL-60 and TNR-1 lines were cultured in RPMI-1640 medium. The nutrient media contained the

following components: L-glutamine (2 mM), gentamicin (50 µg/ml), fetal bovine serum (10%). All reagents were purchased from a domestic supplier (LLC PanEco, Russia). Quality control confirmed the absence of microbial contamination (both extracellular and intracellular) in the cell cultures used.

Virus. The laboratory strain of cytomegalovirus AD169, provided by the viral collection of the N.F. Gamaleya National Research Center for Epidemiology and Microbiology (Moscow), was used in the study. The viral material was passaged on a HELFL cell culture, followed by determining the infectious titer using the plaque assay method. The titer of the de novo obtained virus was 1×10^5 PFU/ml (plaque-forming units/ml).

Dispersed fullerene dC_{60} . was provided by the Institute of Immunology of the FMBA of Russia. Morphological analysis was conducted using a TESCAN MIRA 3 LMH scanning electron microscope (secondary electron mode, accelerating voltage 5 kV, beam current 130 pA). The samples were prepared using air drying without metal coating.

MTT assay. To determine cell viability after exposure to doxorubicin and fullerene dC_{60} , a standard MTT assay was used. Cell cultures were incubated with the tetrazolium dye (MTT, 1 mg/ml) for 2 hours at 37 °C. The obtained formazan was extracted with a 0.04 M hydrochloric acid solution in isopropanol. Quantitative assessment was conducted using spectrophotometry on a TECAN plate reader at 570 nm with background signal correction at 620 nm.

Immunocytochemistry. For the detection of CMV-infected cells, an immunoperoxidase method was used with primary antibodies against viral proteins IE1-p72 and pp65 (Abcam, UK). The prepared substances were visualized using an AxioCam MRc5 microscope (Carl Zeiss, Germany) with 400× magnification and digital image recording.

Immunoblotting. Transfer to nitrocellulose membranes was performed after preliminary electrophoretic separation of proteins in a 12% polyacrylamide gel. Visualization was performed using the chemiluminescence method (Bio-Rad system, USA) followed by quantitative assessment of digital images in the ImageJ program (version 1.52, NIH, USA). β -actin was used for data normalization.

RT-PCR. Total RNA was extracted using Trizol reagent (Thermo Fisher Scientific, USA) according to the standard protocol. cDNA synthesis was performed using 1 µg of total RNA and the MultiScribe commercial reverse transcriptase kit (Applied Biosystems, USA). Primers for amplification were designed based on the genome sequences of the AD169 strain of cytomegalovirus using the Vector NTI Advance 11 program, the thermodynamic prediction algorithm (Themfold Web Server), and the Primer-BLAST tool (NCBI). The GAPDH gene was used as an endogenous control.

qPCR. For the isolation of genomic DNA, the DNA-sorb-B commercial kit (Central Research Institute of Epidemiology of Rospotrebnadzor, Russia) was used according to the standard nucleic acid extraction protocol.

Quantitative determination of CMV DNA was performed using real-time polymerase chain reaction with a specialized reagent kit (Central Research Institute of Epidemiology of Rospotrebnadzor, Russia). The amplification was carried out in a thermocycler with fluorescent signal detection at each cycle.

Statistical analysis was performed using the Prism 9.1.1 (GraphPad Software, USA) and SPSS Statistics 27 (IBM, USA) software. Data processing was carried out in strict accordance with current methodological recommendations.

Results

Preparation and characterization of dC_{60} . Fullerene dC_{60} was obtained using a modified diafiltration method, in which standard dialysis was replaced with tangential ultrafiltration, in accordance with a previously published protocol [18]. The obtained samples were agglomerates approximately 100 nm in size, formed from smaller particles with a diameter of 15–30 nm.

Cytotoxic effect of DOX on Huh 7.5 and HL-60 cells. To determine the cytotoxic effect of DOX, the Huh 7.5 and HL-60 cell lines were incubated in the presence of various concentrations of the antibiotic: 0.1–10 µg/ml for Huh 7.5 (Fig. 1 a) and 0.3–3 µg/ml for HL-60 (Fig. 1 b). It was found that the IC_{50} of DOX for Huh 7.5 cells was 2.6 µg/ml, whereas for HL-60 this value was significantly lower – 0.05 µg/ml.

Characterization of CMV in Huh 7.5 and HL-60 cells. During the study, the content of viral DNA in the Huh 7.5 (hepatocarcinoma) and HL-60 (promyelocytic leukemia) cell lines was assessed using quantitative real-time PCR over a period of 14 days post-infection. Analysis of the obtained data (Fig. 2 a) revealed a decrease in the amount of viral DNA per cell in both studied lines. In HL-60 cells, the viral genome content decreased from 1.22 ± 0.01 lg (1 day post-infection) to 0.78 ± 0.02 lg (14 days post-infection). A similar trend was observed in the Huh 7.5 line, where the level decreased from 1.86 ± 0.03 lg in the first days to 1.22 ± 0.06 lg by the end of the experimental period.

To characterize the course of CMV infection in the cell lines Huh 7.5 (hepatocarcinoma) and HL-60 (promyelocytic leukemia), an analysis of virus-specific proteins corresponding to the immediate early (IE) and early (E) stages of the infectious process was conducted. Cells were infected with CMV at a multiplicity of infection of 2 PFU/cell, followed by monitoring the levels of IE1-p72 and pp65 for 14 days.

The highest number of cells containing IE1-p72 and pp65 proteins was recorded in the HL-60 line on the first day ($37.7 \pm 2.3\%$), whereas in the Huh 7.5 culture, the maximum level of infected cells was noted on the second day ($42.0 \pm 6.5\%$). By day 14, a statistically significant ($p < 0.05$) decrease in the number of cells positive for IE1-p72 and pp65 (1.5 ± 0.9 and 1.6 ± 0.9 , respectively) was observed in both cell lines, indicating the completion of lytic viral replication (Fig. 2 b).

The results of the study revealed a dynamic decrease in viral DNA concentration and a reduction in the population of cells expressing IE and E CMV antigens over a two-week observation period. The observed dynamics indicate the evolution of the infectious process from the active replicative stage to the latent persistence of the virus in both studied cell models.

Cytotoxic effect of DOX on Huh 7.5 and HL-60 cells infected with CMV. Based on the analysis of dose-dependent cytotoxicity, subtoxic concentrations of DOX were selected: 6 µg/ml for the Huh 7.5 cell line and 0.6 µg/ml for HL-60.

A comparative analysis of the cytotoxic effect of DOX on HL-60 and Huh 7.5 cell lines in the presence and absence of CMV was performed. The HL-60 cell line was treated with DOX at a concentration of 0.6 µg/ml 24 hours after viral infection. The Huh 7.5 cell culture was treated with a higher concentration of the antibiotic (6 µg/ml), which was administered 48 hours after infection. Such a differentiated approach allowed for the assessment of the impact of viral infection on the effectiveness of the chemotherapeutic agent in various cell systems. The analysis of the cytotoxic effect was conducted after a 24-hour incubation with the antibiotic. The results are presented in Fig. 3.

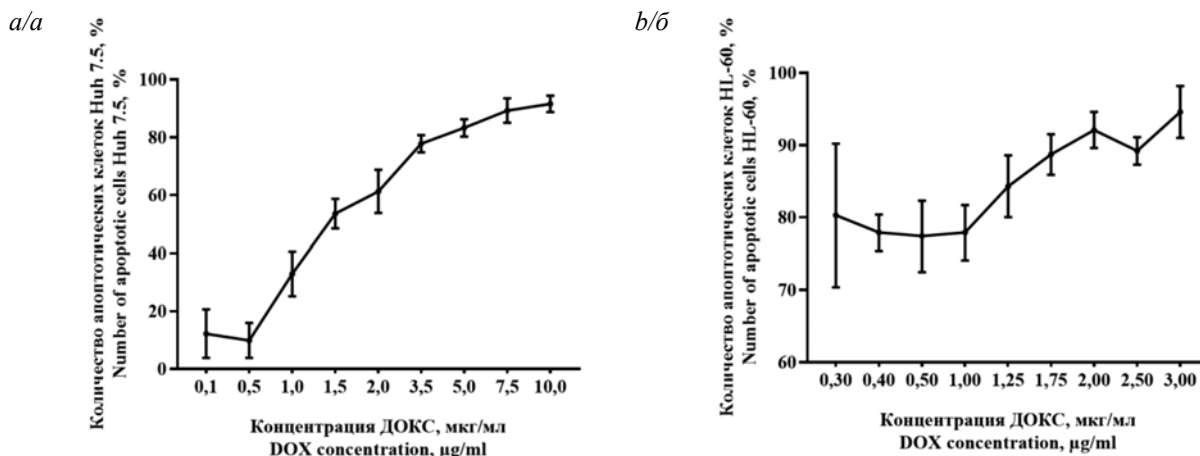


Fig. 1. Evaluation of doxorubicin-induced cytotoxicity in Huh 7.5 (a) hepatocarcinoma and HL-60 promyelocytic leukemia cells (b).

Рис. 1. Цитотоксическое действие ДОКС на клетки Huh 7.5 (a) и HL-60 (б).

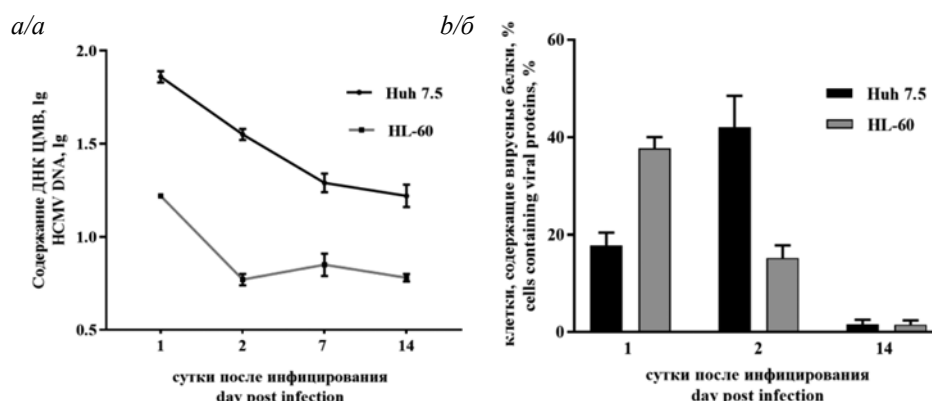


Fig. 2. Longitudinal monitoring of CMV DNA content (a) and IE1-p72/pp65 viral protein expression (b) in Huh 7.5 and HL-60 cell lines during 14 days post-infection.

Рис. 2. Динамика содержания ДНК ЦМВ (a) и вирусных белков IE1-p72 и pp65 (б) в клетках Huh 7.5 и HL-60 с 1-х по 14-е сутки после инфицирования.

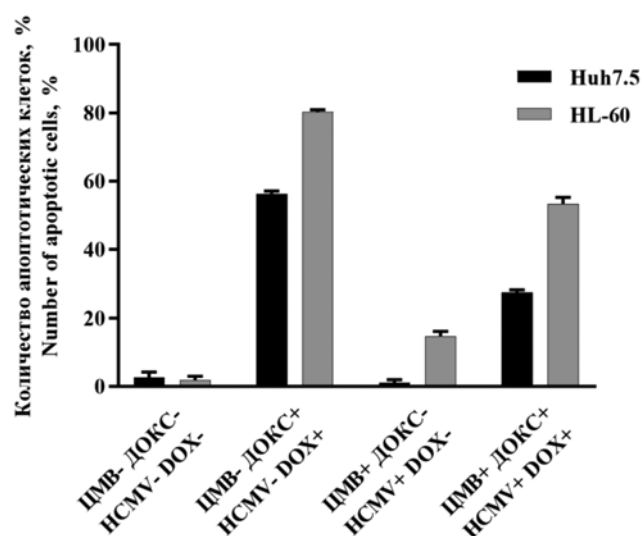


Fig. 3. Doxorubicin-induced cytotoxicity in cytomegalovirus infected Huh 7.5 hepatocarcinoma and HL-60 promyelocytic leukemia cell lines.

Рис. 3. Цитотоксическое действие ДОКС на клетки Huh 7.5 и HL-60, инфицированные ЦМВ.

In HL-60 cells, a significant ($p < 0.05$) reduction in the cytotoxic effect of the antibiotic was observed—the number of non-viable cells decreased from $80.3 \pm 0.6\%$ in the uninfected culture to $53.3 \pm 1.9\%$ in the infected one. A similar protective effect of CMV was observed in Huh 7.5 cells: the cell death rate decreased from $56.3 \pm 0.8\%$ to $27.6 \pm 0.7\%$ ($p < 0.05$). The obtained results indicate a pronounced modulatory effect of CMV, reducing the cytotoxic efficacy of DOX by approximately 30% in both studied cell lines, which may be due to virus-induced changes in cellular metabolism or the activation of protective mechanisms in infected cells.

Antiviral effect of fullerene dC_{60} on THP-1 cells. In earlier studies, a dose-dependent antiviral activity of dC_{60} against CMV was demonstrated in HELF cells [10]. In the present study, we investigated the effect of dC_{60} on viral DNA content using RT-PCR, the expression of

UL123 (immediate early protein IE1-p72) and *UL54* (DNA polymerase) genes using qPCR, and viral proteins (IE1-p72 and pp65) using Western blot in CMV-infected THP-1 cells. The obtained results are presented in **Table 1**.

The results of the study demonstrate a significant impact of dispersed fullerene dC_{60} on molecular markers of CMV infection in THP-1 cells. A significant decrease in the expression of the *UL54* gene by 57% ($p < 0.05$), a reduction in the level of the IE1-p72 protein by 28% ($p < 0.05$), and a significant decrease in viral load ($p < 0.05$) were observed. At the same time, the increase in the expression of the *UL123* gene was not statistically significant ($p > 0.05$), and the level of pp65 protein remained low ($p > 0.05$).

The obtained data indicate the selective inhibitory effect of dispersed fullerene dC_{60} on certain stages of viral replication, which is manifested in the reduction of the early protein level (IE1-p72), decreased expression of late viral genes, and reduced viral load.

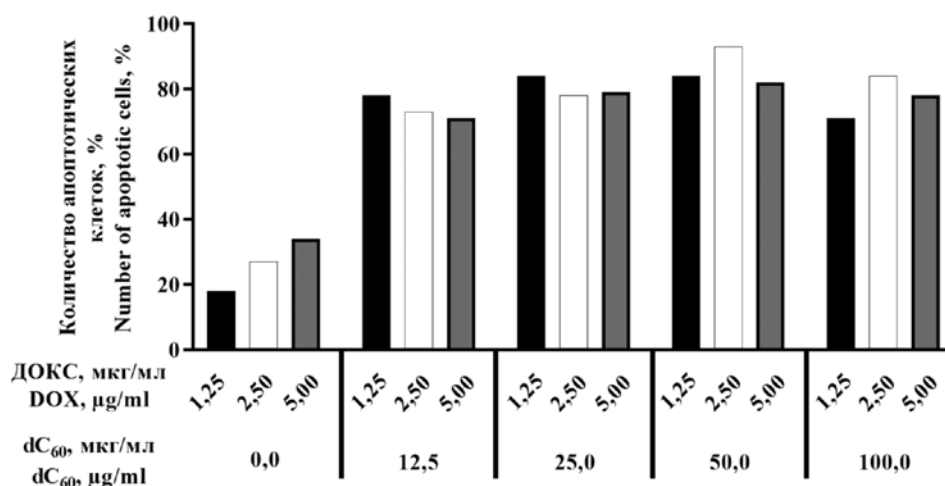
Combined action of dispersed fullerene dC_{60} and DOX on CMV-infected THP-1 cells. In order to study the potential synergistic interaction, the combined effect of dispersed fullerene dC_{60} and DOX on CMV-infected THP-1 cell line was investigated. The study used the following concentration ranges: 12.5–100 $\mu\text{g/ml}$ for dispersed fullerene dC_{60} ; 1.25–5 $\mu\text{g/ml}$ for DOX. The experimental design involved a systematic assessment of the cytotoxic effects of all possible combinations of the specified compounds to identify potentially synergistic interactions between the studied agents. To assess the synergistic effect, a comprehensive study was conducted on the combined action of dispersed fullerene dC_{60} at concentrations of 12.5, 25.0, 50.0 and 100.0 $\mu\text{g/ml}$, and DOX at concentrations of 1.25, 2.50, and 5.00 $\mu\text{g/ml}$ on CMV-infected THP-1 cells. The results of the study demonstrate a pronounced synergistic effect of the combination of dispersed fullerene dC_{60} with DOX, manifested in a significant increase in cytotoxic activity against CMV-infected THP-1 cells. A significant reduction in the number of non-viable cells was observed at all investigated concentrations of DOX, while in the infected culture, the cytotoxic effect was almost 2.5 times

Table 1. Quantitative analysis of aqueous fullerene dC₆₀ nanoparticles impact on human cytomegalovirus replication kinetics and infectivity in THP-1 cells**Таблица 1.** Влияние дисперсного фуллерена dC₆₀ на течение цитомегаловирусной инфекции в клетках THP-1

| Parameter Параметр | UL54, CU/усл. ед. | UL123, CU/усл. ед. | IE1-p72, CU/усл. ед. | pp65, CU/усл. ед. | DNA copies/ml (lg) ДНК, копий/мл (lg) |
|-------------------------------|-------------------|--------------------|----------------------|-------------------|--|
| dC ₆₀ ⁻ | 1.01 ± 0.16 | 1.01 ± 0.19 | 1.02 ± 0.1 | 0.04 ± 0.02 | 6.0 ± 0.6 |
| dC ₆₀ ⁺ | 0.43 ± 0.08* | 1.52 ± 0.45 | 0.73 ± 0.08* | 0.02 ± 0.02 | 2.0 ± 0.7* |

Note. * – statistically significant differences ($p < 0.05$).

Примечание. * – статистически значимые различия ($p < 0,05$).

**Fig. 4.** Evaluation of combination treatment with doxorubicin (DOX) and aqueous fullerene dC₆₀ nanoparticles in cytomegalovirus infected THP-1 cells.**Рис. 4.** Сочетанное действие ДОКС и дисперсного фуллерена dC₆₀ на клетки THP-1, инфицированные ЦМВ.

less pronounced compared to non-infected cells. The results of the study indicate a significant potentiation of the cytotoxic effect of DOX when used in combination with the nanodispersed fullerene dC₆₀ against CMV-infected THP-1 cell line. The obtained experimental data revealed a clear dose-dependent synergy of the studied compounds: the use of minimal effective concentrations (1.25 µg/ml of DOX in combination with 12.5 µg/ml of dC₆₀) significantly increased the sensitivity of infected cells to chemotherapeutic effects ($p < 0.05$). At the same time, the maximum cytotoxic effect, characterized by the death of $93 \pm 2.5\%$ of the cell population, was achieved using the optimal combination of concentrations – 2.5 µg/ml of DOX and 50 µg/ml of nanodispersed fullerene dC₆₀ (**Fig. 4**). The obtained results demonstrate the promise of using dispersed fullerene dC₆₀ to enhance cytotoxic therapy in CMV-associated oncohematological diseases.

The conducted factor analysis of the data using the principal component method followed by varimax rotation allowed for the identification of two dominant factors of chemotherapy effectiveness, the main parameters of which are systematized in **Table 2**. These components explain the largest share of variance in the studied sample and can be considered key factors determining the observed patterns.

The results of the factor analysis revealed a significant contribution of key components to the overall variability of the effectiveness of chemotherapeutic intervention. The first factor explained 49.3% of the observed variance, the second 38.5%, demonstrating the pronounced dominant role of these components. The cumulative contribution of the two factors reached 87.9%, indicating their decisive role in shaping the variability of the chemotherapeutic response.

For a quantitative assessment of the relationships between the studied parameters and the identified factors, a factor load analysis was conducted. **Table 3** presents the corresponding matrix, where the most significant correlations (with maximum load values highlighted for clarity) are shown.

The first component corresponded to high values of DOX concentration (0.801) and a greater number of non-viable cells (0.916), which allows it to be designated as the “Cytotoxic Action of DOX Component.” The second component (0.968) had the most pronounced correlations with the concentrations of dispersed fullerene dC₆₀, therefore it was interpreted as the “dC₆₀ Concentration Component.” The interpretation of the factor analysis results confirms its validity, as the identified components have a clear substantive explanation, indicating the adequacy of the applied analytical approach. The verification of initial assumptions using Bartlett’s test of sphericity showed a statistically significant

Table 2. Characteristics of Key Components

Таблица 2. Характеристики компонент

| № | Key Components Компонента | Eigenvalues Собственные значения | Rotation Sums of Squared Loadings, % Удельный вклад в дисперсию, % | |
|---|---|-------------------------------------|---|---------------------------|
| | | | variance каждой компоненты | cumulative накопленный |
| 1 | DOX-induced cytotoxicity Цитотоксическое действие ДОКС | 1.480 | 49.3 | 49.3 |
| 2 | dC ₆₀ concentration Концентрация dC ₆₀ | 1.156 | 38.5 | 87.9 |

Table 3. Factor loading matrix for parameters influencing chemotherapy efficacy

Таблица 3. Матрица факторных нагрузок для показателей, влияющих на эффективность химиотерапии

| Parameter Показатель | Components Компонента | |
|---|--------------------------|--------------|
| | 1 | 2 |
| Non-viability cells Нежизнеспособные клетки | 0.801 | 0.433 |
| Concentration DOX Концентрация ДОКС | 0.916 | −0.180 |
| Concentration dC ₆₀ Концентрация dC ₆₀ | 0.015 | 0.968 |

result ($p < 0.001$), which justifies the appropriateness of applying factor analysis to the studied data. The obtained p -value indicates the presence of significant relationships between the variables, sufficient for conducting this type of multivariate analysis.

The correlation between the obtained components and the effectiveness of chemotherapy was assessed using the Spearman correlation coefficient. A statistically significant direct correlation was established between the notable closeness of component 1 “Cytotoxic action of DOX” and the number of non-viable CMV-infected cells ($\rho = 0.641$; $p = 0.003$), and a statistically significant direct correlation was established between the notable closeness of component 2 “dC₆₀ Concentration” and the number of non-viable CMV-infected cells ($\rho = 0.595$; $p = 0.007$).

Discussion

According to data from recent studies, about 20% of malignant tumors in humans have a viral etiology. To date, the oncogenic role of several viruses has been proven, such as Epstein–Barr virus, hepatitis B and C viruses, human T-lymphotropic virus type 1, human papillomavirus, herpesvirus type 8, and Merkel cell polyomavirus. Epidemiological and molecular biological studies confirm their significant role in the development of lymphoproliferative diseases, hepatocellular carcinoma, cervical cancer, and other malignant neoplasms [19, 20].

CMV is a widely distributed opportunistic pathogen in the human population. Numerous studies confirm the high frequency of detection of viral DNA and specific CMV proteins in the tissues of various malignant neoplasms [21].

The established correlation between congenital CMV infection and an increased risk of developing acute lymphoblastic leukemia is of particular clinical significance [22].

The conducted studies revealed a complex interaction between CMV and the cytotoxic effect of DOX in various tumor cell lines, such as THP-1 (acute monocytic leukemia) [6, 7, 23, 24], HL-60 (acute promyelocytic leukemia), and Huh 7.5 (hepatocarcinoma). The results obtained in this study indicate a pronounced difference in the sensitivity of the Huh 7.5 and HL-60 cell lines to DOX, which is confirmed by a significant difference in IC₅₀ values (2.6 µg/ml vs. 0.05 µg/ml, respectively). This may be related to the peculiarities of cellular metabolism in different types of tumor cells, which requires further study at a molecular level. The dynamics of CMV infection in the studied cell lines were characterized by a gradual decrease in viral DNA content and a reduction in the number of cells containing immediate early (IE1-p72) and early (pp65) viral proteins, indicating a transition from the lytic to the persistent phase of infection. Notably, the maximum expression of viral proteins was observed at different times: in HL-60 cells on day 1, whereas in Huh 7.5 cells on day 2 post-infection. These differences may reflect the characteristics of intracellular processes in different types of cells during CMV infection. Thus, it is suggested that CMV cannot productively infect cancer cell lines expressing oncogenic alleles. This is consistent with the results of other researchers who have shown that certain oncogenic alleles, including the T antigen (TAg), inhibit CMV [25].

Particular attention should be given to the identified effect of a 30% reduction in the cytotoxic action of DOX in both cell lines after CMV infection. This phenomenon may be due to virus-induced changes in cellular metabolism and/or the activation of protective mechanisms, which opens new avenues for studying the mechanisms of drug resistance in virus-associated tumors.

Modern antiviral therapy for CMV, primarily based on viral DNA polymerase inhibitors (ganciclovir and its analogs), demonstrates limited effectiveness, acting exclusively on the lytic stage of the infectious cycle and having no impact on the latent forms of the virus. In our previous studies, it was established that the combination of ganciclovir with doxorubicin does not overcome the reduced sensitivity of CMV-infected THP-1 cells to chemotherapy [7]. The in-depth analysis of the molecular mechanisms of virus-mediated drug resistance conducted allowed for the identification of new classes of compounds with the potential to restore the chemosensitivity of CMV-infected cells [6, 26, 27].

Among innovative antiviral drugs, carbon nanoparticles, particularly the aqueous dispersion of fullerene C₆₀ (dC₆₀), which exhibit pronounced activity against herpesviruses, including CMV [13–18], are of particular interest. One of the advantages of dC₆₀ is the possibility of its industrial production using standard ultrafiltration technology, which ensures the stable production of highly concentrated solutions with reproducible characteristics. This technology is characterized by high economic efficiency and is easily scalable to production volumes. Along with its favorable safety profile and pronounced antiviral activity, this makes dispersed fullerene dC₆₀ a promising candidate for the development of new therapeutic agents, particularly relevant in the context of increasing resistance to traditional antiviral drugs and for the treatment of persistent viral infections.

The study of the antiviral activity of dispersed fullerene dC₆₀ revealed its selective action on various stages of viral replication in THP-1 cells infected with CMV. The most pronounced inhibitory effect was observed on the expression of the UL54 gene (DNA polymerase), the level of the immediate-early protein IE1-p72, and the content of CMV DNA.

The present study revealed a fundamentally important phenomenon of synergistic interaction between the antitumor drug DOX and the nanostructured form of fullerene C₆₀ within the selected concentration range, where no cytotoxic effect was observed (up to 100 µg/ml). The obtained data demonstrate two key aspects: firstly, the combined application of the mentioned compounds even at minimal concentrations contributed to overcoming virus-induced resistance in tumor cells; secondly, the optimal cytotoxic effect, characterized by the death of more than 90% of the cell population, was achieved with the combined use of DOX at a concentration of 2.5 µg/ml and nanodispersed fullerene at a dose of 50 µg/ml. The conducted factorial analysis confirmed the significance of both components (DOX and dC₆₀) for the effectiveness of the therapy, with their combined contribution explaining 87.9% of the variability in the results.

The results of the conducted study open up new opportunities for the development of therapeutic strategies for oncological diseases associated with CMV, including both hematological and solid tumors. The obtained data justify the need for further study of the use of dispersed fullerene dC₆₀ to potentiate chemotherapy in CMV-associated oncological diseases.

Conclusion

CMV induces resistance to DOX in hematopoietic (promyelocytic leukemia, monocytic leukemia) and solid (hepatocarcinoma) tumor models. It is noteworthy that the combined action of DOX with dispersed fullerene dC₆₀ not only overcomes virus-mediated drug resistance in monocyte leukemia cells but also achieves a pronounced cytotoxic effect at reduced concentrations of DOX, opening up prospects for the development of combined therapeutic regimens with reduced toxicity.

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