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ACTIVATION OF STORE – OPERATED Ca^{2+} ENTRY IN CISPLATIN RESISTANT LEUKEMIC CELLS AFTER TREATMENT WITH PHOTOEXCITED FULLERENE C_{60} AND CISPLATIN

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Ca^{2+}-regulating system in cancer cells is suggested to be remodulated particularly by reduced store-operated Ca^{2+} entry (SOCE) through plasma membrane in order to maintain moderately reduced cytosolic Ca^{2+} concentration and to avoid apoptosis. The endoplasmic reticulum (ER) Ca^{2+} pool content and the size of SOCE in leukemic wild type (L1210) and resistant to cisplatin (L1210R) cells in control, after treatment with either cisplatin (1 μg/ml) or photoexcited fulleren C_{60} (10^{-5} M) alone, or their combination were estimated with the use of Indo-1 AM. The SOCE in resistant to cisplatin L1210R cells was found to be lower than in the wild-type cells. After treatment with cisplatin the decrease of thapsigargin (TG)-sensitive ER Ca^{2+} pool with no significant increase of SOCE was observed in L1210 cells, while no changes were detected in L1210R cells. Photoexcitation of intracellular accumulated fullerene C_{60} in the visible range of spectrum (410-700 nm) was accompanied by increase of SOCE not only in sensitive, but in resistant cells as well. In resistant L1210R cells treated with photoexcited C_{60} essential effect of cisplatin on Ca^{2+} homeostasis became obvious: the size of SOCE proved to be higher than after treatment with photoexcited C_{60} alone. The data obtained allow suggesting the influence of photoexcited C_{60} not only on Ca^{2+}-regulating system, but on those involved in controlling cisplatin entry into drug resistant cancer cells.

K e y w o r d s: calcium, SOCE, leukemic cells, cisplatin, drug resistance, fullerene C_{60}.

Ca^{2+} is a ubiquitous signaling messenger involved in cell cycle, differentiation, proliferation and apoptosis regulation. Eukaryotic cells regulate Ca^{2+} concentration in cytosol ($[Ca^{2+}]_{cyt}$) by its release from intracellular stores (endoplasmic reticulum and mitochondria) or influx through plasma membrane Ca^{2+} channels. In non-excitable cells the major mechanism of Ca^{2+} influx into intracellular space is store-operated calcium entry (SOCE). SOCE is controlled by filling the endoplasmic reticulum (ER) Ca^{2+} store. Its depletion stimulates the opening of plasma membrane store-operated Ca^{2+} channels (SOCCs), that allows refilling the ER Ca^{2+} pool. The canonical components of store-operated Ca^{2+} entry are the integral ER membrane protein STIM-1, which acts as a Ca^{2+} sensor and plasma membrane protein ORAI1, which fulfils channel function after juxtaposition with STIM [1, 2].

The moderate increase of cytosolic Ca^{2+} level promotes proliferation, while high amplitude elevation of $[Ca^{2+}]_{cyt}$ induced, in particular, by SOCE can be followed by uncontrolled increase of Ca^{2+} concentration in mitochondria and cell death by apoptosis [3, 4].

In cancer, normal relationships among extracellular, cytosolic, endoplasmic reticulum and mitochondrial Ca^{2+} become distorted and Ca^{2+}-dependent signaling pathways are deregulated in a way to promote cancer hallmarks such as enhanced proliferation, survival and invasion [5]. Cancer cells have remodulated Ca^{2+} buffering system which allows maintaining $[Ca^{2+}]_{cyt}$ constantly at the relatively low level and to avoid apoptosis [6, 7]. Store-operated Ca^{2+} entry through plasma membrane and its release from ER in cancer cells are reduced due to increased expression of IP3R channels and decreased expres-

sion of ER Ca^{2+} ATPase [8,9]. It is shown that prostate cancer cells, upon transition to more aggressive androgen-independent phenotype, downregulate their SOCE by decreasing the expression of the principal plasma membrane SOC-channel-forming subunit, ORAI1 protein [10],

That is why searching for agents, which could activate Ca^{2+}-dependent apoptosis by restoring SOCE in cancer cells, is promising.

The widely used antitumor drug cisplatin (cis-Pt) could induce Ca^{2+}-dependent apoptosis via IP3R-mediated increase of cytosolic Ca^{2+} level, induction of ER stress and caspase-12 activation, but chemotherapeutic effect of cisplatin is limited by development of cancer cells multidrug resistance [11, 12]. Modulation of signaling pathways involved in development of drug resistance is considered to be a perspective approach for anticancer therapy optimization.

The representative of carbon nanostructures fullerene C_{60} demonstrates unique physicochemical properties: nanosize, ability to penetrate into cytoplasm and compatibility with biological molecules [13-15]. Fullerene C_{60} *per se* is biologically inert and becomes biologically active after its exposure to light. Due to extended π-conjugated system of molecular orbitals fullerene C_{60} absorbs UV/visible light efficiently and is able to generate cytotoxic reactive oxygen species (ROS) [16, 17]. Taking into account that components of cells' Ca^{2+} buffering system are sensitive to ROS [18, 19], redox regulation of their activity seems to be one of the ways to modulate Ca^{2+} homeostasis in cancer cells and to activate apoptosis program.

As it was previously shown by us with the use of fluorescent labeled C_{60} and confocal microscopy, leukemic cells could effectively uptake fullerene C_{60} from the medium [20]. Combined treatment of leukemic cells with photoexcited fullerene C_{60} and 1 μg/ml cisplatin allowed us to enhance cytotoxic effect and to accelerate cell death of both sensitive and resistant to cisplatin cells as compared with each agent to be used alone [20, 21], but the biochemical mechanisms of this effect need further elucidation. A substantial increase of $[Ca^{2+}]_{cyt}$ in leukemic cells which was detected 3 h after combined treatment with photoexcited C_{60} and cisplatin [21] could be one of the determining factors in this effect.

The aim of this study was to estimate the values of ER Ca^{2+} pool and store-operated calcium entry in sensitive and resistant to cisplatin leukemic cells in control and after treatment with either cisplatin or photoexcited fulleren C_{60} alone, or their combination.

Materials and Methods

Two murine leukemic cell lines – wild type, sensitive (L1210) and resistant (L1210R) to cisplatin were obtained from the Bank of Cell Lines from Human and Animal Tissues of R. E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, NAS of Ukraine. The both cell lines were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS, Sigma-Aldrich, Germany), 50 μg/ml penicillin and 100 μg/ml streptomycin at 37 °C in a 5% CO_2 humidified atmosphere. Cisplatin in a range of 0.1-10 μg/ml was shown to decrease the viability of L1210 in a dose dependent manner up to 90% during 72 h incubation with no effect on L1210R cells [21].

Homogeneous stable water colloid solution of fullerene C_{60} (10^{-4} M, purity >99.5%, nanoparticle average size 50 nm) was obtained at Technical University of Ilmenau (Germany) [22, 23]. Cells were incubated in RPMI 1640 medium for 2 h with or without fullerene C_{60} (10^{-5} M). Photoactivation of fullerene C_{60} accumulated by cells was done by probes irradiation with light-emitting diode lamp (410-700 nm light, irradiance 100 mW, during 2 min) in 12-well plate. After irradiation cells were incubated for 3 h and used for estimation of $[Ca^{2+}]_{cyt}$ and SOCE. In the case of combined treatment with photoexcited fullerene and cisplatin (Sigma, USA) the drug in concentration of 1 μg/ml was added to incubation medium.

Free cytosolic Ca^{2+} concentration was measured using fluorescent probe Indo-1 (Sigma, USA). Cells (3×10^7/ml) in buffer A consisting of (mM): KCl – 5, NaCl – 120, $CaCl_2$ – 1, glucose – 10, $MgCl_2$ – 1, $NaHCO_3$ – 4, HEPES – 10, pH 7.4 were loaded with Indo-1AM (1 mM) in the presence of 0.05% Pluronic F-127 (Sigma, USA) for 40 min at 25 °C, then washed by centrifugation (600 g, 10 min) and resuspended in buffer A. Cells loaded with Indo-1 (2.5×10^6 cells/ml) were treated with C_{60}, cisplatin or both as indicated above. Following incubation the cells were transferred to nominally Ca^{2+}-free buffer A containing 0.1 mM EGTA. ER Ca^{2+} content was estimated after addition of 1 μM thapsigargin (TG), store-operated Ca^{2+} entry was examined by adding 1 mM $CaCl_2$ to incubation medium. Indo-1 fluorescence in cells was recorded using spectrofluorometer (Shimadzu RF-510, Japan), λ excitation – 350 nm,

λ emission – 410 and 495 nm. The concentration of free cytosolic Ca^{2+} was calculated as described in [24].

The data were represented as mean ± SD of more than four independent experiments. Mean (M) and standard deviation (SD) were calculated for each group. Statistical analysis was performed using one-way ANOVA followed by post Tukey test. A value of $P < 0.05$ was considered statistically significant. Data processing was performed by IBM PC using specialized applications GraphPad Prism 7 (GraphPad Software Inc., USA).

Results and Discussion

The results of estimation of ER Ca^{2+} pool and store-operated calcium entry in sensitive and resistant to cisplatin L1210 cells in control are presented on Fig. 1 and Table. The ER Ca^{2+} pool content was estimated indirectly after Indo-1 loaded cells transfer into Ca^{2+}-free medium and addition of ER Ca^{2+}-ATPase inhibitor thapsigargin. The equilibrium concentration of cytosolic Ca^{2+} after 10 min incubation of L1210 and L1210R cells in Ca^{2+}-free medium was 110 ± 8 and 72 ± 4 nM respectively. It was shown that 1 μM TG caused transient low amplitude increase of $[Ca^{2+}]_{cyt}$, indicating the depletion of ER calcium pool (Fig. 1). The TG-induced increase of $[Ca^{2+}]_{cyt}$ above the equilibrium level at zero calcium ($\Delta[Ca^{2+}]_{cyt}$) was considered as the measure of ER Ca^{2+} pool content (Table). Subsequent readmission of Ca^{2+} into incubation medium of TG-treated cells allowed examining extracellular Ca^{2+} influx pathway. The size of Ca^{2+}-induced increase of $[Ca^{2+}]_{cyt}$ above

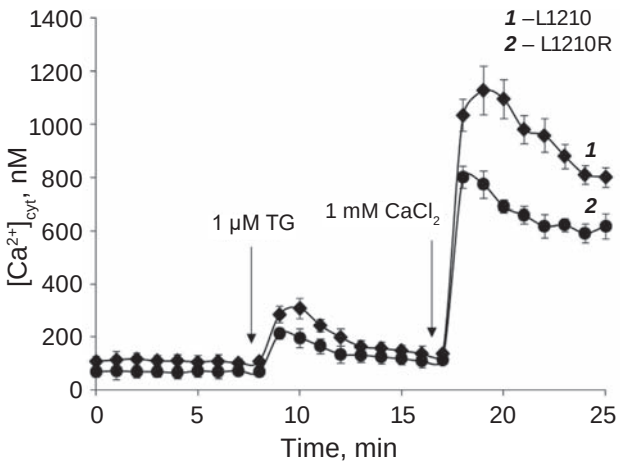

Fig. 1. Store-operated Ca^{2+} entry following thapsigargin-induced depletion of ER Ca^{2+} pool in sensitive and resistant to cisplatin L1210 cells

Table. ER Ca^{2+} pool and SOCE in leukemic cells

Preparations	L1210	L1210R
Thapsigargin-induced depletion of ER, $\Delta[Ca^{2+}]_{cyt}$, nM	190 ± 7	140 ± 4*
SOCE, $\Delta[Ca^{2+}]_{cyt}$, nM	794 ± 18	595 ± 20*

*$P < 0.05$ in comparison with L1210 cells

the equilibrium level after TG addition was considered as the measure of SOCE. Addition of 1 mM $CaCl_2$ caused high amplitude increase of $[Ca^{2+}]_{cyt}$, which was smaller in L1210R cells than in L1210 cells (Fig. 1). The size of SOCE was found to be 1.3 times lower in resistant than in sensitive to cisplatin L1210 cells (Table).

The difference of SOCE value in resistant and sensitive to anticancer drug cells was also demonstrated in [25], where SOCE in resistant to cisplatin lung cancer cells A549 was found to be reduced as compared with wild-type cells A549. It is assumed that reduced activation of SOCE may contribute to the cisplatin resistant phenotype of L1210 cells [26].

As it was earlier shown by us, a substantial increase of $[Ca^{2+}]$cyt in leukemic cells was detected 3 h after combined treatment with photoexcited C_{60} and cisplatin [21]. To investigate the possible reason of this event Ca^{2+} liberation from intracellular stores into the cytosol of leukemic cells was examined. The basal equilibrium concentration of cytosolic Ca^{2+} was estimated after cells transfer into Ca^{2+} free medium. It should be noted that fullerene C_{60} or light irradiation each applied separately had no evident effect on $[Ca^{2+}]_{cyt}$, TG-sensitive Ca^{2+} pool or SOCE (Figs. 2-4).

We have found that treatment of wild-type L1210 cells with cisplatin in concentration 1 μg/ml was followed by the 1.7 times increase of basal equilibrium cytosolic Ca^{2+} concentration after incubation in Ca^{2+} free medium in comparison with control. No elevation of basal equilibrium $[Ca^{2+}]_{cyt}$ in resistant to cisplatin L1210R cells was detected (Fig. 2).

In contrast to cisplatin, photoexcited fullerene C_{60} induced a considerable rise of basal equilibrium $[Ca^{2+}]_{cyt}$ in cells of both lines (Fig. 2).

More pronounced increase of $[Ca^{2+}]_{cyt}$ in the cells of both lines in the Ca^{2+} free medium was detected after combined action of photoexcited fullerene C_{60} and cisplatin. The level of cytosolic Ca^{2+} reached 317 ± 15 and 607 ± 24 nM in L1210 and L1210R cells, respectively (Fig. 2). The data obtained allowed us to suggest that enhancement of $[Ca^{2+}]_{cyt}$

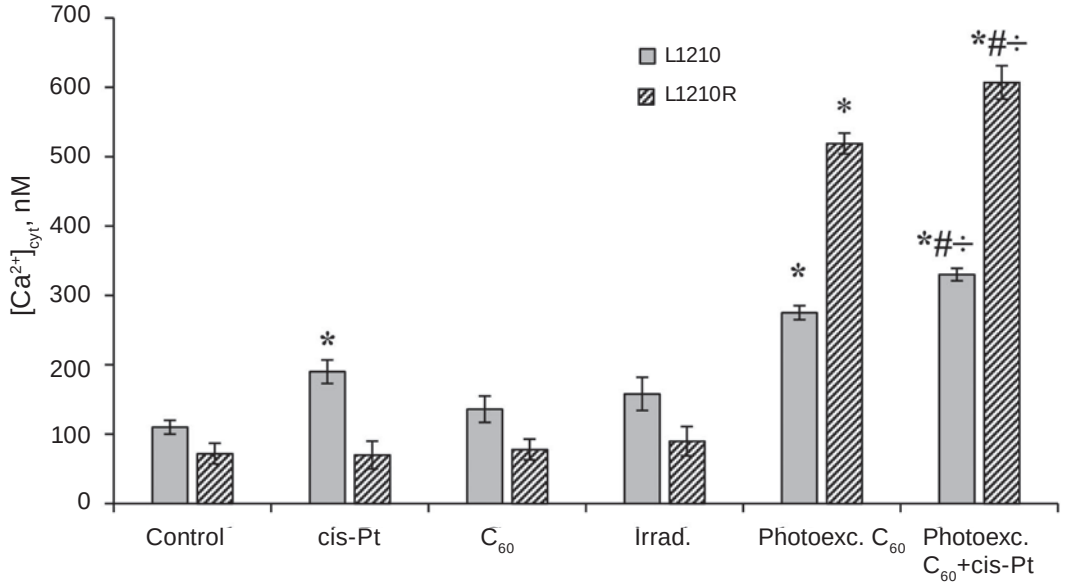

*Fig. 2. Concentration of cytosolic Ca^{2+} (nM) in leukemic cells transferred into Ca^{2+}-free medium 3 h after treatment. *$P < 0.05$ in comparison with control, $^{÷}P < 0.05$ in comparison with cisplatin, $^{\#}P < 0.05$ in comparison with photoexcited C_{60}*

in the Ca^{2+} free medium is the result of enhanced ER Ca^{2+} leak and/or reduced ER Ca^{2+} uptake. To confirm this the values of ER Ca^{2+} pool and store-operated calcium entry in leukemic cells 3 h after treatment with photoexcited fullerene C_{60}, cisplatin, and its combination were studied.

After treatment of wild-type L1210 cells with 1 μg/ml cisplatin the TG-induced increase of $[Ca^{2+}]_{cyt}$ above the equilibrium level was found to be somewhat reduced (Fig. 3) with no significant change of SOCE in comparison with control (Fig. 4). No change of either ER Ca^{2+}-content (Fig. 3) or SOCE (Fig. 4) was observed in L1210R after treatment with cisplatin.

After photoexcitation of accumulated fullerene C_{60} TG-sensitive ER Ca^{2+} pool was found to be decreased with simultaneous increase of SOCE both in sensitive and resistant to cisplatin leukemic cells. The TG-induced increase of $[Ca^{2+}]_{cyt}$ above the equilibrium level in L1210 and L1210R was 3.5 and 2 times lower (Fig. 3), while the size of SOCE was 2.2 and 1.8 times higher than in control, respectively (Fig. 4). As it was previously shown, photoexcitation of fullerene C_{60} accumulated by human lymphoma Jurkat cells was also accompanied by enhancement of SOCE and cell death by apoptosis [27]. We assume that the observed enhancement of SOCE in leukemic cells of both lines could be mediated in part by intense ROS production after fullerene C_{60} photoexcitation [28]. Prevoius studies have revealed a cross-talk between ROS and components of Ca^{2+}-regulating system [29]. Thus, functional activity of both IP3R and STIM appeared to be dependent on oxidation of their reactive thiol groups. Oxidation of IP3R thiol groups was shown to be followed by activation of IP3 receptors and Ca^{2+} release from ER [30, 31], while H_2O_2-induced modification of STIM Cys56 residue was followed by SOCE intensification [32].

After combined treatment of L1210 cells with photoexcited fullerene C_{60} and cisplatin the additive effect of both agents was detected, the ER Ca^{2+} content, as probed by TG application, was lower (Fig. 3) and the size of SOCE was higher (Fig. 4) compared with the respective values after treatment with photoexcited C_{60} or cisplatin separately.

It is interesting that the evident effect of cisplatin on Ca^{2+} homeostasis characteristics in L1210R cells treated with photoexcited C_{60} became evident: the TG-sensitive ER Ca^{2+} pool was lower (48 ± 4 vs. of 70 ± 3 nM) (Fig. 3) and the size of SOCE higher (1351 ± 35 vs. 1042 ± 40) (Fig. 4). These data suggest that photoexcited C_{60} may act not only on components of Ca^{2+} regulating system, but also on those involved in controlling antitumor drug influx and accumulation in cancer cells.

Lower TG-sensitive ER Ca^{2+} pool content in the presence of photoexcited C_{60} and cisplatin could

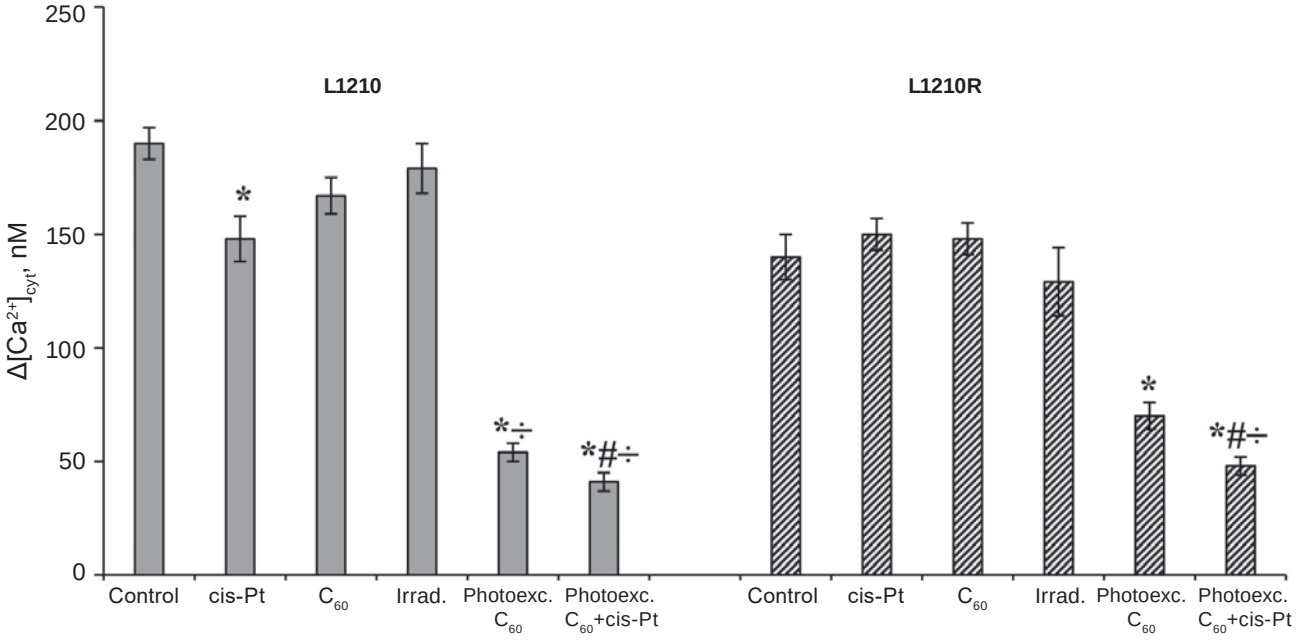

*Fig. 3. Thapsigargin sensitive ER Ca^{2+} pool in treated leukemic cells. *P < 0.05 in comparison with control, ÷P < 0.05 in comparison with cisplatin, #P < 0.05 in comparison with photoexcited C_{60}*

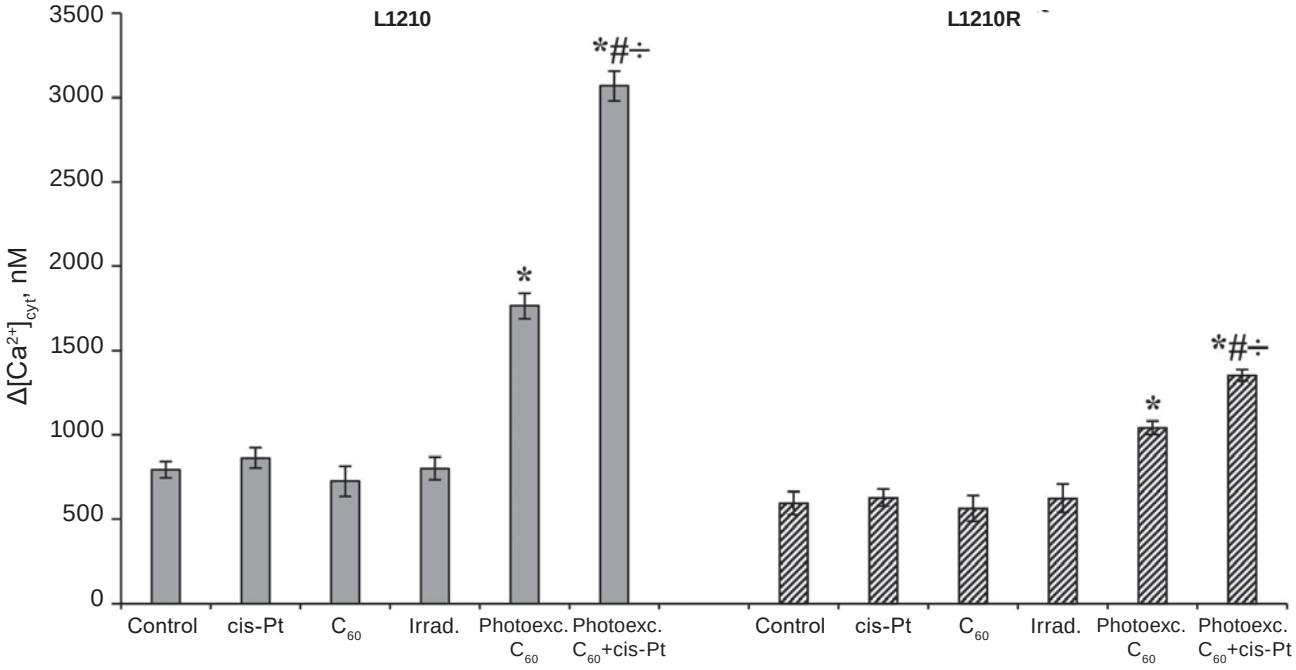

*Fig. 4. SOCE in treated leukemic cells. *P < 0.05 in comparison with control, ÷P < 0.05 in comparison with cisplatin, #P < 0.05 in comparison with photoexcited C_{60}*

result in a higher values of SOCE and $[Ca^{2+}]_{cyt}$ in leukemic cells. But it should be noted that the high level of $[Ca^{2+}]_{cyt}$ in cells of both lines, particularly in L1210R cells transferred into Ca^{2+}-free medium after combined action of photoexcited C_{60} and cisplatin (Fig. 2) could be caused not only by leak of Ca^{2+} from the ER, but from mitochondria as well. This assumption is confirmed by the data of mitochondrial membrane potential dissipation in L1210 and L1210R cells after treatment with photoexcited C_{60} [20].

In summary, we could conclude that photoexcitation of accumulated fullerene C_{60} allowed to enhance cisplatin cytotoxic effects and activate Ca^{2+}-dependent apoptotic pathway not only in sensitive leukemic cells, but also in leukemic cells resistant to cisplatin.

АКТИВАЦІЯ ЄМНІСНОГО ВХОДУ Ca^{2+} В РЕЗИСТЕНТНИХ ДО ЦИСПЛАТИНУ ЛЕЙКЕМІЧНИХ КЛІТИНАХ ЗА ДІЇ ФОТОЗБУДЖЕНОГО ФУЛЕРЕНУ C_{60} ТА ЦИСПЛАТИНУ

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Припускають, що у злоякісно трансформованих клітинах Ca^{2+}-регуляторна система є ремодульованою, зокрема, внаслідок послаблення входу катіона крізь плазматичну мембрану за ємнісним механізмом (SOCE), що дозволяє утримувати концентрацію цитозольного Ca^{2+} на помірно підвищеному рівні та уникати апоптозу. У роботі з використанням зонда Indo-1AM оцінено відносні величини Ca^{2+}-пулу ендоплазматичного ретикулума та ємнісного входу Ca^{2+} у лейкемічних клітинах дикого типу (L1210) та резистентних до цисплатину (L1210R) у контролі, за дії цисплатину (1 мкг/мл) або фотозбудженого C_{60} (10^{-5} М) окремо, чи за їх комбінації. Показано, що величина SOCE в резистентних до цисплатину клітинах L1210R була нижчою, ніж у клітинах L1210. За дії цисплатину величина тапсигаргін (TG)-чутливого Ca^{2+} пулу ЕПР у клітинах L1210 знижувалась без підвищення SOCE, тоді як у клітинах L1210R не було відмічено змін. Фотозбудження акумульованого фулерену C_{60} у видимому діапазоні спектра (410–700 нм) спричиняло посилення SOCE не тільки в чутливих, але й в резистентних до дії цисплатину клітинах. У резистентних клітинах L1210R за дії фотозбудженого фулерену C_{60} цисплатин впливав на Ca^{2+} гомеостаз: величина SOCE зростала більше, ніж за дії тільки фотозбудженого C_{60}. Одержані дані вказують на вплив фотозбудженого C_{60} не тільки на Ca^{2+}-регуляторну систему, але й на компоненти систем, що контролюють надходження цисплатину в резистентних до препарату злоякісно трансформованих клітинах.

Ключові слова: кальцій, SOCE, лейкемічні клітини, резистентність до цисплатину, фулерен C_{60}.

АКТИВАЦИЯ ЁМКОСТНОГО ВХОДА Ca^{2+} В РЕЗИСТЕНТНЫХ К ЦИСПЛАТИНУ ЛЕЙКЕМИЧЕСКИХ КЛЕТКАХ ПРИ ДЕЙСТВИИ ФОТОВОЗБУЖДЕННОГО ФУЛЛЕРЕНА C_{60} И ЦИСПЛАТИНА

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Предполагается, что в злокачественно трансформированных клетках Ca^{2+}-регуляторная система ремодулирована, в частности, вследствие ослабленного входа катиона через плазматическую мембрану по ёмкостному механизму (SOCE), что позволяет поддерживать концентрацию цитозольного Ca^{2+} на умеренно повышенном уровне и избегать апоптоза. В работе с использованием зонда Indo-1AM оценены относительные величины Ca^{2+}-пула эндоплазматического ретикулума и ёмкостного входа Ca^{2+} в лейкемических клетках дикого типа (L1210) и резистентных к цисплатину (L1210R) в контроле, при действии цисплатина (1 мкг/мл) или фотовозбужденного C_{60} (10^{-5} М) отдельно, или в комбинации. Показано, что величина SOCE в резистентных к цисплатину клетках L1210R была ниже, чем в клетках L1210. При действии цисплатина величина тапсигаргин (TG)-чувствительного Ca^{2+}-пула ЭПР в клетках L1210 снижалась без усиления SOCE, тогда как в клетках L1210R не было отмечено изменений. Фотовозбуждение аккумулированного фуллерена C_{60} в видимом диапазоне спектра (410–700 нм) приводило к усилению SOCE не только в чувствительных, но и в резистентных к цисплатину клетках. При действии фотовозбужденного фуллерена C_{60} в резистентных L1210R клетках наблюдалось влияние цисплатина на Ca^{2+} гомеостаз: величина SOCE возростала больше, чем при действии только фотовозбужденого C_{60}. Полученные данные указывают на

действие фотовозбужденного C_{60} не только на Ca^{2+}-регуляторную систему, но и на компоненты систем, контролирующих поступление цисплатина в резистентных к препарату злокачественно трансформированных клетках.

Ключевые слова: кальций, SOCE, лейкемические клетки, резистентность к цисплатину, фуллерен C_{60}.

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