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EFFECT OF ANTICANCER DRUGS ON PRODUCTION OF TRANSFORMING GROWTH FACTOR B AND EXPRESSION OF P53 AND BCL-2 PROTEINS BY MCF-7 AND T47D CELL LINES OF HUMAN BREAST CARCINOMA

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Aim: **To compare the capability of methotrexate, cisplatin, doxorubicine and vincristine to induce production of the transforming growth factor β_1 (TGF-β_1) in two cell lines — MCF-7 and T47D — of human breast carcinoma, as well as to study sensitivity of these cells to TGF-β_1 and mentioned anticancer drugs.** ***Materials and Methods:*** **ELISA for detection of TGF-β content in conditioned culture media and Western-blot analysis of the proapoptotic p53 and antiapoptotic Bcl-2 proteins were applied.** ***Results:*** **t47d cells showing higher resistance to growth inhibiting effect of TGF-β_1 were also refractory to cisplatin. There was no difference between MCF-7 and T47D cells in their sensitivity to methotrexate and doxorubicine, although T47D cells were more sensitive to vincristine. It was found that methotrexate and vincristine did not affect TGF-β_1 production, while doxorubicine used at a dose of 1–100 ug/ml, significantly induced TGF-β_1 production in both cell lines. p53 expression in T47D cells was higher than in MCF-7 cells where only doxorubicin induced strongly p53 expression. It should be noted, that Bcl-2 was better expressed in MCF-7 cells, while it was almost undetectable in T47D cells.** ***Conclusion:*** **In cells of human mammary carcinoma of MCF-7 and T47D lines doxorubicine, unlike vincristine and methotrexate, in dose depending manner induces production of TGF- β_1. TGF- β_1 production in carcinoma cells was associated with doxorubicine-mediated p53 expression in MCF-7 cells or high basal level of p53 in T47D cells. The cells of MCF-7 line were more sensitive to growth inhibition by exogenous TGF- β_1 and to cisplatine action than T47D cells, but there was no difference between these cell lines in sensitivity to other anticancer drugs.**

Key Words: **human breast carcinoma, MCF-7 and T47D cell lines, anticancer drugs, transforming growth factor β, apoptosis, p53, Bcl-2.**

A continuous application of chemotherapy at cancer treatment was found to cause development of resistance to anticancer drugs in more than one third of cancer patients [1]. This phenomenon was explained by the expression of proteins that ensure multi-drug resistance in tumor cells [2]. However, in many cases the resistance of tumor cells to different drugs was not dependent on that mechanism [3]. Recently, we discovered cross-resistance of tumor cell to the anticancer drug cisplatin and to growth inhibitory cytokine transforming growth factor β_1 (TGF-β_1) [4]. While the cisplatin-sensitive parental line of murine leukemia L1210 cells possessed intact TGF-β_1 signaling pathway, the cisplatin-resistant L1210/R cells were characterized by a decreased level of type-I receptor of this cytokine and an increased level of expression of Smad6 protein that inhibits post-receptor TGF-β_1 signaling [4]. Thus, the regulatory pathways of the leukemia cells resistant to growth inhibiting effect of cisplatin are also violated, which makes these cells refractory to the inhibiting action of TGF-β_1.

Earlier, we found [5] that such anticancer drugs as cisplatin, doxorubicine, and methotrexate affected human lung adenocarcinoma A549 cells. These drugs not only induced the target cells to produce more TGF-β_1, but also affected expression of mRNA coding for type II receptor of TGF-β_1. Besides, they caused changes in the post-receptor Smad-dependent TGF-β_1 signaling pathway, namely: 1) decreased expression of Smad2, Smad3 and Smad4 proteins that ensure transduction of TGF-β_1 regulatory signals from its specific receptors on the target cell surface to the nucleus; 2) increased expression of Smad7 protein that inhibits Smad-dependent TGF-β_1 signaling pathway. Furthermore, it was discovered that doxorubicine repressed a capacity of TGF-β_1 to induce phosphorylation of Smad2 and Smad3 proteins in A549 cells. Such modification of Smad2 and Smad3 proteins is required for their activation [5]. Thus, it might be suggested that doxorubicine inhibits transduction of TGF-β_1 signaling in A549 cells by inducing both TGF-β_1 production and action. That effect was specific for TGF-β_1 signaling pathway, since phosphorylation of Erk-1 and Erk-2 protein kinases participating in another regulatory pathway, was not changed under the effect of doxorubicine [5].

Thus, regardless of the capacity of anticancer drugs to induce TGF-β_1 production by tumor cells, in some cases, this inhibitory cytokine is not capable of displaying its negative effect towards tumor cells, because of impairment in its signaling pathway.

Since an assumption about a potential role of TGF-β_1 produced by cancer cells, in realization of their response

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Abbreviations used: TGF-β_1 – transforming growth factor β_1.

to the effect of anticancer drugs, was based on studying a limited number of tumor cell lines, it was expedient to continue such study using other human cancer cell lines. To address that aim, MCF-7 and T47D lines of human breast carcinoma cells were used. In addition to measuring TGF-β_1 production by these cells in response to the anticancer drugs (doxorubicine, cisplatin, methotrexate and vincristine), an expression of proapoptotic p53 protein and antiapoptotic Bcl-2 proteins was studied which could be helpful in discovering novel mechanisms of the antineoplastic effect of those drugs.

MATERIALS AND METHODS

Cell lines. MCF-7 and T47D cell lines of human breast carcinoma were obtained from cell culture collection at Ludwig Institute for Cancer Research (Uppsala, Sweden). The cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Sigma Chem. Co., USA), supplemented with 10% fetal bovine serum (FBS, Sigma Chem. Co.). In some experiments (noted in Figure legends), final concentration of FBS in the culture medium was lowered to 2% or 0.1%. Murine leukemia cells L1210 (L1210/S and L1210/R) were obtained from the cell culture collection at R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, National Academy of Sciences of Ukraine (Kyiv, Ukraine).

Reagents. A majority of used reagents were produced by Sigma, Fluka, Serva and Difco companies. Other reagents were of high qualification standards. TGF-β_1 and reagents for TGF-β_1 ELISA were manufactured by R & D Systems, Inc. (USA). The following anticancer drugs were used: adriamycin (doxorubicine; Ebeve, Austria), cisplatin (Ebeve), methotrexate (Ebeve) and vincristine (Faulding Pharmaceuticals, Australia).

Measurements of cell proliferation and viability. Cell number and viability was defined by the trypan blue exclusion test. The numbers of dead (stained) cells and alive (unstained) cells were counted in hemocytometer after 5 min incubation with this dye. The effects of TGF-β_1 and specific anticancer drugs on growth and survival of MCF-7 and T47D cells were studied using different concentrations of these drugs (24 h incubation) or various time of their action (noted in the figure legends).

ELISA measurement of TGF-β_1 production. TGF-β_1 content in the conditioned medium was defined by ELISA (Quantikine DB100, R&D Systems Inc., USA) using the manufacturer's recommendations.

Western-blot analysis. Tested cell lysates (30 µg of protein per well) were subjected to vertical denaturating electrophoresis in 10% polyacrylamide gel. After electrophoresis, proteins were transferred by electrophoresis onto a polyvinylidenedifluoride membrane, that was incubated overnight at 4 °C with anti-p53 rabbit polyclonal antibodies at ratio 1:2000 or anti-Bcl-2 rabbit polyclonal antibodies (both Santa Cruz Biotechnology, USA) at ratio of 1:1000. Secondary antibodies against rabbit IgG conjugated with horseradish peroxidase (Sigma, USA) were used in ratio 1:5000 (1 h, 4 °C, at rocking). The membrane was exposed to the X-ray film (Fuji Film) for 10 min that was developed under standard procedure.

Statistical analysis. All experiments were repeated three times with three parallel tests in each variant. Two variables were compared on the basis of difference certainty *t*-index (Student's criterion). The difference was considered certain when difference certainty *p* was less than 0.05.

RESULTS

Effect of TGF-β_1 and anticancer drugs on growth and survival of breast carcinoma cells. It is shown in Fig. 1 that TGF-β_1 inhibits growth and induces death of MCF-7cells. TGF-β_1 effect on cell growth becomes distinct only on the 3rd–5th day of the cytokine action, and can be clearly disclosed only at the conditions of FBS deficiency (0.1% or 2%) in cell culture medium. In the presence of 10% FBS, growth-inhibiting effect of TGF-β_1 was not observed (the data are not presented). Cell death induction under the effect of TGF-β_1 was also distinct only at the conditions of 2% FBS in the culture medium (see Fig. 1).

The character of TGF-β_1 effect on growth and survival of T47D cells was different comparing to MCF-7 cells. TGF-β_1 did not show significant impact on cell growth and survival even at low FBS content in the culture medium (Fig. 2).

Methotrexate dose-dependently inhibited growth of the MCF-7 or T47D cells, while methotrexate did not demonstrate significant effect on survival of cells of both cell lines (Fig. 3). Doxorubicine and vincristine were shown to possess similar dose-dependent cytostatic action towards both studied cell lines. However, the strongest effect of vincristine towards T47D cells was achieved at much lower concentrations of this drug, comparing to such effect of the drug in case of the MCF-7 cell testing (see Fig. 3). No significant difference between MCF-7 and T47D cells upon 24 h treatment was found in the intensity of cell death under the action of all studied cytostatics.

Effect of anticancer drugs on TGF-β_1 production by MCF-7 and T47D cells. The results of present study proved that doxorubicin (1–100 µg/ml) induced a secretion of TGF-β_1 by both MCF-7 and T47D cells (Fig. 4). The effect of methotrexate and vincristine was not significant here because of considerable variations in TGF-β_1 level in separate samples of culture medium (see Fig. 4).

Expression of p53 and Bcl-2 proteins by MCF-7 and T47D cells. The results of our experiments showed that the cells of both studied lines expressed p53 protein but T47D cells expressed p53 on higher level than MCF-7 cells (Fig. 5). The level of expression of p53 in the MCF-7 cells was insignificantly changed under the effect of vincristine, methotrexate, and cisplatin, while the doxorubicine induced p53 expression considerably. In this experiment, cisplatin-sensitive murine leukemia L1210/R cells as a positive control and cisplatin-resistant L1210/S cells as a negative control for p53 expression were used [4]. It was found that

the above mentioned anticancer drugs did not affect significantly p53 expression in T47D cells.

As far as Bcl-2 protein is concerned, vincristine induced its expression in the MCF-7 cells, while the other anticancer drugs under study had no effect on it. Different situation was observed in T47D cells, where the expression of Bcl-2 was found to be at a very low level. In that experiment, Jurkat T-cells were used, as a positive control for Bcl-2 expression. None of the anticancer drugs under study was capable of affecting Bcl-2 expression in T47D carcinoma cells.

DISCUSSION

This work is a continuation of our former study [4] devoted to the interrelations between the action of anticancer drugs on specific tumor cells, their production of TGF-β_1 in response to the drug effect,

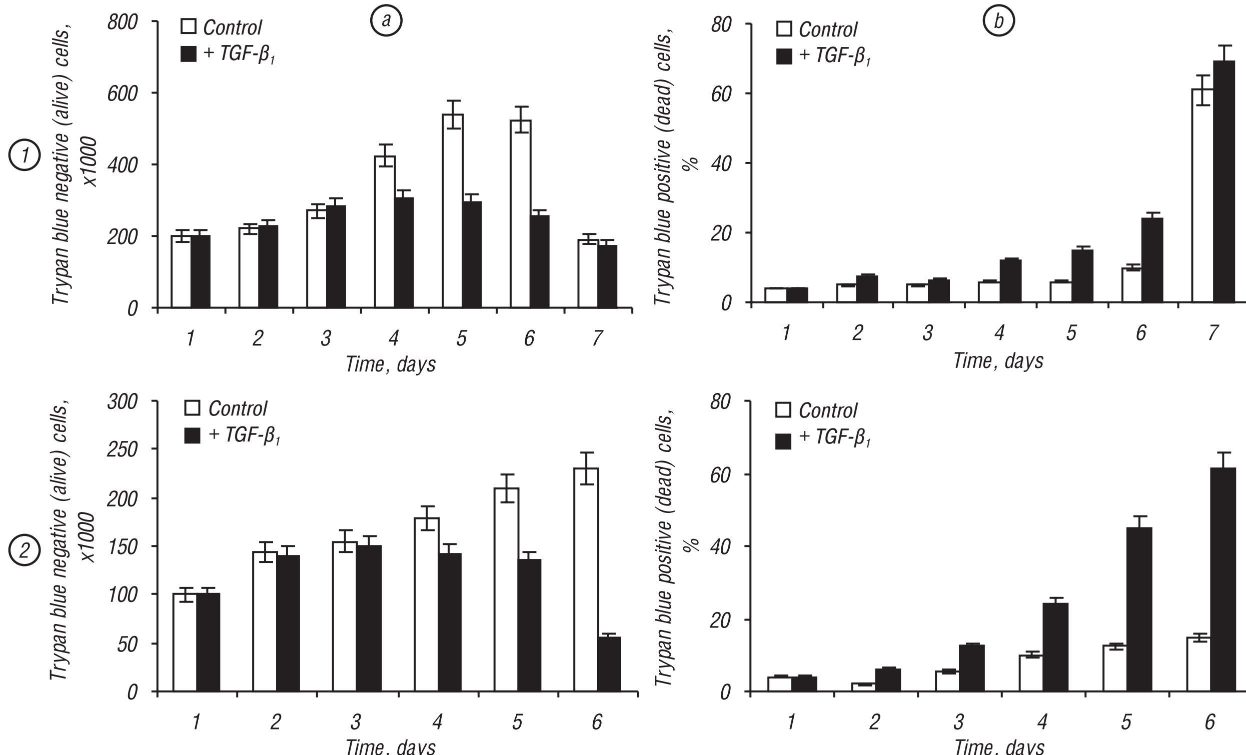

Fig. 1. Effect of TGF-β (10 ng/ml) on growth *(a)* and survival *(b)* of human breast carcinoma cells of MCF-7 line; (1) in the presence of 0.1% FBS; (2) in the presence of 2.0% FBS

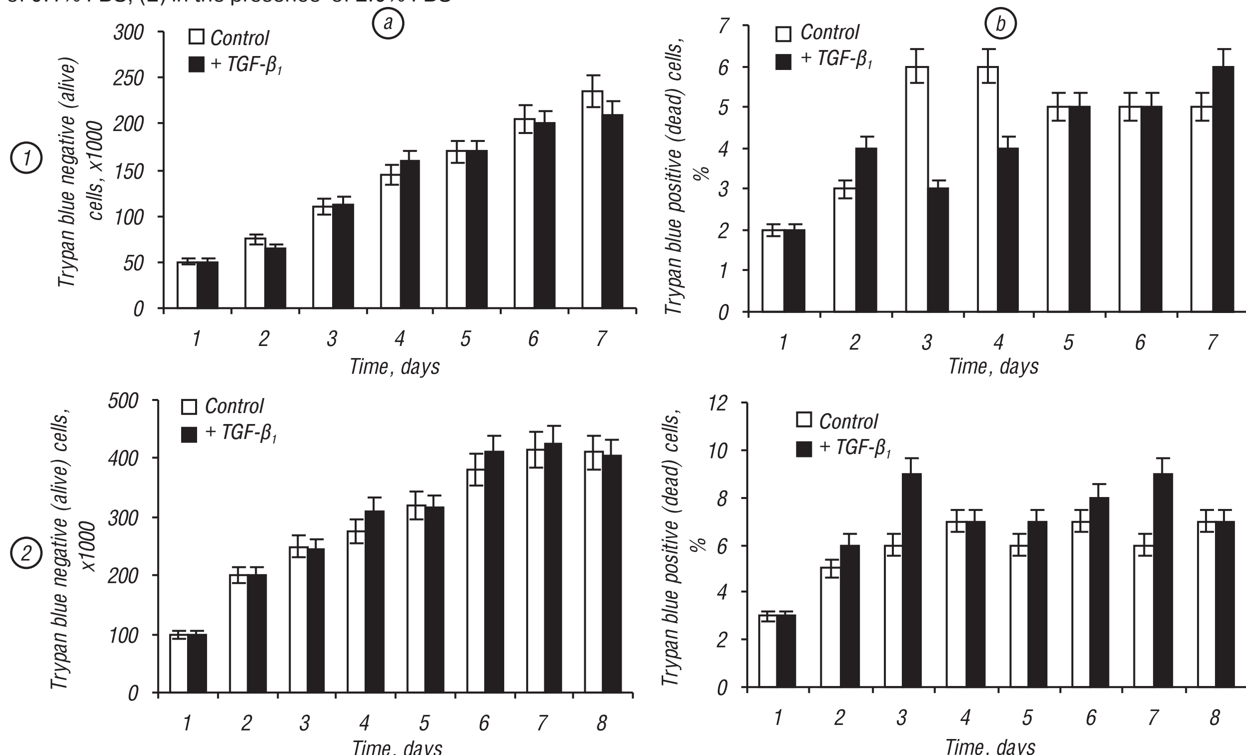

Fig. 2. Effect of TGF-β_1 (10 ng/ml) on growth *(a)* and survival *(b)* of human breast carcinoma cells of T47D line; (1) in the presence of 0.1% FBS; (2) in the presence of 2.0% FBS

and the intactness of TGF-β_1 signaling system in the target tumor cells. Two lines — MCF-7 and T47D — of human breast carcinoma cells were used as experimental models. We studied the effects of methotrexate, cisplatin, doxorubicine and vincristine towards growth and viability of those cells, as well as on their production of TGF-β_1, and the expression of p53 and Bcl-2 proteins.

TGF-β_1 is one of the most ubiquitous in human body natural inhibitors of proliferation of cells of epithelial origin that give rise to a majority of human tumors, including breast cancer [16]. Earlier, we have shown that various cytotoxic agents, in particular anticancer drugs, specific lectins, X-rays, and hyperthermia [4, 7], induced a significant rise in the level of TGF-β_1 secretion by different malignant cells. In present study, it was found that MCF-7 cells possessed higher sensitivity to growth-inhibiting action of TGF-β_1 comparing to T47D cells. At the same time, there was no significant difference between these two cell lines regarding their sensitivity to other anticancer drugs, such as doxorubicine, methotrexate, or vincristine.

We also discovered that TGF-β_1 secretion induced by the anticancer drugs in breast carcinoma cells was dependent on dose and duration of drug action. An emphasis on measuring specific cytokines' level is based on their potential role as diagnostic or prognostic indicators, in particular at estimating an effectiveness of cancer treatment. In this field, most attention has been paid to TGF-α, TGF-β_1, endothelial growth factor, and some other cytokines [8]. TGF-β and endothelial growth factor have been considered as important indicators of both malignant growth and regenerative processes in the organism. At the same time, it is not so easy to evaluate the role of changes in production of active form of TGF-β_1, or the role of impairment in its intracellular signal transduction mechanisms that were observed in cancer patients and in patients with severe immunological disorders. These indicators are not so uniform, as those found for the TGF-β and endothelial growth factor, and, thus, it is not so easy to explain their role in the mechanisms of tumor development [9].

An elevated TGF-β_1 content was revealed in blood plasma of breast [10], lung [11, 12], and prostate

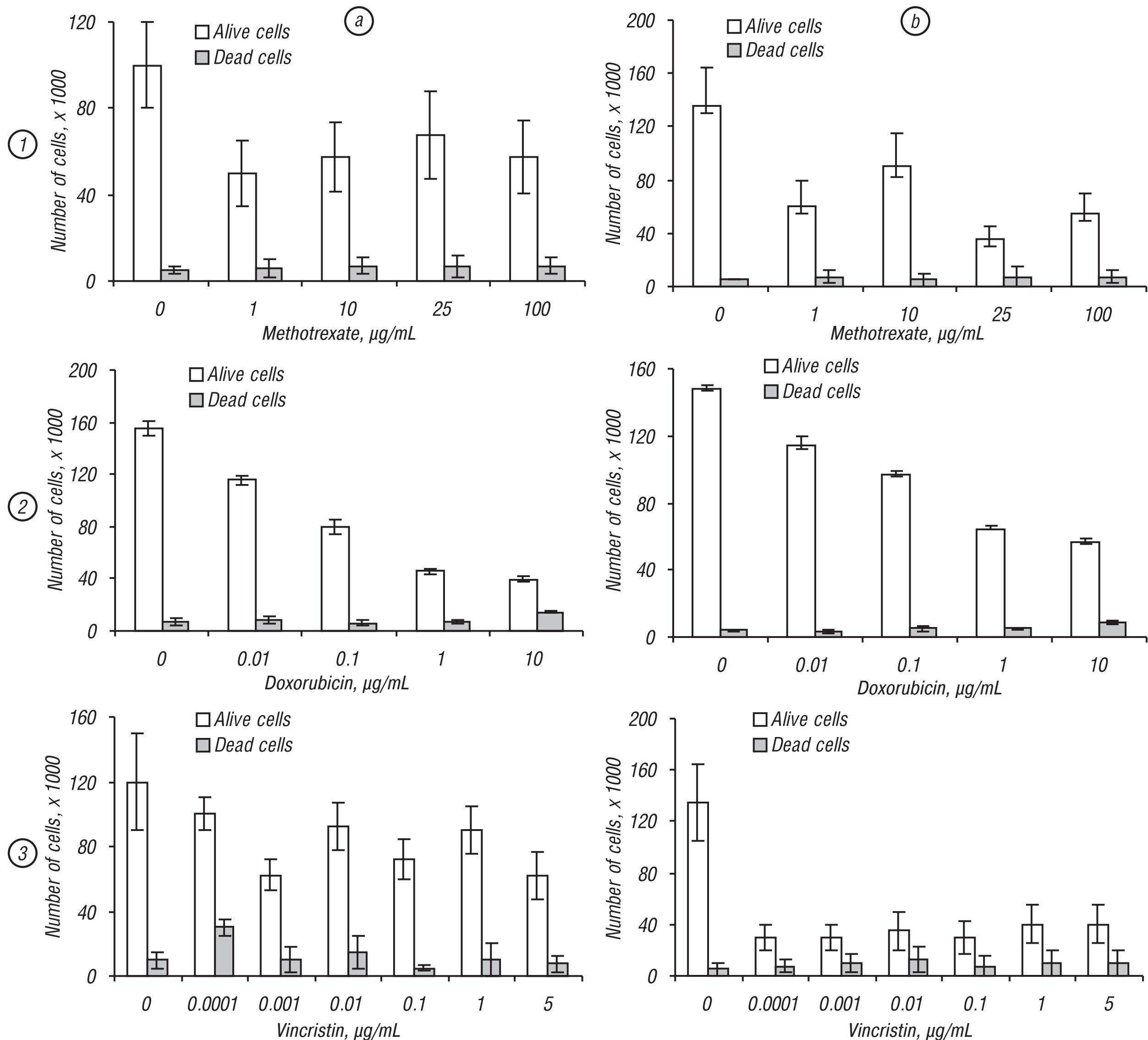

Fig. 3. Effect of methotrexate (1), doxorubicine (2) and vincristin (3) on growth and survival of human breast carcinoma cells of MCF7 *(a)* and T47D *(b)* after 24 h of co-incubation

cancer patients [13], as well as in patients with hepatocellular carcinomas [14]. Moreover, in a series of experimental animal models of breast and prostate cancers, the interdependence between the TGF-β_1 expression level, from one side, and tumorigenesis, increased invasiveness, and drug resistance, from another side, was demonstrated [15]. A similar regularity has been discovered in patients bearing tumors of rectum, stomach, endometrium, ovary, neck area, and in glioma and melanoma patients [15]. A heightened level of TGF-β_1 production was also observed in nude rats inoculated with various human tumors [15].

However, data have been also found in literature, although not so evident, that cancer patients, e.g. with chronic lymphocytic leukemia, have a decreased plasma level of TGF-β_1 [8]. Since in one group of studies a heightened level of this cytokine in lung cancer patients positively correlated with better health prognosis [16, 17], while in another group of studies it correlated with a worse prognosis [12], an issue of the role of increased production of this cytokine at tumor growth requires further clarification. One of plausible explanations for such a state of things might be a development of resistance of malignant cells to the TGF-β_1 growth inhibiting effect. It was found that despite of small-cell lung carcinoma cells were very actively producing TGF-β_1 [18], at the same time, they were resistant to its growth inhibiting effect [19].

Since it has been established that MCF-7 and T47D cells differ in their sensitivity to the apoptosis-inducing action of certain anticancer drugs, it was worth to compare the effect of those drugs on the expression of proapoptotic p53 protein and antiapoptotic Bcl-2 protein in the above mentioned cells. Earlier, we have demonstrated a loss of p53 expression and a higher level of Bcl-2 expression in the L1210/R cells, cross-resistant to the apoptosis-inducing effect of cisplatin and TGF-β_1 [4]. However, there is also evidence that p53 malfunctions and cell resistance to the action of DNA-damaging agents inducing apoptosis, are independent phenomena in certain types of malignant cells [20].

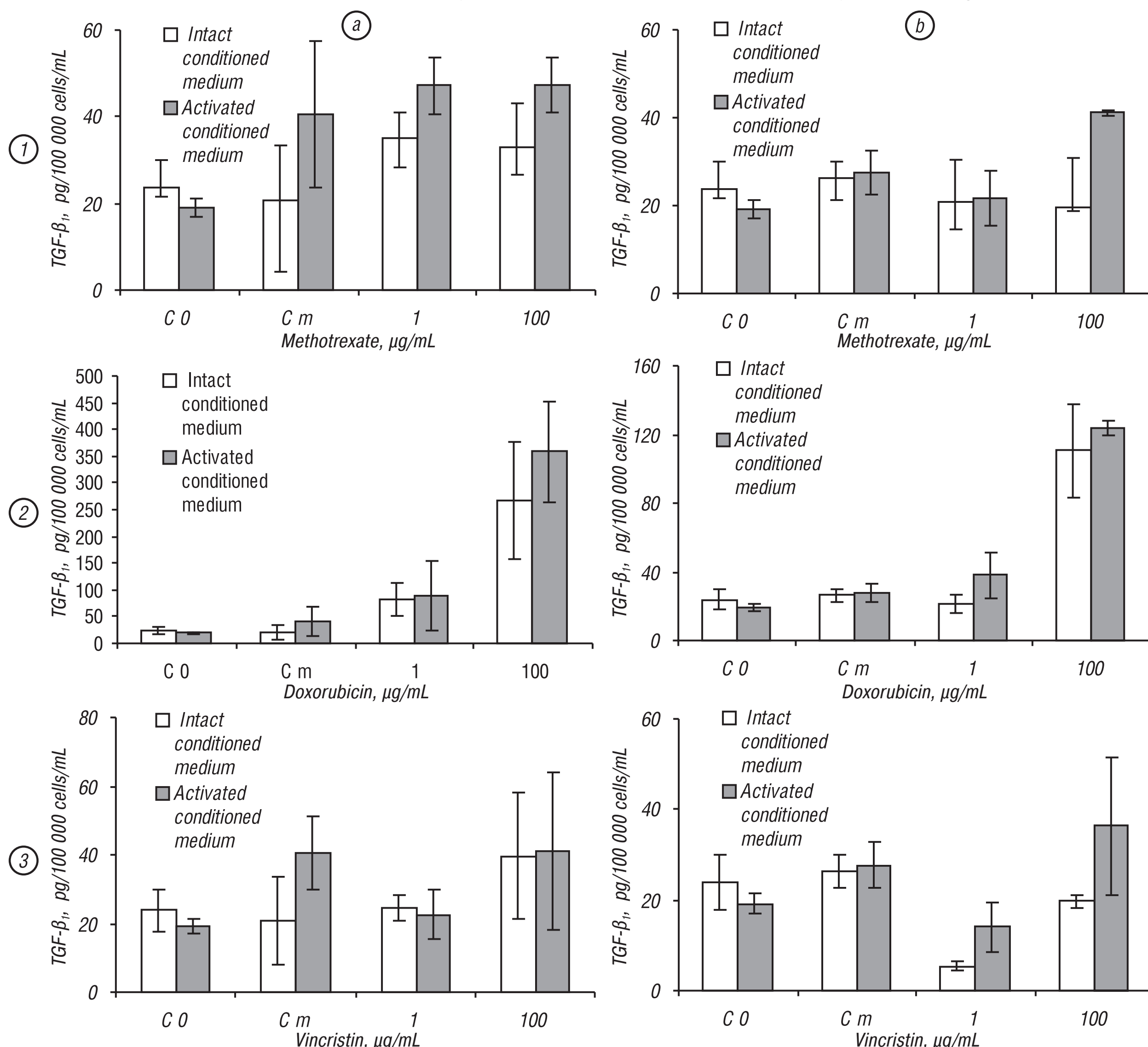

Fig. 4. Effect of methotrexate (1), doxorubicine (2) and vincristin (3) on the production of TGF-β by human breast carcinoma cells of MCF7 *(a)* and T47D *(b)* after 24 h of co-incubation. C0 — fresh cultural medium; Cm — conditioned cultural medium obtained from the intact cells of MCF-7 *(a)* and T47D *(b)* respectively

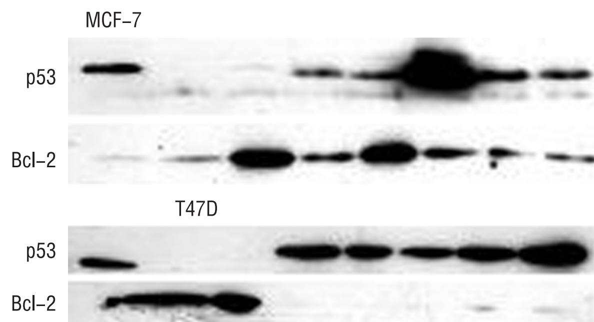

Fig. 5. Effect of anticancer drug on the expression of pro-apoptotic protein p53 and anti-apoptotic protein Bcl-2 in human breast carcinoma lines MCF7 and T47D (expression of these proteins in murine leukemia cells of L1210 line was used as positive (L1210/S) and negative (L1210/R) controls for p53 expression, and human Jurkat T cells were used as positive control for Bcl-2 expression). 1 — L 1210/S; 2 — L1210/R; 3 — Jurkat T cells; 4 — control (MCF7 or T47D cells); 5 — vincristin, 10 ng/ml; 6 — doxorubicine, 1 µg/ml; 7 — methotrexate, 10 µg/ml; 8 — cisplatin, 1 µg/ml

We found a decreased basal level of p53 expression in the MCF-7 cells compared with T47D cells, and a very low level of Bcl-2 expression in T47D cells, comparing to MCF-7 cells. These data do not correspond to similar sensitivity of two carcinoma cell lines to doxorubicine, methotrexate, and vincristine. Altogether, these facts suggest the unreliability of using p53 and Bcl-2 expression as the biological indicators for apoptosis monitoring. It seems reasonable to use additional biological indicators for that purpose, such as the state of caspase system, redistribution of the cytochrome C between mitochondria and cytoplasm, etc. that could better characterize a development of drug-induced apoptosis in tumor cells.

Thus, following conclusions can be suggested taking into account the results of present study: a) in case when the malignant cells are sensitive to TGF-β_1 inhibitory action, an induction of production of this cytokine by the anticancer drug might cause a stronger inhibitory effect of the drug towards growth of tumor cells because of an additional input of TGF-β_1 via an autocrine regulatory loop; b) if the anticancer drug affects malignant cells resistant to the inhibitory action of TGF-β_1, the effect of the autocrine TGF-β_1, induced by the drug, will be absent.

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ВЛИЯНИЕ ПРОТИВООПУХОЛЕВЫХ ПРЕПАРАТОВ НА ПРОДУКЦИЮ ТРАНСФОРМИРУЮЩЕГО ФАКТОРА РОСТА В И ЭКСПРЕССИЮ БЕЛКОВ P53 И BCL-2 КЛЕТКАМИ ЛИНИЙ MCF-7 И T47D КАРЦИНОМЫ МОЛОЧНОЙ ЖЕЛЕЗЫ ЧЕЛОВЕКА

Цель: провести сравнительный анализ способности метотрексата, цисплатина, доксорубицина и винкристина индуцировать продукцию трансформирующего фактора роста (ТФР)-β_1 клетками рака молочной железы человека (линии MCF-7 и T47D), а также исследовать чувствительность этих клеток к ТФР-β_1 и указанным противоопухолевым препаратам. _Материалы и методы:_ для определения содержания ТФР-β_1 в кондиционированной среде использовали иммуноферментный анализ. Уровень белков p53 и Bcl-2 оценивали методом иммуноблоттинга. _Результаты:_ клетки t47d, которые характеризовались большей резистентностью к ростингибирующему действию ТФР-β_1 по сравнению с клетками MCF-7, оказались менее чувствительными к цисплатину. Не выявлено различий между чувствительностью клеток MCF-7 и T47D к действию метотрексата или доксорубицина, хотя клетки T47D были более чувствительными к винкристину. Метотрексат и винкристин не влияли на продукцию ТФР-β_1 клетками MCF-7 и T47D, тогда как доксорубицин в дозе 1–100 мкг/мл существенно усиливал продукцию ТФР-β_1. Экспрессия белка p53 была более интенсивной в клетках T47D, по сравнению с клетками линии MCF-7, и лишь в случае действия доксорубицина на клетки линии MCF-7 было выявлено значительное повышение его уровня. При этом белок Bcl-2 был выявлен только в клетках MCF-7. _Выводы:_ в клеточных линиях карциномы молочной железы человека (MCF-7 и T47D) доксорубицин, в отличие от винкристина и метотрексата, дозозависимо индуцирует продукцию ТФР-β_1. Индукция доксорубицином ТФР-β_1 в клетках карцином ассоциирована с индукцией экспрессии p53 в клетках MCF-7 или повышенным базальным уровнем этого белка в клетках T47D. Клетки линии MCF-7, более чувствительные к рост-ингибирующему действию экзогенного ТФР-β_1, чем клетки линии T47D, отличаются и более выраженной чувствительностью к действию цисплатина, но не отличаются по чувствительности от других цитостатиков.

Ключевые слова: рак молочной железы человека, линии клеток MCF-7 и T47D, противоопухолевые препараты, трансформирующий фактор роста-β, апоптоз, p53, Bcl-2.

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