ACTION OF SARCOLYSIN ON NUCLEIC ACID SYNTHESIS IN MONOLAYER CULTURES OF HUMAN TUMOR CELLS

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Using stable monolayer cultures of human tumor cells (carcinoma of the stomach, ovary, and pancreas, angiosarcoma, mesenchymoma) the action of sarcolysin in various concentrations on the incorporation of labeled precursors into nucleic acids and proteins was studied. Sarcolysin inhibited the incorporation of labeled adenine into nucleic acids of tumor cells by between 74 and 52% and incorporation of labeled lysine into protein by between 60 and 66%.

Disturbance of the synthesis of nucleic acids and protein by antitumor chemotherapeutic compounds can be used as an objective criterion of their action.

The object of the investigation described below was to determine the action of sarcolysin on human tumor cells, using inhibition of synthesis of nucleic acids and protein in the experimental material as the test.

EXPERIMENTAL METHOD

The effect of sarcolysin on incorporation of adenine-8-C^{14} (21 mCi/g), uridine-2-C^{14} (26 mCi/g), DL-lysine-1-C^{14} (56 mCi/g) into nucleic acids and protein was studied in stable monolayer cultures of cells from carcinoma of the stomach (CaVe), carcinoma of the ovary (CaOv), carcinoma of the pancreas (CaPa), angiosarcoma (Sa"709"), and mesenchymomas (Sa"129" and Sa"19") in a stage of logarithmic growth. Altogether 94 experiments were carried out: 33 with labeled adenine, 18 with uridine, and 43 with lysine. Except for the duration of incubation of the samples (4 h at 37°), the experimental conditions were the same as in the previous investigation [1].

Viability of the cells was determined by subculture and counting the number of living cells after contact with sarcolysin under experimental conditions.

The results relating to incorporation of labeled precursors into the macromolecules were plotted graphically.

EXPERIMENTAL RESULTS

The results of experiments of series I to study the effect of sarcolysin on incorporation of adenine-8-C^{14} into nucleic acids in tumor cells of 6 listed cell lines are shown in Fig. 1.

These results show that sarcolysin (100 μg/ml) considerably inhibits the incorporation of the labeled nitrogenous base into nucleic acids of the tumor cells (by between 74 and 52% depending on the cell line).

Cells of carcinoma of the stomach (CaVe) and angiosarcoma (Sa"709") were most sensitive to the action of sarcolysin, and inhibition of nucleic acid synthesis occurred to the degree of 74-73% in the cells of

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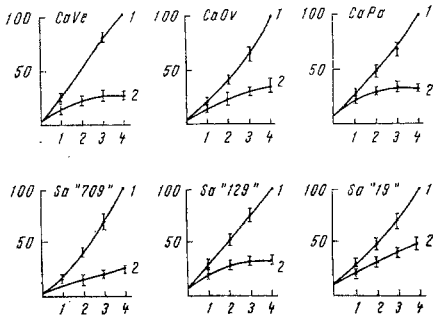

Fig. 1

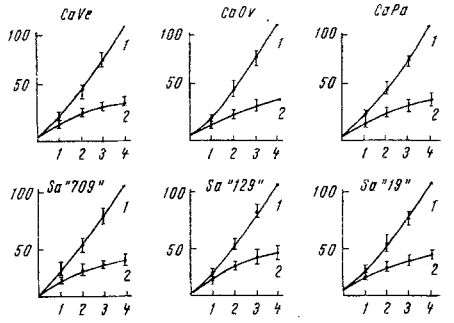

Fig. 2

Fig. 1. Effect of sarcolysin (100 μg/ml) on incorporation of adenine-8-C^{14} into nucleic acids of tumor cells. 1) Control; 2) experiment. Abscissa, incubation time (in h); ordinate, incorporation of adenine-8-C^{14} (in percent of control).

Fig. 2. Effect of sarcolysin (100 μg/ml) on incorporation of DL-lysine-1-C^{14} into proteins of tumor cells. 1) Control; 2) experiment. Abscissa, time of incubation (in h); ordinate, incorporation of labeled lysine (in percent of control).

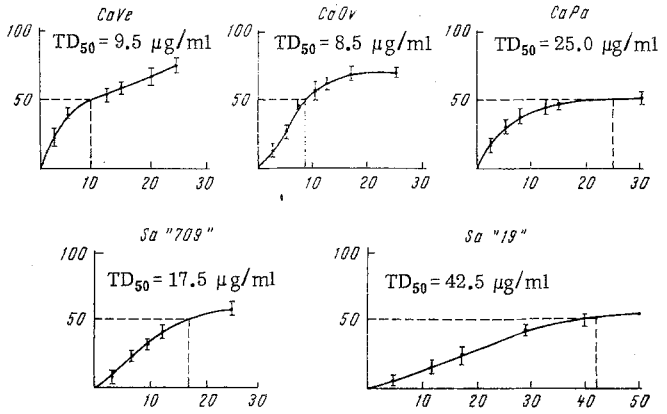

Fig. 3. Inhibition of RNA synthesis in tumor cells under the influence of different concentrations of sarcolysin. Abscissa, concentration of sarcolysin (in μg/ml); ordinate, percentage inhibition of RNA synthesis.

these lines. Cells of the mesenchymoma (Sa"19") were least sensitive (inhibition of the incorporation of labeled adenine was 52%).

To compare the action of sarcolysin on nontumor cells, cultures of cells of human embryonic skin and muscle tissue (3rd-4th subculture) were used, and these proved even more resistant to the action of sarcolysin (inhibition of nucleic acid synthesis 37%).

In the experiments of series II the action of sarcolysin was determined in the same concentration (100 μg/ml) on protein synthesis of cells of the 6 tumor lines mentioned above (Fig. 2). In these experiments sarcolysin also inhibited protein synthesis strongly (60-66%). Inhibition of protein synthesis after contact between embryonic cells and sarcolysin under the same experimental conditions was less (47%).

In the experiments of series III the effect of sarcolysin on incorporation of uridine-2-C^{14} into RNA of the cells of 5 tumor lines was studied using the compound in a lower concentration. For example, for lines CaVe, CaOv, CaPa, and Sa"709" sarcolysin was used in doses of between 2.5 and 25 μg/ml, while in the experiments with Sa"19" cells, which were most resistant to the action of sarcolysin (Fig. 1), the concentration was from 2.5 to 50 μg/ml.

Results in the literature [2] indicating that cells of different tumors may exhibit differential sensitivity to the action of small doses of sarcolysin formed the starting point of these investigations.

It will be clear from Fig. 3 that the character of the curves of inhibition of RNA synthesis in different lines of tumor cells varied a little. This was particularly true of experiments with CaOv and Sa"19" where 50% inhibition of incorporation of labeled precursor into RNA was obtained by sarcolysin in a concentration of 8.5 and 42.5 μg/ml respectively in the sample.

The use of sarcolysin in doses of 2.5-50 μg/ml revealed differential sensitivity of the cells to this compound.

In the current literature considerable attention is being paid to the development of tests for individual selection of chemotherapeutic compounds in clinical practice. Instead of morphological criteria for determination of the sensitivity of tumor cells to chemotherapeutic compounds, biochemical tests, which more adequately reflect the biological activity of the cells [3-5], are being used at the present time on a wide scale.

Hence, the use of sarcolysin in doses of 2.5-50 μg/ml revealed differential sensitivity of the tumor cells of the tested lines.

When identical doses of sarcolysin (100 μg/ml) were used, human embryonic cells showed greater resistance to this compound than tumor cells.

LITERATURE CITED

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