810 POSTER

Expression of the multidrug resistance-associated protein (MRP) and chemoresistance of human non-small-cell lung cancer cells

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Purpose: Human non-small-cell lung cancer (NSCLC) is considered a chemotherapy-refractory malignancy. Using 11 unselected NSCLC cell lines, expression and drug-transporting activity of the multidrug resistance-associated protein (MRP), mediating a multidrug resistance (MDR) phenotype, as well as its correlation with chemoresistance were analysed.

Methods: MRP mRNA and the corresponding protein were detected by RT-PCR and immunoblot, respectively. Southern hybridisation was used to analyse MRP gene amplification. Functional activity of MRP was determined by drug accumulation studies using ^{3}[H]daunomycin and calcein as MRP substrates and probenecid, genistein, benzbromarone, N-ethylmaleimide and verapamil as MRP-modulators. Chemosensitivity was evaluated by an MTT-based survival assay.

Results: The MRP gene is intrinsically expressed at markedly varying intensity in NSCLC cells. Two cell lines expressed MRP at levels comparable to those detected in drug-selected control cell lines (GLC4/ADR, HL-60/AR), however, without MRP gene amplification. Functional analysis revealed a transporting activity of MRP, correlating significantly with the gene expression data. Moreover, a significant correlation between MRP expression and chemoresistance against daunomycin, doxorubicin, etoposide and vinblastin, but not cisplatin was detected.

Conclusion: Our data suggest that MRP may be involved in the intrinsic MDR phenotype of NSCLC cells.

811 POSTER

Influence of melatonin on mutagenicity and anti-tumor effect of cyclophosphamide and nitrosomethylurea in mice

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Purpose: We examined the ability of pineal hormone melatonin (MLT) to modulate the mutagenicity of N-nitrosomethylurea (NMU) and cyclophosphamide (CP) in the tests for chromosome aberrations (ChA) in bone marrow cells and sperm head anomalies (SHA) in mice.

Methods: Animals were killed 24 h (for ChA) or 17 days (for SHA) after single injections of MLT (5 mg/kg, s.c.), NMU (50 mg/kg, i.p.), CP (200 mg/kg, i.p.) or co-administration of MLT and NMU or CP.

Results: MLT reduced the level of ChA (%) from 15.9 (NMU) and 13.7 (CP) to 4.5 and 4.3, respectively ($p < 0.05$). Similarly, SHA frequency (%) was reduced from 18.6 (NMU) and 17.7 (CP) to 9.9 and 6.1. Exposure to MLT (20 mg/l, in drinking water at night) alone or in combination with NMU (50 mg/kg, i.p. ×1) or CP (200 mg/kg, i.p. ×1) failed influence s.c. transplanted carcinoma Ehrlich size in comparison to relevant controls. However, MLT significantly increased the life-span of CP-treated mice.

Conclusion: MLT has antimutagenic effect and potentiates anti-tumor action of CP.

812 POSTER

Inhibitory effect of radiosensitizer AK-2123 on experimental hepatic metastases and CA^{2+} active transport

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The purpose of the work is identification of new active agents for treatment colorectal cancer hepatometastases.

The effect of radiosensitizer AK-2123 (nitro-triazole) on hepatometastases and on Ca^{2+} active transport was studied.

The metastases were induced by intrasplenic injection of colon adenocarcinoma cells in singenic mice. The average number of colonies in control and treated groups was estimated on day 22. The active transport of calcium ions by the (Ca^{2+}-Mg^{2+})-dependent ATP-ase of sarcoplasmic reticulum was evaluated pH-metrically.

The average number of metastases in control and treated (10 mg/kg) groups was 15.8 ± 2.1 and 3.8 ± 1.5 respectively. The part of treated animals was free of metastases. 100% of inhibition of Ca^{2+} active transport was observed.

The AK-2123 radiosensitizer exhibits significant antimetastatic effect which is suggested to be related to the inhibition of active calcium transport.

813 PUBLICATION

In vivo resistance of murine leukemia P388 towards platinum complexes

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Numerous attempts have been done to synthesize novel platinum drugs with improved therapeutic features. We synthesized previously the platinum complex with diaminonitroxyl radical-PtII(DAPO)Ox, which displayed the more antitumor activity in tumor-bearing mice and less overall and specific toxicity than CDDP. The purpose of this work was to examine comparatively development of P388 leukemia resistance to these drugs. The resistance was induced by successive transplantations of tumor cells from mice treated by each drug, with the stepwise increase of doses. There were obvious differences in duration of resistance development to CDDP and PtII(DAPO)Ox – at 5th and 11th generations respectively. Resistant substrains exhibited the mutual cross resistance to CDDP and Pt(DAPO)Ox. Tumorogenicity of resistant and parent strains was similar. Resistance was not disappeared during 16 generations in the absence of own drug. The resistant substrains retained the high sensitivity to ADR, DAU, VCR. They had the cross resistance to ThioTEPa. One substrain (P388/DAPO) maintained the high sensitivity to MTX whereas the other showed the cross resistance to this drug. P388/DAPO, but non P388/CDDP, had a collateral sensitivity to etoposide. Thus, the introduction of nitroxyl radical in platinum complex results in the delay of resistance development and certain changes of chemosensitivity.

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814 PUBLICATION

Antitumor effect oxygenic complexes of cobalt

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Purpose: The main objective in this work was to study the toxicity and antitumor activity of transition metal complexes (oxygen carriers); since it is supposed that these substances concrete as sources of superoxide and hydroxyl radicals that can destroy DNA. The 3 new cobalt complexes, containing jointly a molecular oxygen, amino acids and tetraazomacrocyclic ligands were examined.

Methods: These compounds: I. (cobalt, imidazole, lysine and molecular oxygen), II. (cobalt, histidine and molecular oxygen), III. (cobalt, tetraazomacrocyclic ligand and molecular oxygen) were synthesized by J. Bratuško and J. Stukalina, Institute of Physical Chemistry, Ukraine. The acute toxicity was determined in the intact mice. Ascite and solid tumor models were used: leukemia L 1210 (L 1210), Ehrlich ascite carcinoma (EAC) and Lewis lung carcinoma (LLC). Mice were injected intraperitoneally with compounds in various dose levels during 4–5 days. The antitumor effect of the compounds was measured as percentage tumor growth or metastases inhibition and percentage increase in life span.

Results: In acute toxicity test was determined that maximal tolerated doses were I and II-200 mg/kg, III-400 mg/kg. Treatment L 1210 and EAC failed to increase the life span, in spite of EAC marked inhibitory effect on ascite volume (40–90%). All compounds didn't inhibit the growth of primary tumor LLC, and only one of them (III) showed a significant reduction in the development of metastases LLC (80.6%).

Conclusion: One of the oxygenic complexes III (cobalt, tetraazomacrocyclic ligand and molecular oxygen) was found to have therapeutic effect on mouse Lewis lung carcinoma inhibiting the metastases growth.

815 PUBLICATION

8-Cl-cAMP induction of differentiation and apoptosis in Y-79 human retinoblastoma cell line

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Purpose: Treatment of retinoblastoma cells with certain agents induces a