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ANTI-IDIOTYPIC ANTIBODIES FOR IMMUNIZATION AGAINST TUMOR ASSOCIATED ANTIGENS IN HUMANS.

Fagerberg J., Steinitz M., Wigzell H., Persson M., Gigliotti D., Askelöf P., Rudén U., Wahren B. and Mellstedt H.
Karolinska Institute & Hospital, Stockholm, Sweden.

Induction of immunity against antigens expressed on tumor cells might be a way to prevent or delay relapse of the disease in cancer patients. The tumor associated antigen (TAA) GA733-2 is a 40 kDa glycoprotein expressed in most human colorectal tumors. Human monoclonal anti-idiotypic antibodies (ab2) mimicing part of GA733-2 was produced from EBV transformed cell lines from a patient treated with a mouse monoclonal antibody against the TAA. To evaluate the possibility of ab2 to induce immunity against the nominal antigen, GA733-2, a pilot study including six patients operated on for colorectal cancer was carried out. The patients were immunized with unconjugated ab2 or ab2 conjugated to pertussis toxin peptides. The preparations were precipitated in alum.

All patients developed a specific T cell response against ab2 as well as against the nominal antigen. Five of the six patients mounted a humoral response against ab2 and GA733-2. Overlapping peptide sequences of the external domain of GA733-2 were used to detect B and T cell epitopes. T cell epitopes of GA733-2 have sequence homology with the hypervariable regions of ab2.

The study showed that immunization of cancer patients with anti-idiotypic antibodies seemed to induce a cellular as well as a humoral response against the nominal tumor cell antigen. Primary sequence homologies between the CDR regions of ab2 and the nominal antigen might be the common denominator for induction of an anti-TAA immunity at immunization with ab2. To evaluate the clinical effect of the induction of an anti-TAA immunity a randomized study is needed.

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AN IMMUNOMODULATORY ROLE FOR TAURINE IN HOST ANTI-TUMOR DEFENCE

Finnegan N., Redmond H.P.,Watson W., Duggan S., Bouchier-Hayes D.
Dept. of Surgery, Beaumont Hospital, Dublin 9.

The role of taurine (T), an abundant sulphur-containing amino acid, as a modulator of immune function. has been neglected until recently. The aim of this study is to analyse the effects of altered T availibility on anti-tumour function of monocytes (Mø) and natural killer (NK) cells. Human Mø and NK cells were obtained from peripheral blood taken from healthy volunteers. The cells were isolated and incubated with varying concentrations of T for a controlled period of time. Cytotoxicity was assessed by lysis of Mø- sensitive and NK-sensitive tumour target cells at an E:T ratio of 20:1 using a standard ^{51}Cr-release assay.

Taurine conc^{n} mg/ml								control
10	5	1	0.5	0.25	0.14	0.07	0.035	0.0018	0
% Mø cytotoxicity following a 24hr T incubation									
20.5	20	16.5	22	24					20.7
		-	12.7	17.1	26.5	24.5	-	-	15.3
		18	12.6	-	12.6	22.6	22.6	-	21
% NK cytotoxicity following a 36hr T incubation									
		26.1	22.8	28.6	27.5	22.3	21.1	22.8	20.3
		91.3	90.9	57.0	56.0	70.1	86.0	91.6	66.7
		96.3	91.1	53.7	48.24	58.2	70.9	79.5	62.6

Initial results indicated that T concentrations ranging from 0.1 - 0.04 mg/ml enhanced Mø and NK cytotoxicity against effector-sensitive tumour targets. Thus, an immunomodulatory role for T in cell-mediated immunity, as a dose-dependent enhancer of tumoricidal capacity, is proposed. Manipulation of this property may prove T to be therapeutically beneficial in host defense against malignant disease.

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INFLUENCE OF TGF β_1 AND CHEMOTHERAPY ON CYTOKINE SECRETION IN SCLC

Fischer JR, Krammer PH[1], Drings P. Thorax Hospital, Heidelberg, Germany, [1]German Cancer Research Center, Tumor Immunology Programm, Heidelberg, Germany

We investigated effects of soluble mediators secreted by Small cell lung cancer (SCLC) lines on cytokine-induced growth of lymphocytes. We found that IL-2 mediated T cell growth is suppressed by a cytokine secreted by the SCLC line NCI-N417. TGF β_1 severely suppressed IL-2 mediated T cell growth. Anti-TGF β_1 antibody neutralized immunosuppressive activity secreted by NCI-N417, indicating serological identity of NCI-N417-derived factor with TGF β_1. SCLC line H69 does not secrete this immunosuppressive activity. TGF β_1 mRNA was found in NCI-N417 but not in H69. TGF β_1 inhibits secretion of IL-2, IFNα, IFNγ, TNFα, but not of IL-1α and IL-1β in immune cells from normal individuals. To investigate the clinical relevance of these findings, we evaluated ex vivo cytokine secretion capacity for IL-1α, IL-1β, IL-2, IFNα, IFNγ, TNFα in whole blood cell culture from 58 patients with SCLC and 95 patients with NSCLC. Compared to 44 normal controls, cells from SCLC patients secreted significantly lower amounts of IL-2, IFNα, IFNγ upon mitogen-stimulation. TNFα-secretion was significantly reduced in extensive disease SCLC, but not in limited disease SCLC. Secretion of IL-1α and IL-1β was not reduced. In patients with NSCLC, the amount of secreted IL-2 and IFNα was significantly reduced. Secretion of IFNγ was significantly reduced in disseminated NSCLC, but not in localized NSCLC. Secretion of TNFα, IL-1α and IL-1β was not impaired. Thus, selective immunosuppression was found in patients with SCLC that correlates to the cytokine pattern induced by TGF β_1, depends on tumor stage, and is different from immunosuppression found in NSCLC. In addition, cytokine secretion in SCLC patients was dramatically improved upon successfull chemotherapy, but not after ineffective chemotherapy. Thus, tumor derived immunosuppression may be crucial for in vivo growth of SCLC.

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EFFECT OF INHALANT FUNGOTHERAPY ON LEWIS LUNG CARCINOMA SPREADING IN MICE

Kuznetsovs S., Gurvich I., Research Group "Stimuls", Riga, Latvia,

This study is aimed to examine the possibilities of inhalant antimetastatic therapy in Lewis lung carcinoma using small particle *Phallus impudicus* juice spray (Pharmex, Latvia). The experiments were carried out on C57Bl/6 strain male mice. Carcinoma cells in $2x10^5$ dose were injected into a foot plantar. The tumor was ablated under hexenal narcosis. The volume and the number of metastases in the lungs were determined by Lucke method (1952). The preparation was inhaled for 5 days starting from day 7 after innoculation of tumor cells. Alveolar macrophages were extracted by Fidler method (1980). Adenosine deaminase (AD) and 5' nucleotidase (5-N) activity was estimated in lysate. Surgical ablation resulted in a sudden increase of the volume and number of metastases. 5 days' inhalation was beneficial for reducing the number of metastases by 3,5 times, depressing the metastases volume by 9,8 times. The studies of the enzyme activity of adenosine metabolism in alveolar macrophages, directly contacting metastatic cells in mice lungs reveal that by spray inhalation of *Phallus impudicus* juice the activity of AD increased while that of 5-N decreased against the values in nontreated animals. The obtained results suggest that the action of the spray inhalation give rise to the restoration of the disordered functions and activation of alveolar macrophages as affected by stress reactions. The features noted make it possible to offer *Phallus impudicus* spray inhalation for antimetastatic therapy, including preoperative and postoperative correction of alveolar macrophage function.

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INTERLEUKIN-2 (IL-2) AND ALPHA-2 INTERFERON IN METASTATIC RENAL CELL CARCINOMA (MRCC): ANALYSIS OF 22 CASES.

Landonio G., Baiocchi C., Cattaneo D., Majno M., Scanzi F., Rassu G.
Divisione di Oncologia. Ospedale Niguarda Cà Granda Milano (Italy)

Objective: to evaluate the efficacy of Biological response modifiers ((BRM) in the treatment of MRCC.

Patients and methods:

We treated 22 patients affected by MRCC with IL-2 (18 M/day/x 3-5 days i.v. continuous infusion, every 4 weeks) and Alpha-2-Interferon (9 M/3 times the week) in the period 1991-1993. 16 were males, 6 females; median age 55 yrs (r: 42-66): all patients had been nephrectomized; metastases were present at the time of diagnosis in 8/22 patients; they were multiple in 9/22; median follow up 16 months (r: 3-36).

Results:	Responses	dead	alive	
CR	0	-	-	
PR	5	1	4	(1 maintained PR, 3 "slow" PD)
SD	5	2	3	(3 CR after surgery)
PD	8	6	2	(2 PR with FUDR)
NE	4	2	2	(2 still in therapy)

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Conclusions: IL-2 and Alpha-2 Interferon confirmed as a valid step in the treatment of MRCC: PR+SD accounted for 56% of evaluable responses. NO CR was achieved by BRM alone: nevertheless 3 patients obtained CR after surgery (lung -2- and adrenal -1- metastases) and 1 shows a prolonged PR.

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EFFECT OF FILGRASTIM ON GRANULOCYTOPENIA INDUCED BY CHEMOTHERAPY IN PATIENTS WITH MULTIPLE MYELOMA

Poglòd R., Kraj M., Maj S.
Institute of Haematology and Blood Transfusion, Warsaw, Poland

11 multiple myeloma patients suffering from severe granulocytopenia after cytotoxic therapy were treated with filgrastim (GCSF- Neupogen, Roche). Neupogen was given s.c. in dose of 5 ug/kg/day for 7-14 (mean :10) days. In all cases there was observed an increase in granulocyte count. On one day after completing a whole therapy granulocyte counts ranged from 4,9 to 19,7 (median : 10,9)x 10^9/L. In two cases a peak of granulocytes appeared on the 2-nd and 4-th day of treatment, in one - after 10 days of therapy. The granulocyte count usually rapidly decreased after discontinuing treatment; examinations performed in 8 patients during the first week and in 3 cases - three weeks after treatment revealed granulocyte counts ranging from 0,8 to 2,4 (median : 1,8)x 10^9/L. Side events observed in 6 cases were moderate and reversible. The study revealed the efficiency and good tolerance of Neupogen, but also its short-term action in the treatment of granulocytopenia.