Symposium no. 1: Effector Cells against Cancer

1.019

NATURAL KILLER AND MONOCYTE FUNCTIONS IN BREAST CARCINOMA

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We examined activities of peripheral blood natural killer (NK) cells, monocytes, and lipopolysaccharide (LPS) induced production of tumor necrosis factor-alpha (TNF-a) in a group of breast carcinoma patients (infiltrating ductal carcinoma - stage II) before and after operation and radiotherapy. Normal individuals (16) and verified mastopathia patients (4) were controls.
We found NK cell and monocyte numbers preserved, but NK activity and killing by monocytes significantly reduced ($p<0.05$ and $p<0.003$ respectively). Upon LPS stimulation, cancer and mastopathia patients and normal individuals released similar amounts of TNF-a: 65 U/ml/2×10^6 monocytes.
Early disturbance in some functions of immunocytes capable of coping with tumor was shown.

1.020

DEFENITION OF OPTIMAL CULTURE REQUIREMENTS FOR ANTIBODY-TRIGGERED T CELLS FOR IMMUNOTHERAPY OF OVARIAN CANCER

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Adoptive immunotherapy of cancer patients with activated T lymphocytes requires relative large amounts of cells. We have developed an activation procedure and a culture medium composition, which allows activation and expansion of large numbers of T cells from PBL. These activated and expanded PBL can be triggered for cytolysis by bispecific antibodies (bsAb), e.g. with specificity for the T cell receptor complex (CD3) on the one hand and an ovarian tumor specific antigen (MOV18) on the other, to be used for immunotherapy of patients with ovarian carcinoma. In summary: PBL are optimally activated by PHA (1 ug/ml) + IL2 (150 IU/ml), and expanded by IL2 (600 IU/ml); the optimal medium composition to be used is: 78% RPMI-1640, 20% AIM-V medium, and 2% autologous plasma. Activation and expansion of PBL is done in culture bags. The bsAb-targeted activated PBL are beeing used for intraperitoneal treatment of ovarian cancer patients in a phase I-II study. Further, preliminary clinical data will be presented.

1.021

INHIBITION OF ANTIBODY-TRIGGERED CYTOTOXICITY BY HAMA IN PERITONEAL FLUID; RELATION TO HAMA KINETICS AND AFFINITY

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Ovarian carcinoma patients are treated intraperitoneally with in vitro activated and expanded T lymphocytes, targeted with anti-CD3 x anti-MOV18 bispecific antibody (bsAb). BsAb-targeted lymphocytes are administered daily for 5 days after which a rest period of 2 weeks is followed by a second cycle of treatment. HAMA was measured in serum and peritoneal fluid, respectively from 2 and 3 weeks of treatment onwards. No inhibition of bsAb-triggered cytotoxicity (CTX) occurred during the treatment period, only after 5 weeks from start of therapy inhibition as result of HAMA in peritoneal fluid was found. These results are in agreement with our published data that only relative large amounts of anti-CD3 or anti-MOV18 mAb, in relation to the amount of bsAb, inhibit bsAb-triggered CTX. Moreover, the possibility of developent of HAMA with increasing affinity as function of time during the in vivo administration of bsAb will be discussed. These results have important implications for the design of future studies using bsAb-mediated adoptive immunotherapy.

1.022

IMMUNOLOGICAL STATE AFTER INFECTION WITH BOVINE LEUKEMIA VIRUS (BLV)

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Enzootic bovine leukosis (EBL) is the chronic B-cell lymphoprolipherative disease caused by retrovirus. In a general way it is known that many retroviruses bring about immunosuppression in the infected organism. In connection with BLV infection are inconsistent observations because according to some authors after virus infection is possible to observe immunosuppression and by another we do not observe this state. From this reason we followed immunologic response of the cows infected with BLV using test of phagocytic activity, migration-inhibition test, E-rosette test and quantitative assay of the tetrazolium reductase activity of phagocytes (INT-test). Besides we also investigated biopsies of the prescapsular lymph nodes by histologic examination. Our observations refer to state of the immune system after natural infection of the organism of cows with chronic leukemogenic virus - BLV.

1.023

BIOLOGICAL RATIO OF IL-3 USE IN IL-2 IMMUNOTHERAPY.

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Cortisol rise and macrophage-mediated suppression,observed during IL-2 immunotherapy,may reduce the efficacy of IL-2 itself.This study was performed to analyze the influence of IL-3 on IL-2-induced stimulation of adrenal function and macrophage activation.We have evaluated in mice the effect of IL-3 pretreatment on IL-2-induced corticosterone(CTS)rise;CTS was stimulated by IL-2,while IL-3 did not cause CTS release,and decreased CTS peak induced by IL-2.In another experiment,we have evaluated in vitro the influence of IL-3 on monocyte-mediated release of soluble IL-2 receptors(SIL-2R)in response to IL-2.The preincubation with IL-3 reduced the stimulatory effect of monocytes on SIL-2R release from lymphocytes after IL-2 activation. These preliminary results would suggest that IL-3 may be used in association with IL-2 in the immunotherapy of cancer to manipulate some suppressive events,which occur during IL-2 therapy.

1.024

Flavone acetic acid potentiates the induction of endothelial procoagulant activity by tumour necrosis factor.

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Flavone acetic acid (FAA) and TNF both cause rapid regression in a number of murine tumour models. In each case vascular damage is thought to be a component of antitumour action. While TNF has been shown to enhance endothelial procoagulant activity *in vitro*, little is known about the mechanism of action of FAA. We have compared the effects of FAA on human umbilical vein endothelial cells (HUVEC) *in vitro* with those of TNF, specifically examining the expression of procoagulant activity, using a two-stage clotting assay. Treatment of HUVEC with flavone acetic acid (FAA) at 1.0 mg/ml for 4h resulted in a 3-7 fold increase in procoagulant activity. This increase was due to enhanced tissue factor expression on the endothelial cell surface. Combined treatment with FAA at 1 mg/ml and TNF at 100pg/ml produced a 600-fold (range 200-1500) increase in tissue factor activity, compared to 7-fold and 50-fold increases for the individual agents respectively. Northern blotting of total RNA from cells treated with the combination of agents or either agent alone, followed by probing with a cDNA to human tissue factor demonstrated a synergistic increase in tumour factor mRNA after combination treatment. *In vivo*, the combination of FAA and TNF would be shown to induce greater growth delay in two murine tumours than would be predicted on the basis of the activity of either agent alone. We conclude that the specificity of action of FAA may be in part conferred by the presence of TNF, the combination promoting coagulation on the surface of tumour endothelial cells.