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0213

IN VITRO STAT1-REACTIVATION BY INTERFERON GAMMA IN INTERFERON RESISTANT RENAL CELL CARCINOMA-CELLS

Susanne Axer[1], Iris Dallmann[1], Jens Grosse[1], Tanja Boeker[2], Andreas Emmendoerffer[2], Arnold Ganser[1] and Jens Atzpodien[1,3,4]
[1]Department of Hematology and Oncology, Medizinische Hochschule Hannover, Germany, [2]Fraunhofer Institute, Hannover, Germany, [3]Robert Janker Tumorcenter, Bonn, Germany, [4]European Institute for Tumor Immunology and Prevention, Bonn, Germany

Interferon alpha (IFN-·) treatment in the therapy of human malignancies often causes a relative resistance to IFN-·. Important for the signal transduction of IFN-· is the Jak-STAT pathway, where STAT1 plays an important role. Long-term IFN-· treatment of renal cell carcinoma (RCC) cells causes a secondary resistance to the antiproliferative effect of IFN-·.
In our experiments we examined the secondary IFN-· resistance of A498 cells. IFN-· resistant subclones of the A498 cell line were generated by culturing the cell lines continously in the presence of IFN-·2 (1000U/ml). Based on the hypothesis of a defective signal transduction pathway in resistant cells, electromobility shift assays (EMSA) were performed to measure STAT1-activation in association with IFN-· resistance.
We could demonstrate IFN-·2 induced STAT1 activation in the sensitive subclone, the resistant subclone was associated with a defective STAT1 activation.
Besides we were able to reactivate STAT1 in the resistant subclone. This activation was induced by treatment with Interferon gamma1b (10ng/ml) for a term of half an hour.
These data might provide the idea of new therapeutic strategies for IFN-· resistance in human neoplasms.

0214

INREASE IN PROLIFERATION RATE AND NORMALIZATION OF TNF-ALPHA SECRETION BY BLOCKAGE OF GENE TRANSFER INDUCED APOPTOSIS IN LYMPHOCYTES USING LOW DOSE CYCLOSPORINE A

O. [illegible]ert, G. Röpke, P. Buttgereit, A. Märten, I.G.H. Schmidt-Wolf
Medizinische Klinik und Poliklinik I, Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany

Efficient gene transfer of lymphocytes is extremely difficult. Apoptosis may play a role in this gene transfer resistance of lymphocytes and cell loss induced by transfection of lymphocytes via non-viral vectors. With respect to apoptosis, addition of anti-CD3 antibody can be used as a surrogate for receptor-mediated gene transfer induced apoptosis since anti-CD3 antibody has been shown to be the causative agent of apoptosis in receptor-mediated gene transfer. Here, we show that blockage of apoptosis leads to a significant increase in the proliferation rate of lymphocytes. TNF-alpha secretion which is elevated after addition of anti-CD3 was completely normalized by further addition of low dose cyclosporine A (CsA; 2ng/ml). In contrast, addition of 2ng/ml of CsA had no effect on cytotoxic activity of cytokine-induced killer (CIK) cells. Therefore, addition of low-dose CsA seems to be effective in preventing induction of apoptosis in receptor-mediated gene transfer without interfering with the cytotoxic activity of lymphocytes. In conclusion, gene transfer techniques led to apoptosis and necrosis of lymphocytes. In receptor-mediated gene transfer, apoptosis and necrosis could be blocked by addition of CsA. Blockage of apoptosis after gene transfer should have an impact on the use of lymphocytes transfected with cytokine genes as immunologic effector cells in cancer gene therapy protocols.

0215

LSC – LASER SCANNING CYTOMETRY AS AN APPLICATION FOR THE DETECTION OF TUMOUR CELLS IN THE PERIPHERAL BLOOD. AN EXPERIMENTAL STUDY

G. P. Tilz, K. Pachmann, U. Demel
Clinical Immunology and Jean Dausset Laboratory, Graz University Medical School, Klinikum LKH, Auenbruggerplatz 8, A-8036 Graz, Austria

Introduction: Tumour cells circulate under various situations in the peripheral blood of patients and can be quantified there gy various methods. One of them is the LSC allowing the detection of fluorescent signals and attributing them to morphology.
Material and Methods: A Laser scanning cytometer Compucyte was used in all experiments apart from traditional UV-light fluorescent microscopy and FACS-analysis.
BR-SK 3 Cells were cultured in RPMI-Medium and harvested and added to the PB of healthy controls and tumour bearers. Tumour cells were concentrated by the MACS-technigque using a monoclonal antibody from Miltenyi with anti HEA activities. A second step of characterisation was ollowed gy a FITC-labelled antibody before controlling the harvest of tumour cells in the "spiked blood"
Results: Tumour cells could be found in all conditions down to a dilution of 10 times to minus 6. Enrichment gy the immunomagnetic column method resulted in a 50 to 100 fold increase of sensitivity.
Conclusion: The system investigated is particularly suitable for the detection of contaminating cells in "otherwise celan suspensions" and can be easily adapted for other purposes of experimental tumour immunology.

0216

T CELL RECEPTOR ANALYSIS REVEAL OLIGOCLONAL EXPANSION OF CD4 AND CD8 T CELLS IN PATIENTS WITH LARGE GRANULAR LYMPHOPROLIFERATIVE DISORDER (T-LGL)

Eva M. Weissinger 1, Jos J. Melenhorst2, Martha Kirby2 and A. John Barrett2
1 Medizinische Hochschule Hannover; Abteilung Hämatologie/ Oncologie;Hannover, Germany,
2 National Institutes of Health, NHLBI, Bethesda , USA

The etiology of large granular lymphoproliferative disorder (LGL) is not yet known. There is evidence for a non-resolved T cell immune response rather than a leukemic process. The analysis of the T cell repertoire with sensitive techniques may allow to gain insight in the etiology of LGL. We demonstrated clonal predominance of certain variable beta-chains in CD8+ T cells in all 9 patients studied and preferred expression of particular v-beta chain genes in the CD 4+ subpopulation of the T cells in 7 of 9 patients at presentation at the Institute. Peripheral blood samples of 9 patients with LGL were analyzed for T cell receptor (TCR) expression using spectratyping, a PCR based method identifying the TCR beta chain usage by difference in length of the third complementarity-determining region (CDR 3). All patients presented with typical features of anemia and/or neutropenia associated with circulating CD 8+ LGL cells, which were found to be clonal for TCR rearrangement by Southern blot. Preferential expression of particular v-beta chains of the TCR in CD 8+ cells was shown for all 9 patients. In 7 of 9 patients additional abnormalities of the TCR in the CD 4+ subpopulation of T cells were found, showing skewing of the same v beta chain, but in some cases the CDR 3 length differed. These results suggest an immune mechanism, rather than a malign process in the etiology of T-LGL.