

VHe 04**INFLUENCE OF RECOMBINANT HUMAN INTERFERON-GAMMA ON PLATELET FUNCTION AND COAGULATION FACTORS IN VITRO AND IN PATIENTS TREATED FOR HEMATOLOGIC MALIGNANCIES**

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A large number of cell functions in normal and malignant cells are influenced by interferons such as induction of MHC-genes, specific intracellular enzymes as 2'5' oligoadenylatcyclase or suppression of cellular oncogenes. Since more and more phase II trials with IFN's not only as monotherapy, but also in combination with cytotoxic agents are designed, it is of preferential interest to investigate a possible influence of interferon on platelet function and coagulation factors. In a recent study (J.Mirro et al., Cancer Treat. Rep. 69:315, 1985) it was demonstrated for the first time that IFN-alpha-treatment did induce a coagulopathy in children with myelocytic leukemia. Prolonged activated partial thromboplastin time and depressed activity of factor II, VII, IX, X and XII were demonstrated. Since we started a phase II trial with recombinant human Interferon-gamma in patients with hematologic malignancies, we were interested in the question, whether IFN-gamma might influence platelet function or coagulation factors. Therefore, we investigated platelet function by ADP Collagen- and Ristocetin-induced platelet aggregation as well as platelet factor 3. Platelet rich plasma from normal donors were incubated for 30 min with different doses of IFN-gamma, NaCl or salicylic acid. There was no significant difference in platelet aggregation in the IFN-gamma group as compared to NaCl, while salicylic acid caused dramatically reduced aggregation, as expected. Additionally, we measured the activity of several coagulation factors (II, VII, IX, X, XII, XIII) under the same conditions without evidence to be influenced by IFN-gamma.

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VHe 05**PLATELET SECRETION AND THROMBIN GENERATION IN MALIGNANCY**
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To assess whether or not a relationship between hemostatic disorders and extent or activity of malignant proliferation exists, we studied 38 pts. (49+15 yrs.) with histologically proven neoplasia (carcinoma n=24; malignant melanoma n=5; malignant lymphoma n=9), but without bleeding. Platelet activity and thrombin generation were evaluated by plasma levels of B-thromboglobulin (BTG), platelet factor 4 (PF4) and fibrinopeptide A (FPA). - The mean level of FPA (7.1+5.1, range 1.7-17.5 ng/ml) was significantly increased in tumor pts. (normal range 0-2.5 ng/ml, p<0.001). Fourteen pts. with malignancy revealed pathologically increased levels of BTG (>30 ng/ml) and PF4 (>6 ng/ml); their mean concentration of BTG was 49+11 ng/ml, that of PF4 12+6 ng/ml. These data differed significantly from those of 38 normals (BTG 19+7, PF4 4+2 ng/ml), or those of the other 24 pts. with malignancy (BTG 19+8, PF4 4+2 ng/ml, p<0.001), respectively. However, when dividing the total group of pts. in (A) subjects with progressive disease (n=20) and in (B) those with limited disease or those with remission (n=18), there was no significant difference between mean plasma levels (ng/ml) of BTG (A: 31+17, B: 24+16), PF4 (A: 7+5, B: 8+6) or FPA (A: 7.0+4.9, B: 8.3+5.7). The sensitivity and specificity of BTG and PF4 measurements were tested in subgroup A (i.e. pts. with extensive disease). In 9 of 20 pts. with tumor progression a significant increase of BTG and PF4 occurred revealing a sensitivity of 45%. The specificity or the prognostic value of significantly elevated BTG and PF4 plasma levels (i.e. percentage of really abnormal data related to tumor progression) was 64%. - This study confirms that activation of platelets and coagulation occurs in neoplastic disease. However, the sensitivity and specificity of platelet secretion and thrombin generation are rather low related to the extent of tumor progression. We therefore conclude that measurements of BTG, PF4 and FPA do not allow any estimation of the disease activity in individual patients with solid tumors or malignant lymphomas.

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VHe 06**LEU 7 (HNK 1)-A MARKER FOR SURFACE-DERIVED EPITHELIAL CELLS IN THYMOMA AND THYMIC CARCINOMA**
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Thymic epithelial tumours can be divided in thymomas and thymic carcinomas. Based on light microscopic and immunohistochemical features of the normal thymus, thymomas of cortical, medullary and mixed types were distinguished. Other authors previously observed, that the Leu-7-antigen is expressed in normal thymic surface epithelium and also in some epithelial cells of thymomas. For this reason we investigated the reactivity of 6 epithelial thymic tumours comprising 5 thymomas and 1 thymic carcinoma with anti-Leu-7 (Becton-Dickinson, USA) using the PAP-method on frozen sections.

No expression of Leu-7-antigen was found in 2 thymomas of common mixed type, but all 3 thymomas of cortical or predominant cortical type included Leu-7-positive cells. In 1 of these cases anti-Leu-7 was reactive only at the lobule boundary. 2 thymomas of predominant cortical type showed a reticular and focal confluent staining of epithelial cells with a conspicuous lining of positive cells around perivascular spaces. The most extended Leu-7-reactivity was observed in the epithelial cells of a well differentiated thymic carcinoma, in which Leu-7+ cells formed sheets bordering perivascular spaces. These findings suggest, that the Leu 7+ thymic surface epithelium may represent the proliferating cell layer for some types of thymomas or thymic carcinomas and that the intensity of the Leu-7-expression may indicate the amount of less differentiated surface epithelium derived tumor cells.

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VHe 07**Ploidy pattern of megakaryocytes in patients with metastatic tumors and in controls**

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An altered platelet heterogeneity could be one of the reasons for thrombotic events in malignancy. Although there is evidence that this heterogeneity depends on the different ploidy of megakaryocytes very little is known about these cells in patients with malignant tumors.

We studied the DNA-content of megakaryocytes of the following patients: 30 patients with metastatic tumors - 15 with and 15 without paraneoplastic thrombosis, 15 patients with localized cancer, 15 patients with thromboses but without tumors, and 15 healthy controls.

In both groups of patients with metastatic tumors a largely increased ploidy of the megakaryocytes with an average ploidy index of 3.54 and 3.56 compared with 3.06 of the controls was found. Ploidy index of patients with localized cancer was 3.18 and the ploidy index of patients with thromboses only was 3.15. This means that patients with metastatic tumors have significantly (p<0.0001) increased ploidy of megakaryocytes independent of whether they suffer from thromboses or not. This shift is less pronounced in patients with localized cancer implying a possible correlation between ploidy of the megakaryocytes and tumor mass. Thrombosis alone does not alter ploidy patterns significantly (p<0.1).

The consequence of higher ploidy of megakaryocytes is a larger cytoplasmic mass of these cells. This means an increased platelet production and leads to an alteration in the heterogeneity of circulating platelets. A thus altered platelet population could favour but not necessarily provoke thrombotic complications in malignancy. Besides an overcompensation for increased platelet consumption a mitogenic or thrombopoietin-like factor produced by the tumor itself or by macrophages must be considered.

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