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FIBRONECTIN-FIBRIN-COMPLEXES : AN IMMUNOASSAY TO EVALUATE THEIR FUNCTION IN COAGULATION DISORDERS AND TUMOR SITUATION .

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Fibronectin and fibronectin degradation products interact with fibrin(ogen) by non-covalent and by factor XIII catalyzed covalent binding. In certain physiological or pathophysiological situations these complexes may be of considerable importance. It was the aim of this study to accumulate more information of the function of this proteininteraction. Immunoadsorption in combination with Westernblotting with different monoclonal and polyclonal antibodies demonstrate several fibronectin-fibrin(ogen)-complexes in tumor ascites. For further information we established an immunoassay to measure these complexes. As the capture antibody we used a polyclonal fibronectin antibody and as the tag antibody a monoclonal fibrin(ogen) antibody. In this immunoassay we observed a decrease of these complexes from very high values during the therapy of disseminated intravascular coagulation besides also a decrease of high molecular weight fibrin derivatives and fibronectin split products. We also found elevated levels in ascitic fluid and plasma of patients with advanced ovarian cancer ($\bar{x}$=202,3± SD 45,1 ng/ml fibrinogen equivalent) in comparison to a control group with benign gynecological diseases ($\bar{x}$= 102,9± SD 14,9 ng/ml fibrinogen equivalent). In conclusion we suggest that during intravascular coagulation fibronectin binds fibrin derivatives for elimination from plasma. In the tumor situation these complexes may stem from the fibronectin-fibrin-gel-matrix surrounding the tumor by proteolytical degradation and subsequent release into the ascites. (supported by Deutsche Forschungsgemeinschaft,SFB207,A2).

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INTERFERENCE OF MONOCLONAL IMMUNOGLOBULINS ON PLATELETS AND WHOLE BLOOD AGGREGATION.

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We studied 31 patients with monoclonal gammopathy (MG), 10 of them secreting monoclonal antibodies (MoAb) of the G class, 13 of them IgM and 8 IgA. We also studied 15 healthy age- and sex-matched control subjects. On each subject we evaluated whole blood aggregation (WBA) in response to ADP, collagen, epinephrine and arachidonic acid in parallel with PRP aggregation according to the method of Born. We wondered whether WBA could provide us further information on the interference of MoAb on platelet function. Agonists and concentrations which yielded statistically significant results in comparison with controls will be reported.

IgM MG: Increased WBA to epinephrine 5 and 10 µM ($p < 0.01$) and ADP 4 and 6 µM ($p < 0.001$). Increased PRP aggregation to ADP 1 µM ($p < 0.001$) and collagen 1 µg/ml ($p < 0.001$).

IgA MG: increased WBA to ADP 1 µM ($p < 0.001$). No difference in PRP aggregation.

IgG MG: no difference in WBA. Reduced PRP aggregation in response to ADP 1 µM ($p < 0.01$) and arachidonic acid 0.5 mM ($p < 0.01$).

We conclude that high molecular weight Ig (IgM pentamers and IgA dimers) seem to play a role in WBA, causing an increased aggregatory response when measured as impedance variation; on the other hand, low molecular weight Ig (IgG) seem to interfere directly with platelet function, causing a decreased aggregation. The mechanism underlying this phenomenon is still unclear.

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**PLATELET ASSOCIATED IMMUNOGLOBULINS IN PATIENTS WITH NON - HODGKIN'S LYMPHOMAS .**

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**Levels of platelet associated IgG and IgM were studied in 42 patients with non-Hodgkin's lymphomas / NHL / using rocket immunoelectrophoresis in agarose gel . Twenty percent of patients with NHL had elevated PAIgG and fifty percent had elevated PAIgM levels .**

| | Normal | Grade of malignancies low | high |
|---|---|---|---|
| PAIgG | 11.96 ± 1.79* | 16.51 ± 1.99 | 22.04 ± 11.55 |
| PAIgM | 2.50 ± 0.50* | 6.77 ± 1.06 | 8.42 ± 3.12 |

* mean values ± SE

**Both , PAIgG and PAIgM were strongly correlated with the extend of disease . When patients with NHL and elevated PAIgM levels were treated by chemotherapy , PAIgM levels normalized as tumor load diminished . No similar correlation exsited between response to the therapy and levels of PAIgG in patients with NHL. These data suggest that PAIgM may be useful as a marker for disease activity and may be an early indicator of relapse when measured periodicaly in patients who have completed therapy .**

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TUMOR CELLS INTERACTIONS WITH SUBENDOTHELIAL EXTRACELLULAR MATRIX IN A PERFUSION SYSTEM: ROLE OF PLATELETS.

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It has been suggested that platelets may facilitate tumor metastasis by increasing tumour cell (TC) adhesion to vascular endothelium mainly through the formation of platelet/TC aggregates. In order to further investigate this we have utilized an in vitro model combining extracellular matrices (EM) from cultured vascular endothelial cells and two neoplastic clones from a mFS6 murine fibrosarcoma: one expressing high metastatic potency (M4) and one with low metastatic potential (M9). These two sublines express an in vitro platelet aggregating activity which has previously been characterized and which correlates with in vivo metastasizing capacity. To reproduce the in vivo flow conditions a flat perfusion chamber was used (*). Glass coverslips, carrying the EM were perfused for 10' at a wall shear rate of 450 $sec^{-1}$ with reconstituted heparinized human blood containing $3x10^5$/ml TC, with or without platelets. Coverage of the EM with adherent TC was evaluated by a morphometric method and expressed as percent TC coverage. M4 cells adhered to EM more than did M9 cells: 4.3% TC coverage for M4, versus 2.5% TC coverage for M9. In the presence of platelets, TC adherence was greatly increased, being 9.7% for M4 and 7.8% for M9. In the experiments performed in the presence of thrombocytes no platelet/TC thrombi were found onto the EM and no TC-induced platelet aggregation was detected in blood after perfusion. Our results confirm that platelets favour the occurrence of metastasis and suggest that other mechanisms than platelet/TC aggregates formation might be involved in this process.

(*) K.S. Sakariassen et al. J.Lab.Clin.Med. 102:522, 1983.