DISSEMINATED INTRAVASCULAR COAGULATION (DIC) AND ACUTE LEUKEMIA: IDENTIFICATION OF A NEW CELLULAR PROCAGULANT. A. Falanga (1), R.D. Alessia (2), M.B. Donati (2) and T. Barbar (2). Istituto Mario Negri, Milano (1) and Ospedali Riuniti di Bergamo, Bergamo (2), Italy.

There is an enhanced incidence (>50%) of severe coagulopathy in association with several types of acute leukemias. Cell associated procagulants are considered important in this context. So far only a Tissue Factor (TF)-type procagulant has been described in leukemic cells. We have set up here the experimental conditions to identify other possible cellular procagulants in leukemia. We have tested blast cell extracts from 2 patients with 5 different cytological subtypes (from M1 to M5 of acute non lymphoid leukemia (ANLL), according to the FAB classification, in order to assay whether they express "cancer procagulant" (CP), a F VII-independent FX activating cysteine proteinase (Falanga & Gordon, 1985; Donati, et al. 1986). All the samples shortened the recalcification time of normal human plasma, the effect being significantly greater (p<0.001) in the M3 group. The activity was 20% to 100% independent from the presence of FVII, and was susceptible to 2 cysteine proteinase inhibitors (Iodoacetamide, 2 mM, and HgCl2, 0.1 mM) in all the extracts but the M5 type. In addition, M2 and M3 samples directly activated pure FX in a two stage clotting assay. Control cell extracts from 10 healthy donors did not show any procagulant activity, under the same conditions. This study provides evidence for a new procagulant expressed by cells of ANLL: the peculiar characteristics of this procagulant (i.e. its confinement to the malignant phenotype, its shedding into the plasma, its possible modulation by vitron K antagonist) make this observation of potential interest in the development of new diagnostic and therapeutic tools in ANLL.

EFFECT OF INTERFERON GAMMA ON PROCAGULANT ACTIVITY FROM HUMAN PROMYELOCYTIC CELL LINE (HL 60).

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Interferon gamma (IFN), a lymphokine acting as biological response modifier, can induce morphological and phenotypic differentiation of some leukemic cell lines, specially along the monocytic pathway.

Furthermore, myeloid leukemic cells and normal monocytes have been demonstrated to possess procagulant activity (IFN, IL-1).

The aim of this study was to investigate the modulation of PCA induced by treatment with IFN on human promyelocytic cells from HL 60 cell line. Cells were cultured in suspension for 5 days in RPMI 1640 medium supplemented with 10% fetal calf serum in the absence or in the presence of different concentrations of IFN (100-10.000 u/ml) at 37°C and 5% CO2.

Differentiation was assessed by morphological and cytochemical methods (MGG, ANAE, CAE, MP0) on cytopsin preparations and surface marker analysis with monoclonal antibodies (OKM1, M02, M19, M17, M4).

IFN activated the cytoplasm and membrane staining of HL 60 cells. The activity of PCA was directly correlated to the degree of IFN induced differentiation. The increase in PCA both in the cells and in the conditioned medium was not further affected by higher concentrations of IFN, unable to determine cell maturation.

In conclusion the modulation by IFN seems to be dependent on monocytic differentiation of HL 60 cells.

HEPARIN AND NON-ANTICOAGULANT HEPARINS INHIBIT HEPARANASE ACTIVITY IN NORMAL AND MALIGNANT CELLS: POSSIBLE THERAPEUTIC USE IN PREVENTION OF EXTRAVASATION AND DISSEMINATION OF BLOOD BORNE CELLS. S. Deck, N. Delher, M. Ruter-Kagami, J. Hamburger, H. Puthen, E. Puech and I. Donnadieu. Hadassah University Hospital, Jerusalem, Israel and Beilinson Medical Center, Petah Tikvah, Israel.

Degradation of vascular subendothelium occurs in vivo during the process of inflammation and tumor invasion. Various observations suggest that the capacity of some blood-borne cells to extravasate may depend in part on their ability to enzymes heparanase activity. Incubation of human platelets, human fibroblasts, or highly metastatic mouse lymphoma cells with sulfate-labeled extracellular matrix (ECM) results in heparanase mediated release of labeled heparan sulfate cleavage fragments (0.5-9 kDa, 0.85 on Sepharose 6B) (2. Clin. Invest. 74: 1842 and 75: 1506; Cancer Res. 43: 2704). The present study was undertaken to test the heparanase inhibitory effect of heparin and non-anticoagulant species of heparin that might have a potential therapeutic use in preventing heparanase mediated extravasation of blood-borne cells. We prepared totally or N-desulfated heparins which were either left with their N-position exposed or were subsequently N-acetylated or N-resulfated. These heparins exhibited less than 5% of the anti-coagulant activity of native heparin. It was found that total desulfation of heparin abolished its heparanase inhibitory activity while desulfation was followed by N-acetylation or not. Inhibitory effect was restored by resulfation of the N-position. When only the N-sulfate group was desulfated, inhibitory activity was lost but could be restored by acetylation of the N-position. These results indicate that N-sulfate groups of heparin are necessary for its heparanase inhibitory activity but can be substituted by an acetyl group provided that the N-sulfate groups are retained. Low Mr heparins (main Mr species of 2500 and 4500 daltons) and heparin fragments as small as the tetrasaccharide inhibited degradation. These heparins in vivo inhibited cell extravasation. These results suggest that non-anticoagulant heparins interfere with tumor metastasis and experimental autoimmun diseases (some heparins were kindly provided by Inst. Clow, Farlia and Kabi Vitrum, Stockholm).