DISSEMINATED INTRAVASCULAR COAGULATION (DIC) AND ACUTE LEUKEMIA: IDENTIFICATION OF A NEW CELLULAR PROCOAGULANT. A. Falanga (1), M.D. Alessio (2), M.B. Donati (2) and T. Barbui (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 leukemia. Cell associated procoagulants are considered important in this context. So far only a Tissue Factor (TF)-type procoagulant has been described in leukemic cells. We have set up here the experimental conditions to identify other possible cellular procoagulants 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 procoagulant" (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 M4 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 612 of 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 procoagulant activity, under the same conditions. This study provides evidence for a new procoagulant expressed by cells of ANLL: the peculiar characteristics of this procoagulant (i.e. its confinement to the malignant phenotype, its shedding into the plasma, its possible modulation by vitro kinases) make this observation of potential interest in the development of new diagnostic and therapeutic tools in ANLL.

EFFECT OF INTERFERON GAMMA ON PROCOAGULANT 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 monocyctic pathway.

Furthermore, myeloid leukemic cells and normal monocytes have been demonstrated to possess procoagulant activity (Hart et al., 1986). The aim of this study was to investigate the modulation of PCA induced by treatment with IFN on human promyeocytic cells from HL 60 cell line. Cells were cultured in suspension for 5 days in RPMI 1640 medium supplemented with 1% 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 cytoplasm preparations and surface marker analysis with monoclonal antibodies (OKM1, M02, M19, M7, M4).

PCA was measured as capacity to shortening ricalcification time of normal plasma and of factor VIII, VII and X deficient plasma by the cells and the conditioned media.

Untreated HL 60 cells exhibit high tissue factor-like PCA, related to the cell number. IFN treatment (1000 u/ml) induced a decrease of the same time. A similar difference in PCA both in the cells and in the conditioned media.

The PCA was not further affected by higher concentrations of IFN, unable to determine cell naturalation. 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 EKSTASIS AND DISSIMULATION OF BLOOD BORNE TUMORS. M.C. Falanga, A. Falanga, A.P. Bolognesi Dalassandro, B. Canali and M.B. Donati. Istituto Mario Negri, Milano, Italy.

Involvement of the hemostatic system in tumor metastasis growth has been repeatedly suggested and several tumor-associated platelets have been described. We studied procoagulant activity (PCA) of tissue extracts from 4 murine metastasizing tumors, Lewis Lung Carcinoma (3LL), B16 melanoma (B16), JM sarcoma (JMS) and the M4 variant of the 3M Skeletal Sarcoma (M4). The experiments were designed to identify cancer procoagulant (CP) in a FVII-dependent FX activating cysteine proteinase or tissue factor (TF) in these tumors. Tissue extracts from 3LL, B16 and JMS initiate coagulation both in the presence and absence of FVII (FVII independent activity ranging from 70% to 90% of the total activity). The PCA of the same tumors was significantly decreased (p < 0.01) by cysteine proteinase inhibitors (1 mM iodoacetamide (IA) and 0.1 mM HgCl2) and the inhibition by HgCl2 was reversed by -SH group activators (di-thiureal, KCN, EDTA). In addition these samples were able of directly activating pure bovine FX in a two stage clotting assay. The PCA of M4 extract was dependent on FVII, was not significantly affected by IA and HgCl2 and was inhibited by concanavalin A, a known TF inhibitor. An Ouchterlony double immunodiffusion study showed immunological cross-reactivity of 3LL, B16 and JMS to a polyclonal antibody to purified CP (from rabbit V3 carcinoma; obtained from S.G. Gordon, Denver, USA). No cross-reactivity was present between this antibody and M4. This study shows that the PCA of M4 is TF, whereas the procoagulant(s) of 3LL, B16 and JMS are enzymatically and immunologically indistinguishable from CP.