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UROKINASE-TYPE PLASMINOGEN ACTIVATOR IN PLASMA FROM BREAST CANCER PATIENTS

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An enzyme-linked immunosorbent assay (ELISA) using both monoclonal and polyclonal antibodies was developed for the measurement of human u-PA in plasma and serum. The assay was used to measure the concentration of u-PA in plasma from 34 healthy donors and 92 breast cancer patients. The breast cancer patients were divided into (A): 44 patients in complete remission according to the WHO criteria. (B): 48 patients with clinically detectable disease. The latter were further subdivided into 3 groups according to tumor burden. Of these, 18 patients had minimal tumor burden (B1), 20 moderate (B2), and 10 maximal tumor burden (B3). The mean value of u-PA for the healthy donors was 1.1 ng/ml ± 0.3 ng/ml (SD). The mean value for the breast cancer patients (A+B) was 1.3 ng/ml ± 0.4 ng/ml. This moderate increase was statistically significant at the 1% level. There was a positive correlation between the mean u-PA plasma concentration and the extent of disease (e.g. u-PA conc. in group B3: 1.7 ng/ml ± 0.5 ng/ml). It is possible that breast cancer patients with an elevated plasma u-PA, represent a group with particularly aggressive disease, and that determination of plasma u-PA therefore could be of prognostic value.

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LOCALISATION OF PLASMINOGEN ACTIVATORS AND PLASMINOGEN ACTIVATOR INHIBITOR (TYPE 1) IN LEWIS LUNG CARCINOMA

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Extracellular proteolysis initiated by proteases secreted from neoplastic cells is thought to be one of the characteristics of the invasive, degradative and metastasizing cellular phenotype. Plasminogen activators initiate proteolysis by activating the proenzyme plasminogen present in the extracellular compartment. Previously it was found that areas of Lewis lung primary tumors with tissue degradation also contain high amounts of urokinase-type plasminogen activator (u-PA). A parallel immunohistochemical analysis for u-PA, tissue-type plasminogen activator (t-PA) and a specific plasminogen activator inhibitor (PAI-1) have now shown that the overall distribution of u-PA and PAI-1 is simillar in the primary tumors and that only very few tumor cells contain detectable t-PA immunoreactivity. However, in all primary tumors analysed (n=12) one or several areas showing strong u-PA, but low PAI-1 immunoreactivity was found. The tumor cells in these areas were surrounding muscle tissue being degraded by the invading tumor cells. The immunohistochemical findings were supported by biochemical analysis of tumor extracts and by the use of immunoblotting. These findings suggest that PAI-1 may play a role in the regulation of extracellular proteolysis in these tumors.

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ONE-CHAIN UROKINASE-TYPE PLASMINOGEN ACTIVATOR FROM HUMAN SARCOMA CELLS IS A PROENZYME WITH LITTLE OR NO INTRINSIC ACTIVITY.

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We have compared the plasminogen activating capacity of one- and two-chain urokinase-type plasminogen activator (u-PA) from HT-1080 fibrosarcoma cells in a radiolabeled plasminogen conversion assay and in two types of coupled assays in which generated plasmin was measured with a synthetic substrate. In all the assays the initial rate of plasminogen activation with one-chain u-PA was lower than that of a 250-fold smaller concentration of two-chain u-PA. On the basis of these and previous results, it is concluded that one-chain u-PA has a variety of properties similar to the one-chain proenzyme forms of other serine proteases, and that it should therefore be considered as a genuine proenzyme form of u-PA. The findings are discussed in the view of a recent detection of a Mr 55-60,000 receptor for u-PA at the surface of the HT-1080 cells (Nielsen et al., J. Biol. Chem. 1988, in press), and the cytochemical observation of pro-u-PA/u-PA immunoreactivity being distinctly located at cell-cell and focal cell-substratum contact sites in these cells (Pöllänen et al., J. Cell Biol. 104, 1085-1096, 1987; Pöllänen et al., J. Cell Biol. 1988, in press). Activation of receptor bound pro-u-PA may be an important regulatory step in the breakdown of contact sites during migration of cancer cells.

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RISK OF NON-OCULAR CANCER AMONG RETINOLASTOMA PATIENTS AND THEIR PARENTS - A POPULATION-BASED STUDY IN DENMARK 1943-1984.

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The risk of non-ocular cancer among survivors of retinoblastoma has been investigated in a population-based study in Denmark, 1943-1984. None of the survivors had been treated with chemotherapeutic drugs. Forty-eight patients were treated with X-rays, and 102 patients were primarily treated with surgical removal of the eye(s). The overall relative risk (RR) for a new primary cancer was 4.2 (95% confidence limits, 1.1-11.5). In the subgroup of hereditary retinoblastoma the risk was 15.4 (95% confidence limits, 2.6-50.8) and in the group of non-hereditary cancer the risk was 1.7 (95% confidence limits, 0.1-8.5). For all retinoblastoma patients the relative risk of bone cancer was 100 (95% confidence limits, 17-330). Parents not suffering from retinoblastoma themselves were not at increased risk for non-ocular cancer.