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THE REGULATORY REGION OF THE HUMAN PLASMINOGEN ACTIVATOR INHIBITOR-TYPE 1 (PAI-1) GENE

A.Riccio, L.R.Lund*, P.A.Andreasen^, K.Dano* and F.Blasi
Institute of Microbiology, University of Copenhagen, *Finsen Laboratory, Rigshospitalet Copenhagen, ^Institute of Biochemistry C, University of Copenhagen, Denmark.

PAI-1 synthesis is influenced by several growth factors and hormones. In order to study the molecular mechanisms of PAI-1 regulation we have cloned the human PAI-1 gene, identified its promoter region, and found that glucocorticoids, transforming growth factor-ß and the tumor promoter phorbol myristate acetate (PMA) enhance PAI-1 transcription rate acting at a unique transcription initiation site. The analysis of the promoter region has revealed the presence of a moderately repetitive (Alu-like) sequence, containing a TATA box, a GRE consensus, a Z-DNA forming sequence and two imperfect direct repeats at the extremities, few nucleotides 5' of the transcription initiation site. We have also found that 415 5' flanking nucleotides of the PAI-1 gene contain information enough to promote transcription and to respond to glucocorticoids when fused to the reporter CAT gene and transfected into human fibrosarcoma cells. These findings raise the hypothesis that the human PAI-1 gene has been activated, by DNA insertion, during the evolution.

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REPEATED IN VIVO P-31-NMR-SPECTROSCOPY OF HUMAN SMALL CELL LUNG CANCER (SCLC) ON NUDE MICE DURING UNTREATED GROWTH.

Paul E.G. Kristjansen, E. Jonas Pedersen, Mogens Spang-Thomsen, Finsen Institute, University Institute of Pathology, University Institute of Physical Chemistry, Copenhagen.

Time dependent variations in the relative concentrations of endogenous high-energy phosphates (ATP) in SCLC was evaluated during untreated growth. Six human SCLC-tumours (54A and 54B) on nude mice were examined six times with one weeks interval at a BRUKER 250 MHz magnet. Home build two-turn surface coils 6 and 10 mm were used. The mice were unanesthetized during recording.
The ATP/(Inorganic phosphate) ratio of tumours tended to decrease with in-creasing size and age of the transplant. The configuration of the individual tumour spectra remained fairly constant, whereas a great inter-tumour variation was found.
Conclusion: The method seems useful in studying alterations in the energy metabolism of individual tumours. The future role in preclinical drug testing is yet to be defined.

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COMBINATION CHEMOTHERAPY AS PRIMARY TREATMENT OF BRAIN METASTASES FROM SMALL CELL LUNG CANCER (SCLC).

P.E.G. Kristjansen, L. Damstrup, P. Soelberg Sørensen, H.H. Hansen. Dept. of Oncology ONB, Finsen Institute, and Dept. of Neuromedicine, Rigshospitalet, Copenhagen.

Since 1985 14 SCLC-pts. with initial brain metastases were treated with combination chemotherapy and no concomitant radiotherapy. Two schedules were used: CCNU (Lomustine), Cyclophosphamide, Vincristine, VP-16 (Etoposide) q. 4 weeks and Cis-platinum, VM-26 (teniposide), Vincristine q. 4 weeks. All patients were evaluated by successive cranial CT-scans. Seven of them were included in an ongoing phase II study, with careful prospective neurologic evaluation, including assessment (scoring) of the functional status of patients. Three patients were ineligible due to early death within 3 weeks. The remaining 11 all responded (7 CR and 4 PR). Median duration of brain response was 16 weeks, range (6 - 74).
Conclusion: Initial brain metastases from SCLC are sensitive to combination chemotherapy.

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MOLECULAR STUDIES OF THE CELLULAR RECEPTOR FOR UROKINASE-TYPE PLASMINOGEN ACTIVATOR.

N. Behrendt*, L.S. Nielsen*, E. Rønne*, G.M. Kellerman*, F. Blasi° and K. Danø*
*Finsen Laboratory, Rigshospitalet, Strandboulevarden 49, 2100 Copenhagen Ø., Denmark. °Mikrobiologisk Institut, University of Copenhagen, Øster Farimagsgade 2A, 1353 Copenhagen K., Denmark.

A recently discovered receptor (Vassalli et al. (1985) J. Cell Biol. 100, 86-92) for urokinase-type plasminogen activator (u-PA) was studied with respect to polypeptide chain composition, glycosylation and binding properties in solution. Detergent lysates from human cultured cells holding the receptor were incubated in the presence of radiolabeled ligand. After the incubation, a chemical cross linker was added, and components bound to the radiolabeled ligand were visualized by SDS-PAGE and autoradiography. Pilot studies on purification were performed using affinity chromatography on pro-u-PA-Sepharose. The binding capability of the purified receptor was conserved. An about 2000-fold purification was obtained. The molecular weight of the receptor was determined by SDS-PAGE to be 55 kD. The same molecular weight was found irrespective of whether the disulfide bridges were cleaved or not. The receptor could be enzymatically deglycosylated to yield an about 35 kD polypeptide. The polypeptide part of this heavily glycosylated protein has a lower molecular weight than most known cellular receptors.