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TRANSFORMING GROWTH FACTOR-β AND GLUCOCORTICOID REGULATION OF PLASMINOGEN ACTIVATOR INHIBITOR TYPE-1.

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Urokinase-type (u-PA) and tissue-type (t-PA) plasminogen activators catalyze the conversion of the abundant proenzyme plasminogen to the broad-spectrum protease plasmin. Cellular release of plasminogen activators is therefore able to initiate localized extracellular proteolysis, and has been implicated in tissue destruction and tumor spread in cancer. Plasminogen activation is regulated at several levels. Human plasminogen activator inhibitor type-1 (PAI-1) is an Mr ~ 54,000 protein which belongs to the serpin superfamily and has arginine at the reactive center. We have studied the mechanisms of the stimulation of PAI-1 activity by transforming growth factor-β (TGF-β) and the synthetic glucocorticoid dexamethasone in cultured human cells. By the use of PAI-1 cDNA, TGF-β and dexamethasone were found to cause rapid increases in PAI-1 mRNA levels; the 3.4 as well as the 2.4 Kb-PAI-1-mRNA species were increased. Quantitative studies on the effect of these agents on PAI-1 protein levels in cell extracts and culture media by ELISA, as well as immunocytochemical stainings, gave results consistent with the effects on PAI-1 mRNA. These studies suggest that TGF-β and glucocorticoids may exert important controls over plasminogen activation-mediated extracellular proteolysis, and thus over tissue destruction and tumor spread, through an enhancement of PAI-1 gene transcription.

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GLUCOCORTICOID HORMONE EFFECTS ON MHC CONTROL OF CARCINOGEN-INDUCED LUNG TUMORIGENESIS IN MICE

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Genes from the Major Histocompatibility Complex (H-2) are involved in tumorigenesis in the mouse. We have shown that the H-2 influence on carcinogen-induced lung tumors is not confined to tumor incidence only but comprises also their histological type and growth rate.

It has been reported that the glucocorticoid hormone (GC) mediated control of differentiation of fetal lung is also under H-2 influence. We decided to study the relationship between GC action on fetal lung, the H-2 genotype and lung tumorigenesis. Mice from the strains B10.A and B10, sharing all genes except those of the H-2 complex and known to differ in (1) their susceptibility to lung carcinogenesis and (2) GC mediated control of fetal lung differentiation, were prenatally treated with either GC plus the carcinogen ethylnitrosourea (ENU) or with ENU alone. Assay of tumor development showed that (1) for the alveolor type of lung tumor both treatments result in a highly significant difference in incidence between strains; (2) for the papillary type of lung tumor the GC/ENU treatment (versus ENU alone) results in a higher number of tumors in strain B10, whereas in strain B10.A the reverse was found. An analogous strain specific effect of GC treatment on papillary lung tumor size is indicated as well.

Thus in these H-2 congenic strains GC treatment has a differential effect on prenatally-induced lung tumors: the H-2 linked influence on alveolar lung tumorigenesis remains unaltered, whereas for papillary tumors an H-2 haplotype specific increase or decrease in tumor number (and probably also size) was found.