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CHARACTERIZATION OF ANDROGEN RECEPTORS IN A TRANSPLANTABLE HUMAN PROSTATIC ADENOCARCINOMA (PC.82).

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The transplantable human prostatic adenocarcinoma, PC.82, has been shown to be a suitable model for the study of several aspects of androgen-regulated tumour growth. This tumour contains an androgen receptor (AR) and the purpose of the present investigation was the characterization of this AR with respect to hormone specificity, sedimentation coefficient, dissociation constant, Stokes radius, ionic properties and molecular mass. Cytosol was prepared from tumour tissues permanently growing as subcutaneous grafts in athymic nude mice, which were castrated 2 days before isolation of the tumour. Scatchard plot analysis revealed a binding protein with the characteristics of AR. The AR showed the highest affinity for methyltrienolone, testosterone and 5α-dihydrotestosterone, respectively. Progesterone and oestradiol receptor concentrations in the cytosol preparation were below the detection level. In the presence of 10 mM molybdate the AR from PC.82 eluted at the same ionic strength (0.3 M KCl) from an FPLC anionexchange column (Mono Q) as AR from rat prostate and calf uterus. Photoaffinity labelling of the AR eluted from the FPLC-column with ^{3}H-R1881 resulted in a specific covalently labelled protein with a molecular mass of approx. 50 kD after SDS-polyacrylamide gelelectrophoresis. The AR of the PC.82 tumour had a sedimentation coefficient of 4S in a 5-20% linear sucrose gradient and a Stokes radius of 3.3 nm after gelchromatography on ACA-34. It is concluded that the PC.82 tumour contains a binding principle which shows the properties characteristic for AR in other androgen target cells.

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INTERFERON α INCREASES OESTROGEN RECEPTOR EXPRESSION IN THE ZR-75-1 HUMAN BREAST CANCER CELL LINE.

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There is some evidence that interferon, (IFN), may increase the expression of oestrogen receptor, (ER), in target tissues, including breast carcinoma, (Pouillart et al, Eur J Cancer Clin Oncol, 18, 929, 1982). If this were confirmed it might be expected that IFN would increase the sensitivity of breast carcinoma cells to the anti-oestrogen tamoxifen (TAM). We have previously shown that growth inhibitory concentrations of IFN and TAM are additive rather than synergistic in their effects on ZR-75-1 human breast cancer cells, (Br J Cancer, 52, 3, 428, 1985). In this study we have examined the ability of IFN to modulate ER expression in this cell line.

Human recombinant IFNα (10-1000 U/ml) increased ER levels as measured in a whole cell binding assay and this effect was inversely proportional to dose. Specific binding at a single subsaturating ligand concentration, (1nM ^{3}H-oestradiol), was increased up to 10-fold by a two day pre-exposure of cells to 10 U/ml IFNα. This concentration of IFN alone had no effect on cell proliferation. IFNα induced increases in specific binding of oestradiol by ZR-75-1 cells was observed maximally when cells were treated at a low cell plating density - a factor which also increases the anti-proliferative effects of higher concentrations of the agent (500-1000 U/ml).

Despite marked increases in detectable ER following IFNα treatment, preliminary experiments have failed to show enhanced sensitivity of ZR-75-1 cells to TAM following pre-treatment with IFNα.

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DEMONSTRATION OF OESTROGEN-AND PROGESTERONE-RECEPTORS IN A HUMAN INSULINOMA.

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Oestradiol has been shown to modulate insulin secretion and plasma insulin response to glucose administration in animal model systems. In the human no evidence showing the endocrine pancreas to be a target organ for steroid hormones has hitherto been obtained. Since steroid receptors seem a prerequisite for steroid hormone action a search was made for the presence of such receptors in human pancreatic tissue. Fresh tissue was homogenized in tris-HCl buffer containing molybdate (10 mM) and a serine protease inhibitor (phenyl-methyl-sulphonyl-fluoride). High-affinity, saturable binding of both oestradiol and promegesterone (R 5020) could be demonstrated in tumour tissue by a dextran-coated-charcoal assay and by sucrose density-gradient ultracentrifugation. Both receptors sedimented predominantly as 8S-complexes. The amount of 8S-estrogen receptor present was low (4.2 fmol/mg cytosol protein) compared to the levels of progestin receptor (110 fmol/mg); a combination quite often seen in benign breast tumours. Androgen receptor was absent as judged by the lack of specific or saturable binding of methyltrienolone (R 1881). No receptors could be detected in normal pancreatic tissue surrounding the insulinoma. Progesterone receptor is generally believed to be produced by an oestrogen receptor-mediated mechanism. Our findings support the hypothesis that oestrogens excert an action in pancreatic β-cell tissue.

This work was supported by the Norwegian Society for Fighting Cancer.

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OESTROGEN RECEPTOR DISTRIBUTION IN THE CANCEROUS BREAST

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It is not clear how the expression of oestrogen receptors (ER) in human breast tumours relates to that in the normal tissue. In this study, a comparison has been made between the ER content of tumours and the remainder of the breast obtained at mastectomy. At mastectomy the removed breast was divided into 16 equal sectors from which specimens were taken for receptor assay and histology. The position of the tumour had been previously ascertained. The ER content in each of the specimens was measured by a single saturating dose, dextran coated charcoal assay, and receptor content of the specimen was expressed as fmol H-oestradiol bound/mg cytosol protein, tumours containing >5fmol/mg protein were considered to be ER+ve. Data was obtained from 8 patients whose primary tumours were ER+ve, of these patients, 2 were premenopausal, 1 was perimenopausal and 5 were postmenopausal. In all cases the ER concentration was much higher in the tumour than in the non-malignant specimens. Three of the patients had multifocal tumours, distinct by histological criteria, receptor content and relative position. The non-malignant tissue was not homogeneous and contained areas of benign breast disease as well as normal tissue although there were no differences in the ER contents of these tissues. There appear to be no previous studies where breast tumour ER content is directly compared to that of the whole of the remaining non-malignant breast. The data suggests that the expression of ER in the breast tumours is quantitatively different from the other tissue and supports the hypothesis that the ER concentration in ER+ve tumours reflects the transformed function of neoplastic tissue.