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TUMOUR ASSOCIATED GONADOTROPHIN RELEASING HORMONE RECEPTORS

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We report high affinity binding (kd=50M) of a gonadotrophin releasing hormone (GnRH) analogue resulting in biphasic growth modulation of the human androgen-sensitive prostatic cancer cell line LNCaP. This was in contrast to low affinity, non specific binding (kd=10uM), without biological effect in the human androgen insensitive line DU145. GnRH-like immunoreactivity was demonstrated in the concentrated culture media from both cell lines by a GnRH radioimmunoassay, and this peptides elution profile on HPLC was identical to native GnRH. Nineteen of 22 malignant tumours and 49 of 54 benign prostatic tumours exhibited high affinity binding. Fourteen of 19 malignant tumours and 17 of 49 benign tumours exhibiting high affinity binding contained GnRH-like immunoreactivity suggesting that this system may be involved in prostatic epithelial growth in vivo.

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HORMONAL AND GROWTH FACTOR MANIPULATION OF HUMAN PROSTATE CANCER IN THE NUDE MOUSE MODEL.

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The relevance of low levels of testosterone (T) and adrenal androgens on human prostatic cancer tissue was investigated using the transplantable androgen dependent human prostatic tumor models, PC-82 and PC-EW. Mice bearing growing tumors were supplemented with various plasma levels of T or with the adrenal androgens, androstenedione (A) and dehydroepiandrosterone (DHEA). Both the PC-82 and PC-EW tumor burden remained stable at a plasma T level of 0.8 nmol/l, whereas tumor growth occurred at higher levels of plasma T and tumor regression was observed at lower levels. This critical level of circulating androgen corresponded with intratumor concentrations of T and dihydrotestosterone (DHT) which were significantly above the levels found in castrated animals. Growth of the PC-82 tumor in DHEA implanted mice was not stimulated. Substitution with A resulted in substantially elevated intratumor DHT levels leading to an increase of the tumor burden. Apparantly, in these experimental models adrenal androgens can be converted in tumor growth stimulatory levels of androgens. The clinical relevance of this observation remains to be established.

Receptors for epidermal growth factor (EGF) were demonstrated in tumor tissue of both androgen dependent and independent prostatic tumor models, with concentrations varying from 10-65 fmol/mg protein. EGF appeared to play a role in the development of tumors of the hormone independent PC-135 prostate tumor in nude mice.

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LONG-TERM TREATMENT WITH ANTIANDROGENS

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Since the first report in 1966 by Scott and Schirman on the clinical use of antiandrogens in patients with prostatic cancer, several studies have been published. Most of these deal with short-term treatment and include only a limited number of patients.

Steroid antiandrogens (cyproterone acetate and megestrol acetate) have demonstrable progestational and antigonadotrophic effects, whereas the nonsteroid 'pure' antiandrogens (flutamide, anandron, and casodex) mainly act peripherally on androgen-dependent accessory genital organs and thus preserve libido and sexual potency in most patients.

Short-term treatment with antiandrogens have exerted responses similar to those achieved with conventional endocrine therapy. Because of relatively fewer side effects of these drugs, there is an increasing interest in assessment of the long-term effect, and some studies have been initiated.