158

A POSSIBLE ROLE FOR EPIDERMAL GROWTH FACTOR AND ITS RECEPTOR IN THE GROWTH OF HUMAN PROSTATIC AND RENAL CELL CARCINOMA CELL LINES IN ATHYMIC NUDE MICE.

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The epidermal growth factor receptor (EGFr) concentration was estimated in tissues of various human prostatic (PC) and renal cell carcinomas (RCC) heterotransplanted into nude mic. Membrane preparates of all PC and RCC tumor tissues contained saturable binding sites for EGF, the concentrations varying from 10-65 and 30-170 fmol/mg protein, respectively. The hormone unresponsive PC-133 and PC-135, containing a relatively low and high number of EGF binding sites respectively, were transplanted in male nude mice and in mice that were sialoadenectomized (removal of the submandibular glands) causing decreased levels of circulating EGF. Neither the take nor the growth rate of the PC-133 tumor were affected by sialoadenectomy (SX). This treatment, however, significantly retarded the take rate of PC-135 tissue (58 and 92 per cent for the control and SX treated mice, respectively). Substitution of EGF appeared to abolish the effect of SX on the development of PC-135 tumors. Tumors once developed did not differ with respect to their respective growth rates. By contrast, the growth rate of the RC-43 renal cell cancer cell line was substantially delayed when transplanted in SX nude mice. The present results indicate that EGF is involved in the take and growth of some transplantable human PC and RCC carcinoma cell lines in nude mice.

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159

EGF-RECEPTOR EXPRESSION AND EGF-DEPENDENT GROWTH OF MOUSE BLADDER CELLS IN VITRO.

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The basal cells of the normal human bladder have high epithelial growth factor receptor (EGFR) expression, which is in contrast with the superficial cells and the intermediate cells. Conflicting data have been reported on EGFR expression in human transitional cell cancer (TCC).
We have studied EGFR expression in TCC using monoclonal antibody 2E9 directed against the EGF-binding site of EGFR, and polyclonal antibody 281-7 directed against the tyrosine kinase part of EGFR. Grade I tumours showed EGFR expression in basal cells only, while in grade II tumours EGFR was detectable in basal and intermediate cells. Grade III tumours were either strongly positive or negative for EGFR expression in all cells.
A proliferation-inducing effect of EGF in rat bladder seems to be confined to the basal cells. A correlation between EGF-induced cellular effects and EGFR expression in bladder cells, in vitro, has been shown by few authors. We whish to correlate the level of EGFR expression in cultures of spontaneously immortalized mouse urothelial cells, developped in our laboratory, with EGF-dependent proliferative activity. One cell line, NUC-1, showed a dose-dependent EGF-induced proliferation, but could not proliferate without EGF. The other cell line, NUC-5, also showed EGF-induced dose-dependent proliferation, but could proliferate without addition of EGF. This may be explaned by synthesis and probably secretion of EGF-like factors. Scatchard analysis of EGF-binding indicated high affinity binding sites for EGF. The number of sites varied from 20.000 to 100.000 sites per cell. A possible correlation between EGFR expression and EGF-dependent cellular effects awaits further study.

160

ESTROGEN AND PROLACTIN REGULATION OF RAT DORSOLATERAL PROSTATE IN ORGAN CULTURE

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Besides androgens, estrogen and prolactin are thought to be involved in the regulation of normal growth and pathology of the prostate. We have established organ cultures of rat dorsolateral prostate for the in vitro studies of the mechanisms of hormone interactions.
Explants of dorsal and lateral prostate were prepared separately and cultivated without serum in a chemically defined medium M199, which was supplied with insulin and cortico sterone. The gas atmosphere was a mixture of O_2, CO_2 and air (40:5:55). Under these conditions the viability and overall integrity of the tissue was maintained for at least 14 days although there were castration-like changes in morphology. Wet weights and DNA concentration of the explants also declined.
Addition of testosterone prevented the involutive changes in morhology. The weights and DNA contents of the explants were also better maintained. The rate of (^{3}H)thymidine incorporation significantly increased by the addition of either testosterone, estrogen or prolactin.
The hormone responsiveness of tissue specific functions was evaluated by measuring the expression of the genes M-40 and RWB encoding two androgen-regulated secretory proteins (Matusik et al.,1986, Biochem. Cell Biol. 64, 601). The steady-state levels of mRNA:s were estimated by Northern blotting and hybridization of total RNA to specific DNA probes. The expression of both genes was almost undetectable when the explants were grown in the basal medium but testosterone, estradiol and prolactin were each able to maintain high mRNA levels and to potentiate the effect of the others.
The results show that estrogen and prolactin do have direct effects on rat dorsolateral prostate in organ culture which should thus prove an important model for the studies of the mechanisms of hormone regulation of the prostate.

161

SANDOSTATIN,A LONG ACTING SOMATOSTATIN ANALOGUE,IN THE TREATMENT OF ADVANCED METASTATIC PROSTATIC CANCER.

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As reported for somatostatin the long-acting analogue,sandostatin or SMS 201-995 exerts remarcable number and variety of actions in different part of the body.In addition to the hormonal effects these agents show specific direct inhibitory actions on cell differentiation and division.Various factors have been implicated in the evolution of the prostatic cancer:in fact higt prolactin or GH levels and tumors DNA ploidy have been linked with a poor prognosis,moreover a number of growth factors like epidermal growth factor (EGF),platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and other are involved in the proliferation of malignant cells.As known somatostatin suppresses prolactin and GH levels and inibits DNA syntesis and growth factors effects.On these basis an associated therapy with sandostatin and pharmacological castration with zoladex plus eulexin have been devised for the prostatic andvanced metastatic cancer.All the patients had mesurable disease and pain secondary to the cancer.The protocol included the following drugs:Sandostatin fl 0.1mgx3/die by subcutaneous injection,Zoladex 1 fl every 28 days by subcutaneous injection and Eulexin cpr 250mgx3/die.From november 1989 to january 1990,7 patients median age 68 (range 59-80) with histologically confirmed adenocarcinoma,have been selected.Three of these patients were already in therapy with the only Zoladex plus Eulexin.As expected in all patients not pretreated a significant reduction of pain was observed but also two of the three patients already in therapy showed a remarcable reduction of pain.Clinical side effects were minimal:hot flushes in 2 patients.In conclusion these data although preliminary suggest that this combination therapy is well tolerated,without significative side effects and of good efficacy in reducing pain.These results seem appears encouraging in go on testing this protocol.