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Androgen regulation of Gonadotropin releasing hormone type II in prostate cancer

S Darby, J Stockley, C N Robson, R J Edmonson, H Y Leung, V J Gnanapragasam

Northern Institute for Cancer Research, Newcastle, United Kingdom

Analogues of type I Gonadotrophin Releasing Hormone (GnRH I) are known to exert a direct anti-tumourigenic effect on prostate cancer cells. Recently type II GnRH has been shown to exert potent extra-pituitary anti-proliferative effects. GnRH II expression was first studied in a panel of cancer cell lines by quantitative PCR. High expression was detected in LNCaP cells and low expression in DU145, PC3 and PC3M cells. GnRH II protein expression was next tested by immunohistochemistry in the CWR22 prostate xenograft model. GnRH II expression was decreased in tumours from castrated animals compared to controls and was correspondingly over-expressed in tumours from androgen supplemented mice. In invitro studies GnRH II mRNA and protein expression were decreased in LNCaP cells following androgen withdrawal. In contrast, treatment with androgens significantly increased GnRH II levels. Co-treatment with the anti-androgen casodex completely reversed this effect suggesting direct recruitment of the androgen receptor (AR). In addition, co-incubation with the protein inhibitor cyclohexamide had no effect on GnRH II induction suggesting a direct effect on gene transcription. Finally, in chromatin immunoprecipitation experiments binding of the AR protein to GnRH II upstream sequence was demonstrated in androgen treated cells but not in corresponding controls. These results show first evidence of AR regulation of the GnRH II gene. Further work is underway to assess the role of GnRH II in prostate carcinogenesis.