1

STRUCTURE AND FUNCTION OF STEROID RECEPTORS: MODULATION BY ANTISTEROIDAL AGENTS.

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The oestrogen receptor is a member of a supergene family that includes receptors for steroid and thyroid hormones, vitamin D3, and retinoic acid. A number of additional members of the family have been cloned where the putative ligand remains to be identified. The oestrogen receptor is a ligand-activated transcription factor that modulates specific gene expression by binding to short DNA sequences (oestrogen response elements) located in the vicinity of oestrogen-regulated genes. Regions of the receptor responsible for hormone-binding, DNA-binding and activation of transcription, have been identified.

The antioestrogen, tamoxifen (Nolvadex), behaves as a weak oestrogen agonist. A model, based upon our current understanding of the molecular mechanism of oestrogen action, will be presented to explain the cell and gene specific effects of some anti-oestrogens.

2

TRANSITION OF HUMAN BREAST CANCER CELLS FROM ESTROGEN RESPONSIVE TO UNRESPONSIVE STATE

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The progression of tumor cells from a state of steroid sensitivity to one of insensitivity presents a major clinical problem in the endocrine therapy of breast cancer. Growth of cloned estrogen responsive breast cancer cell lines in vitro in the long-term absence of steroid results in progression to steroid autonomy and thus provides a model system to study this phenomenon. Loss of estrogen response results not from a loss of the estrogen-stimulated growth rate but rather from an increased basal growth rate without steroid. For ZR-75-1 cells the effects are clonal but occur at high frequency (1 in 1,000 cells) and synchronously between clones, suggesting a phenotypic/epigenetic mechanism. The question of how this altered cell growth might be achieved at a molecular level will be discussed in relation to steroid receptor function and involvement of growth factors.

3

SENSITIVITY AND INSENSITIVITY OF BREAST CANCER TO TAMOXIFEN

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Tamoxifen is the endocrine treatment of choice for breast cancer. In several laboratory models in vivo tamoxifen is a tumoristatic agent. When MCF-7 breast cancer cells are inoculated into athymic mice, palpable tumors do not grow unless the animals are treated with estrogen and tamoxifen inhibits estrogen-stimulated growth. If tamoxifen is stopped tumors regrow. These results suggest that adjuvant tamoxifen therapy should involve long periods (even lifetime) to prevent tumor recurrence. Resistance to therapy and patient relapse inevitably occur, and such disease recurrence involving tamoxifen resistance is difficult to treat successfully. A laboratory model of endocrine therapy failure has been developed. When athymic mice with MCF-7 tumors are treated for 6-8 months with tamoxifen several tumors grew and continued to grow in tamoxifen-treated mice. Tumors contained estrogen receptors are grown with either tamoxifen or estradiol Growth can be inhibited with the pure antiestrogen ICI 164,384 or withdrawal of tamoxifen. Tamoxifen-stimulated tumor growth has been observed in human endometrial tumors implanted into athymic animals. There is a suggestion from the clinical literature that long-term tamoxifen therapy for breast cancer may stimulate occult endometrial carcinoma.

4

THERAPEUTIC POTENTIAL OF PURE ANTIOESTROGENS IN THE TREATMENT OF BREAST CANCER

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Novel 7a-analogues of 17b-oestradiol like **ICI 164,384**, differ from all antioestrogens described previously in being entirely free of partial agonist activity. In adult rats, ICI 164,384 blocks completely the stimulatory effects of endogenous or exogenous oestrogens and produces a castration-like involution of the uterus without affecting the hypothalamic-pituitary-ovarian axis. If analogous effects were achieved in patients, peripherally-selective **complete** oestrogen withdrawal would occur, which presents a novel pharmacological option not achieved by any current treatment. Studies with human breast cancer cells showed that ICI 164,384 reduced to a greater extent than did tamoxifen, the mitotic fraction. This difference may reflect a synergistic stimulatory interaction between serum growth factors like insulin, and the partial agonist effect of tamoxifen which is not seen with ICI 164,384. In long-term culture in the presence of ICI 164,384 no resistant cell lines developed, as has been observed previously in studies with tamoxifen. Pure antioestrogens might thus have a further therapeutic advantage over partial agonists like tamoxifen in reducing the probability of treatment failure due to the regrowth of tumours from resistant cells.