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Tamoxifen-resistant breast carcinoma xenograft

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Keywords

Breast cancer, cathepsin D, oestrogen receptor, pS2, tamoxifen resistance, xenograft

Introduction

At diagnosis, approximately 60% of breast tumours express oestrogen receptor (ER) and are considered hormone-responsive. The current first choice endocrine therapy is the antioestrogen tamoxifen (TAM); however, around one third of breast tumours do not respond to this treatment. Of those that do respond, development of TAM resistance can occur after continued treatment. Most studies examining the development of antioestrogen resistance have used cell lines that have been made resistant by continuous culture in the presence of antioestrogens. These have certain limitations, however; they are not representative of the internal microenvironment of a tumour *in vivo* and may select for specific subpopulations. As an alternative model, development of a xenograft of a human TAM-resistant mammary tumour, MaCa 3366/TAM, is described.

Aims

To develop a TAM-resistant subline of an originally sensitive breast cancer xenograft (3366) by long-term treatment of tumour-bearing nude mice with antioestrogen.

Comments

The development of antioestrogen resistance in breast cancer is a considerable clinical problem. Mechanisms associated with a resistant phenotype have mainly been addressed by the development of resistant cell lines *in vitro*, but these have some drawbacks as the tissue architecture seen *in vitro* is lost when cells are placed in culture. Here, a tamoxifen-resistant breast cancer xenograft has been developed and some initial characterisation performed. Because this retains many of the features seen in breast tumours *in situ*, this is a more clinically relevant model to study antioestrogen resistance. Further studies

using this model to address some of the mechanisms associated with antioestrogen resistance are keenly awaited.

Methods

Xenografts of the TAM-sensitive 3366 breast cancer cell line were established in the flanks of NMRI-nu/nu female mice. Mice received increasing doses of TAM (1-50 mg/kg) over a 3 year period until the development of TAM resistance. Thereafter they were treated regularly with 50 mg/kg TAM during passage. For histological investigation, standard procedures were employed. ER and progesterone receptor content of xenografts was determined by commercial immunoassay and the expression of ER-regulated genes was by northern blot analysis. Finally, the hormone binding domain of ER was analysed by sequence analysis to look for mutations associated with TAM resistance.

Results

Histological examination of the TAM-sensitive 3366 xenograft showed a solid ductal invasive carcinoma with moderate differentiation. After treatment with 17ÃŽÂ±-estradiol (E2), histology changed to reveal a ductal pattern of growth. These more differentiated structures were not seen in the resistant subline after E2 treatment.In comparison to the parental TAM-sensitive xenograft, TAM failed to induce growth inhibition in the resistant xenograft. Similar inhibition was seen with the pure antioestrogen ICI 182780, indicating cross-resistance.Both sensitive and resistant tumours expressed similar levels of ERα, ERβ and progesterone receptor. In the sensitive xenografts, ERα was upregulated following E2 treatment, and upregulation of progesterone receptor was also observed. The ER-regulated genes pS2 and cathepsin D were regulated by E2/antioestrogen in the sensitive 3366 tumours, but this was lost in the 3366/TAM cells. Sequence analysis of the ER ligand-binding domain showed no differences between the sensitive and resistant cells.

Discussion

An *in vivo* model of TAM resistance has been developed by long-term treatment of nude mice bearing xenografts of the cell line 3366. This model has been characterised in comparison with the TAM-sensitive parental cell line and has applicability as a more clinically relevant model to study antioestrogen resistance.

References

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