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Modulation of endometrial transforming growth factor β (TGFβ) by tamoxifen

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Abstract

Transforming growth factor β (TGFβ) immunoreactivity was determined in endometria from non-drug-therapy and tamoxifen-treated patients. Sections were scored for pathology and quantity image analysis performed to determine levels of glandular- or fibrosis-associated TGFβ1. Tamoxifen-treated patients displayed greater levels of endometrial dysplasia and glandular hyperplasia, in addition to a statistically significant ($P < 0.0001$) elevation in gland-associated TGFβ1 protein.

Keywords: TGFβ; Tamoxifen; Breast; Endometria

1. Introduction

Although tamoxifen is of immense value in the treatment of breast cancer, epidemiological evidence has linked its usage with endometrial cancer [1]. We speculate that epigenetic mechanisms of carcinogenicity, involving growth factor modulation, may be responsible [2].

Tamoxifen competes with and inhibits the mitotic actions of oestradiol, yet also appears to modulate growth factors such as TGFα and TGFβ. Indeed, tamoxifen exerts some very beneficial effects on TGFs in the breast as a component of its anti-oestrogenic activity, including the downregulation of the expression of the mitogen TGFα and enhancement of the expression of TGFβ with its negative growth factor influence [3]. Hence, with regard to the pro-oestrogenic action of tamoxifen in the human uterus, a hypothesis of uterine TGFβ dysregulation appears plausible.

2. Experimental

Tissue was obtained by operative hysteroscopy or from hysterectomy and snap-frozen prior to processing. Patient ages ranged from 52 to 64 years for 10 drug-therapy-free patients and 56 to 71 years for 10 tamoxifen-treated patients. Treatment with tamoxifen (20 mg/day) was for between 25 and 91 months. Sections were prepared to provide sequential slides for both TGFβ1 immunostaining and comparative haematoxylin and eosin (H&E) staining. Sections were coded, blinded and microscopically examined/graded for areas of dysplasia, fibrosis and glandular hyperplasia.

Statistical analysis of pathology scoring using a Mann–Whitney two-tailed test, demonstrated significantly greater dysplasia and glandular hyperplasia in tamoxifen-treated patients as compared with drug therapy-free controls. A similar, but non-statistically significant, finding was found with respect to endometrial fibrosis.

Examination of slides stained for TGFβ1 immunoreactivity demonstrated that staining in tamoxifen-treated patients was mainly confined to the apical border of the epithelium together with inflammatory cell infiltrates, although some cytosolic and basolateral staining was present. Immunoreactivity associated with glandular or fibrotic elements was assessed using quantity image analysis. Fig. 1 shows the results and demonstrates the significantly greater level of gland-associated TGFβ1-staining measured in tamoxifen-treated patients, compared with drug therapy-free controls ($P < 0.0001$).

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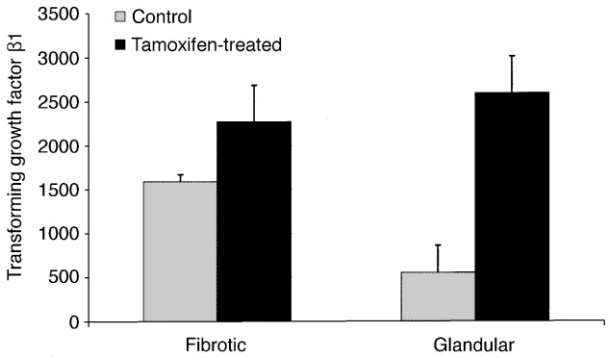

Fig. 1. Transforming growth factor β immunoreactivity in human endometrium.

A non-statistically significant difference was seen for fibrosis-associated TGFβ1-staining.

3. Discussion

The data presented demonstrate that (as seen in breast) tamoxifen treatment results in an induction of TGFβ1 in the endometrial glands. Although such an upregulation has been hypothesised to be beneficial in the treatment of breast cancer [3] the role of TGFβ in tumorigenesis is somewhat paradoxical. TGFβ acts as a potent growth inhibitor in some cancer cells, but can also act as a selective growth promotor when tumour cells acquire resistance to TGFβ-mediated growth inhibition [4].

Endometrial cancer arises from the glandular epithelial cells of the basal layer of the endometrium. The regulation of TGFβ isoforms during the transition of normal proliferative endometria to complex hyperplasia and progression to endometrial carcinoma has been investigated in human endometrium by Gold and colleagues [5]. Glandular epithelium showed a step-wise increase in the expression of all three subtypes progressing from normal proliferative endometrium to simple hyperplasia and on to complex hyperplasia. The simultaneous overexpression or accumulation of the TGFβ isoforms from normal to hyperplastic state may indicate dysregulated growth control, which may contribute to the development of endometrial cancer [5]. These data concur with the data presented in this paper which demonstrate that tamoxifen-induced upregulation of glandular TGFβ1 is accompanied by a greater level of endometrial pathology.

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Inhibition of oestrogen receptor activity by the co-repressor HET/SAF-B is relieved by blockade of histone deacetylase activity

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The oestrogen receptor (ER) is a member of a superfamily of nuclear transcription factors. When the ER binds oestrogen it undergoes a conformational change that results in dimerisation, binding to specific elements of DNA, and finally altered gene transcription [1]. While this model of ER action has held true for the last 30 years, a more complete understanding has revealed that activation of the ER is extremely complex, with regulation by a diverse set of signals and nuclear factors. A poorly described modulator of hormone action is the nuclear matrix, which is a dynamic structure

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