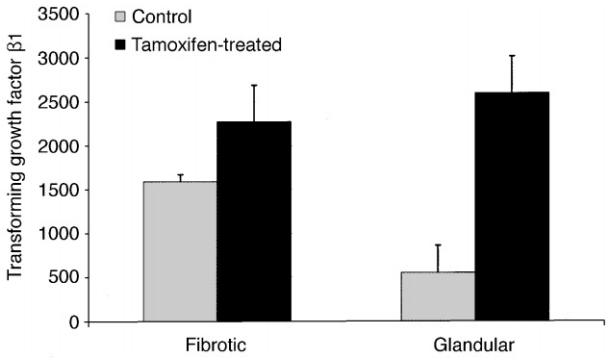

Fig. 1. Transforming growth factor β immunoreactivity in human endometrium.

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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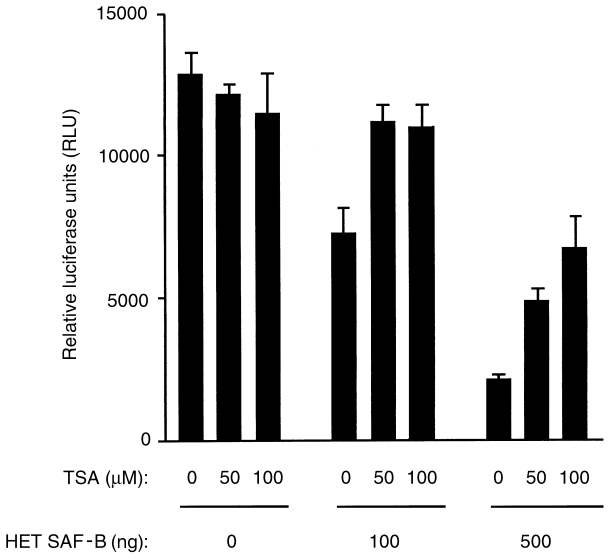

Fig. 1. MCF-7 cells were transiently transfected with ERE-*tk-luc* (0.5 μg), HET/SAF-B, ER (25 ng) and B-gal (200 ng) plasmids. Cells were stimulated with oestradiol for 24 h in the presence or absence of trichostatin A (TSA). Luciferase activities were corrected for B-gal, and represent the average of triplicate wells −/+ standard error of the mean (SEM).

involved in DNA replication, transcription, repair and RNA processing [2]. A role for the nuclear matrix in hormone receptor action was postulated many years ago but only recently have specific nuclear matrix proteins been characterised which directly bind to hormone receptors and modulate their activity [3,4].

We have recently shown that the nuclear matrix protein HET/SAF-B can bind the ER [5]. This was shown by *in vitro* (GST-pulldown) and *in vivo* (co-immunoprecipitation) association of ER with HET/SAF-B. HET/SAF-B binds the ER in both the DNA binding domain (DBD) and the hinge region, and the association of ER with HET/SAF-B occurs in the absence of ligand, but is increased by the anti-oestrogen tamoxifen. HET/SAF-B can enhance the anti-oestrogenic effect of tamoxifen, but when overexpressed at high levels can repress both oestrogen and tamoxifen agonist activity on the ER. These data implicate HET/SAF-B as a co-repressor for the ER and suggest that it may play a role in the anti-oestrogenic activity of tamoxifen.

The majority of identified corepressors bind to histone modifying enzymes, or display intrinsic histone deacetylase (HDAC) activities. To analyse whether the HET/SAF-B-mediated repressive effect is also associated with changes in histone acetylation, we examined the effect of trichostatin A (TSA), a specific inhibitor of HDAC on HET/SAF-B-mediated repression. As shown in Fig. 1, in the absence of TSA, the overexpression of increasing amounts of HET/SAF-B (100 and 500 ng) resulted in a decrease of ER activity.

In the presence of TSA, the repression by HET was partially or completely relieved. Thus, in the presence of TSA, ER is capable of activating transcription from an ERE-tk-construct even in the presence of increasing amounts of HET/SAF-B, indicating that HET/SAF-B partially lost its ability to repress ER-mediated transcription. These data suggest that HET/SAF-B-mediated repression requires histone deacetylase activity, presumably through the formation of a complex with HDAC, or HET/SAF-B itself having HDAC activity, and indicate that HET/SAF-B may act as a co-repressor for the ER in manner similar to that described for other co-repressors.

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