

I.4 Effects of Anti-oestrogens on Insulin-like Growth Factor (IGF-I) Physiology Systemically and in the Uterus

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Insulin-like growth factor-I (IGF-I) is a potent mitogen for normal and neoplastic breast epithelial cells. It has been shown that anti-oestrogens decrease IGF-I levels and gene expression, but it is not clear to what extent this contributes to their antineoplastic activity. In the uterus IGF-I is also a mitogen and has been shown to be an important mediator of the uterotrophic effect of oestrogens. The effect of 'anti-oestrogens' on the expression of IGF-I in the uterus is closely related to their uterotrophic action. For example, tamoxifen induces uterine hypertrophy and upregulates uterine IGF-I expression, while ICI 182780 causes uterine involution and is associated with suppression of uterine IGF-I expression. In studies of novel oestrogen receptor ligands, it will be of interest to determine their effect on IGF-I expression both systemically and in the uterus.

IN 1990, WE published the first randomised, blinded study that demonstrated that anti-oestrogens reduce circulating levels of insulin-like growth factor-I (IGF-I), a potent mitogen for both normal and neoplastic breast epithelial cells [1]. The degree of suppression of IGF-I associated with tamoxifen use was modest (approximately 30%) but was statistically significant and reproducible in many subsequent studies for example, [2].

We subsequently showed that tamoxifen has inhibitory effects *in vitro* [3] and *in vivo* [4] on growth hormone (GH) secretion, which likely accounts for at least a portion of the suppression of IGF-I levels. However, we also showed [5] that even in hypophysectomised animals with GH levels maintained constant by recombinant GH administration, tamoxifen suppressed IGF-I levels, suggesting a separate,

pituitary-independent mechanism for suppression of IGF-I gene expression.

Interestingly, tamoxifen was seen to suppress IGF-I gene expression in several target organs for breast cancer metastasis [5], a result which may be relevant to the activity of the compound in adjuvant treatment of breast cancer, as such an action would be expected to make the organ a less fertile 'soil' for metastasis to progress. The co-administration of a somatostatin analogue such as octreotide with tamoxifen has been shown experimentally to enhance both the antineoplastic activity [6] and the IGF-I suppressive actions [7] of tamoxifen and this contributes to the rationale for major adjuvant clinical trials (NCIC MA14 and NSABP B29) that are comparing tamoxifen to the combination of tamoxifen and octreotide in adjuvant breast cancer treatment. Apart from its

suppressive effects on IGF-I gene expression and serum levels, tamoxifen also has other properties which would be expected to reduce the proliferative and anti-apoptotic actions of IGF-I on breast cancer cells. These include down-regulation of IGF-I receptors on tumour cells [8] and up-regulation of secretion of inhibitory IGF binding proteins [9, 10].

While in general tamoxifen acts to suppress IGF-I gene expression, in the uterus tamoxifen increases IGF-I gene expression, an action which correlates with the uterotrophic action of this compound [11]. In contrast, oestrogen receptor ligands that are 'complete blockers', such as ICI 182780, lead to uterine involution and to down-regulation of uterine IGF-I expression. Interestingly, the uterine expression of IGFBP3, an IGF binding protein that attenuates IGF action, is regulated in a reciprocal fashion: it is increased by ICI 182780 and decreased by tamoxifen [12]. Thus, it appears that oestrogen receptor ligands that cause uterine hypertrophy up-regulate expression of IGF-I and down-regulate expression of an inhibitor of IGF bioactivity, while those that cause uterine involution have the opposite effect. It will be of interest to determine the effect of other ER ligands, such as raloxofene, on IGF-I and IGFBP-3 expression in uterus, bone and mammary gland tissues.

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