(HRT). Through the preparation of sequential cryotone sections we are diagnostically grading the pathologies/histology present in a large number of biopsies, scoring for percentage tissue involvement and relating pathology with TGFβ status by histomorphometry using a range of TGFβ-specific antibodies and probes. In addition, we are using laser capture microdissection to determine the expression of TGFβI, II and III and their cognate receptors using RNA protection assays. Furthermore, we are exploring the TGFβ activation pathway and investigating the endometrial expression of M6P/IGF2r. We hypothesise that tamoxifen causes dysregulation of the TGFβ signalling pathway in preneoplastic and normal cells creating an environment which selects, preferentially, for cells with genetic alterations in the TGFβ signalling pathway, i.e. M6P/IGF2r, TGFβIIr. Cells with mutations in this pathway become non-responsive to normal cellular mito-inhibitory signals and develop into end stage neoplasms.

1. Carmichael PL, Ugwumadu AHN, Neven P, Hewer AJ, Poon GK, Phillips DH. Lack of genotoxicity of tamoxifen in human endometrium. *Cancer Res* 1996, **56**, 1475–1479.
2. Hemminki K, Ranjaniemi H, Lindahl B, Moberger B. Tamoxifen-induced DNA adducts in endometrial samples from breast cancer patients. *Cancer Res* 1996, **56**, 4374–4377.
3. De Souza A, Yamada T, Mills J, Jirtle R. Imprinted genes in liver carcinogenesis. *Faseb J* 1997, **11**, 60–67.
4. Butta A, MacLennan K, Flanders KC, *et al.* Induction of transforming growth factor β1 in human breast cancer *in vivo* following tamoxifen treatment. *Cancer Res* 1992, **52**, 4261–4264.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S11–S12, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00087-2

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

M. Pollak

Departments of Medicine and Oncology, McGill University, Montreal, Quebec, Canada

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.

1. Pollak M, Costantino J, Polychronakos C, *et al.* Effect of tamoxifen on serum insulin-like growth factor I levels in stage I breast cancer patients. *J Natl Cancer Inst* 1990, **82**, 1693–1697.
2. Friedl A, Jordan VC, Pollak M. Suppression of serum IGF-I levels in breast cancer patients during adjuvant tamoxifen therapy. *Eur J Cancer* 1993, **29A**, 1368–1372.
3. Malaab SA, Pollak M, Goodyer CG. Direct effects of tamoxifen on growth hormone secretion by pituitary cells *in vitro*. *Eur J Cancer* 1992, **28A**, 788–793.
4. Tannenbaum GS, Gurd W, Lapointe M, Pollak M. Tamoxifen attenuates pulsatile growth hormone secretion: mediation in part by somatostatin. *Endocrinol* 1992, **130**, 395–3401.
5. Huynh HT, Tetenes E, Wallace L, Pollak M. *In vivo* inhibition of insulin-like growth factor-I gene expression by tamoxifen. *Cancer Res* 1993, **53**, 1727–1730.
6. Weckbecker G, Tolcsvai L, Stolz B, Pollak M, Bruns C. Somatostatin analogue octreotide enhances the antineoplastic effects of tamoxifen and ovariectomy on 7,12-dimethylbenz(a)anthracene-induced rat mammary carcinomas. *Cancer Res* 1994, **54**, 6334–6337.
7. Huynh HT, Pollak M. Enhancement of tamoxifen-induced suppression of insulin-like growth factor I gene expression and serum level by a somatostatin analogue. *Biochem Biophys Res Comm* 1994, **203**, 253–259.
8. Huynh HT, Nickerson T, Pollak M, Yang XF. Regulation of insulin-like growth factor I receptor gene expression by the pure antiestrogen ICI 182, 780. *Clin Cancer Res* 1996, **2**, 2037–2042.
9. Huynh HT, Yang XF, Pollak M. Estradiol and antiestrogens regulate a growth inhibitory insulin-like growth factor binding protein 3 autocrine loop in human breast cancer cells. *J Biol Chem* 1996, **271**, 1016–1021.
10. Huynh HT, Yang XF, Pollak M. A role for insulin-like growth factor binding protein 5 in the antiproliferative action of the antiestrogen ICI 182780. *Cell Growth and Differ* 1996, 7, 1501–1506.
11. Huynh HT, Yang XF, Pollak M. IGF-1 gene expression in the uterus is stimulated by tamoxifen and inhibited by the pure antiestrogen ICI 182780. *Cancer Res* 1993, **53**, 5585–5588.
12. Huynh HT, Pollak M. Uterotrophic actions of estradiol and tamoxifen are associated with inhibition of uterine IGF binding protein 3 gene expression. *Cancer Res* 1994, **54**, 3115–3119.

Acknowledgement—Supported by the National Cancer Institute of Canada.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S12–S13, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00088-4

I.5 Does the Human Uterus Agree with Existing Models? Experiences with Insulin-like Growth Factor (IGF)

E. Tomás

Department of Obstetrics and Gynaecology, University of Oulu, Finland

The insulin-like growth factor (IGF) system is believed to be an important mediator of oestrogen action and may also be involved in mediating and modulating the actions of anti-oestrogens. In circulation, the majority of IGFs are bound to specific IGF binding proteins (IGFBP-1 to 6), which modulate the biological effects of IGFs. Low plasma IGF-I concentrations have been reported in breast cancer patients during tamoxifen treatment. IGFs are also believed to be involved in the regulation of oestrogen-induced cellular proliferation in the normal endometrium. © **1998 Elsevier Science Ltd. All rights reserved.**