Pergamon

0960-0760(94)E0001-2

J. Steroid Biochem. Molec. Biol. Vol. 48, No. 5/6, pp. 419–423, 1994

0960-0760/94 $26.00 + 0.00

General Review

Growth Factors and Steroid Hormone Action in Endometrial Cancer

Liam J. Murphy

Departments of Internal Medicine and Physiology, Faculty of Medicine, University of Manitoba, Winnipeg, Canada, R3E 0W3

There is compelling evidence that growth factors are involved in mediating estrogen action in target tissues. The role of growth factors in the development and progression of endometrial cancer is less clear. Steroid hormones can regulate the expression of the transforming growth factors and epidermal growth factor receptors in endometrial cancer cells in culture. It is also possible to demonstrate that these growth factors function in an autocrine fashion to regulate proliferation of endometrial cancer cells in culture. Constitutive expression or overexpression of such autocrine/paracrine factors and/or their receptors may be important in the growth progression of endometrial neoplasia. However, to date the evidence to support the hypothesis is limited.

J. Steroid Biochem. Molec. Biol., Vol. 48, No. 5/6, pp. 419–423, 1994

ESTROGENS AND ENDOMETRIAL CANCER

In the past few decades there has been a rapid increase in the incidence of cancer in steroid hormone dependent tissues such as the uterus, breast and prostate. These cancers now comprise approximately one third of all cancer death. Endometrial cancer has surpassed cancer of the cervix as the most common form of cancer of the female reproductive tract [1]. Unlike cancers in other hormone dependent tissues there is compelling evidence for a sequential progression of abnormal endometrial proliferative changes from adenomatous polyps to cystic hyperplasia, anaplasia, carcinoma-*in-situ* and invasive endometrial carcinoma [2]. Although the vast majority of patients with endometrial cancer have early stage disease and are cured by hysterectomy and/or local radiotherapy, approx. 10% of patients have advanced or recurrent disease and ultimately die of this disease [3].

Endometrial cancer represents one of the few cancers where there is a clear relationship between excessive hormone stimulation and malignant transformation. The evidence that prolonged unopposed estrogenic stimulation of the uterus, whether as a result of endogenous estrogen overproduction or exogenous estrogen given as hormone replacement therapy, is associated with increased risk of endometrial cancer is compelling [4]. Endometrial cancer is a disease which occurs predominantly in the postmenopausal age group with more than 75% of patients presenting after the age of 50 years [5]. In this age group, there is little ovarian production of progesterone and the effects of estrogen on the uterus are largely unopposed. In hormone replacement therapy of postmenopausal women, progestin treatment particularly when associated with menstruation is widely believed to have a protective effect in terms of risk of development of endometrial cancer. However, definitive proof of this has yet to be reported.

The molecular mechanisms whereby prolonged estrogenic stimulation of the endometrium can result in malignant transformation and the mechanisms underlying the apparent protective effect of progestin therapy remains unclear. A simplistic view would be that estrogen simply serves to expand the potential cells which would be susceptible to other oncogenic events. The pathogenesis of many cancers is thought to involve a multi-step process whereby oncogenic events accumulate and with clonal expansion, rapidly proliferating cell types predominate. If such a multi-step process is involved in malignant transformation of the endometrium then one could envisage a situation where cells which have undergone one or more oncogenic events would remain estrogen responsive and the population of these premalignant cells could be further expanded under continuing unopposed estrogenic

Received 30 Nov. 1993; accepted 28 Dec. 1993.

stimulation. Endometrial shedding associated with normal menstruation or progestin induced withdrawal bleeding would serve to remove many of these potentially malignant cells. Estrogen like other steroid hormones has dramatic effects on chromatin structure in responsive cells and it is possible that these changes in chromatin may enhance oncogenic events or affect mutation rates by exposing potential hot spots or genomic sequences where there is a high rate of mutation and/or recombination. As yet there is no convincing data that estrogen enhances mutation rate in uterine tissue.

PROGESTERONE AND ENDOMETRIAL CANCER

In the endometrium, progesterone antagonizes estrogen action by a variety of mechanisms. Progesterone downregulates estrogen receptor (ER) [6], enhances conversion of 17β-estradiol to the less active estrone by increasing 17β-hydroxysteroid dehydrogenase activity and to estrogen sulfates by increasing arylsulfotransferase activity [7, 8]. However, progesterone stimulates proliferation of endometrial stromal cells *in vitro* and *in vivo*. In the deep glands of the basal layer of the primate endometrium, the DNA labeling index in the epithelial cells increases following ovulation suggesting that the glandular cells in the basal layer may escape progesterone inhibition and/or that under appropriate circumstances progesterone may be able to stimulate proliferation of epithelial cells [9]. Furthermore, under certain conditions progestins can stimulate proliferation of human endometrial cancer cells [10, 11].

STEROID HORMONE ACTION IN THE NORMAL AND MALIGNANT ENDOMETRIUM

Steroid hormones interact with specific intracellular receptors which function as *trans*-acting factors and bind to specific DNA sequences in steroid hormone responsive genes. In the endometrium some of these hormone responsive genes encode oncogenes such as c-*fos*, c-*myc* and *jun* which are also important in transcription modulation [12–14]. In addition, steroid hormones either directly or indirectly activate expression of growth factors, their receptors, components of signal transduction pathways and proteolytic enzymes with modulate growth factors function [15]. Many of these growth factors also activate expression of some of the same early response genes such as c-*myc*, c-*fos* and *jun* protooncogenes which may be directly regulated by estrogen and may enhance or complement estrogen action in this way. For example, in estrogen responsive MCF-7 cells, it is possible to demonstrate synergism between insulin-like growth factor-I (IGF-I) and estradiol. van der Burg *et al.* [16] have shown that estradiol, in the absence of IGF-I or insulin which is able to act through the IGF-I receptor, is able to stimulate c-*fos* and c-*myc* expression but has no effect on c-*jun* expression and results in only a modest stimulation of DNA synthesis. In these cells, however, IGF-I alone stimulates both c-*jun* and c-*fos* expression and markedly enhances the mitogenic effect of estrogen. Thus, there is the potential for autocrine amplification of steroid hormone induced proliferation via activation of components common to the signal transduction pathways of both steroid hormones and peptide growth factors.

Steroid hormone enhancer sequences are usually located in the upstream flanking region of responsive genes. Estrogen-responsive elements (EREs) have been identified in a number of genes and a consensus nucleotide sequence $^{5'}$GGTCAnnnTGACC$^{3'}$ has been derived from comparison of the relatively small number of estrogen responsive genes so far examined. Even fewer progesterone responsive genes have been investigated and the current consensus sequence for progesterone response element demonstrates considerable overlap with response elements for other steroid hormone. Steroid hormone receptors can also interact synergistically with several other *trans*-acting factors including AP-1, CP1, Sp1, OTF, and NF1 [17–19]. Thus, indirect mechanisms may be involved in steroid hormone activation of expression of some genes which appear to be devoid of classical hormone response elements.

The interaction of steroid hormone receptors with other components of the transcription machinery may be important in modulating steroid hormone action and may be of clinical relevance in the treatment and progression of endometrial cancer. We have recently demonstrated that the action of medroxyprogesterone acetate, a potent progestin, in Ishikawa cells can be dramatically altered by modulating the AP-1 activity in the cell [11]. Under normal conditions these estrogen responsive cells are growth inhibited by this agent and medroxyprogesterone acetate decreases c-*jun* expression and endogenous AP-1 activity. However, when this decrease in c-*jun* expression is prevented by transfection with a c-*jun* expression construct the effects of medroxyprogesterone acetate are changed from growth inhibition to growth stimulation [11]. Thus, the emergence of progestin resistant endometrial cancer cells in patients treated with progestins, or initial failure to respond to progestins may not necessarily require the loss or absence of progesterone receptors. Implicit in the transformation of the growth-inhibiting effect of progestins to one of growth stimulation is an alteration in the balance of growth factors and inhibitors produced in response to this hormone.

Another mechanism which may be important in the synergistic interactions of steroid hormones and growth factors may involve cross-talk between receptors. Recently, Ignar-Trowbridge *et al.* [20] have demonstrated epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α) activation of a receptor gene containing a classical ERE. This activation was ER dependent and synergism between estrogen and these peptide growth factors was observed.

containing 5% fetal bovine serum both progestins and tamoxifen, which are growth inhibitory under these conditions, significantly reduced TGF-α expression in Ishikawa cells while they had no effect on TGF-α expression in HEC-50 cells [32, 34]. In Ishikawa cells, estradiol increased TGF-α expression and decreased EGF receptor concentration whereas tamoxifen and progestins enhanced EGF binding [32, 34]. These changes could result from direct effects on EGF receptor expression or from downregulation of the receptor as a result of enhanced TGF-α expression. Both TGF-α and EGF stimulate cellular proliferation. However, under certain circumstances both of these growth factors at high concentrations can inhibit growth in certain cell lines which overexpress the EGF receptor [36]. Thus, the efficacy of progestins in endometrial cancer may depend upon the actual level of expression of these growth factors and their receptors in particular cell populations present in the tumor.

TGF-β_1, the most ubiquitous TGF-β, is expressed in normal human endometrium and in endometrial cancer cells [24]. In the human endometrium TGF-β_1 is expressed in both epithelial and stromal cells [24]. TGF-β_1 is usually inhibitory to normal cells while malignant transformation is often associated with a reduced sensitivity to the inhibitory effects of this agent. Resistance to the growth inhibitory effects of TGF-β_1 appears to increase with malignant progression and in a small number of cancer cell lines, TGF-β_1 actually stimulates cell proliferation. Estrogen responsive Ishikawa cells which are only moderately tumorigenic in nude mice are growth inhibited by TGF-β whereas the estrogen unresponsive HEC-50 cell line which is highly tumorigenic is growth stimulated by TGF-β [33]. In a more extensive study of eight endometrial cancer cell line reported by Boyd and Kaufman [37], TGF-β_1 was found to inhibit growth in five cell lines while it stimulated growth in three cell lines. Interestingly, the cell lines in which TGF-β_1 stimulated growth demonstrated the highest levels of TGF-β_1 mRNA. In HEC-50 endometrial cancer cells, antisense oligonucleotides which block expression of TGF-β_1 inhibit cell proliferation suggesting that TGF-β_1 functions as an autocrine growth factor in this cell line [33]. Although expression of TGF-β_1 in normal human endometrium appears to be similar in the follicular and the luteal phase of the menstrual cycle it is possible to demonstrate regulation by steroid hormones in a variety of cell lines including human endometrial adenocarcinoma cells [33, 35]. Estradiol reduced TGF-β_1 expression in Ishikawa cells but not in HEC-50 cells whereas progestins enhanced TGF-β_1 expression in both cell lines [33].

The IGFs are expressed in the normal endometrium. Expression of both IGF-I and -II is upregulated by estrogen in a variety of species [38]. Stromal rather than epithelial cells appear to be the site of synthesis of IGF-I in the endometrium. Although endometrial cancer cells express IGF-I receptors and respond to IGF-I, the majority of endometrial cancer cells do not express IGF-I or -II. Endometrial cancer cells do express a variety of IGF binding proteins which probably function to modulate IGF action. Expression and regulation of the IGF binding proteins in the various endometrial cancer cells which we have tested is quite variable with different cell lines showing both differential expression and regulation [39]. Expression of a number of other growth factors, including platelet derived growth factor, fibroblast growth factors and heparin binding epidermal growth factor has been demonstrated in the normal endometrium but the role of these growth factors in endometrial cancer has yet to be examined.

CONCLUSIONS AND FUTURE DIRECTIONS

There is compelling evidence to implicate growth factors in steroid hormone action in normal uterine tissue. Their role in the regulation of proliferation of endometrial cancer cells is less clear. However, steroid hormones can regulate the expression of growth factors and their receptors in endometrial cancer cells in culture and in some circumstances it is possible to demonstrate autocrine regulation of proliferation. Constitutive expression or overexpression of such autocrine/paracrine factors and/or their receptors may be important in the growth progression of endometrial neoplasia. Constitutive expression or altered activity of transcription factors normally regulated by steroid hormones may lead to altered steroid hormone responsiveness and deregulated growth. These mechanisms may be important in the failure of some endometrial cancers to respond to progestin therapy. The exciting challenge for the future is the unravelling of the molecular mechanisms mediating the interactions between growth factors and steroid hormone action in endometrial cancer. Such knowledge is important for the development of new treatment strategies for endometrial cancer.

REFERENCES

1. Creasman W. T. and Eddy G. L.: Recent advances in endometrial cancer. *Seminars Surg. Oncol.* **6** (1990) 339–342.
2. Hertig A. T. and Sommers S. C.: Genesis of endometrial carcinoma-I. Study of prior biopsies. *Cancer* **2** (1949) 946–956.
3. Moore T. D., Phillips P. H., Nerenstone S. R. and Cheson B. D.: Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. *J. Clin. Oncol.* **9** (1991) 1071–1088.
4. Fu Y. S., Gambone J. C. and Berek J. S.: Pathophysiology and management of endometrial hyperplasia and carcinoma. *West. J. Med.* **153** (1990) 50–61.
5. Barber H. R. K.: Uterine cancer (prevention). *Cancer* **47** (1981) 1126–1132.
6. Tseng L. and Gurpide E.: Effects of progestins on estradiol receptor levels in human endometrium. *J. Clin. Endocr. Metab.* **41** (1975) 402–404.
7. Tseng L. and Gurpide E.: Induction of human endometrial estradiol dehydrogenase by progestins. *Endocrinology* **97** (1975) 825–833.
8. Tseng L. and Lui H. C.: Stimulation of arylsulfotransferase activity by progestins in human endometrium in vitro. *J. Clin. Endocr. Metab.* **53** (1981) 418–421.
9. Padykula H. A.: Regeneration in the primate uterus: the role of stem cells. *Ann. N.Y. Acad. Sci.* **622** (1991) 47–56.

HORMONE RECEPTOR STATUS IN ENDOMETRIAL CANCER

Assessment of estrogen and progesterone receptor status has become a widespread practice in predicting prognosis in breast cancer, however, assessment of receptor status in endometrial cancer has still not been widely accepted. Approximately two thirds of endometrial cancers are ER positive as determined by classical ligand binding assays [21]. The well and moderately differentiated tumors are more likely to be ER positive than the poorly differentiated tumors and are likely to have a better long term prognosis [22]. Progesterone receptor status is a good predictor of clinical responses to progestin therapy and ER and progesterone receptor status together appears to be as good as, or superior to, histological grade in predicting long term prognosis [21]. Receptors for a variety of other hormones and growth factors have also been demonstrated in normal and malignant endometrium. However, with the exception of EGF receptors' there is as yet little data addressing the clinical significance of these receptors in endometrial cancer.

GROWTH FACTORS AND ENDOMETRIAL CANCER

The major role of estrogen as a promoter of endometrial cancer is likely to be related to its role in stimulating cellular proliferation whereas the apparent protective effect of progestins may be related to the antiproliferative effects of these agents. A variety of growth factors have been found to be expressed in normal endometrial tissue. In many cases, steroid hormones influence the expression of these growth factors and some evidence indicates that a number of these growth factors, most notably EGF and IGF-I, are involved in the estrogen induced proliferative response. As in the case of breast cancer, it has been suggested that autocrine expression of growth factors, their receptors and mediators may be important in the pathogenesis and progression of endometrial cancer. Overexpression of components of autocrine or paracrine growth factor loops would allow for the clonal expansion of cells which could eventually become steroid hormone unresponsive and less dependent on the stromal–epithelial cell interactions which have been shown to be important in the maintenance of the steroid hormone dependent phenotype [23]. As discussed above, the poorly differentiated endometrial cancers are more likely to be steroid hormone receptor negative and unresponsive to progestin therapy. A critical question is whether these less well differentiated tumors express higher levels of growth factors than their more differentiated counterparts. Furthermore, endometrial cancer cell lines which are estrogen independent should express more growth factor or respond differently to these growth factors than estrogen responsive endometrial cell lines. Unfortunately, unlike breast cancer there are only a limited number of established human endometrial cancer cell lines which have been characterized in detail and few of these cell lines are estrogen responsive. Much of the data so far reported in the literature is conflicting.

Both EGF and TGF-α are expressed in normal endometrium and endometrial cancers [24]. EGF and EGF receptors were detectable in approximately half of the endometrial biopsies whereas TGF-α was detectable in the majority of endometrial cancer biopsies [25]. A recent immunohistochemical study suggests that in human endometrium EGF is predominantly localized to the stromal cells and that the intensity of staining increases after ovulation suggesting that progesterone rather than estrogen may have a role in regulating expression of EGF in human endometrium [26]. These data contrast with data from the rodent where EGF is predominantly localized to luminal and glandular epithelium and is up-regulated by estradiol [27]. EGF receptor expression in endometrial cancer as determined by ligand binding and immunohistochemical techniques appears to be less than in normal endometrium and EGF receptor abundance in endometrial cancer does not correlate with histological grade, myometrial invasion or the presence of extrauterine metastases [28–30]. In contrast, TGF-α, a ligand for the EGF receptor is more highly expressed in endometrial cancer biopsy samples where there is myometrial invasion [25]. Thus, it is possible that the apparent inverse correlation between histological grade and EGF receptor concentration may be due to receptor occupancy and/or downregulation by TGF-α or some other ligand. Alternatively the lower concentration of EGF receptors in the less differentiated tumors may reflect a lower fraction of stromal cells.

In the endometrial cancer cell lines which we have examined there are very low levels of expression of EGF, not easily detectable by Northern blotting. In contrast, TGF-α mRNA is moderately abundant in most of the cell lines [31]. TGF-α mRNA abundance is approx. 2-fold higher in the less tumorigenic, estrogen responsive Ishikawa cells compared to highly tumorigenic, estrogen unresponsive HEC-50 cells [32]. Furthermore, the growth promoting activity of TGF-α was more marked in Ishikawa cells than in HEC-50 cells. Antiserum to the EGF receptor is able to block proliferation in Ishikawa cells but not in HEC-50 cells [33]. These data suggest that an autocrine loop involving TGF-α or some other EGF receptor ligand is likely to be important in Ishikawa cell but not in HEC-50 cell proliferation. HEC-1A endometrial cancer cells which are highly tumorigenic in nude mice in the absence of estrogen supplementation, express TGF-α at higher levels than Ishikawa cells [34]. Thus, there is no clear cut relationship between TGF-α expression and tumorigenicity or estrogen responsiveness.

The effects of a variety of steroid hormones on TGF-α expression in Ishikawa and HEC-50 cells has been reported [32, 34]. In full growth medium

10. Holinka C. F. and Gurpide E.: Growth promoting effect of progesterone in a human endometrial cancer cell line. *J. Steroid Biochem. Molec. Biol.* **43** (1993) 635–640.
11. Alkahalaf M., Murphy L. J. and Murphy L. C.: Enhanced c-jun activity alters progestin responsiveness in ishikawa human endometrial carcinoma cells. *Molec. Endocr.* **7** (1993) 1634–1641.
12. Murphy L. J., Murphy L. C. and Friesen H. G.: Estrogen induction of N-myc and c-myc proto-oncogene expression in the rat uterus. *Endocrinology* **120** (1986) 1806–1812.
13. Weisz A. and Bresciani F.: Estrogen induces expression of c-fos and c-myc protooncogenes in rat uterus. *Molec. Endocr.* **2** (1988) 816–824.
14. Chiappetta C., Kirkland J. L., Loose-Mitchell D. S., Murthy L. and Stancel G. M.: Estrogen regulates expression of the jun family of proto-oncogenes in the uterus. *J. Steroid Biochem. Molec. Biol.* **41** (1992) 113–123.
15. Brigstock D. R.: Growth factors in the uterus: steroidal regulation and biological responses. *Bailliere's Clin. Endocr. Metab.* **5** (1991) 791–808.
16. van der Burg B., van Selm-Miltenburg A., deLaat S. and van Zoelen E. J.: Direct effects of estrogen on c-fos and c-myc protooncogene expression and cellular proliferation in human breast cancer cells. *Molec. Cell. Endocr.* **64** (1989) 223–228.
17. Schule R., Muller M., Kaltschmidt C. and Renkawitz R.: Many transcription factors interact synergistically with steroid receptors. *Science* **242** (1988) 1418–1420.
18. Meyer M-E., Gronemeyer H., Turcotte B., Bocquel M. T., Tasset D. and Chambon P.: Steroid hormone receptors competes for factors that mediate their enhancer function. *Cell* **57** (1989) 433–442.
19. Kato S., Tora L., Yamauchi J., Masushige S. and Bellard M.: A far upstream response element of the ovalbumin gene contains several palindromic 5′-TGACC-3′ motifs acting synergistically. *Cell* **68** (1992) 731–742.
20. Ignar-Trowbridge D. M., Teng C. T., Ross K. A., Parker M. G., Korach K. S. and McLachlan J. A.: Peptide growth factor elicit estrogen receptor-dependent transcriptional activation of an estrogen-response element. *Molec. Endocr.* **7** (1993) 992–998.
21. Creasman W. T., Soper J. T., McCarty K. S. Jr, McCarty K. S. Sr, Hindshaw W. and Clarke-Pearson D. L.: Influence of cytoplasmic steroid receptor content on prognosis at early stage endometrial carcinomata. *Am. J. Obstet. Gynec.* **151** (1985) 922–932.
22. Geisinger K. R., Homesley H. D., Morgan T. M., Kute T. E. and Marshall R. B.: Endometrial adenocarcinoma: a multiparameter clincopathological analysis including the DNA profile and sex steroid hormone receptors. *Cancer* **58** (1986) 1518–1525.
23. Cooke P. S., Uchima F. D. A., Fujii D. K., Bern H. A. and Cunha G. R.: Restoration of normal morphology and estrogen responsiveness in cultured vaginal and uterine epithelia transplanted with stroma. *Proc. Natn. Acad. Sci. U.S.A.* **83** (1986) 2109–2114.
24. Murphy L. J., Gong Y., Murphy L. C. and Bhavnani B.: Growth factors in normal and malignant uterine tissue. *Ann. N.Y. Acad. Sci.* **622** (1991) 383–391.
25. Leake R., Carr L. and Rinaldi F.: Autocrine and paracrine effects in the endometrium. *Ann. N.Y. Acad. Sci.* **622** (1991) 145–148.
26. Reynolds R. K., Talavera F., Roberts J. A., Hopkins M. P. and Menon K. M. J.: Regulation of epidermal growth factor and insulin-like growth factor I receptors by estradiol and progesterone in normal and neoplastic endometrial cell cultures. *Gynec. Oncol.* **38** (1990) 396–406.
27. DiAugustine R. P., Petrusz P., Bell G. I., Brown C. F., Korach K. S., McLachlan J. A. and Tebg C. T.: Influence of estrogens on mouse uterine epidermal growth factor precursor protein and messenger ribonucleic acid. *Endocrinology* **122** (1988) 2355–2363.
28. Berchuck A., Soisson A. P., Olt G. T., Soper J. T., Clarke-Pearson D. L., Bast R. C. and McCarty K. S.: Epidermal growth factor receptor expression in normal and malignant endometrium. *Am. J. Obstet. Gynec.* **161** (1989) 1247–1252.
29. Reynolds R. K., Talavera F., Roberts J. A., Hopkins M. P. and Menon K. M. J.: Characterization of epidermal growth factor receptor in normal and neoplastic human endometrium. *Cancer* **66** (1990) 1967–1974.
30. Bigsby R. M., Li A. X., Bomalaski J., Stehman F. B., Look K. Y. and Sutton G. P.: Immunohistochemical study of HER-2/neu, epidermal growth factor and steroid receptor expression in normal and malignant endometrium. *Obstet. Gynec.* **79** (1992) 95–100.
31. Anzai Y., Gong Y., Holinka C. F., Murphy L. J., Murphy L. C., Kuramoto H. and Gurpide E.: Effects of transforming growth factors and regulation of their mRNA levels in two human adenocarcinoma cell lines. *J. Steroid Biochem. Molec. Biol.* **42** (1992) 449–455.
32. Gong Y., Ballejo G., Murphy L. C. and Murphy L. J.: Differential effects of estrogen and antiestrogen on transforming growth factor gene expression in endometrial adenocarcinoma cells. *Cancer Res.* **52** (1992) 1704–1709.
33. Murphy L. J., Gong Y. and Murphy L. C.: Regulation of transforming growth factor gene expression growth factor gene expression in human endometrial adenocarcinoma cells. *J. Steroid Biochem. Molec. Biol.* **41** (1992) 309–314.
34. Gong Y., Murphy L. C. and Murphy L. J.: Hormonal regulation of proliferation and transforming growth factors gene expression in human endometrial adenocarcinoma xenograft. *J. Steroid Biochem. Molec. Biol.* **50** (1994) In press.
35. Gong Y., Anzai Y., Murphy L. C., Ballejo G., Holinka C. F., Gurpide E. and Murphy L. J.: Transforming growth factor gene expression in human endometrial adenocarcinoma cells: Regulation by progestins. *Cancer Res.* **51** (1991) 5476–5481.
36. Stoscheck C. M. and King L. E.: Role of epidermal growth factor in carcinogenesis. *Cancer Res.* **45** (1986) 1030–1037.
37. Boyd J. A. and Kaufman D. G.: Expression of transforming growth factor β_1 by human endometrial carcinoma cell lines: Inverse correlation with effects of growth rate and morphology. *Cancer Res.* **50** (1990) 3394–3399.
38. Murphy L. J. and Ghahary A.: Uterine insulin-like growth factor-I: Regulation of expression and its role in estrogen-induced uterine proliferation. *Endocrine Rev.* **11** (1990) 443–453.
39. Gong Y., Ballejo G., Alkhalaf B., Molnar P., Murphy L. C. and Murphy L. J.: Phorbol esters differentially regulate expression of insulin-like growth factor binding proteins in human endometrial carcinoma cells. *Endocrinology* **131** (1992) 2747–2754.