During the luteal phase, the endometrium continues to increase in thickness. The ER continues to be demonstrable, even when the pending influence of progesterone causes retronuclear brightness in endometrial glands. In the following days the increase of progesterone results in the steady decline of the ER expression. Starting at day 21, the oestrogen receptor can no longer be demonstrated.

Glandular epithelium is effected by these changes more distinctly than stroma. Nevertheless, stroma stains less strongly than the epithelia. The above changes predominantly take place in the functional endometrium. The basal zone, as well as the epithelial surface, undergo little histological change.

3. Postmenopause

The postmenopausal endometrium is characterised by atrophy. The scarce glands are either receptor-negative or display only isolated oestrogen receptor-positive cells. The same applies to the stroma.

Under the influence of oestrogen, during the climacteric either as a result of follicle persistence or exogenous hormone application, a renewed proliferation occurs up to the point of glandular-cystic hyperplasia. Glands and stroma again become ER-positive. Only the pressure-atrophic epithelia of cystically altered glands do not react.

The glandular epithelium in adenomatous hyperplasias, originating under the influence of oestrogen, also displays a high concentration of ERs. Yet, this only applies to grade 1 and grade 2 adenomatous hyperplasias.

Hyperplasias with nuclear irregularities (grade 3) do not display ERs. Evidently the cell's endeavours towards autonomy are so strong in these cases, that the receptor production becomes secondary.

Endometrial carcinoma shows different behavioural patterns depending on its genesis and histological grades (Fig. 1). Type I carcinomas, which originate in hyperplasia, generally show a receptor-rich behaviour. Type II carcinomas, which originate *de novo* and usually display a low histological grade, are receptor-poor.

4. Conclusion

The expression of oestrogen receptors in the endometrium is controlled by oestrogens and progesterones. This applies to both normal as well as pathological tissue. ER expression can completely disappear during the transition to a carcinoma. In invasive carcinoma, the ER concentration is dependent upon the histological grade.

References

1. King WJ, Greene GL. Monoclonal antibodies localize oestrogen in the nuclei of target cells. *Nature* 1984, **307**, 745–747.
2. Neis KJ, Ulrich-Winkelspecht K, Riehm S, Ulrich U. Rezeptor-expression des prä- und postmenopausalen endometriums. In Römer Th, Muek AO, eds. *Endometrium und Hormonsubstitution*. Stuttgart, Thieme Verlag, 1998, 13–18.
3. Zaino RJ, Clarke ECL, Mortel R, Satyaswaroop PG. Heterogenity of progesterone receptor distribution in human endometrial adenocarcinoma. *Cancer Res* 1988, **48**, 1889–1895.

The oestrogen receptor (ER) in vulva, vagina and ovary

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Abstract

The oestrogen receptor (ER) has been identified in normal and neoplastic epithelia of the vulva, vagina and ovary using biochemical, immunohistochemical (IHC) and molecular techniques. Its presence has not translated into effective antineoplastic therapy for malignancies arising from these sites.

Keywords: Oestrogen receptor; Immunohistochemistry; Vulva; Vagina; Ovary

1. Introduction

While oestrogen receptor (ER) has been identified in the epithelium of the vulva, vagina and ovary by biochemical, immunohistochemical (IHC) and molecular techniques, none of the epithelial malignancies arising from these sites are routinely hormonally sensitive [1–10]. This presentation will review the ER status of normal and neoplastic epithelial tissues derived from these sites.

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2. ER in vulvar tissue

Biochemical techniques have demonstrated ER in normal vulvar epithelium, the positivity rate ranging from 33–100% [1–4]. ER levels were 8–650 fmoles/mg cytosol protein (fmoles/mg cp) in one study and 7–10 fmoles/mg cp in another [2,3]. ER was identified in 4 of 6 dysplasias, 3 of 5 carcinoma *in situ* and 10 of 15 vulvar cancers [3]. Vulvar cancer ER content ranged from >5 to 1000 fmoles/mg cp in one study and 2–23 fmol/mg cp in another [2,3].

IHC demonstrated ER in 17 of 22 non-keratinising but in only 2 of 17 keratinising squamous epithelia [4]. No ER was identified by IHC in 9 dysplastic epithelia or in 18 squamous cell carcinomas [4].

3. ER in vaginal tissue

IHC demonstrated ER in the nuclei of basal and suprabasal differentiated epithelial cells of the normal vagina [5]. No significant difference was demonstrated in ER concentrations between the follicular and luteal phases or between regularly cycling and postmenopausal women [6]. All 12 vaginal samples from premenopausal and all four samples from postmenopausal women contained ERα-mRNA [7]. ERβ-mRNA was detectable in all 12 samples from premenopausal women. ERβ-mRNA was absent in all postmenopausal samples [7]. Minimal ER was present in one of seven vaginal carcinomas analysed biochemically [11].

4. ER in ovarian tissue

Biochemical studies have demonstrated ER in normal ovary and in ovarian malignancies [12]. Brandenberger and colleagues found equal amounts of ERα- and ERβ-mRNAs in normal ovaries in all age groups from 33–75 years [8]. ERα-mRNA levels in ovarian cancer were similar or slightly higher, but ERβ-mRNA levels were markedly decreased. Pujol and colleagues reported ERβ-mRNA was the predominant ER form in normal ovaries [9]. In ovarian cancers the ERα- to ERβ-mRNA ratio was markedly increased [9]. Lau and colleagues observed co-expression of ERα- and ERβ-mRNA in ovarian surface epithelial cells and disruption of ERα-mRNA expression but not ERβ-mRNA in most ovarian cancer cell lines [10].

No objective clinical responses to tamoxifen were reported in a series of women with advanced recurrent ovarian cancers [13]. Disease stabilisation was evident lasting 3–7 months [13]. No survival advantage was demonstrated in a prospective randomised trial of 100 women with previously untreated, advanced stage epithelial ovarian cancers randomised postoperatively to doxorubicin and cisplatin with or without tamoxifen [14]. The clinical significance of ER in ovarian cancer remains to be determined.

References

1. Forcucci-Zulli M, Gaglione R, Gentiloni N, Scambia G, De-Stafani L, Iacobelli S. Sex steroid receptors in normal and malignant human vulvar tissue. *Gynecol Obstet Invest* 1985, **19**, 103–106.
2. Omsjø IH, Wright PB, Bormer OP. Estrogen and progesterone receptors in normal and malignant vulvar tissue. *Gynecol Obstet Invest* 1984, **17**, 281–283.
3. Zippel HH, Sander W, Würz H. Steroidhormon-rezeptoren in normalen, dystrophischen, dysplastichen und karzinomatösen vulvagweben. *Geburtsh Frauenheilk* 1985, **45**, 220–225.
4. Mosley DS, Brito F, Bender HG. Immunohistochemical investigations of estrogen receptors in normal and neoplastic squamous epithelium of the vulva. *J Reprod Med* 1990, **35**, 1005–1007.
5. MacLean AB, Nica LA, Hodgins MB. Immunohistochemical localization of estrogen receptors in the vulva and vagina. *J Reprod Med* 1990, **35**, 1015–1016.
6. Perez-Lopez FR, Campo Lopez C, Alos L, Juste G, Ibanez F, Martinez-Hernandez H. Oestrogen and progesterone receptors in the human vagina during the menstrual cycle, pregnancy and postmenopause. *Maturitas* 1993, **16**, 139–144.
7. Chen GD, Oliver RH, Leung BS, Lin LY, Yeh J. Estrogen receptor alpha and beta expression in the vaginal walls and uterosacral ligaments of premenopausal and postmenopausal women. *Fertil Steril* 1998, **71**, 1099–1102.
8. Brandenberger AW, Tee MK, Jaffe RB. Estrogen receptor alpha (ER-α) and beta (ER-β) mRNAs in normal ovary, ovarian serous cystadenocarcinoma and ovarian cancer cell lines: down regulation of ER-β in neoplastic tissues. *J Clin Endocr Metab* 1998, **83**, 1025–1028.
9. Pujol P, Rey JM, Nirde P, *et al*. Differential expression of estrogen receptor-α and-β messenger RNA's as a potential marker of ovarian carcinogenesis. *Cancer Res* 1998, **58**, 5367–5373.
10. Lau KM, Mok SC, Ho SM. Expression of human estrogen receptor-α and -β, progesterone receptor and androgen receptor mRNA in normal and malignant ovarian epithelial cells. *Proc Natl Acad Sci* 1999, **96**, 5722–5727.
11. Ford LC, Berek JS, Lagasse LD, Hacker NF, Heins YL, DeLangers J. Estrogen and progesterone receptor sites in malignancies of the uterine cervix, vagina and vulva. *Gynecol Oncol* 1983, **15**, 27–31.
12. Schwartz PE, LiVolsi VA, Hildreth N, MacLusky N, Naftolin F, Eisenfeld AJ. Estrogen receptors in human ovarian epithelial carcinoma. *Obstet Gynecol* 1982, **59**, 229–238.
13. Schwartz PE, Keating D, MacLusky N, Naftolin F, Eisenfeld A. Tamoxifen therapy for advanced ovarian cancer. *Obstet Gynecol* 1982, **59**, 583–588.
14. Schwartz PE, Chambers JT, Kohorn EI, *et al*. Tamoxifen in combination chemotherapy with cytotoxic chemotherapy in advanced epithelial ovarian cancer: a prospective randomized trial. *Cancer* 1989, **63**, 1074–1078.