

The estrogen and progesterone receptors in endometrial carcinoma - an update

Abstract

Immunohistochemistry of estrogen (ER) and progesterone (PR) receptors in breast cancer is an established method of predicting responsiveness to hormonal treatment and calculating the prognosis and disease free survival rates. However the utility of immunohistochemistry of ER and PR in endometrial cancer (EC), another hormone dependent neoplasia has not yet been well defined and is not a routine in treatment algorithms. Their changing levels in various stages of menstrual cycle and action by alteration of genes regulating endometrial cell cycle have been extensively studied. This knowledge is gradually being integrated in selection of management protocols in terms of initial risk stratification and selection of hormonal and or cytotoxic agents as primary treatment modality or as adjuvants following surgery. This review looks into the molecular basis of ER and PR receptor alterations in EC together with its clinical implications.

Keywords: estrogen receptors, progesterone receptors, isoforms, endometrial carcinoma, progesterone

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Abbreviations: ER, estrogen receptor; PR, progesterone receptor; EC, endometrial carcinoma

Introduction

In the developed countries (eg United States) endometrial cancer (EC) is the most common gynaecologic malignancy, the fourth leading type of cancer overall and the eighth leading cause of death due to cancer. About 2% to 3% of women develop EC during their lifetime.¹ With an increase in the incidence of this malignancy over the years our understanding of its pathophysiology is evolving. The association of a prolonged exposure to endogenous or exogenous estrogen unopposed by progesterone.²⁻⁴ due to various risk factors is the underlying endocrinopathy in cancer development of type 1 ECs. This interplay of estrogen and progesterone through their receptors (ER or PR) in the progression of the disease from endometrial proliferation to hyperplasia and malignancy like in breast cancer has evoked extensive studies exploring ER and PR receptors in carcinogenesis, disease prognosis as well as prediction of responsiveness to hormonal therapy of EC. But immunohistochemistry of ER and PR in EC management algorithms are not in practise. This mini review endeavours to analyse the present concept of ER and PR and their isoforms in carcinogenesis of endometrium and attempts to extrapolate this concept in management of this malignancy.

Discussion

To understand the role of estrogen and progesterone in endometrial carcinoma we have to have a basic understanding of the receptors (ER and PR) through which they exert their actions and their physiological alterations in the different phases of menstrual cycle.

ER and PR receptors and their functions

ER and PR belong to the nuclear receptor superfamily. They are ligand-dependent transcriptional factors, which can bind to different

DNA sites to initiate the expression of specific genes. ER exists in 2 main isoforms, ER- α and ER- β . They have a distinct pattern of expression in the tissues,⁵ which varies during cellular proliferation and differentiation.⁶ ER- α binds to estrogens with high affinity and low capacity. It is predominantly present in the endometrium and is required for the basic development of estrogen sensitive tissues. ER- β binds to estrogens with low affinity and high capacity and inhibits transcription. It is required for organization and adhesion of epithelial cells and hence for differentiated tissue morphology and its functional maturation.^{7,8}

Progesterone receptor (PR) also has 2 isoforms PR-A and PR-B which are basically two functionally distinct transcription factors. That PR-A modulates the anti-proliferative effects of progesterone in uterus i.e. estrogen antagonistic action and PR-B in absence of PR-A induces cell growth i.e. estrogen agonist.⁹

It is well documented in the literature that the transcription of PR gene is induced by estrogen and inhibited by progesterone in the majority of estrogen responsive cells, so the expression of ER and PR is considered to be coordinated.¹⁰⁻¹²

ER and PR in cyclic endometrium

In a normal menstrual cycle estrogens induce proliferation of the epithelial and stromal elements of the endometrium during the preovulatory proliferative phase and postovulation. Progesterone is involved in glandular differentiation and glycogenesis as well as stromal proliferation and the development of predecidual cells. Thus, ER increases in the endometrial epithelium and stroma during the follicular phase and decreases after ovulation to reach a low level in the late luteal phase.

Both PR-A and PR-B also increase during the follicular phase probably under the influence of estrogen and decreases in the epithelium in the luteal phase, but it stays at a higher level in the stroma (predominant isoform-PR-A) until menstruation.¹³⁻¹⁵

ER and PR in endometrial carcinoma

Since EC is sex steroid hormone dependant, the presence of steroid receptors ER- α , PR-A and PR-B has been quantitatively associated with histologic differentiation,^{16,17} response to therapy,¹⁸ and metastatic potential.¹⁹ It has been shown that a loss of sex steroid receptors is an early event in endometrial carcinogenesis, and endometrial carcinoma generally has a lower level of steroid receptors than does normal endometrium or endometrial hyperplasia.²⁰ ER- α expression is decreased in EC.^{21,22} in both glands and stroma in relation to non-malignant tissue and is further decreased as EC grading is advanced.²⁰⁻²⁴ The expression of ER- α is lower in the stroma than in the glands of EC, indicating that stroma cells are significantly more affected than the epithelial cells. PR expression of either one or both of the two PR isoforms PR-A or PR-B is also reduced or absent in EC.^{21,25} PR-A shows the exact same pattern of expression as ER- α in the gland and stroma cells, as well as in the different portions of EC specimens.

PR-A may be associated with a cell and promoter specific repression of PR-B.²⁶ and imbalance in PR-A to PR-B ratio is frequently associated with carcinogenesis.²⁷ The relative over-expression of PR-B, which is referred to as an endometrial estrogen agonist,²⁸ without transcriptional repression by PR-A, may be related to the metastatic potential and partially cause deviation from sex steroidal dependency in endometrial cancers.¹⁹ The ratio of PR-A to PR-B, if <1, has a shorter disease-free survival and a shorter overall survival.²⁹ Whether the ratio of PR-A and PR-B could be used as a prognostic tool to determine progesterone responsiveness is unknown. There are conflicting evidences regarding the PR status in EC. Evidence shows that PR-B is predominant in advanced EC,³⁰ or there is loss of both isoforms in advanced EC.²⁵ Few researchers indicate that only PR-A is expressed in poorly differentiated EC cells.³¹

ER and PR status relationship with disease progression and prognosis

Molecular tumor classification, which includes PR and ER expression, is an integral part of the EC characteristics. Five-year survival rate (stage I) and median survival time (stages II-IV, recurrences) for patients with ER+/PR+ and ER-/PR+ EC i.e. PR+ were reported to be significantly better than for ER-/PR- and ER+/PR- i.e. PR- patients. Thus, ER has no significant prognostic relevance.³² The reduced expression of ER- α and PR-A in the tumor cells, particularly the significantly reduced expression in the stroma cells, may indicate an invasive characteristic of the tumor.³³ Loss of hormone receptors in preoperative EC biopsies independently predicts lymph node metastasis.³⁴ A double negative ER/PR significantly adds predictive and prognostic information for patients otherwise categorised as the lowest risk group; with endometroid grade 1 or 2 tumours subjected to lymphadenectomy, and also for patients without lymph node sampling, thus providing important information when addressing need for adjuvant therapy.³⁴

Tumor progesterone receptor status has significant correlation between PR-positive tumors and grade, surgical stage, histology, adnexal spread, disease free survival and recurrence.³⁴⁻³⁶ No such association has been found between ER status and stage, grade, histology and myometrial invasion.³⁵

Losses of steroid receptors cause deregulation of signalling pathways thereby causing tumorigenesis. ER receptor loss includes PTEN inactivation,³⁷ de novo methylation of ER- α gene and aberrant methylation of CpG islands.^{38,39} These epigenetic alterations occur in a wide variety of tumors, including EC.³⁹⁻⁴¹

There is a correlation between decreased PR expression in EC tumors and the expression of E-cadherin and myometrial invasion.^{42,43} The state of PR-B dominance, like in the cell line HEC-1A, is less invasive than cell lines with predominantly PR-A expression.⁴⁴

Thus, PR/ER immunohistochemistry appears to be a reliable means for predicting survival in endometrioid adenocarcinoma of the endometrium, independent of other clinicopathological parameters.⁴⁵

Hormonal therapy in endometrial cancer

Essentially the treatment of EC is hysterectomy with lymph node sampling. Logically, ER or PR positive tumors should be amenable to hormonal therapy. Hence primary medical therapy with hormones has been tried in Stage IA endometrioid carcinoma.^{35,46-49} and also in recurrent disease.

Progestins, which are considered to be estrogen antagonists have been tried as first line treatment in early disease with a 50 to 70% overall response rate.⁵⁰ There is a need for close follow-up upto 6months even in the responders because of the substantial rate of recurrence because of persistence of ongoing risk factors (obesity, anovulation) so eventually most women undergo total abdominal hysterectomy with bilateral oophorectomy.

However, experience with progestin therapy in recurrent disease is not very encouraging with only about 15-20% response rates.^{51,52} Other drugs that have been tried with varied results are Tamoxifen (response rate 10%),⁵³ Tamoxifen+progestin (response rate 33%),⁵⁴ SERMs (arzoxifene -not commercially available, response rates 25%-31%),⁵⁵ aromatase inhibitors (used in recurrent/ metastatic disease-letrozole, anastrozole-very poor response).⁵⁶

The clinical response to treatment with progesterone has been correlated with ER and PR status. Since ER induces PR receptors both positive ER and PR tumors responded well to hormonal therapy. However, certain PR-negative ECs also showed clinical response.^{35,52} Hence, immunohistochemistry for ER and PR in biopsy specimens remain imperfect predictors of hormonal response.

Behaviour and regulation of genes

In vitro studies using EC cell lines have provided insight into the effect of progesterone directly on cancer cell behaviour by the regulation of genes affecting the various phases of cell cycle, apoptosis, cell adhesion, differentiation, and inflammation.

Numerous genes have been implicated in the progestin-mediated responses observed in endometrial cancer cells eg cyclin D1, MMP-1, -2, -7 and -9, and Ets-1.⁵⁷ In EC cells, the liganded PR decreases the transcriptional activity of the activating protein-1 (AP-1) transcription factor family and c-Jun in particular. In addition, progesterone strongly inhibited total AP-1 as well as c-Jun recruitment to the cyclin D1 promoter, whereas it enhanced AP-1 occupancy on the p53 and p21 promoters, as shown by chromatin immunoprecipitation assays. This modulation of AP-1 activity in EC cells is a potential pathway of progesterone-induced growth inhibition in EC cells.⁵⁸

In addition progesterone upregulates COMT protein expression through PR-A which converts genotoxic catecholestrogens to anticarcinogenic methoxyestrogens (2-ME2) in the endometrium.⁵⁹

Thus, the mechanism by which PR activates or represses this gene involves transcription factors and coregulators that are numerous and gene specific. Research is still going on in this field. It is still an enigma how some PR negative tumors respond to progestin treatment.

Conclusion

The ER and PR receptors play a pivotal role in the pathogenesis and disease progression of endometrial carcinoma. However, their quantitative estimations in management of early stage disease or recurrent disease are not yet a routine protocol.

Pre-operative ER and PR immunohistochemistry in endometrial biopsy specimens may be able to predict probability of lymph node metastasis or even myo invasion and adnexal involvement and hence, aid in planning the extent of surgery and lymph node dissection. However, their role in predicting response to progestin therapy is not accurate, as some ER and PR-tumors may have good response to progestins.

Research is on in determining new markers whereby the biological nature of the EC can be predicted. This may open up newer avenues in management options especially in high grade lesions and ER/PR – tumors especially with the lesser cytotoxic hormonal agents.

Thus, female sex steroid receptors have been expected to serve as a new basis for categorization of patients with EC with reconstruction of treatment algorithms incorporating ER and PR immunohistochemistry as a routine.

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Conflicts of interest

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