Steroid Receptors in Normal Endometrium and in Endometrial Cancer

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Introduction

The endometrium, composed of endometrial glands and stroma with its subjacent myometrium, constitutes a dynamic functional unit. From monthly preparation in anticipation of implantation to pregnancy, sex steroid hormones, especially estrogen and progesterone, have an integral role in endometrial physiology. Endogenous estrogenic hormones include estrone (E1), estradiol (E2), and estriol (E3). E2 is the most potent estrogen in premenopausal women, ovaries being the main site of production. In postmenopausal state, E1 derived from adipocytic conversion of adrenal dehydroepiandrosterone predominates [1]. Hence, study of estrogen receptor (ER) and progesterone receptor (PR) is essential for appreciating their role in healthy endometrial biology and its carcinogenesis. Recent discovery of new ER types and PR isoforms is expected to add to our current understanding of their role in endometrial function and carcinoma.

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Role of Estrogen in Endometrial Carcinogenesis

Endometrial carcinoma is the most common malignancy of the female genital tract in developed countries [2]. Even in developing nations including India, its incidence is said to be increasing [3]. Traditional risk factors of endometrial carcinoma include those associated with chronic hyperestrogenic states, anovulation, and obesity. Early menarche, late menopause, nulliparity, and low parity prolong estrogen exposure duration [2, 4]. Chronic hyperestrogenism coupled with lack of progesterone as occurs in chronic anovulatory states like polycystic ovarian syndrome (PCOS) and estrogen-only hormone replacement therapy (without progestational agents, as was common earlier) also predisposes to endometrial carcinoma [5, 6]. In a longitudinal study of Swedish women, the odds ratio of developing endometrial cancer after 5 or more years of estradiol or conjugated estrogens was found to be 6.2 and 6.6, respectively, as against 1.6 of using estrogen-progestin combination [5]. Patients of PCOS are three times more likely to develop endometrial carcinoma compared with women without the condition [6]. Excess body weight (body mass index >25 kg/m^2) with or without association with PCOS too increases the relative risk of endometrial cancer by at least 1.6 times, primarily by increased adipocytic conversion of circulating androgens to estrogens [2–4, 7].

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Types of Sex Steroid Receptors

Nuclear Sex Steroid Receptors

The conventional ER and PR are members of nuclear receptor family, others being receptors for androgen, glucocorticoid, vitamin D, thyroxine, etc. [8, 9]. In general, the unbound receptor monomer resides in the cell cytoplasm; upon ligand binding, it dimerizes and translocates to the nucleus. The ligand-receptor dimer complex attaches to specific sequences of DNA (hormone response element), in association with transcriptional cofactors (activators or repressors) in the promoter region upstream of target genes. The eventual outcome is modulation of gene expression. The target genes of ER include proto-oncogenes like c-myc, n-myc, c-jun, etc. Most literature on ER expression in human tissues including the endometrium is on this type of ER [10–12]. In 1996, another ER type was isolated from rat prostatic epithelium [13]. It was found to be encoded by ESR2 gene on chromosome 14q23-24.1, unlike the earlier known receptor whose gene, ESR1, was known to be located on chromosome 6q25.1. The new ER was called ER beta (β), and the earlier known ER was redesignated as ER alpha (α). Not only is the systemic distribution of ERβ distinct from ERα, their cellular localization in a given tissue and biologic effects are also at variance from each other [14, 15]. Gene expression profiling studies following activation of ER have identified a vast number of target molecules like growth factors, cell adhesion molecules, and cell cycle regulators, some with differential results between ERα and ERβ [16, 17]. Both types of ER have several functional domains (named A to F). While their structural homology at the DNA binding site (C domain) is more than 90 %, they share only 55 % and 20 % of their structure at the ligand binding domain (E domain) and domains A and B, site for other protein interactions, respectively. Although both ER types bind to E2 and antiestrogens like tamoxifen with comparable affinity, they have differential role in endometrial function. The differences in their functional outcomes could be attributed to significant differences between their amino acid sequences at domains A, B, and F where protein-protein interactions take place, variable posttranslational modifications, and variable dimer formation (α-α, β-β homodimer or α-β heterodimer). The detailed downstream effects of ERβ are still undetermined [16, 17]. PR too occurs in two isoforms, PRA and PRB. Both isoforms are products of PR gene located on chromosome 11, unlike ER types which are products of different genes. They differ in their polypeptide length owing to differential promoter sites, PRB having a 165-amino acid longer domain A and being heavier by 30 kDa than PRA [18–20]. Both isoforms of PR are expressed in the human endometrium. While PRB isoform has stronger transcriptional activity than PRA, the latter exerts direct dominant negative effect on ER function [13, 14]. Most published work on PR is actually on PRA isoform as early antibodies did not recognize PRB.

Sex Steroid Receptors Outside the Nucleus

The concept of sex steroid receptors having exclusively nuclear transcriptional modulatory action, as mentioned above, has been challenged for long [21]. Experimental work has shown estrogen to be capable of mediating cellular responses like vasodilation and regulate blood pressure and insulin signaling in periods as short as few minutes. These rapid cellular events involve activation of intracellular kinases and second messengers like Ca+ [2] ions and cAMP within seconds or minutes of estrogen exposure [22]. Modulating gene transcription requires a minimum of few hours and effects may last for up to a few days. This implies nongenomic (pregenomic) estrogen action mechanisms. Moreover, these outcomes have been shown to be unaffected by transcriptional inhibitors. While the genomic mechanism of action of sex steroid receptors is most widely studied, nongenomic mechanisms are the current area of research.

At least two types of non-nuclear ER are known. A new type of ER has been localized to cytosolic fraction, in the endoplasmic reticulum and to some extent on the plasma membrane, in association with organelle membrane G protein.

It is said to be structurally different from the mERα and named as G protein-coupled ER (GPER) [23–25]. Nuclear ERα and GPER have differing binding affinities toward various estrogenic substances. Its affinity for estrogen is said to be ten times that of nuclear ER [26]. Its expression is regulated by progesterone. Among its major actions, GPER controls epidermal growth factor receptor activation and Ras protein phosphorylation [23–25]. By cell fractional techniques, classic ERα, similar to nuclear ERα, has been isolated from the cell membrane fraction as well. Subsequent to membrane receptor internalization, dimerization occurs akin to nuclear ERα. The mERα forms a complex with various cell signaling proteins leading to the formation of signalosome, leading to immediate cellular events independent of nuclear transcription. Further details of mERα are still unresolved [27]. Other recently discovered new types of membrane ER include ERα-36, a truncated form of ERα, and ER-X [28, 29]. Functional cross talk between GPER, nuclear ER, and mERs is expected although the details are not known yet [23].

Sex Steroid Receptor Expression in Healthy Endometrium

All sex steroid receptors show rhythmic changes in their expression status during a healthy menstrual cycle.

ERα

In the proliferative phase of the menstrual cycle, ERα is expressed on both endometrial glands and stroma of the stratum functionalis. The expression of ERα (as measured by staining intensity, percentage of cells, or a combinational score) is higher in glandular cells than stromal cells. ERα expression increases steadily reaching its peak in preovulatory period, wherein almost all endometrial cells show strong nuclear reactivity. This increase occurs in response to ovarian estrogen production. After ovulation, both glandular and stromal cells show downregulated ERα expression, but the fall is discordant. The decline in ERα expression is gradual in glandular cells, but rather abrupt in stromal cells. The declining trend continues unabated in the glandular compartment to negligible expression in the late secretory phase, which is even lower than the expression during menstruation. On the other hand, stromal cells after their nadir in the early secretory phase show a gradual increment in ERα expression in mid- to late secretory phase. Pre-decidualized stromal cells are known to express ERα in small amounts, albeit at lower levels than those during active bleeding [11, 12, 30–37].

ERα expression in the stratum basalis is as high as the stratum functionalis of the proliferative phase and remains unaltered throughout the menstrual cycle [11]. The sub-endometrial myometrium too expresses ERα; the expression and trends parallel those of the functional endometrium. The bulk of myometrium shows high ERα expression through all phases of the menstrual cycle, without any cyclic change [12]. Postmenopausal women with atrophic endometrium continue to express ERα, levels of which are comparable to those in the late proliferative phase of young women [11]. This implies that ERα expression in the endometrium and to some extent in the myometrium is constitutive; the decline as observed in postovulatory state is induced by rising levels of progesterone secreted by the corpus luteum. This simplistic view is however put to test by results of an interesting study on postmenopausal women on hormone replacement therapy [38]. The authors failed to find a decline in ERα expression in women with breakthrough bleeding. They suggested that the mechanisms underlying bleeding in these patients were different from the physiologic ones operative in the reproductive period.

ERβ

ERβ, the recently discovered another ER, has differential endometrial expression than ERα [14, 36, 37]. Its absolute quantity is also much lower than ERα. Its expression is more intense in the proliferative than secretory phase. However, its peak occurs in the peri-ovulatory period, i.e., days 14–15 lasting for a very short while. Thus, there is

a brief period just prior to the ovulation, when both endometrial glandular ERα and ERβ expressions are at their peak. Besides the minimal temporal lag between ERα and ERβ, spatial expression of ERβ also differs from ERα. While ERα glandular expression is independent of topology, ERβ shows gradual decrease in staining intensity from epithelial cells near the lumen to near total absence in deeper glands. The endometrial stromal cell ERβ expression peaks in the late secretory phase, between days 25 and 27 of the menstrual cycle. The increase is more prominent in stromal cells in perivascular location. Thus, in the late secretory phase, glandular cells of the stratum functionalis have hardly any expression of ERβ, while the expression in stromal cells is maximum. The variance between endometrial stromal ERα and ERβ expression especially in the secretory phase suggests ERβ as probably having a role antagonistic to ERα or modulating the expression of the latter. One significant observation is the presence of ERβ in endothelial cells of endometrial blood vessels, including spiral arterioles [36, 37]. The receptor has also been found in smooth muscle fibers of spiral arterioles. Experimental work on endometrial endothelial cells has confirmed the role of ERβ in vascular biology [39]. This observation has clinical relevance. It is possible that endometrial vascular ERβ expression underlies the beneficial effect of some estrogenic compounds in cases of abnormal uterine bleeding. ERβ is also expressed in the stratum basalis; its expression does not differ between pre- and postovulatory phases.

GPER

Being a relatively new receptor, literature of endometrial GPER expression is limited. A cyclic change in GPER mRNA expression has been reported by few authors [40, 41]. Maximum gene expression was detected in the proliferative phase with a decline in the secretory phase. This pattern is similar to that of ERα expression but different from ERβ. In the proliferative phase, the glandular cells have both apical and basal staining, which became limited to basal regions in the secretory phase. The stromal GPER expression was diffuse and did not differ significantly between the proliferative and secretory phase. The GPER receptor was not detected in blood vessels or myometrium [40].

PR and Its Isoforms

PR exists in two isoforms, PRA and PRB, which are products of the variable promoter region of the same gene. These isoforms differ in their structure, transcriptional efficiency, and potential for modulation of ER-mediated cellular events. Relative levels of both determine nature and magnitude of cellular response to progesterone [19, 20]. Earlier studies on endometrial PR expression used antibodies with higher affinity toward PRA isoform [11, 12, 35]. As a whole, PR levels continue to rise in endometrial glandular cells from day 1 of the menstrual cycle. The peak expression is reached in the early secretory phase, following which there is a sudden fall in the mid-secretory phase and negligible receptor amount in the premenstrual period. Both PRA and PRB isoforms are expressed simultaneously and in comparable amounts in the proliferative phase. By the mid-secretory phase, only PRB persists in the glandular cells [18, 42]. By confocal microscopy, the nuclear distribution of PR has been shown to change with progression of the menstrual cycle from even to focal, the change being related to rising progesterone levels [43]. In contrast to the dramatic fold changes in PR glandular expression, changes in stromal PR levels in the menstrual cycle are insignificant [11, 12, 35]. PRA is the predominant stromal receptor isoform [18, 42]. These observations suggest that there is biologic segregation of PRB and PRA functions in endometrial glands and stroma, respectively. PR expression is also documented in endothelial cells and vessel wall smooth muscle fibers [36, 44]. PR expression in the stratum basalis shows similar trends as the functional layer, albeit with smaller range of change. Atrophic endometrial PR expression is pronounced similar to ER expression [11, 12]. Presence of PR on endometrial stem cell has been confirmed by clonal culture techniques [45].

Other Steroid Receptors: Androgen Receptor (AR), Glucocorticoid Receptor (GR)

Endometrial expression of receptors for androgens and glucocorticoids has also been studied. The hormone interconversion, especially between estrogens and androgenic hormones, suggests a possible role of AR in the cyclic changes of healthy endometrium. Endometrial AR expression changes are cyclical, similar to ER [46–49]. In the proliferative phase of the menstrual cycle, AR is expressed predominantly in the stromal cells; epithelial receptor expression is minimal. This fact is corroborated by upregulation of stromal AR following exogenous estrogen exposure [50]. Androgens acting via AR have been shown to induce prolactin, a marker for endometrial differentiation [51]. The receptor levels decline with progression of the menstrual cycle; in the late secretory phase, the receptor is no longer detected in both cell types. Administration of antiprogestational drugs results in expression and enhancement of AR in endometrial glandular and stromal components, respectively [47]. Endometrial GR expression differs strikingly from other steroid receptors. It is completely absent from glandular epithelial cells. Stromal GR expression is strong throughout the menstrual cycle, with only slight decrease in the secretory phase. Endothelial cells too express GR [52]. Despite these results, the exact role of AR and GR remains incompletely understood in endometrial physiology.

Sex Steroid Receptors in Endometrial Carcinoma: Expression Status and Clinical Implications

Endometrial carcinogenesis is considered dualistic [53]. Type 1 carcinomas outnumber type 2. The former (endometrioid type) arise often in premenopausal, obese women with evidences of hyperestrogenism. These patients typically have preceding endometrial hyperplasia progressing to atypia. The tumors are likely to be low grade and low stage with preserved hormonal responsiveness. Type 2 carcinomas occur in postmenopausal ladies without hyperestrogenic association. The lesions are aggressive, have high-grade morphology, and present at advanced stage.

Receptor Levels in Type 1 and Type 2 Endometrial Carcinomas

Type 1 endometrial carcinomas due to their preceding estrogenic stimulatory conditions are significantly (and expectedly) more likely to express both ER and PR (average 70 %) than type 2 carcinomas (average 20 %) [54]. Carcangiu et al. too noted declining expression levels from endometrioid type to clear cell type through adenosquamous and serous type [55]. The expression of sex steroid receptors as detailed below refers to type 1 endometrial carcinomas, unless specified otherwise.

Receptor Levels in Type 1 Endometrial Carcinoma Compared to Healthy Endometrium

The expression of ER in endometrial glands shows progressive decrease from proliferative endometrium to invasive carcinoma; endometrial hyperplasia shows intermediate levels. While the declining trend is noted universally, only few authors have found the difference between groups to be significant [30, 31, 33]. Another observation is loss of ER staining with appearance of nuclear atypia in the setting of endometrial hyperplasia [31].

Similar to ER total, ERα shows decreasing expression trend from proliferative endometrium to hyperplasia without atypia, atypical hyperplasia, and invasive carcinoma. The reduction in ERα level in carcinoma compared to proliferative endometrium has been found to be consistently significant by several authors [34, 35]. Bircan et al. noted almost all cells (96 %) in proliferative endometrium to be positive for ERα; in endometrial carcinoma, only 31.6 % of cells expressed the protein [34]. However, intra-spectrum comparative studies between proliferative endometrium and hyperplasia without atypia, simple and complex hyperplasia

without atypia and atypical hyperplasia, and atypical hyperplasia and invasive carcinoma have shown variable results, few reporting significant differences and others showing a trend toward reduced protein levels with advancing lesion, but insufficient to achieve statistical significance [34, 56, 57]. It may hence be concluded that loss of ERα is associated with progressive malignant potential of the lesion. Grade II tumors have lower protein content compared to grade I cancers [35].

With increasing severity of lesions from proliferative endometrium to invasive carcinoma, there is significant loss of ERβ expression [35, 56, 57]. While most authors have recorded this trend across groups, Cai et al. demonstrated the reduction in ERβ content in atypical hyperplasia and carcinoma compared to adjacent uninvolved endometrial areas [56]. It is noteworthy that although both ERα and ERβ types are reduced in endometrial carcinoma compared to proliferative endometrium, the decline is more marked for ERα. This results in reversal of ERα/ERβ ratio from >1 in proliferative endometrium to <1 in endometrial carcinoma [35, 57, 58]. In fact, several authors have suggested that it is the reversal of ERα/ERβ ratio which determines the neoplastic progression rather than absolute values themselves. It should also be highlighted that ERβ-expressing tumors almost invariably express ERα, but the reverse is less likely to be true [59].

Total PR expression and its isoforms PRA and PRB expression, all are reduced in endometrial carcinomas compared to healthy endometrium [35, 60]. Arnett-Mansfield et al. demonstrated the difference between PRA and PRB between invasive carcinoma, normal endometrium, and areas of complex hyperplasia within same patient samples to be significant [60]. Mylonas et al. however did not find PR difference between healthy endometrium and endometrial carcinoma to be significant [35]. Unlike healthy endometrium, in which PRA and PRB isoforms are co-expressed and often co-localize within the same cell, endometrial carcinomas often express only one receptor isoform. The intranuclear pattern of reactivity too differs between healthy endometrium and endometrial carcinomas [43]. GPER is expressed in endometrial carcinoma but in reduced amounts compared to healthy endometrium; up to sixfold reduction has been described [61]. Up to 40 % of endometrial carcinomas express AR [49]. Staining is observed in malignant epithelial cells; this is unlike the healthy endometrium wherein glandular AR expression is minimal. The exact significance of this observation is not known, but is likely to be low as androgens do not play a central role in endometrial functioning.

Receptor Expression in Type 1 Endometrial Carcinoma: Correlation with Clinicopathological Factors

High/positive ER expression in invasive endometrial carcinoma correlates with the degree of tumor differentiation [54, 55, 62–64]. Carcangiu et al. demonstrated significant correlation between ER-positive status and low FIGO grade and low nuclear grade ($p<0.001$ and 0.0001, respectively) [55]. ER-positive tumors are more likely to be well differentiated than poorly differentiated. Conversely, poorly differentiated tumors are unlikely to express ER. Kounelis et al. found all endometrioid carcinomas to be ER (and PR) positive [54]. McCarty et al. found 85 % of well-differentiated tumors to be ER positive, while only 13 % of poorly differentiated tumors had detectable protein level [64].

ER expression in endometrial carcinoma also shows significant positive correlation with low tumor stage ($p \leq 0.026$–0.001) [54, 55, 62, 65, 66]. Chambers et al. found that early stage tumors were more likely to be ER positive. They pointed out that tumor grade was a co-variable in their study, the effect of which could not be excluded [62]. Deeply invasive cancers are less likely to be ER positive [65]. ER expression correlation with other evidences of tumors' aggressive nature has been variable. Geisinger et al. reported inverse correlation between ER positivity and lymphovascular invasion. More than 80 % of their tumors lacking lymphovascular invasion were ER expressing, while majority of tumors with such invasion were receptor negative [67]. However, Iwai et al. found no correlation between ER expression and lymph node metastases [68].

Expression of ERα and ERβ in endometrial carcinoma has been correlated with tumor grade and stage by various authors [34, 35, 56–59, 69, 70]. Jongen et al. found significant correlation between preserved ERα expression and early tumor stage ($p<0.02$) [70]. High-stage cancers have significantly lower ERα content than early stage tumors ($p<0.002$) [56]. Significant correlation between ERα expression and histologic grade too has been described in several publications. ERα-expressing tumors are significantly more likely to be of low grade [69, 70]. However, Bircan et al. did not find significant correlation between ERα expression status and any clinicopathological feature [34]. Mylonas said that loss of ERβ was associated with myometrial invasion; however, results of Jongen et al. did not find such correlation [35, 70]. Hu et al. too did not find any prognostic implication of either ERα or ERβ expression [57].

PR immunostaining like ER expression has been found to correlate significantly with well-differentiated tumor histology ($p=0.026$–0.003) [54, 62, 63, 66, 71]. With tumor dedifferentiation, there is loss of PR. Positive association between PR and early tumor stage is also widely reported [59, 65, 66]. Deeply invasive tumors (> half of the myometrium) are likely to have undetectable PR levels ($p=0.006$). However, Chambers et al. did not find correlation between PR status and disease stage to be significant [62]. PR negativity has been found to be significantly associated with lymphovascular invasion and lymph node metastases [55, 67, 68]. Upon multivariate analysis, Iwai et al. found negative PR to be a significant prognostic variable for lymph node metastases, independent of other clinicopathological parameters [68]. Most endometrial carcinomas express predominantly only one PR isoform; however, dual expression is described in low-grade tumors. With increasing tumor grade, there is loss of either isoform. Arnett-Mansfield et al. found no difference between PRA and PRB frequency within the carcinoma group (30 % versus 28 %) [60]. In vivo GPER expression in endometrial carcinoma has been studied only recently. GPER expression has been reported to occur more frequently in high-grade, aggressive histologic type, advanced-stage, and PR-negative endometrial cancers [72].

Receptor Expression in Type 1 Endometrial Carcinoma as a Prognostic Factor

Many authors have found significant correlation between ER expression and final patient outcome [62, 66, 73–76]. Pertschuk et al. concluded that their ER-negative endometrial carcinoma patients were almost four times more likely to die of the disease than those who expressed the receptor [74]. In several studies, ER-positive cases have had significantly longer disease-free survival than ER-negative patients [62, 73, 74, 76]. However, others found the difference between the groups to be insignificant [66, 77].

ER is considered to be a favorable feature by almost all researchers, although literature on its role as an independent prognostic factor in endometrial carcinoma is still not clear. Using multivariate and multi-regression analysis, many authors have suggested it to be so [73, 76]. However, others did not conclude the same [62, 66]. Tornos et al. compared ER and PR expression status between two sets of patients with stage I and grade I endometrial carcinoma – those who died within 4 years and those who survived beyond 10 years. ER expression did not differ significantly between groups [77]. Fanning et al. found tumor stage and grade but not ER expression as a predictor of recurrence in high-risk endometrial carcinoma [78]. Loss of ERα in endometrial carcinoma has been reported to be associated with poor survival [69]. Absence of ERα was found to be an independent factor associated with death due to disease (odds ratio = 7.28) by Jongen et al., but not by Shabani et al. [69, 70]. Loss of ERβ has not been found to have any effect on survival figures [69].

Positive PR status is also known to be a significant prognostic factor for disease-free survival (DFS) ($p=0.0025$–0.001) [66, 76, 77]. Its performance as a predictor of DFS ($p<0.001$) is independent of other clinicopathological factors and exceeds that of ER-positive status ($p<0.01$) [76]. Tornos et al. found the absence of PR to be one of the four statistically significant adverse prognostic factors in stage I grade I adenocarcinoma, others being myometrial invasion, vascular invasion, and high mitoses. Patients who died within 4 years

of diagnosis were significantly more likely to have absent PR than those who survived >10 years [77]. PR-positive status confers better chances of overall survival too. These patients live significantly longer than PR-negative patients [62, 67]. Positive PR status identifies advanced carcinoma patients for progestin therapy. Reported response rates in PR-positive cases (82–91 %) are significantly better than those of PR-negative patients (11 %) [79, 80]. Ehrlich et al. have reported 94 % of their nonresponders to be PR poor [71]. However, in high-risk endometrial carcinoma (those with high stage and poor differentiation), PR positivity may not protect against tumor recurrence [78]. PRA loss has been found to be an independent prognostic factor for disease relapse [70]. Although loss of both PRA and PRB has been associated with poor survival, loss of PRB isoform only achieved independent adverse prognostic factor status for cause-specific survival [70]. It has also been suggested that negative PRB immunostaining result may help in identifying potentially worse-outcome patients for more aggressive adjuvant therapy.

Significantly poor survival has been reported in GPER-expressing cancers by Smith et al. [72]. In endometrial cell lines with downregulated GPER levels, exposure to exogenous estrogen has been found to induce GPER expression [41, 81]. Significantly upon progesterone transfection of the same cell line, the increment failed to occur [41]. This may probably explain the mechanism of action of non-ovarian-origin circulating estrogens on endometrial cancers including ER-negative ones in postmenopausal women and beneficial effects of progestins in endometrial cancers. Skrzypczak et al. found G-1, a compound, to have significant downregulatory effect on GPER expression in endometrial cancer cell lines, implying a potential therapeutic target [61].

Conclusions

The dynamic interplay of sex steroid hormones is evident in healthy endometrial biology. The discovery of novel sex steroid receptor types including those at extranuclear sites has renewed interest in endometrial physiology and carcinogenesis. Recently described ERs include ERβ, G protein-coupled ER, and cell membrane ERα. PRB is a relatively recently discovered isoform of PR. ERβ differs from ERα in its cyclic variation during menstrual cycle, lower quantum of expression, topologic distribution, and downstream cellular events. GPER and mERα are implicated in mediating rapid effects of estrogen, which cannot be explained by the conventional roles of nuclear ER as a nuclear transcription factor.

Endometrial cancers express lower levels of sex steroid hormones than proliferative endometrium. The decline in ERβ exceeds ERα leading to reversal of ERα/ERβ ratio. All receptor expressions show positive association with early stage, low-histologic grade, type 1 cancers and better patient outcome in terms of disease-free survival, overall survival, and response to hormone therapy.

Key Points

1. Estrogen is implicated in both endometrial physiology and carcinogenesis.
2. ERβ is a novel nuclear receptor for estrogen. It differs from ERα (the classical ER) in its cyclic variation during menstrual cycle, lower quantum of expression, topologic distribution, and downstream cellular events. Unlike ERα, it is expressed in endothelial cells.
3. Both ERα and ERβ show their peak tissue expression in the late proliferative phase; in healthy endometrium, ERα/ERβ ratio remains >1 throughout the menstrual cycle.
4. Progestational agents induce secretory activity. Healthy endometrium co-expresses PRA and PRB, the two isoforms of progesterone receptor. Maximum tissue expression is seen in the early secretory phase.
5. Type I endometrial carcinomas very often express ERα, ERβ, and PRs, respective expression levels being significantly lower than proliferative

endometrium. Selective ERα loss results in reversal of ERα/ERβ ratio in endometrial cancers. Of PR isoforms, only one type predominates.

6. Tissue expression of these receptors correlates with well-differentiated phenotype, early tumor stage, low proliferation, disease-free survival, and overall survival.
7. ERα and PRB have been reported to be independent predictors of disease-free and overall survival, respectively. Absent PR expression is likely to identify worse-outcome patients for aggressive adjuvant therapy.
8. Recently new ER types (G protein-coupled ER, mERα, and ER-X) on cell and organelle membranes have been discovered. Their role in mediating typical transcriptional effects and rapid cellular events is a current area of research.

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