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Targeting Female Hormone Receptors as Cervical Cancer Therapy

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Abstract

While preventive methods for cervical cancer are effective, available therapies for advanced cervical cancers are ineffective. New experimental evidence points to weaknesses of prior studies and provides fresh molecular insights on the opposing roles of ERα and PR, which may be translated into valuable treatment for a subset of cervical cancers.

Keywords

human papillomavirus (HPV); estrogen receptor α (ERα); progesterone receptor (PR); cervical cancer; hormonal therapy

Cervical Cancer and Human Papillomavirus

Cervical cancer is the fourth most frequent cancer and fourth leading cause of cancer death in women, worldwide. Cervical intraepithelial neoplasia (CIN) premalignant lesions precede cervical cancer. CINs (CIN1-CIN3) are effectively treated by simple surgeries, but they increase the risk for complications in future pregnancy. Current therapies for cervical cancer are ineffective for advanced or recurrent cervical cancer. Thus, the development of more effective therapy for cervical cancer and CIN is urgently needed.

High-risk human papillomavirus (HPV) is a major etiological factor and HPV vaccines reduce the likelihood of CIN and cervical cancer [1]. The HPV oncogenes E6 and E7 are necessary for HPV-induced cervical carcinogenesis. Persistent HPV infection is occasionally established when the immune system fails to resolve initial infections. CIN3 develops only in 14-40% of women with persistent HPV infections, and the rate of progression from CIN3 to invasive cancer is approximately 30% in unscreened population, suggesting that CIN lesions can regress spontaneously [1-3]. Consequently, less than 0.1%

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of HPV-infected women succumb to cervical cancer. Despite the oncogenic activities of E6 and E7, primary rodent cells are transformed by high-risk HPV DNAs only in the presence of other factors such as a glucocorticoid or activated Ras [1]. Furthermore, cervical neoplastic diseases do not develop spontaneously in transgenic mice expressing E6 and E7 [2]. These observations indicate that other factors, in addition to HPV, are required for cervical carcinogenesis.

This article focuses on the roles of the female sex hormones estradiol (E_2) and progesterone (P_4) in cervical carcinogenesis, and describes how their receptors and/or downstream gene products may be targets for therapy.

Female Hormones and Their Receptors in Cervical Cancer

Long-term oral contraceptives use or multiple parities increases the risk for cervical cancer in HPV-infected women [2]. Since most oral contraceptives contain E_2 and synthetic P_4, and high levels of E_2 and P_4 are maintained during pregnancy, these observations implicate the female hormones in cervical cancer. E_2 and P_4 bind to and activate the estrogen (ERα and ERβ) and progesterone (PR-A and PR-B) receptors, respectively, ligand-dependent transcription factors that play key roles in numerous processes, including cancer. ERβ expression in the cervix is undetectable [4]. Thus, the E_2–ERα and P_4–PR signaling pathway may be involved in the progression and/or development of cervical cancer. Although the association between E_2 replacement or selective ER modulator (SERM) therapy and cervical cancer is controversial [2], recent animal model studies, discussed below, support an oncogenic role of E_2–ERα in cervical cancer.

Epidemiological studies looking at associations between medroxyprogesterone acetate (synthetic P_4) and cervical cancer have been inconclusive, because data have not been stratified based on HPV infection. Although the results need verification, one study indicates that the use of medroxyprogesterone acetate decreases the risk of high-grade CINs among HPV-infected women [5]. Expression levels of ERα and PR do not necessarily reflect their activities, which depend on hormone concentrations. In addition, the levels of female hormones and hormone receptors continuously change due to biological (menstrual cycle), behavioral (hormonal contraceptive use) and environmental factors (estrogenic chemicals). Therefore, it is challenging to gain insight on a role for ERα and PR using studies based on a single measure of these receptors. Biomarkers for ERα, PR-A and PR-B activity in the cervix should be developed. It is also difficult to evaluate the role of E_2–ERα or P_4–PR in cervical cancer from several published *in vitro* studies, because of non-physiologic hormone doses and use of cervical cancer cell lines (e.g., SiHa, CaSki and HeLa) that do not express the receptors [2]. Published clinical trials also are not informative because of short follow-up periods, poor drug choice or underpowered statistical analyses [2, 6].

Mouse Model of Cervical Cancer

The Role of E_2–ERα

Transgenic mice expressing HPV16 E6 (*K14E6*) or E7 (*K14E7*) have been extensively characterized in the context of cervical cancer [2]. Consistent with the notion that HPV

alone is not sufficient, cervical cancer arises at high frequency only after chronic low-dose E_2 treatment. The cervical diseases that arise in these mice recapitulate key aspects of human cervical cancer, including progressive development (CIN1, CIN2, CIN3 and cancer), cancer development in the transformation zone, and expression patterns of biomarkers similar to those of human malignancy [2]. In the HPV transgenic mice, ERα is necessary for cervical cancer development, and SERMs are efficient in treating the disease [2]. In the same mouse model, ablation of ERα expression in stromal cells results in complete regression of cervical neoplastic diseases [7], suggesting a paracrine mechanism. Since ERα is expressed in most cervical cancer stroma, this appears relevant to human cervical cancer [4, 8]. I speculate that ERα activates expression of secretory factors such as growth factors and cytokines in stromal cells that then activate oncogenic growth factor receptor signaling in neoplastic epithelial cells (Fig. 1). Identification of a growth factor receptor transmitting stromal ERα signal to epithelial cells would help the development of a targeted therapy for cervical cancer (Fig. 1). In this regard, amphiregulin—an epidermal growth factor receptor ligand—mediates paracrine effects of ERα during mammary gland development and carcinogenesis, and insulin-like growth factor 1 mediates E_2-induced endometrial cell proliferation [9-11].

ERα expression is gradually lost in neoplastic epithelial cells as cervical neoplastic disease progresses [4, 12]. Knockdown of ERα enhances invasion of the chick chorioallantoic membrane by cervical cancer cells [12]. These observations raise the possibility that stromal ERα is oncogenic, whereas epithelial ERα has dual functions, oncogenic in early stages and tumor-suppressive in late stages of cervical carcinogenesis (Fig. 1). This model further implies that stromal E_2–ERα signaling promotes ERα-negative cervical cancer. Using the Cre-lox technology and the HPV transgenic mouse model, disease stage-specific function of ERα can be addressed by temporal ablation of ERα expression in neoplastic epithelial cells.

The Role of P_4–PR

The cervical neoplastic disease burden in *K14E7/PR*$^{+/+}$ mice is similar to that in *K14E7/PR*$^{-/-}$ mice [13]. This is as expected, since chronic E_2 treatment inhibits the P_4 surge (i.e., low P_4 levels throughout a study period), and thus deletion of PR would have little effect (Fig. 2a). However, activation of PR by medroxyprogesterone acetate causes regression of CIN and cervical cancer in the HPV transgenic mouse model [13]. Based on these results, I hypothesize that PR acts as a ligand-dependent tumor suppressor in cervical cancer as in endometrial cancer [11]. While PR is expressed in 100% of cervical cancers arising in this mouse model, only 20-40% of human cervical cancers express PR [13, 14]. This difference may reflect hormonal status and/or other factors during neoplastic disease development. I speculate that PR$^-$ cancers are frequent in humans because women with high P_4 levels are more common than those with persistently high E_2 levels. Persistently high P_4 levels or cyclic P_4 surges may provide selective pressure for rare PR$^-$ cells (Fig. 2b-c); however, PR$^-$ cervical cancer would rarely occur when high P_4 levels persist because ERα activity would be minimal due to continuously low E_2 levels. Such selection would not occur under a persistent E_2 stimulation condition (Fig. 2a). Cervical carcinogenesis would be highly efficient under this hormonal condition as shown in the HPV transgenic mouse model [2]. In this regard, it might be important to determine whether HPV-infected women who do not

have P_4 surges are at higher risk (e.g., women with polycystic ovarian syndrome) for cervical cancer similar to endometrial cancer [11].

The results in the mouse model system suggest that proper use of ERα and PR ligands could be useful in the treatment of cervical cancer. If the cancer stroma expresses ERα, treatment with SERMs such as faslodex might be effective, regardless of expression of ERα in the cancer cells (Fig. 1). Co-treatment with SERMs and selective PR modulators (SPRMs) such as medroxyprogesterone acetate may be synergistic if both ERα and PR are expressed in appropriate cells.

Conclusions

Although there has been substantial improvement in our understanding of ERα and PR functions over the last decade, their function and mechanism in physiology and pathophysiology of the cervix is still underappreciated. Studies using the HPV transgenic mouse model have expanded understanding of the molecular pathogenesis of cervical cancer, and some of the underlying mechanisms that involve readily targetable hormone receptors. These advances support the hypothesis that epithelial P_4–PR is tumor suppressive and that E_2–ERα is oncogenic and tumor suppressive depending on cell types in which it functions. Next is to see if these findings are translatable to human disease via clinical trials evaluating the efficacy of SERMs and/or SPRMs in treating cervical cancer and CINs. As many of these classes of drugs are already in clinical use, the results could be translated quickly to clinical application, whereas further understanding of ERα and PR functions in cervical carcinogenesis will reveal new therapeutic targets for the disease.

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Abbreviations

HPV	human papillomavirus
E_2	estradiol
P_4	progesterone
ER	estrogen receptor
PR	progesterone receptor
CIN	cervical intraepithelial neoplasia

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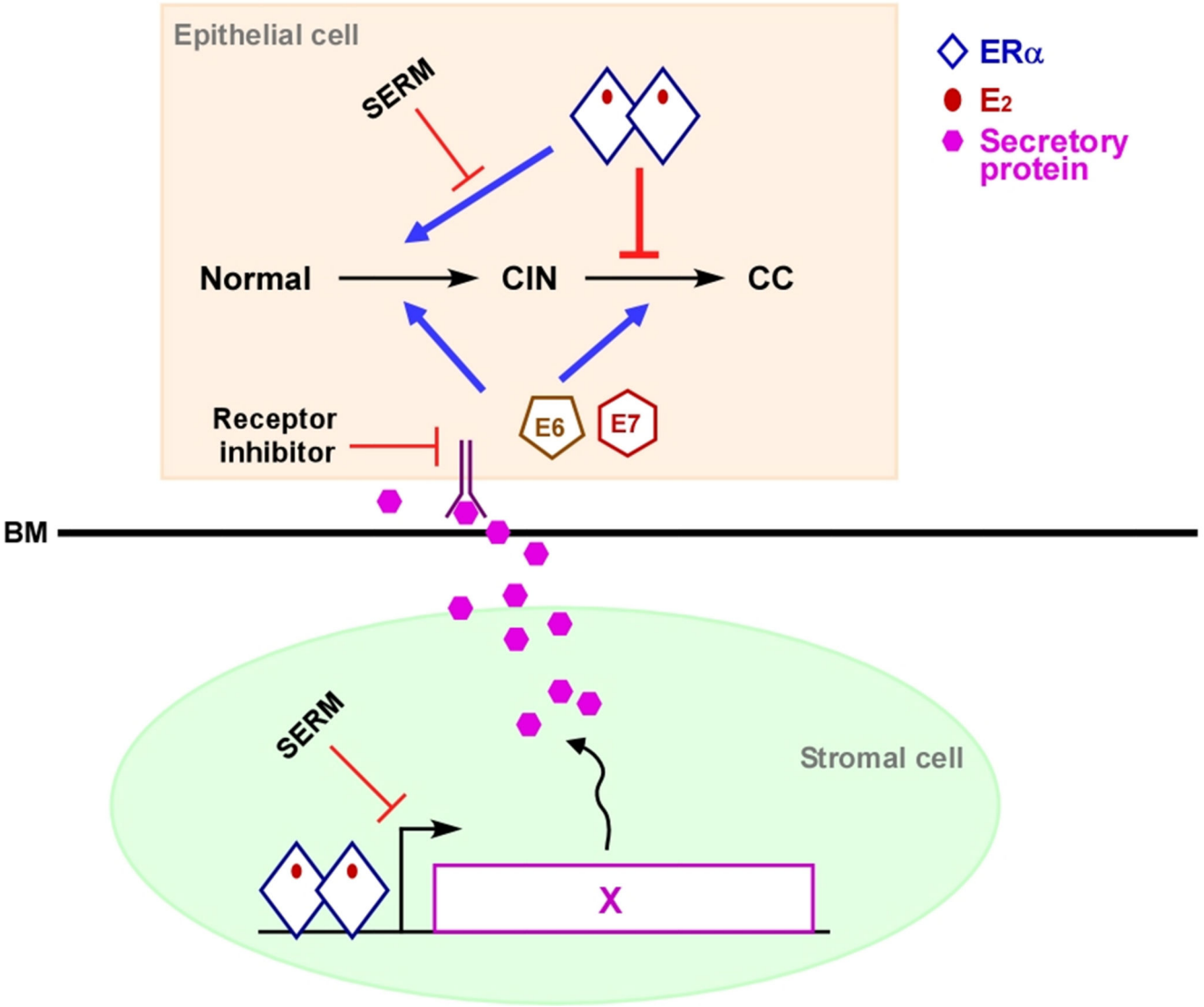

Figure 1. A proposed model of ERα mechanism in cervical cancer

A gene(s) denoted as X that encodes for a secretory protein(s) is activated by ERα in stromal cells. The secretory protein activates a membrane receptor-mediated pathway in epithelial cells, which, in conjunction with E6 and E7, promotes initiation and progression of cervical cancer (CC). SERMs and receptor inhibitors could be effective in treating CC. It is proposed that E_2-liganded ERα promotes the development of CIN, but the activated ERα in neoplastic epithelial cells inhibits further progression of CIN. BM, basement membrane.

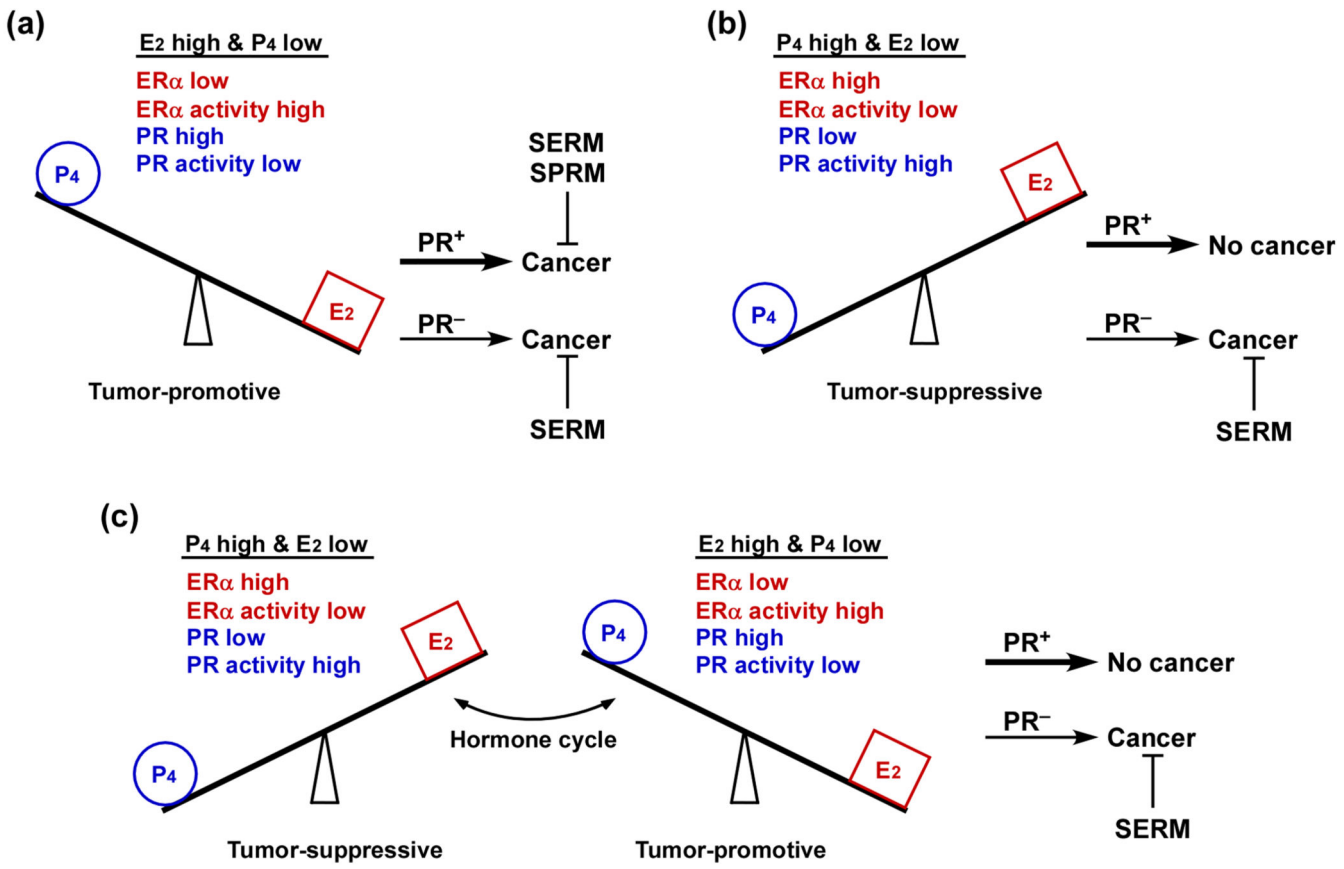

Figure 2. A model of the impact of the balance between E_2 and P_4 on cervical cancer

An E_2 surge promotes epithelial cell proliferation in female reproductive tracts and a following P_4 surge reverses it [2, 11]. While E_2 surges activates ERα and increases PR expression in the cervix [7], the activity of PR remains minimal because P_4 levels are low during E_2 surges. PR activity is heightened and ERα activity decreases during the following P_4 surge. As ERα and PR downregulate their own expression, their expression levels are lower when activated by the hormones. These regulations occur in both stroma and epithelium. A model of the impact of normal and impaired hormonal cycle on cervical cancer is proposed. Tumor-promotive E_2 action is mainly through stromal ERα (see Fig. 1). Epithelial PR likely mediates, at least in part, tumor-suppressive function of P_4 and thus high P_4 has little effect on PR^- cancer cells.

(a) Persistently high levels of E_2 (high ERα activity) maintains low P_4 levels (low PR activity). Under this hormonal condition, the development of PR^+ cancers is more likely because there is no selective pressure for PR^- cancers.

(b) Cancer development is unlikely under this hormonal condition because of persistently low ERα activity. If it occurs nonetheless, it is likely PR^- cancer.

(c) E_2 and P_4 peak sequentially in turn and are never high concurrently during hormone cycle (*left*, luteal phase; *right*, proliferative phase). PR^- cells have advantage to become cancerous.

The thickness of arrows indicates the relative likelihood of an event. Note that HPV must be present in all three hormonal conditions for cancer development.