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Review

Steroid receptors and metastatic potential in endometrial cancers

Jiro Fujimoto *, Hideki Sakaguchi, Ikumi Aoki, Sufia Khatun, Hiroshi Toyoki, Teruhiko Tamaya

Department of Obstetrics and Gynecology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu City 500-8705, Japan

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Abstract

The relative overexpression of estrogen receptor (ER)-α exon 5 splicing variant, the disrupted synchronization of ER-β and ER-α expressions, and the suppression of progesterone receptor (PR) form A expression as a transcriptional repressor might be related to metastatic potential of uterine endometrial cancers, leading to poor patient prognosis related to estrogen refractoriness.

Keywords: Endometrial cancer; Estrogen receptor-α and β; Isoform; Metastasis; Progesterone receptor; Splicing variant

Contents

1. Introduction

Most uterine endometrial cancers in the early stage conserve sex steroid hormone dependency in growth as normal uterine endometrium does. Furthermore, metastatic potential in well-differentiated endometrial cancers is partially modulated by sex steroid hormones in various steps of metastasis; the detachment of cancer cells [1], invasiveness to the basement membrane and interstitium [2,3] related to plasminogen activator inhibitor 1 [4,5], and angiogenesis activated by basic fibroblast growth factor [6–8], vascular endothelial growth factor [9,10], and platelet-derived endothelial cell growth factor [11–13]. Among the various steps in the metastasis of gynecological cancers, angiogenesis is an extremely important process for growth related to patient prognosis in other gynecological cancers too [14–19].

During advancement of endometrial cancers, the cancer cells transform to gain metastatic potential while losing sex steroidal dependency. This prompted us to study the molecular mechanisms of metastatic potential acquisition from the aspect of steroid receptors.

2. Estrogen receptor-α (ER-α) splicing variants

Single exon splicing variant ER-α, exon 2 splicing variant ER-α (ER-α E2SV) [20,21], ER-α E3SV [20,22],

* Corresponding author. Tel.: +81-58-2672631; fax: +81-58-2659006.

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ER-α E4SV [21,23–25], ER-α E5SV [21,26,27], ER-α E6SV [22], ER-α E7SV [20–22,24,28], and double splicing variant ER-α E4,7SV were plausibly observed as positive or negative transactivators [29]. ER-α E4SV [23,25] and ER-α E5SV mRNAs [26] have been found in normal tissues from human uterus and rat uterus and brain, while it is likely that ER-α E4SV has no biological function [25] and ER-α E5SV is transcriptionally active without ligand binding [26].

There was no significant difference in the ratio of ER-α E5SV to ER-α wild type (ER-α WT) mRNA expression among normal uterine endometria and primary tumors of uterine endometrial cancers classified according to grades of histological differentiation and clinical staging. The ratio of ER-α E5SV to ER-α WT mRNA expression significantly increased in four of eight metastatic lesions of uterine endometrial cancers, while there was no decrease in any case. Therefore, the relative overexpression of ER-α E5SV might be related to metastatic potential with the loss of sex steroidal dependency in uterine endometrial cancers [30].

3. Estrogen receptor-β (ER-β)

Novel rat ER-β (rER-β) [31] and human ER-β (hER-β) [32,33] were identified in cDNA libraries from rat prostate and human testis, respectively. The rER-β consists of 485 amino acids, and distinctly expresses in epithelial cells of prostate, granulosa cells of ovary [34], and osteoblastic cells of bone [35]. The hER-β consists of 530 amino acids [34]. ER-β has high affinity for estradiol-17 β [36,37] and characteristics similar to ER-α in specific binding to various estrogenic substances and antagonists [34]. Although the phosphorylation site for mitogen-activated protein kinase is conserved in the activation function (AF)-1 region of ER-β as in ER-α [37], both AF-1 and AF-2 regions of ER-β are shorter than those of ER-α. Furthermore, the transcription at an AP1 element was inhibited by estradiol and activated by antiestrogens via ER-β cascades [38]. This indicates some difference in the transcriptional efficiency and regulatory potential of the target genes. ER-β specifically expresses in testis, ovary, thymus, spleen [32], osteoblasts [39] and fetus [40].

The ratio of ER-β to ER-α mRNA expression was in the range of 1.5–10:100 in normal ovaries. In a 48-month survival rate, the patient prognosis for ovarian cancers with a ratio of ER-β to ER-α mRNA expression out of the normal range was significantly worse than that for ovarian cancers with a normal ratio [41]. In normal endometrium, the ratio of ER-β to ER-α mRNA expression is very stable, indicating that ER-β coexpressed with ER-α might contribute to intact estrogen dependency [42]. ER-β mRNA was expressed in a wider range and significantly higher in ovarian endometriomas than in normal uterine endometria during the menstrual cycle, while ER-α mRNA was expressed relatively lower and randomly [42]. Therefore, the disrupted synchronization of ER-β and ER-α expressions might be related to a unique estrogen-dependent growth and spreading in ovarian cancers and endometriomas.

The ratio of ER-β to ER-α mRNA expression in most primary uterine endometrial cancers was similar to that in normal uterine endometria. On the other hand, in 14 of 20 metastasis-positive cases of uterine endometrial cancers, the ratio in the metastatic lesion was significantly higher than that in the primary tumor of the corresponding case, and patient prognosis in these cases was extremely poor. This analysis suggests that the intact synchronized expression of ER-β interacting with ERα might be disrupted in most metastases of uterine endometrial cancers, leading to poor patient prognosis related to estrogen refractoriness.

4. Progesterone receptor (PR) isoforms

Progestational effects are demonstrated on cellular proliferation and differentiation in the target tissues after progesterone binds to PR [43]. Two distinct PR forms, A (PR-A) and B (PR-B, wild type), have been proposed to exist in chick oviduct [44] and T47D human breast cancer cells [44]. Human PR-A, initiated from in-frame AUG present in the PR-B mRNA, lacks the N-terminal 164 amino acids of PR-B [45–48], and acts as a progestindependent, trans-dominant repressor of PR-B functions and other steroid receptor functions [49]. PR-A and PR-B are equally present in normal female genital tract [50]. Variable expressions of those two isoforms were demonstrated in gynecologic cancers, and the dominancy of PR-B mRNA expression might be a biological marker of malignant phenotype in ovarian cancers [50].

In the primary tumor of uterine endometrial cancers, approximately equal expression of PR-A and PR-B mRNAs or dominant expression of PR-B mRNA was demonstrated. In all metastatic lesions of uterine endometrial cancers, the expression of PR-A mRNA was suppressed and PR-B mRNA was dominantly expressed [51]. Additionally, NIH3T3 cells transfected with ER-α and PR-B genes, under the influence of independent viral promoters, form abundant colonies in an agar culture and tumors in nude mice [52]. Therefore, the relative overexpression of PR-B, caused by the altered expression of PR-A, might be related to metastatic potential and tumorigenesis with the loss of intact progesterone dependency in endometrial cancers.

5. Conclusion

Unique alterations of ER and PR cascades might be related to metastatic potential of uterine endometrial cancers. This motivates us to analyze transcriptional alteration associated with co-factors, not only to AF-2 but also to AF-1, in target cells as a future study.

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