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Local estrogen formation and its regulation in endometriosis

Taisuke Mori | Fumitake Ito | Akemi Koshiba | Hisashi Kataoka | Osamu Takaoka | Hiroyuki Okimura | Khaleque N. Khan | Jo Kitawaki

Department of Obstetrics and Gynecology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Correspondence
Taisuke Mori, Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, 602-8566, Japan.
Email: moriman@koto.kpu-m.ac.jp

Abstract

Background: It has been well established that endometriosis is an estrogen-dependent disease. Although the exact pathogenesis of the disease is still unclear, it is known to be characterized by estrogen-dependent growth and maintenance of the ectopic endometrium and increased local estrogen production.

Methods: The authors reviewed studies on local estrogen production and estrogen activities mediated by estrogen receptors in endometriotic tissues.

Main findings: Aberrant expression of several enzymes in local endometriotic lesions contributed to the production and metabolism of estrogens. Aromatase was one of the key therapeutic targets for the regulation of local estrogen formation. Our findings suggest that PGC-1a, a transcriptional coactivator-modulating steroid hormone, regulates aromatase expression and activity. Estrogen activities mediated by different types of estrogen receptors abnormally elevated in local tissues could also be involved in the development of endometriosis. The authors demonstrated that the isoflavone aglycone, a partial agonist of the estrogen receptor, suppressed the formation of endometriotic lesions.

Conclusions: Local estrogen production and estrogen activity mediated by estrogen receptors are important potential therapeutic targets for endometriosis.

KEYWORDS

aromatase, endometriosis, estrogen, estrogen receptors, PGC-1α

1 | INTRODUCTION

Endometriosis is a common benign gynecological disease characterized by the presence of functional endometrium-like tissues at extra-uterine sites. It affects approximately 6%-10% of females of reproductive age.[1] It is associated with various clinical symptoms including chronic pelvic pain, dysmenorrhea, and infertility, seriously affecting women's health and quality of life.[2] Our understanding of the etiology of endometriosis includes some established hypotheses, and several regulatory factors are known to support the development or maintenance of the disease. However, its exact etiology remains poorly understood.

It is well accepted that endometriosis is foremost an estrogen-dependent disease.[3] It is characterized by estrogen-dependent growth and maintenance of ectopic endometrium and by increased local estrogen production. Indeed, endometriosis symptoms and endometriotic lesions are relieved after menopause in many cases. Additionally, the lesions usually contract in a low-estrogen environment such as after treatment with GnRH agonist.[4] Accumulating evidence has shown that estrogen concentration is elevated in

endometriotic lesions, although serum estrogen levels are not elevated in women with endometriosis.[5-8] Notably, the biological effects of estrogens are mediated by the estrogen receptors (ERs). Estrogen responsiveness depends on the balance of ER expression, distribution, and ER protein function, which are different between endometriotic tissues and normal endometrium, contributing to the pathological characteristics of endometriosis.[9] Thus, previous studies suggest the existence of a proliferative signaling mechanism in endometriotic tissues mediated by the estrogen-estrogen receptors axis.[10] Here, we provide current insight into the biological process of estrogen-mediated signaling in endometriosis and into the development of therapeutic strategies targeting local estrogen formation.

2 | EXPRESSION OF ENZYMES INVOLVED IN LOCAL ESTROGEN FORMATION IN ENDOMETRIOSIS

Recently, in situ estrogen synthesis and metabolism have been considered to play an important role in the development and progression of the estrogen-dependent disease.[11,12] Estrogen is one of the steroid hormones synthesized from cholesterol (Figure 1). Two of the most important enzymes involved in the process of estrogen biosynthesis are steroidogenic acute regulatory protein (StAR) and aromatase. StAR is expressed in adrenal glands and gonads. Its expression is stimulated initially by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secreted from the pituitary. The function of StAR in the regulation of steroidogenesis involves introducing the entry of cholesterol for estrogen production.[13] Previous studies showed that StAR is highly expressed at the levels of protein and mRNA in peritoneal endometriosis and endometriotic stromal cells, compared with normal endometrium.[14,15] Treatment with prostaglandin E_2 (PGE_2) significantly increased StAR expression in human endometriotic stromal cells. This response could be mediated via phosphorylation of cAMP response element binding protein (CREB) and binding of CCAAT/enhancer-binding protein (C/EBP) to a cis-element of the StAR promoter.[16,17] Thus, aberrant expression of StAR in endometriotic stromal cells plays a critical role in the development of endometriosis.

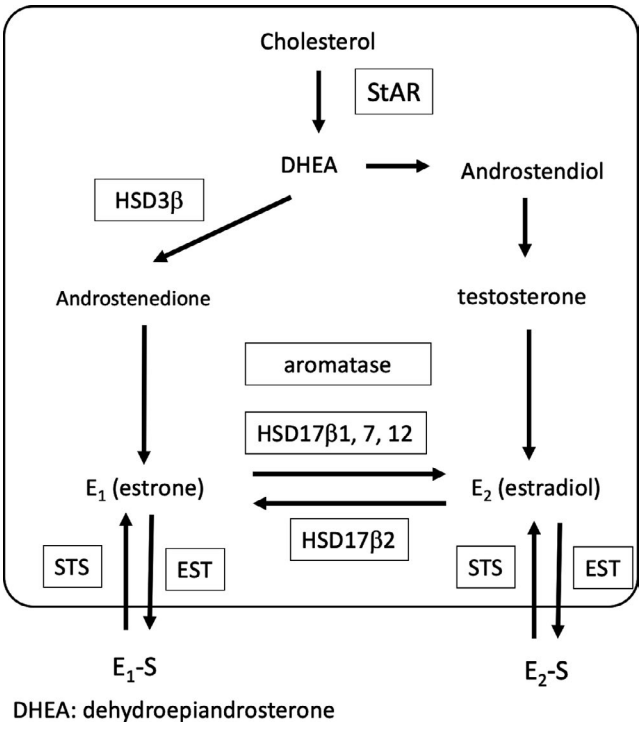

FIGURE 1 Biosynthesis and metabolism of estrogens

Aromatase is the enzyme converting testosterone and androstenedione to estradiol (E_2) and estrone (E_1), respectively. Aromatase is expressed in a number of human tissues and cells, such as ovarian granulosa cells, adipose tissue, skin fibroblasts, placental trophoblasts, osteoblasts, and brain. In women of reproductive age, aromatase is most potently and periodically secreted by the ovary. Ovarian granulosa cells express high levels of aromatase under the influence of FSH.[18] In contrast, in postmenopausal women, estrogen formation takes place in extra-glandular sites such as adipose tissue and skin.[19] The main substrate of aromatase in adipose and skin tissues is androstenedione secreted from adrenal tissues.

Interestingly, previous evidence demonstrates that aromatase is highly expressed in endometriosis.[5-8,20] Aromatase was detected in endometriotic implants in much larger amounts than in eutopic endometrium, although it was not detected in normal endometrium from disease-free women. Our group showed that local estrogen production by aberrantly elevated aromatase takes place in endometriosis and adenomyosis, but not in normal endometrium using immunohistochemical analysis.[5] Conversely, some studies have shown an absence of aromatase activity in endometriotic samples. This discrepancy may be caused by a difference in specificity of antibodies used or differences between biopsy specimens investigated. Recently, Huhtinen et al showed that intratissue estrogen concentrations in ovarian endometriotic lesions were much higher than those in normal endometrium, peritoneal, and deep endometriosis.[8] The group also showed that the mRNA level of aromatase was significantly more abundant in the proliferative/secretory menstrual phase of ovarian endometrioma and in the proliferative phase of deep endometriosis.[8] These findings suggest that aromatase plays a critical role in local estrogen production, especially in ovarian endometriosis, and indicate the existence of autocrine and paracrine sources of estrogens in local lesions.

A prominent influence on these processes is the 17β-hydroxysteroid dehydrogenase (HSD17β) enzyme family. These enzymes are involved in the formation of biologically active steroid hormones, including testosterone, estrone (E1), and estradiol (E2). They function by catalyzing the reversible interconversion of E1 and E2. Specifically, HSD17β type 1 (HSD17β1) catalyzes the 17β-reduction of biologically inactive E1 to E2, while HSD17β2 preferentially catalyzes the oxidation of E2 to E1. In endometriotic tissues, HSD17β1 expression and enzyme activity are increased compared with those in normal endometrium without endometriosis.[21,22] Our recent study showed that HSD17β1 is highly

expressed at mRNA and protein levels in endometriotic tissues, including deep infiltrating endometriosis (DIE) lesions, than in normal endometrium. We also showed that progesterone therapy significantly suppressed the catalytic activity of HSD17β1 ovarian endometrial stromal cells.[23] In contrast, evidence regarding the expression and enzyme activity of HSD17β2 in endometriotic tissues is inconsistent. Some studies demonstrated that HSD17β2 expression is decreased in endometriotic tissues including eutopic and ectopic endometrium, resulting in the inactivation of E2. In contrast, our group reported that the expression in secretary endometrium was increased with endometriosis.[24] Other investigators also showed that there were no observable differences in the expression of HSD17β2 between normal endometrium and endometriosis.[25]

The major source of estrogens is estrone sulfate, an inactivate conjugate form abundant in the peripheral tissues such as circulating serum. Estrogen sulfate is de-sulfated to estrone, an active form, by steroid sulfatase (STS), and estrone is inactivated by estrogen sulfotransferase (EST).[22,26] STS is highly expressed in the endometriotic tissues and has been shown to correlate with disease severity.[27] EST is highly expressed in ovarian endometrioma, though its expression is not detectable in normal and eutopic endometrium. Thus, these findings indicate how the aberrant expression of these enzymes in endometriosis contributes to local production and metabolism of estrogens.

3 | AROMATASE REGULATION IN ENDOMETRIOSIS

The human aromatase gene is tissue-specifically regulated through the alternative use of multiple untranslated isoforms of its exon I (I.1, I.2, I.3, I.4, I.5, I.6, I.7, and PII). Various exon I-containing mRNAs are present at different levels in different aromatase-expressing tissues. For example, exon I.I transcripts, located most distally upstream from the coding region, were found to be elevated in placental tissue.[28] The major exons in breast cancer specimens are I.3 and PII.[29] In contrast, normal breast adipose tissues show very low levels of exons/promoters I.3 and II, and a low level of exon/promoter I.4.[30] These findings suggest different aromatase expression regulatory mechanisms between normal breast adipose and cancer tissues.

In endometriotic tissues, our group and other investigators demonstrated that the promoters corresponding to exons I.3 and PII are the gene's main promoters.[31,32] Prostaglandin E_2 (PGE_2) stimulates aromatase expression in endometriotic stromal cells.[33] PGE_2 formation is then caused by the enzyme activity of cyclooxygenase type 2 (COX-2) in endometriotic stromal cells.[34] Notably, estrogen-mediated induction of various cytokines in cells has been directly linked to the hormone and the promotion of inflammation.[35] The inflammatory cytokines, including interleukin (IL)-6 and IL-8, activate pro-survival signaling pathways.[36] PGE_2 also enhances the expression of StAR in endometriotic stromal cells as described above. These findings suggest the existence of a feed-forward mechanism

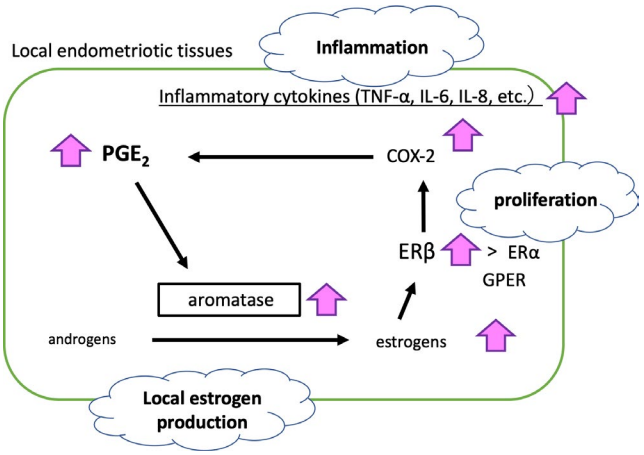

FIGURE 2 The feedback mechanism of local estrogen production during endometriosis through estrogen receptors

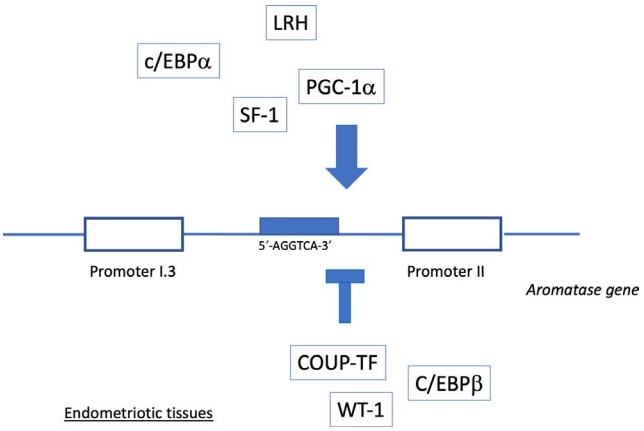

FIGURE 3 A schematic diagram of positive and negative transcriptional regulation of aromatase expression in endometriotic tissue

among estrogen production, PGE_2, and cytokines promoting the persistence of endometriotic lesions[37] (Figure 2).

A previous report showed that steroidogenic factor-1 (SF-1) binds to the nuclear receptor half-site upstream of the aromatase promoter II to regulate aromatase expression.[32] Conversely, chicken ovalbumin upstream promoter-transcription factor (COUP-TF) inhibits aromatase expression (Figure 3). SF-1 is expressed in endometriosis but not in normal eutopic endometrial cells, while COUP-TF is expressed in both normal and eutopic endometrium. In aromatase promoter II, SF-1 competes for the same binding site as COUP-TF. Additionally, evidence has shown that various types of transcriptional factors, including CCAAT/enhancer-binding protein (C/EBP) α C/EBPβ Wilms' tumor-1 (WT-1), DAX-1, and liver receptor homolog-1 (LRH-1),[6] could be involved in the regulatory expression of aromatase. WT-1 acts as a corepressor of SF-1 at the nuclear half-site of aromatase promoters I.3 and II. C/EBP α and C/EBPβ bind to the cAMP response element between aromatase PI.3 and II. C/EBPα functions as an enhancer, and in contrast, C/EBPβ inhibits aromatase expression.[6] C/EBPβ is expressed at a lower level in endometriosis

but not in eutopic endometrium. DAX-1 regulates SF-1 transcription in a dominant-negative manner and inhibits SF-1-dependent expression of aromatase in endometriosis.[38,39] Thus, these findings suggest that transcription factors play important roles in the regulatory expression of aromatase in endometriotic tissues and eutopic/normal endometrium.

Another important factor is PGC-1α, a multifunctional coactivator that interacts with various nuclear receptors to regulate genes in multiple biological responses including oxidative metabolism, mitochondrial biogenesis, adaptive thermogenesis, and steroidogenesis.[40,41] For example, in brown adipose tissue, PGC-1α cooperates with peroxisome proliferator-activated receptor gamma (PPARγ) to stimulate adipocyte differentiation.[42] In addition, PGC-1α promotes progesterone production in ovarian granulosa cells as a coactivator of SF-1 and LRH-1.[41] It has also been shown that PGC-1α downregulates the expression of insulin-sensitive glucose transporter type 4, and is involved in glucose uptake, in skeletal muscle cells.[43] Thus, PGC-1α is differentially expressed in different tissues and functions as a coactivator interacting with tissue-specific transcription factors. Our group previously showed that aberrantly elevated expression of PGC-1α in ovarian endometrioma was correlated with the localization of aromatase in the endometriotic tissues. PGC-1α elevated aromatase expression at the mRNA level in ovarian endometriotic stromal cells (OESCs) through the usage of aromatase promoter I.3/II.[31] Endogenous PGC-1α bound to the nuclear receptor half-site 5′-AGGTCA-3′ was recruited by a chromatin immunoprecipitation assay. It is also notable that TNF-α produced by peritoneal macrophage and endometriotic tissue can stimulate PGC-1α in OESCs. It is clear that a full understanding of the regulation of aromatase in endometriosis will require further investigation.

4 | ESTROGEN RECEPTORS IN ENDOMETRIOSIS

Estrogens promote physiological activities after binding to the steroid receptor estrogen receptor (ER) subtypes, ERα and Erβ. These receptors exhibit tissue-specific expression. ERα is highly expressed in bone, kidney, liver, mammary glands, and reproductive organs, whereas ERβ is expressed in the prostate, ovary, bladder, uterus, and central nervous system.[44] The estrogen response occurs after binding of ERs to estrogen-responsive elements (EREs) followed by the nuclear activation complex for the transcription of each target gene. Estrogen can also exert its effects through nongenomic signaling via cell membrane ERs. GPER (a seven-pass transmembrane G protein-coupled estrogen receptor) has been identified as a novel receptor with binding ability to E2 in cell membranes and endoplasmic reticulum.[45] The response is regulated by downstream molecules including the phosphatidylinositol 3-kinase (PI3K) and MEK/ERK mitogen-activated protein kinase (MAPK) pathways.[46] Here, we review the expression and significance of each estrogen receptor in endometriosis.

4.1 | Estrogen receptors (ERα and ERβ) in endometriosis

In the normal endometrium, expression of ERα is significantly higher than that of ERβ. The main activity of ERα is thought to be to promote cell proliferation.[47] On the other hand, in endometriosis, expression of ERα is attenuated compared with normal endometrium, and in contrast, ERβ is upregulated.[25,48,49] Although the detailed mechanisms of the attenuation of ERα and the increase in ERβ remain unclear, previous studies showed hypomethylation of the ERβ promoter could be associated with upregulation of protein level in endometriotic tissues.[49] Maekawa et al reported the aberrant DNA methylation of tissue-dependent and differentially methylated region (T-DMR) in ERα contributes to its impaired expression in the ovarian endometrioma.[50,51] On the other hand, in contrast to a previous report, they concluded DNA methylation is not involved in the upregulation of ERβ in endometriosis.[50] Interestingly, other investigators showed that ERβ downregulates ERα expression in the stromal cells from ovarian endometrioma.[52] Importantly, a loss-of-function experiment using siRNA showed that ERβ inhibited proliferation of endometrial stromal cells. This indicates that, in addition to ERα ERβ plays a critical role in the development of endometriosis. Furthermore, a recent study demonstrated that ectopic proliferation, survival, and inflammatory activity of endometriotic tissues were mediated by ERβ.[53] The potential of ERβ as a therapeutic target in endometriosis has been recognized. One study showed that a selective ERβ agonist achieved lesion size regression in a mouse model of endometriosis.[54]

Isoflavones, a subgroup of the phytoestrogens found in soybeans, exert estrogen-like activity. They have similarities in structure with E_2, but exert anti-estrogenic effects in reproductive-age women with high estrogen levels.[55] There have been a few studies to investigate the effect of isoflavones on endometriosis. Treatment by two flavonoids, puerarin and parthenolide, inhibited proliferation of human endometriotic stromal cells.[56,57] Other investigators showed that genistein caused regression of an endometriotic implant in a rat model.[58] Our group recently demonstrated that daidzein-rich isoflavone aglycones (DRIAs) inhibited the proliferation of OESCs at clinically feasible concentrations[59] (Figure 4). Additionally, DRIAs suppressed the formation of endometriosis-like lesions in a mouse model.[59] Clinical trials will be carried out to clarify the effect of DRIAs in patients with endometriosis.

We noticed that isoflavone is a partial agonist of the estrogen receptor, and DRIA supplement suppresses inflammatory cytokines and aromatase expression/enzyme activity in endometriosis. Furthermore, when an endometriosis model mouse was given DRIA, cyst formation decreased.[59]

4.2 | GPER

GPER mediates the balance between nongenomic rapid cell signaling mechanisms and genomic slow transcriptional activity in the response to estrogens. GPER is expressed in most tissues, for

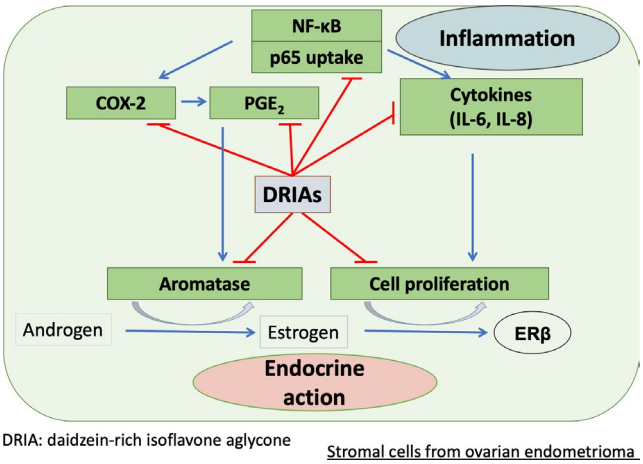

FIGURE 4 Daidzein-rich isoflavone aglycones inhibit cell proliferation, local estrogen production, and inflammation in endometriotic tissue

example, heart, brain, placenta, and liver. GPER is also located not only in the cell membrane but also in the surface membrane of intracellular organelles including endoplasmic reticulum and the Golgi apparatus. It stimulates the phosphatidylinositol 3-kinase (PI3K) and MEK/ERK mitogen-activated protein kinase (MAPK) pathways. Although there have been few previous studies on GPER in endometriosis, evidence has shown that it is expressed relatively highly in endometriotic tissues compared with normal endometrium [60] and in the endometrium of patients with endometriosis compared with healthy women.[61] Furthermore, the aberrant expression of GPER in estrogen-dependent diseases suggests its potential involvement in the pathogenesis of endometriosis.[62-64] To further understand the mechanism of GPER activity in endometriosis, we conducted experiments using the GPER agonist G-1. We found that G-1 inhibited proliferation in a dose-dependent manner and caused G2/M cell cycle arrest of endometrial stromal cells, leading to induction of caspase-3–dependent apoptosis.[65] Interestingly, these inhibitory effects might unexpectedly be caused independently of GPER.[65] Although our findings imply that G-1 might be applicable as a therapeutic drug for endometriosis, further careful investigation to understand the functional mechanism of GPER will be needed.

5 | CONCLUSIONS

Although the pathogenesis of endometriosis remains unclear, it is apparent from previous basic studies and clinical evidence that it is an estrogen-dependent disease. However, the disease cannot be explained by simple proliferative activity mediated by the classical estrogen receptor. In addition to the expression of several estrogen receptors, the activities mediated by numerous regulatory factors could play important roles in disease development by forming a complicated network. Nonetheless, it still appears that the most important target factors for treatment and future research are local estrogen production in endometriotic tissues and estrogen activities via the estrogen receptors. Further investigation of these is required.

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DISCLOSURE

The study with human and animal patients was approved by the Institutional Review Board of the Kyoto Prefectural University of Medicine (ERMR-C-1180-1, ERB-E-306). All authors declare that they have no conflict of interest.

ORCID

Taisuke Mori https://orcid.org/0000-0002-9792-4132
Khaleque N. Khan https://orcid.org/0000-0002-9493-3340

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