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Review Article

The elusive and controversial roles of estrogen and progesterone receptors in human endometriosis

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Abstract: Endometriosis is a complex and challenging disease that involves aberrant adhesion, growth, and progression of endometrial tissues outside of the uterine cavity, and there is evidence to suggest that estrogen plays a key role in its development and progression. Numerous in vivo clinical studies have described the ectopic expression and regulation of estrogen receptor (ER) and progesterone receptor (PR) in the different types of endometriosis compared to normal or eutopic endometrium. However, we have noticed that conflicting and contradictory results have been presented in terms of ER subtype (ERα and ERβ) and PR isoform (PRA and PRB) expression. Both ER and PR are transcription factors and ER/PR-mediated responses depend on the coordinated, opposing, and compensatory functions of ER subtypes and PR isoforms. Moreover, analysis of the uterine phenotypes of ERα/ERβ and PRA/PRB knockout mice indicates that different ER subtypes and PR isoforms mediate distinct responses to steroid hormones and play different roles in uterine function. In this review, we outline studies that have elucidated the molecules and signaling pathways that are linked to ER and/or PR signaling pathways in the development and progression of endometriosis.

Keywords: Estrogen receptor subtypes, progesterone receptor isoforms, endometrium, endometriosis

Introduction

Endometriosis is the most common gynecological disorder [1]. It affects 6%-10% of all women of reproductive age (from the onset of menstruation to menopause) in the Western world [2] and is strongly associated with infertility [3, 4]. It has major clinical implications in addition to infertility, including chronic pelvic pain, dysmenorrhea, and deep dyspareunia, and it has significant socioeconomic impacts around the world [5]. Endometriosis can be treated with pain medications, hormonal treatments, and surgery [1]. Although the etiology and pathophysiology of this disease are still not completely understood, the published data have given rise to several theories to explain the causal mechanisms behind the disease, including theories of endometrial or Müllerian duct origin and embryonic cell rest [6]. Several other disease-related risk factors have been proposed [1], and it is likely that multiple factors including genetics, epigenetics, environmental modifications, and aging are involved in the development of endometriosis [7]. It is notable that women are rarely diagnosed in the early stages of endometriosis, and no treatments currently available are capable of providing a permanent cure [1]. It has also been reported that 47% of endometrial lesions appear again after removal of endometriotic tissue in patients [8].

Endometriosis is defined as the presence of estrogen-stimulated lesions [9] that contain endometrial glands and stroma that are located outside the uterine cavity [1]. Endometrial tis-

sue implants can be located in the pelvis, abdominal cavity, or other organs including the brain, lungs, and bladder (http://endometriosis.org/endometriosis/). There are different forms of pelvic endometriosis such as ovarian, superficial peritoneal, and deep infiltrating endometriosis [10], and in the clinic the most common sites of endometriosis are the ovaries, the broad and uterosacral ligaments, and the pouch of Douglas [3]. The two processes of migration and invasion appear to be critical for the establishment of endometriosis, but there is limited knowledge about the events that lead to the aberrant adhesion, growth, and progression of endometrial tissues outside the uterine cavity [2, 5]. Although animal studies have contributed significantly to our understanding of the development and progression of endometriosis [11], the absence of spontaneous endometriosis in animal models continues to make it difficult to define the cellular and molecular mechanisms that underlie the disease.

The pathogenesis of endometriosis is multifactorial, but endogenous and exogenous estrogens are considered to be the potential modulators in the pathophysiology and/or pathogenesis of endometriosis [9, 12]. The human uterine endometrium is a complex and highly active organ that participates in reproductive functions [13]. The uterine endometrium includes epithelial cells, stromal cells, immune cells, and blood vessel cells that are targeted by ovarian steroid hormones including estrogen (principally 17β-estradiol) and progesterone [13]. Both estrogen and progesterone exert their functions by binding to their intracellular receptors, the estrogen receptor (ER) and progesterone receptor (PR), which are members of the steroid/nuclear receptor superfamily [14]. In this short review, we provide a brief of overview of ectopic ER and PR expression and regulation in endometriosis lesions compared to normal ER and PR expression in the eutopic endometrium. We also outline the studies that have described the possible ER- and PR-mediated signaling pathways that contribute to the disease.

ER subtype expression in human endometriosis

There are two structurally related ER subtypes, ERα and ERβ, that appear to have overlapping, but different, tissue expression and localization profiles and ligand specificities [15, 16]. In general, binding of the ligand to the ER results in the dissociation of heat shock proteins from the ER that allows the receptors to form dimers (ERα/ERα, ERβ/ERβ, or ERα/ERβ) [17]. These dimers can either bind to the estrogen response elements in the promoter regions of ER-regulated genes or tether themselves to the regulatory regions of target genes through interaction with other nuclear transcription factors such as activator protein complex-1 [14]. Interestingly, while hormone-activated ERα and ERβ recognize the same estrogen responsive element, the two subtypes can display diverse transactivational properties in a ligand-dependent manner when they are co-expressed [18]. In addition, ERβ also has the capacity to regulate ERα activity in estrogen target cells [19, 20].

The localization and regulation of ER subtype expression has been investigated in human endometrium during the normal menstrual cycle [13]. Although both ERα and ERβ are present in endometrial glands and stroma, ERα is likely to be the primary mediator of the estrogenic action in this tissue [21]. During the secretory phase, the levels of ERα are decreased in all endometrial cell components, but the levels of ERβ are decreased only in endometrial epithelial cells. Although the roles of estrogen in endometriosis are obvious [9], there have been controversies regarding the levels of ER subtype expression in different types of endometriosis (**Table 1**). While several studies have demonstrated that expression of ERα mRNA [12, 22-27] and protein [23, 27-35] is decreased in endometriosis lesions compared to normal uterine tissues (except for one report [36]), the regulation of ERβ mRNA and protein in ovarian endometriosis has been shown either to be similar [24, 29-32, 35, 37], or the opposite [12, 25, 38] compared to normal uterine tissues. Moreover, in peritoneal endometriosis mRNA and protein expression both ER subtypes fails to follow a consistent and regular pattern [12, 23-27, 33, 34]. Although the decreased expression of both ER subtype mRNA has been found in deep infiltrating endometriosis [9, 12], the regulation of the protein levels of the receptor has not been studied. Furthermore, an increased ratio of ERβ mRNA to ERα mRNA in ovarian [22, 33] and peritoneal [39] endometriosis compared to normal endometrial tissues indicates that regulation of relative expression levels of the ER sub-

Table 1. Estrogen and progesterone receptor expression in different types of endometriosis

Steroid hormone receptor	Gene Symbol	Types of endometriosis		References
		Ovarian (extra-ovarian)	Peritoneal	
Estrogen receptor	ERα, ESR1	ERα mRNA decreased in the stroma (qRT-PCR, SB)		[22]
		ERα mRNA decreased (qRT-PCR)	ERα mRNA was unchanged (qRT-PCR)	[12]
		ERα mRNA decreased (qRT-PCR, ISH)	ERα mRNA decreased (qRT-PCR, ISH)	[24]
		ERα mRNA decreased (qRT-PCR)		[23, 26, 27]
			ERα mRNA increased (qRT-PCR)	[25]
		ERα protein decreased (WB)		[27, 28]
			ERα mRNA (ISH) and protein (IHC) increased in the glands	[38]
		ERα protein decreased in the glands (IHC)	ERα protein decreased in the glands (IHC)	[32]
		ERα protein decreased (IF, EIA, DCC)	ERα protein decreased (IF, EIA, DCC)	[29, 30]
			ERα protein decreased in the glands (ICC)	[31]
		ERα protein decreased (ELISA)		[23]
		ERα protein decreased in both the glands and the stroma (IHC)		[33, 34]
		ERα protein decreased in the stroma (IHC)	ERα protein decreased in the stroma (IHC)	[35]
		ERα protein increased in both the glands and the stroma (IHC)		[36]
			ERα protein increased (IHC)	[25]
			ERα protein decreased in the stroma (IHC)	[37]
	ERβ, ESR2	ERβ mRNA increased (qRT-PCR, SB)		[33]
		ERβ mRNA increased (qRT-PCR)	ERβ mRNA was unchanged (qRT-PCR)	[12]
		ERβ mRNA increased during the secretory phase (qRT-PCR, ISH)	ERβ mRNA decreased during the proliferative phase (qRT-PCR, ISH)	[24]
		ERβ mRNA increased (qRT-PCR)		[23, 26, 27]
			ERβ mRNA increased (qRT-PCR)	[25]
		ERβ protein increased (ELISA)		[23]
		ERβ protein decreased in both the glands and the stroma (IHC)		[33]
		ERβ protein increased in both the glands and the stroma (IHC)		[34]
			ERβ protein increased (IHC)	[25]
		ERβ protein increased (WB)		[27]
	ERβ:ERα	ERβ:ERα mRNA ratio increased		[22, 33]
			ERβ:ERα mRNA ratio increased	[39]

Progesterone receptor	PRA/B, PGR	PR mRNA was unchanged (qRT-PCR)		[26]
		PR mRNA decreased in the stroma (qRT-PCR)		[23, 27]
		PR protein decreased in the glands (IHC)	PR protein decreased in the glands (IHC)	[32]
		PR protein decreased (IF, EIA, DCC)	PR protein decreased (IF, EIA, DCC)	[29, 30]
			PR protein decreased in the glands (ICC)	[31]
			PR protein was present in both the glands and the stroma (IHC)	[39]
		PR protein decreased (IHC)		[23]
		PR protein decreased in the stroma, but increased in the glands during the secretory phase (IHC)		[36]
			PR protein increased in the glands (IHC)	[38]
			PR protein was unchanged (IHC)	[35]
	PRA	PRA protein decreased (WB, IP)		[28]
			PRA protein was present in the stroma (IHC)	[39]
			PRA protein decreased in both the glands and the stroma (IHC)	[37]
	PRB	PRB mRNA decreased in the stroma (qRT-PCR)		[27]
		PRB protein was absent (WB, IP)		[28]
			PRB protein was present in the stroma (IHC)	[39]

qRT-PCR, quantitative real-time reverse transcription polymerase chain reaction; SB, Southern blotting; ISH, in situ hybridization; WB, western blotting; IHC, immunohistochemistry; ICC, immunocytochemistry; IF, isoelectric focusing in polyacrylamide gels; EIA, enzyme immunoassay; DCC, dextran-coated charcoal assay; IP, immunoprecipitation.

types seems to differ between normal, eutopic, and ectopic endometria.

Although recent studies have led to the identification of a G-protein-coupled ER (GRER) that specifically mediates endometrial proliferation in mice and myometrial contractility in humans under physiological conditions [40], the regulation and possible functions of GRER in endometriosis have not yet been defined.

PR isoform expression in human endometriosis

The uterine response to progesterone is dependent on PRs [41, 42]. Like ERs, ligand binding causes release of the heat shock protein complex and the PR undergoes a conformational change that allows the receptor dimer to interact with specific progesterone response elements located within the regulatory regions of its target genes [43]. The two predominant isoforms of the PR, PRA and PRB [44], are both encoded by the same PR gene but use alternative promoters and translation start sites. PRA lacks the N-terminal 164 amino acids of PRB [45]. When expressed in an equimolar ratio in cells, PRA and PRB can either homodimerize (PRA/PRA and PRB/PRB) or heterodimerize (PRA/PRB) [46], and the relative expression of the two isoforms varies dramatically in different tissues, cell types, physiological states, and diseases [43, 44]. It has been shown that the two PR isoforms are not functionally equivalent, and in vitro experiments show that PRA functions as a transcriptional inhibitor of PRB when PRA and PRB are co-expressed [45].

In human endometrium, the levels of PR isoform expression are differentially regulated during the normal menstrual cycle [13]. For example, PRA is the predominant PR isoform and persists in the stroma, but the expression of both PR isoforms is decreased in endometrial epithelial cells during the secretory phase [13]. Similar to ER subtype expression, contradictory results have been reported for PR isoforms in different types of endometriosis (**Table 1**). PRA/B, PRA, or PRB mRNA and protein expression are decreased or absent in ovarian endometriosis [23, 26-30, 32] in a cell-type specific manner [36]. Again, PRA/B mRNA and protein expression fails to show a consistent and regulated pattern in peritoneal endometriosis [29-32, 35-39]. Interestingly, in addition to regulation by progesterone, the expression of PR subtypes is up-regulated by estrogen stimulation in the endometrium [13]. For example, it has been shown that treatment with 17β-estradiol induces PRB expression more than PRA expression in human endometrium [47]. However, it has not yet been established why a decreased expression of PR subtypes occurs in estrogen-dependent endometriosis.

Progesterone also acts through different membrane-bound PRs that mediate non-genomic activities [48]. Several studies have shown that membrane-bound PRs appear to be expressed and regulated not only in normal human endometrium in a cycle-dependent manner [49] but also in the endometriosis lesions [50, 51].

Progesterone resistance implies a decreased responsiveness of target tissue to bioavailable progesterone [52], and such an impaired progesterone response is seen in women with endometriosis and is suggested to contribute to the pathogenesis of this disease [21, 53]. Thus, further research on the mechanism of PR regulation and progesterone resistance in endometriosis is warranted.

Regulation of ER and PR expression in human endometriosis

There is compelling evidence that DNA methylation [54] is involved in the regulation of endometrial changes in women during the menstrual cycle [55-57]. It has been reported that the levels of DNA methyltransferase (DNMT) 1, 3a, and 3b mRNA are increased in endometriosis compared to normal and eutopic endometria [58]. Besides transcription and translation, ER and PR undergo post-translational modifications, and several studies have shown that DNA methylation of ERβ and PRB is altered in endometriosis [27, 59]. Thus, there is considerable evidence to suggest that aberrant DNA methylation status might contribute to the aberrant regulation of ERβ and PRB expression in endometriosis.

Alterations of uterine function in ER- and PR-knockout mice

Studies of mutant mice lacking two ER subtypes have provided important insights into the physiological function of ER subtypes in the regulation of uterine function [60]. For example, deletion of ERα and ERβ together or deletion of

just ERα inhibits endometrial growth and leads to a decrease in estrogen target gene expression, whereas deletion of ERβ does not affect the biological responses of the uterus to estrogen. Recently, Burns and colleagues have used the reciprocal uterine transfer technique to create different ER subtype knockout mice and have demonstrated that estrogen-regulated signaling responses are predominately mediated by ERα in endometriosis-like lesions [61].

PRA/B knockout studies have revealed that endometrial epithelial cells become hyperplasic, which is the opposite of estrogen-induced cell proliferation [62]. Moreover, mice specifically lacking uterine PRA but not PRB fail to display progesterone-induced inhibition of estrogen-induced cell proliferation, and this results in uterine dysfunction and infertility [63]. PR knockout mice created with the reciprocal uterine transfer technique show an increase in the size of endometriosis lesionss, and this estrogen-dependent growth effect is unable to be suppressed by progesterone [64].

Cross talk between ER and PR in mice is known to occur. For example, treatment with estrogen in ERα and ERβ knockout mice is not able to up-regulate uterine PR expression [65, 66]. Whether ER subtypes and PR isoforms are co-expressed and how they interact each other in the same cells in endometriosis remains to be addressed, but animal studies indicate that imbalances in ER and PR expression and aberrant interactions between the two receptor signaling pathways might be involved in the ectopic implantation and growth of uterine tissue. These knockout mouse models provide a useful experimental system for unraveling the steroid hormone receptor-induced ectopic implantation process of uterine tissues and affect the development and progression of endometriosis. These mouse models have also helped to identify ER- and PR-mediated signaling pathways in the endometriotic tissue.

Possible signaling pathways in human endometriosis

The exact role of the peritoneum in the establishment and maintenance of endometriosis has been elusive, as recently reviewed [4]. Multiple molecules and signaling pathways have been speculated to participate in the pathogenic progression of endometriosis lesions [3-5, 7], including 17β-hydroxysteroid-dehydrogenases [67, 68], steroid receptor coactivator-1 [69], adhesion/attachment/invasion proteins [70, 71], disintegrin and metalloproteinases [72], nuclear factor-kappa B [73], Wnt/β-catenin [74], and the mitogen-activated protein kinase and phosphatidylinositol 3'-kinase/AKT [75] signaling pathways. These molecules and signaling pathways are either directly linked to estrogen synthesis and ER and PR activation or interact with ER and PR signaling pathways at different levels through signaling molecules downstream of the receptor. Therefore, it is interesting to determine to what extent ER subtype and PR isoform-mediated pathological effects are connected to these molecules and signaling pathways in the development and progression of endometriosis.

Conclusion and future directions

Endometriosis is an estrogen-dependent gynecological disease that originates from anatomical and biochemical aberrations in endometrial function [1, 2]. The unclear etiology and pathophysiology of this disease hampers successful endocrine therapies, and previous studies suggest that the responses of different endometrial cells to estrogen and progesterone differ under physiological conditions. However, in reviewing the literature it is somewhat difficult to obtain a clear picture of ER subtype and PR isoform expression in human endometriosis. We suggest that the possible existence of differential regulation of ER subtype and PR isoform expression in endometriotic tissues found in the literature might be accounted for by the different types of endometriosis, unmatched phase comparison during the menstrual cycle, endometriotic tissue heterogeneity, differences in sample sizes and analytical methods, and the use of different antibodies. Given that different forms of pelvic endometriosis might have different cell origins [10], the localization and regulation of cell-type specific ER subtypes and PR isoforms in different types of endometriosis are speculative and remain to be investigated. Because of the diverse dimerization and transactivational properties of ER subtypes and PR isoforms, it is worthwhile to determine if the aberrant ratios of ER subtypes and PR isoforms contribute to, or are a consequence of, endometriosis. Furthermore, the molecular mechanisms underlying ER- and PR-mediated endometriotic tissue responses need to be better

understood. Elucidation of the functionality of ER subtypes and PR isoforms will be the turning point in our understanding of the aberrant adhesion, growth, and progression of endometrial tissues outside of the uterine cavity.

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Disclosure of conflict of interest

The authors have nothing to disclose.

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