


Endometriosis and nuclear receptors

Bahar D. Yilmaz  and Serdar E. Bulun *

Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, 250 E. Superior Street, Chicago, IL 60611, USA

*Correspondence address. Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, 250 E. Superior Street, Room 3-2306, Chicago, IL 60611, USA. E-mail: s-bulun@northwestern.edu  orcid.org/0000-0003-0850-8637

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BACKGROUND: Endometriosis is recognized as a steroid-dependent disorder; however, the precise roles of nuclear receptors (NRs) in steroid responsiveness and other signaling pathways are not well understood.

OBJECTIVE AND RATIONALE: Over the past several years, a number of paradigm-shifting breakthroughs have occurred in the area of NRs in endometriosis. We review and clarify new information regarding the mechanisms responsible for: (i) excessive estrogen biosynthesis, (ii) estrogen-dependent inflammation, (iii) defective differentiation due to progesterone resistance and (iv) enhanced survival due to deficient retinoid production and action in endometriosis. We emphasize the roles of the relevant NRs critical for these pathological processes in endometriosis.

SEARCH METHODS: We conducted a comprehensive search using PubMed for human, animal and cellular studies published until 2018 in the following areas: endometriosis; the steroid and orphan NRs, estrogen receptors alpha (ESR1) and beta (ESR2), progesterone receptor (PGR), steroidogenic factor-1 (NR5A1) and chicken ovalbumin upstream promoter-transcription factor II (NR2F2); and retinoids.

OUTCOMES: Four distinct abnormalities in the intracavitary endometrium and extra-uterine endometriotic tissue underlie endometriosis progression: dysregulated differentiation of endometrial mesenchymal cells, abnormal epigenetic marks, inflammation activated by excess estrogen and the development of progesterone resistance. Endometriotic stromal cells compose the bulk of the lesions and demonstrate widespread epigenetic abnormalities. Endometriotic stromal cells also display a wide range of abnormal NR expression. The orphan NRs NR5A1 and NR2F2 compete to regulate steroid-synthesizing genes in endometriotic stromal cells; NR5A1 dominance gives rise to

excessive estrogen formation. Endometriotic stromal cells show an abnormally low ESR1:ESR2 ratio due to excessive levels of ESR2, which mediates an estrogen-driven inflammatory process and prostaglandin formation. These cells are also deficient in PGR, leading to progesterone resistance and defective retinoid synthesis. The pattern of NR expression, involving low ESR1 and PGR and high ESR2, is reminiscent of uterine leiomyoma stem cells. This led us to speculate that endometriotic stromal cells may display stem cell characteristics found in other uterine tissues. The biologic consequences of these abnormalities in endometriotic tissue include intense inflammation, defective differentiation and enhanced survival.

WIDER IMPLICATIONS: Steroid- and other NR-related abnormalities exert genome-wide biologic effects via interaction with defective epigenetic programming and enhance inflammation in endometriotic stromal cells. New synthetic ligands, targeting PGR, retinoic acid receptors and ESR2, may offer novel treatment options.

Key words: endometriosis / nuclear receptors / stem cells / SF-1 / ESR2 / NR2F2 / PGR / progesterone resistance / retinoids

Introduction

The traditional definition of endometriosis, i.e. the presence of endometrial tissue outside of the endometrial cavity, narrowly focuses on the anatomical disease, yet lesions may not always be visualized with laparoscopy, and the extent and severity of the pelvic disease may not correlate with its often debilitating symptoms, including chronic pelvic pain and infertility (Stovall *et al.*, 1997; Milingos *et al.*, 2003). In view of recent clinical and molecular advances in our understanding of pelvic endometriosis, it is more appropriately defined as an estrogen-dependent and inflammatory disorder associated with

reconditioning of the peripheral and central nervous systems for pain perception and infertility (Giudice and Kao, 2004; Bulun, 2009).

Repeated episodes of ovulatory menses represent the single most important risk factor for developing endometriosis (Vercellini *et al.*, 2014). Even macroscopically invisible implants may lead to persistent pain yet respond to suppression of ovulation (Khan *et al.*, 2014). The disruption of menses usually provides relief from endometriosis symptoms (Fang *et al.*, 2002; Vercellini *et al.*, 2011). Inhibition of local estrogen production via aromatase inhibitors may further improve symptom relief (Takayama *et al.*, 1998; Soysal *et al.*, 2004). This emphasizes the paramount importance of estrogen to the pathogenesis of endometriosis: estrogen promotes endometriotic cell survival, inflammation and lesion progression (Bulun *et al.*, 2010; Monsivais *et al.*, 2016).

In addition to estrogen dependence, another striking feature of endometriosis is the availability of the full set of steroidogenic enzymes enabling de-novo synthesis of estradiol (Attar *et al.*, 2009; Bulun, 2009). It was also proposed that estrone sulfate may act as a reservoir for local estradiol formation in endometriotic tissue (Smuc *et al.*, 2007). Current treatment regimens focus on total interruption of estrogen signaling and ovulation suppression via hormonal agents (Johnson and Hummelshoj, 2013). An ideal therapy for endometriosis would be a high-precision approach that targets local production or action of estrogen or other steroids. Steroid hormones act primarily via binding to their nuclear receptors (NRs). Understanding the distinct roles of NRs in the pathogenic processes of endometriosis may reveal opportunities for development of novel therapeutic approaches. This review focuses on key NRs that play crucial roles in local estrogen synthesis, steroid hormone action and steroid hormone availability in the pathogenesis of endometriosis.

NRs comprise a superfamily of conserved transcription factors, mostly regulated by small lipophilic ligands and cellular signaling pathways (Germain *et al.*, 2006). There are 48 members of the NR superfamily in humans (Yin *et al.*, 2013). These receptors function as monomers and homo/heterodimers that directly regulate transcription of hormone-inducible genes (Germain *et al.*, 2006) (Fig. 1). Estrogen receptors alpha and beta (ESR1 and ESR2) and progesterone receptor (PGR) are the key steroid receptors involved in the pathophysiology of endometriosis (Attia *et al.*, 2000; Monsivais *et al.*, 2014). In endometrial stromal cells, progesterone regulates retinoic acid production and action (Pavone *et al.*, 2010). Retinoids also act via a number of NRs and are involved in normal endometrial function

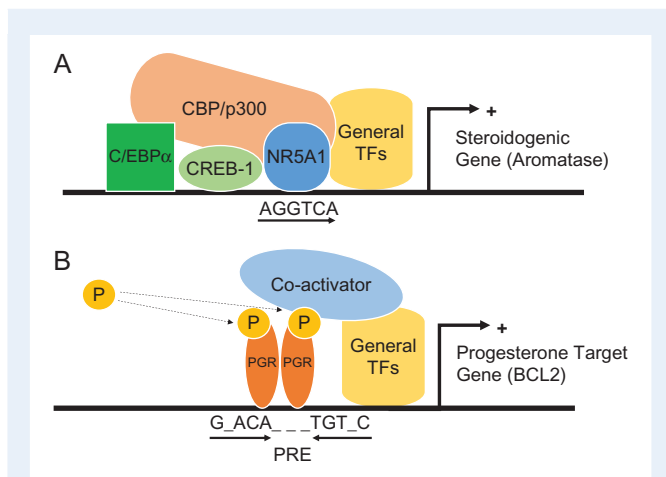


Figure 1 Examples of nuclear receptor action in endometriotic and normal uterine cells. (A) NR5A1 is an orphan nuclear receptor that directly binds to DNA as a monomer. It assembles a transcriptional complex capable of initiating the expression of steroidogenic genes in endometriotic stromal cells (Yang *et al.*, 2002; Bulun *et al.*, 2005). (B) In leiomyoma smooth muscle cells, a homodimer of PGRs liganded with progesterone (P) bind to a specific progesterone response element (PRE) and assemble a specific complex including a co-activator to start transcription of progesterone target genes such as BCL2 (Bulun, 2013). BCL2, B-cell lymphoma-2; C/EBPα, CCAAT/enhancer binding protein-α; CREB-1, cAMP response element binding protein 1; CBP, CREB-binding protein; PGR, progesterone receptor; NR5A1, steroidogenic factor-1; TFs, transcription factors.

and endometriosis (Pavone *et al.*, 2011). The NRs without known ligands, i.e. orphan NRs, steroidogenic factor-1 (NR5A1) and chicken ovalbumin upstream promoter-transcription factor II (NR2F2) also play critical roles in regulating local estrogen concentrations in endometriosis (Zeitoun *et al.*, 1999; Attar *et al.*, 2009; Bernardi *et al.*, 2018).

Methods

A comprehensive search of the PubMed database was conducted to identify peer-reviewed literature published in English until June 2018, pertinent to the roles of NRs in endometriosis pathogenesis and progression. The search included the keywords either alone or in combination with 'endometriosis': estrogen receptor alpha, estrogen receptor beta, retinoic acid receptor (RAR), PGR, steroidogenic factor-1, chicken ovalbumin upstream promoter-transcription factor II, endometrial stem cells. Both animal and human studies were reviewed for this article.

NR5A1 and NR2F2

NR5A1, also known as SF-1, is an orphan NR because it does not have a well-defined natural ligand (Luo *et al.*, 1994). NR5A1 plays a critical role in regulating steroidogenic pathways in the adrenal gland, testis and ovary (Luo *et al.*, 1994; Hanley *et al.*, 2000). While NR5A1 expression is barely detectable in the eutopic endometrium, its mRNA level is ~12 000-fold higher in endometriosis (Xue *et al.*, 2007b). In the endometriotic stromal cells, NR5A1 is essential for supporting high levels of proteins and enzymes that drive the serial conversion of cholesterol to estradiol (Attar *et al.*, 2009; Bernardi *et al.*, 2018). NR5A1 binds the promoters and stimulates the expression of steroidogenic acute response protein (StAR), side chain cleavage enzyme (CYP11A1), 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2), 17 β -hydroxylase/17,20-lyase (CYP17A1) and aromatase (CYP19A1) (Attar *et al.*, 2009; Bernardi *et al.*, 2018).

NR5A1 serves as a key downstream mediator of prostaglandin E₂ (PGE₂) action (Sirianni *et al.*, 2009). Estradiol- and cytokine-induced stimulation of cyclooxygenase-2 (COX-2) leads to overproduction of PGE₂, which in turn binds to its receptor on endometriotic stromal cells and elevates intracellular levels of cAMP (Noble *et al.*, 1997; Tamura *et al.*, 2002, 2004; Sun *et al.*, 2003; Wu *et al.*, 2005). Downstream of the PGE₂-cAMP pathway, NR5A1 binds to the promoters of multiple steroidogenic genes such as StAR and aromatase, which leads to formation of large quantities of estradiol (Bulun *et al.*, 2005; Attar *et al.*, 2009).

PGE₂-induced expression of aromatase is opposed by various transcriptional repressors in the healthy endometrium, such as NR2F2 (also known as COUP-TFII) (Zeitoun *et al.*, 1999). NR2F2 is another orphan NR that regulates a subset of genes involved in cell adhesion, angiogenesis and inflammation; these genes are also important for endometriosis progression (Li *et al.*, 2013). Silencing *Nr2f2* in cell lineages of mouse uterus results in decidualisation failure (Kurihara *et al.*, 2007), whereas the depletion of NR2F2 in the human endometrial stromal cells selectively upregulates genes involved in inflammation and cell adhesion (Li *et al.*, 2013). In contrast to high levels of NR5A1, NR2F2 mRNA and protein levels are significantly lower in ectopic endometriotic lesions compared with normal eutopic

endometrium (Li *et al.*, 2013; Lin *et al.*, 2014). This downregulation may be due to the inflammatory cytokines and interleukins in peritoneal fluid in women with endometriosis, as IL-1, TNF- α and TGF- β 1 have been shown to reduce NR2F2 transcript and protein levels (Lin *et al.*, 2014). In the normal endometrium, the promoter regions of the aromatase and StAR genes are occupied by NR2F2 and not by NR5A1. Promoter-bound NR2F2 inhibits expression of steroidogenic genes, while endometriotic stromal cells override this inhibition via NR5A1 binding to chromatin with higher affinity (Zeitoun *et al.*, 1999).

Thus, when NR5A1 is absent, NR2F2 carries out its inhibitory action on the steroidogenic pathway at various steps simultaneously to create a fail-safe system for the maintenance of normal endometrial stromal cell function in healthy endometrium (Bulun, 2009). When substantial levels of NR5A1 are present, however, NR5A1 binds to steroidogenic gene promoters with higher affinity, thus successfully competing with NR2F2 in endometriotic cells to activate the steroidogenic cascade, resulting in an estrogen-producing cell phenotype similar to that of ovarian granulosa cells.

Regulation of NR5A1 expression and activity in endometriotic cells

The remarkably higher expression of NR5A1 in the endometriotic stromal cells compared with normal endometrium is maintained via various epigenetic mechanisms such as DNA methylation, histone modification and post-transcriptional regulation (Bulun, 2009). Genome-wide methylation studies show that functionally important genes in endometriosis are differentially expressed in accordance with their aberrant methylation status (Dyson *et al.*, 2014; Yotova *et al.*, 2017). Hypomethylation of a critical CpG island at the promoter region of *NR5A1* is accompanied by remarkably high *NR5A1* mRNA expression in stromal cells collected from ovarian endometriomas (Xue *et al.*, 2007b; Yamagata *et al.*, 2014). In contrast, hypermethylation of two specific intragenic regions of the *NR5A1* gene in endometriotic stroma compared to normal endometrium also increase *NR5A1* expression: one CpG island spans from exon II to intron III and another is located in intron I (Xue *et al.*, 2011, 2014). Correlation between the location of CpG islands and *NR5A1* expression demonstrates that methylation of different genomic regions generates opposite effects on transcriptional activity; expression of *NR5A1* increases with hypermethylation of intragenic CpG islands and hypomethylation of CpG islands around the promoter site (Dyson *et al.*, 2014). Additionally, treating normal endometrial stromal cells with the demethylating agent 5-aza-2'-deoxycytidine induces a 55-fold increase in *NR5A1* mRNA expression, reinforcing the crucial role of methylation status in determining *NR5A1* expression (Xue *et al.*, 2007b). In addition to the differential methylation status, enrichment of acetylated histones 3 and 4 in the *NR5A1* promoter in endometriotic tissues shows that differential acetylation of histones may also contribute to *NR5A1* overexpression (Monteiro *et al.*, 2014). These epigenetic aberrations alter chromatin availability, allowing various transcription factors such as upstream stimulatory factor-2 to interact with the promoter region of *NR5A1* in endometriotic stromal cells (Xue *et al.*, 2007b; Utsunomiya *et al.*, 2008).

Post-transcriptional modifications may also have a role in regulating NR5A1 levels. Micro RNAs (miR) interact with mRNAs to accelerate their degradation or interfere with their translation (Bartel, 2009). Several types of miR have altered gene expression in the eutopic endometrium of women with endometriosis compared to disease-free women (Pan and Chegini, 2008; Ohlsson Teague et al., 2009; Filigheddu et al., 2010). miR23a and miR23b levels are lower in endometriosis and in the eutopic endometrium of women with endometriosis, and they inversely correlate with NR5A1 levels, yet NR5A1 is not a direct target of miR23a and miR23b (Shen et al., 2013). As an example of a post-translational regulatory mechanism, direct phosphorylation of NR5A1, via selective stimulation of the membrane-bound estrogen receptor GPR30, increases NR5A1 transcriptional activity, leading to induction of aromatase expression in endometriotic stromal cells (Lin et al., 2009).

Estrogen receptor beta

The biologically active estrogen estradiol acts via nuclear estrogen receptors to regulate growth of the endometrial tissue (Huhtinen et al., 2012). The nuclear estrogen receptor subtypes are ESR1 and ESR2, which are encoded by different genes but have 96% similarity in their DNA binding domains (Mosselman et al., 1996). While ESR1 and ESR2 are both present in the endometrium, ESR1 expression dominates, and estrogen-dependent proliferation is mediated mainly through ESR1 (Matsuzaki et al., 2001; Shang, 2006). Upon ligand binding, the estradiol/ESR1 complex acts as a transcription factor and binds to the promoters of estrogen-target genes such as the PGR to induce their expression (Weihua et al., 2000; Carroll et al., 2005; Lin et al., 2007).

Several groups have reported significantly lower levels of ESR1 both in endometriomas and cultured endometriotic stromal cells obtained from cyst walls of ovarian disease (Brandenberger et al., 1999; Fujimoto et al., 1999; Smuc et al., 2007). ESR1 mRNA expression is ~7-fold lower in stromal cells from ovarian endometriomas compared to normal endometrial stromal cells (Xue et al., 2007a). In various cancer types, methylation of CpG islands in the promoter region of the ESR1 gene is associated with gene silencing (Issa et al., 1994; Ottaviano et al., 1994). Reduced expression of ESR1 is correlated with hypermethylation of the ESR1 gene near its 3' promoter in endometriotic stromal cells (Dyson et al., 2014). Additionally, ESR2 directly downregulates ESR1 in stromal cells derived from ovarian endometriosis (Trukhacheva et al., 2009). ESR2 binds to alternatively used promoter regions of the ESR1 in the presence of estradiol and suppresses its expression (Grandien, 1996; Donaghue et al., 1999; Trukhacheva et al., 2009).

In endometriotic tissue, there is a switch from ESR1 to ESR2 dominance. RNA expression of ESR2 is 40- to 140-fold higher in stromal cells obtained from ovarian endometriomas compared to healthy eutopic endometrial stromal cells (Smuc et al., 2007; Xue et al., 2007a; Yang et al., 2015). ESR2 expression is also higher in the eutopic endometrium of women with endometriosis compared to disease-free women; suggesting that high levels of ESR2 in the endometrium increase the risk of developing endometriosis (Han et al., 2012; Monsivais et al., 2014). The abnormally high ESR2:ESR1 mRNA ratio in endometriotic stromal cells reaches an ~800-fold difference compared with normal endometrial stromal cells (Xue et al., 2007a).

The ESR2:ESR1 protein ratio is also higher in endometriotic versus endometrial stromal cells (Xue et al., 2007a).

Cause of high ESR2 expression in endometriotic cells

Studies investigating the association between ESR2 polymorphisms and endometriosis risk have reported inconsistent results; a meta-analysis comparing eight studies concluded that the previously suggested polymorphisms were associated with bias rather a real risk for endometriosis (Guo et al., 2014). Hypomethylation of a CpG island in the promoter of the ESR2 gene was seen in endometriotic stromal cells, whereas the same sequence was hypermethylated and therefore silenced in normal endometrial stromal cells (Xue et al., 2007a). Treatment of endometrial stromal cells with the demethylating agent, 5-aza-2-deoxycytidine, significantly increased ESR2 mRNA levels, suggesting that differential methylation is a major mechanism driving ESR2 upregulation in endometriosis (Xue et al., 2007a). DNA methyltransferase (DNMT) 1 and DNMT3B mRNA and protein are differentially expressed in endometriotic cells or lesions in comparison to normal endometrium from disease-free women (van Kaam et al., 2011; Dyson et al., 2015; Hsiao et al., 2015). Differential binding activity of DNMT3B to NR5A1 and ESR1 promoters in endometriotic versus normal endometrial stromal cells suggests that this enzyme might play a role in abnormal gene expression in endometriosis (Dyson et al., 2015). The relationship between DNMT expression levels and ESR2 promoter hypomethylation in endometriosis remains to be discovered.

Biological consequences of ESR2 overexpression in endometriosis

Aberrantly high ESR2 levels regulate several pathological processes in endometriotic tissue including proliferation, inhibition of apoptosis, inflammation and pain transmission (Monsivais et al., 2014; Han et al., 2015). Genome-wide chromatin immunoprecipitation approaches identified a total of 70 genes that had an ESR2 binding site and that also were differentially expressed in normal endometrium versus endometriosis (Monsivais et al., 2014; Han et al., 2015). In particular, estradiol induces ESR2 enrichment at the promoter region of the Ras-like and estrogen-regulated growth inhibitor (RERG) gene. PGE₂, via protein kinase A, phosphorylates RERG and enhances its nuclear translocation, inducing the proliferation of primary endometriotic cells (Monsivais et al., 2014). Another estradiol-regulated ESR2 target gene, serum and glucocorticoid-regulated kinase (SGK1), is also induced by PGE₂ and contributes to survival of endometriotic cells via inhibition of apoptosis (Monsivais et al., 2016). The key role of ESR2 in proliferation and survival of endometriotic cells is further supported by studies in a mouse model of endometriosis expressing high levels of ESR2 in endometriosis lesions. The inhibition of ESR2 activity by an ESR2-selective estrogen antagonist suppresses lesion growth in these animals, whereas gain of ESR2 function stimulates the progression of endometriosis (Han et al., 2015). Mechanistically, this work also reveals that ESR2 interacts with components of the cytoplasmic inflammasome to increase IL-1 β , thus contributing to cellular adhesion and proliferation (Han et al., 2015).

Endothelial cells in the human endometrium express ESR2 but not ESR1 (Critchley et al., 2001; Tamura et al., 2004). In addition, estradiol

via ESR2 rapidly induces COX-2 expression in uterine endothelial cells (Critchley *et al.*, 2001; Tamura *et al.*, 2004). Thus, it is tempting to speculate that ESR2 may have a major role in regulating COX-2 levels in endometriosis. ESR2 signaling integrates inflammatory and pain pathways; macrophage infiltration of endometriosis increases in response to estradiol (Greaves *et al.*, 2015). ESR2-immunoreactive macrophages contribute to inflammation by mediating nerve-growth in a mouse model (Greaves *et al.*, 2015). Treatment of sensory neurons with diarylpropionitrile (DPN), an ESR2-selective estrogen agonist, results in upregulation of the capsaicin receptor, TRPV1, which may contribute to inflammation-associated pain perception in endometriosis (Caterina *et al.*, 2000; Greaves *et al.*, 2014).

A recently developed ESR2 ligand with anti-inflammatory properties, chloroindazole, prevents lesion establishment via suppression of inflammation, and inhibits angiogenesis and neurogenesis in a mouse model without disturbing fertility (Zhao *et al.*, 2015). Moreover, the SRC-1 inhibitor bufalin, which leads to ESR2 protein degradation, induces apoptosis in endometriotic epithelial cells and inhibits proliferation of stromal cells (Cho *et al.*, 2018). Agents that inhibit ESR2-mediated inflammation may be promising novel treatment options for endometriosis without interfering with fertility. Future preclinical studies are required to determine the efficacy and safety of these agents.

Progesterone receptor

In the endometrium, progesterone exerts its effects through intracellular PGRs PGR-A and PGR-B, both of which are encoded by a single gene (Kastner *et al.*, 1990). PGR-A is a 94 kDa protein, whereas PGR-B is 114 kDa protein with 164 additional amino acids at its N-terminal (Lessey *et al.*, 1983; Alexander *et al.*, 1989). In mice, selective ablation of PGR-A results in uterine and ovarian abnormalities and female infertility, while ablation of PGR-B halts breast development only (Mulac-Jericevic *et al.*, 2000, 2003). While PGR-A is sufficient for endometrial and ovarian function in mice, in humans, the roles of PGR-A and PGR-B seem to be more complex (Mote *et al.*, 1999). Transcriptional activities of different PGR isoforms depend on the cell type as well as the promoter; e.g. in the endometrium, only PGR-A exerts repressor actions on *ESR1* (Vegeto *et al.*, 1993). Through PGR-A, progesterone acts like a brake on estradiol action in endometrial epithelium. It inhibits estrogen-induced growth and proliferation and can even reverse hyperplasia (Yang *et al.*, 2011; Kim *et al.*, 2013). This inhibitory action is mediated through stromal cells in a paracrine fashion, as *PGR* knockout endometrial tissue recombinants show that stromal PGR is essential for progesterone to antagonise estrogen-induced epithelial proliferation (Kurita *et al.*, 2000). In response to progesterone, endometrial stromal cells also take up retinol and produce retinoic acid, which induces the enzyme 17 β -hydroxysteroid dehydrogenase type 2 (HSD17B2) in endometrial epithelial cells, possibly in a paracrine fashion (Cheng *et al.*, 2008). Thus, in endometrial epithelial cells, progesterone not only antagonises the action of estrogen but also induces HSD17B2, the enzyme that converts estradiol to the less potent estrone (Yang *et al.*, 2001).

Progesterone resistance in endometriosis

The gene expression profile of endometriotic cells during the window of implantation reveals that progesterone-responsive genes such as

that for glycodelin are significantly downregulated in women with endometriosis compared to endometrial cells from disease-free women (Kao *et al.*, 2003). Further comparisons at various points during the menstrual cycle show dysregulated gene expression in the early secretory phase, with increased survival and mitotic activity (Burney *et al.*, 2007). This attenuation of progesterone responsiveness can be explained by decreased PGR levels in endometriotic cells. Despite the ability of these cells to produce large amounts of progesterone through locally expressed steroidogenic enzymes, very low levels of PGR-A are present, while PGR-B is undetectable in endometriotic tissues obtained from peritoneal lesions (Attia *et al.*, 2000). In eutopic endometrial tissue, both PGR isoforms increase throughout the proliferative phase and peak before ovulation under the influence of increasing estrogen levels; in endometriosis, PGR levels remain very low to undetectable, possibly due to an abnormally low ESR1:ESR2 ratio in endometriotic stromal cells (Bulun *et al.*, 2012).

Defective epigenetic programming may also contribute to progesterone resistance (Xue *et al.*, 2007b). Endometrial mesenchymal stem cells (eMSC) isolated from the eutopic endometrium of women with endometriosis do not properly decidualise *in vitro* in response to hormone treatment; this suggests that progesterone resistance in endometriotic tissue may be inherited from defectively programmed stem cells (Barragan *et al.*, 2016). A decreased progesterone response in mature stromal cells impedes HSD17B2 induction in epithelial cells, thus contributing to high levels of local estradiol by hindering its conversion into the biologically less active steroid estrone (Bulun *et al.*, 2006).

Mechanisms affecting PGR expression in endometriotic tissue

Associations of *PGR* gene polymorphisms with endometriosis have been reported but results are inconsistent (Wieser *et al.*, 2002; Lattuada *et al.*, 2004; De Carvalho *et al.*, 2007; van Kaam *et al.*, 2007). A meta-analysis comparing 12 studies concluded that the link between a *PGR* variant and endometriosis risk was only observed in European subjects (Pabalan *et al.*, 2014). Therefore, polymorphisms directly affecting PGR function do not likely explain the development of progesterone resistance in endometriotic tissue. The *PGR-B* promoter is hypermethylated in ectopic endometrial epithelium, which may suppress its expression in endometriosis (Wu *et al.*, 2006). In fact, treatment of an immortalized endometriotic epithelial cell line with the pro-inflammatory cytokine TNF induces hypermethylation of the *PGR-B* promoter (Wu *et al.*, 2008). Gene expression profiling in a baboon endometriosis model shows that as the disease progresses, a progesterone-resistant phenotype appears not only in the ectopic lesions but also in the eutopic endometrium (Afshar *et al.*, 2013). These observations collectively suggest that inflammation may regulate PGR expression via epigenetic reprogramming.

Additionally, miR-196a, miR-29c and miR-194-3p have been shown to be associated with progesterone resistance. miR-194-3p hinders decidualization in endometrial stromal cells via direct regulation of PGR expression (Pei *et al.*, 2018). miR-196a downregulates PGR expression via the ERK/MEK pathway and inhibits decidualisation (Zhou *et al.*, 2016). miR-29c, which is also overexpressed in eutopic endometrium of women with endometriosis and in baboon models, downregulates *PGR* by decreasing FK506-binding protein 4 (FKBP4)

levels (Yang *et al.*, 2012; Joshi *et al.*, 2017). Surgical excision of endometriosis lesions may help overcome the development of progesterone resistance by alleviating the inflammatory milieu (Joshi *et al.*, 2017).

ESR2 binds to alternatively used promoters in the *ESR1* gene and suppresses its expression in endometrial stromal cells (Trukhacheva *et al.*, 2009). *ESR1* suppression by high levels of *ESR2* in endometriosis may thus hinder *E2/ESR1*-mediated induction of *PGR* in this tissue (Trukhacheva *et al.*, 2009). It is possible that *ESR2* may also directly bind to *PGR* promoters to suppress its transcription.

Retinoids

Retinoic acid signaling and function in the endometrium

Retinoic acid is traditionally known to have anti-inflammatory effects (Schug *et al.*, 2007). Transcriptional activation through RARs may trigger differentiation, cell-cycle arrest and apoptosis (Altucci *et al.*, 2001; Kitareewan *et al.*, 2002; Donato and Noy, 2005). Alternatively, retinoic acid can activate transcription to promote cell survival through an orphan NR, peroxisome proliferator-activated receptor beta/delta (*PPAR-β/δ*) (Shaw *et al.*, 2003). Shuttling of retinoic acid to the NRs is regulated by the intracellular lipid binding proteins, cellular retinoic acid-binding protein 2 (*CRABP2*) and fatty acid-binding protein 5 (*FABP5*), which transfer retinoic acid to *RAR* or *PPAR-β/δ*, respectively (Tan *et al.*, 2002; Schug *et al.*, 2007). Thus, the ratio of *CRABP2* and *FABP5* in a particular cell regulates retinoic acid signaling to exert either pro-apoptotic or pro-survival effects (Schug *et al.*, 2007; Çakiroğlu *et al.*, 2017).

Retinoic acid production and metabolism are crucial for endometrial decidualisation and the crosstalk between stroma and the glandular epithelium. Progesterone via *PGR* induces retinoic acid production in endometrial stromal cells, which then acts on epithelial cells to induce *HSD17B2* expression (Casey *et al.*, 1994; Cheng *et al.*, 2008). In endometriotic tissue, defective retinol uptake and retinoic acid metabolism resulting from progesterone resistance compromises the crosstalk between the stroma and epithelium (Çakiroğlu *et al.*, 2017).

Retinoic acid deficiency

Retinol uptake and retinoic acid action are impaired in endometriotic stromal cells collected from ovarian endometriomas (Pavone *et al.*, 2010). The cell surface receptor stimulated by retinoic acid 6 (*STRA6*), which is the main receptor for retinol uptake by endometrial stromal cells, is downregulated in endometriotic stromal cells compared to normal endometrial stromal cells (Pavone *et al.*, 2011). Impaired intracellular conversion of retinol to its active form, all-trans retinoic acid, and deficiency of retinol binding protein 1 (*RBPI*) also contribute to decreased availability of retinoic acid (Pavone *et al.*, 2011; Pierzchalski *et al.*, 2014). Moreover, endometriotic stromal cells express the oxidizing enzyme *CYP26B1* at higher levels, which causes a more rapid clearance of retinoids (Pavone *et al.*, 2017). Decreased availability of retinoic acid gives rise to deficiency of *HSD17B2* in the epithelial compartment. *HSD17B2* deficiency impairs the conversion of potent estradiol to its less active form estrone,

further contributing to the hyperestrogenic environment in endometriosis (Pavone *et al.*, 2011).

Anti-apoptotic effects of altered retinoid metabolism

Retinoic acid deficiency can enhance cell survival pathways in endometriosis via at least two different ways. First, decreased retinoic acid levels lead to increases in inflammatory cytokines such as *IL-6* (Wang *et al.*, 2007). In an immunocompetent mouse model, retinoic acid was shown to inhibit the development of peritoneal endometriotic implants while reducing *IL-6* and monocyte chemoattractant protein 1 levels and increasing macrophage differentiation (Wieser *et al.*, 2012). Second, retinoic acid deficiency can lead to cell growth and protect against apoptosis due to a switch in cell signaling pathways from *CRABP2/RAR* to *FABP5/PPAR-β/δ* (Schug *et al.*, 2007). *CRABP2* expression is induced by progesterone, and progesterone resistance in endometriosis severely decreases the *CRABP2:FABP5* ratio (Pavone *et al.*, 2010). *FABP5* dominance promotes the shuttling of retinoic acid to *PPAR-β/δ*, which promotes cell survival and impairs apoptosis (Pavone *et al.*, 2010). Recently, it was shown that expression of the retinoic acid-regulated autophagy marker *Beclin1* is reduced in endometriotic tissue compared to endometrium, and attenuation in autophagy may contribute to enhanced endometriotic stromal cell proliferation (Lu *et al.*, 2018). Collectively, decreased availability of retinoic acid and a switch in its intracellular signaling may favor anti-apoptotic pathways and cell survival in endometriosis.

Endometrial stem cells

The endometrium undergoes cyclical regeneration in response to the steroid hormones estradiol and progesterone (Jabbour *et al.*, 2006). The extraordinarily high regenerative capacity of this dynamic tissue led to the search for stem cell-like endometrial cell populations, characterized by the capacity for colony formation, self-renewal and differentiation. Rare stromal and epithelial cells (1.25 and 0.22%, respectively) with high proliferative capacity were identified, providing the first evidence of endometrial stem cells (Chan *et al.*, 2004; Schwab *et al.*, 2005). Following these reports, several putative endometrial stem cell populations were identified including side population cells, eMSCs and bone marrow-derived mesenchymal stem cells (BMDSCs) (Gargett *et al.*, 2016).

The side population phenotype is a universal marker for adult stem cell activity in various tissues (Challen and Little, 2006). Side population cells express ATP-binding cassette transporter (*ABCG2/Bcrp1*) on the cell surface and have the ability to efflux the DNA binding dye Hoechst 33342 (Zhou *et al.*, 2001). These perivascular cells comprise ~2% of the human endometrium distributed in the functionalis and the basalis layers and display an endothelial-cell phenotype with migration and angiogenesis abilities (Masuda *et al.*, 2010). When injected into subcutaneous tissue or the kidney capsule of *NOD-SCID* mouse, side population cells regenerate human endometrial stroma, glandular epithelium and endothelium (Cervello *et al.*, 2010, 2011; Miyazaki *et al.*, 2012). While the side population may harbor endometrial stem cells, this population is heterogeneous and isolation techniques are impractical for further applications due to isolation-associated toxicities (Cousins *et al.*, 2018).

eMSCs are self-renewing, multipotent, clonogenic stem cells that can give rise to mesodermal lineages *in vitro*. eMSCs were first isolated from the endometrium as CD146(+)/PDGFRB(+) dual positive cells and later by a novel single cell surface marker, sushi domain containing-2 (SUSD2) (Gargett and Masuda, 2010). Similar to the side population, eMSCs are located in the perivascular region and they are present in both functionalis and basalis layers (Schwab and Gargett, 2007; Masuda *et al.*, 2012). Comparison of post-menopausal and premenopausal endometrial tissues revealed eMSCs with similar self-renewal capacity and expression of SUSD2 (Ulrich *et al.*, 2014).

In addition to endogenous stem cells of the endometrium, BMDSCs may also contribute to endometrial regeneration. Endometrial biopsy of HLA-mismatched bone marrow donor recipients demonstrated donor-derived cells in the stroma and the epithelium (Taylor, 2004; Ikoma *et al.*, 2009). BMDSCs were also shown to serve as progenitor cells for endometriotic lesions (Du and Taylor, 2007). Later studies suggested that BMDSCs may differentiate into stroma or epithelium but do not contribute to the endometrial progenitor population (Cervello *et al.*, 2012). Recently, a study of a chimeric irradiated mouse model transplanted with immunofluorescent labeled marrow showed that bone marrow-derived cells that infiltrate into the epithelial and vascular compartments may be F4/80(+) macrophages (Ong *et al.*, 2018). As macrophages secrete vimentin and are weakly positive for leukocyte marker CD45, they could easily be mistaken for endometrial cells (Mor-Vaknin *et al.*, 2003; Ong *et al.*, 2018). Thus, recent evidence suggests that BMDSCs may not contribute to endometrial regeneration via trans-differentiation. Regardless, BMDSCs seem to enhance endometrial regeneration. Endometrial injury increases the engraftment of these cells to the tissue independent of sex steroid hormones (Du *et al.*, 2012). Cell therapy with autologous peripheral blood CD133+ BMDSCs significantly improves endometrial thickness and the duration and intensity of menstruation and decreases adhesion scores in patients with refractory Asherman syndrome (Santamaria *et al.*, 2016). Thus, it is conceivable that BMDSCs may improve endometrial regeneration via secreting paracrine factors to stimulate endogenous endometrial stem cells.

Stem cells in endometriosis

Based on clinical and molecular evidence, retrograde menstruation is the most plausible theory explaining the development of endometriosis, with some of the endometrial tissue effluxed to the peritoneum during menstruation (Sampson, 1927; Bulun, 2009). Yet, it is not known why endometriosis occurs only in 10% of women while retrograde menstruation through the fallopian tubes occurs in ~90% of women (Halme *et al.*, 1984). Therefore, predisposing factors are likely involved, either in the shed endometrial cells that enable survival in the peritoneal cavity or in the immune response that leads to impaired clearance of the migrated cells.

Similar to endometrium, endometriotic lesions also harbor multipotent, colony-forming MSCs (Chan *et al.*, 2011). Remarkably, MSCs and epithelial progenitor cells isolated from ovarian endometriomas do not show increased clonogenicity or self-renewal compared to endometrial stem cells, which might have explained the increased survival capacity in endometriosis (Chan *et al.*, 2011; Li *et al.*, 2014). However, because *in-vitro* culture lacks the paracrine factors unique

to the stem cell niche, it is unable to recapitulate normal physiology. It was shown that cytokines such as colony-stimulating factor-1 secreted from macrophages increase the proliferation and invasion activity of endometriotic stem cells (Chan *et al.*, 2017). Other molecular qualities of endometriotic stem cells, such as aberrant NR expression, could also give rise to a resilient phenotype.

NRs in endometrial stem cells

Endometrial side population cells are ESR2-positive, but they do not express ESR1 or PGR (Cervello *et al.*, 2011). Similarly, SUSD2(+) eMSCs are also ESR1-negative (Ulrich *et al.*, 2014). Based on their perivascular location, it is tempting to speculate that these MSCs represent the first cell type that comes into contact with steroids and growth factors transported by blood. These stem cells may respond to circulating estradiol primarily via ESR2, the predominant estrogen receptor type. In post-menopausal women, estradiol treatment increases the total number of SUSD2(+) eMSCs and the endometrial thickness proportionally (Ulrich *et al.*, 2014). This proliferation in response to estradiol could be due to ESR2-mediated growth or paracrine signaling between ESR1/PGR-positive mature stromal cells and neighboring stem cells.

The proposed stem cell signaling theory for leiomyomas can be taken as a model for the endometrium. For the stimulation of clonal expansion and growth of leiomyoma, sex steroids and steroid hormone receptors are necessary; yet, leiomyoma stem cells express barely detectable levels of ESR1 or PGR (Mas *et al.*, 2012; Ono *et al.*, 2012). The suggested mechanism for hormone action on leiomyoma stem cells proposes that differentiated stromal cells respond to circulating steroid hormones by secreting paracrine factors, which in turn stimulate stem cell proliferation and tumor expansion (Bulun, 2013). Supporting this model, it was recently shown that a PGR-positive group of cells in uterine leiomyomas secrete receptor activator of nuclear factor kappa-B ligand (RANKL) following progestin treatment, which induces proliferation of leiomyoma stem cells through its receptor RANK (Ikhenia *et al.*, 2018). Endometrial or endometriosis stem cells, which are also deficient in steroid receptors, may also be stimulated via unique paracrine signaling originating from the surrounding steroid receptor-positive cells.

Epigenetically programmed populations with stem cell characteristics may be present in eutopic endometrial tissue of women predisposed to develop endometriosis. These cells may inappropriately express high levels of pro-inflammatory (e.g. ESR2) or steroidogenic (e.g. NR5A1) factors that increase their capacity to survive outside of the uterine cavity. Upon arrival in the peritoneal cavity via retrograde menstruation, these cells would be more likely to form endometriotic lesions (Fig. 2). Thus, a combination of defective epigenetic programming combined with larger numbers of cells with stem cell characteristics could constitute a significant risk factor for developing the symptoms of pelvic endometriosis.

Novel therapeutic approaches targeting steroid receptors

Current available medical treatment options for endometriosis include combined oral contraceptives, gonadotropin-releasing hormone agonists

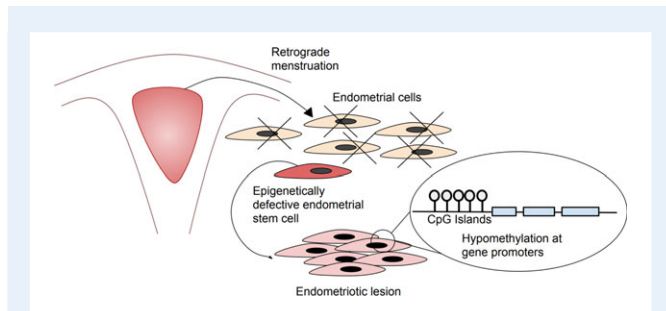


Figure 2 Role of endometrial stem cells in endometriosis pathogenesis. Normal mature endometrial cells that are shed in the peritoneal cavity through retrograde menstruation fail to attach and are absorbed. Epigenetically defective endometrial cells with stem cell characteristics display enhanced cell survival and lead to lesion formation. These endometriotic cells have hypomethylated CpG islands at promoters that regulate genes encoding critical nuclear receptors such as ESR2 and NR5A1. These nuclear receptors alter estrogen production and action and also the response to progesterone.

and antagonists, oral or injectable progestins and aromatase inhibitors (Dunselman *et al.*, 2014). Almost all available agents result in only temporary symptom relief (Bedaivy *et al.*, 2017). Since the basis of therapy is ovulation interruption and estrogen suppression, non-steroidal anti-inflammatory drugs are the only treatment option for women who wish to maintain fertility. In addition, there is no evidence to show that pregnancy outcomes improve following ovulation suppression therapy for endometriosis (Hughes *et al.*, 2007). Thus, novel therapeutic approaches with better sustainable outcomes and higher tolerability are needed.

Since estradiol is known to promote proliferation of the endometrium, several studies have tested selective estrogen receptor modulators (SERMs) to drive endometriotic lesion regression. Raloxifene and bazedoxifene both result in lesion regression and inhibition of proliferation in murine models (Yao *et al.*, 2005; Kulak *et al.*, 2011; Naqvi *et al.*, 2014). Nonetheless, a prospective randomized clinical trial of post-excision raloxifene for biopsy-proven endometriosis showed that those who received raloxifene following surgical lesion excision experienced pain sooner than the placebo arm and raloxifene did not inhibit lesion growth (Stratton *et al.*, 2008). This discrepancy may have several possible explanations. First, while ESR2 mediates estradiol-dependent anti-apoptosis and proliferation in human lesions, its expression is variable in murine models of endometriosis with ESR1 dominance in most models (Kulak *et al.*, 2011; Naqvi *et al.*, 2014). Second, raloxifene decreases proliferative markers in the epithelium of lesions in rodent models but not in the stroma, yet the stromal component is the major contributor to endometriotic lesions (Altintas *et al.*, 2010). Finally, estradiol agonism or antagonism may have direct effects on nociceptors or pain perception. ESR2 ligands acting as estrogen antagonists in endometriotic tissue show promising results in murine models and should also be considered as potential therapeutics (Zhao *et al.*, 2015).

Selective PGR modulators (SPRMs) are synthetic steroids that exert agonistic and antagonistic properties upon binding to PGR in a tissue-specific manner (Madauss *et al.*, 2007). SPRMs induce amenorrhea without causing a hypoestrogenic state or associated bone loss (Chabbert-Buffet *et al.*, 2005). These agents also reduce abnormal

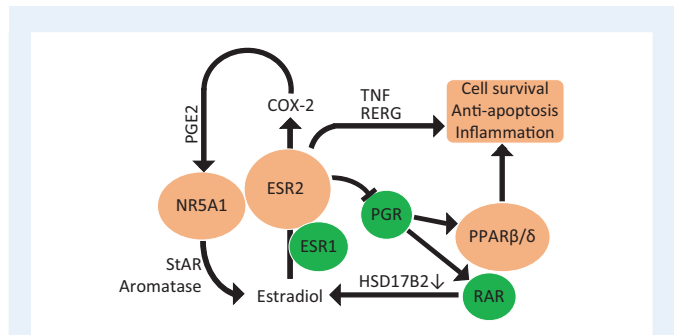


Figure 3 Molecular characteristics of steroid hormone receptors in endometriotic tissue. In endometriotic tissue, high levels of local estradiol are maintained by the upregulation of various nuclear receptors such as NR5A1 and ESR2, which are connected via feedback loops involving inflammatory factors. The abnormally low ESR1:ESR2 ratio in endometriotic stromal cells is associated with low levels of PGR, which leads to progesterone resistance and further contributes to a hyperestrogenic environment via an abnormal retinoic acid signaling pathway. COX-2, cyclooxygenase-2; ESR1, estrogen receptor alpha, ESR2, estrogen receptor beta; HSD17B2, 17 β -hydroxysteroid dehydrogenase type 2; PGE2, prostaglandin E2; PPAR β/δ , peroxisome proliferator-activated receptors beta/gamma; PGR, progesterone receptor; RAR, retinoic acid receptor; RERG, RAS-like estrogen-regulated growth inhibitor; NR5A1, steroidogenic factor 1; StAR, steroidogenic acute regulatory protein; TNF, tumor necrosis factor.

uterine bleeding that is observed with progestin treatment (Donnez *et al.*, 2015). SPRMs that primarily act as progesterone antagonists are ulipristal acetate (UPA), asoprisnil and mifepristone. UPA decreases lesion size, attenuates cell proliferation, and induces apoptosis in murine endometriosis models (Huniadi *et al.*, 2013; Liang *et al.*, 2018). Mifepristone also reduces lesion size in animal models and patients (Kettel *et al.*, 1996; Mei *et al.*, 2010). In parallel with these findings, a systematic review of 10 randomized controlled trials assessing the efficacy of SPRMs for relief of endometriosis-associated pain concluded that mifepristone relieves dysmenorrhea and dyspareunia, with insufficient evidence of efficacy and safety of other SPRMs (Fu *et al.*, 2017). SPRMs may be a promising new type of medication for clinical use, but their long-term efficacy remains to be proven (Whitaker *et al.*, 2014).

Discussion

A woman with first degree relatives with endometriosis is seven times more likely to develop endometriosis compared to those who have unaffected relatives (Simpson *et al.*, 1980). Despite some evidence that endometriosis may be an inheritable disease, no germ-line or causative somatic mutations have been reported to date (Montgomery *et al.*, 2008; Rahmioglu *et al.*, 2012). While nucleotide variants or mutations were noted sporadically in the epithelial component of ovarian endometriomas or deep-infiltrating endometriosis, stromal cells consistently lack any somatic mutations (Anglesio *et al.*, 2017). Epigenetic aberrations in endometriotic stromal cells seem to be the main contributors to the pathogenesis and progression of

endometriosis (Dyson *et al.*, 2014; Kokcu, 2016; Koukoura *et al.*, 2016). Among these epigenetic abnormalities, differential methylation of the ESR2 promoter seems to have a crucial impact. The shift from ESR1 to ESR2 dominance changes the estradiol responses and blunts estradiol induction of PGR in stromal cells, leading to reduced expression of PGR isoforms. The decreased ESR1:ESR2 ratio likely reshapes eMSC chromatin organization, giving rise to an acquired heritable progesterone resistance. Repeated exposure of the peritoneum to epigenetically defective eMSCs via menstruation precipitates formation of endometriotic lesions. Following lesion formation, estrogen via ESR2 and pro-inflammatory factors increase inflammation and survival of endometriotic cells within the lesion.

The ability of endometriotic stromal cells to express the full set of steroidogenic enzymes as well as sulfatase pathway enzymes results in remarkable amounts of local estradiol production (Rizner, 2016). Inflammation and increased PGE₂ induce steroidogenic enzymes, including aromatase and StAR, via translocation of NR5A1 to their promoter regions, which competes with NR2F2. Activation of this cascade communicates back with ESR2 through increased local estradiol, further reinforcing inflammation by increasing COX-2 levels, and creating a vicious cycle (Fig. 3). It is important to note that not only the interaction between hormone receptors and sex steroids, but also the change in hormone levels during the menstrual cycle, are the key factors of this phenotype. SPRMs seem to be effective in alleviating endometriosis-associated pain without creating a hypoestrogenic state, suggesting that repeated menstruation and ovulation may be more critical to reinforce this inflammatory environment than continuous estrogen exposure. It is possible that de-escalating the inflammatory environment will lead to epigenetic reprogramming of stem cells and help overcome progesterone resistance in the long term. New synthetic ligands targeting ESR2, PGR and RAR are promising future treatments for endometriosis. Expanding our understanding of the NR signaling mechanisms in relation to hormonal fluctuations could guide development of other novel non-hormonal therapeutic agents without disturbing fertility.

Authors' roles

B.D.Y. performed the literature search and wrote the initial draft of the article. S.E.B. revised the article. Both authors reviewed and approved the submission of the article.

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Conflict of interest

The authors declare they have no conflicts of interest.

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