Human Reproduction Update, Vol.20, No.4 pp. 467–484, 2014
Advanced Access publication on March 14, 2014 doi:10.1093/humupd/dmu002

human reproduction update

The dynamics of nuclear receptors and nuclear receptor coregulators in the pathogenesis of endometriosis

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Submitted on November 14, 2013; resubmitted on December 23, 2013; accepted on January 7, 2014

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BACKGROUND: Endometriosis is defined as the colonization and growth of endometrial tissue at anatomic sites outside the uterine cavity. Up to 15% of reproductive-aged women in the USA suffer from painful symptoms of endometriosis, such as infertility, pelvic pain, menstrual cycle abnormalities and increased risk of certain cancers. However, many of the current clinical treatments for endometriosis are not sufficiently effective and yield unacceptable side effects. There is clearly an urgent need to identify new molecular mechanisms that critically underpin the initiation and progression of endometriosis in order to develop more specific and effective therapeutics which lack the side effects of current therapies. The aim of this review is to discuss how nuclear receptors (NRs) and their coregulators promote the progression of endometriosis. Understanding the pathogenic molecular mechanisms for the genesis and maintenance of endometriosis as modulated by NRs and coregulators can reveal new therapeutic targets for alternative endometriosis treatments.

METHODS: This review was prepared using published gene expression microarray data sets obtained from patients with endometriosis and published literature on NRs and their coregulators that deal with endometriosis progression. Using the above observations, our current understanding of how NRs and NR coregulators are involved in the progression of endometriosis is summarized.

RESULTS: Aberrant levels of NRs and NR coregulators in ectopic endometriosis lesions are associated with the progression of endometriosis. As an example, endometriotic cell-specific alterations in gene expression are correlated with a differential methylation status of the genome compared with the normal endometrium. These differential epigenetic regulations can generate favorable cell-specific NR and coregulator milieus for endometriosis progression. Genetic alterations, such as single nucleotide polymorphisms and insertion/deletion polymorphisms of NR and coregulator genes, are frequently detected in ectopic lesions compared with the normal endometrium. These genetic variations impart new molecular properties to NRs and coregulators to increase their capacity to stimulate progression of endometriosis. Finally, post-translational modifications of NR coregulators, such as proteolytic processing, generate endometriosis-specific isoforms. Compared with the unmodified coregulators, these coregulator isoforms have unique functions that enhance the pathogenesis of endometriosis.

CONCLUSIONS: Epigenetic/genetic variations and posttranslational modifications of NRs and coregulators alter their original function so that they become potent 'drivers' of endometriosis progression.

Key words: nuclear receptor / nuclear receptor coregulator / endometriosis

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Introduction

Endometriosis is an estrogen-dependent pro-inflammatory disease defined as the colonization and growth of endometrial tissue at anatomic sites outside the uterine cavity, primarily the pelvic peritoneum and ovaries (Bulun, 2009). Up to 15% of reproductive-aged women in the USA chronically suffer from the symptoms of endometriosis (Bulun, 2009; Karaman *et al.*, 2012), which include infertility, pelvic pain, menstrual cycle abnormalities and increased risk of certain cancers, such as ovarian, lymphatic, breast and skin cancers (Swiersz, 2002; Giudice and Kao, 2004; Bertelsen *et al.*, 2007). Due to the severe and chronic morbidity associated with this gynecological disorder, past studies have attempted to identify distinguishing molecular features of the endometriotic lesions with the aim of developing more effective prognostic, diagnostic and/or treatment strategies for the clinical management of this debilitating disease. Despite such efforts, however, many current clinical treatments are inadequate for symptom relief and have unacceptable side effects. Thus, more detailed molecular studies are needed in order to identify novel essential molecular pathways for endometriosis progression. Nevertheless, it is clear from currently available data that estrogen-mediated cell signaling and inflammatory signaling both are essential for the progression of endometriosis. A summary of data implicating nuclear receptors (NRs) and NR coregulators in these processes and in the progression of ectopic lesion growth is given below. We have attempted to catalog all published contributory causes of this complex disease with a short discussion of how each might influence survival/progression of endometriotic lesions. At the end, however, we will provide our best opinion as to the key regulators that deserve major attention for therapeutic development in the future.

The role of NRs and coregulators in estrogen signaling in endometriosis

Compared with the normal endometrium, endometriotic tissues have higher concentrations of estradiol-17β (E_2) and locally elevated levels of steroidogenic factor 1 (SF-1) and aromatase, along with reduced activity of 17β-hydroxysteroid dehydrogenase-2 (Zeitoun and Bulun, 1999; Bulun, 2009; Bulun *et al.*, 2009, 2010a, b). In response to these aberrant E_2 levels in endometriotic tissues, a unique NR pattern is maintained in endometriotic tissues compared with the normal endometrium. For example, estrogen receptor (ER)β levels in endometriotic tissues are much higher than in the normal endometrium, whereas ERα levels are not substantially different in endometriotic tissue versus normal endometrium; often they are reduced in endometriotic tissues compared with the normal endometrium (Fujimoto *et al.*, 1999). ERα and ERβ knockout mice with surgically induced endometriosis revealed that the ERα gene is required for normal uterine growth and for ectopic lesion growth; in addition, the ERβ gene is involved in ectopic lesion growth (Burns *et al.*, 2012). However, in mice with surgically induced endometriosis the numbers and size of ERα knockout ectopic lesions are smaller than those of ERβ knockout ectopic lesions. Furthermore, endometriotic tissues have decreased progesterone signaling, and this 'progesterone resistance' is commonly observed in women with endometriosis (Aghajanova *et al.*, 2010; Fazleabas, 2010). Interestingly, elevated ERβ enhances progesterone resistance in endometriotic tissues (Bulun *et al.*, 2012). Therefore, these two different ER isoforms have unique functions in endometriosis progression.

To precisely regulate NR-mediated gene expression caused by external stimuli, NRs recruit specific coregulators in tissue-, temporal- and spatially specific manners. Accordingly, alteration of the NR coregulator milieu is very frequently associated with the progression of human disease (Lonard *et al.*, 2007). In the case of endometriosis, alternations in the molecular properties of NR coregulators, such as RA-binding protein 2 (Pavone *et al.*, 2010), Breast Cancer 1 (Goumenou *et al.*, 2003), tumor protein 53 (TP53) (Paskulin *et al.*, 2012), hydrogen-peroxide inducible clone 5 (Hic-5) (Aghajanova *et al.*, 2009), DNA (cytosine-5-)-methyltransferase (DNMT) (Wu *et al.*, 2007a, b), steroid receptor coactivator-1 (SRC-1) (Han *et al.*, 2012), heat shock protein 70 (HSP70) (Chehna-Patel *et al.*, 2011) and Cyclin D1 (Pellegrini *et al.*, 2012), are detected more frequently in endometriotic tissues compared with the normal endometrium. The altered molecular properties of these NR coregulators change estrogen-mediated signaling pathways to increase ectopic lesion growth.

The role of NRs and coregulators in inflammatory signaling in endometriosis

In addition to estrogen dependency, pro-inflammatory signaling plays an essential role in endometriosis progression because levels of tumor necrosis factor (TNF)α, prostaglandin E_2, cyclo-oxygenase (COX)-2 and various cytokines are highly elevated in endometriotic tissues relative to normal endometrium and these factors synergistically stimulate ectopic lesion growth (Tseng *et al.*, 1996; Noble *et al.*, 1997; Berkkanoglu and Arici, 2003; Szyllo *et al.*, 2003; Bulun, 2009). Therefore, this pro-inflammatory response is a major component of endometriosis progression.

How do NRs modulate inflammatory signaling in ectopic lesions leading to the development of endometriosis and *vice versa*? In addition to ligands of NRs, pro-inflammatory cytokines can enhance the activities of NRs by modulating functional interactions between NRs and coregulators in the absence of the normal cognate NR ligands (Barish *et al.*, 2005). This observation suggests that the activation of cytokine signaling by endometriosis induces ligand independent NR activation in ectopic lesions to support NR-dependent ectopic lesion growth. Alternatively, ligand-bound NRs also can modulate inflammatory signaling in ectopic lesions. Previous studies have revealed that certain types of NR family members, such as Liver X Receptor (LXR), peroxisome proliferator-activated receptor (PPAR) and glucocorticoid receptor (GR), negatively modulate inflammatory signaling pathways by ligand-dependent binding of NRs to negative regulatory elements of inflammatory genes or by positively regulating the expression of inflammatory inhibitor genes in a ligand-dependent manner (Delerive *et al.*, 2001; Galon *et al.*, 2002; Joseph *et al.*, 2003; Welch *et al.*, 2003). Therefore, activation of PPAR-γ with thiazolidinedione (PPAR-γ agonists) inhibits the progression of endometriosis by preventing activation of inflammatory genes in ectopic lesions (Lebovic *et al.*, 2013).

Alternative isoforms of NR coregulators also have been implicated in the regulation of inflammatory signaling in endometriotic tissues. For example, six DNA variants of the receptor-interacting protein 140 (RIP140) gene were identified in endometriosis patients (Caballero *et al.*, 2005). Therefore, different molecular properties of RIP140 variants might be involved in the progression of endometriosis by differentially regulating inflammatory signaling in endometriotic tissues compared with wild-type RIP140. In recently published work dealing with the SRC-1 coactivator, we demonstrated that a 70-kDa SRC-1 isoform generated by matrix metalloprotein (MMP) 9 from full-length SRC-1 is highly elevated in mouse and human endometriotic tissues. This SRC-1 isoform, but not full-length SRC-1, prevents TNF alpha-mediated apoptosis and sustains the ectopic endometriotic lesions (Han *et al.*, 2012).

Collectively, NRs and NR coregulators differentially contribute to effectively modulate the process of endometriosis. In this manuscript, we summarize available data dealing with NRs and their coregulators that have been associated with endometriosis (such as altered protein levels, genetic variations and post-translational modifications). These altered molecular properties often present opportunities to develop new molecular therapeutic approaches for the next generation of endometriosis therapies.

Methods

To identify NRs and NR coregulator genes that are differentially expressed between endometriotic tissues and normal endometrium, genes were selected from Gene Expression Omnibus (GEO) profiles using the NCBI database (http://www.ncbi.nlm.nih.gov/geoprofiles/), with the following key words: 'endometriosis and nuclear receptor', 'endometriosis and coactivator' and 'endometriosis and corepressor'. The lists of NR and NR coregulator genes were taken from the Nuclear Receptor Signaling Atlas (NURSA; http://www.nursa.org/) database. Integrations of GEO profile data and the NR and coregulator gene lists generated a list of NRs and coregulators that have differential expression patterns between endometriotic tissues and normal endometrium (Tables I and II). Based on this list, a systematic literature search was conducted in PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) of articles published on or before 1 September 2013 using the search terms 'endometriosis and NR gene name listed Table I' or 'endometriosis and NR coregulator gene listed in Table II'. These data provide NR and NR coregulator genes that have aberrant gene expression in endometriotic tissues and could be involved in the progression of endometriosis.

To identify NR and NR coregulator genes that have genetic variations or post-translational modifications in endometriotic tissues, a systematic literature search was conducted in PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) of articles published on or before 1 September 2013, using the search terms 'endometriosis plus polymorphism' and ' endometriosis plus post-translational modification'. In all of the above cases, only papers that included information on both case and controls were included.

Table I The list of NRs that have different expression levels in endometriotic tissue when compared with the normal endometrium.

Gene	Average fold[a]	GEO file name[b]
PGR	0.25	GDS2835, GDS3092, GDS3975
RORB	0.36	GDS2835, GDS3060, GDS3092, GDS3975
ESR1	0.43	GDS2385,GDS3060, GDS3092, GDS3975
RORC	0.47	GDS2835, GDS3092, GDS3975
NR2F6	0.50	GDS3092, GDS3975
NR5A1	0.55	GDS3092
DNMT2	0.59	GDS2835
NR4A3	0.61	GDS3092
NR2E1	0.62	GDS3092
PPARG	0.64	GDS2737
NR2F1	0.65	GDS3060
ESRRG	0.65	GDS2835, GDS3092
ESRRB	0.66	GDS3092
DNMT1	0.67	GDS3975
RXRG	0.68	GDS3060
NR2C1	0.69	GDS3092
NR2F1	1.50	GDS2835
RARB	1.55	GDS3060
NR1D2	1.56	GDS3975
NR2E3	1.64	GDS3060
NR2F2	1.64	GDS3060
NR4A1	1.66	GDS2737, GDS2835, GDS3060, GDS3975
VDR	1.67	GDS2737, GDS2835, GDS3975
ESR2	1.69	GDS3060, GDS3975
HNF4A	1.81	GDS3060
THRA	1.83	GDS3975
NR3C2	2.27	GDS2835, GDS3060, GDS3092
NR5A2	2.29	GDS2835, GDS3060
NR1H4	2.61	GDS2835, GDS3092, GDS3975
NR1I2	2.65	GDS3060
NR5A1	2.97	GDS3975
NR4A3	3.02	GDS2835, GDS3975
NR0B1	3.28	GDS2835, GDS3092
NR4A2	3.73	GDS2835, GDS3975
THRB	4.02	GDS3092

NR, nuclear receptor.
[a]Average fold: average fold expression levels for endometriotic tissue/normal endometrium.
[b]GEO data file: these data are from Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/).

Results

Alterations in levels of NRs and NR coregulators in endometriosis

Because NRs and their coregulators play essential roles in maintaining normal cellular physiology in various tissues, their levels are precisely regulated. Consequently, dysregulation of NR and coregulator levels is highly associated with the progression of human diseases (Lonard *et al.*, 2007; Dasgupta *et al.*, 2013). In this content, aberrant levels of NRs and their coregulators also could be associated with the progression of endometriosis due to up-regulated estrogen and inflammation-mediated signaling in endometriotic tissues. Based on the integrative analysis described in the methods section, NRs and NR coregulators that exhibit >1.5-fold changes in the expression between endometriosis

Table II The list of coregulators that have different expression levels in endometriotic tissue when compared with the normal endometrium.

Gene ID	Average fold[a]	GEO file name[b]
BRCA1	0.33	GDS3092, GDS2835, GDS3975
CRABP2	0.35	GDS2835, GDS3092, GDS3975
CCNE1	0.37	GDS3092
MED24	0.41	GDS2835, GDS3975
MUC-1	0.42	GDS2835, GDS3092, GDS3975
NRIP1	0.49	GDS3092, GDS2835
COPS5	0.51	GDS3092
PPARGC1A	0.54	GDS3975
TP-53	0.54	GDS2835, GDS3092
TADA3	0.57	GDS3092
CDK7	0.61	GDS3092
DDX17	0.61	GDS3975
SMARCA4	0.63	GDS2835, GDS3975
RARA	0.66	GDS2737
RAN	0.67	GDS3092, GDS2835
KDM1A	0.69	GDS3092
PSMC3	0.69	GDS2835
GMEB2	0.70	GDS3092
SRC-1	1.3	GDS2835
PIAS1	1.5	GDS2835
SMARCA2	1.5	GDS2835
SRC-3	1.5	GDS3060
PPARGC1A	1.5	GDS3092
RB1	1.6	GDS3060
PRMT2	1.6	GDS2835, GDS3975
TGFB1I1	1.7	GDS3060, GDS3092
CCND1	1.8	GDS3060
DCAF6	1.8	GDS3060
KAT2B	1.9	GDS2835
CITED2	2.0	GDS2835, GDS3092, GDS3975
TRERF1	2.0	GDS3060
SRCAP	3.0	GDS3060
FHL2	4.0	GDS2835, GDS3092, GDS3975
ISL1	4.4	GDS3092
ZFPM2	6.1	GDS2835, GDS3060, GDS3092, GDS3975

[a]Averag fold: average fold expression levels in endometriotic tissue/normal endometrium.
[b]GEO data file: these data are from Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/).

groups and normal controls were selected and classified as 'endometriosis-specific NRs (ESNRs)' and 'endometriosis specific coregulators (ESCRs)' (Tables I and II). Using these tables and the PubMed database, only those NRs and coregulators that have aberrant expression patterns in endometriotic tissues and are involved in the progression of endometriosis are selected and described as below.

NRs associated with endometriosis progression

Progesterone receptor. The progesterone receptor (PR) plays an essential role in normal female reproductive function, such as initiation and maintenance of pregnancy (Wetendorf and DeMayo, 2012). To dynamically modulate progesterone-mediated cellular processes, PR has two isoforms, PR-A and PR-B, and the ratio of PR-B to PR-A is tissue-specifically regulated (Vegeto *et al.*, 1993; Condon *et al.*, 2006; Bellance *et al.*, 2013). Notably, PR-A and PR-B govern distinct endogenous gene networks in progesterone-responsive cells (Richer *et al.*, 2002). More importantly, studies with PR isoform-specific gene ablation mice have revealed that only PR-A plays a crucial role in ovarian and uterine function, whereas PR-B, but not PR-A, is required for mammary gland development (Conneely *et al.*, 2002; Mulac-Jericevic *et al.*, 2003). Because of their crucial roles in female reproductive tissues, alterations of the progesterone levels and/or PR-mediated signaling pathways are closely associated with human endometrial disease progression. Endometriotic tissues do not respond well to progesterone stimuli; this progesterone resistance is associated with infertility in women with endometriosis (Bulun *et al.*, 2006). How do endometriotic tissues become resistant to progesterone? One possible mechanism leading to progesterone resistance is loss of PR expression in endometriotic tissues compared with normal endometrial cells (Al-Sabbagh *et al.*, 2012). The comparative analysis of PR RNA levels via quantitative RT–PCR and PR protein level assessment using immunohistochemistry revealed that endometriotic tissues have a lower ratio of PR-B/PR-A compared with the normal endometrium (Hayashi *et al.*, 2012). This suggests that a reduction of PR-B levels in endometriotic tissue could be associated in part with the development of progesterone resistance. Interestingly, the proliferative activity of immortalized endometrial stromal cells has been reported to be significantly enhanced by knockdown of PR-B using small interfering RNA (Wu *et al.*, 2008). In addition to the progression of progesterone resistance in endometriotic tissues, the down-regulation of PR-B might be responsible for some of the increased proliferative activity observed in endometriotic tissues in women with endometriosis. In general, the down-regulation of PR-B generates a tendency toward progesterone resistance in endometriosis and may promote proliferative activity in endometriotic tissues and survival of ectopic lesions *in vivo*.

Another question is how PR-B gene expression is down-regulated in endometriotic tissues when compared with normal? This may be due to hypermethylation of the PR promoter region leading to transcriptional repression and silencing; the methylation status of the PR-A and PR-B promoter regions in endometriotic tissues has been investigated and it is reported that the promoter region of PR-B, but not PR-A, is hypermethylated in endometriosis compared with the normal endometrium (Wu *et al.*, 2006). This hypermethylation of the PR-B-specific promoter can be a cause for the down-regulation of PR-B gene expression and the development of progesterone resistance in endometriotic tissues (Fig. 1).

In contrast with the above observations, however, some studies reported higher levels of PR-B in endometriotic tissues (Misao *et al.*, 1999; Bukulmez *et al.*, 2008). For examples, ovarian endometrioma inner lining samples had significantly higher levels of PR-B mRNA when compared with the eutopic endometrium (Misao *et al.*, 1999), and endometrioma capsules manifested robust immunoreactivity for PR-B, whereas PR-A immunoreactivity was barely detectable (Bukulmez *et al.*, 2008). However, how and why PR-B gene expression is highly

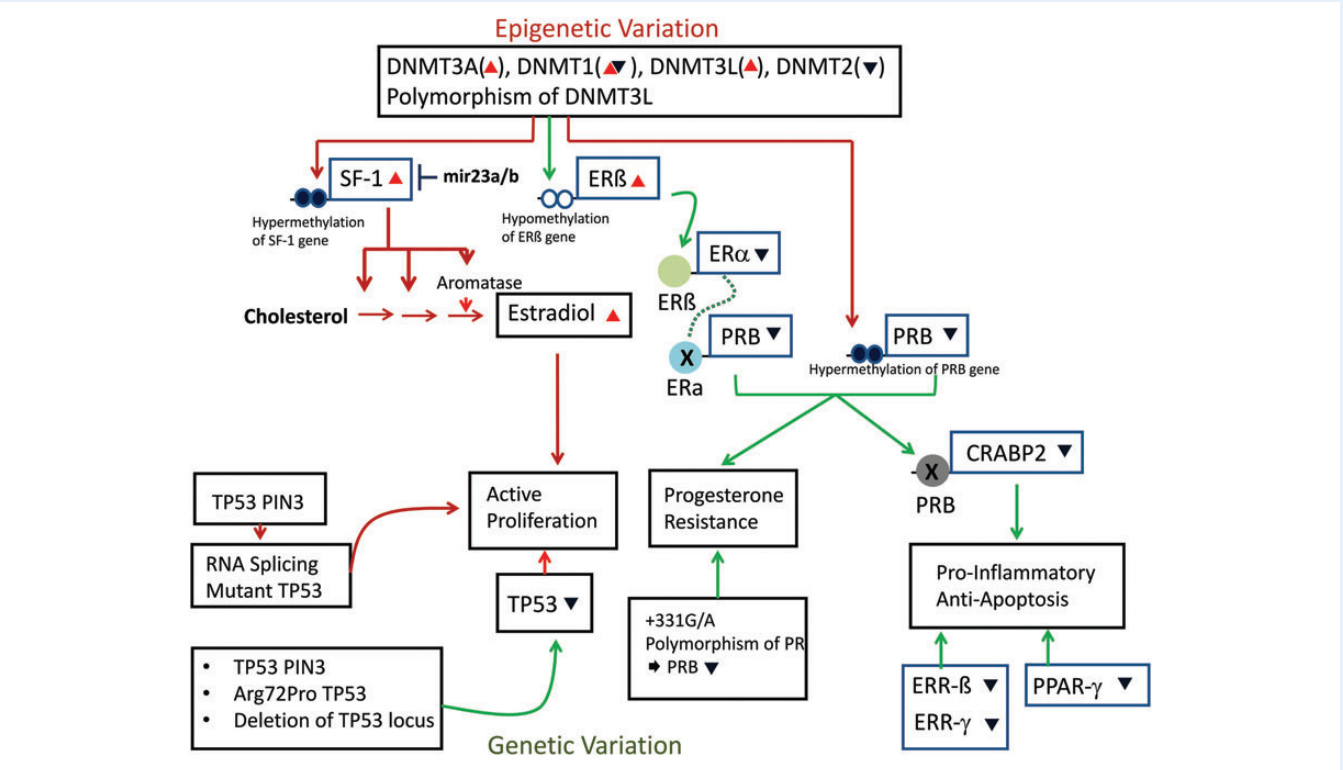

Figure 1 Epigenetic and genetic variation involved in the progression of endometriosis. (1) Epigenetic variation: the endometriotic tissues have aberrant levels of DNA methyltransferase (DNMT)s and polymorphism of DNMT3L compared with the normal endometrium. The alternation of DNMTs might be associated with hypermethylation of the SF-1 gene to enhance its expression in endometriotic tissues. The overexpression of SF-1 actively involves in estradiol production for the ectopic lesion proliferation. In contrast to SF-1, the alternation of DNMTs is correlated with hypomethylation of the estrogen receptor (ER)β gene to increase ERβ expression in endometriotic tissues. The increased ERβ binds to ERα promoter region to down-regulate ERα in endometriotic tissues. The reduced levels of ERα did not induce progesterone receptor (PR) gene expression in endometriotic tissue in response to estradiol. The alteration of DNMTs also may be directly involved in the hypomethylation of the PR gene promoter to down-regulate PR gene expression in endometriotic tissues. Therefore, both types of down-regulation of PR gene are associated with the development of progesterone resistance in endometriotic tissues. In addition to progesterone resistance, down-regulation of the PRB gene is associated with reduction of CRABP2 gene expression in endometriotic tissues to enhance pro-inflammatory signaling for survival of the ectopic lesion. (2) Genetic variation: the tumor protein 53 (TP53) PIN3 mutant, Arg72Pro TP53 mutant and deletion mutant of TP53 locus were frequently detected in endometriotic tissues. These TP53 mutations are correlated with the reduced levels of TP53 in endometriotic tissues. In addition, a PIN3 mutant can generate an RNA splicing mutant of TP53 lacking the N-terminal activation domain. Therefore, both types of alterations of TP53 induce proliferation activity of endometriotic tissues compared with wild-type endometrium. The +331G/A polymorphism of the PRB gene is correlated with the alteration of PRB gene expression in endometriotic tissues that might be associated with the development of progesterone resistance. (3) Unknown mechanism: estrogen receptor-related (ERR)-β, ERR-γ and PPAR-γ levels are reduced in endometriotic tissues compared with the normal endometrium, with an unknown mechanism preventing apoptosis signaling resulting in the survival of ectopic lesions. (Red triangles): increasing, (dark blue inverted triangles): decreasing, (red arrows): positive regulation and (green arrows): negative regulation.

elevated in these endometriotic tissues is not clear. In addition, Smuc *et al.* (2009) have reported that there is no difference in the expression of the PR-B isoform at both mRNA and protein levels in endometriotic tissue versus normal endometrium. Therefore, varied expression patterns have been reported for PR-B among endometriotic tissues.

Estrogen receptor α. ERα is the classical human ER that was cloned in 1986 (Green *et al.*, 1986). Because ERα recognizes estrogen and modulates estrogen-mediated cellular processes in various estrogen-target tissues, dysregulation of ERα gene expression is associated with human disease progression, including cancers and endometrial disease (Burns *et al.*, 2012). In the case of endometriosis, ERα expression has been identified in endometriotic tissues as well as in the normal endometrium (Lyndrup *et al.*, 1987; Lessey *et al.*, 1989; Prentice *et al.*, 1992; Bergqvist and Fernö, 1993; Jones *et al.*, 1995), and the relative expression pattern of ERα in endometriotic tissues versus the normal endometrium is dynamically regulated. In the case of endometriosis progression, ERα mRNA expression levels have been reported to be increased in ectopic tissues in comparison with both normal and eutopic endometrial tissue (Pellegrini *et al.*, 2012). Recent studies using the ERα null mouse with surgically induced endometriosis have revealed that the ERα gene is required for the development of endometriosis because ectopic lesions in ERα knockout animals are smaller and fewer in number compared with wild-type ectopic lesions (Burns *et al.*, 2012). Therefore, ERα expression in ectopic lesions is required for the full growth of ectopic lesions in mice with endometriosis. However, why endometriotic cells have a higher level of ERα is not yet clear.

Because of the essential role that ERα plays in endometriosis progression, selective ER modulators can be employed to suppress ERα activity in ectopic lesions and to obtain growth regression. For example, raloxifene and bazedoxifene, which inhibit endometrial ERα activity, have caused significant regression of experimental endometriosis in an animal model (Yao *et al.*, 2005; Altintas *et al.*, 2010; Kulak *et al.*, 2011). These data suggest that targeting ERα activity could be an alternative endometriosis treatment that could reduce some of the side effects of current total systemic estrogen depletion therapy. In a clinical trial, however, raloxifene treatment did not impact ectopic lesion growth and shortened the time before pelvic pain returned (Stratton *et al.*, 2008).

In addition to elevations of ERα, however, certain previous studies have revealed that endometriotic cells have a lower level of ERα than normal endometrium (Matsuzaki *et al.*, 2001; Smuc *et al.*, 2009; Trukhacheva *et al.*, 2009) (Table I). This is confusing at first glance. For example, ERα levels are significantly down-regulated in endometriotic tissues that exhibit progesterone resistance. Reduced ERα is associated with lower PR levels in endometriotic tissues because PR gene expression is directly regulated by ERα in the endometrium (Boney-Montoya *et al.*, 2010), and the down-regulation of PR is correlated with progesterone resistance and progression in endometriotic tissues. How do endometriotic cells down-regulate ERα levels during the progression of progesterone resistance? Decreased ERα levels are closely associated with increased ERβ levels in endometriosis (Trukhacheva *et al.*, 2009; Bulun *et al.*, 2010a, b). In endometriotic tissues, increased ERβ may be recruited to the ERα promoter to suppress ERα expression (Trukhacheva *et al.*, 2009) (Fig. 1). It is possible that ERα expression patterns differ depending upon the endometriotic sites (Matsuzaki *et al.*, 2001; Colette *et al.*, 2013).

ER-related receptors. ER-related receptors (ERRs) are members of the orphan NR family. ERRs can bind to estrogen response elements in DNA to modulate target gene expression. However, endogenous ligands for the ERR have not yet been clearly identified. The ERR family consists of three members: ERR-α, ERR-β and ERR-γ (Heard *et al.*, 2000). Expression of ERRs has been detected in the normal endometrium; however, their expression was not clearly detected in endometriotic lesions (Bombail *et al.*, 2008; Fujimoto and Sato, 2009). Consistent with these observations, our ESNR analysis also revealed that endometriotic tissues have a lower level of ERR isoforms when compared with the normal endometrium (Table I). Overall, expression of ERRs is down-regulated in the ectopic endometrium compared with the normal endometrium. However, the molecular mechanism of down-regulation of ERRs in endometriotic tissue has not been clearly elucidated.

Why might the down-regulation of ERRs be associated with endometriosis? A previous study revealed that increased ERR-γ expression promotes mesenchymal-to-epithelial transition (MET), suppressing breast cancer progression (Tiraby *et al.*, 2011). Endometriosis progression itself is associated with an epithelial-to-mesenchymal transition (EMT) in order to infiltrate target tissues and organs. Therefore, down-regulation of ERRs might inhibit MET processes in endometriotic tissues and encourage the induction of EMT. Generally, endometriotic lesions have apoptotic resistance and a modified protein pattern in their mitochondrial membranes because most apoptotic proteins are anchored to the mitochondrial membrane (Agic *et al.*, 2009; Ding *et al.*, 2010). Interestingly, ERRβ and ERRγ modulate the expression of the mitochondrial genes involved in apoptotic processes (Giguere, 2008). Therefore, decreased levels of ERR isoforms may provide a beneficial effect for ectopic lesions, allowing for their survival by preventing mitochondria-mediated apoptosis signaling (Fig. 1).

Peroxisome proliferator-activated receptors. Three subtypes of PPARs have been identified and characterized (α, β and γ), and the activity of PPARs is regulated by polyunsaturated fatty acids and eicosanoid metabolites (Willson and Wahli, 1997; Michalik and Wahli, 1999). Their specific endogenous ligands are yet to be identified.

ESNR pattern analysis has revealed that endometriotic tissues have a lower level of PPAR-γ compared with the normal endometrium (Table I). In the case of cancer, expression of the PPAR-γ gene is modulated by DNA methylation (Pancione *et al.*, 2010). However, whether an alteration of the methylation status of the PPAR-γ gene is correlated with a down-regulation of PPAR-γ in endometriotic tissues has not been elucidated.

Does down-regulation of PPAR-γ in endometriotic cells play a role in endometriosis progression? During endometriosis progression, the chemokine Regulated Upon Activation Normal T Cell Expressed and Secreted (RANTES) plays an essential role in endometriosis because it has been shown to mediate inflammatory cell chemotaxis (Wang *et al.*, 2010; Yang *et al.*, 2013). Therefore, high levels of RANTES excreted from endometriotic tissues recruit macrophages and can contribute to progression of endometriosis. Interestingly, PPAR-γ inhibits RANTES production from human endometriotic stromal cells (Pritts *et al.*, 2002, 2003). Moreover, ciglitazone, a PPAR-γ agonist, significantly decreased the attachment of endometrial cells to peritoneal mesothelial cells in an *in vitro* model of the early endometriotic lesion (Kavoussi *et al.*, 2009). In addition, rosiglitazone and pioglitazone (PPAR-γ agonists) significantly decreased the size of ectopic uterine tissues and the mean wet weight of explants (Lebovic *et al.*, 2004, 2010; Demirturk *et al.*, 2006). Activation of PPAR-γ with agonists suppressed ectopic lesion growth in rat and baboon models of endometriosis (Aytan *et al.*, 2007; Lebovic *et al.*, 2010). For the survival of ectopic cells with activated inflammatory signaling, the ectopic lesions could suppress PPAR-γ gene expression to encourage further endometriosis progression (Fig. 1).

NR subfamily 5, group A, member 1 (NR5A1)/SF-1. SF-1 has been known to be a key modulator of steroidogenesis since the early 1990s (Lala *et al.*, 1992; Morohashi *et al.*, 1992; Giguere, 2008). SF-1 is involved in controlling many physiological pathways to precisely regulate adrenal and reproductive functions; many essential factors involved in the development of adrenal and reproductive tissue are controlled by SF-1 (Morohashi *et al.*, 1992; Lin and Achermann, 2008; Schimmer and White, 2010). Therefore, dysregulation of SF-1 gene expression might be associated with estrogen-dependent endometriosis progression. ESNR expression profiling analysis revealed that levels of SF-1 RNAs were highly elevated in endometriotic tissues compared with the normal endometrium (Table I). Consistent with RNA levels of SF-1, protein levels of SF-1 were also significantly elevated in the ectopic endometrium compared with normal endometria, and the elevation of SF-1 levels was significantly correlated with the severity of endometriosis (Tian *et al.*, 2009).

The above observation raises the question of how endometriotic tissues maintain a higher level of SF-1 compared with the normal endometrium. A previous study revealed that aberrant alteration of DNA methylation and alteration of the gene expression of DNA methyltransferases, which regulate DNA methylation, are correlated with endometriosis progression (Nasu *et al.*, 2011). Based on this observation, the

methylation status of the SF-1 gene in endometriotic tissue and the normal endometrium was investigated. Bisulfite sequencing revealed more intense methylation in CpG islands that span from exon II to intron III of the SF-1 gene in endometriotic cells compared with normal endometrial cells (Xue *et al.*, 2011). There was a strong correlation between mRNA levels of SF-1 and the percentage of methylation of exon II/intron III of the SF-1 gene. Therefore, the methylation of a coding exon/intron sequence in the SF-1 gene may enhance gene expression in endometriotic tissues, enhancing lesion survival; whereas hypomethylation of exon II/intron III of the SF-1 gene in the normal endometrium was associated with drastically lower levels of SF-1. In addition, a recent study revealed that the methylation status of the intron I region of the SF-1 gene is strongly correlated with SF-1 mRNA in endometriotic cells (Xue *et al.*, 2013). Collectively, published data suggest that the methylation of CpG islands in intron I and exon II/Intron III of the SF-1 gene increases SF-1 gene expression in endometriotic tissues (Fig. 1).

How are these endometriotic-specific DNA methylation patterns in the SF-1 gene generated in endometriotic tissue? Interestingly, expression levels of DNMT3A and DNMT3B are highly elevated in the ectopic endometrium compared with the normal endometrium or the eutopic endometrium of women with endometriosis (Wu *et al.*, 2007a, b; van Kaam *et al.*, 2011). Therefore, increased DNMT3A and DNMT3B gene expression might be actively involved in methylation of intron I and exon II/Intron III of the SF-1 gene, leading to enhanced SF-1 gene expression in endometriotic tissues. In addition to DNA hypermethylation, levels of SF-1 RNA are post-transcriptionally regulated by microRNAs (miRNAs) in endometriotic tissues. For example, both miR23a and miR23b are down-regulated in endometriotic tissues compared with the normal endometrium, and their expression levels are inversely correlated with SF-1 mRNA levels (Shen *et al.*, 2013) (Fig. 1). Therefore, mRNA levels of SF-1 are significantly reduced when eutopic endometrial stromal cells overexpress miR23a/b, whereas SF-1 levels are highly up-regulated when miR23a/b levels are down-regulated in normal endometrial stromal cells (Shen *et al.*, 2013). However, the detailed molecular mechanism of endometriotic cell-specific down-regulation of miR23a/b has not been clearly elucidated.

Since the induction of SF-1 gene expression could drive the initiation, development and establishment of endometriosis, reducing SF-1 levels or inhibiting SF-1 activity could be possible molecular therapeutic approaches for endometriosis treatment. For example, the Scripps Research Institute has synthesized small molecule inhibitors against SF-1 based on isoquinolinore scaffolds to improve potency and selectivity and to lower cellular toxicity (Roth *et al.*, 2008). Therefore, such a small molecule inhibitor against SF-1 could be employed in endometriosis treatment.

Estrogen receptor β. E_2 is a key component of ectopic lesion growth and in the persistence of endometriotic tissue, as well as for the inflammation and pain associated with the disease. In addition to E_2, its cognate ERs play crucial roles in the development of endometriosis (Burns and Korach, 2012; Burns *et al.*, 2012). In contrast to the modest changes in ERα expression described above, markedly elevated levels of ERβ are detected in endometriotic tissues in mice with endometriosis and in human endometriotic tissues compared with normal endometrial tissues (Brandenberger *et al.*, 1999; Han *et al.*, 2012).

ERβ has several alternatively spliced forms, and each ERβ isoform has a tissue- and disease-specific expression pattern (Gaskell *et al.*, 2003; Leung *et al.*, 2006). ERβ1, ERβ2 and ERβ5 isoforms are expressed in human endometrium; a decreased ratio of ERα/ERβ1 has been detected in the proliferative endometrium of endometriosis patients compared with the normal endometrium (Juhasz-Boss *et al.*, 2011). This observation suggests that elevated levels of ERβ1, but not ERβ2 or ERβ5, might be associated with the pathogenesis of endometriosis.

The above observation raised the question of how endometriotic tissues maintain higher levels of ERβ compared with the normal endometrium. The methylation status of the ERβ gene promoter is differentially maintained between endometriotic cells and normal endometrial cells, similar to SF-1 (Xue *et al.*, 2007a, b). For example, a CpG island in the promoter region (−197/+359) of the ERβ gene is hypomethylated in endometriotic tissues compared with the normal endometrium, and the activity of the ERβ promoter containing this CpG island is strongly inactivated by *in vitro* methylation (Xue *et al.*, 2007a, b). In general, it appears that hypomethylation of the ERβ gene promoter increases ERβ gene expression in endometriotic tissues compared with the normal endometrium. How do endometriotic cells induce hypomethylation of the ERβ gene? Interestingly, down-regulation of DNAMT1 and DNMT2 has been detected in ectopic lesions compared with the normal endometrium (Eyster *et al.*, 2007; Borghese *et al.*, 2008). Therefore, reductions of DNAMT1 and DNMT2 might be causal for hypomethylation of the ERβ gene promoter region, leading to increased ERβ gene expression in endometriotic tissues (Fig. 1).

What is the role of overexpressed ERβ in the progression of endometriosis? Chromatin immunoprecipitation assays have demonstrated that ERβ binds to the promoter locus of the ERα gene, which has non-classical activator protein 1 and specificity protein 1 binding motifs and a classic estrogen response element; together they function to suppress ERα expression in endometriotic stromal cells (Trukhacheva *et al.*, 2009). This repressive role of ERβ on ERα gene expression in endometriotic cells also has been confirmed by experiments knocking down and overexpressing ERβ (Trukhacheva *et al.*, 2009). Because ERα directly regulates endometrial PR gene expression (Boney-Montoya *et al.*, 2010), ERα deficiency in endometriotic tissues might be responsible for the failure of E_2 activity to induce PR gene expression. This secondary PR deficiency in turn causes progesterone resistance in women with endometriosis (Bulun *et al.*, 2012). Therefore, the ERα deficiency mediated by overexpressing ERβ could promote the progesterone resistance in endometriotic tissues (Fig. 1).

A study on ERβ knockout mice with surgically induced endometriosis revealed that the ERβ gene is required for ectopic lesion growth, even though the impact of an ERβ gene knockout is less than ERα gene deletion in the suppression of ectopic lesion growth (Burns *et al.*, 2012). This observation suggests that ERβ could have other functions that support the growth and/or maintenance of ectopic lesions in addition to the development of progesterone resistance in endometriotic tissues. Thus, questions regarding the roles of ERβ in endometriosis have not been fully addressed to date.

Vitamin D receptor. The vitamin D receptor (VDR) is expressed in cycling human endometrial tissues (van Kaam *et al.*, 2008), and vitamin D_3 plays a functional role in fertility and uterine growth (Kwiecinksi *et al.*, 1989; Yoshizawa *et al.*, 1997). Therefore, the vitamin D3/VDR signaling axis could play some role in normal female reproductive function. In addition, VDR-mediated cellular pathways might be involved in endometriosis progression, as immunohistochemistry has shown stronger staining for

VDR in endometriotic tissues and endometrial cancer compared with the normal endometrium (Agic *et al.*, 2007; Zelenko *et al.*, 2012). Although the role of VDR in the progression of endometriosis has not been clearly elucidated, VDR-agonist treatment inhibits leukocyte infiltration into inflammatory sites and this VDR-agonist-mediated anti-inflammatory effect is associated with inhibition of nuclear factor (NF)-kB-mediated cell survival signaling (Griffin *et al.*, 2003). Since endometriosis is known as an inflammatory disease, and anti-inflammatory drugs suppress ectopic lesions in mouse models of endometriosis (Efstathiou *et al.*, 2005), an inhibition of NF-kB activity by ligand-bound VDR should suppress ectopic lesion growth because ectopic lesions maintain higher levels of VDR expression. As expected, elocalcitol, a VDR agonist, was claimed to inhibit ectopic lesion growth in a validated mouse model of endometriosis (Mariani *et al.*, 2012). Although the role of increased levels of VDR in ectopic lesion growth is not clear, endometriotic VDR expression might be targeted by alternative therapies to lessen the side effects of current endometriosis treatments.

NR coregulators associated with the development of endometriosis

Cellular retinoic acid-binding protein 2. Retinoic acid (RA) is a dual effector that determines cell fate in a tissue type-dependent manner (Schug *et al.*, 2007, 2008). In normal cells, for example, RA classically enhances differentiation and apoptosis and inhibits proliferation. RA binds to cellular RA-binding protein 2 (CRABP2) to deliver RA to the RA receptor (RAR)α, which eventually enhances differentiation and apoptosis and inhibits proliferation (Schug *et al.*, 2007). In pathological cell types, however, RA paradoxically induces cell survival signaling pathways because RA binds to fatty acid-binding protein 5 (FABP5), which delivers RA to a different NR, PPAR β/δ and induces the expression of pro-survival genes (Schug *et al.*, 2008).

Endometriosis-specific coregulator (ESCR) expression pattern analysis revealed that levels of CRABP2 are lower in endometriotic tissues compared with the normal endometrium (Table II). How can endometriotic cells maintain lower levels of CRABP2? PR is actively involved in the up-regulation of CRABP2 expression in endometrial stromal cells to control retinol uptake and to support the growth-suppressor actions of RA (Pavone *et al.*, 2010). In contrast to the normal endometrium, however, endometriotic cells with progesterone resistance have low levels of PR. Therefore, the reduction of PR could lead to down-regulation of CRABP2 levels, and down-regulation of CRABP2 could lead to enhancement of FABP5-mediated pro-survival activity in response to RA (Pavone *et al.*, 2010).

The above observation suggests that if CRABP2 is up-regulated in ectopic lesions, it could suppress the growth of the lesion by causing CRABP2/RARα-mediated apoptosis in response to RA. Therefore, regulation of the pathway leading to CRABP2 gene expression could be a potential molecular therapeutic target for endometriosis treatment. For example, simvastatin enhances the inhibitory effects of RA on cell growth by increasing apoptotic effects because simvastatin stimulates the expression of CRABP2 but not FABP5 (Sokalska *et al.*, 2013). Therefore, the combination of simvastatin with RA could be employed for endometriosis treatment to increase the CRABP2/RARα-mediated apoptosis pathway in ectopic lesions and to suppress ectopic lesion growth.

Breast cancer 1, early onset gene. The Breast Cancer 1, Early Onset (*BRCA1*) gene was identified as a tumor suppressor because its main function is to repair damaged DNA and ensure genomic stability (Chen and Parmigiani, 2007). When the BRCA1 gene is mutated or its expression levels are altered, DNA damage is not repaired properly. As a result, cells develop additional genetic alterations that can lead to diseases such as cancer (Satagopan *et al.*, 2002). The ESCR gene expression pattern analysis revealed that BRCA1 RNA is significantly reduced in endometriotic tissues compared with the normal endometrium (Table II). Therefore, endometriotic tissues have a higher potential to acquire genetic variations in their genomes due to the down-regulation of BRCA1. Why do endometriotic tissues have a lower level of BRCA1 compared with the normal endometrium? In the case of breast cancer, hypermethylation of the BRCA1 gene promoter is detected in breast cancer cells compared with normal breast cells, and hypermethylation of the BRCA1 gene is strongly correlated with a reduction of BRCA1 mRNA levels in some clinical breast cancer specimens (Rice *et al.*, 2000; Xu *et al.*, 2013). As with cancer, endometriosis-specific aberrant genomic DNA methylation patterns also are found in endometriotic tissues (Nasu *et al.*, 2011). As described previously, some genes, such as PRB (Wu *et al.*, 2006), E-Cadherin (Wu *et al.*, 2007a, b) and HOXA10 (Wu *et al.*, 2005), show hypermethylation in their promoter and other regions in endometriosis compared with the normal endometrium. However, ERβ (Xue *et al.*, 2007a, b), SF-1 (Xue *et al.*, 2007a, b) and aromatase (Izawa *et al.*, 2008) genes are hypomethylated in endometriotic tissues. Although the methylation status of the BRCA-1 gene in endometriotic tissues has not been investigated, altered methylation of the BRCA-1 gene potentially could be associated with the development of endometriosis.

Tumor protein 53. TP53 has been described as a tumor suppressor gene because it has anticancer functions and plays a role in apoptosis, genomic stability and inhibition of angiogenesis (Matlashewski *et al.*, 1984; Isobe *et al.*, 1986). The level and/or activity of TP53 is significantly down-regulated in most types of cancer cells compared with normal tissues (Semczuk *et al.*, 2010). As in cancer, TP53 levels also are down-regulated in endometriotic tissues compared with the normal endometrium (Arimoto *et al.*, 2003) (Table II). Why do endometriotic tissues have a reduced TP53 level compared with normal the endometrium? Notably, alterations of chromosome 17 in general and the p53 locus in particular are frequently detected in severe and late-stage endometriosis (Bischoff *et al.*, 2002). Therefore, somatic genome perturbation of the TP53 locus might be associated with down-regulated TP53 levels in endometriotic tissues compared with the normal endometrium (Fig. 1). How does a TP53 deficiency lead to the development of endometriosis? Unfortunately, detailed studies to address this question have not yet been conducted. However, down-regulated TP53 might lead to uncontrolled proliferative activity and the development of ectopic lesions in women with endometriosis, as it does in cancer.

Transforming growth factor beta 1 induced transcript 1Hic-5. Hic-5 is also known as 55 kDa androgen receptor-associated protein or transforming growth factor β1-induced transcript 1 (TGFB111). Functionally, Hic-5 is involved in cellular senescence (Fujita *et al.*, 1998). In the case of NR signaling, Hic-5 potentiates transactivation of the GR, androgen receptor, mineralocorticoid receptor and PR, but it does not alter ER activity (Yang *et al.*, 2000). Interestingly, expression levels of Hic-5 are significantly reduced in human endometrial stromal fibroblasts from women with endometriosis compared with the normal endometrium (Aghajanova

et al., 2009). Therefore, a deficiency in Hic-5 gene expression appears to be closely associated with the development of endometriosis. However, the molecular mechanisms leading to down-regulation of Hic-5 levels in endometriotic tissue have not yet been elucidated. What is the physiological meaning of the down-regulation of Hic-5 levels in endometriotic tissues? Endometriotic tissues display progesterone resistance due to low levels of PR. However, some endometriotic tissues have higher levels of PR-B expression compared with the normal endometrium (Misao et al., 1999; Bukulmez et al., 2008). Since Hic-5 works as a PR coactivator in certain PR-mediated cellular processes (Aghajanova et al., 2009), down-regulation of Hic-5 might impair PR activity in ectopic lesions and promote progesterone resistance in PR-positive ectopic lesions. Hic-5 also has a differential expression pattern between ectopic lesions related to their location (Table II) (Colette et al., 2013).

DNA (cytosine-5-)-methyltransferase. The genome-wide profiling of methylation patterns in gene promoter regions has revealed an unbalanced and unique distribution of DNA methylation patterns in endometriotic tissues when compared with the normal endometrium (Borghese et al., 2010). For example, subtelomeric hypermethylated regions are associated with endometriotic tissues, whereas hypermethylated regions are uniformly distributed on the chromosomes of normal endometrium (Borghese et al., 2010). This endometriotic cell-specific DNA methylation pattern could be associated with variations in DNMT gene expression. For example, levels of *DNMT1* and *DNMT2* are down-regulated in endometriotic tissues compared with the normal endometrium (Borghese et al., 2008) (Table II). In addition to aberrant levels, altered activity of these DNMTs could induce defective methylation of gene promoter regions during the genesis and/or progression of endometriosis. Therefore, deletion of DNMT1 and DNMT2 might be associated with the hypomethylation of the ERβ gene in endometriotic tissues, which could induce ERβ gene expression for the survival of ectopic lesions.

In contrast to *DNMT1* and *DNMT2*, DNMT3A and DNMT3B are over-expressed in the ectopic endometrium compared with the normal endometrium as well as in the eutopic endometrium in women with endometriosis (Wu et al., 2007a, b; Borghese et al., 2008) (Table II). The hypermethylation of CpG islands in intron I and exon II/Intron III of the SF-1 gene is associated with elevated SF-1 gene expression in endometriotic tissues. In contrast to SF-1, however, the hypermethylation of the PR-B-specific promoter is associated with low levels of PR-B in endometriotic tissues, causing progesterone resistance. Therefore, overexpression of DNMT3A and DNMT3B genes could influence hypermethylation of SF-1 and PR-B for the development of endometriosis (Fig. 1).

Cyclin D1. The typical function of cyclin D1 (CCND1) is to regulate the cell cycle by modulating cyclin-dependent kinases (CDKs). In addition to cell cycle control, CCND1 synergistically regulates ERα-mediated cellular processes in a ligand-independent fashion with SRCs; CCND1 recruits SRCs to ERα in the absence of ligand so as to enhance ERα activity (Zwijsen et al., 1998). Therefore, CCND1 works as an ERα coregulator to modulate ERα-mediated cellular processes. Interestingly, CCND1 expression levels are highly elevated in endometriotic tissues compared with the normal endometrium (Pellegrini et al., 2012). This observation suggests an essential role for CCND1 in the progression of endometriosis. However, how endometriotic tissues achieve a higher level of CCDN1 has not yet been elucidated. What could be the functional link between overexpression of the CCND1 gene and the progression of endometriosis? Because CCDN1 works as an ERα coactivator, the elevated activity of the CCDN1/ERα functional axis could up-regulate ERα-mediated signaling in endometriotic tissues in a feed-forward manner. In this way, elevated levels of CCDN1 might increase the activity of ERα in ERα-mediated cellular processes required for ectopic lesion progression.

Because CCDN1 plays an essential role in estrogen signaling in ectopic lesions, targeting CCDN1 also could be employed as an alternative endometriosis treatment. For example, Dienogest, a specific PR agonist, has been used for endometriosis treatment because it directly inhibits the proliferation of human endometrial epithelial cells by suppressing CCND1 gene expression (Shimizu et al., 2009). In addition to Dienogest, Puerarin causes regression of the growth of endometriotic implants in animal models of endometriosis by preventing CCDN1-mediated estrogen signaling (Chen et al., 2011). Puerarin also suppresses proliferative activity of human endometriotic stromal cells via the down-regulation of CCDN1 (Cheng et al., 2012). Therefore, the regulation of CCDN1 expression levels in ectopic lesions could be another novel molecular therapeutic approach for endometriosis treatment by preventing ERα-mediated cellular processes.

NR coactivator 1 (NCOA1)/SRC-1. The estrogen/ER signal axis plays a crucial role in endometriosis progression (Bulun, 2009; Burns et al., 2012). For the precise regulation of ER-mediated gene regulation, ERs recruit various coregulators onto ER at target gene promoter regions (Foulds et al., 2013). Therefore, the discovery of an endometriosis-specific partnership between ERα and coregulators could shed new light onto the molecular mechanisms of estrogen-dependent endometriosis progression. SRC-1 is an ERα coregulator, and alterations in SRC-1 levels in specific tissues is correlated with the progression of human disease, such as prostate, breast and other cancers (Lonard et al., 2007). In the case of endometriosis, expression levels of SRC-1 and the number of SRC-1-positive cells in ovarian endometriosis lesions have been reported to be greater than those of SRC-2 and SRC-3. In addition, immunohistochemistry has revealed that SRC-1 is co-localized with ERα in almost all glandular and many stromal cells in ovarian endometriotic tissues (Kumagami et al., 2011).

The proliferative activity is significantly lower in endometriotic epithelia than eutopic endometrial epithelia in the proliferative phase of the menstrual cycle in the absence of alterations in ER and PR (Suzuki et al., 2010). Notably, the expression of SRC-1 in endometriotic epithelia in the proliferative phase is significantly lower than in eutopic endometrioma (Suzuki et al., 2010). This observation of reduced proliferative activity in endometriotic epithelial cells can be correlated with reduced expression of SRC-1 levels. At first glance, the meaning of this correlation may be unclear. However, in a later section below, we will explain the important interactions of the SRC-1 gene in endometriosis. SRC-1 has a predominant role in endometriosis progression compared with other SRC family members.

Genetic variation of NR and coregulator genes in endometriosis

In addition to identifying alterations in expression levels of NRs and their coregulators, a number of different studies revealed that genetic

variations in genes encoding NRs and their coregulators also are associated with endometriosis susceptibility (Stefansson *et al.*, 2002; Rotman *et al.*, 2013). For example, the rate of endometriosis among the relatives of endometriosis patients is higher than controls in both hospital-based (Kennedy *et al.*, 1995; Simpson and Bischoff, 2002) and population-based (Stefansson *et al.*, 2002) control samples. In addition to studies of relatives, twin studies of endometriosis have revealed an increased concordance of endometriosis in monozygotic twins compared with dizygotic twins (Treloar *et al.*, 1999, 2002). Collectively, the above observations strongly suggest that a genetic component(s) is associated with the progression of endometriosis. To this end, various factors have been identified across the genome and investigated to determine how genetics may play a role in endometriosis progression (Montgomery *et al.*, 2008; Rahmioglu *et al.*, 2012). For example, rs10965235, located in an intron of CDKN2BAS on chromosome 9p21, is closely associated with a Japanese endometriosis cohort (Uno *et al.*, 2010), and the intergenic single nucleotide polymorphism (SNP) rs12700667 on chromosome 7p15.2 is associated with a European endometriosis cohort (Painter *et al.*, 2011). Using the PubMed database, we investigated whether genetic variation in NRs and their coregulators is associated with the progression of endometriosis.

NRs that show genetic alterations in endometriotic tissue

Estrogen receptor α. The human ERα gene has 8 exons spanning >140 kb on chromosome 6q25 (Ponglikitmongkol *et al.*, 1988). Notably, polymorphisms of ERα are associated with estrogen-dependent progression of human diseases, such as breast cancer, osteoporosis and Parkinson's disease (Hill *et al.*, 1989; Kobayashi *et al.*, 1996; Isoe-Wada *et al.*, 1999). In addition, ERα polymorphisms have been hypothesized to be associated with the risk of endometriosis in many epidemiological studies. For example, the PvuII and XbaI polymorphisms of the ERα gene that are located in intron 1 are reported to be associated with an increased risk of endometriosis (Govindan *et al.*, 2009). However, another meta-analysis revealed that the PvuII and XbaI polymorphisms in the ERα gene may not be associated with endometriosis risk (Hu *et al.*, 2012; Li *et al.*, 2012). Therefore, it is uncertain whether PvuII and XbaI polymorphisms of the ERα gene are associated with endometriosis progression. In addition to SNPs, a polymorphic (TA)n repeat insertion 1174 bp upstream of the human ERα gene was reported in a patient with endometriosis (Georgiou *et al.*, 1999; Hsieh *et al.*, 2005), but the functional correlation between the polymorphic (TA)n repeat and endometriosis is far from clear.

Estrogen receptor β. Several genetic polymorphisms in the ERβ gene have been identified: (i) a 21 bp deletion encompassing codon 238 and 244 in exon4; (ii) a 846G>A transition in exon 4 that substitutes the amino acid G (250) to S(250); (iii) a 1421T>C transition in exon 7 that is a silent mutation; (iv) a 1082G>A transition within the LDB in exon 5 and finally, (v) a 1730 (A>G) mutation in the 3′ untranslated region of exon 8 (Rosenkranz *et al.*, 1998; Wang *et al.*, 2004). However, there are no significant differences in the frequency of either AluI polymorphism in exon 8 or the RsaI polymorphism in exon 5 of the ERβ gene between endometriosis patients and control group (Wang *et al.*, 2004; Trabert *et al.*, 2011; Hu *et al.*, 2012). In a Japanese population, however, a positive association was reported between the AluI polymorphism in the ERβ gene and stage IV endometriosis (Wang *et al.*, 2004).

Progesterone. Progesterone is a potent antagonist of estrogen-induced endometrial proliferation. Therefore, alterations in progesterone-mediated signaling may be associated with the pathogenesis of endometriosis. For example, a lower level of PR-B gene expression is associated with the progression of progesterone resistance in endometriotic tissues. Interestingly, a genomic polymorphism analysis detected a 306-base pair insertion from the PV/HS-1 Alu subfamily into intron G of the PR gene (PROGINS) (Rowe *et al.*, 1995). This polymorphism is closely associated with the progression of breast and ovarian cancer as well as the progression of endometriosis (Wieser *et al.*, 2002; Lattuada *et al.*, 2004; Pearce *et al.*, 2005; Hu *et al.*, 2012). However, other studies reported that PROGINS is not associated with endometriosis when compared with healthy women (Treloar *et al.*, 2005; Trabert *et al.*, 2011).

In addition to PROGINS, a +331G/A polymorphism in the PR gene was detected in endometriosis patients (van Kaam *et al.*, 2007). The +331G/A polymorphism is located in the promoter region of the PR gene (De Vivo *et al.*, 2002). Interestingly, the +331G/A polymorphism enhances the synthesis of PR-B by generating an additional TATA box, thereby altering the ratio of PR-A to PR-B (De Vivo *et al.*, 2002), leading to higher expression levels of PR-B in the endometrial epithelium of +331A carriers (Berchuck *et al.*, 2004). Therefore, the presence of the +331A allele is considered to reduce the risk of developing deep infiltrating endometriosis and clear cell ovarian cancers (Berchuck *et al.*, 2004; van Kaam *et al.*, 2007) (Fig. 1).

Coregulators that have genetic modifications in endometriotic tissue

Tumor protein 53. As described above, endometriotic cells have lower levels of TP53 than normal endometrial cells. In addition to alterations of TP53 levels, genetic alteration of the TP53 gene is associated with the pathogenesis of endometriosis. Gene-specific PCRs have revealed that codon 72 in TP53 has a polymorphism (Arg/Arg, Arg/Pro, Pro/Pro) in women with severe endometriosis but not in women without endometriosis and this polymorphism is closely associated with the progression of endometriosis in Taiwanese and Mexican populations (Chang *et al.*, 2002; Gallegos-Arreola *et al.*, 2012). For example, p53 Arg/Arg homozygotes have a lower risk for endometriosis, whereas Arg/Pro heterozygotes and Pro/Pro homozygotes have a higher risk for endometriosis progression. How the Arg72Pro TP53 polymorphism changes the molecular properties of TP53 leading to endometriosis progression has not been elucidated. In contrast to the Taiwanese and Mexican populations, however, the Arg72Pro TP53 polymorphism was not associated with a higher risk of endometriosis in Italian and Brazilian populations (Vietri *et al.*, 2007; Bianco *et al.*, 2011).

In addition to the Arg72Pro TP53 polymorphism, a polymorphism in Intron 3 of the TP53 gene (PIN3, rs17878362, 16 bp duplication) was claimed to be associated with the progression of endometriosis (Paskulin *et al.*, 2012). How does the TP53-PIN3 mutation impact the progression of endometriosis? A previous study revealed that lymphoblastoid cell lines with the *TP53*-PIN3 allele have reduced levels of *TP53* mRNA (Gemignani *et al.*, 2004). In a previous section, we reported that endometriotic cells have lower levels of TP53 compared with the normal endometrium. Therefore, the TP53-PIN3 mutation might be associated with reduced TP53 levels in endometriotic tissues, contributing to the progression of endometriosis (Fig. 1).

In addition to down-regulation of TP53 levels, PIN3 can change TP53 splicing patterns in endometriotic tissues because the PIN3 region is

involved in splicing intron 2 of the TP53 gene. *In silico* models predict that PIN3 may alter the topology of *G-quadruplex* structures, generating alternatively spliced p53 mutants retaining intron 2 (Gemignani *et al.*, 2004; Marcel *et al.*, 2011). This TP53 splice variant lacks the N-terminal domain containing the transactivation motif of p53 (Gemignani *et al.*, 2004; Marcel *et al.*, 2011). Therefore, the TP53-PIN3 mutant gene might produce an N-terminally truncated TP53, which binds DNA but does not activate transcription through p53-response elements. This TP53-PIN3 mutant could work as a dominant negative mutant of TP53 to enhance the progression of endometriosis. Together, the down-regulation of TP53 gene expression and loss of transactivation ability of TP53 in endometriotic tissues might be associated with the TP53-PIN3 mutation (Fig. 1).

DNA (cytosine-5-)-methyltransferase 3. Epigenetic mechanisms have been proposed to play a role in endometriosis progression since expression levels of DNMTs are regulated differentially in endometriotic tissues versus normal endometrium. In addition to aberrant expression, genetic polymorphisms of DNMT genes have been identified (Borghese *et al.*, 2012; Szczepanska *et al.*, 2013). For example, a rare DNMT3L variant (rs113593938), located in exon 10, is associated with significant hypomethylation of subtelomeric regions (El-Maarri *et al.*, 2009). Among polymorphisms of DNMT genes, the rs8129776 polymorphism in intron 9 of the DNMT 3L gene is significantly associated with an increased risk of ovarian endometrioma progression (Borghese *et al.*, 2012). However, the rs8129776 polymorphism of DNMT3L was not reported to be associated with alterations in DNMT3L levels in endometriotic tissues (Huang *et al.*, 2012). Therefore, even though the functional consequence of the rs8129776 polymorphism of the DNMT 3L gene in endometriosis progression is not clear at present, the role of polymorphism of DNMT3L should remain a consideration due to the reported methylation status of NR genes in endometriosis (above and in Fig. 1).

Receptor-interacting protein 140. RIP140 is a bi-functional coregulator for multiple members of the NR super-family, such as ER, PR, RAR and GR. RIP140 null male mice are viable, but RIP140 null females are infertile because of the complete failure of mature follicles to release oocytes at the ovulation stage (White *et al.*, 2000). Therefore, RIP140 clearly plays an essential role in female reproductive biology. A small case–control study revealed that some SNPs, such as *Gly75Gly*, *Arg448Gly* and *Ser803Leu of RIP140*, are present in the RIP140 gene locus (Caballero *et al.*, 2005). Among them, the Arg448Gly polymorphism of RIP140 appears to be weakly associated with endometriosis (Caballero *et al.*, 2005). It is possible that an Arg448Gly polymorphism could act as a low penetrance allele contributing to human endometriosis progression. However, the molecular mechanism of how this mutation impacts the development of endometriosis is not well understood. This mutation might affect a protein–protein interaction of RIP140 because the carboxyl terminal-binding protein interacting motif of RIP140 is located close to the Arg448 region.

Post-translational modifications of NR coregulators in the pathogenesis of endometriosis

To modulate diverse cellular processes with limited gene numbers, the molecular properties of NR and NR coregulators, such as stability, structure, function, activity, intracellular localization and interaction with other proteins, are dynamically regulated by post-translational modifications via reversible chemical reactions (e.g. phosphorylation, acetylation, methylation, hydroxylation, glycosylation and nitrosylation) and structural changes (e.g. disulfide-bridge formation and proteolytic cleavage) or the addition of small protein tags (e.g. ubiquitination and neddylation) (Han *et al.*, 2009). These alterations in the molecular properties of a specific target protein by post-translational modifications are associated frequently with human disease progression. For example, estrogen-induced phosphorylation of SRC-3 by atypical protein kinase Cζ protects SRC-3 from proteosomal degradation, promoting increased estrogenic gene activity and proliferation of breast cancer cells through increased SRC-3 stability and levels (Yi *et al.*, 2008). In the case of endometriosis, a proteomic approach identified proteins with aberrant levels in the eutopic endometrium of endometriosis patients in the mid-secretory phase of the menstrual cycle (Stephens *et al.*, 2010). Interestingly, alterations in protein abundance do not always correlate with microarray RNA data, and there is no reason to think that endometriosis is an exception. This suggests that further proteomic analyses are required. It also suggests that, considering the extensive interplay between signaling pathways and kinases in endometriosis, extensive post-translational modification changes likely play a significant role in endometriotic tissues to change the stability and function of regulatory proteins so as to promote endometriosis progression. Although a comprehensive PubMed analysis revealed that some NR coregulators have endometriotic cell-specific post-translational modifications, the number of such NR coregulators published in PubMed to date was quite small. These are summarized below.

The 20 kDa fragment of HSP70

HSP70 proteins function as molecular chaperones that protect and assist the folding process of newly synthesized proteins, helping in translocation, function and general quality control (Morishima, 2005). A 20-kDa fragment of HSP70 has been detected in ectopic tissue lysates isolated from endometriosis patients when compared with the normal endometrium (Chehna-Patel *et al.*, 2011). The 20 kDa fragment of HSP70 is generated from full-length HSP70 by subtilisin/kexin isozyme (SKI)-1 in ectopic tissue. Interestingly, SKI-1 and HSP70 are spatially proximal in endometriotic tissues, but not in the normal endometrium (Chehna-Patel *et al.*, 2011). These findings suggest that the 20 kDa fragment of HSP70 is generated by SKI-1, and may contribute to survival of endometriotic cells. What could be a role for the 20 kDa fragment of HSP70 in endometriosis progression compared with full-length HSP70? HSP70 is designed to interact with transcription factors, such as NF-γB and non-ligand-bound steroid receptors, and to maintain them in an inactive form by physically restricting them within the cytoplasmic compartment (Guzhova *et al.*, 1997; Malhotra and Wong, 2002; Ran *et al.*, 2004). Thus, full-length HSP70 can minimize the NF-κB mediated signaling. In contrast to full-length HSP70, however, the 20 kDa fragment of HSP70 does not interact with transcription factors such as NF-κB. Unrestricted NF-κB then can freely translocate into the nucleus to enhance NF-κB-mediated inflammation. In response to inflammatory signaling, endometriotic tissues could further activate SKI to generate more of the 20 kDa fragment of HSP70 (Fig. 2). In addition, the 20 kDa fragment of HSP70 might be actively involved in the development of endometriosis in ways that have not yet been investigated.

The 70 kDa isoform of SRC-1 coactivator

As described in the previous section, SRC-1 is a major coregulator involved in endometriosis progression (Kumagami *et al.*, 2011). We have recently shown that a specific 70 kDa isoform of SRC-1 is selectively generated at high levels in both human and mouse ectopic endometriotic lesions, whereas the parent full-length SRC-1 is 'reduced' in endometriotic tissues (Han *et al.*, 2012). Molecular and biochemical analyses revealed that this SRC-1 isoform is a 70-kDa SRC-1 C-terminal fragment that is proteolytically generated from full-length SRC-1 by MMP9. Typically, MMP9 is secreted from cells and is involved in tissue remodeling during cell migration and invasion. Because of its tissue remodeling activity, MMP9 is actively associated with cancer initiation and metastasis. In addition to its role in the development of cancer, MMP9 is up-regulated in endometriotic cells during their migration and implantation into distant anatomic sites. Interestingly, we found that MMP9 also has an intracellular function to generate the 70 kDa fragment of SRC-1 from full-length SRC-1 in endometriosis conditions.

How is MMP9 specifically activated in endometriotic tissues but not in the normal endometrium? MMP9 is activated by increased levels of TNF-α (TNFα), a cytokine that is secreted from activated peritoneal leukocytes as part of the pro-inflammatory response to ectopic menstrual effluents during endometriosis progression. Therefore, this newly identified TNFα-MMP9-SRC-1 isoform signaling axis appears to be a key module for the pathogenic progression of endometriosis. What is the specific role of the SRC-1 isoform rather than full-length SRC-1 in the pathogenesis of endometriosis? During endometriosis progression, retrograde menstrual tissue usually activates an inflammatory response and the host immune surveillance system attacks and flushes the unwelcome cells from the pelvic area. In patients with endometriosis, however, these cells escape the immune surveillance system by generating the SRC-1 isoform in ectopic lesions because the SRC-1 isoform prevents TNFα-mediated apoptosis in the endometriotic cells. This non-genomic mechanism of action of the cytoplasmic SRC-1 isoform involves an interaction between the isoform and cytosolic caspase 8 that prevents

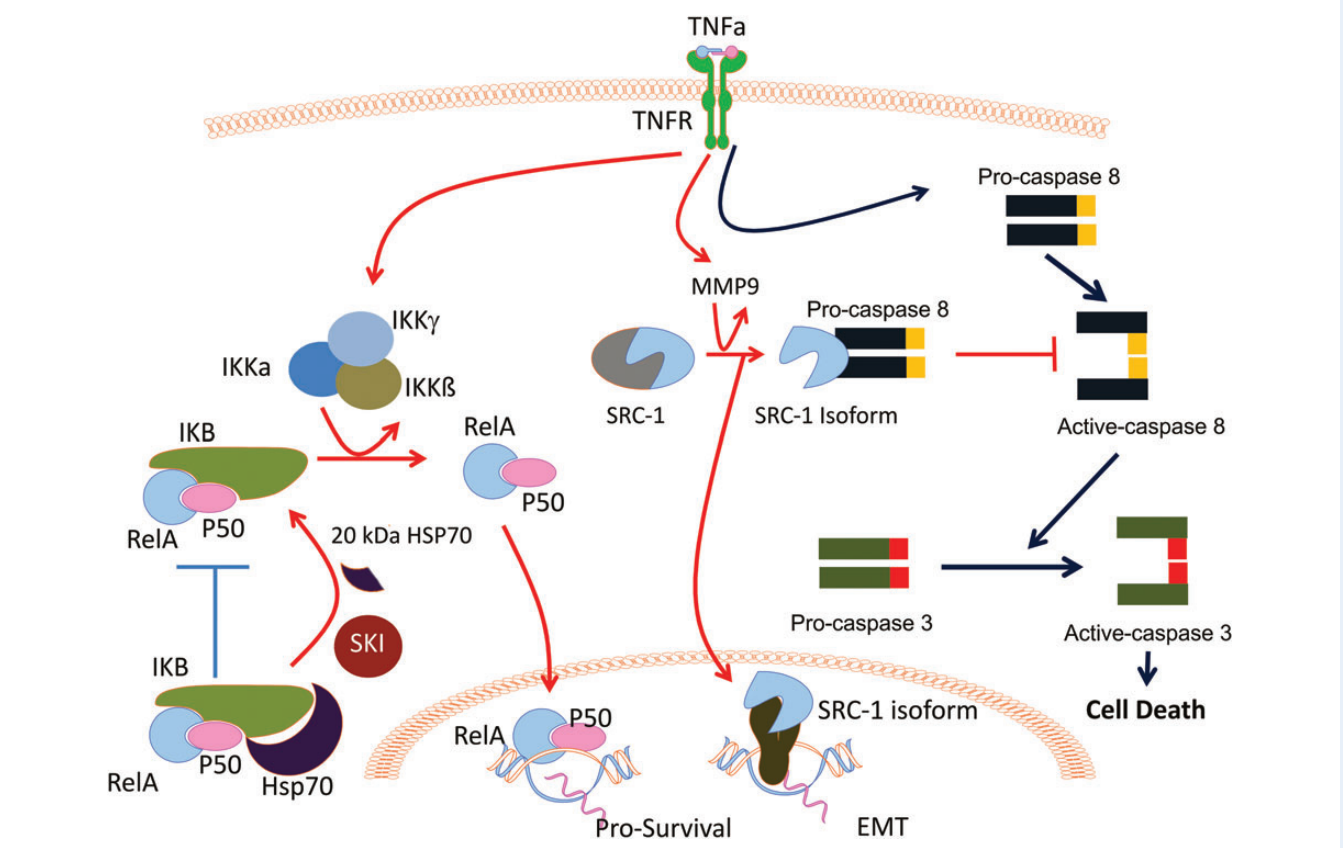

Figure 2 Post-translational modification of NR coregulators in endometriotic tissues. (1) 20 kDa HSP70: in endometriotic tissue, SKI-1 protease actively processes HSP70 to the 20 kDa HSP70 isoform that does not bind I-kappa-B (IKB) protein. Therefore, V-Rel reticuloendotheliosis viral oncogene homolog A (RelA) and P50 easily are generated by the IκB kinase (IKK) complex activated by TNFα in endometriotic tissues. Therefore, RelA/P50 translocate into the nucleus to activate pro-survival gene expression in endometriotic cells. (2) 70 kDa steroid receptor coactivator (SRC)-1 isoform: in normal endometrial cells, TNFα activates caspase8/caspase3 cell death signaling to induce apoptosis (blue line). In endometriotic cells, however, TNFα-activated matrix metallopeptidase (MMP) 9 to proteolytically process the SRC-1 full-length protein to the 70 kDa SRC-1 C-terminal isoform (red line). The resulting 70 kDa SRC-1 isoform interacts with pro-caspase 8 to prevent its activation in response to TNFα. Therefore, inactivation of caspase 8 by the SRC-1 isoform effectively prevents apoptosis progression in ectopic lesions. In addition to anti-apoptosis, the SRC-1 isoform enhances gene expression involved in epithelial-to-mesenchymal transition (EMT) progression in ectopic lesions, supporting their survival.

caspase 8 activation and acts to block TNFα-induced apoptosis (Han *et al.*, 2012) (Fig. 2). In contrast to the SRC-1 isoform, however, full-length SRC-1 does not prevent, but rather allows TNFα-mediated apoptosis in human endometrial cells because nuclear full-length SRC-1 does not interact with caspase 8 (Han *et al.*, 2012). Evading TNFα-induced apoptosis, endometriotic cells are then free to undergo the EMT process that drives cell motility and invasion, phenotypic hallmarks of aggressive endometriosis in women at high risk for this debilitating disease. In fact, overexpression of the SRC-1 isoform enhances EMT processing in endometriotic tissues to support the growth of ectopic lesions (Han *et al.*, 2012) (Fig. 2). Full-length SRC-1 does not induce the EMT process. Consequently, for survival, ectopic tissues change the molecular properties of SRC-1 by proteolytic processing, leading to anti-apoptosis activity and enhanced EMT activity by the SRC-1 isoform. This pathological dysregulation of a nuclear coactivator appears to be a critical predisposing event for establishment and survival and growth of endometriotic lesions.

Conclusion

Many of the current clinical endometriosis treatments are not sufficiently effective and have unacceptable side effects. For example, levels of prostaglandin E_2, COX-2 and various cytokines are highly elevated in endometriotic tissue relative to normal endometrium (Tseng *et al.*, 1996; Noble *et al.*, 1997; Bulun, 2009), suggesting that a heightened pro-inflammatory response is a major component of this disease. Selective COX-2 inhibitors are often used as the first line of conventional treatment for this disorder (Ebert *et al.*, 2005; Ozawa *et al.*, 2006). However, the COX-2 selective inhibitors have gastrointestinal side effects (such as bleeding or perforation of an ulcer), even though their side effects are much less than older non-steroidal anti-inflammatory drugs (Jarupongprapa *et al.*, 2013). Cox-2 inhibitor treatment also increases the risk of dyspepsia, and even may increase the risk for cardiovascular conditions (Mendes *et al.*, 2012; Jarupongprapa *et al.*, 2013). Since it is well established that increased concentrations of E_2 arise in endometriotic tissues from locally elevated levels of aromatase along with reduced activity of 17β-hydroxysteroid dehydrogenase-2 (Brosens *et al.*; Bulun *et al.*, 2010a, b), current endometriosis treatments also involve suppressing E_2 levels through the use of GnRH agonists (Descamps and Lansac, 1998), oral contraceptives, synthetic progestins and/or aromatase inhibitors (Attar and Bulun, 2006). These therapies cause infertility and may have harmful side effects in other estrogen-target tissues such as bone and brain (Shepherd, 2001). In severe cases of endometriosis, however, a total hysterectomy may be the only current option when inflammatory and estrogen suppression therapies are ineffective.

To improve efficiency and overcome the side effects of current endometriosis treatments, there is a great need to identify the 'key molecular driver mechanisms' for this disease. Herein, we summarized how changes in the molecular properties of NRs and their coregulators might specifically contribute to endometriosis progression, and we suggest that these currently represent the highest probability for effective 'driver targets' for new alternative endometriosis treatments. For example, endometriotic cells have higher levels of SF-1 and ERβ because steroidogenesis plays an essential role in ectopic lesion growth. Therefore, regulation of these NR genes seems to be a good therapeutic target for endometriosis. In the case of DNMTs, aberrant levels and genetic variations can impact the expression levels of PR, ERβ, SF-1 and PPAR-γ in endometriotic tissues. Development of DNMT-specific inhibitors or activators might change the epigenetic status of endometrial cell-specific NR genes and suppress ectopic lesions in women. For example, 5-aza-2′-deoxycytidin (5-aza-dC), Zebularine, Procainamide, Procaine and Epigallocate chin-3-3-gallate have been used in cancer treatment to modulate DNMT activity (Miyamoto and Ushijima, 2005; Manoharan *et al.*, 2007). The 5-aza-dC forms irreversible covalent bonds with DNMT1 after its incorporation into DNA, thereby inducing degradation of DNMT1 (Christman, 2002). This DNMT activity modulator could be employed to prevent endometriotic cell-specific NR gene expression for the suppression of ectopic lesion growth.

In addition to regulating endometriosis-specific levels of NRs, modulation of their activity could be employed for alternative endometriosis treatments. Small molecule inhibitors (SMIs) that impact SF-1 protein stability and/or inhibit SF-1 activity could be employed to enhance SF-1 activity in endometriotic tissues. A previous study revealed that two isoquinolinone analogs, SID7969543 and SID7970631, have submicromolar efficacy and selectivity for SF-1 via a panel of NR functional assays (Madoux *et al.*, 2008). These SMIs could be applied for SF-1 targeted endometriosis treatment. Importantly, expression of ERβ is specifically and dramatically elevated in endometriotic tissues compared with the normal endometrium. This is especially notable because ERβ is generally expressed only at low levels in all tissues, and is very low in normal uterus. Therefore, ERβ-specific modulators could be employed to regulate endometriosis-specific ERβ activity for the suppression of endometriosis progression. ERB-041 is a selective ERβ agonist that has anti-inflammatory activity in preclinical models of arthritis and inflammatory bowel disease. ERB-041 treatment suppresses ectopic lesion growth by 40–75% compared with vehicle in a mouse endometriosis model (Harris *et al.*, 2005). ERβ also may be involved in the progesterone resistance seen in endometriotic tissues. The combination of an ERβ antagonist plus progesterone might lead to greater suppression of ectopic lesions by reactivating the PR-mediated anti-proliferative activity in ectopic lesions. In any event, antagonists of ERβ remain a major target approach for future drug combinations for this disease.

In addition to NR-specific target drugs, NR coregulators can change their molecular properties in the face of active inflammation to enhance the progression of endometriosis. Compared with the direct regulation of NR function, modulation of coregulator molecular properties might have more dramatic effects on endometriosis due to the fact that NR coregulators systematically and globally regulate multiple endometriosis progression pathways, whereas an NR drug is likely to only modulate a restricted cellular pathway(s). Consequently, an endometriosis treatment based on down-regulation of a specific NR activity may not be as effective because the cell can activate alternative escape pathways to overcome the NR deficiency. In the case of NR coregulators, however, multiple important cellular pathways can be targeted simultaneously to prevent endometriosis progression. For example, the SRC-1 isoform prevents TNFα-mediated apoptosis and also modulates the EMT required for ectopic lesion maintenance and growth (Han *et al.*, 2012). Since anti-apoptosis and EMT are two of the main essential cellular processes involved in the development of endometriosis, inhibition of the SRC-1 isoform could block these two essential cellular processes at the same time plus inhibit growth (by blocking full-length SRC-1) to completely shut down the essential endometriosis pathogenesis pathways. From this perspective, targeting endometriosis-specific coregulators

may be the most effective method to prevent endometriosis progression. In that vein, our best guess is that the SRC-1 isoform may be the prime molecular therapeutic target for endometriosis treatment because normal endometrium (and other tissues) does not have the SRC-1 isoform. If 'off-target' effects of inhibitors are minimal, SRC-1 isoform-targeted treatment could significantly reduce side effects in normal tissues. Our laboratory has developed SMIs that selectively inhibit SRC-1 activity in various cancer cell lines (Wang *et al.*, 2011). Based on these SRC-1-specific SMIs, SRC-1 isoform-specific SMIs can now be identified and are being used in laboratory trials for endometriosis treatment in animals.

Collectively, the NR/NR coregulator functional axis plays a critical role in the pathogenesis of endometriosis and the discovery of new molecular mechanisms for NR and NR coregulator functions that drive or maintain growth of endometriotic cells should generate new ideas for the next generation of therapies for endometriosis.

Authors' roles

Both of the authors (S.J.H. and B.W.O.) conceived the study, and participated in study design, collection, analysis of data, and in drafting and revising the manuscript.

Funding

Research supported by Eunice Kennedy Shriver NICHD through cooperative agreements U54HD007495; and as part of the Specialized Cooperative Centers Program in Reproduction and Infertility Research of NICHD (B.W.O.).

Conflict of interest

None declared.

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