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Review

Estrogen metabolism and action in endometriosis

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ABSTRACT

Endometriosis is a complex estrogen-dependent disease that is defined as the presence of endometrial glands and stroma outside the uterine cavity. The etiology of endometriosis is multifactorial and includes complex interactions of genetic, immunological, hormonal and environmental factors. Many theories have been proposed, but no single theory can explain all aspects of endometriosis, suggesting that endometriosis is a heterogeneous disease. This review presents the current theories on the pathogenesis of endometriosis, followed by an overview on estrogen metabolism in normal and diseased endometrium of endometriosis patients. The potential role of aberrant expression of individual estrogen-metabolizing enzymes is discussed, and a model mechanism for increased formation of estradiol is presented separately for different types of endometriosis. The disturbed expression of estrogen receptors in endometriosis is detailed, and the estrogen biosynthetic enzymes and receptors are discussed as novel therapeutic targets for the treatment of endometriosis.

Contents

1. Introduction

Endometriosis is a complex disease that is defined as the presence of endometrial glands and stroma outside the uterine cavity (Guidice and Kao, 2004). It is most commonly diagnosed in women of a reproductive age, and affects up to 10% of all premenopausal women. This incidence increases from 35% to 50% in women with

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infertility, pelvic pain, or both (Eskenazi and Warner, 1997; Guidice and Kao, 2004). Symptoms of endometriosis include several types of severe pain and infertility, which significantly impair the quality of life in these women (Berkley et al., 2005; Hompes and Mijatovic, 2007). The diagnostic methods that are available include ultrasonography and magnetic resonance imaging of the pelvis, while the gold standard for definitive diagnosis still remains surgical assessment by laparoscopy (Olive and Barrie Schwartz, 1993; Kennedy et al., 1998; Guidice and Kao, 2004; Carbognin et al., 2006). Ectopic endometrial tissue can be present on the ovaries, the pelvic peritoneum and the rectovaginal septum, and also in other pelvic sites (fallopian tubes, vagina, cervix and uterosacral ligaments). More rarely, extra pelvic sites are involved, such as the pleura and even the brain, thus forming at least three different entities: ovarian endometriosis, peritoneal endometriosis and deep-infiltrative endometriosis (Guidice and Kao, 2004; Nap et al., 2004).

This review aims to present the current theories on the pathogenesis of endometriosis, followed by an overview of the local production of estrogens in peripheral tissues, with the emphasis on the diseased endometrium of endometriosis patients (henceforth referred to as endometriotic or ectopic endometrium). The potential role of aberrant expression of individual estrogen-metabolizing enzymes will be discussed, and a model mechanism for the increased formation of estradiol will be presented separately for all of the three types of endometriosis. The disturbed expression of estrogen receptors in endometriosis will also be detailed, and finally, estrogen biosynthetic enzymes and receptors will be discussed as potential therapeutic targets for treatment of endometriosis.

2. The pathogenesis of endometriosis

Neither the etiology nor the pathogenesis of endometriosis is fully understood. Endometriosis is a polygenic, heritable disease, and surgically confirmed disease occurs six- to nine-fold more commonly in first-degree relatives of affected women than in those of unaffected women (Kenedy et al., 1998; Hompes and Mijatovic, 2007). The immune system is also involved in the pathogenesis of endometriosis (Guidice and Kao, 2004). Peritoneal fluid in women with endometriosis is marked by increased inflammation with increased concentrations of cytokines, such as interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor alpha (TNFα), and various other growth and angiogenic factors, which probably contributes to the survival of ectopic endometrium (Kyama et al., 2003; Matarese et al., 2003). An evolving body of evidence suggests that endometriosis also has an environmental origin (Hompes and Mijatovic, 2007). Indeed, many theories have been proposed, but no single theory can explain all of the aspects of endometriosis. This thus suggests that endometriosis is a heterogeneous disease, where different types of endometriosis have different etiologies and pathogenesis (Story and Kennedy, 2005).

Peritoneal endometriosis comprises superficial lesions over the peritoneal and other serosal membranes, and includes red, black and white implants. The development of such lesions can be explained in part by Sampson's theory of retrograde menstruation of the endometrial tissue through the fallopian tubes and into the peritoneal cavity, and its subsequent implantation (Sampson, 1927). However, most women do not develop endometriosis even though retrograde menstruation is a common phenomenon. Therefore, other factors appear to be involved, such as the amount of menstrual effluent present in the periotoneal cavity, and aspects affecting the adherence, implantation, and proliferation of endometriotic tissue, including changes in immunological mechanisms (Olive and Barrie Schwartz, 1993; Story and Kennedy, 2005).

In ovarian endometriosis, lesions appear as endometriotic cysts (endometrioma) in which endometriotic foci are surrounded by a fibrous capsule. The pathogenesis of ovarian endometriosis is still controversial, but the majority of data support the theory of coelomic metaplasia, which states that the original coelomic membrane undergoes metaplasia, forming typical endometrial glands and stroma (Story and Kennedy, 2005). According to this theory, the mesothelium overlying the ovary invaginates, to form mesothelial inclusions, followed by a metaplastic process that results in the formation of endometriomas (Story and Kennedy, 2005). The finding of endometrioma in a patient with Rokitansky–Küster–Hauser syndrome who did not have a uterus suggests that ovarian endometriosis cannot be explained by the retrograde menstruation theory, thus further supporting the coelomic metaplasia theory (Rosenfeld and Lecher, 1981).

Deep infiltrating endometriosis is characterized by lesions that penetrate to a depth of 5 mm or more, with multi-focal distribution (on bowel, bladder, vagina, ureter, uterosacral ligaments). This can be explained to be a result of a metaplastic process, through the metaplasis of Müllerian remnants (Story and Kennedy, 2005). The other two hypotheses for the pathogenesis of deep infiltrating endometriosis suggest that these lesions originate from secondary infiltration of peritoneal endometriosis or uterine adenomyosis (Story and Kennedy, 2005). Koninckx and Martin (1992) suggested that deep endometriosis should also be divided into three types, with different pathogenesis. The recent detection of endometriosis in lymph nodes of patients with deep infiltrating rectovaginal endometriosis has suggested the lymphatic spread of this disease (Mechsner et al., in press).

In addition to the above-described theories, other hypotheses and theories have been proposed to explain other aspects of the pathogenesis of different types of endometriosis. The induction theory proposes that the menstrual endometrium produces substances that induce peritoneal tissue to form endometriotic lesions (Nap et al., 2004; Nissole and Foidart, 2005). The lymphatic and vascular metastasis theory proposes a dissemination of endometrial cells through lymphatics and blood vessels and explains the development of extra pelvic endometriosis at distant sites, such as the pleura and the brain (Ichida et al., 1993; Nissole and Foidart, 2005; Augoulea et al., 2008).

3. Endometriosis is an estrogen-dependent disease

Endometriosis primarily affects women of reproductive age and is occasionally diagnosed in postmenopausal women, usually in those with relatively high estrogen levels, or who are treated with estrogen-replacement therapy. Suppression of estrogen levels using gonadotropin-releasing hormone (GnRH) agonists can provide regression of the lesions. However, the recovery of estrogen levels after the discontinuation of the therapies causes a relapse of the lesions, which suggests that endometriosis grows and regresses in an estrogen-dependent manner (Kitawaki et al., 2003). Higher levels of estradiol (E2) have been reported in menstrual blood of endometriosis patients, in comparison with healthy women, suggesting that in these endometriosis patients E2 is formed locally in the endometrium (Takahashi et al., 1989). In addition, the successful treatment of several cases of endometriosis using aromatase inhibitors, which prevent the local formation of estrogens, further supports the estrogen dependency of endometriosis (Takayama et al., 1998; Razzi et al., 2004). Moreover, several case reports of histological endometriosis in elderly men undergoing high-dose estrogen therapy for prostate cancer also support this estrogen dependency (Martin and Hauck, 1985; Giannarini et al., 2006). In these men, endometriotic tissue was present on the bladder, the prostate, the lower abdominal wall and in the paratesticular region (Giannarini et al., 2006).

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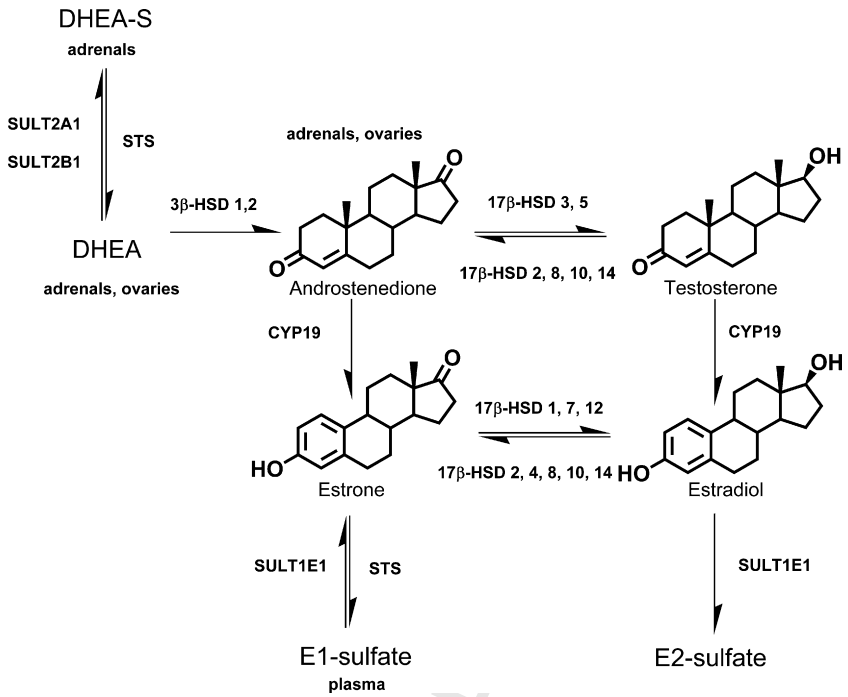

Fig. 1. Local metabolism of estrogens. Estrogen formation from androgens of adrenal and ovarian origin, the circulating levels of estrone sulfate, and estrogen inactivation by estrogen sulfotransferase and oxidative 17β-hydroxysteroid dehydrogenases. DHEA, dehydroepiandrosterone; E1, estrone; E2, estradiol; STS, steroid sulfatase; SULT1E1, estrogen sulfotransferase; SULT2A1, SULT2B1, DHEA sulfotransferases; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; CYP19, aromatase.

4. The local production of estrogens

In premenopausal women, estrogens can be synthesized in the ovaries and in peripheral tissues (e.g. adipose tissue, skin) (Labrie, 1991; Fang et al., 2002; Simpson, 2003). In target tissues, estrogens can originate from three main sources: (1) ovarian secretion via an endocrine mechanism; (2) peripheral formation that increases the concentrations of circulating estrone sulfate, which is converted in the target tissue; and (3) local formation in the target tissue (Fang et al., 2002). Locally, estrogens can be formed from the inactive precursors of adrenal dehydroepiandrosterone sulfate (DHEA-S), dehydroepiandrosterone (DHEA) and androstenedione, and they can be of ovarian origin (DHEA, androstenedione); they can also be formed from circulating levels of estrone sulfate (Fig. 1). Estrogens can thus be produced via the so-called aromatase pathway, from DHEA-S, DHEA or androstenedione and testosterone, by the actions of steroid sulfatase, 3β-hydroxysteroid dehydrogenases (3β-HSDs), aromatase and the reductive 17β-hydroxysteroid dehydrogenases (17β-HSDs), and via the so-called sulfatase pathway, from estrone sulfate by the actions of steroid sulfatase (STS) and reductive 17β-HSDs (Fig. 1; Tables 1 and 2).

5. Estrogen metabolism in normal endometrium

All of the enzymes necessary for the local production of estrogens from DHEA-S, DHEA, androstenedione and estrone sulfate are expressed in human endometrium. DHEA sulfatase activity that can convert DHEA-S to DHEA has been detected in human endometrium (Hausknecht et al., 1982; Prost et al., 1983). A small percentage of DHEA can also be converted to androstenedione, demonstrating the presence of 3β-HSD activity (Collins et al., 1969; Hausknecht et al., 1982). Early studies showed that human endometrium also possesses aromatase, oxidative 17β-HSD and sulfotransferase activities: when endometrial tissue fragments were incubated with testosterone, E2, estrone, E2-sulfate and estrone sulfate were formed (Tseng et al., 1982, 1984; Tseng, 1984). When androstenedione and estrone are incubated with endometrial tissue, these

Table 1
Kinetic characteristics of STS, SULT and 3β-HSDs.

Enzyme	Substrate	K_m (μM)	V_{max} (nmol/min mg)	References
STS	DHEA-S	9.59	1.89[a]	Hernandez-Guzman et al. (2001)
	E-S	72.75	9.55[a]	
SULT1E1	E	5–10[b]		Falany et al. (1995)
	E2	30 ± 5[b]	26.8 ± 4.4[c]	Adjei et al. (2003)
SULT2B1a	DHEA	2.27 ± 0.21	4.31 ± 0.01	Geese and Raftogianis (2001)
SULT2B1b	DHEA	4.37 ± 0.59	1.61 ± 0.01	
3β-HSD type 1	DHEA	4.5	53	Thomas et al. (2001)
3β-HSD type 2	DHEA	47	82	Simard et al. (2005)

SULT2B1a and SULT2B1b are isozymes.
[a] μmol/min mg.
[b] nM.
[c] nmol/h U.

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Table 2
Kinetic characteristics of CYP19 and 17β-HSDs.

Enzyme	Substrate	K_m (μM)	V_{max} (nmol/min mg)	k_{cat} (min^{-1})	References
CYP19	A	62 ± 24[a]			Zhang et al. (2002)
	T	166 ± 27[a]			Krekels et al. (1991)
17β-HSD type 1	E	0.07		1.5[b]	Gangloff et al. (2001)
17β-HSD type 7	E	3.25	0.89		Törn et al. (2003)
17β-HSD type 12	E	3.5			Luu-The et al. (2006)
17β-HSD type 2	Eol	0.35 ± 0.09		3.9 ± 0.5[b]	Lu et al. (2002)
	T	0.61 ± 0.06		3.4 ± 0.4[b]	
17β-HSD type 4	Eol	0.81			Adamski et al. (1995)
	T	UD			
17β-HSD type 8	Eol	118.5	4.67		Ohno et al. (2008)
	T	46.4	0.07		
17β-HSD type 10	Eol	43.0 ± 2.1		0.66 ± 0.01	Yang et al. (2005)
	T	ND			
17β-HSD type 14	Eol	5.6 ± 1.7	2.5 ± 1.0	0.076 ± 0.03	Lukacik et al. (2007)
	T	470	2.6		
AKR1C3	E	ND			
	A	5.3		0.31	Penning et al. (2006)

UD, undetectable; ND, not determined.
[a] nM.
[b] s^{-1}.

can be reduced to form testosterone and E2, respectively, showing androgenic and estrogenic 17β-HSD activities (Collins et al., 1969). However, here more products were formed from testosterone and E2, suggesting that the oxidative 17β-HSD activity prevails in normal endometrial tissue (Collins et al., 1969). In addition to estrone sulfotransferase, a sulfatase activity that converts estrone sulfate to estrone has also been detected in human endometrium (Prost et al., 1983; Adessi et al., 1984). Steroid metabolism studies on endometrial tissue, intact endometrial epithelial glands, and stromal cells have thus shown that in the endometrium of premenopausal women, in addition to ovarian estrogens, a small quantity of estrogens, mainly as estrone, can be formed locally from DHEA-S, DHEA, androstenedione and estrone sulfate. However, as noted already by Kitawaki et al. (1997), some of the above-mentioned studies obtained endometrial specimens after hysterectomies for different, mostly gynaecological, diseases (endometriosis, leiomyomas). Therefore, these results may not completely reflect the situation in normal endometrium.

6. Estrogen metabolism in endometriosis

In ectopic endometrium, aberrant expression of several estrogen-metabolizing enzymes has been reported, which can lead to high E2 biosynthesis and low E2 inactivation, and to an excess of local E2, which results in further proliferation of ectopic endometrium (Guidice and Kao, 2004). In addition to the biochemical disturbances seen in eutopic endometrium of endometriosis patients, the local microenvironment of ectopic endometrium might further affect gene expression in a paracrine manner, which might result in the differences seen between the three different types of endometriosis.

6.1. Aromatase

Increased aromatase expressions at the mRNA and protein levels have been detected in the ectopic endometrium of patients with ovarian, peritoneal, and deep infiltrating endometriosis (Noble et al., 1996; Matsuzaki et al., 2006a; Dassen et al., 2007; Šmuc et al., 2007; Bukulmez et al., 2008; Borghese et al., 2008; Aghajanova et al., in press). Expression did not differ according to the menstrual phase (Bukulmez et al., 2008). Expresssion of aromatase has also been seen in the eutopic endometrium of endometriosis patients, while in normal endometrium, no transcript, or very low levels of transcript were detected (Noble et al., 1996; Kitawaki et al., 1997; Bukulmez et al., 2008). When comparing aromatase expression in different types of endometriosis, significantly higher levels of aromatase mRNA have been found in ovarian endometriosis, with less seen in peritoneal endometriosis and deep endometriotic nodules (Heilier et al., 2006). Here, Heilier et al. (2006) indicated that these differences support the theory of distinct clinical endometriosis entities. In contrast to these studies, Bukulmez et al. (2008) demonstrated increased aromatase mRNA levels in red implants, followed by black implants and the endometrioma cyst capsule. They also indicated that the highest expression correlates with the chronic inflammatory stage of endometriosis.

Zeitoun et al. (1999) detected aromatase activity in cultured stromal cells derived from ovarian endometriomas, and Banu et al. (2008) also reported high expression of aromatase in human immortalized endometriotic stromal cells. In contrast to these studies, several other studies have detected aromatase expression mainly in glandular epithelial cells of ovarian and peritoneal endometriosis, and in deep infiltrating endometriosis (Kitawaki et al., 1997; Matsuzaki et al., 2006a; Fechner et al., 2007; Hudelist et al., 2007; Bukulmez et al., 2008).

6.2. 17β-Hydroxysteroid dehydrogenase type 2

Most studies on the expression of 17β-HSD type 2 have shown its deficient expression in endometriotic tissue. Low levels of 17β-HSD type 2 mRNA or protein, or indeed no expression at all, have been demonstrated in ectopic endometrium in ovarian and peritoneal endometriosis, and in deep-infiltrative endometriosis (Zeitoun et al., 1998; Matsuzaki et al., 2006a,b; Dassen et al., 2007; Borghese et al., 2008). Studies on immortalized cells have also reported barely detectable expression of 17β-HSD type 2 in endometriotic epithelial and stromal cells (Banu et al., 2008). Since progesterone stimulates the inactivation of E2 via 17β-HSD type 2, the decreased expression of 17β-HSD type 2 might be caused by impaired progesterone action (Zeitoun et al., 1998). It has been shown that stromal endometriotic cells fail to produce paracrine factors that are necessary for the

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production of transcription factor Sp1, which further induces 17β-HSD type 2 in epithelial cells (Cheng et al., 2007).

Surprisingly, Matsuzaki et al. (2006b) detected 17β-HSD type 2 mRNA in all of their samples of ovarian endometriosis after laser-capture microdisection, suggesting that E2 levels might be higher in deep infiltrating and peritoneal endometriosis, than in ovarian endometriosis, and growth of epithelial cells might be stimulated via paracrine mechanisms. We have detected no significant differences in 17β-HSD type 2 mRNA levels in ovarian endometriosis compared to control endometrium (Šmuc et al., 2007). Moreover, recently Carneiro et al. (2007) even detected higher levels of 17β-HSD type 2 mRNA by semi-quantitative analysis in ectopic endometrium of patients with peritoneal and ovarian endometriosis, as compared to the control group endometrium. The same study also used immunohistochemistry to detect 17β-HSD type 2 in ectopic and eutopic endometrium, but not in the control group endometrium (Carneiro et al., 2007).

Although decreased levels of 17β-HSD type 2 mRNA have been seen in all three types of endometriosis, at the protein level, decreased expression has been confirmed only in extraovarian endometriotic implants (Zeitoun et al., 1998). Furthermore, other studies that have shown no differences in expression, or increased transcript levels, suggest that the expression of 17β-HSD type 2 still needs further clarification.

6.3. 17β-Hydroxysteroid dehydrogenase type 1

17β-HSD type 1 has a pivotal role in E2 formation. Zeitoun et al. (1998) detected expression of 17β-HSD type 1 by RT-PCR and Northern blotting in the majority of undefined extraovarian endometriotic and eutopic endometrial tissue samples. There were no apparent differences in the steady-state levels of 17β-HSD type 1 mRNA between endometriotic and eutopic endometrial samples in different cycle phases (Zeitoun et al., 1998). Later, along with Borghese et al. (2008) we ourselves (Šmuc et al., 2007) have shown higher levels of 17β-HSD type 1 mRNA in endometriomas, as compared to control endometrium, and Dassen et al. (2007) in deep-infiltrative endometriosis, as compared to normal endometrium, while Aghajanova et al. (in press) showed no differences in expression. In contrast to the results at the mRNA level, Dassen et al. (2007) detected significantly lower immunostaining intensities in epithelial and stromal cells of the eutopic and ectopic endometrium of endometriosis patients, compared with normal endometrium. Expression of 17β-HSD type 1 was also examined in immortalized human endometriotic epithelial and stromal cells, in comparison to endometrial epithelial and stromal cells: here, high levels of 17β-HSD type 1 mRNA were shown for endometrial stromal cells, moderate levels for two out of four endometriotic epithelial cell samples and in endometriotic stromal cells, while no expression were detected in endometrial epithelial cells (Banu et al., 2008).

It is clear that the expression of 17β-HSD type 1 in endometriosis has not been sufficiently studied. Currently there are data showing up-regulation of 17β-HSD type 1 at the transcription level in ovarian endometriosis and in deep endometriotic lesions, while expression in peritoneal endometriosis has not yet been reported. Importantly, there is only one study that has shown immunohistochemistry data (Dassen et al., 2007). The paramount importance of 17β-HSD type 1 in local E2 formation should be sufficient argument for further expression analyses at the protein level in different types of endometriosis.

6.4. Sulfatase and sulfotransferase

High sulfatase activities within the ectopic endometrium would suggest that this tissue can form high levels of estrone from the serum pool of estrone sulfate. The data on expression of STS are rather contradictory. Although metabolism studies have revealed significantly lower sulfatase activities in ectopic rather than eutopic endometrium of patients with ovarian endometriosis (Carlström et al., 1988), we have seen significantly higher levels of STS mRNA in samples of ovarian endometriosis, as compared to control endometrium (Šmuc et al., 2007). Also in peritoneal endometriosis, STS activity has been shown to be lower in ectopic, rather than eutopic, endometrium (Purohit et al., 2008). However, in deep infiltrating endometriosis, Dassen et al. (2007) showed no differences in STS expression between ectopic and eutopic endometrium of patients, and also for normal endometrium of the control group, while they found significantly lower STS protein levels in epithelial cells of eutopic endometrium, compared to normal endometrium. Interestingly, Purohit et al. (2008) recently reported that STS activity in peritoneal endometriotic implants correlates with the severity of this disease; moreover, the STS activity in peritoneal ectopic implants and eutopic endometrium was higher than the aromatase activity, thus suggesting that the sulfatase pathway is important in endometriosis.

Although previously it was reported that there were no significant differences in expression of estrogen sulfotransferase (SULT1E1) at the mRNA level in ectopic endometrium of patients with ovarian and peritoneal endometriosis and in deep infiltrating endometriosis (Šmuc et al., 2007; Dassen et al., 2007; Hudelist et al., 2007), recently Borghese et al. (2008) showed decreased mRNA levels in ovarian endometriosis, supporting the potential importance of the sulfatase pathway.

6.5. Other estrogen-metabolizing enzymes

Expression of other enzymes involved in estrogen formation and inactivation has also been studied in endometriosis. We have examined the expression of reductive 17β-HSD type 5 (AKR1C3) and 17β-HSD types 7 and 12 (Šmuc et al., 2007, in press). Here we showed significantly higher mRNA levels in ovarian endometriosis, *versus* control endometrium, while Borghese et al. (2008) recently detected no differences in expression of 17β-HSD type 7, when compared to eutopic endometrium of the same patients. Among the oxidative 17β-HSDs, Dassen et al. (2007) and Borghese et al. (2008) showed decreased levels of 17β-HSD type 4 mRNA in ovarian endometriosis and deep infiltrating endometriosis. As with Borghese et al. (2008), we did not see significant differences in expression of 17β-HSD type 8 in ovarian endometriosis, compared to control endometrium (Šmuc et al., in press).

Also, 3β-HSD type 2 is expressed in ovarian and peritoneal endometriosis (Tsai et al., 2001). Recently, Borghese et al. (2008) even showed higher expression of 3β-HSD types 1 and 2 in ovarian endometriomas, as compared with eutopic endometrium. The expression of 3β-HSDs and STS further supports the hypothesis that E2 in ectopic endometrium can be formed from the inactive precursors of adrenal and ovarian origin, not only from androstenedione, but also from DHEA and DHEA-S. It is known that the adrenal secretion of DHEA and DHEA-S increases and reaches a maximum before menopause, between the ages of 20 and 30 years (Labrie et al., 2003), further supporting the importance of DHEA as a precursor for E2 formation. Interestingly, Tsai et al. (2001) and Bulun et al. (2005) showed that in addition to aromatase and 3β-HSD type 2, steroidogenic acute regulatory protein (StAR) and other steroidogenic enzymes, including steroid side-chain-cleavage enzyme (SCC) and 17-hydroxylase-17-20-lyase, are also expressed in ovarian and peritoneal endometriosis (see also Attar and Bulun, 2006). Recently, Atttar et al. (in press) demonstrated higher mRNA levels of these steroidogenic enzymes in endometriotic tissue of patients with peritoneal endometriosis, and showed significantly higher levels of progesterone, estrone and E2 in endometriotic

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comparing to endometrial stromal cells, suggesting that ectopic endometrium has a capacity to synthesize E2 from cholesterol *de novo*.

6.6. Overview of estrogen biosynthesis in endometriosis

Several E2-forming and E2-inactivating enzymes are aberrantly expressed in endometriosis. However, the majority of the data show differences only at the mRNA level, which often does not correspond to the amount of the active protein. Therefore the below-proposed mechanisms of excessive E2 production in the three different types of endometriosis might still differ from the real situation in ectopic endometrium, and might represent the best estimate from the current data.

In ovarian endometriosis, over-expression has been shown for: aromatase, which catalyzes the conversion of androstenedione to estrone, and to a lower extent, of testosterone to E2; the reductive estrogenic 17β-HSD types 1 and 12, which can activate estrone to form the potent E2; and AKR1C3, which reduces androstenedione to form testosterone. This thus suggests that E2 is formed from androstenedione via the aromatase pathway (Matsuzaki et al., 2006b; Dassen et al., 2007; Šmuc et al., 2007; Bukulmez et al., 2008; Borghese et al., 2008). Data on the expression of 17β-HSD types 7 and 2, STS and SULT1E1 are rather controversial. One study indicated higher levels of 17β-HSD type 7 and STS, and another one indicated lower levels of 17β-HSD type 2 and SULT1E1, which all might affect E2 production (Šmuc et al., 2007; Borghese et al., 2008). The higher levels of STS shown in one study (Šmuc et al., 2007) and the lower levels of SULT1E1 seen in another study (Borghese et al., 2008) indicate the possible importance of the sulfatase pathway. The up-regulation of 3β-HSD types 1 and 2 (Borghese et al., 2008) show that excessive levels of E2 can be formed from DHEA-S and DHEA (Fig. 2a). The expressions of StAR, SCC, 17-hydroxylase-17-20-lyase and 3β-HSD type 2 indicate that androstenedione, a precursor for E2 formation, can also be formed from cholesterol *de novo* (Tsai et al., 2001; Attar and Bulun, 2006).

In peritoneal endometriosis, higher levels of aromatase and decreased levels of 17β-HSD type 2 suggest that E2 can be formed from androstenedione via the aromatase pathway (Matsuzaki et al., 2006a); since 3β-HSD type 2 is expressed in peritoneal endometriosis (Bulun et al., 2005), E2 can also be formed from DHEA. The expression of reductive 17β-HSDs still awaits further studies. Experimental data indicate that the sulfatase pathway does not contribute to E2 formation, as there is no difference in expression of SULT1E1 and there is significantly lower STS activity in ectopic endometrium compared to eutopic endometrium (Purohit et al., 2008) (Fig. 2b). However, knowing that STS activity prevails over aromatase activity in ectopic and eutopic endometrium of patients with peritoneal endometriosis, the sulfatase pathway may still have certain roles in E2 formation in peritoneal endometriosis (Purohit et al., 2008). Up-regulation of the steroidogenic enzymes (StAR, SCC, 17-hydroxylase-17-20-lyase, 3β-HSD type 2 and aromatase) suggests that *de novo* formation of estrone has an important contribution in the increased local levels of estrogens (Atttar et al., in press).

In deep infiltrating endometriosis, aromatase and 17β-HSD type 1 are over-expressed (Dassen et al., 2007), while the oxidative 17β-HSD types 2 and 4 are down-regulated (Dassen et al., 2007). This shows the ability of the ectopic endometrium to form E2 from androstenedione via the aromatase pathway. The expression of 3β-HSD has not yet been examined. Since there is no difference in expression of STS and SUL1E1 (Dassen et al., 2007), it appears that also in deep endometriosis the sulfatase pathway is less important for E2 production than the aromatase pathway (Fig. 2c).

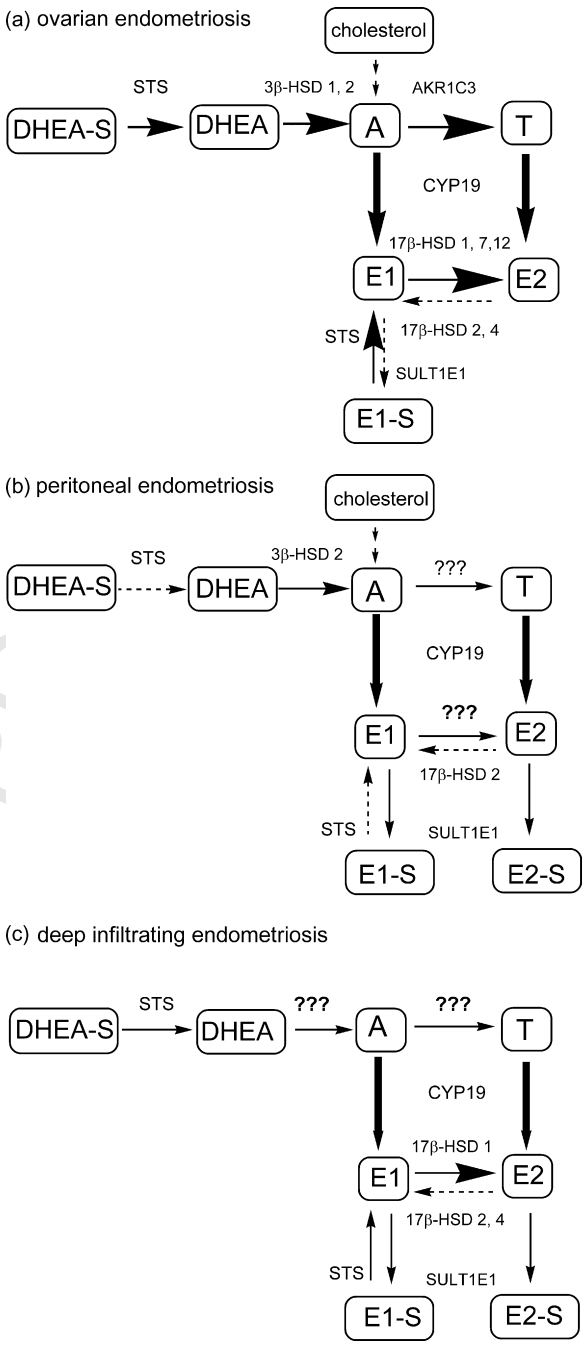

Fig. 2. Estradiol biosynthesis in endometriosis. Proposed mechanisms of excessive E2 formation in ovarian (a), peritoneal (b) and deep infiltrating (c) endometriosis based on the transcriptional levels of the estrogen-metabolizing enzymes. A, androstenedione; T, testosterone; E1-S, estrone sulfate; E2-S, estradiol sulfate; ???, expression of genes not yet examined; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; further abbreviations as for Fig. 1.

7. Estrogen receptors and endometriosis

The E2 that is formed in the endometrium exerts its actions through the estrogen receptors (ERs), of which there are two distinct isoforms: ERα and ERβ. Both of these ERs are members of the steroid receptor superfamily, and they act as ligand-dependent transcription factors. The ERs classically bind to the estrogen response elements (EREs) in the promoter regions of their target genes; however, the ER can also regulate genes that lack an ERE, via protein–protein interactions with other transcription factors, such as activating protein-1 (AP-1) and stimulating protein

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1 (SP1) (reviewed in Cheskis et al., 2007). In addition to the well characterized genomic action, non-genomic actions of E2 have become widely accepted (Young, 2008). These actions can be mediated through ERα, GPR30, a recently described G-protein-coupled receptor, or via mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), calcium influx, and/or cAMP pathways (Levin, 2005; Cheskis et al., 2007; Young, 2008). There are still controversies regarding the nature and location of the receptors mediating the non-genomic actions (Prossnitz et al., 2008; Otto et al., 2008), and due to a limited number of studies on non-genomic actions in endometrium, we are still at the beginning of putting together our understanding of the rapid E2 action in the endometrium.

Studies on ERα and ERβ knock-out mice and the use of ERα- and ERβ-selective ligands have revealed specific roles of each isoform (Couse and Korach, 1999; Harris, 2007). ERα is necessary for the normal functioning of the uterus, with knock-out mice being infertile and not responding to estrogen administration. The ERβ knock-out mouse shows enhanced responses to estrogen stimulation, indicating that ERβ is a modulator of ERα action (Couse and Korach, 1999; Harris, 2007). Both of the ERs are expressed in human endometrium, although ERα predominates over ERβ and their expression differs between the menstrual phases. Aberrant expression of ERs has been reported in estrogen-dependent diseases like endometrial cancer and endometriosis (Utsunomiya et al., 2000; Sakaguchi et al., 2002; Hu et al., 2005).

In the eutopic endometrium of endometriosis patients, ERα and ERβ have been detected throughout the menstrual cycle, where the expression of ERα is much higher than that of ERβ. The mean levels of both isoforms are significantly higher in the proliferative phase than the secretory phase (Matsuzaki et al., 2000). In the ectopic endometrium, the expression of the ERs does not correlate with menstrual phases (Matsuzaki et al., 2000, 2001). Several studies have revealed lower expression of ERα in ectopic endometrium of patients with peritoneal and ovarian endometriosis, as compared to eutopic endometrium, thus showing a decreased ratio of ERα/ERβ (Brandenberger et al., 1999; Fujimoto et al., 1999; Matsuzaki et al., 2001; Hudelist et al., 2005; Šmuc et al., 2007; Bukulmez et al., 2008). There are no studies on the expression of the ERs in deep infiltrating endometriosis. There are also three reports on increased levels of ERβ in ovarian endometriosis, which show similar, or even higher, levels of ERβ than ERα in ectopic endometrium (Fujimoto et al., 1999; Šmuc et al., 2007; Bukulmez et al., 2008). Increased expression of ERβ in ectopic endometrium can be explained by aberrant DNA methylation of the ESR2 promotor; indeed, significantly higher methylation of the ESR2 promoter has been shown in normal endometrium, as compared to endometriotic cells of ovarian endometriosis, where demethylation significantly increased ESR2 mRNA levels (Xue et al., 2007). The consequence of ERβ up-regulation in endometriosis is not yet well understood; however, it has been proposed that its up-regulation has an anti-inflammatory role (Bukulmez et al., 2008). Recently, Trukhacheva et al. (in press) proposed that ERβ modulates the cell cycle, and might thus contribute to proliferation of endometriotic stromal cells.

7.1. Estrogen receptors and proliferative actions

The growth of endometrial cells is stimulated by E2, mainly through the activation of ERα (Vivacqua et al., 2006). However, the levels of ERα decrease in ovarian and peritoneal endometriosis. Does E2 still exert its proliferative effects through ERα? In previous studies in the Ishikawa endometrial cancer cell line it was shown that a 12-h exposure to E2 markedly reduced the content of ERα, but did not affect the expression of ERβ (Vivacqua et al., 2006), suggesting that down-regulation of ERα is a consequence of increased local E2 formation. Recent studies have shown that over-expression of ERβ in endometrial stromal cells results in significant down-regulation of ERα (Trukhacheva et al., in press). So how can the proliferative effects of E2 in ectopic endometrium be explained? Several studies have revealed that in endometrium, E2 can exert its proliferative effects also in a non-genomic manner. In the Ishikawa cell line, E2 induces its growth effect via the GPR30-MAPK pathway, with proliferation reduced in the presence of a GPR30 antisense oligonucleotide, a MAPK kinase inhibitor and a PI3K inhibitor (Vivacqua et al., 2006). Another study in human endometrial cells has shown that E2 can significantly increase serine/threonine kinase (AKT) phosphorylation in stromal cells. This activation was inhibited by a PI3K inhibitor, but not by an ER antagonist, suggesting that E2 exerts part of its proliferative effects through the non-ER mediated AKT signaling pathway (Kayisli et al., 2004). Recently, Trukhacheva et al. (in press) reported that ERβ binds to specific ERα promoter regions, and that ablation of ERβ abolishes E2-induced proliferation, suggesting that ERβ is necessary, but not sufficient, to increase the proliferation of endometriotic stromal cells. Studies on the Ishikawa cell line and recent studies on endometriotic stromal cells thus imply that in ectopic endometrium, E2 exerts its proliferative effect via ERα, the MAPK or AKT signaling pathways, or even via ERβ.

7.2. Estrogen receptors and anti-inflammatory actions

In addition to their well known proliferative effects, estrogens can show anti-inflammatory actions. Most studies have indicated that estrogens exert these actions by repressing genes that promote inflammation, such as *IL-6*, *IL-8*, *TNFα*, through their inhibition of NF-κB activity and DNA binding, or by recruiting SRC-2, which acts as a transcriptional repressor (Ray et al., 1997; Cvoro et al., 2007). E2-dependent repression of inflammatory genes occurs with both ERα and ERβ; however, ERβ is slightly more potent (Cvoro et al., 2007). The inflammation-dependent up-regulation of ERβ relative to ERα has previously been seen in animal models (reviewed in Straub, 2007). Similarly, one would expect differences in ERβ expression between different types of peritoneal endometriosis, in terms of red lesions, which are regarded as early endometriosis and show increased inflammation, and black lesions, which are regarded as advanced endometriosis (Nisolle and Donnez, 1997; Khan et al., 2004). Bukulmez et al. (2008) and Matsuzaki et al. (2001) showed the highest ERβ/ERα ratio in ovarian endometriomas, followed by black lesions and red implants, suggesting that induction of ERβ by inflammation further promotes the local containment of endometriotic lesions.

8. Putative estrogen actions in endometriosis

Based on published data, a hypothesis as to estrogen actions and the crosstalk between inflammation and proliferation in endometriosis can be proposed (Fig. 3). Ectopic endometrium induces inflammation within the peritoneal cavity, which results in the formation of cytokines. IL-1β and the VEGF produced by macrophages or endometriotic lesions can induce COX-2 (Tamura et al., 2002a,b). COX-2 catalyzes the formation of prostaglandin (PG) G2, which is further converted to PGE2 (Bulun et al., 2005). Induction of COX-2 leads to increased levels of PGE2, the most potent stimulator of StAR and aromatase, and a modest stimulator of SCC, 17-hydroxylase-17-20-lyase and 3β-HSD type 2 in endometriotic stromal cells (Noble et al., 1997; Atttar et al., in press). COX-2 induction also indirectly increases the local concentration of E2, which further up-regulates COX-2 and aromatase (Tamura et al., 2004; Bukulmez et al., 2008a) and establishes a positive-feedback loop, as a vicious cycle in favor of continuous estrogen and prostaglandin formation (reviewed in Bulun et al., 2005). Increased levels of E2

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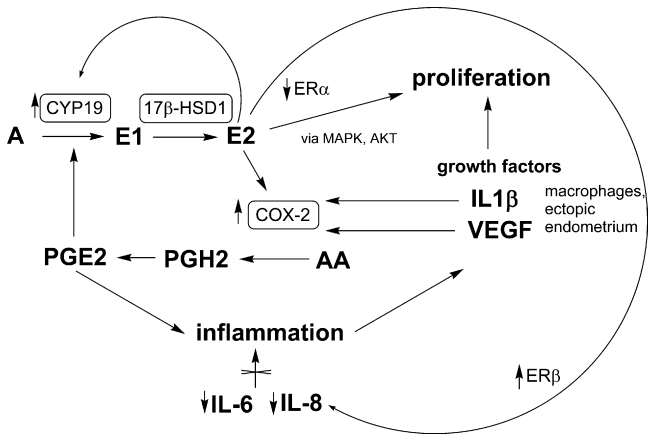

Fig. 3. Estrogens and crosstalk between proliferation and inflammation. Ectopic endometrium induces inflammation within the peritoneal cavity, IL-1β and VEGF produced by macrophages or endometriotic lesions induce COX-2, which catalyzes the formation of PGG2, which is converted to PGE2. The increased levels of PGE2 induce aromatase and indirectly increase the local concentrations of E2, which up-regulate aromatase and COX-2 and establishes a positive-feedback loop in favor of continuous estrogen and prostaglandin formation. This leads to enhanced proliferation and inflammation. Increased levels of E2 exert a proliferative action via ERα or via non-ERα-mediated pathways. Higher levels of ERβ and an increased ERβ/ERα ratio might affect the estrogen proliferative actions via ERα and might elicit anti-inflammatory effects by reducing the expression of pro-inflammatory genes. Abbreviations as for Fig. 1 and main text.

formed in ectopic endometrium can affect the expression of the ERs, and especially ERα (Trukhacheva et al., in press). Due to the decreased levels of ERα seen in ovarian and peritoneal endometriosis (Brandenberger et al., 1999; Fujimoto et al., 1999; Matsuzaki et al., 2001; Hudelist et al., 2005; Šmuc et al., 2007; Bukulmez et al., 2008), the proliferative effects might be achieved either via classical binding to lower levels of ERα, or by binding to other receptors via the MAPK or AKT signaling pathways, or even via ERβ (Vivacqua et al., 2006; Kayisli et al., 2004; Trukhacheva et al., in press). Proliferation might also be stimulated by growth factors and cytokines secreted by peritoneal macrophages, peritoneum and ectopic endometrium. The higher levels of ERβ seen in ovarian endometriosis (Fujimoto et al., 1999; Šmuc et al., 2007; Bukulmez et al., 2008) and the increased ERβ/ERα ratio in peritoneal endometriosis (Brandenberger et al., 1999; Fujimoto et al., 1999; Hudelist et al., 2005) might affect the proliferative actions of estrogen via ERα and might elicit anti-inflammatory effects by reducing the expression of pro-inflammatory genes (Bukulmez et al., 2008).

9. Estrogen biosynthetic enzymes and estrogen receptors as targets for treatment

The current therapy of endometriosis is focused on lowering of the endogenous estrogen levels to pharmacological castration levels, with surgical therapy to remove endometriotic lesions also widely combined with medical therapy to induce a hypo-estrogenic state in patients (Guidice and Kao, 2004). Suppression of the estrogen levels by GnRH agonists provides regression of the lesions; however, this type of treatment cannot be used for prolonged durations because of the severe side effects. In addition, discontinuation of these therapies results in a high recurrence rate (Rice, 2002). Therefore, there is a need for the development new agents that can provide more efficacious therapeutic alternatives combined with fewer side effects (Fechner et al., 2007).

One of the novel therapeutic approaches is focused on local E2 synthesis; therefore, enzymes involved in the increased local production of E2 represent novel drug targets. Inhibitors of these tissue-specific enzymes represent a new class of therapeutics, the selective intracrine modulators, which can prevent the local formation and actions of estrogens. Expression of aromatase in endometriosis has been known since 1996 (Noble et al., 1996), and several aromatase inhibitors have already been used in the treatment of premenopausal and postmenopausal endometriosis. There are also two studies that have shown the effectiveness of this treatment in postmenopausal endometriosis (Takayama et al., 1998; Razzi et al., 2004). For the treatment of premenopausal women, aromatase inhibitors have been used in combination with GnRH agonists, a progestin, progesterone or combination oral contraceptives. There have been four phase II trials here (Amsterdam et al., 2005; Ailawadi et al., 2004; Shippen and West, 2004; Soysal et al., 2004). An aromatase inhibitor with a GnRH agonist, oral progestin or an oral contraceptive resulted in a larger percentage of symptom-free women within 24 months from completion of the treatment (reviewed in Attar and Bulun, 2006).

In addition to aromatase, other enzymes that regulate estrogen actions at the pre-receptor level and are over-expressed in endometriosis represent potential targets for treatment. The reductive 17β-HSDs are pivotal for E2 formation, and since higher levels of 17β-HSD type 1 mRNA were seen in ovarian endometriosis and deep infiltrating endometriosis, this enzyme represents a potential therapeutic target. Although its activity in ectopic endometrium still awaits determination, it appears that inhibitors of reductive 17β-HSDs should be superior over inhibitors of aromatase, since they would more effectively prevent E2 formation by blocking not only the aromatase pathway, but also the sulfatase pathway. Different inhibitors of 17β-HSD type 1 have been synthesized recently and tested using *in vitro* and *in vivo* models (reviewed in Brožič et al., 2008; Day et al., 2008). Inhibitors with different scaffolds have been developed, with the lowest IC_{50} values in the nM range; however these have yet to reach clinical trials (Day et al., 2008).

Inhibitors of STS also have potential for the treatment of endometriosis. One study has shown higher STS mRNA levels in ovarian endometriosis (Šmuc et al., 2007), and in peritoneal endometriosis, the STS activity is considerably higher than the aromatase activity (Purohit et al., 2008). Moreover, only the STS activity correlates with the severity of this disease, and a recent study has shown that the STS inhibitor 667 COUMATE almost completely blocks STS activity in eutopic and ectopic tissue, an effect comparable to the inhibition of aromatase by letrozole (Purohit et al., 2008). Interestingly, also danazol, a compound that has been widely used for the treatment of endometriosis, possesses a weak STS inhibitory activity (Carlström et al., 1984). All of these data suggest that STS inhibitors may be beneficial for the treatment of endometriosis (Purohit et al., 2008).

The ERs are aberrantly expressed in endometriosis. Selective ERβ agonists show anti-inflammatory activities in preclinical models of arthritis and inflammatory bowel disease; these might also be beneficial in endometriosis. When tested in model mice with endometriotic lesions, 40–75% of the mice were completely lesion free after two weeks (Harris et al., 2005). Since no ERβ was detected in the lesions, Harris et al. (2005) hypothesized that the agonist was stimulating the macrophages and/or natural killer cells of the nude mice to recognize the exogenous endometrial tissue as foreign, and to clear it from their system. These data indicate a potential role of ERβ agonists in the treatment of endometriosis, and since ERα appears to be the receptor responsible for mediating the negative feedback to the hypothalamus and pituitary (Couse and Korach, 1999), ERβ selective agonists would not be expected to result in the same side-effect profile as GnRH agonists (Harris et al., 2005).

10. Perspectives and conclusions

Current data on the expression of the estrogen-metabolizing enzymes and the ERs suggest different mechanisms of increased

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local E2 formation in peritoneal and ovarian endometriosis, and in deep infiltrating endometriosis. This further supports the theory of different diseases with different etiologies and pathogenesis. There is still controversy relating to the expression of certain pre-receptor regulatory enzymes, and therefore there remains the need to examine and re-examine the expression of the estrogen-metabolizing enzymes and both of the ERs in different types of endometriosis, separately for glands and stroma, and with special emphasis on pure samples obtained through the help of laser-capture microdissection. As transcription levels do not always correspond to the protein levels, immunohistochemical studies should also be performed. Finally, steroid metabolism studies are indispensable to decipher the complete picture of estrogen metabolism and actions, and thus provide us with a better understanding of the pathogenesis of the separate diseases. A detailed expression analysis at the mRNA and protein levels, together with metabolism studies, should lead to the identification of novel targets for treatment and novel biomarkers for the development of non-invasive diagnostic tests for the different types of endometriosis.

Q5 Uncited references

Prost and Adessi (1983).

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