Is abnormal eutopic endometrium the cause of endometriosis? The role of eutopic endometrium in pathogenesis of endometriosis

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Summary

Endometriosis (EM) is one of the most common diseases which severely affect the health and reproductive function of women of childbearing age. There are fundamental abnormal changes within the eutopic endometrium of women with endometriosis compared to normal endometrium of women without endometriosis. Eutopic endometrium shows enhanced ability of proliferation, implantation and angiogenesis, and greater probability of escaping the unfavorable conditions of the ectopic environment. Therefore, the character of eutopic endometrium determines the fate of the backward-flowing endometrial tissue – to live or to die. The abnormal endometrial tissue in EM patients flows backward to the pelvic cavity, completing a 3-step procedure of pathogenesis (attachment-aggression-angiogenesis), and ultimately develops into EM. Abnormal eutopic endometrium may also play important roles in endometriosis-associated infertility. This recognition regarding the pathogenesis of endometriosis ultimately will help to discover new methods for diagnosis and treatment. Endometrial markers for micro-invasive diagnosis and direct treatment of eutopic endometrium as the origin of the disease should be further investigated.

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BACKGROUND

Endometriosis affects 10–15% of women of reproductive age, appears to be increasing in prevalence, and is also considered as a "mystery disease of the modern age". About 80% of women with endometriosis present with pelvic pain, and 50% co-exist with infertility. This disorder is one of the most common benign diseases which severely affect the health and quality of life of women of reproductive age. Endometriosis is a highly variable condition in terms of age at onset and mode of presentation, range of symptoms, anatomical sites and likelihood of recurrence. In the past few decades, endometriosis has been actively and widely investigated, yet it is still an enigmatic disease. It was first described by Von Rokitansky in 1885 [1]. Sampson proposed the leading theory of retrograde menstruation in 1921 [2]. Several other viable theses are development by metaplasia from Müllerian remnants [3] and distant implantation of menstrual debris [4]. These hypotheses are attractive since they can explain some clinical phenomenon; however, many points argue against them. Especially, Sampson's reflux implantation theory, the most widely accepted hypothesis, faces many doubt and challenge. Why is retrograde menstruation a common event in women with patent fallopian tubes [5], but the morbidity of endometriosis is only 10–15%? The answer to this question may lie in the endometrium itself, since the eutopic endometrium of women with endometriosis shows fundamental differences compared with women without the disease [6]. These differences may contribute to the survival of regurgitated endometrial cells into the peritoneal cavity, and thus to the development of endometriosis. The explanation of this will lead to further understanding of the etiology of this disease and the high rate of recurrence after medical or surgical treatment.

Although the natural process of disease development is not precisely known, endometriosis is established when retrograde endometrial cells engraft within the mesothelium and pelvic cavity. During this process, reflux menses possess the following necessary characteristics: (a) the endometrial debris, including both epithelial and stromal cells, must exist in the reflux menses reaching the pelvis through a patent tube; (b) two components of the endometrial gland and stromal cells must be viable; (c) these cells must have the potential ability to implant into the pelvic organs; (d) the observed anatomical distribution of peritoneal endometrial lesions must correspond to the dynamic mechanism of a tubal reflux. Before the progression into peritoneal endometriosis, the effluent viable endometrial cells must evade the immune attack within the pelvic cavity, attach to the peritoneum and other pelvic organs by the forefront step of adhesion, subsequently break through the extracellular matrix and basement membrane, and ultimately implant at an ectopic location and develop characterized by neo-vascular system formation. Variable and numerous studies indicate that the event sequencing during pathogenesis might be attachment, aggression, and angiogenesis, and we prefer to term it the "3A" model [7].

In this context, we review the published literature on the eutopic endometrium as the origin of endometriosis and its clinical application in diagnosis and treatment.

HOW EUTOPIC ENDOMETRIUM SURVIVE IMMUNE ATTACK?

One important aspect of the physiology of endometriosis is defective immune surveillance. It has been postulated that the clearance of endometrial cells within the pelvic cavity is decreased, and the defective immune surveillance predisposes the susceptible women to develop the disease [8]. However, several mechanisms have been proposed that the intrinsic characteristics of eutopic endometrium participates in the immunotolerance and protects itself from the harmful effects of the immune system.

There is a decreased cytotoxic activity of NK cells in peripheral blood and peritoneal fluid from patients with endometriosis [9,10]. In addition, the reduction is correlated with the severity of the disease and is more obvious in the follicular phase, when retrograde endometrial cells should be cleared by NK cells [11]. The mechanisms that suppress NK cell activity may depend on eutopic endometrium of women with endometriosis. Hirata et al found that cultured endometriosis tissue has inhibitory effects on the cytotoxic activity of NK cells [12]. The supernatants of cultured eutopic endometrial stromal cells had more suppressive effects on NK cell cytotoxicity than those from controls [13]. These findings indicate that substances present in eutopic endometrium of women with endometriosis may suppress NK cell cytotoxicity. One such substance might be the soluble intercellular adhesion molecule-1 (sICAM-1). ICAM-1 is a cell surface molecule, and when it binds with leukocyte function antigen-1 (LFA-1), a surface molecule on NK cells, it activates these cells. sICAM is a circulating fragment of ICAM-1. When sICAM binds with LFA-1, it inhibits NK cells binding with ICAM-1 on target cells and suppresses the activation of NK cells. It has been shown that the expression of sICAM-1 is higher in eutopic endometriotic stromal cells than in those of disease-free women [14].

Several studies demonstrated that there is defective T lymphocyte function in endometriosis. Helvacioglu et al found T lymphocytes had a decreased proliferative response to endometrial cells in women with endometriosis [15]. Steele et al observed T lymphocytes had a reduced cytotoxicity against endometrial cells in women with endometriosis [16]. The mechanism by which endometriotic cells escape from cytotoxic effects of T lymphocyte is attributable to FasL expressed by eutopic endometrium. When a FasL-expressing cell binds a Fas-bearing lymphocyte, it induces the Fas-bearing cell's death by apoptosis. The expression of FasL is increased in eutopic endometrial stromal cells from women with endometriosis compared with women without endometriosis [17].Therefore, eutopic endometrium may cause apoptosis of surrounding lymphocytes and thereby escape from attack by lymphocytes, and further develop into ectopic implants.

Regulatory T lymphocytes (Treg cells) are a special subtype of T lymphocytes. They suppress activation of the immune system and maintain immunostasis and tolerance to self-antigens [18]. Berbic et al demonstrated that the number of Treg cells was substantially decreased in eutopic endometrium of women without endometriosis compared to that of women with the disease. They proposed that the preserved Treg cells seen in eutopic endometrium decreased the ability of immune cells to effectively recognize and target

endometrial antigens during menstruation, allowing the survival of endometrial cells in ectopic sites [19].

Changes of macrophages in the peritoneal cavity of women with endometriosis have been reported by many researchers; however, only recent studies are beginning to clarify changes within the eutopic endometrium. The number of macrophages in proliferative phase is significantly increased in eutopic endometrium of patients with endometriosis compared with that of controls. In addition, there is also an increase in macrophage density in women without endometriosis during the mid-menstrual phase, which was not observed in women with the disease [20]. Khan et al demonstrated that tissue infiltration of macrophages in the eutopic endometrium in women with endometriosis was significantly higher than in control women [21]. Activated macrophages could synthesize and secrete a wide variety of cytokines and growth factors, including interleukin-1 (IL-1), IL-6, IL-8, epidermal growth factor (EGF) and hepatocyte growth factor (HGF), which have been observed to be greatly increased in both eutopic and ectopic endometrium of women with endometriosis but not in disease-free controls [22,23]. These data indicate that macrophages in the eutopic endometrium of women with endometriosis may have similar effects on endometrial cells to those in the peritoneal environment [24], where macrophages have defective scavenger activity and their liberated cytokines and growth factors can promote the growth of endometriosis [25]. Eyster et al recently documented the presence of mutual communications between macrophages and endometrial stromal cells [26]. They speculated that macrophages stimulated the expression of genes in endometrial stromal cells that might support the survival of endometrial cells in ectopic sites.

Apoptosis is a programmed cell death with characteristic morphological and biochemical changes without an inflammatory response, which is another factor that contributes to the survival of endometrial cells in the peritoneal cavity and the development of endometriosis. Eutopic endometria of women with endometriosis demonstrate greatly reduced apoptosis compared to endometria from controls, especially during late secretory/menstrual and early proliferative phases [27]. The mechanism that leads to reduced apoptosis in eutopic endometrium is related with B cell lymphoma/leukaemia-2 (Bcl-2) and Bcl-2-associated X protein (BAX). Bcl-2 is capable of inhibiting apoptosis, while BAX promotes cell death by countering the effect of BCL-2. An increased expression of Bcl-2 protein and decreased Bax expression has been found in proliferative eutopic endometrium compared with normal endometrium from healthy women [28]. The abnormal expression of Bcl-2 and BAX in eutopic endometrium results in decreased apoptosis and survival of regurgitated endometrial cells in the peritoneal cavity.

HOW DO ENDOMETRIAL CELLS ATTACH TO THE PERITONIUM?

The next step in disease development after endometrial cell survival in the pelvic cavity is attachment to the peritoneum. *In vitro* studies have clearly demonstrated that endometrial cells can attach to intact peritoneum and that this process is mediated predominantly by endometrial stromal cells [29]. Eutopic endometrium rather than mesothelium

plays the key role in endometrial cells binding to peritoneal mesothelial cells.

Integrins are proteins known to mediate adhesion of cells to either neighboring cells or to extracellular matrix, and they play an important role in this adhesion process. Recently, increased integrin expression has been observed in eutopic endometrium of women with endometriosis compared with control endometrium [30]. Furthermore, the expression of integrins in both mesothelial and in menstrual effluent has been demonstrated in women with endometriosis [31]. Agents blocking integrins activity could inhibit the attachment process of menstrual endometrium to extracellular matrix *in vitro* [32].

Hyaluronic acid is a major component of the extracellular matrix (ECM) ground substance and is expressed on the membrane of peritoneal mesothelial cells. A recent study indicates that CD44, a key receptor for hyaluronic acid, is highly expressed in endometrial epithelial and stromal cells compared with normal controls without the disease. Menstrual endometrium from women with endometriosis also demonstrates increased adherence to peritoneal mesothelial cells [33]. On the other hand, pretreatment of endometrial fragments by hyaluronic acid prevented the formation of endometriotic lesions in the mouse model. These data suggest that the hyaluronic acid – CD44 binding complex may be involved in the initial attachment of endometrium to peritoneal mesothelial cells [34].

Cadherin is calcium-dependent transmembrane adhesion molecule that mediates cell – cell interaction. Its cytoplasmic part is linked to the actin cytoskeleton via catenin. E-cadherin/catenin complex is pivotal in signal transduction from the outer cell surface to the cytoskeleton, and participates in the in the cell-to-cell attachment between the endometrium and peritoneal mesothelial cells. In one study, the E-cadherin/catenin concentration measured by enzyme immunoassay was significantly higher in the eutopic endometrium of patients with adenomyosis than in the controls [35]. In another study, E-cadherin/catenin expression in the mid-secretory endometrium with endometriosis was significantly higher compared to that of healthy fertile controls [36]. These findings suggest that impaired regulation of E-cadherin/catenin protein expression in eutopic endometrium might be involved in the attachment of endometrial tissue fragments to the peritoneum.

HOW ENDOMETRIAL CELLS INVADE INTO MESOTHELIUM?

Tissue invasion requires destruction of the extracellular matrix. The lysis of the ECM and invasion of mesothelium following attachment could be an important step for the successful invasion of the endometrial cells in endometriosis. In this process, several proteases are involved.

Invasion of endometrial cells into the mesothelium is favored by the endometrial expression of matrix metalloproteinases (MMPs). In eutopic endometrium, several studies have shown an increase in the expression of several MMPs in eutopic endometrium, including MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-11. In addition, reduced levels of the MMP inhibitors – TIMP-1 TIMP-2 and TIMP-3 – have been observed in eutopic endometrial tissues of women with

endometriosis compared to disease-free patients [37–40]. Pretreatment of human endometrial tissue with enhanced MMPs expression can promote the invasion of endometrial cells and establishment of ectopic lesions. In contrast, blocking of MMPs expression and activity by TIMPs results in a significant inhibition of endometriosis development. More importantly, eutopic endometrial tissues from women with endometriosis demonstrate a reduced response to progesterone, allowing a continuous expression of MMPs throughout the secretory phase, which reflects the inherent capacity of endometrial tissue to break down the ECM [41].

Proteolytic status of the fibrinolytic system is determined by the imbalance between plasminogen activators and inhibitors. Plasminogen is activated to plasmin by 2 types of activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), which bind to a specific uPA receptor (uPAR). The activity of the PAs is reduced by specific PA inhibitors (PAIs). Several reports have detected an increase of uPA in the eutopic endometrium from women with endometriosis [42,43]. In addition, peritoneal fluid from women with endometriosis induced even more uPA expression in endometrial cell culture from women with endometriosis [44]. In relation to fibrinolytic receptors, expression of soluble uPAR is greatly increased in eutopic endometrial cells of women with endometriosis [43]. The soluble form of the uPA receptor can increase the activity of uPA by delaying its inhibition by PAI-1 [45].The higher concentration of uPA and soluble uPAR in eutopic endometrium may result in endometrial implants with a higher potential to degrade the extracellular matrix and invasively grow into endometriotic tissue.

HOW ENDOMETRIAL CELLS PROVIDE BLOOD SUPPLY BY ANGIOGENESIS?

The shed endometrial fragments lodged on peritoneum require the establishment of a new blood supply for the survival of implants after local invasion of the basement membrane. There is much evidence indicating that the human endometrium itself is highly angiogenic, which might contribute to the initiation of endometriosis [46]. Among the identified angiogenic factors, vascular endothelial growth factor (VEGF) is the most potent and studied factor in endometriosis. Donnez et al reported that eutopic epithelium of women with endometriosis, as compared to endometrium from healthy women, exhibited significantly increased VEGF levels, particularly during the late secretory phase of the menstrual cycle [47]. The biological activity of VEGF depends mainly on its binding to VEGF receptors (VEGFR), such as VEGFR-1, VEGFR-2, and neuropillin-1 and -2. Some studies have indicated that eutopic endometrium from women with endometriosis had significantly higher expression of VEGF-A (a member of the VEGF family) in glandular epithelium and VEGFR-2 in endometrial blood vessels than that from disease-free controls [48,49].

Epidermal growth factor (EGF) plays fundamental roles in diverse processes such as embryogenesis, development, proliferation, and differentiation. Recently research indicates that it also has an angiogenic activity. The EGF system consists of 4 receptors – human epidermal growth factor receptor (HER) 1-4. It has been shown that EGF and its receptor HER-1 are expressed in normal endometrium [50].

A recently published study using real-time PCR and immunochemistry demonstrated that HER1, HER2, and HER3 were higher in eutopic endometrium from patients with endometriosis compared with endometrium from healthy women, and that HER2 showed a pattern of distribution that differed between eutopic and healthy endometrium. The differences between normal and endometric endometrium were most prominent around the time of menstruation, with a significantly higher expression of HER1 and HER2 in the late secretory phase and HER3 in the proliferative phase, and a significant decrease in expression of HER2 and HER3 from late secretory to proliferative phase in eutopic endometrium [51]. The authors proposed that a high and specific pattern of expression of EGF receptors in menstrual endometrial fragments could aid ectopic implantation and angiogenesis [51].

OTHER ABNORMALITIES IN EUTOPIC ENDOMETRIUM

Aromatase is an important enzyme in estrogen synthesis in target tissues. Expression of aromatase has been detected in the eutopic endometrium of endometriosis patients but not in normal endometrium of disease-free patients [52–54]. The intense inflammatory reaction triggered by retrograde menstrual debris in the pelvic cavity could produce large amounts of prostaglandins and other inflammatory factors that could stimulate aromatase expression [55]. The over-expression of aromatase would in turn induce local production of estrogen, which further induces prostaglandin synthesis by activating the COX II (cyclooxygenase II) enzyme [56,57]. Thus, a feed-back cycle is created between inflammation and estrogen production, involving overexpression of aromatase and COX II, and continuous production of estradiol and prostaglandins [58,59]. Excessive local estrogen would inhibit the phagocytosis of macrophages and NK cells and facilitate the implantation of endometrial cells in the peritoneum [60,61].

Nerve fibres have been identified within the functional layer of endometrium and in increased concentration within the myometrium of women with endometriosis, which could not be observed in women without the disease [62]. Women with endometriosis and pain symptoms have significantly higher nerve fibre density in comparison with women with infertility but no pain. This finding indicates that the nerve fibres in endometriotic plaques may originate from nerve fibre progenitors in the functional layer of the endometrium, which probably provides a mechanism for lesion-specific pain in endometriosis..We also speculate that primary abnormalities in eutopic endometrium of patients have a role not only in the genesis of endometriosis, but also in the genesis of symptoms.

Dendritic cells (DCs) are antigen presenting cells that are highly involved in the initiation and modulation of the immune response. Recently, a study by Schulke et al. showed changes in endometrial DC populations in women with endometriosis, observing increased CD1a immature DC cell populations during the proliferative phase and decreased CD83 mature DC cell populations in the eutopic endometrium of women with endometriosis, compared to the normal controls across all stages of the menstrual cycle [63]. This finding indicates that primary defect in immune cell function in eutopic endometrium of women with endometriosis could predispose these women to develop endometriosis.

Recently, extensive investigations have been performed on the characterization of possible stem cells in the eutopic endometrium. Leyendecker et al found the menstrual flow of women with this disease was composed of significantly more endometrial tissue shed from the basal layer, which is considered the residing site of endometrial stem cells [64]. Götte et al. found increased expression of the adult stem cell marker Musashi-1 in eutopic endometrium of patients with endometriosis, which favors the stem cell origin of endometriosis [65]. Furthermore, endometrial stem cells could regenerate not only endometrial and stromal cells, but also endothelial cells, and form mature blood vessels [66]. The predominant hypotheses proposes that ectopic endometriotic lesions might originate from eutopic endometrial stem cells, which probably abnormally shed from their location in the basal layer of eutopic endometrium from the women with endometriosis, but is not seen in women without this disease [67,68].

Role of Abnormal Eutopic Endometrium in Endometriosis – Associated Infertility

The pathogenesis of endometriosis-related infertility is still unclear. Numerous mechanisms have been proposed to account for fertility impairment in these patients, including altered folliculogenesis, ovulatory dysfunction, poor oocyte quality, luteal phase defects, reduced fertilization, and abnormal embryogenesis. Studies have shown that patients with endometriosis have reduced receptivity due to compromised endometrium [69,70]. It was also found that dysregulation of select genes in eutopic endometrium of patients with endometriosis may lead to impaired embryonic attachment, embryotoxicity, immune dysfunction and apoptosis during the window of implantation [70]. Some researchers also found a reduced decidualization capacity in endometrium from women with endometriosis, and the milieu surrounding the uterine cavity may be involved in impaired eutopic endometrium decidualization [71,72]. The role of eutopic endometrium in endometriosis-related infertility is still unknown due to a lack of understanding about the normal physiologic mechanisms of embryo implantation.

Clinical Implication in Diagnosis and Treatment

There is a general consensus that laparoscopy is the gold standard for the diagnosis of endometriosis. It allows direct visualization of the lesions and histological confirmation. Unfortunately, laparoscopy is a costly invasive procedure requiring general anaesthesia, and it is inevitably associated with potentially severe complications. There is a wide spectrum of symptom severity, and the stage of endometriosis on laparoscopy correlates poorly with the extent and severity of pain. Some patients with minimal disease have severe pain, whereas other women with severe stage III to IV disease are asymptomatic. There is no good noninvasive test for endometriosis even though the evolving genomic and proteomic technologies have been used in the discovery of potential biomarkers of this complex disease [73]. Therefore, there is often a significant delay in diagnosis of endometriosis. In relation to treatment, it is difficult for surgical procedures to succeed in removing the entire implant, and hormonal therapy does not cure endometriosis. The symptoms of the disease are likely to recur once treatment is discontinued. The high recurrence rates may be caused by the basic differences between the eutopic endometrium

of women with endometriosis and disease-free controls, which is not targeted by both medical and surgical treatment. Therefore, the successful diagnosis and treatment of endometriosis may lie in the dysfunctional eutopic endometrium itself. Endometrial biomarkers for diagnosis and treatment of eutopic endometrium as the origin of the disease are promising approaches.

Kitawaki et al. reported that detection of aromatase P450 protein in endometrial biopsy samples strongly correlated with the presence of endometriosis or adenomyosis [74], and suggested that this approach could be used as an outpatient screening test for endometriosis, with sensitivity and a specificity of 91% and 100%, respectively. Another marker being explored for the diagnosis of endometriosis is endometrial biopsy with detection of nerve fibres, which are primarily small unmyelinated sensory C fibers in the functional layer of endometrium. Results from a double blind study yielded a specificity and sensitivity of 83% and 98%, respectively, a positive predictive value of 91% and a negative predictive value of 96%, which is close to the accuracy of laparoscopic assessment by experienced gynecological laparoscopists [62].

Danazol is very effective in controlling endometriosis-associated pain; however, its androgenic side effects such as oily skin, hirsutism, deepening voice, acne and weight gain may affect patient compliance with treatment. These side effects may be diminished by the vaginal route of administration of danazol because the systemic levels of danazol will be lower and the concentration of the drug reaching the uterus may be higher than that achieved by the oral route. A clinical study has indicated that a low dose of vaginal danazol (200 mg/d) for 12 months could result in even greater efficacy in the control of endometriosis-related pain, with far fewer side effects [75]. More importantly, because ovulation is not blocked, over half the patients become pregnant while using the vaginal danazol ring with no harmful effects [76]. The mechanism of these beneficial effects on both fertility and pain of endometriosis may be the result of a direct inhibitory effect of danazol on aromatase expression in eutopic endometrium. The presence of aromatase in eutopic endometrium of patients with endometriosis was reported to be related with pain and decreased endometrial receptivity to implantation [77,78]. In this aspect, inhibition of aromatase expression in eutopic endometrium would explain the pain relief and fertility enhancing effects of vaginal danazol treatment in endometriosis.

Dysmenorrhea is the most frequent symptom in women with endometriosis, and this symptom is decreased in most women using the levonorgestrel intrauterine system (LNG-IUS). Therefore, LNG-IUS has recently been studied as an alternative treatment for endometriosis-associated pain. A recent multicentre randomized, controlled clinical trial to compare the efficacy of LNG-IUS and GnRH-analogue in the control of endometriosis-related pain over a period of 6 months shows that the LNG-IUS and the GnRH-analogue are equally effective in the control of endometriosis-associated chronic pelvic pain [79].Another randomized controlled trial comparing LNG-IUS to depot medroxyprogesterone acetate (MPA) for patients with endometriosis following conservative surgery in symptom control and recurrence prevention shows that LNG-IUS is as effective as MPA in symptom control and prevention of recurrence, and LNG-IUS users show better
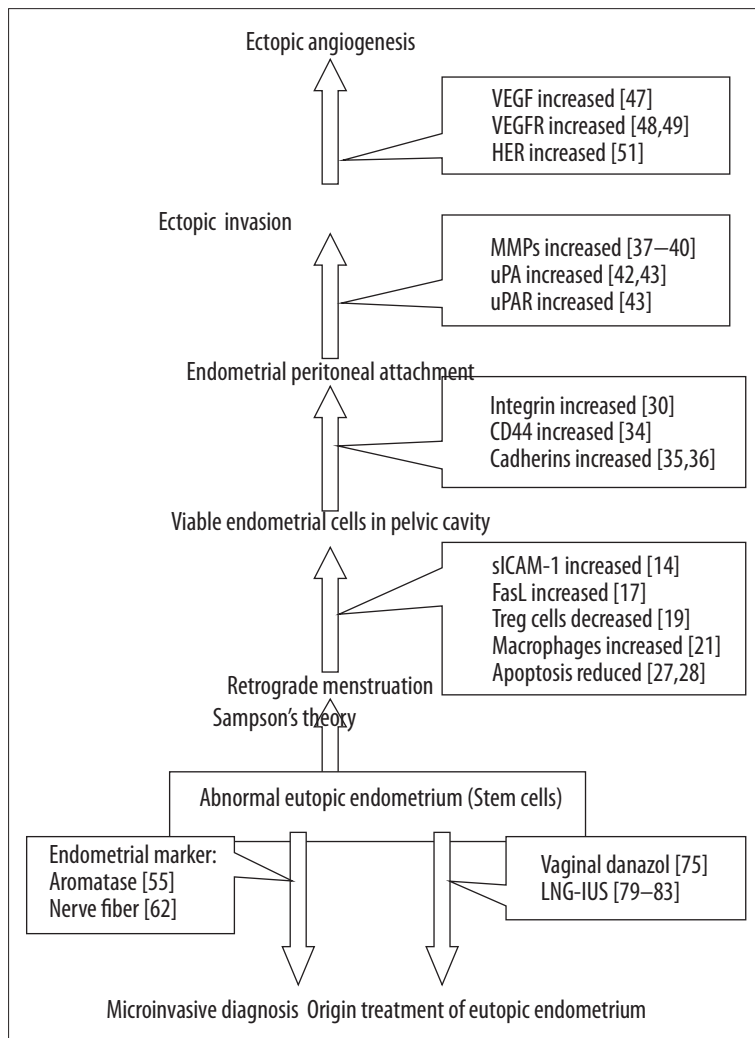
Figure 1. Simplified view of role of eutopic endometrium in pathogenesis of endometriosis(up arrow) and its clincal implications(down arrow). sICAM, soluble intercellular adhesion molecule-1. FasL, Fas ligand. Treg cells, regulatory T lymphocytes. MMPs, matrix metalloproteinases. uPA, urokinase-type plasminogen activator. uPAR, uPA receptor. VEGF, vascular endothelial growth factor. VEGFR, VEGF receptor. HER, human epidermal growth factor receptor. LNG-IUS, levonorgestrel intrauterine system.

compliance [80]. In addition to its effectiveness, LNG-IUS shows fewer side effects associated with hypoestrogenism. More importantly, a recent study also shows that it may increase bone mineral density after use for 3 years, and some cardiovascular risk markers on the lipid profile could be positively impacted [80,81]. All these findings justify long-term treatment of endometriosis-associated pain using LNG-IUS. The mechanism of LNG-IUS in treatment of endometriosis may be a direct effect on eutopic endometrium as the origin of the disease. Our own study indicates that after treatment with LNG-IUS, eutopic endometrium of patients with endometriosis showed increased apoptosis in both endometrial and stromal cells [82]. Another study demonstrated that 6 months of LNG-IUS treatment reduces the expression of the cell proliferation markers estrogen receptor-a (ER-a) and progesterone receptor-a (PRA), and increases the expression of apoptosis markers Fas in eutopic endometrium of patients with endometriosis [83]. These findings explain the mechanism of the clinical improvement observed in endometriosis patients using the LNG-IUS.

CONCLUSIONS

Even though the underlying mechanisms that lead to the development and maintenance of endometriosis are still

an enigma, numerous data indicate that eutopic endometrial glandular and stromal cells may be functioning differently in women with endometriosis compared to normal endometrium in disease-free women. These cells have intrinsic characteristics that favor their survival outside the uterine cavity and precede development of well-documented changes at the peritoneum and other ectopic sites [84]. During menstruation, the sloughing endometrial cells in endometriosis patients could escape immune surveillance from the body and are less susceptible to apoptosis, resulting in an increase in viable cells. After overcoming a phase of immune tolerance, the next step in the development of early endometriosis is the adhesion of endometrial cells to mesothelium and invasion of the extracellular matrix, since the eutopic endometrium of women with endometriosis are more adhesive and invasive then normal endometrium. After the last step of angiogenesis, the endometrial cells establish a new blood supply for the survival of implants, continue to proliferate in ectopic sites, and finally result in endometriosis (Figure 1). During this process of disease development, multiple factors in both the general and local environments have important roles in facilitating the development and maintenance of the disease. Many differences observed between eutopic endometrium and ectopic tissue of patients with endometriosis can

be explained as the direct consequence of a different environment. However, this hypothesis may only apply to peritoneal endometriosis but not to endometrioma and deep endometriosis lesions, because the pathogeneses of endometriosis are different in different lesions [85].

The demonstration of the dysfunctional eutopic endometrium in women with endometriosis might provide the theoretical background for renewed progress in diagnosis and treatment. Endometrial marker for micro-invasive diagnosis and direct treatment of eutopic endometrium as the origin of the disease are promising and should be further investigated.

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