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Pathophysiological Changes in Early Endometriosis

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1. Introduction

Endometriosis is a common but complex gynecological disorder of unknown pathogenesis. It is characterized by ectopic growth of endometrial tissues. Based on Sampson's classical implantation theory, retrograde menstruation, immune escape, adhesion, angiogenesis and growth of endometrial cells are essential milestones in the pathogenesis of endometriosis. The cellular communications of immune, endothelial and endometriotic cells during endometriosis development are mediated via cytokines and chemokines. Many specific cytokines in peritoneal fluid of patients with endometriosis are aberrant from normal women. However, it's not clear at which stage of endometriosis these aberrant cytokines begin to change and owing to the limitation with human study the functions of these cytokines were only investigated in vitro. On the other hand, the onset of angiogenesis is initiated by oxidative stress due to cellular and tissue hypoxia, which is mainly coordinated by the hypoxia-inducible factors (HIFs). HIFs stimulate VEGF transcription and activation in endometriosis lesions in acquiring new blood vessels for survival and growth. Monitoring inflammatory response, oxidative stress and angiogenesis in the endometriosis lesions is of vital importance in understanding the pathophysiological changes during early development of endometriosis.

In our studies, we investigated for the first time the dynamic changes of oxygen reactive species and angiogenesis in the endometriosis implants by in vivo imaging techniques and characterized regulation of cytokines, hypoxia and angiogenesis factors within the first 24 hour of experimental endometriosis in mice. We identified significant oxidative stress and hypoxia responses in the endometriosis implants in early phase only, but specific estrogen-dependent cytokine activations and angiogenesis signaling in late phase. In this chapter, we will describe the non-invasive in vivo imaging method as a valuable tool for monitoring oxidative stress and angiogenesis in endometriosis and to understand its role in the early development and growth of endometriosis. We will also demonstrate oxidative stress preceded hypoxia and cytokine activation and angiogenesis signaling in the pathogenesis of early endometriosis.

2. Development of endometriosis

2.1 Sampson's implantation theory

Endometriosis is one of most common gynecological disorder, but poorly understood condition. As early as in 1860, von Rokitansky (Rokitansky, 1860) is the first one to describe

this disease in detail. Since then, several postulated theories explaining the pathogenesis of endometriosis were raised. The most popular theory is Sampson's classical implantation theory in 1921 (Sampson, 1921). He proposed that the endometrial fragments of uterine endometrium during menstruation can regurgitate through the fallopian tubes and survive in the peritoneal cavity, developing to endometriosis.

There have been numerous studies in human and primate support the implantation theory (Bartosik et al., 1986; Halme et al., 1984). However, this hypothesis cannot explain why only about 10% women suffer from endometriosis, but the incidence of retrograde menstruation should be much higher. What's more, the endometriotic lesion sometimes is present out of peritoneal cavity, such as lungs, brain and heart, instead of peritoneal cavity only (Felson et al., 1960; Joseph et al., 1994; Thibodeau et al., 1987). Besides, genetic, immunological factors and vascular and lymphatic spread are also essential for endometriosis development. Therefore, endometriosis is multifactorial and complicated condition. More studies are needed to explicitly understand the pathogenesis of endometriosis.

2.2 Pathophysiology

With numerous clinical and basic researches on endometriosis, especially peritoneal endometriosis, based on Sampson's retrograde menstruation theory, it's well accepted that the appearance of vital endometrial cells is the first step. Then immune escape, adhesion, implantation, angiogenesis and proliferation are all very important during the development of endometriosis (Fig. 1).

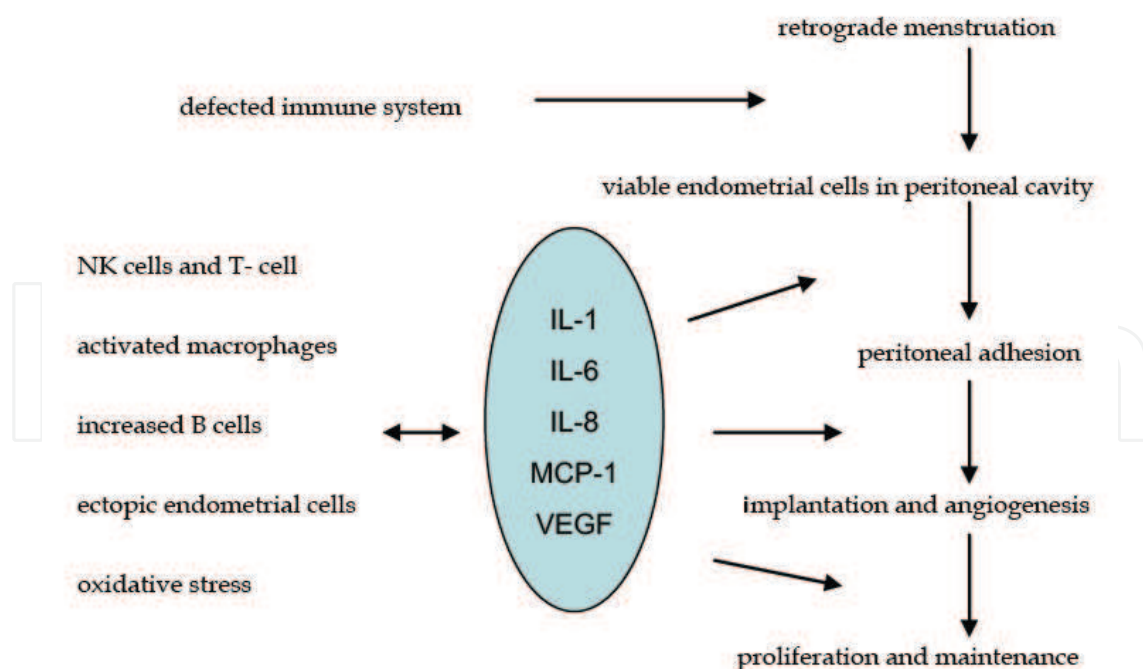


Fig. 1. Summary of the development of endometriosis

In healthy women, macrophages, lymphocytes, natural killer cells and leukocytes eliminate ectopic endometrial cells (Braun *et al.*, 1996). Though the number of immune cells in

peritoneal fluid of women with endometriosis was significantly higher than women without this disease, the function of increased immune cells was decreased (Berkkanoglu *et al.*, 2003). Meanwhile, these defected immune cells may secrete some cytokines and growth factors, such as interleukin-1 (IL-1), interleukin-8 (IL-8), monocyte chemotactic protein 1 (MCP-1) and vascular endothelial growth factor (VEGF) etc., which may help the endometrial cells escape from immune surveillance to adhere to the peritoneum, establish microvessels and finally grow under the stimulation of estrogen cycle (Kyama *et al.*, 2003). However, the reasons causing impaired immune cells are not known. When and what kind of cells as well as molecules taking part in the process from survival to steady growth are still not clear.

2.3 Cellular communications

Endometrial cells have to contact with immune cells, peritoneal lining and vascular endothelial before final growth and maintenance in ectopic location. Cellular immune response is responsible for implantation of the retrograde and vital endometrial cells. The molecules secreted by immune cells would effect the reaction between endometrial cells and other cells.

2.3.1 Macrophages

Macrophages are the most abundant immune cells in peritoneal fluid and their main role is to phagocytose cellular debris and pathogens. They can also promote lymphocytes and other immune cells to respond to pathogens (Tariverdian *et al.*, 2009; van Furth *et al.*, 1979). It has been reported that the number and activity of macrophages in peritoneal fluid significantly increased. However they cannot clear the ectopic endometrial cells and inhibit the development of endometriosis. Modulators of activated macrophages for both immune and non-immune cells promote growth and maintenance of ectopic lesion (Lebovic *et al.*, 2001). There are several evidence to support the change of receptors expression on macrophages leads to impaired scavenger function, which might be caused by abnormal cytokines and growth factors in the peritoneal fluid of women with endometriosis (Berkkanoglu *et al.*, 2003).

2.3.2 Lymphocytes

The two main types of lymphocytes are: B cells accounting for humoral acquired response by secreting soluble antibodies into the body's fluids for eliminating foreign antigens, and T cells responsible for cellular responses. Both of which recognize specific antigen targets. T cells are mainly differentiated into helper T cells promoting antibody production secreted by B cells, regulatory T cells controlling immune response, and cytotoxic/suppressor T cells killing infected cells and cancer cells in the thymus. In endometriosis, it was reported that the proliferation and cytotoxic activity of lymphocytes in peripheral blood is decreased (Dmowski *et al.*, 1981; Steele *et al.*, 1984). Increased T cells, both helper and suppressor T cells, in peritoneal fluid and ectopic endometriotic tissue was observed in women with endometriosis (Dmowski *et al.*, 1994; Hill *et al.*, 1988; Mettler *et al.*, 1996). However, the changes are not consistent. Besides, the function and activity of peripheral T cells might be different from those in peritoneal fluid. In all, it's controversial if the alteration of lymphocytes in peripheral and peritoneal fluid play a role in the development of endometriosis.

2.3.3 Natural killer cells

Natural killer cells (NK cells) constitute a major component of the innate immune system. They have two ways to take part in host defense by expressing different receptors binding to target cells. One receptor type binds immunoglobulin G (IgG). The other includes killer-activating receptors promoting cytotoxic activity and killer-inhibitory receptors (KIR) suppressing cytotoxic activity (Moretta *et al.*, 1995). Oosterlynck and Wilson have found that the cytotoxic activity of peripheral and peritoneal fluid NK cells from women with endometriosis was obviously decreased with the severity of endometriosis (Oosterlynck *et al.*, 1991; Wilson *et al.*, 1994). The decreased NK-mediated cytotoxicity in the peritoneal fluid might contribute to the establishment of endometriosis. The mechanisms that cause aberrant NK cell cytotoxicity are unclear, but seem to be involved in KIR expression (Wu *et al.*, 2000). In a recent study, Maeda *et al.* reported KIR2DL1 as the subclass of KIR overexpressed on NK cells in peripheral and peritoneal fluid of patients with endometriosis.

2.3.4 Peritoneal cells

Several adhesion molecules were found to be expressed in endometrium, which mediate the adhesion and invasion of endometrial cells to peritoneum. Koks found that endometrium preferentially adheres to the extracellular matrix (ECM) of the peritoneum mediated by integrin (Koks *et al.*, 2000). Endometrium expresses various integrins during menstruation shedding and the adhesion can be disrupted by blocking integrin. Integrins are cell-surface glycoproteins acting as receptors for ECM proteins. In normal eutopic endometrium, integrins are important in the interaction between glandular epithelial and stromal cells, and essential for implantation (Lessey *et al.*, 1992). After adherence of endometrial cells to the peritoneum, local degradation of the ECM is required for invasion and implantation. Metalloproteinases (MMPs) causing ECM breakdown, tissue collapse and menstruation was up-regulated in late secretory phase (Salamonsen *et al.*, 1996). This implies that the vital endometrial cells in peritoneal cavity during menstruation shedding already have the potential to invade into peritoneum. What's more, MMPs are present independent of the cycle phase in peritoneal and ovarian endometriosis (Salamonsen *et al.*, 1996), which promotes endometriotic cells to infiltrate into peritoneum further although endometriosis has been established.

2.3.5 Vascular endothelial cells

The ectopic endometrial cells require an accessible blood supply to proliferate and invade through the peritoneum after escaping immune surveillance. Greater angiogenic activity has been found in the peritoneal fluid of women with endometriosis, which are modulated by growth factors and cytokines such as VEGF & IL-8 secreted by ectopic endometrial cells and defected immune cells (Oosterlynck *et al.*, 1993). VEGF is a mitogen for endothelial cells and stimulates the proliferation of both vascular and lymphatic endothelial cells *in vitro* (Joukov *et al.*, 1997) and promotes angiogenesis or hyperplasia of lymphatic vessels *in vivo* (Jeltsch *et al.*, 1997). Increasing evidence indicates that VEGF plays an important role in the angiogenesis of peritoneal endometriosis (McLaren, 2000). VEGF is elevated in the peritoneal fluid and endometriotic lesion of women with endometriosis and correlated with the severity of this disease (McLaren *et al.*, 1996). Its expression is more pronounced around red endometriotic lesions as compared with the more inactive black implants (Donnez *et al.*, 1998).

2.4 Molecular modulations

Cellular communications in endometriosis mediated by inflammatory cytokines and growth factors is mainly regulated by nuclear factor- κ B (NF- κ B) signaling pathway (Fig. 2) (Gonzalez-Ramos *et al.*). NF- κ B mediated gene transcription promoting inflammation, invasion, angiogenesis, and cell proliferation and inhibiting apoptosis of endometriotic cells through p50/p65 dimers and NF- κ B inhibitor I κ B α has been found *in vitro* and *in vivo* studies (Gonzalez-Ramos *et al.*, 2010). Constitutive activation of NF- κ B has been demonstrated in endometriotic lesions and peritoneal macrophages of patients with endometriosis (Laird *et al.*, 2000). Some drugs such as GnRH blocking NF- κ B have been proven efficient at reducing endometriosis-associated symptoms in women (Han *et al.*, 2003). Overload iron produced by erythrocytes from menstruation shedding and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) as well as oxidative stress stimulate NF- κ B activation in macrophages and ectopic endometrial cells, which stimulates synthesis of proinflammatory cytokines, sending a positive feedback loop to the NF- κ B signaling pathway. NF- κ B activation enhances factors of anti-apoptosis, growth, invasion and angiogenesis as well as proinflammatory cytokines such as cyclooxygenase 2 (COX-2), vascular endothelial growth factor (VEGF), macrophage migration inhibitory factor (MIF), interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α), which promote the development of endometriosis. Intercellular adhesion molecule-1 (ICAM-1) and RANTES up-regulated by NF- κ B activity could attract more macrophages to sites of inflammation.

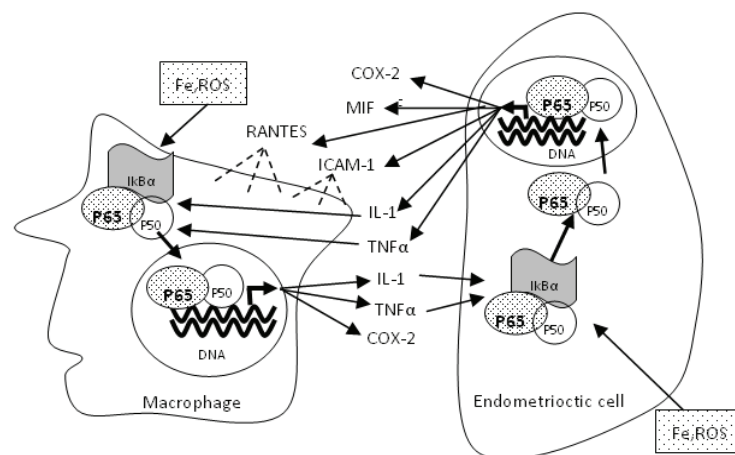


Fig. 2. NF- κ B signaling pathway in endometriosis

3. Early pathogenesis

3.1 Oxidative stress

Oxidative stress has been proposed as a potential factor in the pathogenesis of endometriosis (Van Langendonck *et al.*, 2002). Oxidative stress may occur when the balance of reactive oxygen species (ROS) and antioxidant is disturbed. Several studies have demonstrated that the oxidative stress is involved in endometriosis with increased concentration of ROS, enzymes producing ROS and lower concentration of antioxidant in peritoneal fluid and in the eutopic and ectopic endometrium of women with endometriosis (Ota *et al.*, 2001; Zeller *et al.*, 1987). It's postulated that oxidative stress is stimulated by erythrocytes (Brosens, 1994), apoptotic

endometrial tissue, cell debris and macrophages (Murphy *et al.*, 1998). These inducers may cause activation and recruitment of mononuclear phagocytes which induce oxidative stress. Oxidative stress might lead to a localized pelvic inflammatory reaction with increased pro-inflammatory mediators, cytokines and growth factors (Gupta *et al.*, 2006). These cytokines and growth factors have been widely accepted to promote the immune modulation, adhesion, invasion and angiogenesis of endometriosis. Therefore, understanding of oxidative stress could give a light in the initiation and process of angiogenesis and inflammation during the development of endometriosis. However, two other studies could not find the imbalance between ROS and antioxidant in the peritoneal fluid of women with endometriosis (Ho *et al.*, 1997; Wang *et al.*, 1997). This discrepancy might be due to the use of markers of oxidative stress. Thus, further studies are needed to identify when and how oxidative stress play a role in the pathophysiology of endometriosis in particular during early development.

3.2 Proinflammatory responses

It's widely accepted that endometriosis is a pelvic inflammatory process with defected function of immune system and increased level of abnormal cytokines, chemokines and growth factors in the peritoneal fluid modulating the growth and inflammation of endometriosis. The proinflammatory cytokines and chemokines involved in development of endometriosis include IL-1, IL-6, IL-8, MCP-1 and RANTES (Table 1). These cytokines are mostly secreted by activated immune cells and endometrial cells. They act as paracrine and autocrine messengers in cellular communication. On the one hand, some of these cytokines mediate the adhesion of endometrial cells to peritoneum, such as ICAM-1 and TNF- α and promote proliferation of endometrial cells, such as IL8, as well as stimulate angiogenesis such as VEGF. On the other hand, some cytokines modulate immune cells function: transforming growth factor beta (TGF- β) inhibiting T and B lymphocytes and NK cells which may cause immune tolerance; MCP-1 activating macrophages. The imbalance and abnormal distribution of peritoneal fluid cytokines and their functions imply that inflammation plays a key role in the development of endometriosis.

Whether pelvic inflammation cause endometriosis or endometriosis results in pelvic inflammation is still not well defined. Due to the unsatisfactory diagnostic methods and the limitation of human researches, we are not able to answer this question in human because most patients have had endometriosis for an unknown disease course at the time of diagnosis. Studying endometriosis using animal models complement the understanding endometriosis in human. Chen *et al.* have found that the endometrial cells in the peritoneal fluid induced the production of IL-1 β , TNF- α , VEGF and MCP-1 at 24 hours in the peritoneal fluid of mice. (Chen *et al.*). Similarly, IL-2, IL-4, IL-6, IL-10 and MCP-1, eosinophil chemotactic protein (eotaxin), macrophage inflammatory protein and RANTES as well as CC chemokine receptor (CCR1) were found remarkably expressed in endometriotic lesions on the 4th day in rat model by autologous transplantation of endometrial epithelial fragment to peritoneum (Umezawa *et al.*, 2008). These inflammation cytokines found in early endometriosis is consistent with those found in peritoneal fluid of women with endometriosis. Based on this finding, it can be supposed that endometrial cells in peritoneal cavity might cause inflammation mediating and promoting the development of endometriosis. More studies about early endometriosis are necessary to confirm this hypothesis.

Cytokines	Functions	References
IL-1	Activates T-lymphocytes Differentiates B cells Increase IL-6, sICAM-1, IL-8 & VEGF	(Vigano <i>et al.</i> , 1998) (Lebovic <i>et al.</i> , 2000) (Arici <i>et al.</i> , 1993)
IL-6	Stimulate B cell activity Differentiate T cells Stimulate angiogenesis	(Le <i>et al.</i> , 1989) (Giudice, 1994) (Lin <i>et al.</i> , 2006)
IL-8	Promote proliferation of endometrial and endometriotic stromal cells Stimulate adhesion of endometrial cells to fibronectin Recruit neutrophils and lymphocytes	(Iwabe <i>et al.</i> , 1998) (Arici <i>et al.</i> , 1998) (Garcia-Velasco <i>et al.</i> , 1999)
MCP-1	Activate macrophages Stimulate endometrial cell proliferation	(Oral <i>et al.</i> , 1996) (Arici <i>et al.</i> , 1997)
RANTES	Attract macrophages and lymphocytes	(Khorram <i>et al.</i> , 1993)
ICAM-1	Mediate cell adhesion Inhibit NK cells cytotoxicity	(Oral <i>et al.</i> , 1996) (Koninckx <i>et al.</i> , 1998)
TGF- β	Attract monocytes Inhibit T and B lymphocytes and NK cell activity	(Oosterlynck <i>et al.</i> , 1994)
TNF- α	Initiate the cascade of cytokines and inflammatory response Increase the adherence of cultured endometrial stromal cells	(Laird <i>et al.</i> , 1996) (Zhang <i>et al.</i> , 1993)
VEGF	Stimulate angiogenesis; Attract monocytes	(McLaren <i>et al.</i> , 1996)

Table 1. Functions of cytokines and growth factors involved in endometriosis

3.3 Angiogenesis

The establishment of new blood vessels is essential in growth and survival of endometriosis. Increased angiogenic activity has been demonstrated in peritoneal fluid of women with endometriosis and strong expression of angiogenic factors has been shown in active lesions (Donnez *et al.*, 1998; Nisolle *et al.*, 1993). Moreover, inhibition of endometrial implants by anti-angiogenic agents or VEGF receptors (VEGFR) blocker was observed in animal studies (Dabrosin *et al.*, 2002; Nap *et al.*, 2004). Many anti-angiogenic compounds are studied extensively in animal models of endometriosis. Vlahos stated that pentoxifylline used in the treatment of peripheral vascular disease for many years may cause suppression of endometriotic tissue by inhibiting angiogenesis through VEGF-C and VEGFR-2 expression in rat model (Vlahos *et al.*). Besides, progestins already used in the treatment of endometriosis inhibit human ectopic endometrial lesions in a mouse model by regulating cysteine-rich angiogenic inducer (CYR61), basic fibroblast growth factor (bFGF) and VEGFA (Monckedieck *et al.*, 2009). Endostain, a potent endogenous inhibitor of blood vessel growth, suppress angiogenesis by inhibiting endothelial migration without effecting normal estrous cycles (Becker *et al.*, 2006). What's more, either selective cyclooxygenase-2 (COX-2) inhibitor or immunoconjugate molecule (Icon) suppress angiogenesis in animal models by microvessels density assessment (Krikun *et al.*). However, there is no study to investigate the early process of angiogenesis in endometriosis, which makes new anti-angiogenesis therapy possible for prevention of reoccurrence after surgical treatment.

4. Experimental designs

Oxidative stress, proinflammatory responses and angiogenesis of endometriosis are important during early development of endometriosis. We postulate that the refluxed endometrial tissues in peritoneal cavity could stimulate oxidative stress and proinflammatory cytokines which promote the endometriotic adhesion, angiogenesis and implantation (Fig. 3). The methods we used are complementary to each other's insufficiency (Table 2).

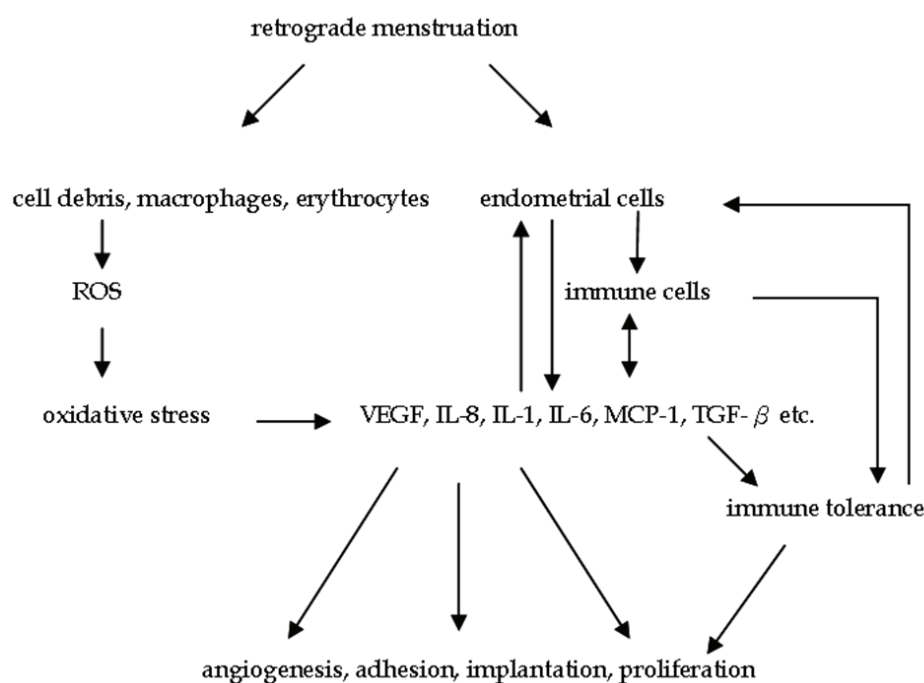


Fig. 3. Summary of early pathogenesis in endometriosis

	Method	Advantage	Disadvantage
Oxidative stress	IVIS	<i>in vivo</i> , longitudinal, semi-quantitative	Expensive
	ROS or RNS markers	<i>in vitro</i> , quantitative, sensitive	non-longitudinal, not stable
Angiogenesis	Cellvizio, IVIS	<i>in vivo</i> , longitudinal, semi-quantitative	expensive, superficial vessels
	Angiogenic markers	<i>in vitro</i> , quantitative	non-longitudinal
Cytokines	Antibody Array	small sample, all cytokines, semi-quantitative	expensive, non-longitudinal
	Multiplex	small sample, selected cytokines, quantitative	expensive, non-longitudinal
	ELISA	large sample, specific cytokines, quantitative, sensitive	non-longitudinal

Table 2. Comparison of available study methods

4.1 Oxidative stress in early endometriosis

In order to monitor the oxidative stress response in early development of endometriosis, an experimental endometriosis model in C57 mice was established by subcutaneous injection of mouse endometrium fragments. A chemiluminescent probe, L-012 (25mg/kg s.c.), was injected to the mice for the noninvasive *in vivo* oxidative stress imaging. L-012 is a new luminol derivative and sensitive chemiluminescence probe reacting with various types of ROS. ROS and reactive nitrogen species (RNS) production in the transplanted lesion can be monitored longitudinally by Xenogen IVIS 200 Imaging System. The results showed that *In vivo* imaging demonstrated significant increased bioluminescence signals for ROS/RNS from the transplanted lesions at the first hour interval. The signal reached a peak after 4 hours of transplantation. Then, the signal gradually decreased and maintained at minimal intensity in the rest of experiment. Immunohistochemistry showed positive lag correlation for the stained Hypoxia-inducible factors (HIF-1) in glandular epithelial cells and stromal tissue from the isolated lesions across the later time after transplantation. For angiogenesis, CD34, VEGF and Von Willebrand factor (vWF) signals were increased in parallel with HIF expression at 1 week thereafter. The non-invasive *in vivo* imaging method provides a valuable tool for monitoring oxidative stress in endometriosis and to understand its role in the early development and growth of endometriosis. The study indicated oxidative stress preceded HIF activation and VEGF angiogenesis in the pathogenesis of early endometriosis.

4.2 Cytokine profiling in early endometriosis

Both donor and recipient BALB/c mice at 7 weeks old were subjected to ovariectomy (OVX) and then were supplemented with 100ug/kg estradiol. Uterine horns from the donor mice were removed into F12 medium. Endometrium was punched into endometrial fragments after peeling off the serosa and myometrium under microscope. Fragments suspended in 0.3ml PBS were injected into peritoneal cavity of recipient mice. Peritoneal fluid was collected at experiment time intervals after transplantation. Cytokines profiles in peritoneal fluid were detected simultaneously. Differentially expressed cytokines were confirmed by ELISA quantification.

The results showed that the levels of CD30, CD36/SR-B3, Dickkopf-related protein (Dkk-1), epidermal growth factor (EGF), Eotaxin, IL-1 receptor antagonist (IL-1ra), IL-6 and Vascular cell adhesion protein 1 (VCAM-1) were significantly increased with the first hour of transplantation. This is the first report to analyze the peritoneal fluid cytokines profiles in experimental endometriosis in mice. The change pattern of cytokines could provide insights in understanding the early development of endometriosis. From the results, we can see that the oxidative stress and abnormal cytokine profiles might contribute to the early development of endometriosis.

4.3 Angiogenesis in early endometriosis

Mice were randomly treated with epigallocatechin-3-gallate (EGCG) extracted from green tea, Vitamin E (antioxidant controls) or vehicle (negative controls) for *in vivo* and *in vitro* microvessel imaging at the end of intervention. Microvascular networks in the endometriotic lesions *in vivo* were imaged by Cellvizio LAB LSU-488 with ProFlex Microprobe S1500. Microvessel length and area were measured using Cellvizio LAB Vessel Detection software and averaged from 4 perpendicular regions of the lesion in replicate.

Endometriotic implants were collected for angiogenesis microarray and pathway analysis after microvessel assessments *in vivo*. Differentially expressed angiogenesis molecules CD34, VEGFA, VEGFB, VEGFC, VEGFD, VEGFR1, VEGFR2 and VEGFR3 were confirmed by quantitative PCR, Western blot and immunohistochemistry. Effects of EGCG on angiogenesis signal transduction were further characterised in human endothelial cell line. Microvessel parameters and angiogenesis VEGFC/VEGFR2 signaling pathway including Jun proto-oncogene (cJUN), interferon-gamma (IFNG), matrix metalloproteinase-9 (MMP9) and chemokine (C-X-C motif) ligand-3 (CXCL3) in endometriotic implants and endothelial cells were studied. The results showed that EGCG, but not Vitamin E, inhibited microvessels in endometriotic implants. EGCG selectively suppressed VEGFC and tyrosine kinase receptor VEGFR2 expression. EGCG down regulated VEGFC/VEGFR2 signaling through cJUN, IFNG and MMP9/CXCL3 pathways for endothelial proliferation, inflammatory response and mobility. EGCG also suppressed VEGFC expression and reduced VEGFR2 and extracellular signal-regulated kinases (ERK) activation in endothelial cells. VEGFC supplementation attenuated the inhibitory effects by EGCG.

5. Prospective and proposal

5.1 Clinical significance and potential applications

Up to date, the only way to diagnose endometriosis is laparoscopy which is minimal invasive but expensive. Non-invasive and cheap diagnostic methods are urgent to be developed. CA-125 is a widely used serum marker for the diagnosis and evaluation of recurrent endometriosis or the success of a surgical treatment. A recent meta-analysis including twenty three studies and assessing the diagnostic performance of serum CA125 has shown that it's a poor diagnostic method with 90% specificity and 28% sensitivity (Mol *et al.*, 1998). One study has found serum IL-6 and peritoneal fluid TNF- α were able to discriminate between patients with and without endometriosis (Bedaiwy *et al.*, 2002). They stated the sensitivity and specificity of serum IL-6 reached 80% and 87% respectively, which is significantly higher than that of CA-125. It indicates that no inflammatory cytokine make a potential biomarker for diagnosis of endometriosis. Its predictive values in early endometriosis require further investigation.

In addition, the recognition of pathogenesis is able to provide new concept to the current unsatisfactory treatments. Hormone medicine is a commonly used drug for prevention of occurrence after surgical treatment. However, lots of patients are not sensitive to these medicines or cannot endure the side effects, such as vomiting and weight gain. New therapy with less adverse effects and more effective function needs to be developed. The study of oxidative stress, inflammation and angiogenesis in the pathogenesis of early endometriosis make it possible. For example, antioxidant therapy with 1200 IU of vitamin E and 1 g of vitamin C for a period of two months lead to a decrease in the inflammation cytokines such as MCP-1, RANTES and IL-6 in peritoneal fluid (Nalini Santanam, 2003). Another drug mifepristone with antioxidant effects was also found to exert an inhibitory effect on endometrial cell growth (Guo *et al.*). As angiogenesis, the VEGF inhibitor and anti-VEGF antibody have been demonstrated to be effective to control and inhibit implant lesion in mice model (Hull *et al.*, 2003). As process of endometriosis contains several steps, the ideal medicine has the potential to control the development of progression of endometrium in early pathophysiological stage (Fig. 4).

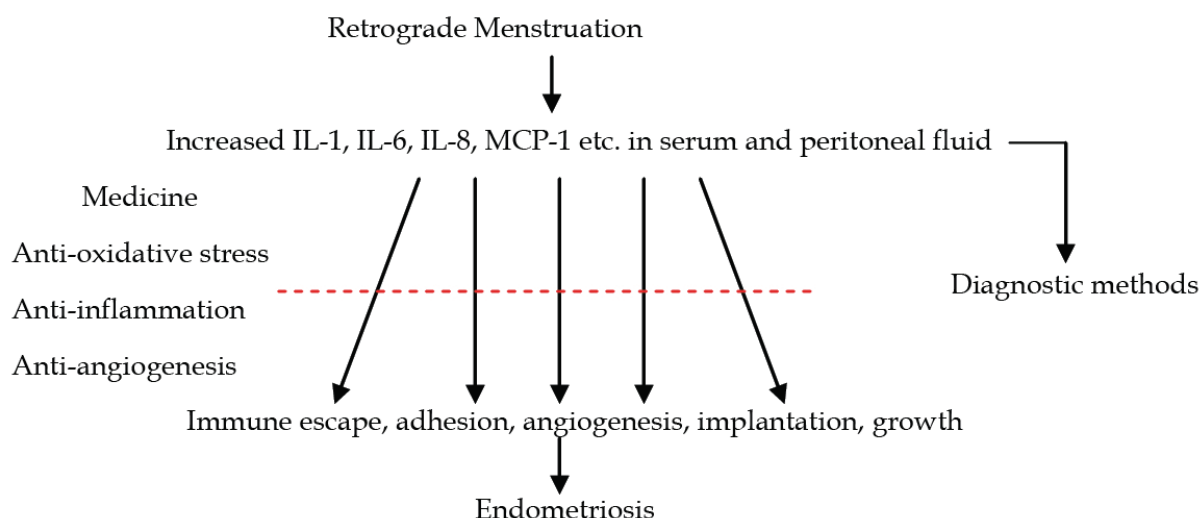


Fig. 4. Hypotheses and clinical potentials of endometriosis

5.2 Study limitations

Due to unavailable systematic studies, the understanding about this disease is still limited although endometriosis has been studied for many years. The limitations and difficulties are as below:

First, at the time of diagnosis endometriosis has already been established with unknown history. Hence, it's impossible to undertake clinical research from the onset to maintenance, which mainly makes the etiology still unknown. Second, it's difficult to have adequate control group. The control women involved in most studies are patients without endometriosis, which means they might have other disease, such as uterine myoma and benign ovarian tumor. The difference between normal eutopic and ectopic endometrium as well as normal pelvic environment and that with endometriosis is impossible to study in human. Third, we have already known genetic, immune system and peritoneal microenvironment are associated with endometriosis, which is supported by different curative effect with the same treatment for different patients and diverse symptoms. Therefore, the clinical treatment is individual and personal which increase the difficulty to observe and compare the different treatments. Fourth, only human and primates suffer from spontaneous endometriosis. The reproductive anatomy, physiology and estrogen cycle characteristics of monkeys are similar to human. Therefore, monkeys are the best animal model to do studies which can not carry out in humans. However, only few centers have the capacity to maintain this expensive animal. The most commonly used animal model is rodents, but there is an enormous phylogenetic gap between these animals and human. Hence, the question is how much data from these rodent models can be extrapolated to human situation. Fifth, primary endometrial and endometriotic epithelial cells cannot be passaged and fall into senescence within 2 weeks, but a stable cell line is necessary for the mechanism study. Until now, there are no stable and commercial normal endometrial and endometriotic glandular and stromal cells available for studying. Several researchers immortalized these cells by using human telomerase reverse transcriptase (hTERT) (Kyo *et al.*, 2003) or transfecting SV40 T-antigen vector (Zeitvogel *et al.*, 2001). However, how much characteristics these immortalized cells are similar to primary endometrial cells are needed to approve.

6. Conclusion

Endometriosis is a multifactorial disorder including retrograde menstruation, immune tolerance, adhesion, transplantation and proliferation modulated by abnormal inflammatory cytokines profile in peritoneal fluid. Future studies are necessary to focus on the whole picture of signaling pathway in early pathogenesis.

The current treatments mainly focus on inhibiting estrogen and its receptors which are not useful for every patient with endometriosis because estrogen is only one factor in the development of endometriosis. The signaling pathway is essential and makes it possible to develop an effective medication which could not only decrease estrogen level but also inhibit inflammation cytokines, ROS and angiogenesis. On the other hand, complete understanding of pathogenesis of endometriosis such as cytokines could provide a new way to diagnose and even to divide the disease into different stages according to pathophysiological characteristics, which makes the treatment individual and personal.

What's more, prevention of endometriosis after surgery is also very important. The current medicines used for prevention of recurrence are not very effective and have various side effects. The understanding of pathogenesis of early endometriosis may produce a better therapy to prevent recurrence. Ultimately, more clinical and basic researches should be carried out to overcome the complicated disease.

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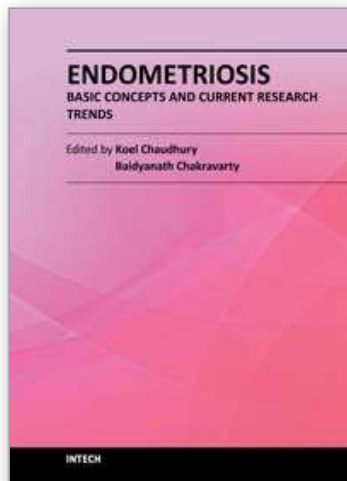
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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies. This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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