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Immune - endocrine interactions in endometriosis

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1. ABSTRACT

Endocrine and immune systems are among the most essential regulators of endometrial physiology, and immune-endocrine interactions are likely to be involved in the pathogenesis of endometriosis. Endometriosis is an inflammatory, estrogen-dependent disease defined by the presence of viable endometrial tissue outside the uterine cavity. Impaired immune response that results in inadequate removal of refluxed menstrual debris has been proposed as a possible causative factor in the development of endometriosis. Moreover, decrease in spontaneous apoptosis of endometrium is the other theory proposed for the development of endometriosis. Endometriotic tissues respond to sex steroids aberrantly and behave differently compared to endometrium in addition to their ability to produce local estrogen. The effects of estrogen on distinct intracellular signaling pathways including MAPK, PI3K/AKT and NF-kappaB may take a role in enhanced endometrial cell survival, altered immune response, and differential cytokine and chemokine expression in endometriosis. Better understanding of immune-endocrine interactions will set the stage for effective immune-targeted therapies not only for endometriosis but also for other endometrial diseases such as adenomyosis, recurrent reproductive failure and implantation-related infertility.

2. INTRODUCTION

Endocrine and immune systems are among the most essential regulators of endometrial physiology. Both systems show menstrual cycle dependent changes and also are widely accepted to participate in morphologic and molecular regulation of endometrium throughout the menstrual cycle and pregnancy. Accordingly, endometrium requires bidirectional interactions with these systems suggesting that the local function of each is dependent on the other (1, 2).

Endometriosis, a common estrogen-dependent disease defined by the presence of viable endometrial tissue outside the uterine cavity, is one of the leading causes of disability among reproductive age women and represents a major personal and public health concern. The prevalence of endometriosis approaches to 6–10% in the general reproductive age female population and to 25-50% in women with infertility (3, 4). Moreover, among women with endometriosis, 30-50% are infertile. In addition to infertility, endometriosis may also cause severe chronic pelvic pain, dysmenorrhea, dyspareunia, and less commonly, affect bowel and bladder functions. It is estimated that 40% of women with pelvic pain has endometriosis (5).

With the results from interdisciplinary studies it is widely accepted that the immune system cooperate with most of the other body systems. One of the most captivating of these inter-systemic communications occurs between immune and reproductive systems. The relationship between thymus and gonads were observed as early as the 1890s by Calzoari (6) and then by Chiodi (7) in 1940s, whose observations are the first clear findings suggesting interaction between the immune system and reproductive hormones. However, scientists were not aware of the importance of their findings and no meticulous studies had been performed on reproductive and immune system interactions until 1970s, when the evidence of involvement of sex hormones in autoimmune diseases and a higher prevalence of autoimmune diseases in women have been reported in 1979. This report by the National Advisory Committee on the Future of Arthritis Research sponsored by the Arthritis Foundation urged that ‘‘an explanation be sought for the remarkable female to male ratio in systemic lupus’’ (8, 9). In the same year, Grossman *et al.* (10) proved that treatment of rats with either estradiol or estrone results in thymic involution regardless of whether the thymus is enlarged due to castration or is of normal size. Moreover, autoimmune diseases such as Grave’s disease, rheumatoid arthritis, Hashimoto’s thyroiditis, systemic lupus erythematosus, Sjögren’s syndrome and scleroderma affect women more commonly (ranging from 75 to 95% of patients are females) (8). Nowadays, estrogens are believed to be involved in a wide range of autoimmune diseases (11, 12) and thought to be responsible for the increased prevalence of these diseases among females (13-16) and that estrogen has notable effects on immunity and inflammatory conditions (17-19).

Pathogenesis of endometriosis has puzzled researchers for more than a century and still remains one of the most enigmatic disorders in gynecology. Numerous theories of the pathogenesis of endometriosis have been proposed. The most widely accepted theory is that the disorder originates from retrograde menstruation of endometrial tissue sloughed through patent fallopian tubes into the peritoneal cavity (20). The development of the disease in the pelvis has been attributed to attachment and invasion of endometrial fragments to the peritoneum, establishment of blood supply, and presence of a suboptimum immune response that does not adequately clear the implants, resulting in their continued survival and growth (21). However, retrograde menstruation is a common phenomenon affecting 76 to 90% of women of reproductive age and does not correlate with the prevalence of endometriosis. Some factors including pro-inflammatory peritoneal environment, immunologic alterations and aberrant response to sex steroids were proposed to render certain women susceptible to attachment and survival of ectopic endometrial tissues in the peritoneal cavity (22-25).

Four main areas of research have provided evidence suggesting that immune-endocrine interactions are likely to be involved in the pathogenesis of endometriosis. These comprise: 1) presence of continuous estrogen production, 2) molecular and cellular alterations in immunologic response 3) presence of proinflammatory microenvironment in ectopic endometrial tissue, and 4) regulation of chemokines by sex steroids. Therefore, in this review we focus in the role of immune and endocrine systems and their possible interactions at cellular and molecular level in the pathogenesis of endometriosis.

3. IMMUNE SYSTEM AND ENDOMETRIOSIS

Endometriosis is associated with changes in cell-mediated and humoral component of innate and acquired immunity. Impaired immune response that results in inadequate removal of refluxed menstrual debris has been proposed as a possible causative factor in the development of endometriosis. Although the peritoneal fluid of women with endometriosis contains increased numbers of immune cells, they seem to facilitate its progression by secreting growth factors and cytokines rather than inhibit the development of endometriosis (26).

3.1. Cellular immunity in endometriosis

3.1.1. Macrophages

Peritoneal macrophages are the major resident cells in the peritoneal cavity, and their number, concentration, and activity is higher in patients with endometriosis than in controls (27). Whereas the increased number and activity of peritoneal fluid macrophages in women with endometriosis would be expected to facilitate the clearance of ectopic endometrial cells and to slow down or inhibit the development of endometriosis, they seem to promote growth of ectopic endometrium. In association with enhanced activation of macrophages, there is an increase in the release of their products, such as cytokines, growth and angiogenic factors, which can promote the survival and growth of ectopic endometrial implants (28).

The phagocytic activity of macrophages is crucial in the face of an invading foreign material or when encountering cellular debris and apoptotic cells. This activity is mediated through surface scavenger receptors, which are regulated by a variety of cytokines and growth factors (29). As these cytokines and growth factors are present in abnormal levels in the peritoneal fluid of women with endometriosis, they may cause defective scavenger receptor function (30). In addition, scavenger receptors play a role in cellular adhesion and non-adherent macrophages do not express type A scavenger receptors. Thus, an increase in non-adherent macrophages without type A scavenger receptors might be another mechanism for abnormally functioning macrophages, which may contribute to the growth of ectopic endometrial cells (31). Classically activated M1 macrophages (i.e. activated by lipopolysaccharide) are potent effector cells that kill microorganisms and tumor cells, and produce copious quantities of pro-inflammatory cytokines (32, 33). In contrast, M2 macrophages tune inflammatory responses and adaptive T helper-1 (Th1) immunity, scavenge debris, and promote angiogenesis, tissue remodeling and repair (32, 33). According to another hypothesis, alterations in the balance between these two subclasses of macrophages may cause an increase in the local production of factors promoting angiogenesis and implantation of endometrial cells (34).

3.1.2. Natural killer cells

Both peripheral and peritoneal natural killer (NK) cells from women with endometriosis display reduced cytotoxicity against autologous and heterologous endometrium (35, 36). Furthermore, the decrease in local NK cell-mediated cytotoxicity in the peritoneal fluid is more pronounced in the moderate and severe stages of endometriosis (37). Alterations in NK cell cytotoxicity in endometriosis appear to be secondary to functional rather than quantitative changes. The percentage of peripheral NK cells is not altered and contradictory reports indicate a decrease, no change, or an increase in peritoneal NK cells (35, 38, 39).

Multiple mechanisms seem to be involved in the suppression of NK cell activity in women with endometriosis. Increased expression of killer inhibitory receptor (KIR), which interact with major histocompatibility complex class I molecules on potential target cells to block NK activity, was demonstrated in NK cells from women with endometriosis (40). In another study, it was shown that the proportion of a subclass of killer inhibitory receptors (KIR2DL1) was increased on NK cells in the peritoneal fluid and peripheral blood suggesting a local and systemic decrease in NK activity (41). Evidence of NK inhibitory factors in ectopic endometrial implants or peritoneal fluid has also been demonstrated. Resection of endometriotic foci increased the percentage of moderately differentiated NK cells, suggesting that endometriosis disturbs differentiation of NK cells (42). The p40 subunit of the NK cell-activating cytokine, interleukin (IL)-12, which is expressed in increased amounts in peritoneal fluid of endometriosis patients, can block NK cell-mediated endometrial lysis (43). Moreover, high levels of peritoneal transforming growth factor (TGF)-beta, typically found in the peritoneal fluid surrounding implants, inhibits NK activity around endometriosis (44).

Interestingly, gonadotropin-releasing hormone (GnRH) agonist treatment causes a progressive increase in both NK cell activity and number in women with endometriosis (39, 45). This might be a direct effect of the GnRH agonist or a consequence of decreased estradiol levels. In contrast, danazol suppresses spontaneous and activated NK cell cytotoxicity *in vitro* (46).

3.1.3. T Lymphocytes

Functional changes in lymphocytes in women with endometriosis were first suggested almost three decades ago. Decreased *in vivo* reactivity to intradermal injection of autologous endometrial antigens and endometrium (measured as the intensity of perivascular lymphocytic infiltration) was demonstrated in Rhesus monkeys with spontaneous endometriosis as compared to healthy controls (47, 48). Similarly, reduced cytotoxic effect of peripheral blood lymphocytes against autologous endometrial cells was observed (48). However, the reports about the peripheral blood lymphocyte profiles are inconsistent. Some studies demonstrated increased CD4:CD8 ratio in peripheral blood of women with endometriosis (27). On the contrary, other studies revealed that peripheral lymphocyte profiles are not markedly affected in endometriosis (38, 49). The biologic activities of peripheral lymphocytes may not reflect the biologic activities of lymphocytes from specific tissue sites. In contrast to peripheral blood, T lymphocyte concentration is increased in the peritoneal fluid and ectopic implants of women with endometriosis (50, 51). Both helper and suppressor subtypes seem to be increased in numbers. However, lymphocyte profiles in the peritoneal fluid of endometriosis patients are still controversial (50, 52, 53).

CD4 T cells are divided into type 1 (Th1) helper T cells which secrete IL-2, IL-12 and interferon gamma and type 2 (Th2) helper T cells, which secrete IL-4, IL-5, IL-6, IL-10, and IL-13 (54). Cell-mediated immunity, including T-cell-mediated cytotoxicity is activated or suppressed by cytokines produced by Th1 and Th2 cells, respectively. In women with endometriosis, Th2 helper cells in peritoneal fluid are reported to aberrantly suppress cell-mediated immunity by up-regulating IL-4 and IL-10 secretions (54, 55). As a result, decreased T cell cytotoxicity may allow implantation of endometrial cells in peritoneum.

The effect of danazol on lymphocyte activation has been measured using peripheral blood mononuclear cell cultures. Danazol significantly inhibited macrophage-dependent T-lymphocyte proliferation in lymphocyte culture systems, however, did not affect macrophage-dependent T lymphocyte activation of B lymphocytes (56). Similar to the effects of danazol, GnRH agonist treatment in women with endometriosis for 2 to 4 months caused a significant increase in T-lymphocyte proliferative activity of peripheral blood lymphocytes but did not have a significant effect on T-cell subsets or B-cell numbers (39).

3.2. Humoral immunity in endometriosis

In addition to alterations in cell-mediated immunity, considerable evidence indicates that endometriosis is associated with polyclonal B-cell activation and an increased incidence of autoantibodies. An increase in B-cell function in women with endometriosis was first suggested in 1980 (57). Later, IgG and complement deposits in the eutopic endometrium and a corresponding reduction in the serum total complement level in women with endometriosis, suggestive of the intra-endometrial antigen–antibody reaction, were demonstrated (58). In a subsequent study, IgG and IgA autoantibodies against endometrial and ovarian tissues were detected in the sera and in cervical and vaginal secretions of women with endometriosis (59). Moreover, antibodies to endometrial transferrin, alpha2-Heremans Schmidt glycoprotein, human chorionic gonadotropin receptor, isoforms I and II of the enzyme carbonic anhydrase, and CA-125 have also been reported in women with endometriosis (59-63). A common carbohydrate epitope, the Thomsen-Friedenreich-like (T) antigen, found on many of these antigens may be involved in the autoantibody response and could indicate an underlying genetic defect (64, 65). The presence of IgG, IgM, and IgA autoantibodies directed against cell-derived antigens such as phospholipids, histones, and polynucleotides in were also detected in women with endometriosis (66). These autoantibodies were hypothesized to be associated with lower pregnancy rates

from *in vitro* fertilization procedures by interfering with embryo implantation. Anecdotal but interesting was the observation that all patients with positive autoantibodies who conceived successfully were on corticosteroid treatment (67). The antibodies against laminin-1, which is a major basement membrane glycoprotein required for initial anchorage and migration of the trophoblast cells into the maternal decidua during implantation through an interaction with integrin receptors, was detected in infertile patient with endometriosis (68).

The postulated autoimmune etiology of endometriosis derives from reports on increased polyclonal B-cell activity, abnormalities in function of B and T cells, reduced NK cell activity, multiple organ tissue damage, altered apoptosis, familial inheritance, presence of autoantibodies to endometrium, tendency to atopic illnesses and increased likelihood of other autoimmune diseases (35, 66, 69-73). In a survey including more than 3600 volunteers with surgically verified endometriosis, high rates of autoimmune and endocrine disorders (fibromyalgia, chronic fatigue syndrome, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and hypothyroidism) and atopic diseases (allergies, asthma, and eczema) were demonstrated in women with endometriosis. The rate of Sjogren's syndrome was 24 times, systemic lupus erythematosus was 20 times, and thyroiditis was six times higher than that expected in the general population (74). Although endometriosis has these characteristics of an auto-immune disease, there are still some missing criteria in postulating and accepting endometriosis as an autoimmune disease. Although a strong genetic component exists in endometriosis, no association with specific HLA haplotypes has been demonstrated yet (75). In order to define a disease truly autoimmune in nature, pathological changes in the tissues of the actively sensitized animal resembling those of the corresponding disease should be demonstrated but there is still no such study performed to investigate this phenomenon.

4. ENDOCRINE SYSTEM AND ENDOMETRIOSIS

Traditional endometriosis treatments have aimed to decrease endogenous estradiol production since it has been well established that endometriotic implants are dependent on estrogen for their maintenance and growth. Although peripheral levels of estrogen are not different between women with or without endometriosis, the amount of local estrogen to which endometriotic tissue is exposed exceeds systemic levels. This is due to the aromatase activity in ectopic endometrium that converts androstenedione to estrone and testosterone to estradiol (76). In the ectopic endometrium, steroidogenic factor-1 (SF-1), a transcription factor capable of stimulating aromatase production, binds more avidly to the aromatase promoter site than does competing binding protein (COUP-TF), a factor that inhibits transcription. Therefore, the aromatase gene is preferentially expressed. Low levels of aromatase mRNA expression were also demonstrated in the eutopic endometrium of women with endometriosis (77). In contrast, normal endometrium does not express SF and therefore does not produce aromatase (78). Prostaglandin E_2 (PGE_2) was found to be the most potent inducer of aromatase activity in endometriotic cells (79). Moreover, estrogen was reported to increase PGE_2 formation by stimulating the cyclooxygenase type 2 (COX-2) enzyme (80). Thus, a positive feedback loop for continuous local production of estrogen and PGs is established, favoring the proliferative and inflammatory characteristics of endometriosis.

The major product of aromatase activity in endometriosis, namely estrone, is only weakly estrogenic and must be converted to a more potent estrogen, estradiol, to exert a full estrogenic effect. The enzyme 17beta-hydroxysteroid dehydrogenase (17beta-HSD) type 1, which converts estrone into estradiol, is expressed in endometriosis (81). The conversion of estradiol to estrone is completed by 17beta-HSD type 2, normally present in normal endometrial cells; however, endometriotic cells lack this enzyme, leading to impaired inactivation of estradiol and increased local concentrations of this steroid hormone (81). It has been shown that progesterone induces the activity of 17beta-HSD type 2 in normal endometrial glandular cells in culture, one of the anti-estrogenic properties of progesterone.

The relative progesterone resistance in endometriotic lesions, which could lead to further escalation of estradiol actions on these lesions, because progesterone down-regulates estrogen receptors, curtailing the effects of estradiol at the cellular level was demonstrated (21). The progesterone receptor (PR) is expressed as A and B isoforms, which differ functionally. Progesterone action on target genes is conferred primarily by PR-B homodimers; truncated progesterone-receptor A represses function of the B isoform (82). It is likely that progesterone resistance is primarily due to a significant reduction of PRs, presence of the inhibitory isoform PR-A and the absence of the stimulatory PR-B in endometriotic implants compared with normal endometrium (83). It can be hypothesized that the lack of PR-B and extremely low levels of PR-A contributes to increased local levels of estradiol, since progesterone fails to induce the estradiol-metabolizing enzyme 17beta-HSD type 2 in endometriotic tissues (84).

5. IMMUNE-ENDOCRINE INTERACTION AT MOLECULAR LEVEL

As discussed above, increased proinflammatory cytokine expression and leukocyte influx, and changes in immune response characterize endometriosis as an immune-inflammatory disease. Ectopic endometrial tissues respond to sex steroids aberrantly and behave differently compared to endometrium in addition to their ability to produce local estradiol. Furthermore, endometriotic implants generally do not demonstrate the typical cyclic histology, and those that do are often asynchronous with the eutopic endometrium (85). The presence of high rates of autoimmune and endocrine disorders and atopic diseases in women with endometriosis (74) further supports immune-endocrine interaction in endometriosis.

5.1. Immune-surveillance and apoptosis

Defective immune surveillance is an interesting concept in the pathogenesis of endometriosis. It has been postulated that endometrial cells in the peritoneal fluid avoid immunosurveillance and implant into peritoneum in women with endometriosis (86). Several mechanisms have been proposed how endometrial cells escape from the leukocyte recognition. It has been speculated that lymphocytes can adhere to endometrial cells through the lymphocyte function-associated antigen-1 (LFA-1) - intercellular adhesion molecule-1 (ICAM-1) dependent pathway and present them as a target to NK cells. Soluble form of ICAM-1 (sICAM-1), which was released from endometriotic lesions, competes with ICAM-1 to bind LFA-1. When sICAM-1 binds LFA-1, it makes lymphocytes less available for binding with cell surface ICAM-1 on target cells, thus preventing the recognition of endometrial cells by these lymphocytes and prevents subsequent NK cell-mediated cytotoxicity (87-89). Furthermore, IL-6 secreted by endometriotic cells in concert with interferon-gamma may upregulate sICAM-1 production by macrophages of patients with endometriosis. As a result, increased secretion of sICAM-1 may allow endometrial fragments to evade immunosurveillance, survive and implant (90).

A decrease in spontaneous apoptosis of human endometrium is one of the theories proposed for the development of endometriosis (91). Previous studies have demonstrated that endometrial apoptosis in the eutopic endometrium is lower in women with endometriosis compared to disease-free women and is further decreased in ectopic endometrial implants (91, 92). Survival of the desquamated endometrial tissue in the peritoneal cavity is crucial for establishment of viable implants. Under normal circumstances, cells that do not adhere to the extracellular matrix enter apoptosis as they receive different signals from their adhesion receptors (93). However, endometrial cells from women with endometriosis have increased ability to implant and survive in ectopic locations. It was reported that the percentage of apoptosis in sloughed endometrial cells was greatly reduced among women with endometriosis, implying that the number of surviving cells that enter the peritoneal cavity is greater in women who develop endometriosis (91). Decreased sensitivity of endometrial tissue to spontaneous apoptosis contributes to the implantation and growth of endometrium at ectopic sites. It was demonstrated that the apoptotic index in ectopic endometrium was significantly lower compared to the autologous eutopic endometrium of the same patients and to the endometrium of fertile controls during the late secretory/menstrual and early proliferative phases. Moreover, the cyclic variability of apoptosis was lost in the ectopic endometrium (94).

The B-cell lymphoma/leukemia-2 (bcl-2) is a proto-oncogene which prevents apoptosis, promoting cell survival by blocking a final common pathway resulting in cell death (95). The action of bcl-2 depends on the expression and concentration of a potential antagonist protein, bax (96). Increased bcl-2 and absence of bax expression were reported in the late proliferative phase of eutopic endometrium from women with endometriosis compared with normal endometrium, whereas bcl-2 was not detected in those tissues during the secretory phase (97). The presence of apoptotic cells as measured by the TUNEL method correlated with bcl-2/bax expression. Decreased apoptosis was found in bcl-2-immunopositive and bax-immunonegative tissues (94, 97). Moreover, bcl-2 was found regardless of the cycle phase in endometriotic implants, and its levels were high in the proliferative and late secretory phases and low in the early secretory phase (94, 97). The variation of apoptosis throughout the menstrual cycle suggests that ovarian steroids may control endometrial apoptosis by up- and down-regulating bcl-2 and bax expressions (98-100). Bcl-2 expression in endometrial glandular cells was related to changes in estrogen receptor and progesterone receptor patterns throughout the cycle (101). Moreover, Critchley *et al.* reported an increase in Bcl-2 protein expression in glandular and surface epithelium of antiprogestin-treated endometrium (102). These findings were supported by the decrease of bcl-2 expression after 30 days of daily exposure to oral contraceptives in women with and without endometriosis. A remarkable increase in the expression of bax was described after contraceptive treatment, which correlated with the increased apoptotic index (103). Possibly, oral contraceptives exert their beneficial effects against endometriosis by increasing apoptosis and diminishing cellular growth in ectopic locations.

Alterations in the Fas-Fas Ligand (FasL) system may also contribute to the defective immune surveillance of endometrial cells in women with endometriosis (104). When a FasL expressing cell binds to a Fas-bearing immune cell, it triggers the Fas-bearing cell's death by apoptosis. Garcia Velasco *et al.* have described FasL modulation in endometrial stromal cells by macrophage-derived growth factors and extracellular matrix, establishing the role of FasL in the pathogenesis of endometriosis (104). Increased levels of macrophage-derived growth factors, such as PDGF and TGF-beta1, in the peritoneal fluid of women with endometriosis have been shown to up-regulate FasL expression in endometrial stromal cells, which in turn may induce apoptosis of activated T cells, thus permitting endometrial cells to survive in the peritoneal cavity (105). Furthermore, the adhesion of endometrial stromal cells to extracellular matrix proteins laminin, fibronectin and collagen IV up-regulated their FasL expression (106). It has been also shown that IL-8 has a regulatory effect on Fas-FasL system. IL-8 up-regulates the FasL protein expression and decrease apoptosis in endometrial stromal cells, which suggests that increased FasL expression by IL-8 may contribute to the apoptosis of T lymphocytes and thus produce an immunotolerant environment for the development of ectopic implants (107). Soluble FasL (sFasL) can be proteolytically cleaved from membrane-bound FasL by metalloproteinases (108). Garcia-Velasco *et al.* have observed that women with moderate-severe endometriosis showed higher levels of sFasL in both serum and peritoneal fluid when compared with healthy control, and they suggest that these higher levels of sFasL may come from shed endometrial fragments or peritoneal fluid

leukocytes (109). Higher levels of soluble FasL in the peritoneal fluid of women with endometriosis may contribute to increased apoptosis of Fas-bearing immune cells in the peritoneal cavity, leading to their decreased scavenger activity. All these findings indicate that Fas-FasL system may be involved in endometrial cell survival and ectopic implantation.

It is still unclear whether the abnormal resistance to apoptosis in the ectopic endometrium from endometriosis patients is primary in origin or secondary after establishment of the pelvic endometriosis process. However, the significant body of evidence suggests that the endometrial cells from women with and without endometriosis have fundamental differences including a variety of anomalies in structure, proliferation, immune components, adhesion molecules, proteolytic enzymes and their inhibitors, steroid and cytokine production and responsiveness, gene expression and protein production (110). These differences could contribute to the survival of the regurgitated endometrial cells into the peritoneal cavity and to the development of endometriosis. On the other hand, many differences observed between the eutopic and ectopic endometrium, which favors the survival of ectopic implant, can be explained as a direct consequence of the inflammatory peritoneal environment (54, 111, 112).

The cellular response to estrogen is classically mediated through the binding of estrogen to its nuclear receptors alpha and beta. These receptors function as ligand dependent transcription factors to modulate gene transcription from promoters by direct binding of the receptor to specific DNA target sequences, designated estrogen response elements (EREs) (1, 113, 114). In spite of the clarity with which the ER has been shown to act as a transcription factor, it has been apparent for several years that not all physiological effects of estradiol are accomplished through a direct effect on gene transcription (115). In many instances, other signaling pathway(s) including PI3K/Akt and p38 MAPK, NF-kappaB signaling may contribute to the estrogenic action (1, 116, 117). Estrogen may activate these signaling pathways before transcription, and these pathways may enhance genomic actions of estrogen or influence cell function before (or in the absence of) classical estrogen-mediated gene transcription (118-122).

This part of the review converses possible interaction of PI3K/Akt, MAPK and NF-kappaB signaling pathways with sex steroids in endometriotic tissue and enlighten the role of these interactions in endometrial cell survival (proliferation/apoptosis), immune response, and cytokine and chemokine expression in endometriosis.

5.2. PI3K/Akt/PTEN signaling and endometriosis

Akt is activated by multiple growth factors and cytokines, and functions as a downstream regulator of PI3K signaling. Once phosphorylated (on serine 473 or threonine 308 residues, or both), Akt promotes cell survival by phosphorylating substrates that decrease the activity of pro-apoptotic proteins or that increase the activity of anti-apoptotic proteins (123, 124). Active Akt phosphorylates, and therefore inhibits, the pro-apoptotic molecules such as Bad, caspase 9, and forkhead family of the transcription factors. Moreover, Akt suppresses apoptotic gene expression such as Fas ligand, the cell cycle inhibitor p27, and it blocks cytochrome c release from the mitochondria through the regulation of Bcl-2 (125). Akt also activates NF-kappaB by phosphorylating inhibitory kappaB (IkappaB) kinase (IKK). Thus, Akt increases the expression of genes participating in cell survival and inflammation (126).

PTEN (phosphatase and tensin homologue deleted on chromosome 10) is a tumor-suppressor protein that inhibits PI3K/Akt signaling (123). PTEN inhibits PI3K/Akt signaling pathway by removing the phosphate in D3-phosphate group of phosphoinositide-3, 4, 5-triphosphate (PIP3) (127). Dephosphorylation of PIP3 is a critical determinant for controlling cell growth, proliferation, and survival. Inhibition of PIP3 causes blocking of Akt signaling, which in turn, ends up with an increased activity of pro-apoptotic molecules such as Bad and caspase-9 (123). PTEN inhibits cell cycle progression by down-regulating cyclin D1 as well. These suggest that PTEN suppresses cell survival and stimulates apoptosis through Akt-dependent and -independent pathways (128).

Endometrial PTEN expression and Akt phosphorylation have temporal and spatial changes, *in vivo*, throughout the menstrual cycle, and sex steroids may be involved in regulation of these changes (113, 129, 130). Guzeloglu-Kayisli *et al.* have shown that phosho-Akt is mostly localized to nucleus during proliferative phase and reaches the highest level during late proliferative phase. In contrast, during early secretory phase phospho-Akt immunoreactivity is weaker (113). However, higher PTEN immunoreactivity was in endometrial stromal and glandular cells during late secretory and early proliferative phases compared to other phases of the cycle (131).

Estrogen typically stimulates cell proliferation by activating genes that promote cell cycle progression, such as cyclin D1 and c-myc (132). It is well known that the proliferative phase of the menstrual cycle is under the dominant effect of estrogen and that cell proliferation reaches its maximal level during this phase. In addition to stimulating proliferation, estrogen acts as a survival factor by inhibiting pro-apoptotic and activating anti-apoptotic molecules. It has been reported that estrogen stimulates Akt phosphorylation in cultured stromal cells in a short-term manner. Furthermore, estrogen may down-regulate PTEN activity by increasing its phosphorylation in endometrial cells (113, 131).

PTEN is frequently inactivated in human cancers. PTEN mutations are seen early in endometrioid ovarian carcinoma and endometrioid ovarian cancer is thought to arise from endometriosis (133, 134). Moreover, mutation of the tumor suppressor gene PTEN has been described in 21% of ovarian endometriotic cysts (135). This may imply that genetic alterations in the PTEN gene may be an early event in endometriotic cells. A very strong support for a role of PTEN in the malignant transformation of

endometriosis came recently from a mutagenesis approach in genetically engineered mice (136). In mice harboring an oncogenic allele of K-ras resulting in the development of benign lesions reminiscent of endometriosis, a conditional deletion of PTEN caused the progression towards the ovarian tumor. In these mice with a combined mutation of K-ras and PTEN, all the tumors appeared to originate from the ovarian epithelium with a disease latency of only 7 weeks, extended into the stroma through a process of infiltrative growth and were diagnosed as endometrioid subtype. It has to be noted that, although the oncogenic activation of K-ras did result in the development of both peritoneal and ovarian lesions with endometrioid morphology, that mouse model is probably not perfect as a genocopy of endometriosis. Indeed, lesions in the ovary showed proliferations of glands but lack a surrounding endometrial-like stroma. However, even if these observations need to be confirmed, this elegant study represents one of the most convincing pieces of evidence supporting a continuum between endometriosis and cancer. These results, based on the combination of two mutations in tumor-related genes, suggest the potential existence of a mechanism of tumorigenesis conforming to a progression model from the benign lesion to the malignant ovarian disease. These very few data suggest an implication of the PTEN gene, more than others, in the progression of endometriosis towards a more severe and invasive form. Thus, it is important to identify therapeutic strategies targeting PTEN activation to inhibit progression of endometriosis. One attractive therapeutic target may be PIP3K and its downstream signaling molecules such as Akt. We have evaluated Akt activity in the endometriosis using anti-phospho Ser 473 Akt and found that phospho-Akt level increase the endometriosis when compared to normal endometrium (unpublished data) supporting that specific Akt inhibitors could be used for endometriosis therapy as suggested in endometrial cancer therapy (137).

5.3. MAPK Pathway and Endometriosis

MAPKs are the family of kinases that transduce signals from the cell membrane to the nucleus in response to a wide range of stimuli, including stress (138). They are serine/threonine kinases that, upon stimulation, phosphorylate their specific substrates at serine and/or threonine residues. Such phosphorylation events can either positively or negatively regulate substrate, and thus the entire signaling cascade activity (139). The MAPK superfamily consists of three well-characterized subfamilies: the extracellular signal-regulated kinase (ERK); the c-Jun NH2-terminal kinase (JNK); and the p38 MAPK, and each family member has its own subfamilies: ERKs (ERK1 and ERK2), JNKs (JNK1, JNK2, and JNK3), and p38-MAPKs (p38-MAPKalpha, p38-MAPKbeta, p38-MAPKgamma, and p38-MAPKdelta) (139).

All MAPK pathways have been implicated in the regulation of cell survival and apoptosis in response to a variety of stimuli. The first seminal work showed that nerve growth factor (NGF) withdrawal caused apoptosis in PC12 cells through activation of JNK and p38 MAPK, while ERK was protective (140). This simple model turned into a very complicated affair as numerous subsequent studies have demonstrated that the MAPK pathways may either promote or prevent apoptosis depending on the cell type, stimuli, and the latency of the activation of MAPKs (141).

The p38 MAPK pathway, also called as “stress-activated kinase”, is simultaneously activated in response to a variety of cellular and environmental stresses such as changes in osmolarity, DNA damage, heat shock, ischemia, inflammatory cytokines, shear stress, UV irradiation, or oxidative stress. It plays important regulatory roles for a variety of downstream molecules such as transcription and translation factors, cell cycle molecules, kinases, or scaffold proteins, and thus exert a variety of cellular outputs, including cytokine production, cell proliferation, cycle arrest, migration, differentiation, senescence, and apoptosis (142). Abundant evidence for p38 MAPK involvement in apoptosis exists and is based on concomitant activation of p38 MAPK, and apoptosis induced by a variety of agents such as NGF withdrawal and Fas ligation (143, 144). Cysteine proteases (caspases) are central to the apoptotic pathway and are expressed as inactive zymogens (145, 146). Caspase inhibitors then can block p38 MAPK activation through Fas cross-linking, suggesting that p38 MAPK functions downstream of caspase activation (143, 147). However, over-expression of dominant active MKK6 (a kinase that specifically activates p38 MAPK) can also induce caspase activity and cell death thus implying that p38 MAPK may function both upstream and downstream of caspases in apoptosis (148, 149). It must be mentioned that the role of p38 in apoptosis is cell type and stimulus dependent. While p38 MAPK signaling has been shown to promote cell death in some cell lines, in different cell lines p38 MAPK has been shown to enhance survival, cell growth, and differentiation (150).

Seval *et al.* (151) have shown that total and phosphorylated p38 MAPK immunoreactivity in normal endometrial cells with a significantly higher phosphorylated/total p38 MAPK ratio in the functional layer compared with the basal layer. Furthermore, estradiol significantly increased p38 MAPK phosphorylation in endometrial stromal cells in culture within minutes. The estrogen receptor antagonist ICI 182,780 reversed the estrogen-induced p38 MAPK phosphorylation in endometrial stromal and epithelial cells, suggesting involvement of the estrogen receptor by a non-genomic interaction of estrogen and P38 MAPK pathways (151). Similarly, both total and phosho-p38 MAPK stainings were observed in endometriotic cells. Interestingly, ectopic endometrial epithelial and stromal cells revealed the highest phospho-p38 MAPK immunoreactivity compared to those in eutopic and normal endometrium. In culture we observed that inhibition of p38 MAPK signaling significantly decreases IL-8 expression but not apoptosis (In press). These findings suggest that estrogen-stimulated p38 MAPK activation may in turn contribute to proinflammatory environment and leukocyte influx of ectopic endometrium by increasing chemokine expression.

5.4. NF-kappaB signaling and Endometriosis

NF-kappaB, first identified as an enhancer binding protein for immunoglobulin κ light chain gene

expression in B cells, is well known to positively regulate expression of many molecules regulating immune response, inflammation, cell division, and apoptosis (152). Normally, NF-kappaB is mainly localized in the cytoplasm of unstimulated cells and is associated with an inhibitory protein, IkappaB. After an appropriate stimulation, IkappaB is rapidly phosphorylated by IkappaB kinase (IKK) complex, which in turn causes ubiquitin-mediated degradation of IkappaB and let NF-kappaB move to the nucleus where it regulates gene transcription (153). The wide variety of genes regulated by NF-κB includes cytokines (IL-1, IL-2, IL-6, IL-12), chemokines (IL-8, monocyte chemotactic protein-1 (MCP-1), regulated on activation, normal T cell expressed and secreted (RANTES), adhesion molecules (ICAM, VCAM), cell proliferation (cyclin D1, c-myc), and apoptotic molecules (Fas ligand, Bcl-XL) (154, 155).

Several functions of the human endometrium are associated with inflammatory-like response, e.g. implantation and menstruation. These events involve the increased expression of proinflammatory molecules, the infiltration of leukocytes and tissue remodeling (2, 156). Inappropriate activation of inflammatory pathways is also likely to be associated with pathophysiological situations.

King *et al.* investigated the expression of NF-kappaB pathway intermediates in human endometrium and first-trimester decidua. In that study, IkappaBα mRNA was increased in the peri-menstrual phase of the menstrual cycle. Because NF-kappaB activation increases IkappaB transcription, with their finding they suggested that premenstrual progesterone withdrawal stimulated the NF-kappaB activation. When progesterone concentrations increased in early pregnancy, IKKbeta mRNA levels declined, whereas IKKalpha mRNA levels increased in the decidua, suggesting that NF-kappaB is activated during early pregnancy. Thus, NF-kappaB may regulate the expression of molecules vital for implantation and successful pregnancy (156) and its activity is modulated by steroid hormone receptors.

Recent studies have shown several mechanisms by which steroid hormone receptors take part in NF-kappaB inactivation. These include IkappaB degradation, competition between steroid receptors, and NF-kappaB to bind to nuclear cofactors, and physical interaction between steroid receptors and NF-kappaB (157, 158). An inhibitory effect of ER on NF-kappaB activity was reported in many tissues but not in endometrial or endometriotic tissues. A study showed that ERalpha inhibits IL-6 expression, and that inhibition is mediated via protein–protein binding of ERalpha and NF-kappaB. This mechanism may also be important in the endometrial pathophysiology. Moreover, investigating if this relationship is bidirectional may be biologically important (159, 160). In this manner we have found that both NF-kappaB and ER antagonize each other and inhibit each other's transcriptional activities. We observed that both ERalpha and ERbeta inhibit the DNA binding affinity of p50 and p65. This is likely to be an important mechanism for the regulation of many cytokines by estrogen in human endometrial (unpublished data). On the other hand, the p50 subunit of NF-kappaB is not capable of repressing ERalpha binding to DNA, suggesting other mechanisms, such as nuclear cofactors, that may co-modulate ER- and NF-kappaB–related transcriptions. Although these findings are obtained from normal endometrial cells it is still unknown if the same interactions occur in endometriotic cells or not. Thus far, according to our preliminary results we would speculate that endometriotic cells may respond differently than endometrial cells in terms of NF-kappaB and ER interactions. This may be due to continuous activation of ER and NF-kappaB by estrogen and proinflammatory cytokines, respectively, in ectopic loci. An alternative hypothesis is that the IkappaB production and/or degradation may be regulated by sex steroids. Therefore, investigating how the regulation of NF-kappaB is different in endometriotic cells may advance our understanding of endometriosis pathogenesis. Another possible mechanism that may affect this crosstalk is the presence of co-activators and/or co-suppressors involved in the activation/suppression of transcription factors.

6. CONCLUSION

There is clear evidence for multiple interactions between steroid hormones and immune mediators in the development and growth of ectopic endometrium tissue. We hope that better understanding of these interactions will set the stage for effective immune-targeted therapies not only for endometriosis but also for other endometrial diseases such as adenomyosis, recurrent reproductive failure and implantation-related infertility. The changes in leukocytes number and subtypes in both eutopic and ectopic endometrium suggest a characteristic of an immunologically active tissue for endometriosis. These changes and differential regulation of endometrial cytokines and chemokines in endometriosis are also related with the estrogenic microenvironment. Besides, it is also widely accepted that not only do endometrial cytokines and chemokines mediate the recruitment of leukocytes into the endometrium, but also they seem to mediate some of the proliferative and secretory actions of ovarian steroids. However, the effects of estrogen on distinct intracellular signaling pathways including MAPK, PI3K/AKT and NF-kappaB and other possible immunologic molecules require further studies. These studies will enable us to better understand many molecular and cellular mechanisms such as cell survival, apoptosis, interaction of estrogen signaling with the other secondary signaling cascades and its effect in immunologic response in endometriotic tissue.

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Abbreviations: IL: Interleukin; NF-kappa B: Nuclear factor-kappa B, Th: T helper; NK cell: natural killer cell; TGF-beta: transforming growth factor-beta; 17beta-HSD: 17beta-hydroxysteroid dehydrogenase; ICAM-1:

intercellular adhesion molecule-1; FasL: Fas ligand, PTEN: phosphatase and tensin homologue deleted on chromosome 10.

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