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Role of cytokines in the endometrial-peritoneal cross-talk and development of endometriosis

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1. ABSTRACT

A clear picture of the dynamic relationship between the endometrium and peritoneum is emerging as both tissues may participate in the spontaneous development of endometriosis. Various adhesion molecules, pro-inflammatory cytokines and chemoattractants cytokines have emerged as central coordinators of endometrial-peritoneal interactions. The peritoneal microenvironment which consists of the peritoneal fluid, normal peritoneum and peritoneal endometriotic lesions may play an active role in the pathogenesis of endometriosis, by harbouring most inflammatory responses that are triggered by the presence of endometrial cells, leading to recruitment of activated macrophages and leukocytes locally. Menstrual endometrium has the ability to bond and invade the peritoneal tissue. In baboons intrapelvic injection of menstrual endometrium permits the study of early endometrial-peritoneal interaction in an *in vivo* culture microenvironment and can lead to important insight in the early development of endometriotic lesions. In this review, we discuss the roles of the endometrial-peritoneal interactions, not only in disease development but also in the broader process of aetiopathogenesis.

2. INTRODUCTION

Endometriosis is a benign gynaecological disease characterised by endometrial like stromal cells and glands. The clinical presentation depends on the location (peritoneal, ovarian or rectovaginal) and the extent of the disease. Clinical symptoms may include but are not limited to cyclic pelvic pain, dysmenorrhea, dyspareunia and infertility (1). The natural process of disease development is still poorly explored. Although the aetiology is not precisely known, endometriosis is proposed to occur when refluxed endometrial cells end up into the peritoneal cavity during menstruation (2). Limited information still exists regarding early endometrial-peritoneal attachment and invasion in the development of endometriosis, and is mainly derived from *in vitro* studies (3 - 7). To study how endometriosis evolves, it is important to understand the pathophysiology of the two tissues involved and how they interact with each other during the transition process from ectopic endometrium to endometriosis (8), i.e how the endometrial cells engraft within the mesothelial lining, intermesh with the peritoneum and ultimately colonise the peritoneal microenvironment.

A key step in the development of endometriosis is the ability of endometrial cells to adhere to mesothelium

and invade the extracellular matrix. The basis of this premise is that the peritoneum may allow ectopic tissue attachment, as has been supported by previous *in vitro* studies (3, 9). However, other investigators have reported that normal mesothelium impedes the attachment of endometrial cells and have proposed that injury or trauma to the peritoneum is necessary for endometrial-peritoneal bonding (10, 11).

The development of endometriosis is an intricate disease process, characterised by presence of several factors including cytokines, growth factors and adhesion molecules (12, 13). Macrophage derived cytokines may contribute to the development of endometriosis by promoting neovascularisation and attachment of endometrial cells to the peritoneum (14, 15). Increased angiogenesis is common around peritoneal explants and increased angiogenic activity has been observed in peritoneal fluid (PF) of women with endometriosis (16). The expression of adhesion molecules like integrins on the surface of mesothelium may play an integral role during the initial attachment of endometrial cells to peritoneum (17. Whereas *in vitro* studies have provided us with a vivid image of the role of endometrial-peritoneal interactions in disease development, the factors that either regulate or propagate these interactions *in vivo* are elusive. It is not clear to what extent these phenomena are either endometrium-dependent or peritoneum-dependent. Recent studies have provided new insight into the role of cytokines, matrix metalloproteinase and adhesion factors that control the regulation of immune activity and the coordination of complex cellular functions in the development of endometriosis. Furthermore, we recently demonstrated that endometrium and macroscopically normal peritoneum are affected by profound biological changes that dependent on the phase of the menstrual cycle and on the either presence or absence of endometriosis (18). The purpose of this review paper is to address the role of eutopic endometrium, peritoneal endometriotic lesions and normal pelvic peritoneum in endometrial-peritoneal adhesion in order to better understand the pathogenesis of endometriosis.

3. ROLE OF ENDOMETRIUM IN ENDOMETRIAL-PERITONEAL ADHESION AND INVASION

Endometrium undergoes remodelling that is characterised by proliferative and secretory processes that lead to regrowth of a functional tissue during the menstrual cycle (19 - 21). Although said to be nonmalignant, endometriosis may exhibit characteristics that are similar to malignancy, including aggressive growth, localized invasion, and spread to various organs. According to the retrograde menstruation theory, endometrial fragments flow back through the fallopian tubes, reach the peritoneal cavity, attach on the pelvic mesothelium, invade the peritoneum and develop into endometriotic lesions (2). Indeed women who have undergone tubal ligation have been associated with less severity of endometriosis (22) an indication of menstrual reflux interruption. However, it is not clear how endometrium can survive outside the uterine cavity and implant, although endometrium exhibits biological characteristics that may favour this process of adhesion and invasion.

3.1. Eutopic endometrial factors promoting adhesion: integrins and CD44

In vitro studies have clearly shown that endometrial cells can adhere to normal peritoneum (3, 9, 23) and that this process is mediated predominantly by endometrial stromal cells (3). Integrins are proteins known to mediate adhesion of cells to either neighbouring cells or to extracellular matrix (24) and play an important role in this adhesion process. The expression of integrins (Figure 1) in both mesothelial (17) and in endometrial (25) cells has been demonstrated in women with endometriosis (25). The $alpha_V beta3$ integrins transmit signals to the cytoskeletal structures of cells and usually mediate the expression of fibronectin and vibronectin (26), and have been localised in endometriotic lesions and endometrium of women with and without endometriosis in both follicular and secretory phases (27). However, agents blocking $alpha_V beta3$ integrin activity minimally reduce the adhesion of menstrual endometrium to extracellular matrix *in vitro* (28). On the other hand CD44, a key receptor for hyaluronic acid, has been demonstrated in endometrial cells and pretreatment of mesothelial cells by hyaluronidase diminishes the binding of endometrial cells to mesothelium (29). These data suggest that the hyaluronic acid–CD44 binding may have a role in the initial attachment of endometrium to peritoneal mesothelial cells (29).

3.2. Eutopic endometrial factors promoting invasion: metalloproteinases and cytokines

An active role of the endometrium in peritoneal invasion is supported by significant biological differences in eutopic endometrium between women with and without endometriosis (18, 30, 31). The cellular mechanisms of ectopic endometrial growth involve invasive events similar to metastatic neoplasms that require extracellular matrix degradation (32, 33). Invasion of endometrial cells into the mesothelium follows after initial attachment to the peritoneal wall and is favored by the endometrial expression of matrix metalloproteinases (MMPs) (34) that remodel the mesothelial lining of the peritoneum (30). In eutopic endometrium, several MMPs and tissue inhibitors of matrix metalloproteinase (TIMPs) are highly expressed during menstruation and may play an important role in both tissue breakdown and repair processes (35, 36). In contrast, endometrial expression of MMP-3 is low during the follicular and the luteal phases (37, 38). The expression of MMPs is suppressed by progesterone during the luteal phase (37). However, in women with endometriosis, an enhanced endometrial expression of MMPs has been observed during the secretory phase, suggesting that women with endometriosis are either insensitive or resistant to the inhibiting effect of progesterone on endometrial MMP expression (21).

Cytokines such as interleukin (IL)-1beta stimulate endometrial MMP-1, MMP-2 protein secretion and MMP-1 gene expression in a time dependent manner *in vitro* (30). Another cytokine, tumor necrosis factor-alpha (TNF-alpha), also induces endometrial MMP-1, MMP-2

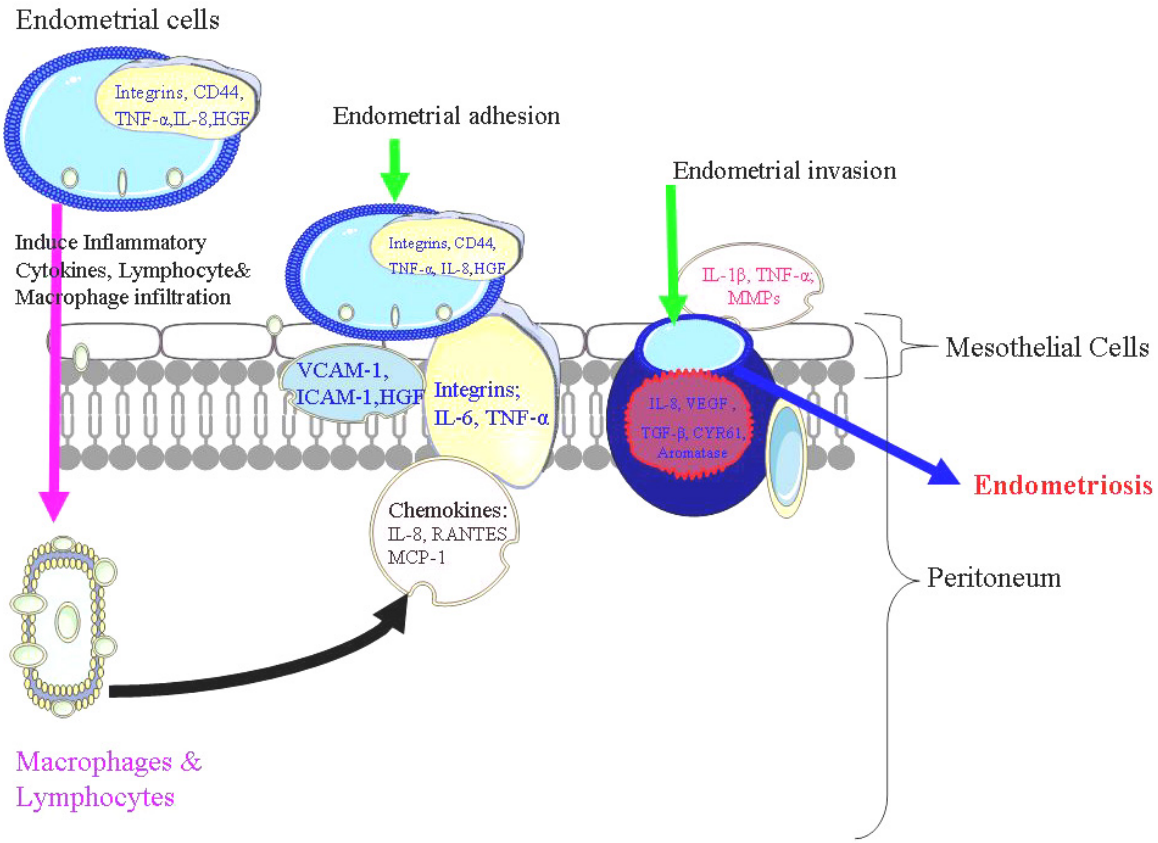

Figure 1. Endometrial-peritoneal adhesion and invasion in the pathogenesis of endometriosis. The presence of endometrial cells in pelvic cavity may induce infiltration of immune cells like lymphocytes or macrophages into the peritoneal cavity. Chemokines like IL-8 that are associated with endometrial proliferation may activate integrins, expressed by endometrium or mesothelial cells. Adhesion of these integrins to intercellular adhesion molecules (ICAMs) such as ICAM-1 or vascular cell-adhesion molecule 1 (VCAM-1) may consequently mediate firm adhesion of endometrial cells to mesothelial cells. Attached endometrial cells invade the extracellular matrix through remodelling of mesothelial lining of peritoneum by MMPs that are upregulated by presence of inflammatory cytokines such as TNF-α and IL-1β. Another molecule, HGF, may enhance the degradation of the extracellular matrix and stimulate cellular change and motility. The establishment and growth of endometriotic lesions is further supported by increased angiogenesis and local presence of oestrogens.

and MMP-3 protein secretion and MMP-1 and MMP-3 gene expression in a time dependent manner *in vitro* (30). Recently, we have demonstrated that women with endometriosis express increased endometrial mRNA of TNF-alpha, IL-8 and MMP-3 during the menstrual phase compared to the luteal phase (18), which could partly explain the increased invasiveness of endometrial fragments in women with endometriosis (34). Moreover, increased levels of both MMP-3 and MMP-7 have been reported in the eutopic endometrium of baboons with induced endometriosis during the window of implantation when compared to controls (34). The results of this study agree to *in vitro* studies showing increased MMP-3 and -7 mRNA levels in the secretory eutopic endometrium of women with endometriosis when compared to controls (39).

3.3. Ectopic endometrial factors promoting invasion: metalloproteinases, angiogenic factors and cytokines

There is substantial evidence that ectopic endometrium has the capacity to invade the surrounding tissue. Viable endometrial cells from human endometriotic biopsies as opposed to human endometrial biopsies are invasive in an *in vitro* collagen invasion assay, probably because they have a higher proportion of potentially invasive E-cadherin-negative epithelial cells (41). In human endometriotic lesions, an abnormal expression of specific members of the MMP and TIMP families has been identified (35). In baboons with experimental endometriosis, high levels of MMP-7 are expressed in ectopic endometriotic lesions (39). Furthermore, the expression of cathepsin D, an acidic protease promoting cellular growth and invasion through the destruction of basal membranes and extracellular matrix (ECM), is increased in ectopic endometrial tissues compared to eutopic endometrium (42). We recently demonstrated that transgelin a smooth muscle actin binding protein, is upregulated in peritoneal endometriotic lesions when compared to macroscopically normal peritoneum (43). Similarly transgelin 2 has been reported to be overexpressed in gastric cancer and hepatocellular carcinoma (44, 45). This protein is thought to be involved

Table 1. Factor that may play a central role in the endometrial-peritoneal cross-talk

Factors that promote endometrial adhesion • Integrins: e.g alphavbeta3 • CD44 • ICAM-1 • VCAM-1 • Macrophages
Factors that promote invasion • MMP-1, MMP-2, MMP-3 & MMP-7 • IL-1beta • TNF-alpha • IL-8 • Cathepsin D • Transgelin • HGF • VEGF • CYR61
Factors that may alter the peritoneal microenvironment • HGF • Macrophages • IL-1beta • IL-6 • ICAM-1 • TGF-beta • VCAM-1 • MMP-3 • TNF-alpha • RANTES

in cell proliferation and migration, suggesting that its overexpression may be implicated in tumour progression (45) and in the invasion process of endometriosis.

Furthermore, endometriotic stromal cells are reported to be a source of Hepatocyte growth factor (HGF) (46), which can induce critical changes on the morphology of mesothelial cells and enhance endometrial cell attachment and invasion. (Table 1).

4. ROLE OF PELVIC PERITONEUM IN ENDOMETRIAL-PERITONEAL ADHESION AND INVASION

The peritoneum is an integral part of the endometriosis microenvironment. The peritoneum comprises of a single layer of mesothelial cells at the surface of the intra-abdominal organs (47, 48), and has the structural and functional role of maintaining their integrity (47). The surface epithelium of the serous membrane of the peritoneum is attached to a basement membrane underlying extracellular matrix comprised of collagen, blood vessels, and lymphatic and nerve fibres (17, 47). The structural and functional configuration of the peritoneum allows for an important homeostatic role through rapid mobilization of inflammatory mechanisms that efficiently localize either peritoneal injury or trauma.

4.1. Pelvic inflammation and endometriosis

The development of endometriosis requires endometrial cells to attach to peritoneum and invade the extracellular matrix (Figure 1). Refluxed menstrual debris into the pelvic cavity can spur an inflammatory response that result in the release of diverse chemoattractants that recruit peripheral blood mononuclear cells into the peritoneal environment (49, 50). Cell adhesion molecules are transmembrane receptors involved in cell–cell interaction and mediate various immune and inflammatory processes (51). Thus, they may play a role in both the interaction of endometrial cells with the peritoneal surface and in the inflammation and immunologic reactions that accompany the disease process. Studies have reported the possible involvement of intercellular adhesion molecule-1 (ICAM-1) (18) and several types of integrins (24, 25, 52, 53) in the pathogenesis of endometriosis. Aberrant expression of adhesion molecules in endometrium and peritoneum may facilitate endometrial-peritoneal adhesion (27, 28). Integrins are cell-surface receptors that mediate adhesion of endometrial cells to mesothelial cells (51). Each integrin consists of an alpha-subunit and a beta-subunit. In the immune system, integrins have essential roles, which includes leukocyte attachment to endothelial cells and extravasation of cells into tissues (54). The adhesive interactions of immune cells are usually transitory. Unstimulated lymphocytes are non-adherent but, in response to encountering chemokines, they become adherent to other cells and ECM components after a short period. Fundamental to this process is the ability of integrins to alter their avidity through intracellular signalling (54). This process may be associated with the presence of immune cell infiltration in endometriosis and its microenvironment (49,55). It has been conjectured that lymphocytes 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 natural killer (NK) cells. But soluble forms of ICAM-1 (s-ICAM-1) are upregulated in PF of women with endometriosis (56) and also can bind to LFA-1 presenting lymphocytes and thereby preventing the recognition of endometrial cells by these lymphocytes (57-59) resulting in an impaired immunesurveillance.

Macrophages harboured by either peritoneal fluid or intact tissues can produce proinflammatory mediators in response to any exogenous or endogenous stimuli like endometrial cells (60-62). Women with endometriosis have both an increased concentration of white blood cells and macrophages in PF and an increased activation status of these macrophages (63).

4.2. Active role of normal pelvic peritoneum

Peritoneal endometriosis occurs frequently, but only limited data are available on the role of normal peritoneum in harbouring endometrial cell attachment and invasion. It is possible that critical alterations in the peritoneal surface and stroma precede endometrial attachment on the ectopic sites. Increased levels of HGF in PF have been observed in women with endometriosis when compared to controls (46). HGF is recognized as a potential inducer of proliferation, migration and cellular change which acts on epithelial cells (64). In endometriosis, sources of HGF are suggested to be endometriotic stromal cells and peritoneum rather than peritoneal macrophages, that serve as the main sources of most cytokines in PF (46, 65). The HGF is said to enhance the degrading of extracellular matrix (ECM) and stimulate cell motility (66). In a recent study the surface mesothelium of pelvic

peritoneum adjacent to active endometriosis was shown to undergo a sequence of reactive change from flat cell to cuboidal or columnar epithelium. (67,68). These changes were manifested through increased accumulation of macrophages and higher expression of HGF in the adjacent cuboidal or columnar cells of pelvic endometriosis, which may be involved in the transformation of peritoneal mesothelium (68,69). *In vitro* studies have also shown that cells isolated from menstrual effluent have a similar effect on mesothelial morphology without causing apoptosis and necrosis (70), as well as in cancer cells (71). Thus women with endometriosis, may have substantial alterations in the peritoneal microenvironment (50,72) including overtly enhanced angiogenesis (73) and exacerbated inflammatory infiltrates comprised of different leukocyte populations, proteolytic and adhesions factors (49,50,63,74). Furthermore, increased intraperitoneal inflammation has been reported in women with endometriosis and baboons with induced endometriosis (61,62,75-77).

Until recently, the role of macroscopically normal peritoneum in this inflammatory process was not well investigated. However, our recent research has shown that macroscopically normal peritoneum taken outside the pelvic brim is an active player and not a passive recipient in the development of endometriosis, especially during menstruation (8, 18, 78). Firstly, during the menstrual phase, peritoneal expression of IL1-beta, intercellular adhesion molecule-1 (ICAM-1), transforming growth factor-beta, (TGF-beta) and IL-6 mRNA is upregulated in women with endometriosis when compared with controls (8, 18). Secondly, in women with or without endometriosis, the expression levels of mRNA for aromatase and for vascular cell-adhesion molecule-1, (VCAM-1) are lower in endometrium than in peritoneum (78). In women with endometriosis, the peritoneal mRNA expression of VCAM-1 is significantly higher during the menstrual phase when compared to the luteal phase (78), possibly promoting peritoneal lymphocyte migration and inflammation. Indeed, previous studies have shown that alpha4beta1-integrin or Very Late Antigen 4 –VCAM-1 (VLA4–VCAM-1) interactions have central roles in the migration of lymphocytes to inflammatory tissue (79). Thirdly, we demonstrated increased peritoneal mRNA expression of TNF-α and MMP-3 in women with endometriosis when compared with controls during the luteal phase (18). Fourthly, in women with endometriosis, peritoneal mRNA expression of regulated on activation, normal T-Cell expressed and secreted (RANTES) is significantly higher during the menstrual phase when compared to the luteal phase (8, 78). Local pelviperitoneal inflammation can lead to a reorganization of the collagen based ECM and promote endometrial-peritoneal attachment and invasion (80). Since pelviperitoneal serosal membranes lie in proximity to ectopic endometrial cells present in PF, cytokines or chemokines (Table I) present in normal peritoneum and/or in PF also can possibly prime endometrial cells toward proliferation, peritoneal attachment and invasion (49).

5. ROLE OF CYTOKINES AND CHEMOKINES IN ENDOMETRIAL-PERITONEAL ATTACHMENT AND INVASION

Profound alterations on the levels of cytokines secreted by lymphocytes infiltrating endometriotic lesion have been reported (81). Large numbers of macrophages are also present in peritoneal fluid secreting increased amounts of inflammatory cytokines in women with endometriosis (49, 50). Inflammatory infiltrates have also been observed in endometriotic lesions (81). Furthermore, macroscopically normal peritoneum also shows signs of increased inflammation in women with endometriosis, especially during the menstrual phase, as described previously by Kyama *et al*, (8 ,18).

Increased knowledge in endometrial migration and attachment has aroused a focus on inflammatory as well as non-inflammatory cell infiltrates and their contribution to endometriosis (Figure 1). Chemokines and cytokines have potent local functional properties, such as chemotaxis and proangiogenesis, and may contribute to the migration of leukocytes into the endometriotic environment. Substantial amounts of certain CC and CXC chemokines including CXCL8 (IL-8), CCL2 (MCP-1) have been demonstrated in endometriotic lesions (18, 82). CXCL8 (IL-8) is very pleiotropic and is induced by TNF-alpha (39, 83,84). Transcripts for CCL5 (RANTES) have also been demonstrated in endometriotic lesions (85, 86). Another cytokine, IL-6 is increased in the serum and normal peritoneum of women with endometriosis (18, 86) and also enhances endometrial attachment and proliferation of endometrial cells (88).

There is increasing recognition that infiltrating immune cells may contribute to endometrial growth and invasion of endometriotic lesions (49, 50, 81). Both activated macrophages and T cells may have this dual role, and it remains a challenge to inhibit the activity of these immune cells towards an effective antiendometriosis response *in vivo*. The prevention of endometrial-peritoneal attachment is an important target in the prevention of endometriosis. *In vitro* studies have shown increased endometrial stromal cell adhesion to mesothelial cells pretreated with TNF-alpha (89). Similarly, *in vitro* incubation of endometrial stromal cells with increasing concentrations of IL-8 has been reported to stimulate their adhesion to fibronectin (90). Also *in vivo* adhesion of human endometrial cells to mouse peritoneum was moderately increased by treatment with TNF-alpha and IL-6 (88,91). In contrast a recent study showed TNF-alpha, IL-8 and IL-6 failed to stimulate, *in vitro* adhesion between endometrial epithelial cells and mesothelial cells in a dose dependent fashion (7).

The functional characterization of peritoneal - endometrial inflammatory and non-inflammatory cell infiltrates is important for understanding the pathogenesis of endometriosis. In this respect, the chemical composition and dynamics of the ECM also deserve more careful research, because chemokines may "stick" to other proteins

in the peritoneal microenvironment and enhance chemoattraction of immune cells (Table 1).

6. ANIMAL MODELS FOR ENDOMETRIAL-PERITONEAL INTERACTIONS

Animal models are important to study endometrial-peritoneal interactions *in vivo*. Both rodents and non-human primates (92 - 94) have been used for endometriosis studies. The baboon model has been validated for more than 15 years as the best animal model for the preclinical study of endometriosis. Endometriosis occurs spontaneously in baboons, but for research purposes it is more practical to induce endometriosis by intrapelvic injection of endometrium (95, 96). Laparoscopic appearances, pelvic localization (97) and microscopic aspects (98) of endometriosis are similar in women and in baboons.

Intrapelvic injection of menstrual endometrium in baboons allows the possibility to study early endometrial-peritoneal interaction at short term intervals in an *in vivo* culture system. These studies will give very important insight in the early development of endometriotic lesions (96, 99), and offer better understanding of the role of endometrium, peritoneum and peritoneal fluid in the onset of endometriosis. Interesting data have recently emerged from research using the baboons model while exploring the role of inflammation and angiogenesis in the pathogenesis of endometriosis.

In baboons, both spontaneous retrograde menstruation and experimental intrapelvic injection of endometrium are associated with intrapelvic inflammation which is marked by increased PF volume and increased PF concentration of white blood cells and inflammatory cytokines (12, 76, 77). This peritoneal inflammatory effect is observed within one month after intrapelvic injection of endometrium (76), but disappears after 2 to 3 months (100]. The WBC concentration and proportion of macrophages and cytotoxic T cells is increased in the PF of baboons with spontaneous endometriosis (100, 101]. Furthermore, neutralization of TNF-alpha activity with anti- human Tumor Necrosis Factor –alpha can prevent or treat endometriosis in baboons (102 - 104), probably by reversing the chronic inflammatory state associated with spontaneous or induced endometriosis in baboons

It has been shown in the baboon model with induced endometriosis that endometrial changes in Cyteine-rich, angiogenic inducer, 61 CCN1 (CYR61) may occur after intrapelvic seeding of endometrium (105), suggesting that endometriosis causes secondary endometrial changes. Increased angiogenic activity is well documented in women with endometriosis (73). In women with endometriosis opaque red lesions exhibit a higher activity than nonopaque red lesions in PF and ectopic endometrium (106). In baboons with induced endometriosis, increased levels of VEGF in ectopic lesions have been observed in the more active red lesions [105]. The angiogenic factor CYR61, a member of the CCN family of growth factors involved in development, proliferation and tumorigenesis, has been shown to be up-regulated in eutopic and ectopic endometrium of women with endometriosis [107]. The increased levels of these angiogenic factors in endometriotic lesions may enhance the peritoneal vascularisation, hence promoting endometrial survival and growth.

7. CONCLUSIONS

Critical alterations in peritoneum precede early endometrial-peritoneal attachment in women with endometriosis as opposed to women without endometriosis. The observed changes reflect alterations in cytoskeletal and signaling pathways that suggest regional activity from integrins, cytokines and hormone growth factors. Enhanced collagenase activity would contribute to remodeling of the stromal compartment and create a favorable environment for infiltration of leukocytes as well as other cells, such as fibroblasts and endothelial cells. More studies are needed that focus on early endometrial-peritoneal attachment and invasion. Gene and protein profiling of endometrium and peritoneum may provide hints about early transition steps of either endometrial cells to endometriosis or provide insight into peritoneal changes that may actually facilitate the development of endometriosis. The baboon is an ideal model to study early endometrial-peritoneal interaction at short term intervals in vivo. These research efforts could help to identify critical alterations in the peritoneal environment surrounding endometriosis lesions and might ultimately lead to advances in diagnosis, prognosis, and novel approaches to new therapeutic targets.

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Abbreviations: PF: peritoneal fluid, MMPs: matrix metalloproteinases, TIMPs: tissue inhibitor of metalloproteinases, ECM: to extracellular matrix, IL-: interleukins -, ICAM-1: intercellular adhesion molecule-1, VCAM-1: vascular cell-adhesion molecule-1, TNF-alpha: tumour necrosis factor –alpha, TGF-beta: transforming growth factor-beta, RANTES: regulated on activation, normal T-Cell expressed and secreted, NK cells: natural killer cells, VEGF: vascular endothelial growth factor, MCP-1: monocyte chemotactic protein-1, CC chemokines: chemokines with adjacent cysteines, CXC chemokines: chemokines with an amino acid in between the cysteine residues, LFA-1: Lymphocyte Function-Associated Antigen-1, Very Late Antigen -4 : VLA-4, CYR61: Cyteine-rich, angiogenic inducer, 61 CCN1, HGF: Hepatocyte growth factor

Key Words: Endometriosis, Endometriotic Lesion, Endometrium, Cytokines, Chemokines, Adhesion Factors, Matrix Metalloproteinases, Peritoneal Fluid, Peritoneum, Review

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