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Role of chemokines in the pathogenesis of endometriosis

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1. ABSTRACT

Chemokines, proteins that operate within the body's immune system, play numerous roles in menstruation, bacterial infection, implantation of embryos, and the maintenance of early pregnancy. They are also strongly related to the pathogenesis of endometriosis. Several chemokines including interleukin (IL)-8, growth-related oncogene (GRO) alpha, regulated on activation, normal T expressed and secreted (RANTES), and macrophage inflammatory protein (MIP)-1 are reported to be elevated in the peritoneal fluid (PF) of women with endometriosis. Chemokines IL-8 and GRO alpha as well as epithelial cell-derived neutrophil-activating protein (ENA)-78, eotaxin, and interferon-inducible protein (IP)-10 might be involved in macrophage activation, inflammatory reaction, and adhesion of endometriotic tissues in the peritoneal cavity, and enhanced angiogenesis in the progression of endometriosis. The chemokines closely related with the pathogenesis of endometriosis form a complex network locally and systemically in women with the disease. Understanding this network is a key to improving our understanding of endometriosis as well as developing new, more effective therapies.

2. INTRODUCTION

Endometriosis, defined by the presence of viable endometrial tissue outside the uterine cavity, is a common chronic inflammatory disease affecting 3–10% of women of reproductive age, and is associated with chronic pelvic pain, dysmenorrhea, and infertility (1). Although numerous theories regarding the histogenesis of endometriosis have been proposed by investigators, the underlying fundamental mechanisms of this disease remain unknown. According to the most widely accepted theory, the pathogenesis of endometriosis is a consequence of the implantation of viable endometrial tissues in the pelvis via retrograde menstruation (1-4). The disease is also associated with infertility: in addition to the obstruction of fallopian tubes due to adhesion, chemokines produced from macrophages and endometriotic tissues induce other factors that negatively affect both sperm motility and embryo implantation as well as early-stage development, which suggests the involvement of immunological change associated with endometriosis (5-7).

That estrogen encourages the development of endometriotic lesions and progesterone inhibits disease

Table 1. Different types of chemokines and their receptors

Name	Other name(s)	Receptor
CC chemokines		
CCL1	I-309, TCA-3	CCR8
CCL2	MCP-1	CCR2, CCR2
CCL3	MIP-1alpha	CCR1
CCL4	MIP-1beta	CCR1, CCR5
CCL5	RANTES	CCR5
CCL6	C10, MRP-2	CCR1
CCL7	MARC, MCP-3	CCR2
CCL8	MCP-2	CCR1, CCR2B, CCR5
CCL9/CCL10	MRP-2, CCF18, MIP-1gamma	CCR1
CCL11	Eotaxin	CCR2, CCR3, CCR5
CXC chemokines		
Name	Other name(s)	Receptor
CXCL1	Gro alpha, GRO1, NAP-3, KC	CXCR2
CXCL2	Gro-beta, GRO2, MIP-2 alpha	CXCR2
CXCL3	Gro-gamma, GRO3, MIP-2alpha	CXCR2
CXCL4	PF-4	CXCR3B
CXCL5	ENA-78	CXCR2
CXCL6	GCP-2	CXCR1, CXCR2
CXCL7	NAP-2, CTAPIII, PEP	CXCR1
CXCL8	IL-8, NAP-1, MDNCF, GCP-1	CXCR1, CXCR2
CXCL9	MIG, CRG-10	CXCR3
CXCL10	IP-10, CRG-2	CXCR3
C chemokines		
Name	Other name(s)	Receptor
XCL1	Lymphotactin alpha, SCM-1 alpha, ATAC	XCR1
XCL2	Lymphotactin beta, SCM-1beta	XCR1
CX3C chemokines		
Name	Other name(s)	Receptor
CX3CL1	Fractalkine, Neurotactin, ABCD-3	CX3CR1

progression is well known (8). Besides these ovarian steroid hormones, recent studies have reported that a variety of chemokines form a complex network and play important roles in the growth and proliferation of endometriotic lesions. The enhanced immunological status and neovascularization induced by chemokines in the pelvic cavity of women with endometriosis are important in the fundamental pathogenesis of the disease. In this review, we describe the roles of various chemokines in the pathogenesis of endometriosis.

3. CHEMOKINES

Chemokines are a large superfamily of structurally and functionally related molecules demonstrating chemotactic activity targeted at specific leukocyte populations. They are 70–90 aa in length and are divided into four subfamilies based on the relative position of their cysteine residues (CC, CXC, C, CXC3) (9-11); members of three of these subfamilies, CC, CXC, and CXC3 appear to be involved in endometriosis. The CC chemokine subfamily, with two adjacent cysteines, includes macrophage inflammatory proteins (MIP)-1 alpha, MIP-1 beta, MIP-3 alpha, macrophage chemoattractant protein (MCP)-1, regulated on activation, normal T expressed and secreted (RANTES), eotaxin, I-309, and human caspase (HC)14, all of which predominantly chemoattract and activate mononuclear cells (10, 12). In contrast, the CXC chemokine subfamily, in which two terminal cysteines are separated by another amino acid includes interleukin(IL)-8, neutrophil-activating protein (NAP)-2, platelet factor 4, ß-thromboglobulin, growth-related oncogene (GRO) alpha, GRO beta, GRO gamma, inducible protein (IP)10, and epithelial cell-derived neutrophil-activating protein (ENA)-78, many of which have been shown to chemoattract and activate neutrophils (9, 10, 13). In addition, CX3C cysteine motif was named fractalkine, and this chemokine is produced by endothelial and neurons cells. Fractalkine exists as a cell-surface-bound as well as a cleaved soluble protein. The extracellular domain of this molecule is released into the supernatant of transfected cells as a 95-kDa glycoprotein. The expression of this protein has been reported to be upregulated by inflammatory signals.

Human endometrial epithelial cells (EEC), endometrial stromal cells (ESC), and endometriotic cells have been reported to produce and secrete various chemokines, including IL-8 (15-18), ENA-78 (19), GRO alpha (20), MCP-1 (16-18, 21, 22), MIP-1 alpha (17, 23), RANTES (24, 25), and eotaxin (26, 27). A role for these chemokines has been implied in a number of human diseases, which are characterized histologically by the presence of neutrophils (28). Chemokines are produced by various cell types including leukocytes, hematopoietic cells, endothelial cells, fibroblasts, and tumor cells in response to viruses, bacteria, lipopolysaccharides (LPS), and pro-inflammatory cytokines such as tumor necrosis factor (TNF)-alpha and IL-1 (13). The responding cell can undergo morphological changes, intracellular calcium mobilization, release of intracellular stored enzymes, respiratory bursts, and increased adhesion to extracellular matrix proteins (10, 12, 13). The expression of these chemokines has been further suggested to be important in menstruation, bacterial infection, embryo implantation, and the maintenance of early pregnancy (29, 30). In addition to these roles, chemokine play important roles in the pathogenesis of endometriosis. Table 1 shows the classification of each chemokine and its receptor.

4. IMMUNOLOGICAL ENVIRONMENT IN THE PERITONEAL CAVITY OF ENDOMETRIOTIC WOMEN

4.1. Inflammatory reaction in endometriosis

Many researchers have suggested that the pathogenesis of endometriosis has inflammatory aspects, and that the activation of many participating cells is caused by chemokines and other cytokines such as IL-1 and TNF-alpha, called inflammatory cytokines. IL-8, classified as a CXC chemokine, can induce the chemotaxis of neutrophils and acts as a potent inflammatory factor in the pathogenesis of endometriosis. There are many other inflammatory chemokines and cytokines, including IL-1, IL-4 (31, 32), IL-5 (33), IL-6 (34), IL-8 (35, 36), MIP-1alpha (37, 38), RANTES (39), INF-gamma (40), IP-10 (41, 42), and TNF-alpha, which form a complex network and stimulate other cells such as

macrophages, stromal cells, epidermal cells, and smooth muscle cells. Inflammatory cytokines and chemokines such as TNF-alpha, IL-1, IL-8, and INF-gamma stimulate the peritoneal macrophage in endometriosis. And this stimulated macrophage produces prostaglandin E_2, which cause pelvic pain and dysmenorrhea. Moreover, the expression of angiogenetic factors increase in the pelvic cavity of endometriotic women, and these factors cause intra-pelvic adhesion. This phenomenon is also the cause of the pain and dysmenorrhea. Thus, these inflammatory reactions in endometriosis produce various clinical symptoms in endometriotic women including chronic pelvic pain, dysmenorrhea, and infertility.

The peritoneal macrophages (PMs), which produce several chemokines and other cytokines, are the major resident cells in the peritoneal cavity of women with or without endometriosis. In normal conditions, they kill harmful cells such as retrograde endometrial tissues, and their presence is commonly associated with an inflammatory environment. Most researchers have demonstrated increased numbers of PMs and their activity in endometriosis (43-57). The presence of ectopic endometrial tissues in the peritoneal cavity of endometriotic women induces the production and activation of PMs and leads to an inflammatory condition that favors progression of the disease. These activated PMs might synthesize and secrete other types of chemokines and cytokines into the peritoneal fluid (PF) including IL-1 (43, 44), IL-6 (44, 45), IL-8 (46, 47), IL-13 (48, 49), IL-15 (48), TNF-alpha (50), transforming growth factor (TGF)-beta (51, 52), ENA-78 GRO alpha (53, 54), and vascular endothelial growth factor (VEGF) (55). The cytokines IL-1beta and TNF-alpha, which are secreted by activated macrophages, have potent inflammatory, cytotoxic, and angiogenic properties (56, 57). Levels of IL-1beta and TNF-alpha in the PF of women with endometriosis have been significantly elevated in most studies (43, 44, 46). Increased levels of IL-8, ENA-78, eotaxin, and GRO alpha, which is a CXC chemokine, play important roles in the neovascularization that surrounds endometriotic lesions by increasing other angiogenetic factors such as VEGF. These chemokines are multifunctional chemokines secreted by lymphocytes, monocytes, fibroblasts, endothelial cells, and endometriotic cells as well as PMs, and are thought to have primary roles in the pathogenesis of endometriosis.

PF levels of MCP-1, which is classified as a CC chemokine and is mainly produced by monocytes, have been shown to increase with the severity of endometriosis (37). Arici *et al.* reported that women with severe endometriosis have higher MCP-1 levels than women with mild endometriosis. It is therefore of interest that women with moderate to severe endometriosis who had not received treatment had higher levels of MCP-1 in their peritoneal fluid than women who had been treated with a gonadotropin-releasing hormone agonist. Akoum *et al.* reported that endometrial epithelial cells from women with endometriosis secrete higher amounts of MCP-1 after 24 h of stimulation with IL-1beta or TNF-alpha, compared with cells from healthy women (38).

Levels of RANTES, which is a CC chemokine, are also elevated in women with endometriosis and highly correlate with the stage of endometriosis (39). RANTES is also a normal constituent secreted by the eutopic endometrium, and its secretion by endometrial stromal cells is stimulated by TNF-alpha and INF-gamma (24). Thus, numerous factors form a signaling network in the peritoneal cavity of endometriotic women, and are closely related with the pathogenesis of endometriosis.

4.2. Endometriotic tissues and chemokines

Recent studies have suggested that endometriotic implants themselves also produce various kinds of chemokines which affect the progression of endometriosis (59, 60). Ulukus *et al.* reported that IL-8 and MCP-1 expressions are high in endometriotic tissues as well as in peritoneal implants, and these chemokines are thought to be involved in the progression of both ovarian and peritoneal endometriosis(48). Moreover, we previously reported that the CXC chemokines IL-8, GRO alpha, and ENA-78 are expressed in endometriotic tissues, and that the expression of these chemokines is elevated after 24 h of stimulation by TNF-alpha in an *in vivo* study (54). These chemokines are thought to cause the inflammatory reaction which results in the advancement seen in endometriotic tissues.

On the other hand, Shi *et al.* reported that estradiol and 2,3,7,8-tetrachlorodibenzo*p*-dioxin can up-regulate CC chemokine receptor 8 expression on the surface of endometrial stromal cells and stimulate monocytes/macrophages to secrete I-309, which is a CC chemokine, and that more monocytes migrate from the blood to the peritoneal cavity under the induction of I-309 and interact with HPMC (human peritoneal mesothelial cell line), which in turn further stimulates I-309 production. Alternatively, a high level of I-309 in the local peritoneal cavity may mediate the adhesion of endometrial stromal cells to HPMC by up-regulating the expression of integrin beta1 on the surface of endometrial stromal cells, thereby contributing to the establishment of peritoneal endometriotic lesions (61). Cultured uterine endometrial stromal cells have been shown to release more intracellular adhesion molecules (ICAMs) in soluble form (sICAM) in endometriotic women (62, 63). The shedding of sICAM-1 from endometrial cells, followed by the binding of sICAM-1 to the lymphocyte function-associated antigen (LFA)-1 receptor, could prevent the lymphocytes from interacting with ICAM-1 on the membrane. More interestingly, sICAM-1 production from the macrophages of women with endometriosis was up-regulated by interferon-gamma and IL-6 administration (64, 65). Thus, sICAM prevents endometriotic cell lysis from occurring, and the refluxed endometrial cells may escape peritoneal immunosurveillance and implant themselves in ectopic sites.

Consequently, in addition to hormonal factors such as local estrogen production, inflammatory processes also may play fundamental roles in the metaplastic transformation of ovarian surface epithelium into

endometriotic lesions and in their own survival and proliferation.

5. ANGIOGENESIS

Angiogenesis, which is the process of generating new capillary blood vessels, occurs in a variety of normal and pathologic processes. In angiogenesis, the basement membrane is first dissolved by protease derived from vascular endothelial cells; endothelial cells then migrate and proliferate, and the capillary tube forms (66-68). Each of these steps is regulated by numerous angiogenic factors. An angiogenic mechanism might be involved in the pathogenesis of endometriosis, and the outgrowth of ectopic endometriotic implants might depend on new capillary growth (69, 70).

VEGF is one of the major growth factors in angiogenesis, and is a potent mitogen, morphogen, and chemoattractant for endothelial cells (71, 72). The angiogenic activity of peritoneal fluid is elevated in women with endometriosis along with the elevated VEGF levels in the peritoneal fluid (73, 74). McLaren *et al.* demonstrated that macrophages in the peritoneal fluid are the principal source of the angiogenic growth factor. An anti-VEGF antibody abolished the enhanced endothelial cell proliferation induced by a macrophage-conditioned medium isolated from the peritoneal cavity of women with endometriosis (74). These findings suggest that activated macrophages are a major source of VEGF, which is directly regulated in endometriosis (75). Since endometriosis is characterized by pronounced vascularization on and around the ectopic tissue, elevated peritoneal fluid levels of the potent angiogenic growth factor VEGF and the presence of VEGF-positive macrophages in the ectopic tissue are clinically important in this disease. Therefore, VEGF-induced angiogenesis might be a critical aspect of the pathophysiology of endometriosis.

In addition to VEGF, several chemokines play important roles in angiogenesis associated with endometriosis. IL-8, a chemoattractant for neutrophils and an angiogenic agent, induces proliferation of endothelial cells (76, 77). Arici *et al.* reported that IL-8 is produced in the healthy endometrium as well as in endometriotic tissue *in vivo* and that IL-8 induces proliferation of endometrial stromal cells as a potential autocrine growth factor (54, 78). Iwabe *et al.* demonstrated that IL-8 exerts its growth-promoting actions in both normal endometrial cells and endometriotic cells (79). TNF-alpha, which is secreted from activated macrophages and is a potent inducer of new blood vessel growth, also stimulates the proliferation of endometriotic stromal cells (79). We have previously reported that endometriotic cells stimulated by TNF-alpha produce ENA-78 and GRO alpha, which are CXC chemokines working as chemotactic factors, and which are closely related with neoangiogenesis (54).

Recently, eotaxin, which belongs to the CC chemokine family, has also been shown to play a critical role in the development of endometriosis as an angiogenetic factor (80, 81). Ouyanget *et al.* reported on the expression of IL-4 in the peritoneal fluid of women with endometriosis; the induced IL-4 increases the expression of eotaxin, which has a role as an angiogenetic factor, in and around the blood vessels in the stroma of endometriotic tissue (80). The eotaxin induced by IL-4 might promote angiogenesis and the subsequent development of endometriosis. On the other hand, Kim *et al.* reported a significant decrease in IP-10 concentrations in the PF of women with advanced-stage endometriosis as compared with that of the early-stage disease (41). In view of the reported evidence that the concentrations of angiogenic factors such as VEGF and HGF are elevated in the PF in the advanced stages of endometriosis, the decrease in IP-10 concentrations may therefore contribute to the enhancement of the angiogenic effect of PF in the advanced stages. The decreased IP-10 concentrations may also stimulate the development of endometriosis by reducing T-cell-mediated antitumor effects.

Thus, neoangiogenesis is closely related with the development of endometriosis, and chemokines appear to play important roles in the angiogenesis of endometriotic cells.

6. INFERTILITY AND CHEMOKINES IN ENDOMETRIOSIS

Sperm toxicity in patients with endometriosis has been addressed by many investigators. To date, only one study has shown increased sperm phagocytosis in the peritoneal fluid of patients with infertility and endometriosis (82). Because numerous kinds of chemokines including IL-8, GRO alpha , ENA-78, RANES, and MIP3 alpha are detected in the peritoneal fluid of women with endometrosis, these chemokines could related with these sperm dysfunction. One research group demonstrated that PMs phagocytized spermatozoa *in vitro* and that macrophages from women with endometriosis were more active than those from women without endometriosis. It is well known that chronic male genital tract infections could be associated with the infertility. Martinez *et al.* reported that the high concentration of IL-8 and other cytokine are detected in the semen with presence of leukocytes and/or pathogens, which associates with infertility (83). On the other hand, Barbonetti *et al.* reported that RANTES is associated with the semen condition (84). The percentage of RANTES-positive spermatozoa may vary under conditions associated with the condition of spermatozoa. A lower expression of RANTES is seen in the semen of patients with asthenozoospermia. Moreover, sperm velocity and the proportion of motile spermatozoa were shown to decrease when peritoneal fluid from women with endometriosis was added to medium *in vitro* (85). Cellular components of seminal fluid appear to mediate the inhibitory action of the peritoneal fluid. The cell-mediated inhibition of sperm motility seems to be a contributor to endometriosis-related infertility (86).

Sueldo *et al.* reported that peritoneal fluid reduces the fertilization of murine oocytes *in vitro* when

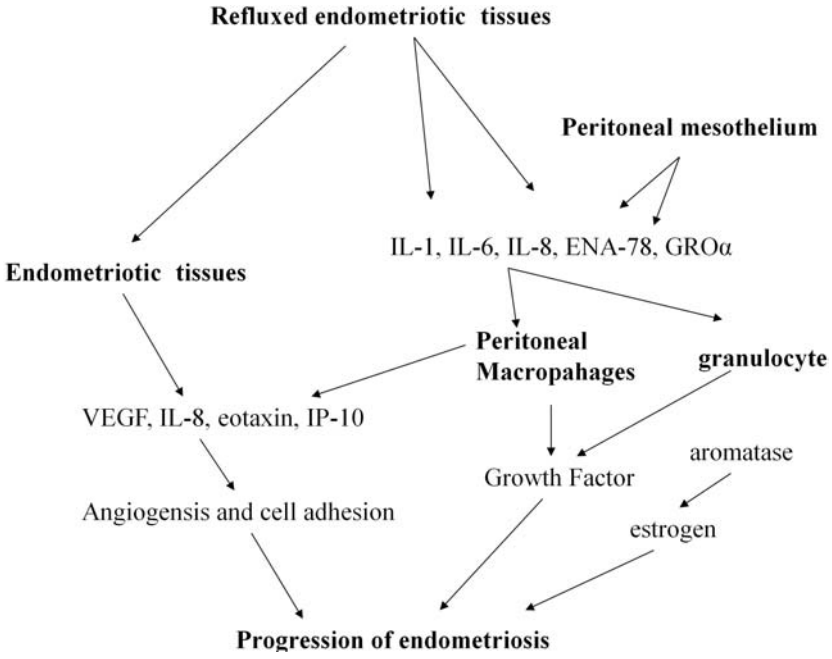

Figure 1. Many kinds of chemokines, including IL-8, GRO alpha, ENA-78, and IP-10, form a complex network with various factors and play important roles in the pathogenesis of endometriosis.

added to macrophage-conditioned medium, and that this effect is enhanced when the fluid is from women with endometriosis (87). It was also reported that penetration assay scores in hamster eggs decreased when spermatozoa were exposed to macrophage-conditioned medium. These studies indicate how the presence of endometriosis can impair egg fertilization and embryo development.

TNF-alpha and IFN-gamma, two of the elevated cytokines in the peritoneal fluid of women with endometriosis, have various effects in human reproduction. TNF-alpha significantly affects sperm motility *in vitro* (88). In addition, Hill *et al.* tested various concentrations of chemokines and found significant embryotoxicity by TNF-alpha and IFN-gamma (89). IFN-gamma significantly inhibits blastocyst implantation *in vitro* (90). Furthermore, it has been reported that the peritoneal fluid from women with endometriosis causes a decrease in the mouse embryo cleavage rate (91). TNF-alpha and INF-gamma induce the expression of chemokines such as IL-8, ENA-78, GRO alpha, and IP-10 (54), and the inflammatory reaction caused by these chemokines negatively affects sperm and embryo conditions which leads to infertility. Moreover, the activity of an embryotoxic factor was directly related to the clinical stage of endometriosis, and medical treatment of endometriosis eliminated the embryotoxicity of the peritoneal fluid (92, 93). On the other hand, some reports have failed to demonstrate an adverse effect of peritoneal fluid from women with endometriosis on fertilization and embryo development in mice (94, 95).

In sum, various chemokines produced in the peritoneal environment of women with endometriosis have been demonstrated to have negative effects upon human reproduction *in vitro* and *in vivo* (96, 97).

7. CONCLUSION

Although the fundamental pathogenesis for endometriosis is not known, there is substantial evidence that chemokines play numerous roles in the pathogenesis and development of endometriosis and endometriosis-associated infertility. Our working hypothesis is that chemokines and other cytokines produced by macrophages and other cells form a complex signaling network in the pathophysiology of this endometriotic condition. In addition, adhesion factors and angiogenetic factors, which would normally be introduced via endometriotic cells, increase the opportunities for their implantation. Figure 1 schematically shows one possibility for the pathogenesis of endometriosis that fits the data collected to date. Further studies into the specific role of each cytokine as well as clinical experiments may improve the understanding of endometriosis and result in novel therapies.

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