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Expression and localization of CXCL16 and CXCR6 in ovarian endometriotic tissues

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Abstract

Purpose Inflammatory mediators, including chemokines, may play crucial roles in the development of endometriosis. Therefore, we investigated the expression and localization of CXCL16 and its receptor, CXCR6, in ovarian endometriotic tissues. We also examined whether CXCL16 induces IL-8 production in endometriotic stromal cells.

Methods We performed immunohistochemical and Western blotting analyses of in vivo and in vitro samples. IL-8 production was assayed using an ELISA.

Results Both CXCL16 and CXCR6 were expressed by endometriotic epithelial cells and stromal cells, but not normal ovarian stroma. A Western blotting analysis using primary cultured endometriotic stromal cells showed a constant expression of CXCL16 and CXCR6 in the proliferative phase, secretory phase and during gonadotropin-releasing hormone agonist therapy. CXCL16 induced IL-8 production in several endometriotic stromal cells in vitro.

Conclusions CXCL16 and CXCR6 might be involved in the pathophysiology of endometriosis through regulation of the inflammatory response.

Keywords CXCL16 · CXCR6 · Endometriosis · IL-8

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Introduction

Endometriosis is a common gynecologic disease which affects 0.5–5% of fertile females and 25–40% of infertile females of reproductive age [1]. Endometriosis is defined as the ectopic growth of endometrium-like tissue in locations outside the uterus, including the ovaries and the pelvic peritoneum, and is an enigmatic disease that deteriorates the health of patients by causing pain, infertility, and adnexal masses. Sampson's theory of implantation of endometrial cells [2] and fragments refluxed during the menstrual period is widely accepted [3]. In addition, a large volume of evidence indicates that inflammatory mediators and immune responses play crucial roles in the development of endometriosis and endometriosis-related pain and infertility [4, 5], although the pathophysiology of endometriosis is not fully understood.

Several studies have reported increased levels of many chemokines in the peritoneal fluid of patients with endometriosis. The majority of such chemokines are induced upon cellular activation by inflammatory stimulation [6–8]. The chemokine superfamily consists of about 50 cytokine members and 20 chemokine receptors [9, 10] involved in the regulation of tumor-associated immunity, blood vessel formation, cancer cell proliferation and metastasis. Over the past few years, there has been emerging evidence that several pairs of chemokines and their receptors play critical roles in the ontogenesis of endometriosis [11, 12].

Recently, CXCL16 has been identified to be a ligand for a chemokine receptor, CXCR6, which is expressed by several types of inflammatory cells, including peripheral blood leukocytes and macrophages [13–16]. CXCL16 exists in both transmembrane and soluble forms and functions as a scavenger receptor for oxidized lipoproteins

and bacteria [17–19]. The expression of CXCL16 has been reported on immune cells like dendritic cells, macrophages, B cells, T cells, and on smooth muscle cells and endothelial cells [17–20], and therefore, it is associated with a number of human inflammatory diseases including rheumatoid arthritis [21, 22], interstitial lung disease [23, 24], and atherosclerosis [25–27].

In the present study, we examined the expression and localization of CXCL16 and CXCR6 in endometriotic ovarian cysts. We also examined whether CXCL16 is able to induce the production of interleukin-8 (IL-8), which has been considered a key molecule underlying endometriosis-related inflammation, in primary cultured endometriotic stromal cells. Our observation raised the possibility that CXCL16/CXCR6 might be involved in the pathophysiology of endometriosis.

Materials and methods

Patients

The endometriotic tissues used for this study were taken from the chocolate cyst linings of the ovaries of patients with endometriosis [$n = 11$; proliferative phase ($n = 4$), secretory phase ($n = 4$), and during gonadotropin-releasing hormone agonist (GnRHa) therapy ($n = 3$)] who had undergone surgery at Nagoya University Hospital. For all of these samples, informed consent was obtained from each patient before the study; this study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

Immunohistochemistry

The immunohistochemical analyses were performed as described previously [28]. Briefly, formalin-fixed, paraffin embedded tissue sections were cut, deparaffinized, and treated at 90°C in a microwave oven for heat-induced epitope retrieval. Immunohistochemical staining was carried out based on the labeled streptavidin-biotin method after incubation with 10% normal rat serum in PBS for 10 min. The primary antibody against CXCL16 (Human CXCL16 Antibody, R&D System Inc., Minneapolis, MN, USA) or CXCR6 (ab8023, Abcam Inc., Cambridge, MA, USA) was diluted 1:100 in PBS. In negative control experiments, the primary antibody was replaced with rabbit IgG. The slides were counterstained with hematoxylin prior to mounting. Staining for CXCL16 and CXCR6 was carried out repeatedly for each sample. Stained sections were observed under an Olympus BH2 microscope (Tokyo, Japan) and photographed using a charge-couple device color camera (CS600; Olympus).

Primary culture of endometriotic stromal cells

Endometriotic stromal cells (ESCs) and endometrial stromal cells were separated as described previously [29]. In brief, endometriotic cysts and endometrial tissue in the late proliferative phase was minced into small pieces ($\sim 1\ mm^3$), and these pieces were filtered through a cell strainer consisting of a 100 µm pore size nylon mesh (Becton Dickinson, Franklin Lakes, NJ, USA) to remove the blood cells. Then, the minced tissue was incubated with stirring at 37°C for 20 min in PBS and 0.5% collagenase (Wako, Osaka, Japan). The tissue digest was vigorously pipetted and passed over a cell strainer consisting of 70-µm pore size nylon mesh (Becton Dickinson). The ESCs collected from the lower receptacle were suspended and plated onto 60 mm sterile dishes. The ESCs were cultured in Dulbecco's modified Eagle's medium (DMEM; Sigma, St. Louis, MO, USA) containing 10% fetal bovine serum (FCS) (Sigma), 100 IU/mL penicillin, and 100 µg/mL streptomycin. The purity of ESCs was assessed by morphological determination using light microscopy. Each cell population was routinely 98% pure, as assessed by phase contrast microscopy.

Western blotting analysis

Cultured ESCs within three times of passage and minced normal ovarian cortex were lysed in a radioimmunoprecipitation buffer (10 mM Tris–HCl, pH 7.4, 150 mM NaCl, 1% Nonidet P-40, 5 mM EDTA, 1% sodium deoxycholate, 0.1% SDS, 1.2% aprotinin, 5 µM leupeptine, 4 µM antipain, 1 mM phenylmethylsulfonylfluoride, and 0.1 mM Na_3VO_4). Cell lysates were clarified by centrifugation at $13{,}000\times g$ at 4°C for 15 min, diluted in 2× sample buffer (125 mM Tris–HCl, pH 6.8, 4% SDS, 10% glycerol, 0.2% bromphenol blue, and 4% 2-mercaptoethanol), resolved by 10% SDS-PAGE, and immunoblotted with a 1:1,000 dilution of an anti-CXCL16 Ab, anti-CXCR6 Ab, or anti-β-actin Ab (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA).

ELISA for IL-8

The ESCs were diluted with DMEM with 10% FBS to a seeding density of 1×10^5 cells per well and suspended in 24-well tissue culture plates (500 µL/well). The cultures were allowed to proliferate until subconfluence (24–48 h). After 24 h serum starvation, CXCL16 (200 ng/mL; PeproTech, Rocky Hill, NJ, USA) was added and cells were incubated for another 24 h. The concentration of IL-8 in the culture supernatants was determined in duplicate using commercially available IL-8 ELISA kits (Quantikine Human CXCL8/IL-8 Immunoasay; R&D System Inc.). The

intra- and inter-assay CV was 4.4–4.7 and 5.2–8.1%, respectively.

Results

CXCL16 and CXCR6 expression in ovarian endometriotic tissue

First, to confirm the expression of CXCL16 and CXCR6 in the ovarian endometriotic tissues, a Western blot analysis and an immunohistochemical analysis were performed. Table 1 shows the patient characteristics. The immunohistochemical analysis revealed that both CXCL16 and CXCR6 were expressed by endometriotic epithelial cells and stromal cells, but not normal ovarian stroma (Fig. 1). No obvious differences in the localization or intensity of staining were found among the samples from the proliferative phase, secretory phase and during GnRHa therapy (data not shown). Both CXCL16 and CXCR6 were detected in the primary cultured ESCs by a Western blotting analysis. The immunoreactive bands of CXCL16 and CXCR6 were conspicuous and had almost constant expression in ESCs from the proliferative phase (P1–P4), secretory phase (S1–S4), and during GnRHa therapy (G1–G3; Fig. 2). Both CXCL16 and CXCR6 were negligible in the normal ovarian cortex (Ov; Fig. 2). CXCL16, not CXCR6, in the physiological endometrial stromal cells showed a weaker immunoreactivity compared with those in ESCs (E; Fig. 2).

The effects of CXCL16 on IL-8 production by ESCs

Next, we investigated whether CXCL16 affects the IL-8 production of primary cultured ESCs. Measurement of IL-8 in culture supernatant by ELISA showed that 200 ng/mL CXCL16 increased the IL-8 production in the most of the cultured ESCs (P1, P2, S1, S2, S3, S4, G1, G2). However, a few of the cultured ESCs (P3, P4, G3) did not show an increase in IL-8 with CXCL16 (Fig. 3).

Table 1 Patient characteristics

	Age (years)	Cyst size (cm)	GnRHa
P1	33	8	–
P2	34	6	–
P3	45	15	–
P4	25	8	–
S1	32	8	–
S2	38	4	–
S3	28	7	–
S4	35	7	–
G1	37	10	L, 4 mo
G2	37	4	N, 2 mo
G3	34	5	L, 5 mo

L leuprorelin acetate, *N* nafarelin acetate

Discussion

In the present study, we first found that both CXCL16 and its receptor, CXCR6, are expressed in the epithelial cells and stromal cells in the ovarian endometriotic tissues. It has been reported that CXCR6 is expressed on several types of inflammatory cells, such as CD4+ T cells, CD8+ T cells [15], NKT cells [30], and NK cells [31]. On the other hand, CXCL16 has been reported to be expressed in activated endothelial cells [32], Hodgkin's disease-derived tumor cells and tumor-associated macrophages in rectal cancer [33, 34]. It has recently been reported that CXCL16 and CXCR6 co-localized on prostate cancer cells and showed the highest expression in cancer cells surrounded by inflammatory stroma [35]. CXCL16 has been also demonstrated to stimulate the growth of prostate cancer cell lines via CXCR6.

CXCL16 is synthesized as a transmembrane molecule that is transported to the cell surface. There are two forms of CXCL16 resulting from cleavage at the cell surface [17, 19]. The soluble form of CXCL16 functions as chemoattractant to promote cell migration [36]. The remaining transmembrane CXCL16 can function as a cell adhesion molecule for cells expressing CXCR6 [17, 19], and has also been demonstrated to function as a novel scavenger receptor for phosphatidylserine and oxidized lipoprotein [18]. Studies using inhibitors revealed that the two disintegrin-like metalloproteinases, ADAM10 and ADAM17, are mainly involved in this release of CXCL16 [37, 38]. ADAM10 has been reported to be expressed by endometrial epithelial cells and stromal cells and a higher expression of ADAM10 mRNA in epithelial and stromal cells of patients with endometriosis has been observed in comparison to patients without endometriosis [39]. Recently, Baston-Büst et al. [40] reported that syndecan-1-knockdown decidualized human endometrial stromal cells showed a higher secretion of chemokines, including CXCL16 to the culture medium compared with wild-type endometrial stromal cell lines. Based on both previous findings and our present results, the expression of CXCL16 by endometrial and endometriotic stromal cells might thus be regulated by inflammatory response. However, our results also showed that GnRHa treatment did not affect the expression of CXCL16 and CXCR6 in ESCs in vitro. An extended culture of these cells might impair their properties and, therefore our results might not reflect the actual situation in vivo.

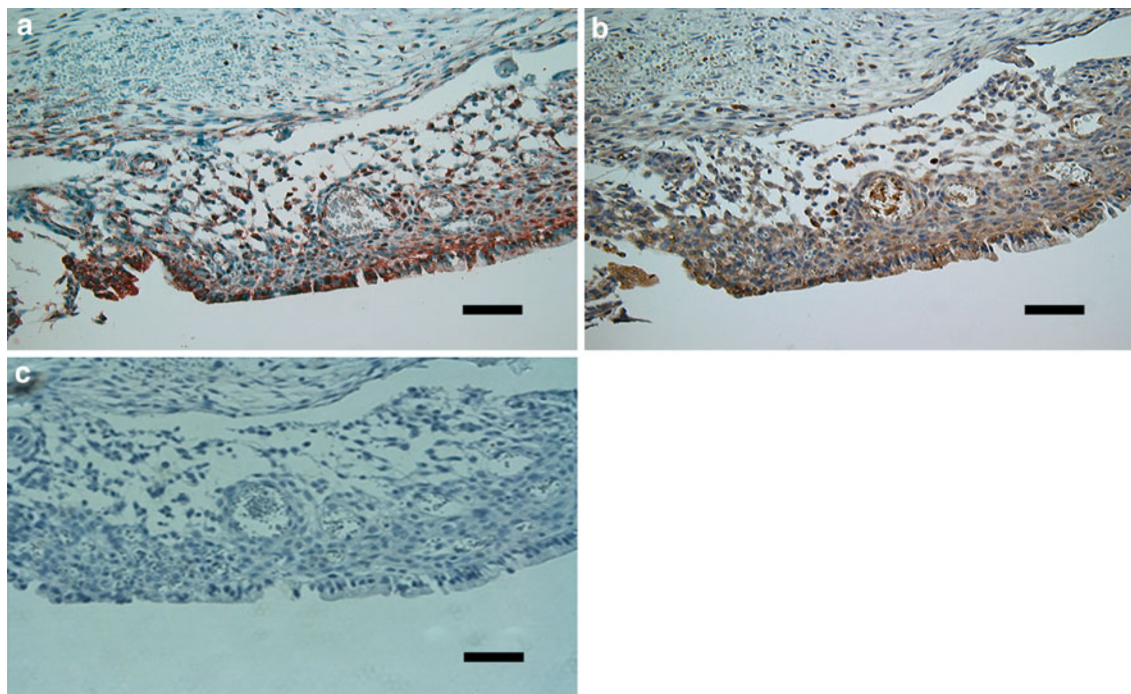

Fig. 1 Immunohistochemical localization of CXCL16 and CXCR6. **a** CXCL16 and **b** CXCR6 are expressed in the epithelial and stromal cells of the ovarian endometriotic tissues. **c** Negative control. The *bars* indicate 25 μm

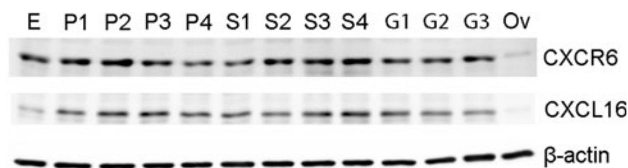

Fig. 2 The expression of CXCR6 and CXCL16 in ovarian endometriotic stromal cells, physiological endometrial stromal cells and normal ovarian cortex. Ten micrograms of samples were subjected to SDS-PAGE, and an immunoblot analysis using an anti-CXCR6 Ab (*upper panel*), anti-CXCL16 Ab (*middle panel*) or anti-β-actin Ab as an internal control (*lower panel*). P1–P4, S1–S4, and G1–G3 cells were derived from the samples excised during the proliferative phase, secretory phase and during GnRHa therapy, respectively. *E* and *Ov* represent endometrial stromal cells and normal ovarian cortex, respectively

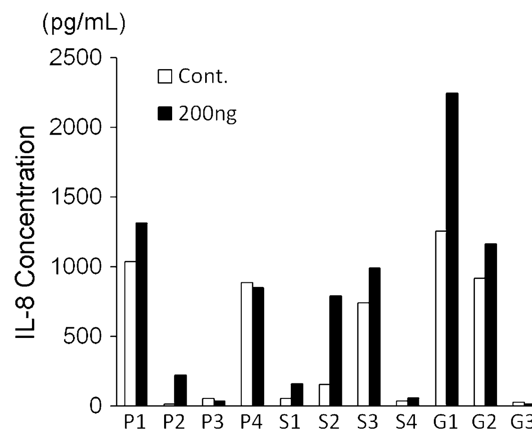

Fig. 3 CXCL16 stimulation of IL-8 production by ovarian endometriotic stromal cells. IL-8 production was increased by the addition of 200 pg/mL CXCL16 in the P1, P2, S1–S4, G1, and G2 stromal cells. The P1–P4, S1–S4, and G1–G3 cells were derived from the samples excised during the proliferative phase, secretory phase and during GnRHa therapy, respectively. Three independent experiments produced similar results

It is generally believed that local inflammation occurs in the peritoneal cavity in endometriosis and therefore, affects immunological and inflammatory factors, which play an important role in the pathogenesis of endometriosis [4]. IL-8 is an angiogenic, proinflammatory and growth-inducing cytokine [41]. IL-8 has also been reported to be produced in the human endometrium in vivo, and that IL-8 induces the proliferation of endometrial stromal cells as an autocrine growth factor [42]. Moreover, Iwabe et al. [7] demonstrated that tumor necrosis factor-α stimulates the proliferation of endometriotic stromal cells through induction of IL-8 gene and protein expression. Our current results showed that CXCL16 may induce IL-8 production in ESCs. Taken together, the CXCL16 expressed by endometriotic tissues might be involved in the inflammatory aspect of endometriosis though the increase in IL-8 production.

In conclusion, we have herein demonstrated that CXCL16 and CXCR6 are expressed by ovarian endometriotic tissues in vitro and in vivo, and that CXCL16 induces IL-8 production in endometriotic stromal cells.

Therefore, CXCL16 and CXCR6 might be key molecules involved in the regulation of the inflammatory response and proliferation in endometriosis. Further studies will be required to provide a more detailed functional evaluation of CXCL16 and CXCR6 in endometriosis and to elucidate the pathophysiology of endometriosis.

Conflict of interest None.

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