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Role of Interleukin-6 and Its Receptor in Endometriosis

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Background: Studies have shown that the concentration of interleukin (IL)-6 in peritoneal fluid is increased in patients with endometriosis; however, whether the disorders involving IL-6 contribute to the development of endometriosis is still unclear. In the present study, we evaluated the potential role of IL-6 and IL-6 receptor (IL-6R) in the pathogenesis of endometriosis.

Material/Methods: We examined activated macrophages and the expression of membrane-binding receptor (mIL-6R) in peritoneal fluid using flow cytometry. The levels of IL-6 and the IL-6 soluble receptor (sIL-6R) in peritoneal fluid and plasma in patients with endometriosis was measured by an enzyme-linked immunosorbent assay.

Results: Activated macrophages and mIL-6R in peritoneal fluid were increased in patients with endometriosis. IL-6 and sIL-6R in peritoneal fluid were also increased in patients with endometriosis; however, there was an increase in plasma IL-6 and a decrease in plasma sIL-6R. The endometriosis group was categorized into 2 groups according to the retrospective American Fertility Society Score (r-AFS): group A and group B. Peritoneal fluid sIL-6R in endometriosis group B was significantly higher than in endometriosis group A and the control group.

Conclusions: Disorders involving IL-6 and IL-6R are correlated with the etiology of endometriosis. An increase in sIL-6R in peritoneal fluid promotes the development of endometriosis by enhancing the bioactivity of IL-6.

MeSH Keywords: Endometriosis • Gynecology • Interleukin-6 • Macrophages

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Background

Endometriosis is a common gynecologic clinical entity characterized by aberrant growth of endometrial cells at sites outside the uterus. The etiology of endometriosis is multidimensional; however, the exact etiology is unknown [1,2]. The local pelvic inflammatory process, accompanied by altered function of immune-related cells and changes in cytokine content in the peritoneal cavity, have been shown to be related to the development of endometriosis [3,4]. Studies have shown that cytokines, including interleukin (IL)-6, IL-8, IL-10, IL-1beta, IL-17A, interferon-gamma, and tumor necrosis factor-alpha, are increased in the peritoneal fluid (PF) of patients with endometriosis [2,5–9].

IL-6 is a multi-functional cytokine that is increased in PF and serum of women with endometriosis [2,10]. Macrophages are the predominant cells secreting IL-6 in PF [11]. A number of studies have shown that activated macrophages in the PF of women with endometriosis are significantly increased in number and secrete more cytokines, including IL-6 [2,12,13]. These studies suggest that IL-6 disorders in PF contribute to the pathology of endometriosis. It has been reported that an increased level of IL-6 suppresses NK cell activity in the PF of patients with endometriosis via regulation of SHP-2 expression [2].

IL-6 exerts multiple bioactivities through its receptor (IL-6R). Membrane-binding receptor (mIL-6R) and soluble receptor (sIL-6R) are 2 forms of IL-6R. The biological activity of IL-6 is mainly mediated through binding with the corresponding mIL-6R. sIL-6R exists in body fluids and possesses a characteristic biological significance. The unique property of sIL-6R that mediates and enhances the biological function of IL-6 plays an important role in human disorders [14,15]. Studies showed that IL-6 and IL-6R act as growth regulatory signals for human endometrial stromal cells in dose- and cell density-dependent inhibition. Endometrial stromal cells resist the activity of IL-6 by reducing the expression of IL-6R [16,17].

In the present study, we determined the number of activated macrophages and mIL-6R expression in PF. The levels of IL-6 and sIL-6R in PF and plasma were measured to explore the possible role of IL-6R (mIL-6R and sIL-6R) in endometriosis.

Material and Methods

Patient selection and sample collection

The endometriosis group comprised 47 inpatients with endometriosis confirmed by laparoscopy and histologic examination at the Women's Hospital School of Medicine Zhejiang University. All subjects provided informed consent. The endometriosis group was categorized into 2 groups according to the retrospective American Fertility Society Score (r-AFS): group A (stages I-II [n=19]), with an average age of 34.2±7.1 years; and group B (stages III-IV [n=28]), with an average age of 33.2±6.3 years. The control group comprised 22 inpatients with benign ovarian cystic tumors and uterine malformations confirmed by laparoscopy or histologic examination; the average age was 33.8±6.7 years. There was no significant difference in age among the 3 groups. All of the participants had regular menstrual cycles, had no systemic or celiac inflammatory lesions and immune system disorders, were not taking exogenous hormones, and had not received anti-inflammatory or immunosuppressive therapy 3 months prior to surgery. Our study was approved by the Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University.

Peripheral blood was collected before laparoscopy. Supernatant plasma was stored at –70°C after centrifugation. PF was collected at the time of laparoscopy. The macrophages were isolated and the supernatant fluid was stored at –70°C.

Flow cytometry

Activated macrophages (CD14) and mIL-6R (CD126) in PF were evaluated using flow cytometry. A (PF) monoplast macrophage suspension (100 µl 5×10^5/ml) was added to tubes. Mouse anti-human CD14-FITC (10 µl, CD14, IM0645; Coulter Immunotech, Fullerton, CA) and mouse anti-human CD126-PE (10 µl, CD126, IM1979; Coulter Immunotech) monoclonal antibodies were used to stain the cells. Murine IgG1-FITC and murine IgG1-PE fluorescent antibodies (10 µl) served as controls. The percentage of macrophage cell surface CD14+, CD126+, and CD14+/CD126+ expression was determined using flow cytometry (Beckman Coulter Company, Fullerton, CA).

Enzyme-linked Immunosorbent Assay (ELISA)

Double antibody sandwiched ELISA kits (human IL-6 ELISA [BMS213/2] and human sIL-6R ELISA [BMS214]; Bender MedSystems, Vienna, Austria) were used to detect the levels of IL-6 and sIL-6R in PF and plasma. Samples were tested according to ELISA kit instructions. The ELISA plates were washed and serial dilutions of IL-6, 50 µl of the assay buffer, and 50 µl of the IL-6 sample were added to every IL-6 sample well, while serial dilutions of sIL-6, 80 µl of the assay buffer, and 20 µl of the sIL-6R sample were added to every sIL-6R sample well. The concentration range of the IL-6 standard solution was 1.6–100 pg/ml, and the concentration range of the sIL-6R standard solution was 0.08–5 ng/ml. A pre-prepared biotin-conjugate (50 µl) was added to the IL-6 sample wells and 50 µl of a pre-prepared HRP-conjugate solution were added to the sIL-6R wells. Plates were incubated at 25°C for 2 h after being blocked and shaken. After washing, 100 µl of pre-prepared TMB substrate solution was added, and the plates were placed

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Table 1. Comparison of CD14+, CD126+, and CD126+/CD14+ cells in peritoneal fluid.

	Group A (n=19)	Group B (n=28)	Control (n=22)	F value
CD14+	85.82±9.42*	81.99±7.93*	76.91±8.87	5.911
CD126+	73.66±7.88*	71.39±11.07*	63.56±10.31	5.961
CD126+/CD14+	72.82±8.23*	70.40±11.28*	62.87±10.38	5.448

The results are expressed as the mean ±SD of the histochemistry score (H-SCORE) for CD14+, CD126+, and CD126+/CD14+; n – indicates the number of patients; * represents a P<0.05 versus the control group.

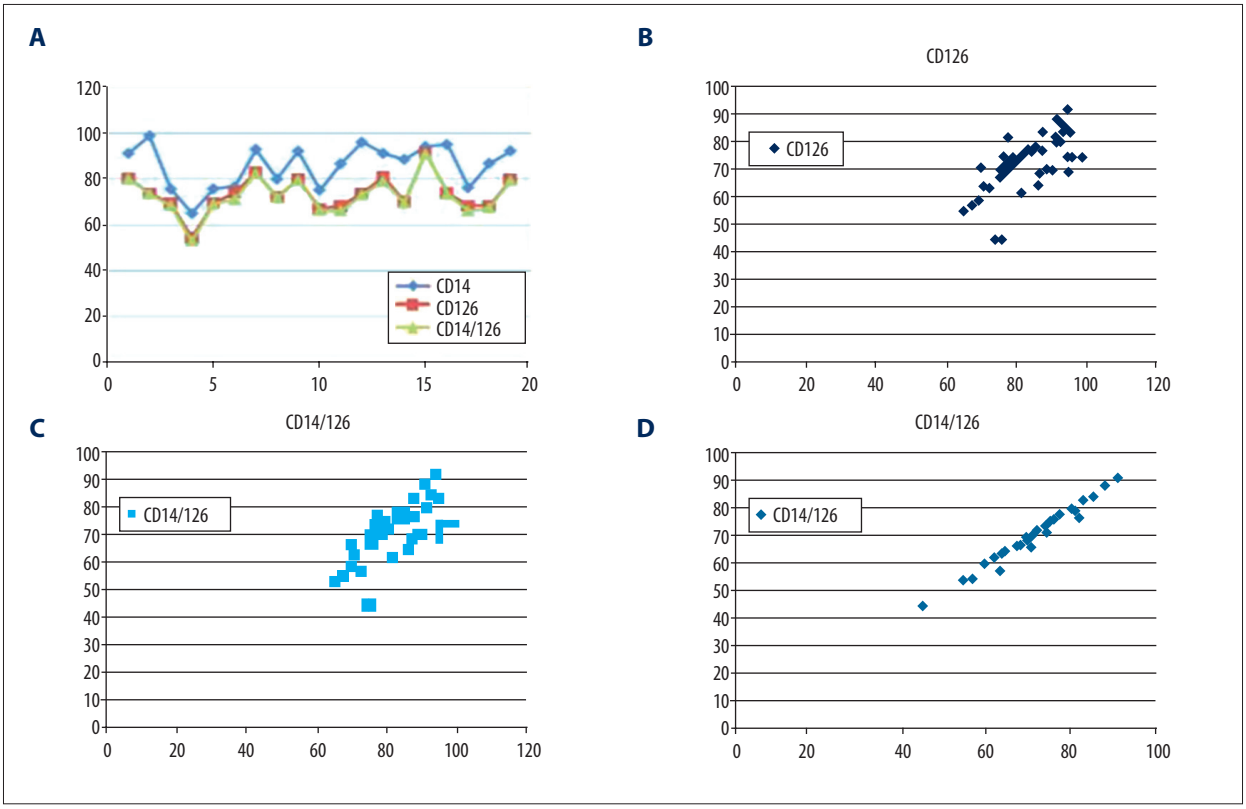

Figure 1. Correlation between the expression of CD14+, CD126+, and CD14+/CD126+ in peritoneal fluid. (**A**) Expression of CD14+, CD126, and CD14+/CD126+. (**B**) Linear correlation between CD14+ and CD126+ (r=0.657; P<0.05). (**C**) Linear correlation between CD14+ and CD14+/CD126+ (r=0.698; P<0.05). (**D**) Linear correlation between CD126+ and CD14+/CD126+ (r=0.991; P<0.05).

in a dark room for 20 min at 25°C. The reaction was stopped with 100 ul of stop solution, and the absorbance value was read at 450 nm. IL-6 and sIL-6R in each sample were calculated according to the absorbance and the standard curve of each case with 620 nm wavelength as a reference.

Statistical analysis

Data are presented as the mean ±SEM and the levels of IL-6 in PF were sealed with a logarithm. ANOVA, Student-Newman-Keuls test, and linear correlation were used for statistical analyses. A two-tailed test with a P<0.05 was considered statistically significant. All data were managed with SPSS 13.0 software.

Results

Immunophenotypic analysis of PF cells

Activated macrophages (CD14+) and the expression of mIL-6R (CD126+) in PF were determined using flow cytometry. The population of macrophages increased in patients with endometriosis compared to the control group (P<0.05), but there were no differences between the 2 endometriosis groups (P>0.05). There was also higher expression of mIL-6R (CD126+) and CD14+/CD126+ in patients with endometriosis than in the control group (P<0.05). There were no demographic differences between the 2 endometriosis groups (P>0.05; Table 1).

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Table 2. Comparison of the percentage of CD126+/CD14+ cells among CD14+ and CD126+ cells in peritoneal fluid.

Group	CD126+/CD14+ cells among CD14+ cells (%)	CD126+/CD14+ cells among CD126+ cells (%)
Group A	84.85	98.96
Group B	85.86	98.61
Control	81.74	98.91

Table 3. Comparison of IL-6 and sIL-6R in peritoneal fluid and plasma.

	Group A (n=19)	Group B (n=28)	Control (n=22)	F value
Peritoneal fluid				
IL-6 (pg/ml)	46.94±3.05*	45.70±2.48*	12.58±2.25	14.33
sIL-6R (ng/ml)	52.42±24.11	69.95±22.54*	54.78±23.55	4.11
Plasma				
IL-6 (pg/ml)	16.96±5.95	22.77±11.02*	17.15±7.29	3.557
sIL-6R (ng/ml)	107.13±20.95	80.09±23.22*	108.20±25.18	11.71

The results are expressed as the mean ±SD of the IL-6 and sIL-6R in peritoneal fluid and plasma; n indicates the number of patients; * represents a P<0.05 versus the control group.

Correlation between the expression of CD14+, CD126, and CD14+/CD126+

The expressions of CD14+, CD126+, and CD14+/CD126+ were closely related. There was a linear correlation between CD14+ and CD126+, CD14+ and CD14+/CD126+, and CD126+ and CD14+/CD126+ (r=0.657, 0.698, and 0.991, respectively; P<0.05; Figure 1).

The ratios of CD14+/CD126+ in CD14-positive cells in the control group, endometriosis group A, and endometriosis group B were 81.74%, 84.85%, and 85.867%, respectively. There was no significant among between these 3 groups (P>0.05; Table 2).

The ratio of CD14+/CD126+ in CD126-positive cells in the control group, endometriosis group A, and endometriosis group B were 98.91%, 98.86%, and 98.61%, respectively. There were no significant differences among the 3 groups (P>0.05; Table 2).

Expression of IL-6 and sIL-6R in PF and plasma

The expression of IL-6 and sIL-6R in PF and plasma from the 3 groups (endometriosis group A, endometriosis group B, and control group) was measured by ELISA. The expression of IL-6 in PF in the 2 endometriosis groups was higher than in the control group (P<0.05), but no difference existed between the 2 endometriosis groups (P>0.05; Table 3 and Figure 2A). The expression of sIL-6R in PF and IL-6 in plasma was higher in endometriosis group B (P<0.05) when compared with endometriosis group A or the control group, but there was no difference between endometriosis group A and the control group (P>0.05; Table 3 and Figure 2A, 2B). The expression of sIL-6R in plasma was decreased in the endometriosis group B (P<0.05) compared with endometriosis group A and the control group, but there was no difference between endometriosis group A and the control group (P>0.05; Table 3, Figure 2B).

Correlation between IL-6 concentration in PF and the expression of CD14+, CD126+, and CD14+/CD126+

IL-6 in PF was increased in the endometriosis groups (Figure 2C); however, there was no significant linear correlation between IL-6 and the expression of CD14+, CD126+, or CD14+/CD126+ (Figure 2D).

Discussion

It has been shown that because of an imbalance in the local pelvic immune microenvironment, countercurrent endometrium escapes from immune surveillance and clearance mechanisms and may be related to endometriosis [18]. In the present study, higher expression of CD14+ in the endometriosis groups revealed an increased number of activated macrophages in PF, suggesting that macrophages participate in the occurrence of endometriosis. Increased IL-6 in PF was consistent with an increased expression of CD14+ in the PF, suggesting that increased PF IL-6 in patients with endometriosis is related to the activation of macrophages. Further correlation analysis showed that there was no significant correlation between the IL-6 level and expression of CD14+. Studies have shown that mature activated T cells, ectopic endometrial stromal cells, and

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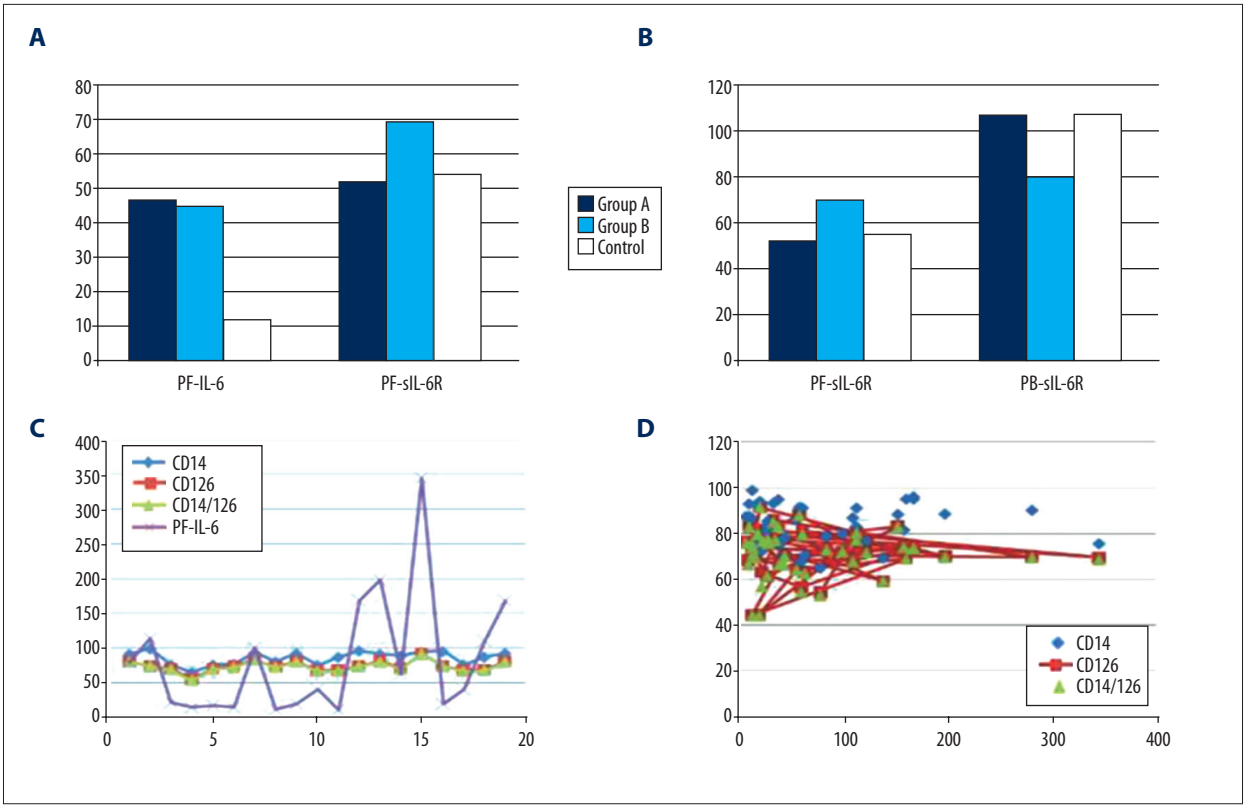

Figure 2. Expression of IL-6 and sIL-6R and the correlation between IL-6 and the expression of CD14+, CD126+, or CD14+/CD126+ in peritoneal fluid. (**A**) The sIL-6R level increased in peritoneal fluid in the endometriosis group B, while peritoneal IL-6 was increased in groups A and B. (**B**) Higher expression of sIL-6R in peritoneal fluid in the endometriosis group B compared with endometriosis group A and the control group (P<0.05). Lower expression of plasma sIL-6R in endometriosis group B compared with endometriosis group A and the control group (P<0.05). (**C**) Peritoneal fluid IL-6 increased in endometriosis groups A and B, along with the increased expression of CD14+, CD126+, and CD126+/CD14+ in the peritoneal fluid. (**D**) There was no significant linear correlation between IL-6 and the expression of CD14+, CD126+, or CD14+/CD126+ in the peritoneal fluid.

epithelial cells can also produce IL-6 and influence the content of PF IL-6 in endometriosis patients [19–22]. Thus, activated macrophages may be one of multiple sources of IL-6.

IL-6 is a multi-functional cytokine that is increased in the PF of women with endometriosis [2,10]. In the present study, PF IL-6 levels in the endometriosis groups were significantly increased, while the plasma IL-6 level was only elevated in endometriosis group B, which indicated that an altered expression of local PF IL-6 had great significance in the pathogenesis of endometriosis. Moreover, IL-6 changes in the abdominal local microenvironment is intuitive when compared with plasma. According to the literature, IL-6 promotes the occurrence and development of endometriosis through the cytokine network as an important pro-inflammatory molecule. In addition, IL-6 also plays a crucial role in the pathogenesis of endometriosis by interfering with cellular immune function [23–29]. Endometriosis patients can synthesize and secrete increased haptoglobin, which helps ectopic endometrial cells escape from immune surveillance and elimination by adhering to the surface of macrophages and decreasing phagocytosis. The release of IL-6 by activated macrophages increases the secretion of haptoglobin and forms a positive feedback loop, which facilitates ectopic endometrium survival and promotes the occurrence and development of endometriosis [30]. Whether the increased level of IL-6 in PF in endometriosis patients is related to endometriosis stage is still controversial. Our study shows that the PF IL-6 level in endometriosis patients is significantly increased, but is unrelated to the r-AFS, which was consistent with a report by Overton [31].

The various biological activities of IL-6 are mainly mediated through binding with the corresponding IL-6R. MIL-6R and sIL-6R are 2 forms of IL-6R. In the present study, we determined the expression of mIL-6R (CD126+) in PF using flow cytometry to acquire in-depth information on the IL-6 mechanism. The results revealed that the expression of CD126+ and CD14+/CD126+ was highly consistent. Nearly 99% of CD126+

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(mIL-6R) is positioned on the surface of CD14+ macrophages, suggesting that macrophages are the major effector cells of IL-6. Expression of CD126+ and CD14+/CD126+ in the endometriosis group was significantly higher than in the control group and had a linear correlation with CD14+ expression. These results suggest that PF macrophages are both major IL-6-producing cells and the main target cells of IL-6, which may have contributed to the occurrence and development of endometriosis.

SIL-6R is another form of IL-6R. We showed that PF sIL-6R in endometriosis group B was significantly higher than in endometriosis group A and the control group, suggesting that PF sIL-6R is involved in the pathogenesis of endometriosis and may be associated with the severity of the disease. In fact, sIL-6R is proteolytically cleaved from IL-6R and exists in body fluids. SIL-6R can enhance the bioactivity of IL-6 by direct binding of the IL-6/sIL-6R complex to gp130 [15]. Thus, the increase in sIL-6R synergistically promotes the development of endometriosis. Whether there is a relationship between sIL-6R and IL-6 warrants further study. Holub [32] studied several kinds of autoimmune diseases and concluded that the content of sIL-6R had no relationship with IL-6, and the same conclusion was reached in a study involving erythematosus and rheumatoid arthritis [33]. In the present study, we showed that the PF IL-6 content in the endometriosis A and B groups was significantly increased, while the PF sIL-6R levels was only increased in the endometriosis group B, indicating that sIL-6R content has little to do with IL-6, which is consistent with these previous reports.

We also found that the PF sIL-6R level was increased in endometriosis group B, and sIL-6R was significantly reduced in plasma. Therefore, it can be assumed that the concentration of mIL-6 in local PF, along with the activation of mononuclear cells in the peripheral blood of endometriosis patients, reduces mIL-6R on plasma mononuclear cell membranes, leading to an increase in the sIL-6R level, while the plasma sIL-6R hydrolyzed by mIL-6R is decreased. This finding also warrants further study.

Conclusions

Our research suggests that disorders of IL-6 and its receptor are correlated to the etiology of endometriosis. The increase in PF sIL-6R promotes the development of endometriosis by enhancing the bioactivity of IL-6.

Conflicts of interest

None.

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