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Research Article

Immunohistochemical Evaluation of CXCL12/CXCR4 and Adiponectin in deep Infiltrating Endometriosis

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Abstract

Chemokine CXCL12 and its receptor CXCR4 are involved in tumor cell migration, invasion and metastasis. Adiponectin is produced by adipose tissue, and exerts anti-inflammatory and anti-angiogenic effects. The aim of this study was to compare the expression of CXCL12, CXCR4 and adiponectin by immunohistochemical staining in intestinal endometriosis (IE, 6 cases) and abdominal wall endometriosis (AE, 12 cases) tissue, to ovarian endometriosis (OE, 12 cases). In addition, the relationship between adiponectin and the CXCL12/CXCR4 axis in these tissues was examined. In IE, CXCL12 expression was detected in 83.3%, and 16.7% of glandular and stromal cells, respectively, but CXCR4 expression was only found in stromal cells (33.3%). In AE, CXCL12 expression was found in 75.0% of glandular and 33.3% of stromal cells, and CXCR4 was found in 50% and 75% of glandular and stromal cells, respectively. There was no difference inCXCL12/CXCR4 expression among three endometriosis groups. The expression of adiponectin isoforms did vary, but there were no differences among the groups. The high molecular weight adiponectin isoform (HMW) was found in both glandular and stromal cells in all three groups. Positive staining for the low molecular weight (LMW) isoform was seen only in stromal cells, and the intermediate molecular weight (IMW) isoform was not found in either glandular or stromal cells. No significant relationship between CXCL12, CXCR4, and adiponectin was found in IE and AE. The CXCL12/CXCR4 axis and adiponectin were not found to be dominant in deep infiltrating endometriosis.

Keywords: Infiltrating endometriosis; CXCL12; CXCR4; Adiponectin

Abbreviations

IE: Intestinal Endometriosis; AE: Abdominal Wall Endometriosis; OE: Ovarian Endometriosis; LMW: Low Molecular Weight; IMW: Intermediate Molecular Weight; HMW: High Molecular Weight

Introduction

Endometriosis is defined by the presence of endometrial tissue outside of uterine cavity. Deep infiltrating endometriosis that penetrates the muscles of pelvic organs, may cause pelvic pain and induce disability and infertility [1]. Immunological factors such as chemokines enhance the implantation of endometrial cells and the progression of disease [2,3], and are elevated in the peritoneal fluid of female patient with endometriosis [4]. Endometriosis in extra-ovarian sites, especially in the intestine (IE) or in the abdominal wall (AE), has infiltrative properties similar to neoplasms, which results in diagnostic difficulties and unnecessary operations.

Chemokines are 8-10kDa cytokines that regulate a variety of immune responses, and are classified into four groups: CXC, CC, C and CX3C. Chemokine CXCL12, also known as stromal cell derived factor-1 (SDF-1), and its receptor CXCR4, are important for the initiation and progression of primary and metastatic cancers, including breast cancer [5-7]. They have also been associated with angiogenesis and cancer cell invasion [8,9]. CXCR4was known to be expressed in normal endometrium [10] and in endometriosis cells [11], but the expression of CXCL12 has not been investigated extensively in normal endometrium or endometriosis tissue. Whether the activation of CXCL12/CXCR4 is associated with deep infiltrating endometriosis remains unclear.

In addition to its function as a lipid storage organ, adipose tissue is known to have endocrine functions. Adiponectin is produced by adipose tissue, and can suppress some of the metabolic arrangements that result in type 2 diabetes, obesity, atherosclerosis and non-alcoholic fatty liver disease [12-14]. In addition to anti-inflammatory and anti-angiogenic properties, adiponectin can also stimulate the expression of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-1, and MMP-13, and is involved in synovitis and joint destruction in RA [15]. In the ovaries and endometrium, adiponectin affects periovulatory remodeling of the ovarian follicle, steroid synthesis/secretion, energy supply, and the inflammatory response of endometrial cells [16]. Adiponectin concentrations in serum and peritoneal fluid are lower in endometriosis patients compared to non-endometriosis patients [17]. Therefore, adiponectin may be an anti-endometriosis factor, but its role in endometriosis is still unclear.

The expression of CXCL12/CXCR4 and adiponectin were evaluated in intestinal, abdominal wall, and ovarian endometriosis by immunohistochemical staining, and the relationship between the three factors was analyzed to determine the nature of deep infiltrating endometriosis.

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Table 1: Immunohistochemical expression of CXCL12 and CXCR4 in endometriosis tissue.

	CXCL12		CXCR4	
	Gland	Stroma	Gland	Stroma
IE (6 cases)	5 (83.3%)	1 (16.7%)	0 (0%)	2 (33.3%)
AE (12 cases)	9 (75.0%)	4 (33.3%)	6 (50.0%)	9 (75.0%)
OE (12 cases)	6 (50.0%)	6 (50.0%)	1 (8.3%)	3 (25.0%)

IE: Intestinal endometriosis; AE: Abdominal wall endometriosis; OE: Ovarian endometriosis

Materials and Methods

Samples from patients who had been surgically treated for IE and AE between 2001 and 2013 (6 cases of IE, and 12 cases of AE) at the Sanggye Paik Hospital, Seoul, Korea, were collected, and compared to resected ovarian endometriosis (12 samples). All specimens were fixed with 10% buffered formalin, and the paraffin-embedded sections were stained with hematoxylin and eosin. Mean age was 37.0±9.7, 33.6±4.6, and 34.8±9.9years in IE, AE, and OE groups, respectively.

Hybridoma production

A monoclonal antibody against adiponectin was produced by hybridoma production and monoclonal antibody purification as follow [15]. Two BALB/c mice were immunized subcutaneously with 100 μL of complete Freund's adjuvant (DIFCO Laboratories, Detroit, MI) containing 100 μg of recombinant human adiponectin expressed in *E. coli* (Prospec, Rehobot, Israel). After 2 weeks, the mice were injected with incomplete Freund's adjuvant as before. The mice were boosted with only antigen, adiponectin (50 μg) i.v. 2 weeks later. Two days after the last boost, the sera were tested for reactivity to recombinant adiponectin by ELISA. The splenic lymphocytes were fused to FO myeloma cells (ATCC) then plated in 96-well plates in DMEM supplemented with 20% FBS (Invitrogen) and HAT component (Sigma-Aldrich). The culture supernatants were tested for reactivity to recombinant human adiponectin by Western blot and ELISA. Monoclonal antibodies were purified from culture supernatants of the screened clones by Protein G-Sepharose column chromatography (GenScript, NJ, USA) according to the manufacturer's protocol. Antibodies to the three adiponectin isoforms were generated; high (HMW), intermediate (IMW) and low (LMW) molecular weight.

Immunohistochemistry

Sections (4 μm) of the endometriosis tissue were cut and stained by an automated system (Vision Biosystem Ltd, Mount Waverly, Australia) with CXCL12 (Santa Cruz, CA, USA), CXCR4 (Santa Cruz, CA, USA), and three adiponectin isoforms (10mg/ml). Antigen was retrieved with epitope retrieval solution 1 or 2 (Leika Microsystem, Newcastle, UK). Slides were incubated with antibody at room temperature for 20 minutes then with a biotinylated secondary antibody for 8 minutes. The resulting complexes were detected with avidin-peroxidase-conjugated polymer. Color was developed using 3,3'-diaminobenzidine (DAB; ScyTek, Logan, UT, USA). Mayer's hematoxylin was used as a counterstain. Positive and negative control stains were used in each run. Nuclear and/or cytoplasmic staining for CXCR4 and adiponectin and cell membrane, nuclear and/or cytoplasmic staining for CXCL12 were considered as positive. Expression scoring was defined as follows; o, no positive cells; 1, <10% positive cells; 2, 10-25% positive cells; 3, 26-50% positive cells; 4, >50% positive cells. Scores of more than 2 were considered positive.

Results

CXCL12 expression was found in 83.3% (5/6 cases) and 16.7% (1/6 cases) of glandular and stromal cells in IE, respectively (Table 1, Figure 1). In AE, 75.0% (9/12 cases) of glandular and 33.3% (4/12 cases) of stromal cells were positive for CXCL12. For OE tissue, 50% (6/12 cases) of glandular and stromal cells were positive for

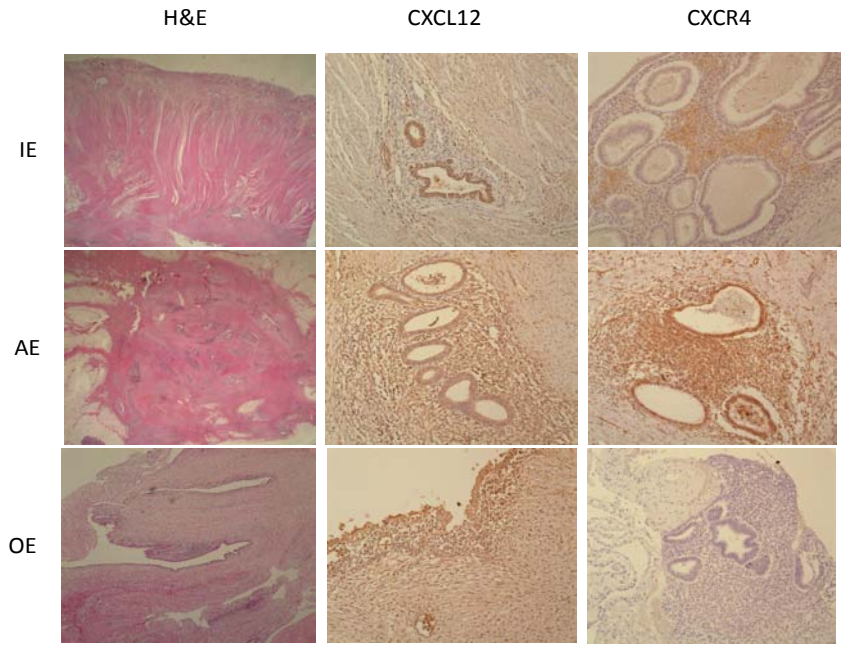

Figure 1: Immunohistochemical expression of CXCL12 and CXCR4 in IE, AE, and OE.

Table 2: Immunohistochemical expression of adiponectin isoforms.

	Adiponectin					
	LMW		IMW		HMW	
	Gland	Stroma	Gland	Stroma	Gland	Stroma
IE (6 cases)	0	6 (100%)	0	0	6 (100%)	6 (100%)
AE (12 cases)	0	12 (100%)	0	0	11 (91.7%)	12 (100%)
OE (12 cases)	0	12 (100%)	0	0	12 (100%)	12 (100%)

IE: Intestinal endometriosis; AE: Abdominal wall endometriosis; OE: Ovarian endometriosis; LMW: Low molecular weight; IMW: Intermediate molecular weight; HMW: High molecular weight

CXCL12. CXCR4 expression was found in 33.3% of IE stromal cells (2/6cases), but not in glandular cells. CXCR4 expression was noted in 50% (6/12 cases) and 75% (9/12 cases) of glandular and stromal in AE, respectively, and in 8.3% (1/12 case) and 25% (3/12 cases) of glandular and stromal in OE. Co-expression of CXCL12/CXCR4 was noted in 66.7% of AE tissue (8/12 cases). There was no difference in expression pattern among the three groups; glandular cells expressed slightly more CXCL12, while stromal cells expressed slightly more CXCR4. CXCL12 protein expression did not correlate with CXCR4 expression in IE or AE.

Adiponectin expression varied by isoforms (Table 2, Figure 2). The HMW isoform was found in both glandular and stromal cells in all groups. The LMW isoform was found only in stromal cells in all groups, whereas the IMW isoform was not found in either glandular or stromal cells. The expression pattern of the adiponectin isoforms was similar among the three groups. There was no relationshipbetweenCXCL12, CXCR4, and adiponectin in the IE and AE groups.

Discussion and Conclusion

The cause of endometriosis has been attributed to the attachment and invasion of the retrograded endometrial fragments to the peritoneum, where they establish a blood supply, triggering a suboptimal immune response that cannot adequately clear the implants. The extra-pelvic occurrence of endometriosis is rare, but it occurs in the abdominal wall, followed by the umbilicus, vulva, appendix, ileum, hernia sac, and colon [18]. Infiltration of endometriosis cells into various pelvic tissues could be compared with certain invasive and metastatic characteristics of cancer.

In this study, CXCL12 expression was examined in both glandular and stromal cells in IE and AE, and glandular expression was slightly higher, which has not been previously seen. However, CXCR4 was mainly expressed in stromal cells, which is consistent with previous reports [19]. It is still unclear which components (glandular or stromal cells) or cytokines are important in deep infiltrating endometriosis.

The CXCL12/CXCR4 axis is known to be involved in cell invasion.CXCL12 stimulated CXCR4 expression and accelerated tumor invasion in gastric cancer [20]. In prostate cancer cells, up-regulation of CXCL12 was a major mechanism underlying SLUG-mediated migration and invasion [21]. CXCR4 expression was significantly associated with depth of invasion and poor survival in gastric carcinomas [22], and it is also known to be a co-receptor for the binding of HIV-1 and HIV-2 to CD4+ cells [23]. In hypoxic tumor areas, CXCL12 and CXCR4 expression were increased, which stimulated tumor cell motility and invasiveness [24]. Two mechanisms were suggested by which CXCL12 promotes tumorigenesis. First, CXCL12 may promote tumor cell growth by directly stimulating tumor cell via CXCR4. Second, CXCL12 may induce the recruitment of endothelial progenitors, which allows for tumor angiogenesis. Other reports have shown no difference in CXCR4 expression between normal endometrium and endometriosis cells [11]. But some studies have reported that CXCR4 is down-regulated in IE stromal cells, which could be explained by intraperitoneal inflammation and hypoxia causing cellular arrest within the peritoneal cavity [25-27]. In this study, CXCL12 was expressed at higher levels in glandular cells, and CXCR4 was expressed more in stromal cells in IE tissue. The role of glandular cells vs. stromal cells is not well understood, however, the different characteristics of these cells may play an important role in the development of deep infiltrating endometriosis.

Some modification processes may be involved in infiltrating endometriosis. Nuclear CXCR4 expression correlated with increased infiltration potential and a poor outcome in gastric cancer [28]. It was suggested that CXCL12 bind to CXCR4 at the membrane level and then translocated to the nucleus becoming more invasive. In this study, focal nuclear staining of CXCL12 and CXCR4 was seen, but cytoplasmic staining was dominant. Another modification process in infiltrating endometriosis was miRNA. miRNA has also emerged as a major regulator of steroid hormone responses. Ovarian steroids and inflammatory factors decreased the expression of miRNA in endometrial stromal cells, and enhanced the invasive potential and inhibited the apoptosis of endometrial stromal cells [29].

In addition to adipose tissue, adiponectin is also produced and secreted by endometrial cells, and could act in an autocrine or

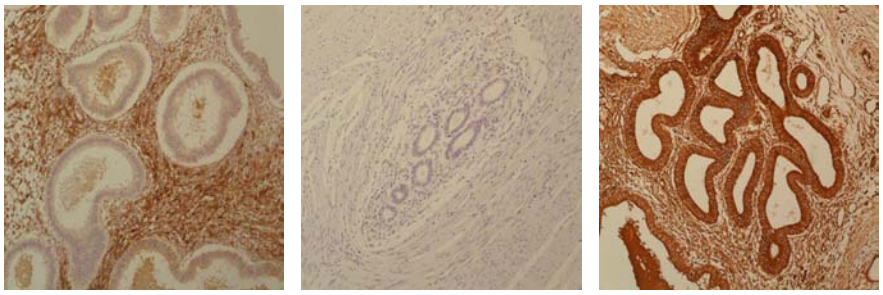

Figure 2: Adiponectin isoform expression in intestinal endometriosis. LMW (A), IMW (B), HMW (C).

paracrine manner to regulate embryo implantation and uterine receptivity [30]. Adiponectin circulates in blood as several isoforms; high (HMW), intermediate (IMW) and low (LMW) molecular weight. Decreasing adiponectin levels had been linked to increased risks of type II diabetes, insulin resistance, and several types of cancer including breast, colorectal, prostate, and digestive system [31,32].

Currently, conflicting data about the role of adiponectin in pathophysiology of endometriosis exists. Adiponectin inhibited endometrial cell proliferation in dose- and time-dependent manner, and caused cell death in one study, which suggests an anti-endometriosis function [31]. Low adiponectin concentration might permit angiogenesis and enhance effect of IGF-1, which would in turn stimulate the development and growth of endometriosis [17]. Adiponectin suppressed IL-1β induced secretion of IL-6, IL-8 and MCP-1 in endometrial stromal cells, which suggests that adiponectin plays an anti-inflammatory role [33]. However, other reports have contradicted these data. Adiponectin levels are comparable in patients with and without endometriosis [34]. In addition, the expression of adiponectin and adiponectin receptor was not different in endometriosis and non-endometriosis tissue [35]. Expression levels of adiponectin in the endometrium are far below than those in adipose tissue, and the physiological implications of locally produced adiponectin in the endometrium are uncertain [33].

There is currently no consensus about the clinical or biological relevance of adiponectin isoforms. HMW adiponectin is considered to be the main determinant of insulin sensitivity [36], and is a better clinical marker after surgical treatment of obesity, coronary artery disease and infertility study [37]. The LMW isoform is known to be biologically active [36]. Some studies have shown that total adiponectin and its isoforms levels do not correlate with cardiovascular disease severity [38]. There was no difference in the expression of adiponectin isoforms between endometriosis groups, and HMW and LMW adiponectin were both found in IE in this study. The role of adiponectin in deep infiltrating endometriosis remains unclear, and further study is needed.

The relationship between CXCL12/CXCR4 and adiponectin expression has been described previously. Adiponectin is used as a surrogate marker in coronary artery disease and diabetes, and CXCL12 was the main chemokine involved in ischemia-directed circulating angiogenic cell mobilization and homing [39]. Although the interaction between adiponectin and CXCL12 affected neither the CXCL12/CXCR4 binding nor the CXCL12 signaling in Jurkat cells, their association might influence the distribution of adiponectin and CXCL12 in inflammatory sites [40]. Adiponectin stimulated migration in endothelial progenitor cells, which led to the activation of PI3K and NF-kB, increased expression of CXCR4, and enhanced migration of circulating angiogenic cells towards CXCL12 [41]. CXCL12 was found to be negatively correlated with blood sugar and peripheral insulin resistance, which suggests that the expression of CXCL12 is closely related to adiponectin [42,43]. Unfortunately, the association between adiponectin and CXCL12 in infiltrating endometriosis was not elucidated in this study.

Though CXCL12/CXCR4 axis is involved in the invasion of the various tumor cells, its role in deep infiltrating endometriosis is not known, and this study was not able to elucidate this relationship. Adiponectin is involved in the pathogenesis of endometriosis, but its association with infiltrative nature is not definitive. The small sample size and lack of molecular mechanism are limitations in this study, however, the evaluation of protein expression in deep infiltrating endometriosis has provided a valuable first step for further studies. Further studies are required to clarify the mechanism behind endometriosis with infiltrative feature.

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