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Review Article

Chemokines Modulate the Activity of Several Cells of the Immune System: Relationship with the Pathogenesis of Endometriosis

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Abstract

Endometriosis is a highly prevalent inflammatory condition associated with impaired immune response in the peritoneal cavity and uterus. Evidence points to an involvement of inflammatory mediators such as chemokines in the pathogenesis of this disease. Chemokines are a large family of structurally homologous cytokines that stimulate leukocyte movement and regulate their migration from blood to tissues, also known as chemotactic cytokines. Several chemokines including interleukin-8, Growth-Related Oncogene (GRO) alpha, RANTES, Macrophage Inflammatory Protein (MIP-1) were described as increased in peritoneal fluid of patients with endometriosis. CCL2 and CCL20 were involved in the activation and migration of inflammatory cells in patients with endometriosis. Moreover, the influences of environmental factors such as dioxin in the development of endometriosis appear to be related to the stimulus that RANTES and thymus-expressed chemokine (TECK) could have on them. Furthermore, the peritoneal fluid of patients with endometriosis seem to have an effect on neutrophils, macrophages and T cells making them to secrete more chemokines, such as CXCL10 and CXCL8. The existences of genetic polymorphisms of chemokines were also studied, and an association between rs2812378 and CCL21 was related to advanced stages of endometriosis.

Chemokines also seem to have effect on the association between endometriosis and infertility. An increase of chemokines in peritoneal fluid of patients with endometriosis would have effect on sperm by decreasing its mobility and its concentration.

The increase in some inflammatory cytokines and chemokines may be responsible for various pain symptoms of endometriosis and even infertility. Although the pathogenesis underlying the development of endometriosis is unknown, there is substantial evidence that chemokines play innumerous roles in the pathogenesis and development of this disease and infertility associated with it. Additional studies evaluating the role of each chemokine along with clinical trials can contribute to a better understanding of the pathogenesis of this disease, as well as be useful in developing a noninvasive diagnosis and feasible therapeutic in the future.

Keywords: Endometriosis; Chemokine; Pathogenesis; Immunology; Cytokine

Introduction

Endometriosis is a common gynecological condition that affects 10 to 15% of women in their reproductive period, and up to 50% of women with chronic pelvic pain and/or infertility [1,2]. It has been regarded as one of the leading causes of gynecological hospitalization [3]. The disease is defined by stroma and/or endometrial glandular epithelium implant in extra-uterine location [4], and is likely to compromise several sites, including ovaries, peritoneum, uterosacral ligaments, retro-cervical region, rectum-sigmoid colon, terminal ileum, appendix, bladder and ureters [3,5-8].

In spite of being one of the most studied diseases in gynecology [9], some aspects of it still remain unclear, especially its etiology [7,8]. Two etiopathogenic hypotheses have prevailed since a century ago: the theories of coelomic metaplasia [10] and retrograde menstruation [11]. The latter may take into account the influence of a favorable hormonal environment and immunological factors on the failure to eliminate endometrial cells from the peritoneal cavity [12,13]. Cells that fall into the endometrial cavity should probably trigger a local immune response. On this regard, the balance between immunity and tolerance is crucial for maintaining immune homeostasis in which many mechanisms are involved in keeping the immune response under control, including the activity of Natural Killer (NK) and T-regulatory (T-reg) cells [14-16]. As in cancer and others autoimmune diseases, chemokines seems to play a key role in immune balance by modulating the activity of inflammatory mediators and allowing the maintenance and progression of these diseases. Likewise, in endometriosis, this role appears to be essential and have been the

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result of study by many authors in the last few years.

In this review, we will address the complexity and challenges of determining the usual behaviour of chemokines in endometriosis.

Methods of Review

A systematic review was conducted in MEDLINE (1966-2012) and PubMed (1966-2012), using endometriosis and chemokines as MeSH (Medical Subject Headings) terms. The abstracts of all articles were read and the manuscripts thoroughly reviewed. The references in all articles were also reviewed for additional information. The articles were selected and reviewed independently by 2 reviewers (PB and SP) to warrant quality.

The search engine returned 233 articles of which 164, published within the last 10 years, were selected. Of these, we excluded all articles that did not correlate chemokines directly in the pathogenesis of endometriosis and those that were not published in English. Besides, we selected those that had a significant sample with proper review, Meta-analyzes and controlled studies, accounting for 44 articles. While reviewing the references of articles, we selected other 13 articles, published more than 10 years ago, but relevant to our review for being pioneering articles.

Chemokines

Chemokines are a large family of structurally homologous cytokines with approximately 8 to 12kD, called chemotactic cytokines, as they stimulate the movement of leukocytes (chemokinesis), and regulate the migration of blood cells to the tissues (chemotaxis) [17].

The chemokine molecules have two internal disulfide loops and are divided into four subfamilies according to the position of their amino terminals cysteine residues: two cysteines directly adjacent (CC), two cysteines separated by one amino acid (CXC), two cysteines separated by three amino acids (C3XC), and finally, the fourth subfamily (XCL1) with a single cysteine (International Union of Immunological Societies/World Health Organization Nomenclature Subcommittee on Chemokine) [18]. In the standardized nomenclature, all chemokines carry an "L"suffix to characterize them as ligands and all receptors use an "R" suffix with the same purpose [19].

Chemokines act through high affinity trans-membrane receptors exposed on the surface of circulating cells. Eleven different receptors for CC chemokines (called CCR1 until CCR11) and six for CXC chemokines (called CXCR1 until CXCR6) were identified [20,21]. Although chemokine receptors have binding sites that may be highly specified (CCR9, CXCR6), as a rule, the same receptor may be the target of binding for various chemokine in the same group (Table 1) [22].

Besides working as lymphocyte chemotactic agent, studies on chemokines and their receptors revealed other important roles for these molecules, such as their relationship with tumor metastases and, conversely, inhibition of tumor cell growth, as well as in infections and autoimmune diseases like rheumatoid arthritis and multiple sclerosis [23-25].

Chemokines play a paramount role in tumor progression. Chronic inflammatory processes may cause tumors formation, and both tumor and stroma cells produce chemokines and other cytokines. They operate both by autocrine and peregrine mechanisms on sustaining tumor cells growth, inducing angiogenesis, and promoting a decrease in immune surveillance [25].

Chemokines and their receptors also play an important role in the development and maintenance of innate and adaptive immunity [25]. Furthermore, they help in the process of wound healing and angiogenesis. However, if the physiological role of chemokines is subverted or chronically enlarged, the disease is likely to develop. Since chemokines are involved in the pathophysiology of chronic inflammation, tumorigenesis and metastasis, as well as autoimmune diseases, the potential use of chemokine antagonists has been evaluated in targeted therapies [21]. The chemokines role of modulating the activity of other cells of the immune system has not been fully studied and elucidated yet, and their role in the pathogenesis of endometriosis is the target of a growing number of studies.

Inflammatory microenvironment in the peritoneal cavity of patients with endometriosis: chemokines role

Many authors have suggested that the pathogenesis of endometriosis entails inflammatory aspects and activation or inactivation of many cells involved in the process would be affected by chemokines. We will show the first and the last report of the involvement of each chemokine with endometriosis, trying to follow a sequence since the first description.

The first article linking endometriosis and chemokines (Khorram et al., 1993) [26] showed that the peritoneal fluid concentration of CCL5 (RANTES or Regulated upon Activation, Normal T cell Expressed and Secreted) was significantly elevated in women with endometriosis compared with controls and that those levels correlated positively with the disease stage. Zhao et al., in 2002 [27], discovered that endometrial stroma cells have receptors for hydrocarbons and could stimulate the production of RANTES through the use of dioxin. It is known that dioxin and its similes (TCDD/PCBs) affects the endometrial physiology, however, its mechanism is speculative and remains uncertain due to the difficulty in evaluating its exposure in intrauterine life, childhood and adulthood, along with the limitations of its reproduction in vitro [28]. This, in turn, could induce the recruitment of inflammatory cells, corroborating to the development and progression of endometriosis.

In 2010, Wang et al. [29] evaluated the relationship between TECK (thymus-expressed chemokine), dioxin and 17α-estradiol in endometrial stroma cell modulation. They found that the combination of dioxin and 17α-estradiol with endometrial stroma cells increases TECK secretion in endometrial cells and allows their invasion through the rise on the expression of matrix metalloproteinase 2 and 9 (MMP-2 and MMP-9). Besides that, the use of neutralizing anti-TECK can effectively decrease the potential of invasion of those cells and expression of MMP-2 and MMP-9. Finally, the authors demonstrated that RANTES can induce surface markers of macrophage tolerance in vitro and inhibit the apoptotic effects of macrophage-like cells on endometrial stroma cells.

In 2012, Li et al. [30] evaluated the invasive ability of endometrial stroma cells under the action of the chemokine CCL2 (MCP-1), applying a dosage by ELISA in patients with and without endometriosis. They found that the secretion of MCP-1 in topical

Table 1: Human Chemokines identified: receptors, ligands (standardized and alternative nomenclature) and gene locus [22].

Family	Chemokine	Original Name	Receptors	Gene Locus
CXC	CXCL1	GROα / MIP-2	CXCR2	24q21
	CXCL2	GRO β	CXCR2	4q21
	CXCL3	GRO γ	CXCR2	4q21
	CXCL4	PF-4	CXCR3-B	4q21
	CXCL5	ENA-78	CXCR2	4q21
	CXCL6	GCP-2	CXCR2	24q21
	CXCL7	NAP-2	CXCR2	4q21
	CXCL8	IL-8	CXCR2 + CXCR1	24q21
	CXCL9	MIG	CXCR3-A	4q21
	CXCL10	IP-10	CXCR3-A	4q21
	CXCL11	I-TAC	CXCR3-A	4q21
	CXCL12	SDF-1	CXCR4	10q11.21
	CXCL13	BCA-1	CXCR5	4q21
	CXCL14	BRAK	?	5q31.1
	CXCL15	*Lungkine*	?	?
	CXCL16	CXCL16	CXCR6	17p13
CC	CCL1	I-309	CCR8	17q11
	CCL2	MCP-1	CCR2	17q12
	CCL3	MIP-1α	CCR1, CCR5	17q12
	CCL4	MIP-1β	CCR5	17q12
	CCL5	RANTES	CCR5	?
	CCL6	C10	?	?
	CCL7	MCP-3	CCR1,CCR2,CCR3	17q11
	CCL8	MCP-2	CCR3, CCR5	17q11
	CCL9	MIP-1γ	?	?
	CCL10	CCL10	?	?
	CCL11	*Eotaxin*	CCR3	17q11
	CCL12	MCP-5	CCR2	?
	CCL13	MCP-4	CCR2, CCR3	17q11
	CCL14	HCC-1	CCR1, CCR5	17q12
	CCL15	HCC-2/MIP-1δ/ *Leotactin-1*	CCR1, CCR3	17q12
	CCL16	HCC-4/LEC	CCR1, CCR2	17q12
	CCL17	TARC	CCR4	16q13
	CCL18	PARC/DC-CK1	?	17q12
	CCL19	MIP-3β/ELC	CCR7	9p13.3
	CCL20	LARC/MIP-3α	CCR6	2q36.3
	CCL21	SLC/6Ckine	CCR7	9p13.3
	CCL22	MDC	CCR4	16q13
	CCL23	MPIF-1	CCR1	17q12
	CCL24	*Eotaxin 2*/MPIF-2	CCR3, CCR5	7q11
	CCL25	TECK	CCR9	19q13.3
	CCL26	*Eotaxin-3*	CCR3	7q11
	CCL27	ESkine/MCC/Ctack	CCR10	9p13.3
	CCL28	MEC	CCR3, CCR10	5p12
XC	XCL1	Linfotactina α	XCR1	1q24
	XCL2	Linfotactina β	XCR1	1q24
CX_3C	CX_3CL1	*Fractalkine*	CX_3CR1	16q13

endometrial stroma cells of patients with endometriosis was increased compared with women without the disease. Also, they found that MCP-1 may enhance the viability, proliferation and invasion of stroma cells depending on the duration and amount of exposure to it. Likewise, the use of anti-MCP-1 and/or CCR2 receptor antagonists could completely abolish the stimulatory function of MCP-1. This chemokine was first studied by Akoum et al. [31], who demonstrated that women with endometriosis have increased peritoneal fluid MCP-1 levels and these results correlate with the severity of disease.

More recently, Margari et al., [32] evaluating the peritoneal fluid concentrations of MCP-1 in patients with different stages of endometriosis and comparing with controls, found a decrease in the concentrations of MCP-1 in stage I endometriosis, which is even larger in stage II, in contrast to stage III and IV, which exhibit concentrations similar to the controls.

In women, serum levels of MCP-1 were compared in infertile women with and without endometriosis and Gmyreket et al. [33] found an increased and significant level of this chemokine in patients with endometriosis when compared with a cohort of infertile women.

Another study showed differences in the follicular fluid in patients undergoing IVF (In Vitro Fertilization) with and without endometriosis. Xu et al. [34] found that a RANTES level in the follicular fluid was significantly higher in patients with endometriosis when compared with patients with tubal infertility.

Antinolo et al. in 2004 [35], evaluated the frequency of polymorphisms in RANTES receptor and MCP-1 in women with and without endometriosis and did not find significant differences, although those chemokines are usually increased in peritoneal fluid of patients with endometriosis. This fact led Na et al. in 2011 [36], to evaluate the effects of the peritoneal fluid of patients with endometriosis in chemokines secretion by leukocytes. In short, they evaluated patients with and without endometriosis and compared the effect of adding peritoneal fluid of these patients to a neutrophils, monocytes and T cells culture. They observed that these cells secrete varying levels of MCP-1, RANTES and MIP-1 α in response to stimulation from the peritoneal fluid of patients with endometriosis.

CX3CL1 (Fraktalkine) is one of the most studied chemokines in endometriosis researches [37,38]. Evaluating healthy women in 2006, Watanabe et al. [38] showed that more CX3CL1 is higher expressed in the endometrial at the secretory phase when compared to the proliferative phase, illustrating that such presence could be responsible for the regulation of the immune environment by attracting cells such as NK, which plays a major role in the immune system of vertebrates. These lymphocytes are capable of differentiating between virus-infected cells, neoplastic cells and normal cells.

In 2010, Hirata et al. [39] evaluated the recruitment and migration of T helper 17 (Th17) cells under the influence of the chemokine CCL20. Using flow cytometry in endometrial of patients with endometriosis, they found that Th17 cells express CCR6, the CCL20 receptor. Using immuno histochemistry they found that CCL20 is also expressed in stroma and epithelial cells of endometrial tissue. Moreover, they found that CCL20 provided selective migration of Th17 lymphocytes, and IL-1α, TNFα -and IL-17A increased the secretion of CCL20 in cultures of endometrial stroma cells.

In 2009, Kim et al. [40] had already published a similar study, however evaluating the secretion of CXCL8 and CXCL10 in cultures of neutrophils, CD4+ lymphocytes, and monocytes. The addition of peritoneal fluid in the culture of these cells led to a significant increase in secretion of CXCL8 and CXCL10. In 2009, Galleri et al. [41] found reduced concentrations of CXCL10 in serum and peritoneal fluid of patients with endometriosis when compared to patients without it.

In 2011, Sudqvist et al. [42] evaluated 1149 samples of 798 Caucasian patients with endometriosis and scanned the presence of genetic polymorphism. They unveiled an association between CCL21 rs2812378 and moderate to severe endometriosis, throwing light on the different forms in the pathogenesis of endometriosis for indicating the type and severity of the disease. Comparing with Rheumatoid Arthritis (RA), both diseases seem to be associated with variants of the CCL21 gene but in different alleles (G in RA and A in endometriosis), suggesting a differentiated functional role of the allele.

In a recent study, our group [43] found a relationship between chemokines that regulate the activity of NK (Natural Killer) and T-reg (T regulatory) cells in patients with endometriosis. We compared the expression of the mentioned chemokines in the topic (patients and controls) and ectopic endometrial (patients). Of those associated with NK cells, CX3CL1 and CXCL12 expression was significantly greater in foci of endometriosis compared to the eutopic endometrium in patients and controls. And of the chemokines associated with T-reg cells, CCL17 expression was significantly greater in the eutopic endometrial of patients with recto sigmoid endometriosis compared to the foci of endometriosis or eutopic endometrial of patients with retro cervical endometriosis or to disease-free women. An NK and T-reg cell seems to play a fundamental role in endometriosis. These cells when inactive, underactive or even when functioning normally, appears to play a fundamental role in the genesis and/or maintenance of this disease. Knowing how these chemokines modulate this inflammatory response represents a special key to understanding the genesis and maintenance of this disease.

Reis et al. [44] published a review which shows the relationship between chemokines and the hormone regulation exercised over them. A complementary and possibly mechanism of endometriosis formation derives from an imbalanced regulation of cell fate with reduced susceptibility to apoptosis. Some chemokines, such as RANTES and IL-8, may be involved in the amplification of the local immune response and the survival of endometriosis cells increasing its proliferation or even attenuating the apoptosis. Despite the sex steroids remains the first line targets for medical therapies, the effects of estrogens and progestagens on endometriosis cells are only partially known. Estrogens are not only proliferative, but also Proinflammatory and ant apoptotic in endometrial cells, and these effects are exacerbated in women with endometriosis through the action of some chemokines, kinases and Bcl-2. Progestogens also are effective in inducing apoptosis in endometrial epithelial cells through the inhibition of Bcl-2 and the stimulation of Bax and ERK pathways. This is an interesting point of view and shows some new possibilities for diagnosis and treatment of this disease, in addition to showing the importance of studying this group of inflammatory mediators.

Several chemokines play a critical role in angiogenesis associated

with endometriosis. IL-8 (CXCL8) that is produced both in the topic and ectopic endometrial induces the proliferation of stroma cells in them, which may be considered an angiogenic inductor [45,-47]. Besides, Nishida et al. [45] also demonstrated that endometriosis cells induced by TNFα produce ENA-78 and GROα, which are CXC chemokines pervaded by chemo attractive factors, and closely related to neoangiogenesis. Moreover, IL-8 is one of the most studied chemokines correlated to endometriosis. The first article regarding this issue [48] correlated the levels of this chemokine in the peritoneal fluid of women with and without the disease. IL-8 concentration was higher in women with endometriosis than in controls with a positive correlation with the stage of the disease. Several other studies had similar results in the past few years [49-51] and Ohata et al. [52] found a correlation between ovarian endometrial and the serum concentrations of this chemokine. Carmona et al. [53] studied serum concentrations of IL-6 and IL-8 in patients with and without endometriosis. They carried out a case control study comparing patients with ovarian endometrium, deep infiltrating endometriosis and healthy women without endometriosis. They found that the presence of ovarian endometrioma is related to an increase in serum concentrations of IL-6 and IL-8.

In 2012, Malhotra et al. [51], evaluating angiogenic cytokines, performed dosage of IL-8 and leptin in the peritoneal fluid of patients with endometriosis and then compared them with fertile controls. They found that both IL-8 and leptin are increased in peritoneal fluid of patients with peritoneal endometriosis in early or advanced stages, but are decreased in patients with ovarian endometrial. In addition, they found no differences related to infertility or chronic pelvic pain.

Contributing to the discussion on IL-8, Manabe et al. in 2011 [54], evaluated the expression of CXCL16, and its receptor CXCR16 in ovarian endometriomas, using immuno histochemistry and Western blot, and found that both stroma cells and epithelial cells in ovarian endometrial expressed continuously to this chemokine, independent of the menstrual cycle phase. They also discovered that the CXCL16 induced the production of IL-8 in endometriosis stroma cells in vitro.

Recently, eotaxin (CCL11), which belongs to the family of CC chemokines, was reported as a neoangiogenic factor in the development of endometriosis [55,56]. Ouyang et al. [55] reported an increase in expression of IL-4 in the peritoneal fluid of women with endometriosis that resulted in an increase in expression of eotaxin. This chemokine plays an important role in the formation of new blood vessels in endometriosis stroma cells, and can be one of those responsible for the subsequent development of the disease. However, the first report showing the correlation of this chemokine with endometriosis [57] found higher levels of peritoneal fluid concentrations of CCL11 in patients with endometriosis and this increase was even more evident in patients with advanced stages of the disease.

Conclusion

Although the pathogenesis of endometriosis is not completely clear, there are several studies including chemokines as likely players in the development of this disease. Additional research evaluating the role of each chemokine along with clinical trials can contribute to a better understanding of the pathogenesis of endometriosis, as well as be useful in developing a noninvasive diagnosis and feasible therapeutic in the future.

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