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Immune interactions in endometriosis

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Abstract

Endometriosis is a common, complex gynecologic disorder characterized by the presence of endometrial glands and stroma at extrauterine (ectopic) sites. In women who develop this disease, alterations in specific biological processes involving both the endocrine and immune systems have been observed, which may explain the survival and growth of displaced endometrial tissue in affected women. In the past decade, a considerable amount of research has implicated a role for alterations in progesterone action at both eutopic and ectopic sites of endometrial growth which may contribute to the excessive inflammation associated with progression of endometriosis; however, it remains unclear whether these anomalies induce the condition or are simply a consequence of the disease process. In this article, we summarize current knowledge of alterations within the immune system of endometriosis patients and discuss how endometrial cells from women with this disease not only have the capacity to escape immunosurveillance, but also use inflammatory mechanisms to promote their growth within the peritoneal cavity. Finally, we discuss evidence that exposure to an environmental endocrine disruptor, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin, can mediate the development of an endometrial phenotype that exhibits both reduced progesterone responsiveness and hypersensitivity to proinflammatory stimuli mimicking the endometriosis phenotype. Future studies in women with endometriosis should consider whether a heightened inflammatory response within the peritoneal microenvironment contributes to the development and persistence of this disease.

Keywords

chemokines; cytokines; dioxin; endocrine-disrupting chemicals; endometriosis; estrogen; immune–endocrine interactions; inflammation; peritoneum; progesterone; TCDD

The human endometrium is a unique adult tissue in that this organ system undergoes steroid-driven cycles of breakdown and regrowth approximately 400 times during a woman's reproductive life. Although the biological purpose of the tissue dynamics associated with the menstrual cycle remains unclear, the etiology of reproductive tract disease processes are generally linked to the physiology of the menstrual cycle. In particular, endometriosis, a common but poorly understood gynecologic disease, occurs when displaced menstrual

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tissues attach and exhibit patterns of cyclic growth outside the uterus, frequently resulting in severe pain and infertility [1]. Symptomatic endometriosis is believed to occur in approximately 10% of reproductive-age women, although endometriosis is probably underdiagnosed given that confirmation of the disease requires visualization by surgeons followed by histological examination. Since first described within the medical literature more than 100 years ago [2,3], multiple hypotheses have been proposed regarding the etiology of this disease, including the retrograde menstruation (implantation) theory [4], coelomic metaplasia theory [5–8], development of ectopic growth following activation of embryonic cell rests [9,10], metastatic (hematogenic or lymphatic transport) theory [11] and the more recent adult stem cell theory [12]. Significantly, no single theory can adequately explain all presentations of this disease, including the rare cases of male endometriosis [13]. Nevertheless, development of endometriosis is confined to menstruating species and retrograde menstruation clearly provides a mechanical means of menstrual tissue displacement into the peritoneal cavity, potentially allowing the establishment of the disease. However, retrograde menstruation is believed to occur in the majority of reproductive-age women [4]; therefore, other mechanisms must also contribute which ultimately determine why only certain women develop endometriosis. Although some investigators have suggested that all menstruating women exhibit some degree of ectopic endometrial growth, robust survival and progressive growth of the displaced endometrial tissue within the peritoneal microenvironment requires that endometrial cells accomplish a number of complex biological processes. Specifically, following retrograde menstruation, viable endometrial tissue fragments must escape apoptosis, evade normal immune surveillance, invade an intact mesothelial surface and rapidly acquire a vascular supply.

Endometriosis is generally considered to be a steroid-sensitive disease; however, defects of the immune system as well as genetic and epigenetic predisposition probably play equally important roles in determining whether an individual will develop this condition [1]. While early studies focused on the concept of endometriosis as an autoimmune disease, recent research has shifted to the possibility that the disease may involve alterations in the function of certain immune cells that are components of cell-mediated immunity. Within the peritoneal cavity of women who develop endometriosis, resident and recruited immune cells are either overwhelmed by the amount of misplaced endometrial tissue or otherwise dysfunctional in their ability to effectively detect and destroy autologous endometrial tissue. In addition, resident and recruited immune cells within the peritoneal cavity of endometriosis patients remain capable of producing proin-flammatory cytokines/chemokines that can trigger inflammatory reactions within endometrial cells that further contribute to the disease process. Specifically, within the peritoneal cavity, initial inflammatory responses to damaged cells (e.g., menstrual tissue) occur through an increased movement of plasma and blood leukocytes into the injured tissues (e.g., site of ectopic endometrial attachment) which normally facilitate tissue repair. This acute inflammatory response incorporates the local vasculature, immune system and various somatic cells comprising the injured endometrial tissue. Importantly, immune cells present within the damaged tissue, including macrophages, dendritic cells and mast cells, contribute significantly to the development of acute inflammation as well as the initiation of repair processes. For example, following activation, these resident immune cells release inflammatory mediators responsible for vasodilation and increased permeability of blood vessels, allowing extravasation of recruited leukocytes (first neutrophils, then monocytes) from blood vessels into the tissue in an effort to dispose of the injured tissue. However, as noted previously, in women with endometriosis, during each episode of menstruation, viable endometrial cells entering the peritoneal cavity via retrograde menstruation interact with an innate immune system that becomes increasingly dysfunctional as the disease progresses. Moreover, the excessive and persistent nature of endometriosis-associated inflammation probably contributes not only to initial ectopic endometrial growth, but also to the comorbidities that endometriosis patients

frequently exhibit (e.g., irritable bowel syndrome, interstitial cystitis, endocrine and autoimmune diseases, allergies and asthma) [14]. While it is currently unknown whether the inflammatory nature of endometriosis is a cause or consequence of the disease process, women who develop endometriosis often exhibit a hypersensitivity to inflammation across multiple organ systems [15].

During surgical confirmation of endometriosis, the presence of disease is classified as stage I–IV, correlating with the extent and location of endometriotic lesions [16]. Severe disease is frequently associated with significant peritoneal adhesions, a comorbidity that can further contribute to both pain and infertility in these women. Although current medical guidelines do not include an assessment of the patient's inflammatory state within the peritoneal cavity, as described previously, inflammation may ultimately determine the severity of the disease. Furthermore, changes in the peritoneal environment involving abnormal cytokine and prostaglandin production as well as the immune dysfunction discussed later, are all believed to interfere with reproductive processes; thereby contributing to the infertility associated with this disease [17–19]. Thus, these dysfunctional immune cells not only fail to effectively clear discarded endometrial tissues but may actually contribute to the development of chronic, peritoneal inflammation as well as subclinical, systemic inflammation [20]. In order to address these issues therapeutically, a better understanding of the potential origin of the overall immunopathophysiology of endometriosis is critically needed. Within the reproductive tract, steroid hormones are important regulators of immune responses; not surprisingly, therapeutic agents acting as steroid hormone agonists and antagonists continue to be explored for the treatment of endometriosis. However, recent research also suggests that certain environmental toxicants are also capable of acting as endocrine disruptors, potentially affecting the development and progression of endometriosis in certain women. Thus, it is becoming increasingly important to examine how various biological agents, capable of acting as steroidal signals within the reproductive tract, may impact immune function related to either promotion or inhibition of this disease. Although ovarian steroids have well-documented roles in the normal regulation of the endometrium in preparation for pregnancy, defects in steroid synthesis or responsiveness clearly play a role in the etiology of reproductive tract diseases. To this end, recognition of ovarian steroids as potential immunological components of endometriosis has only recently begun to be considered. Throughout the normal menstrual cycle, estrogen action promotes endometrial regrowth following menstruation and mediates the selective recruitment of certain populations of immune cells to this tissue. In contrast to estrogen action, progesterone acts not only as a differentiation signal, but also as an immunosuppressive agent during pregnancy, allowing implantation of the semi-allogenic embryo to occur without rejection. Therefore, among women with endometriosis, an endometrial phenotype exhibiting reduced progesterone sensitivity not only compromises tissue differentiation but also affects the immunosuppressive actions of this steroid. For example, within the secretory phase of the menstrual cycle, progesterone normally acts to suppress the action of nuclear factor-κ B (NF-κB), a transcription factor exhibiting both proinflammatory and anti-apoptotic activity in most cells [21]. Importantly, since NF-κB expression can also be activated by an inflammatory stimulus [22,23], the combination of reduced progesterone responsiveness and chronic inflammation in the endometrium of endometriosis patients leads to constitutive expression of this transcription factor [24]. Thus, a significant component of the pathogenesis of endometriosis is the loss of normal patterns of communication between the endocrine and immune systems within the endometrium, effectively disrupting the immunosuppressive microenvironment required for normal reproductive function.

Although the loss of normal patterns of endocrine–immune signaling associated with endometriosis could evolve as a consequence of the disease process itself, a growing body of evidence suggests that human exposure to environmental chemicals may act to disrupt

steroid synthesis or action [25] as well as negatively affect immune function [26]. A potential role for exposure to environmental toxicants capable of both endocrine and immune disruption in the development of endometriosis first emerged with the observation of increased incidence and severity of this disease in a primate colony following chronic dietary exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) [27]. Halogenated aromatic hydrocarbons, including TCDD and other dioxin-like compounds, are not only resistant to degradation within our environment, but also tend to bioaccumulate within the human food chain owing to their lipophilic chemistry. Widespread human exposure to these compounds occurs via our diet and, once consumed, TCDD-like compounds have been shown to elicit a broad range of biochemical responses, resulting in both immune dysfunction and reproductive failure [28]. After publication of the primate study noted earlier, several epidemiologic studies in humans attempted to correlate the incidence of endometriosis to the body burden of TCDD or dioxin-like polychlorinated biphenyls (PCBs) [29–32]. For example, an increased incidence of endometriosis was reported among relatively small cohorts of infertility patients in Belgium, a country in which high levels of TCDD in breast milk have been documented [30,33]. However, other studies failed to demonstrate a correlation between adult body burden of various dioxin-like toxicants and the presence or absence of endometriosis [34,35]. At this juncture, it is difficult to interpret the discrepant conclusions drawn by human studies attempting to correlate the presence of an adult disease with the body burden of various toxicants. Several groups, including our own, have begun to consider whether early-life toxicant exposures may be more relevant to the eventual development of adult diseases, including endometriosis [36,37].

In this article, we will summarize the current knowledge of immunological components of endometriosis with a focus on whether endometrial cells from women who develop endometriosis are uniquely capable of not only escaping immune detection, but also utilizing inflammatory mechanisms within the peritoneal cavity to promote their ectopic invasion and persistent growth.

Altered function of immune cells in endometriosis

During each normal menstrual period, somatic cells present within the functionalis region of the human endometrium begin to undergo programmed cell death, a biological response that reduces the risk that these cells could survive and grow ectopically within the peritoneal cavity despite retrograde menstrual flow. This postdifferentiation pathway normally leads to apoptosis of shed endometrial cells; therefore, tissues entering the peritoneal cavity promote immune cell scavenging of menstrual debris without eliciting a significant inflammatory reaction [38]. The immune cells that play a role in this destruction include macrophages, natural killer (NK) cells and cytotoxic T cells; cell types whose actions must be tightly regulated in order to ensure that the immune response is specific to shed menstrual debris rather than the normal tissue undergoing regrowth within the eutopic endometrium. However, in women with endometriosis, multiple studies have shown that immune surveillance is impaired and the innate immune system appears to be unable to adequately respond to displaced endometrium within the peritoneal cavity [39,40]. Specifically, a decrease in NK cell cytotoxicity [41,42] and an enhanced activation state of monocytes and peritoneal macrophages has been documented in endometriosis patients [43–45]. Thus, a failure of peritoneal immune cells to clear misplaced endometrium may play a central role in providing an opportunity for viable endometrial cells to attach and grow ectopically. Additionally, activation of inflammatory responses within the peritoneal cavity may lead to the local production of cytokines and chemokines that enhance the growth of ectopic endometrial tissue by both inhibiting normal apoptotic processes and promoting localized angiogenesis [46,47]. Once the onset of acute inflammation is initiated by resident peritoneal macrophages, inflammatory mediators are released and are responsible for

increased blood flow and extravasation of leukocytes (neutrophils and monocytes) from blood vessels into the tissue, in an effort to dispose of ectopic endometrium. Thus, current research suggests that, although the ability of immune cells to identify and destroy autologous endometrial tissue is compromised in women with endometriosis, these cells retain their ability to produce cytokines, growth factors and potent angiogenic factors, which ultimately act to support the survival and ectopic growth of endometrial tissue fragments [48].

Immune surveillance within the peritoneal cavity

Following retrograde menstruation, immune surveillance within the peritoneal cavity by resident and migrating immune cells provides an important line of defense against the development of endometriosis through removal of displaced endometrial tissues. Inadequate removal of refluxed menstrual debris, coupled with an enhanced ability of sloughed endometrial tissue to evade immune surveillance and rapidly invade a peritoneal site, may represent the most critical factors in determining an individual woman's risk for developing endometriosis. In this regard, macrophages are the primary resident immune cells within the peritoneal cavity which act to eliminate cellular debris and apoptotic cells, including endometrial tissues deposited via retrograde menstruation. The phagocytic activity of these cells is mediated via secretion and activation of matrix metalloproteinases (MMPs) as well as expression of the scavenger receptor CD36. Collectively, MMPs and CD36 promote the degradation [49] and clearance of nonself cellular debris [50,51]. Importantly, although the number of macrophages is increased within the peritoneal fluid of women with endometriosis compared with disease-free women [52], 'endometriosis' macrophages exhibit a reduction in expression and activity of MMP-9. [53]. In addition, the scavenger receptor, CD36, is downregulated in peritoneal macrophages from women with endometriosis [54], a defect potentially leading to poor phagocytic capacity and decreased uptake and degradation of debris [55–57]. Importantly, activation of PPARγ by a variety of specific ligands induces expression of CD36, [58,59]; thus, numerous PPARγ agonists have been examined for potential therapeutic benefits in endometriosis [60–62]. Finally, a series of sophisticated studies conducted by the Tsai laboratory have implicated prostaglandin (PG) E2 as the major factor present in peritoneal fluid which serves to inhibit MMP-9 activity as well as peritoneal macrophage expression of MMP-9 and CD36 [53,63]. Taken together, these studies demonstrate that endometriosis-related macrophages have reduced phagocytic capacity contributing to the development and severity of disease.

Another mechanism that may allow endometrial fragments to evade immune surveillance, survive and implant involves the lymphocyte function-associated antigen-1 (LFA1)–intercellular adhesion molecule-1 (ICAM-1) pathway. In the peritoneal cavity of disease-free women, it is believed that lymphocytes expressing LFA1 can adhere to misplaced endometrial cells expressing ICAM-1 and present them as targets to NK cells. However, the soluble form of ICAM-1 released from endometriotic lesions competes with ICAM-1, decreasing the availability of LFA1 expressed by lymphocytes, rendering these cells unable to present the endometriotic cell to the target NK cell. Thus, under disease-related conditions, the recognition of endometrial cells by these lymphocytes and subsequent NK cell-mediated cytotoxicity may be prevented [64,65].

Rejecting/accepting endometrial tissue within the peritoneal cavity

As noted previously, a failure of immune cells to appropriately transmit death signals to endometrial cells and/or the capacity of endometrial fragments to avoid cell death may be associated with the development of endometriosis only in certain women. In addition to the defects in macrophages noted previously, dysfunctional NK cells belonging to the innate immune system also affect the clearance of endometrial tissue within the peritoneal cavity of

endometriosis patients. While there are conflicting reports on whether or not the number of peritoneal NK cells is altered in women with endometriosis [66–68], most studies indicate that both peripheral and peritoneal NK cells from these patients exhibit reduced cytotoxicity [67,69]. Specifically, NK cells from women with endometriosis display an increased expression of killer inhibitory receptor, which interacts with HLA class I molecules on potential target cells to suppress NK cell activity [70]. Furthermore, the antigenicity of displaced endometrial cells from women with endometriosis has been shown to be altered owing to overexpression of HLA class I, which acts to protect against lymphocyte cytotoxicity [71,72]. Thus, important cell recognition interactions that normally occur between endometrial tissue fragments and the peritoneal innate immune system may be quite different in women with endometriosis compared with women who avoid this disease. However, further investigation is necessary to dissect the molecular mechanisms responsible for defects in self-recognition signaling between immune cells and endometrial debris related to endometriosis.

Within the peritoneal fluid of women with endometriosis, studies have shown that the cytotoxicity of T lymphocytes is reduced [73], potentially contributing to the survival of displaced endometrium by inducing apoptosis in cytotoxic lymphocytes via the Fas–FasL pathway [74]. Fas-induced apoptosis plays a fundamental role in the regulation of the immune system and is a main mechanism by which cytotoxic T lymphocytes induce cell death in cells expressing foreign antigens. However, in women with endometriosis, FasL expressed by endometriotic cells binds to its Fas receptor on lymphocytes to induce apoptosis of T-lymphocytes. Moreover, the level of soluble FasL, which also induces apoptosis of Fas-expressing cells, is increased in the peritoneal fluid of women with advanced stages of endometriosis [74]. Therefore, Harada proposed in 2004 that “endometriotic cells not only become resistant to Fas-mediated apoptosis, but also acquire the ability to utilize this pathway to their advantage by launching a ‘Fas counter-attack’ against the host’s immune system. The increased expression of FasL by endometriotic cells coincides with their inherent resistance to Fas-mediated apoptosis which protects them from a ‘suicidal’ death” [75].

Although studies have indicated a higher percentage of peritoneal neutrophils in women with endometriosis compared with disease-free women [76], the potential contribution of this immune cell population to disease pathogenesis has not been adequately elucidated. Neutrophils normally constitute approximately 90% of circulating granulocytes and are one of the innate immune system’s first lines of defense against invading pathogens. However, these cells also play a significant role in tissue remodeling and angiogenesis through production and secretion of proinflammatory cytokines, serine proteases, MMPs and vascular endothelial growth factor; thus, these cells are well-positioned to contribute to the pathogenesis of endometriosis. Further supporting this possibility, neutrophils may perform sophisticated regulatory functions in endometriosis, affecting not only the inflammatory and immune responses but also hematopoiesis and wound healing [77]. In order to optimally execute their functions, neutrophils survey their surrounding environment and accept cues from multiple cell types, including other leukocytes. Neutrophil dysfunction associated with endometriosis is suggested by their reduced lactoferrin and myelo-peroxidase concentrations [78]; however, this alteration does not necessarily construe a lack of activation. In particular, epithelial neutrophil-activating peptide-78, is normally increased upon neutrophil activation and there is evidence that this protein is overly abundant in the peritoneal fluid of endometriosis patients [79]. Importantly, the recruitment, activation and migration of neutrophils to most tissues are now believed to be initiated by the inflammatory response from Th17 cells. Recently, Hirata *et al.* demonstrated that the recruitment of Th17 cells to endometriotic tissues was associated with increased production of IL-17, leading to stimulation of IL-8 and cyclooxygenase-2 expression and subsequent proliferation of

endometriotic stromal cells [80,81]. However, it remains to be determined whether IL-17 expression by Th17 cells is the mechanism by which neutrophils are recruited to endometriotic tissue. Further investigations are required to better understand the roles of neutrophils and Th17 cells in the pathophysiology of endometriosis and to determine whether stimulation of their phagocytic properties or inhibition of their proinflammatory properties, respectively, might have therapeutic value.

Cytokine production & ectopic invasion

In women with endometriosis, functional alterations in macrophages, NK cells, cytotoxic T lymphocytes and perhaps neutrophils lead to a more immunotolerant peritoneal microenvironment than should normally exist; thereby enabling the establishment of disease following retrograde menstruation [82]. Furthermore, immune cell production of numerous cytokines and chemokines in the setting of reduced progesterone responsiveness, could facilitate disease progression rather than disease prevention [83]. Cytokines are key mediators of intercellular communication within both the immune and endocrine systems, acting in a pleiotropic fashion on a variety of target cells. Acting via specific receptors, cytokines can exert proliferative, differentiative, cytostatic, chemoattractant or angiogenic effects. These multiple properties implicate cytokine action during not only the initial attachment and invasion of endometrial cells to the mesothelial lining of the peritoneal surface but also to the establishment of a vascular supply that promotes growth-related disease progression. Specifically, resident immune cells such as macrophages produce cytokines in response to the presence of ectopic endometrial tissues that can directly affect angiogenesis and ectopic growth. Moreover, cytokines produced by macrophages recruit additional immune cells which produce their own cytokines, further promoting immunologic aberrations which enhance angiogenesis and ectopic growth. As stated previously, some investigators have viewed endometriosis as an autoimmune disease and their studies have focused on immune cells and cytokines involved in acquired immunity [84–86]. Since the current article focuses on the cell-mediated immunopathogenesis of endometriosis, the known roles of chemokines/cytokines involved in this aspect of immunity are listed in the following paragraphs.

IL-1 is a cytokine produced by activated monocytes and macrophages that is critical for regulation of normal immune and inflammatory responses. Multiple studies have attempted to quantify the peritoneal fluid concentration of IL-1 of patients with endometriosis compared with disease-free women, but results to date are conflicting [87–90]. Vigano *et al*. found that IL-1β increased soluble ICAM-1 shedding from endometrial cells, potentially interfering with peritoneal immunosurveillance, therefore allowing refluxed endometrial tissue to escape removal in the peritoneal cavity as described previously [65]. In addition, IL-1β is able to upregulate RANTES expression in endometriotic stromal cells *in vitro*, suggesting a role for RANTES in induction of monocyte chemotaxis and further production of IL-1 by macrophages.

IL-6 is produced by numerous cell types throughout the body (monocytes, macrophages, fibroblasts, endothelial cells, vascular smooth-muscle cells and endometrial epithelial as well as stromal cells types) [91,92] and is another important regulator of immunity and inflammation. Importantly, this cytokine also appears to mediate cellular communication between the endocrine and immune systems. Specifically, endometrial stromal and epithelial cells produce IL-6 in response to hormones as well as immune activators, such as IL-1α or β, TNF-α or β, PDGF and IFN-γ. Although multiple studies have indicated a link between raised serum levels of IL-6 and the presence of endometriosis [93–98], others have shown no association [64,99–101]. Further studies are required to fully elucidate the potential effect of this important regulator of inflammation.

IL-8, a chemokine produced by monocytes/macrophages, is capable of attracting and activating neutrophils [102]. While Gazvani *et al*. found no difference in serum IL-8 levels in endometriosis patients compared with normal controls [103], Pizzo and colleagues found elevated IL-8 levels in endometriosis patients [104]. This cytokine is potently angiogenic, and therefore could play an important role in endometriotic growth. A study by Kim *et al*. found that treatment of neutrophils with recombinant human IL-8 led to an increase in the cell's release of IL-8 protein [105]. The authors of this study suggest that "neutrophils reaching the peritoneal fluid in response to the chemoattractant IL-8 produced by endometriotic cells or immune cells, generate additional IL-8 which likely results in an amplification of immune cell accumulation and cytokine production" [105].

Monocytes, which are the precursors to macrophages [106], are drawn to sites producing high levels of monocyte chemoattractant protein-1 (MCP-1). As the name states, MCP-1 is a monocyte chemotactic agent and is produced by multiple cell types including endothelial cells, fibroblasts and leukocytes [107–108]. MCP-1 is also an activating factor for these cells and stimulates mature macrophages to secrete growth factors and cytokines which promote endometrial cell proliferation. Not surprisingly, the concentration of this cytokine is higher in the peritoneal fluid of women with endometriosis [109] and correlates with the severity of disease.

RANTES is a potent chemoattractant for eosinophils, monocytes, macrophages and T lymphocytes, both *in vivo* and *in vitro*. *In vitro*, stromal cells isolated from endometriomas, compared with normal endometrium, secrete significantly higher concentrations of RANTES, potentially accounting for the increased peritoneal fluid concentration of this cytokine noted in women with moderate and severe endometriosis [110]. Importantly, an increased level of expression of the high affinity chemokine receptor for RANTES, CD191 (previously known as CCR1) has been reported in peripheral blood leukocytes and peritoneal macrophages of patients with endometriosis compared with controls [111]. Collectively, the increased secretion of RANTES by endometriotic lesions combined with the increased expression of CD191 indicates a possible mechanistic explanation for leukocyte recruitment to the peritoneal cavity.

TNF-α and -β represent another class of inflammatory cytokines which may play a role in the development of endometriosis. TNF-α is produced by multiple immune cells (neutrophils, activated lymphocytes, macrophages and NK cells) as well as several nonhematopoietic cells. However, to date, TNF-β has only been identified as a product of lymphocytes. Both cytokines have been associated with beneficial and deleterious effects, with the outcome dependent upon the quantity produced as well as the prevailing microenvironment. The primary function of TNF-α and -β is to initiate a cascade of cytokines and other factors associated with inflammatory responses. In fact, by inducing IL-8 expression, TNF-α stimulates the proliferation of endometriotic stromal cells, a potentially important aspect of disease initiation [95]. In addition, TNF-α promotes the adherence of cultured stromal cells to the mesothelium [112]. Several investigators have shown that TNF-α concentrations are elevated in the serum [113,114] and peritoneal fluid [115] of patients with endometriosis and the concentration found in the peritoneal fluid correlates with the stage of disease severity [116].

VEGF represents a growth factor that is greatly impacted by proinflammatory cytokines and is an important regulator of the angiogenic process crucial for the development and maintenance of endometriotic implants. VEGF is a potent selective endothelial mitogen produced by activated peritoneal macrophages, migrating neutrophils and by somatic cells within the endometriotic lesions [117–119]. Therefore, it is not surprising that expression of this factor is increased in the peritoneal fluid of endometriosis patients compared with

control women [117], that VEGF levels correlate with the stage of disease [117,119] and that this growth factor appears to play a prominent role in vascularization of endometriotic tissues [120,121]. Moreover, in a collaborative study, we previously demonstrated that soluble flt-1, a VEGF receptor antagonist, blocked the formation of ectopic human lesions in our murine model of experimental endometriosis. Specifically, we found that treating immunocompromised nude mice with the VEGF receptor antagonist was highly effective in preventing the initial establishment of human tissues as ectopic lesions, largely by preventing the formation of chimeric human–murine vessels [122]. Targeting vascular elements continues to interest endometriosis researchers and a recent study demonstrated that cabergoline, a dopamine agonist which inhibits neoangiogenesis via prevention of VEGF–VEGF receptor-2 binding, can also reduce disease burden in mice bearing experimental human endometriotic implants [123].

Although expression of any individual inflammatory cytokine described previously can be expected to exhibit wide variations between patients, it is likely that the resulting cytokine milieu culminates in the recruitment of numerous inflammatory cell types to the peritoneal cavity which contribute to the inflammatory nature of endometriosis [124]. The peritoneal fluid of women with endometriosis has been found to contain abnormally high levels of numerous cytokines, including the potent proinflammatory agents IL-1, IL-8 and TNF-α. These cytokines, produced by activated macrophages and neutrophils, contribute to a heightened inflammatory peritoneal microenvironment which promotes the establishment of ectopic disease [104]. Furthermore, IL-8 and TNF-α may additionally promote cell adhesion to the peritoneal mesothelium, establishment of a vascular supply and cell proliferation. Finally, endometriotic lesions and peritoneal mesothelial cells are also capable of producing cytokines such as TNF-α and IL-1 which can act to amplify the local production of cytokines and chemokines such as IL-8 and RANTES.

Regulators of immune action

Given the dysregulation of immune cells which appears to be a component in the pathophysiology of endometriosis, it becomes appropriate to evaluate regulators of immune homeostasis. A wide array of factors contribute to normal and pathologic immune regulation including Treg cells, steroid hormones (and their agonists and antagonists), endocrine disrupting toxicants and certain MMPs and transcription factors. For instance, steroids normally play a role in matrix remodeling as well as directing the migration and function of endometrial leukocytes; thus, a loss of normal progesterone action, identified in women with endometriosis [125], would compromise immune cell function and additionally contribute to the invasive establishment and progression of disease. Clearly, alterations in immune cell function and action may simply be a consequence of alterations in the regulators of immune cells rather than a defect within the cell itself. Indeed, altered action of immune cell regulators/effectors may help explain the observed variations in the peritoneal fluid cytokine milieu among women with and without endometriosis, as described previously.

Tregs

Tregs play a crucial role in controlling, suppressing and modulating a vast array of immune responses to infection [126,127] and tumors [128]. Specifically, these specialized immunoregulatory cells control a number of immune-related responses, as outlined by Berbic *et al*. [129]: T-cell proliferation [127] and activation [130]; macrophage, B-cell, dendritic cell and NK-cell function [131,132]; mast cell degranulation [130]; cell proliferation and cytokine release [131]. To date, little information is known regarding any specific role of Tregs in the pathogenesis of endometriosis; however, these cells have been characterized in the eutopic endometrium of women with and without this disease. In disease-free women, Tregs are most prominent during the estrogen-dominated proliferative

phase, while the number is significantly reduced during the progesterone-dominant secretory phase of the menstrual cycle. However, Tregs remain abundant within secretory-phase endometrium of women with endometriosis, perhaps reflecting the reduced progesterone responsive endometrial phenotype associated with this disease. Therefore, it is proposed that preservation of Tregs in women with endometriosis decreases the ability of newly recruited immune cell populations to effectively recognize and target endometrial antigens during menstruation, thus contributing to the survival and implantation of shed endometrial cells [129]. Similarly, suppression of local immune responses by a Treg cell-dependent mechanism could underlie deficient clearing of ectopic tissues within the peritoneal microenvironment [133]. Taken together, these data suggest that Tregs may be an attractive therapeutic target; however, the antigen specificity and origin of endometrioisis-associated Treg cells remain to be clarified. Specifically, naturally occurring Tregs are generated in the thymus while induced Tregs are produced in response to a specific microenvironment [134]. This clarification may be important, in that Tregs associated with a reduced progesterone responsive endometrium may be quite different from thymus-derived cells, potentially allowing cell-specific therapeutic targets.

Ovarian steroids

The involvement of ovarian steroids in the immunopathophysiology of endometriosis has long been established, and a woman's risk for developing this disease generally reflects her cyclic exposure to estrogen during the reproductive years. Although endometriosis can occur in young girls, the disease only rarely develops before menarche and the progression of ectopic endometrial growth is generally limited by menopause. In contrast to the role of estrogen, exposure to progesterone, via oral contraceptive use or pregnancy, is a negative risk factor for the development of endometriosis. As stated previously, the pathophysiology of endometriosis is associated with reduced endometrial responsiveness to progesterone; thus, estrogen action becomes the dominant steroidal signal at ectopic sites of growth. Estrogen dominance promotes not only the growth of endometrial tissue but also the establishment of a microenvironment in which proinflammatory cytokines and chemokines continuously recruit and activate certain immune cells. Whether at eutopic or ectopic sites of endometrial growth, loss of appropriate progesterone responsiveness promotes an inflammatory microenvironment; thus the combinatorial effect of increased estrogen action and reduced progesterone action contributes to the hyperinflammatory state associated with endometriosis. Importantly, ectopic sites of endometrial growth are associated with local production of estrogen via PGE2 upregulation of proteins and enzymes: steroidogenic acute regulatory protein, P450 side-chain cleavage enzyme, 3B-hydroxysteroid dehydrogenase type 2, 17B-hydroxylase 17,20 lyase and P450 aromatase, as reviewed by Wu *et al*. [135]. Since the peritoneal fluid concentration of PGE2 is much greater in women with endometriosis than controls [136,137], this eicosanoid is able to negatively affect macrophage's phagocytic ability and positively affect local endometriotic estrogen production, the latter of which further stimulates several mediators of inflammation including RANTES and IL-8 [138,139]. Estrogen-associated proinflammatory cytokine production also induces the recruitment of neutrophils and peritoneal macrophages to the ectopic site [140,141] and this steroid may play a role in impaired NK cell cytotoxicity [142]. These data suggest an important immunoregulatory role of estrogen in this disease in addition to its previously recognized role in stimulating endometrial cell proliferation. Given the critical role of estrogen in the pathophysiology of endometriosis, suppression of the production of this steroid through gonadotropin-releasing hormone (GnRH) analog therapy is a strategy widely used for treatment of this disease. Blocking the effects of estrogen in endometriosis patients not only inhibits the effect of this steroid on the proliferation of endometriotic cells, but also impacts the innate immune system leading to alterations in processes that are equally important to disease development and progression. For example,

GnRH analog treatments have been shown to increase the total number and activity of NK cells and T lymphocytes [69,143–145]. These findings suggest that hormonal therapies currently in use for endometriosis patients not only affect the ectopic growth of endometriotic cells but also alter the immunological microenvironment in ways that may affect, for better or worse, the disease process.

In order for estrogen and progesterone to directly influence the inflammatory microenvironment associated with endometriosis, these hormones must bind to their respective receptors, which act as transcription factors within the promoter region directly regulating gene expression [146]. However, our laboratory and others have shown that eutopic and ectopic endometrial tissues acquired from women with endometriosis exhibit a reduced responsiveness to progesterone occurring as a result of a significant reduction in progesterone receptor (PR) isotype-B expression [147], leading to a change in expression pattern of PRB/PRA [148]. Recent observations suggest that the promoter region of the PR becomes hypermethylated in women with endometriosis [149], probably explaining the diminished protein expression described by several groups [147,148]. Investigations of steroid receptor expression on immune cells have shown that peripheral and endometrial NK cells contain both PR isoforms and estrogen receptor, respectively [150,151]. In addition, one group has recently shown peritoneal and endometrial macrophages express both estrogen receptor and PR [152]. At this juncture, most studies suggest that the reduced responsiveness to progesterone associated with endometriosis would affect the anti-inflammatory action of this steroid on multiple cell types. Thus, it is important to recognize that, at both eutopic and ectopic sites of endometrial growth, the anti-inflammatory effects of progesterone on any individual cell type also affects behavior of other cells within the microenvironment. For instance, progesterone has been shown to antagonize estrogen-regulated endometrial neutrophil recruitment and function within the endometrium [153,154], therefore it remains important to determine whether normal patterns of immune cell trafficking fail to occur in women with endometriosis as a consequence of endometrial progesterone resistance. Clearly, it is possible that reduced progesterone sensitivity associated with endometriosis contributes in important ways to the establishment and maintenance of the proinflammatory environment of the disease. We have shown in an experimental model of endometriosis that the inflammatory phenotype of the eutopic endometrium observed in women with endometriosis increases the capacity of endometrial fragments from these patients to adhere and invade the peritoneal mesothelium as well as acquire a vasculature at ectopic sites of growth [155,156]. Thus, tissue inflammation and invasive behavior are clearly biologically linked to the establishment of experimental endometriosis in our disease model. Certainly, disruptions in the ability of progesterone to appropriately regulate the endometrial MMP system would be expected to contribute significantly to peritoneal inflammation since the MMP system plays a critical role in a wide variety of inflammatory processes [157]. Going forward, a better understanding of the pathophysiology of reduced progesterone sensitivity within the eutopic endometrium should enable researchers to develop targeted therapeutics which can promote the normal anti-inflammatory action of this steroid at ectopic sites.

Environmental endocrine disruptors

The development of endometriosis appears to require the contribution of multiple interactive mechanisms involving both the endocrine and immune systems. Therefore, it must be considered that external, environmental agents that are known to disrupt these systems could contribute to this disease. In this regard, TCDD is a known disruptor of steroid action in reproductive tissues, affecting steroid receptor levels, steroid-sensitive gene expression, steroid metabolism and serum transport [158–160]; thereby disrupting the known immunoregulatory effects of these steroids. It should be noted that multiple epidemiological

studies have examined the adult body burden of TCDD and PCBs with regard to the presence or absence of endometriosis; however, results have not reached a consensus. Although a recent study demonstrated that higher levels of non-dioxin-like PCBs are associated with the disease [161], the specific role of TCDD and dioxin-like PCBs remains to be clarified [35]. Nevertheless, experimental studies to date have shown TCDD to clearly act as an endocrine disrupting chemical in several systems affecting both estrogen and progesterone action. For example, TCDD is a known estrogen antagonist, and thus an altered expression of cytochromes P450 1A1 and 1B1 was noted in human endometrial organ cultures treated with TCDD [162]. In addition, given that the PR contains estrogen response elements, the ability of TCDD to disrupt estrogen signaling may represent a pathway for this toxicant to also affect progesterone action by disrupting the expression of one or both isoforms of the PR (PRA and PRB). In addition to the disruption of estrogen and progesterone action, other etiologic pathways may link exposure to this toxicant and the development of endometriosis [148]. In this regard, we have utilized an *in vitro* stromal-epithelial coculture model system to demonstrate that acute exposure to TCDD activates an inflammatory-like pattern of cell–cell communication that acts to decrease the ratio of PRB/PRA in endometrial stromal cells [148]. As we have noted in a recent article, the ability of TCDD to shift components of cell–cell communication in the human endometrium to an inflammation-like pattern provides a potential mechanistic explanation for the many studies that have linked this toxicant to the pathophysiology of endometriosis [163]. It is also important to note that TCDD and dioxin-like PCBs act through the aryl hydrocarbon receptor (AhR), a ligand-activated orphan nuclear receptor expressed in both endometrial and immune cells, allowing this toxicant to directly regulate genes expressed by both somatic and immune cell types. Since ligand-activated AhR interacts with NF-κB [164–168], it is not surprising that many of the physiological and cellular functions adversely affected by TCDD are regulated by NF-κB, such as immune activation and control of cell proliferation.

In addition to disrupting endocrine signaling, environmental agents such as TCDD and PCBs can cause chemotoxic disruption of cytokine-mediated communication among immune cells. Disruption of cytokine signaling can impair immune responses, reflected within various disease processes by either an increase or decrease in immune function. For instance, TCDD and estrogen together have been shown to increase secretion of RANTES and macrophage inflammatory protein-1α by endometriotic stromal cells [169], thus allowing TCDD to elicit some of its immuno-modulatory effects in this disease through these chemokines. Importantly, reduced NK cell cytotoxic activity and cytokine production *in vivo* and *in vitro* has been shown to correlate with higher serum levels of TCDD, PCBs and p,p'-DDE (a metabolite of dichlorodiphenyltrichloroethane, one of the most well-known synthetic pesticides). Moreover, normal peripheral blood mononuclear cells pulsed with PCBs, p,p'-DDE and their combination showed a significant downregulation of NK cell cytotoxicity [170]. Therefore, the cytotoxic ability of NK cells of women with endometriosis may be impaired, in part, owing to exposure to certain environmental toxicants. In addition, Singh and colleagues showed that TCDD induces upregulation of Fas and FasL in the thymus leading to thymic atrophy, as well as apoptosis in peripheral T cells [171,172], potentially accounting for some of the immunosuppressive effects of TCDD observed in endometriosis. Finally, given that TCDD induces thymic atrophy and deletion of activated T cells by apoptosis, this environmental toxicant may also impact the development of naturally occurring Tregs, potentially providing yet another mechanism by which TCDD exposure could promote the development of endometriosis.

Expert commentary

Despite a high rate of occurrence, endometriosis remains a poorly understood disease that is difficult to diagnose noninvasively or manage appropriately. While reduced endometrial responsiveness to progesterone is currently recognized as a central element of the pathophysiology of endometriosis, only recently has reduced sensitivity to this steroid been considered as an immunological component of the disease process. In this article, we have focused on the potential impact that reduced progesterone responsiveness has on the endocrine–immune interface of the human endometrium at eutopic and ectopic sites of growth. We have also discussed the possibility that human exposure to environmental toxicants may play a role in the development of the endometriosis phenotype. Studies from a number of laboratories, including our own, have shown that endometrial stromal and epithelial cells obtained from women with endometriosis exhibit characteristics that are distinctly different from cells obtained from disease-free women. Our studies, using various *in vitro* model systems, suggest that an inflammatory, wound-like pattern of epithelial-to-stromal cell communication may reduce the progesterone responsiveness of stromal cells, the cell type most responsible for directing endometrial preparation of pregnancy. Importantly, this loss of progesterone responsiveness subsequently disrupts the ability of stromal cells to effectively transmit paracrine signals to adjacent epithelial and immune cells, leading to alterations in the local microenvironment that not only affect the control of inflammatory processes during endometrial differentiation but also affect the dynamics of menstruation as well.

At this juncture, it remains unclear whether the immunological components of endometriosis contribute to the original development of the disease process or reflect the changes in endocrine–immune relationships that evolve as a consequence of disease progression. Although it is difficult to irrefutably link exposure to environmental agents to the development of endometriosis, humans are exposed to an astonishing array of natural and manmade chemicals. Many of these toxicants are persistent, with long half-lives; thus, these agents accumulate within our bodies and have the capacity to be transferred to the developing fetus during pregnancy. Indeed, a recent ana lysis by the Environmental Working Group revealed the presence of 287 different chemicals, including multiple dioxins and dioxin-like PCBs, within human cord blood. Although not every child was exposed to all toxicants, no child was without some exposure [201]. It is difficult to ascertain the combinatorial affects of these numerous chemicals, but certainly individual toxicants have been linked to childhood and adult cancers, immune disorders, developmental delays and alterations in reproductive tract function. Using a murine model of early life TCDD exposure, we recently demonstrated that this toxicant affects the development of the female offspring such that a similar degree of reduced progesterone responsiveness is observed as noted in women with endometriosis [37]. Interestingly, using this murine model we found that female mice exhibiting reduced progesterone responsiveness also exhibit an increased sensitivity to various inflammatory processes that affect reproductive success [173]. Although prospective human studies of early life toxicant exposures are not possible, our studies in mice clearly demonstrate that endocrine disruptors that affect progesterone responsiveness in the reproductive tract are also disruptors of inflammatory processes.

As noted in the current article, many of the alterations of the immune system and immune cell behaviors that have been observed in women with endometriosis may be a consequence of disease-related changes in the normal endocrine–immune relationships within the reproductive tract. However, in women who develop endometriosis, alterations in inflammatory processes and/or immune cell function associated with the innate immune response to retrograde menstruation may play a primary role in the initial development of ectopic endometrial growth (Figure 1). The challenge ahead is to determine whether the

initial trigger for the development of endometriosis comes from the endocrine system, the immune system or both. Importantly, sorting out the potential role(s) that environmental agents, acting as disruptors of the endocrine–immune interface, may play in the development of endometriosis represents an equally critical challenge.

Five-year view

Many researchers who study endometriosis currently view the disease as both an endocrine and immune disorder. Nevertheless, the emerging understanding that alterations in normal endocrine–immune communication pathways within the reproductive tract may predispose women to the development of endometriosis represents a major advance in our understanding of this disease. In particular, reducing the impact of the hyperinflammatory microenvironment that may affect the progression of endometriosis will be key to the development of better therapeutic strategies for this disease. In the next 5 years, our research group expects progress to be made in identifying specific immune cells or immune cell processes that can be effectively targeted for therapeutic design. For example, Tregs produced within the endocrine and immune compromised environment of endometriosis may represent an attractive therapeutic target; however, the antigen specificity and origin of endometriosis-associated Treg cells remain to be determined. Nevertheless, studies outlined herein suggest that therapies which effectively reduce systemic inflammation may also improve progesterone responsiveness within the reproductive tract. Improving endometrial progesterone response at both eutopic and ectopic sites of growth would be expected to not only improve fertility but reduce the need for long-term therapeutic intervention.

Clearly, development of improved diagnostic and treatment strategies will continue to remain at the forefront of endometriosis-associated research in the coming years. However, the recognition that this disease may have its origins within the fetal environment suggests that effective preventive strategies may also be possible. Specifically, we and others have demonstrated epigenetic modifications which may predispose a woman to reduced progesterone response and/or a hyperinflammatory response. Identifying epigenetic therapies which can reverse these modifications has the potential to dramatically reduce the incidence as well as the severity of endometriosis and related diseases. Over the next 5 years, recognition of endometriosis as an epigenetic disorder that alters normal endocrine–immune communication may well revolutionize treatment of this disease.

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Key issues

- Numerous studies have demonstrated significant alterations within the immune system which contribute to the survival and growth of displaced menstrual tissues in women with endometriosis. Although resident and recruited immune cells are dysfunctional, with an impaired ability to clear menstrual debris, these cells retain the capacity to produce proinflammatory cytokines/chemokines, further promoting the inflammatory nature of the disease. Moreover, endometrial cells from women with endometriosis exhibit hypersensitivity to inflammatory stimuli, which may additionally promote their growth inside the peritoneal cavity.
- Improved understanding of the potential origin of the overall immunopathophysiology of endometriosis is required in order to identify therapeutic target areas which may allow the alleviation, or ultimately, the prevention of this disease.
- Tregs and steroid hormones, as well as hormone agonists and antagonists such as endocrine disrupting toxicants and certain transcription factors, are known regulators of the immune response in other tissues. Thus, it is important to examine how each of these factors may contribute, alone or in concert, to immune dysfunction and pathophysiology of endometriosis.
- Our group and others have noted a progesterone-resistant endometrial phenotype in women with endometriosis, which leads to loss of the immunosuppressive actions of this steroid and a failure of appropriate communication between the endocrine and immune systems. We suggest that inflammation and endometrial progesterone resistance are key components in the development and progression of endometriosis and both may be required for establishment of disease. To this end, immune alterations that lead to progesterone resistance may arise in some women, while in other women, an endometrial progesterone-resistant phenotype may allow development of a hyperinflammatory state.
- Experimental studies indicate the developmental exposure to endocrine-disrupting chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin can lead to the development of a progesterone-resistant endometrial phenotype observed in women with endometriosis, which is hypersensitive to inflammatory stimuli, similar to that observed of women with endometriosis. We propose that the peritoneal microenvironment of women with endometriosis also exhibit a similar heightened inflammatory response which contributes to the development and persistence of this disease via promotion of a systemic, hyperinflammatory state within patients.

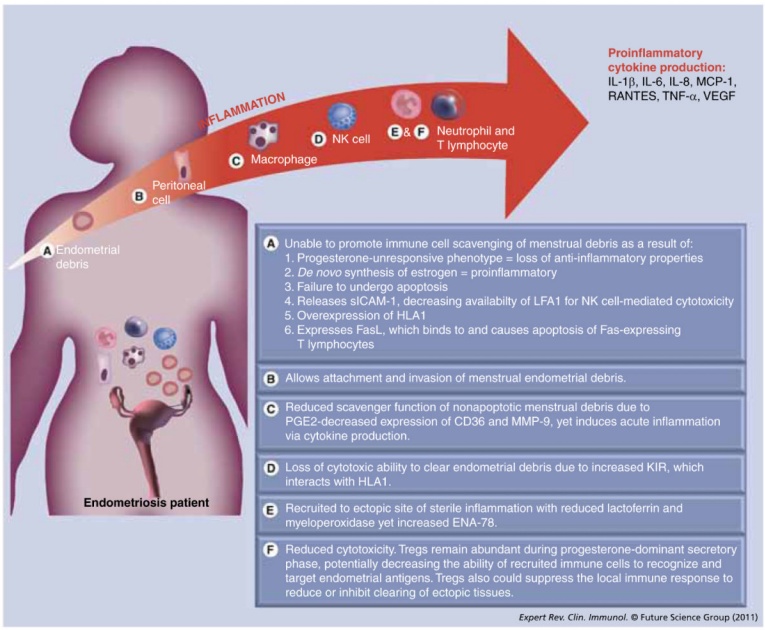

Figure 1. Current understanding of the cross-talk between endometrial cells, peritoneal (mesothelial) cells and multiple immune cells via proinflammatory chemokines/cytokines

Dysregulation of cell-mediated immunity in endometriosis, compared to disease-free women with no clinical evidence of endometriosis, accounts for the survival and growth of endometriotic tissue. Specifically, nonapoptotic menstrual debris escapes detection and elimination by immune cells, initiating an inflammatory cascade via production of chemokines/cytokines.

ENA-78: Epithelial cell-derived neutrophil-activating peptide 78; KIR: Killer-cell immunoglobulin-like receptor; LFA1: Lymphocyte function-associated antigen 1; MCP-1: Monocyte chemotactic protein-1; MMP-9: Matrix metalloproteinase-9; NK: Natural killer; PGE2: Prostaglandin E2; sICAM-1: Soluble ICAM-1.